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The immune system in cardiovascular diseases: from basic mechanisms to therapeutic implications

Xiaoyan Wang^{1,2} , Liming Chen^{1,2}, Jianming Wei³, Hao Zheng⁴, Ning Zhou⁵, Xinjie Xu⁶, Xin Deng^{1,2}, Tao Liu^{4,7,8} and Yunzeng Zou^{1,2,9}

Immune system plays a crucial role in the physiological and pathological regulation of the cardiovascular system. The exploration history and milestones of immune system in cardiovascular diseases (CVDs) have evolved from the initial discovery of chronic inflammation in atherosclerosis to large-scale clinical studies confirming the importance of anti-inflammatory therapy in treating CVDs. This progress has been facilitated by advancements in various technological approaches, including multi-omics analysis (single-cell sequencing, spatial transcriptome et al.) and significant improvements in immunotherapy techniques such as chimeric antigen receptor (CAR)-T cell therapy. Both innate and adaptive immunity holds a pivotal role in CVDs, involving Toll-like receptor (TLR) signaling pathway, nucleotide-binding oligomerization domain-containing proteins 1 and 2 (NOD1/2) signaling pathway, inflammasome signaling pathway, RNA and DNA sensing signaling pathway, as well as antibody-mediated and complement-dependent systems. Meanwhile, immune responses are simultaneously regulated by multi-level regulations in CVDs, including epigenetics (DNA, RNA, protein) and other key signaling pathways in CVDs, interactions among immune cells, and interactions between immune and cardiac or vascular cells. Remarkably, based on the progress in basic research on immune responses in the cardiovascular system, significant advancements have also been made in pre-clinical and clinical studies of immunotherapy. This review provides an overview of the role of immune system in the cardiovascular system, providing in-depth insights into the physiological and pathological regulation of immune responses in various CVDs, highlighting the impact of multi-level regulation of immune responses in CVDs. Finally, we also discuss pre-clinical and clinical strategies targeting the immune system and translational implications in CVDs.

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INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of global mortality and continue to be the primary contributor to the worldwide disease burden.^{1–3} The number of CVDs patients has doubled from 1990 to 2019, and the relevant mortality has increased by 5.5 million over that period.¹ Meanwhile, global trends for disability-adjusted life years (DALYs) and years of life lost also increased significantly.¹ Therefore, it is urgently necessary to elucidate the mechanisms of CVDs progression and, based on these mechanisms, develop new drugs to significantly reduce mortality.³

The immune system, essential for the host defending against pathogens, acts as a double-edged sword in the physiological and pathological processes of CVDs.^{4,5} Both the innate and adaptive immune systems play significant roles in this process.^{6,7} Immune cells such as macrophages, dendritic cells (DCs), T-cells, and B-

cells, which are components of the immune system, are essential for maintaining vascular health and integrity.^{8–10} The multi-level regulatory signaling pathways and mechanisms of the immune regulation also matters in CVDs.^{11–13} In addition, there's great progresses in therapeutic targets and clinical research progress (e.g., FDA-approved drugs and clinical trials) regarding the immune regulations in CVDs' treatment in recent years.^{14,15}

This review aims to illuminate the complex interplay between immune system and cardiovascular health. It offers a systematic exploration of the research achievement that have shaped our understanding of immune regulation in the cardiovascular system. Then the endotypes and immuno-features of CVDs are discussed in terms of both physiological and pathological. Also, the activation and regulation of immune responses in the context of CVDs are highlighted, including both innate and adaptive immune responses that contribute to CVDs progression. Furthermore, the

¹Shanghai Institute of Cardiovascular Diseases, Zhongshan Hospital and Institutes of Biomedical Sciences, Fudan University, Shanghai, China; ²State Key Laboratory of Cardiovascular Diseases, Zhongshan Hospital, Fudan University, Shanghai, China; ³Central Diagnostics Laboratory, University Medical Center Utrecht, University Utrecht, Utrecht, The Netherlands; ⁴Jiangsu Provincial Key Laboratory of Critical Care Medicine and Department of Critical Care Medicine, School of Medicine, Zhongda Hospital, Southeast University, Nanjing, China; ⁵Department of Cardiovascular Medicine, Anzhen Hospital Affiliated to Capital Medical University, Beijing, China; ⁶State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; ⁷Department of Biochemistry and Molecular Biology, School of Medicine, Southeast University, Jiangsu, Nanjing, China; ⁸State Key Laboratory of Respiratory Disease, Joint International Research Laboratory of Respiratory Health, National Clinical Research Center for Respiratory Disease, National Center for Respiratory Medicine, Department of Allergy and Clinical Immunology, Guangzhou Institute of Respiratory Health, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China and ⁹Institutes of Advanced Medical Sciences and Huaihe Hospital, Henan University, Kaifeng, Henan, China
Correspondence: Xiaoyan Wang (xyzheart@163.com) or Tao Liu (liut47@126.com) or Yunzeng Zou (zou.yunzeng@zs-hospital.sh.cn)
These authors contributed equally: Xiaoyan Wang, Liming Chen, Jianming Wei, Hao Zheng, Ning Zhou

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multi-level regulatory signaling pathways and crosstalk between immune and non-immune cells in CVDs are discussed, highlighting the importance of epigenetic, post-transcriptional, and post-translational modifications in modulating immune responses. Additionally, the crosstalk of key signaling pathways, such as G protein-coupled receptor and growth factor receptor pathways, with immune responses are summarized. Importantly, the review outlines preclinical strategies and clinical progress in immune regulation for CVDs, covering potential therapeutic agents, FDA-approved drugs, and ongoing trials. This review will conclude with key insights, future research directions, and the role of immunology in CVD management, highlighting new opportunities for prevention and treatment. The systematic insights provided in this review aim to furnish a current and thorough understanding of the immune response in CVDs. This knowledge is expected to contribute significantly to the future development of the immune response in both basic research and clinical translation in CVDs.

THE PAST AND PRESENT OF IMMUNOLOGY AND IMMUNOTHERAPY IN CVDS

The role of immune response in atherosclerosis was first identified by Rudolf L.C. Virchow and Nikolay Nikolaevich Anichkov more than a century ago.¹⁶ However, for decades, research mainly focused on cholesterol's central role rather than immune response in the development of human atherosclerosis.¹⁷ In 1985, researchers from Cambridge University confirmed Virchow and Anichkov's earlier views by identifying macrophage foam cell clusters forming fatty streaks in human atherosclerotic plaques.¹⁸ That year, Jonasson et al. showed that major histocompatibility complex, class II, DR Alpha (HLA-DRA), nearly absent in normal arterial walls, was significantly expressed in both immune cells and vascular smooth muscle cells (VSMCs) within atherosclerotic plaques.¹⁹ Later evidence identified monocytes, T cells as well as macrophages in these plaques, reinforcing the idea that dysregulated immune response contributes to atherosclerosis development.^{20–22} In 1977, Andreas Grüntzig developed primary percutaneous coronary intervention (PPCI), an effective treatment for preserving viable myocardium and limiting infarct size following an acute myocardial infarction (AMI).^{23,24} However, myocardial reperfusion can cause additional death of previously viable cardiac myocytes, known as myocardial reperfusion injury, which can contribute up to 50% of the final infarct size.²⁵ By the 1980s, researchers identified vascular immune dysregulation in coronary arteries before myocardial infarction (MI) and cardiac inflammation after MI. Furthermore, ischemia-reperfusion injury (IRI) is partly caused by a burst of oxygen free radicals, which leads to lipid peroxidation and membrane damage, with neutrophils as a potential source of these free radicals.^{26–28} While most pre-clinical studies focus on biological processes induced by AMI, Sarah A. Dick and Slava Epelman highlighted that the balance between physiological and pathological immune dysregulation also influences the progression of chronic heart failure (HF).²⁹ In the 1990s, researchers found that low-grade chronic inflammation might contribute to clinical deterioration in patients with non-ischemic heart failure.^{30,31} Moreover, HF, whether ischemic or non-ischemic, is frequently linked to increased plasma levels of pro-inflammatory cytokines like tumor necrosis factor- α (TNF- α) and soluble TNF- α receptor, which are associated with worse clinical outcomes.³² In 1994, Attilio Maseris, a prominent cardiologist in ischemic heart disease, made significant contributions to understanding the inflammatory pathogenesis of unstable angina. His group discovered that elevated acute-phase reactants, like C-reactive protein (CRP) and serum amyloid A (SAA), predicted poor outcomes in unstable angina patients.³³ This observation highlighted the role of immune system in unstable angina, and the findings were soon expanded upon by

another research team. Paul Ridker et al. discovered that prediction models combining inflammatory markers (hs-CRP, SAA, interleukin-6, soluble intercellular adhesion molecule-1 (sICAM-1)) along with lipid levels more accurately predicted cardiovascular risk than models based solely on lipids.^{34,35} These studies established pro-inflammatory cytokines as key prognostic indicators by linking dysregulated immune response to increased cardiovascular risk. Later that year, Paul Ridker and colleagues found that elevated plasma TNF- α in post-MI patients was linked to a higher risk of recurrent coronary events and was predictive of CVDs prognosis.³⁶ In 2003, Roman et al. reported that patients with chronic inflammatory diseases have an increased prevalence of underlying atherosclerosis compared with healthy controls, independent of traditional risk factors, indicating atherogenesis is associated with systemic inflammation that occurs prematurely.³⁷ In 2005, lymphoid follicle-like structures in the aged aorta of *Apoe*^{-/-} mice, now known as tertiary lymphoid organs (TLOs), were characterized by the aggregation of T and B cells.³⁸ Furthermore, in 2015, Andreas' group elucidated the protective role of TLOs against atherosclerosis progression.³⁹ Of note, recent advances in single-cell technologies, such as single-cell mass cytometry, cellular indexing of transcriptomes and epitopes by sequencing, and single-cell RNA sequencing (scRNA-seq), have significantly enhanced our understanding of immune and non-immune cell interactions in atherosclerotic tissue, marking a major leap in studying immune heterogeneity.^{10,40} In 2023, Sun et al. found TLOs present in various CVDs and used 28 single-cell RNA sequencing datasets to investigate their formation and heterogeneity.⁴¹ Also, Rafael Kramann's group utilized single-cell spatially resolved transcriptomics to map gene regulation and cardiac remodeling in human tissue post-MI.⁴² Additionally, immunotherapies for cancer, like immune checkpoint inhibitors (ICIs), which boost immune surveillance against tumors and are increasingly used in various cancers, have been associated with cardiovascular events.⁴³ The CAR-T cells in vivo by delivering modified messenger RNA (mRNA) in T cell-targeted lipid nanoparticles (LNPs) could reduce fibrosis and restore cardiac function after injury.^{15,44,45}

Building on these significant discoveries, numerous clinical trials are currently underway to explore and validate new therapeutic strategies. In 2017, Ridker et al. reported that administering 150 mg of canakinumab every three months significantly lowered the risk of recurrent cardiovascular events compared to placebo in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS).⁴⁶ The CANTOS study was groundbreaking, being the first large-scale trial to show that targeting interleukin-1 β (IL-1 β) with anti-inflammatory treatment significantly reduces cardiovascular events in coronary heart disease patients. In 2019, the Colchicine Cardiovascular Outcomes Trial (COLCOT) underscored the role of inflammation in coronary atherosclerosis by demonstrating that low-dose colchicine reduces cardiovascular events in patients with a history of myocardial infarction.⁴⁷ Overall, these clinical trials emphasize the importance of targeting the immune system in individuals with residual inflammatory risk, highlighting the potential of immune-targeted therapies to improve cardiovascular health (Fig. 1).

IMMUNO-FEATURES IN CARDIOVASCULAR SYSTEM UNDER PHYSIOLOGICAL CONDITIONS

Cardiovascular homeostasis relies on the precise coordination of immune cells, signaling pathways, and cell interactions to maintain an inflammation-free environment essential for optimal cardiac function.⁴⁸ The immune system's role in the heart under physiological conditions involves finely tuned responses from various immune cell types that contribute to tissue repair, maintenance, and immune surveillance without triggering an inflammatory cascade⁴⁸ (Fig. 2).

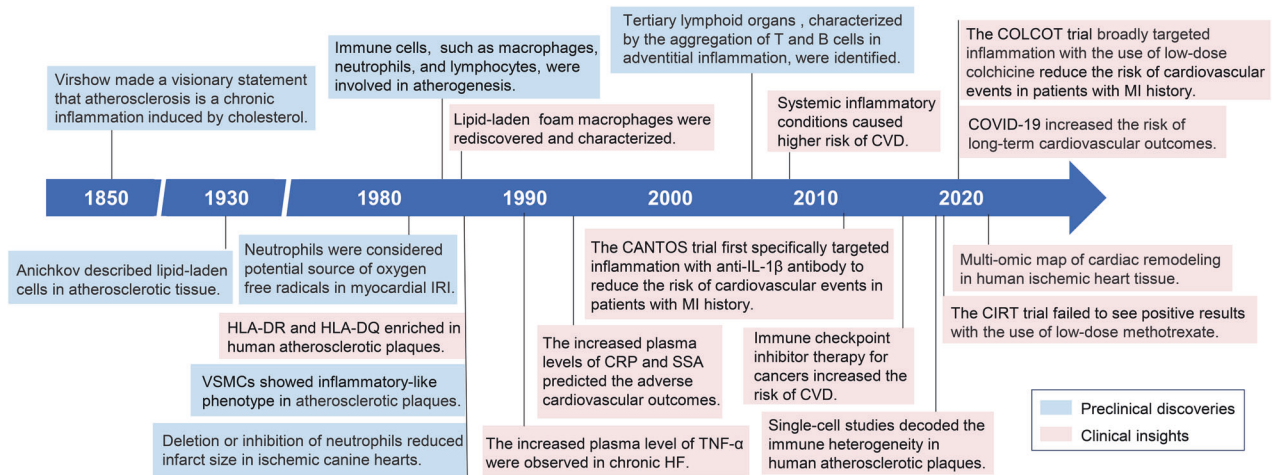


Fig. 1 Timeline of key milestones in the development of immunology and immuno-therapy in CVDs in cardiovascular diseases. IRI ischemia-reperfusion injury, HLA-DR Major Histocompatibility Complex, Class II, DR, HLA-DQ Major Histocompatibility Complex, Class II, DQ, VSMCs vascular smooth muscle cells, TLOs tertiary lymphoid organs, CVDs cardiovascular diseases; CANTOS the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), CRP C-reactive protein, SSA serum amyloid A, TNF- α tumor necrosis factor- α , HF heart failure, COLCOT the Colchicine Cardiovascular Outcomes Trial, COVID-19 Coronavirus Disease 2019, CIRT the Cardiovascular Inflammation Reduction Trial

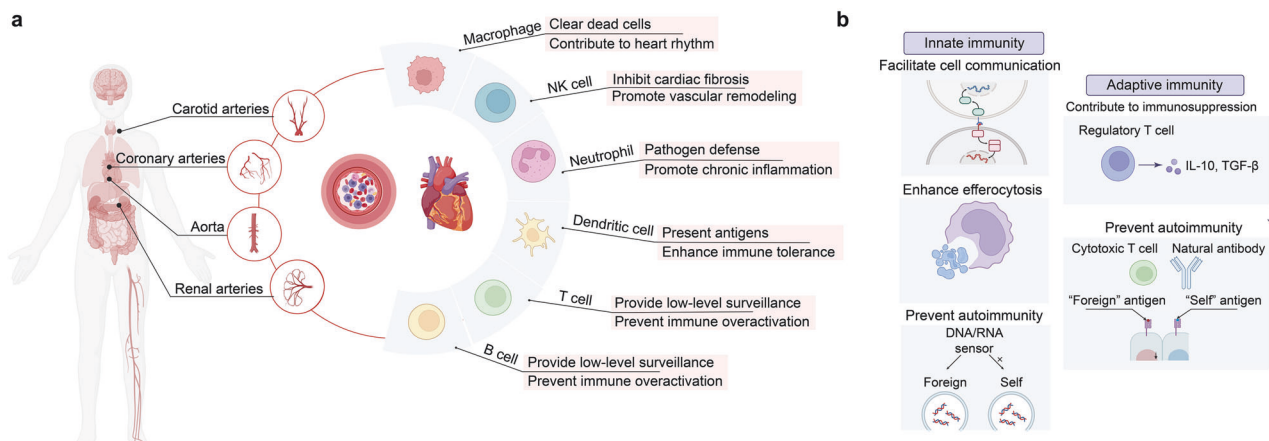


Fig. 2 Immuno-features in cardiovascular system under physiological conditions. **a** Overview of Immune cell in cardiovascular system; **b** Innate and adaptive Immune Signaling Pathways in Cardiovascular Homeostasis (Created with BioRender.com, <https://BioRender.com/i19e947>)

Overview of immune cell in cardiovascular system

Innate and adaptive immune cells play crucial roles in both the homeostasis and pathogenesis of the cardiovascular system.^{49,50} The main types of innate immune cells involved in cardiovascular diseases (CVDs) include neutrophils, monocytes/macrophages, eosinophils, dendritic cells (DCs), mast cells, natural killer cells and innate lymphoid cells.^{49,51} The adaptive immune cells include CD4+ T_{em}, such as effector-memory CD4+ T cells, CD4+ T_{cytox}, CD4+ cytotoxic T cells, CD8+ T_{em}, CD8+ effector-memory T cells, CD8+ T_{cytox}, CD8+ cytotoxic T cells, and B cells, such as marginal zone B cells, and regulatory B cells (Bregs).^{12,49,50,52} The origin of immune cells in the cardiovascular system is diverse.^{53–57} Innate immune cells, like tissue-resident macrophages (C-C chemokine receptor type 2-, CCR2- macrophages), may develop from the yolk sac and fetal liver progenitors,^{8,53,54,57} while CCR2+ macrophages are derived from the recruited monocyte.⁸ Others are continuously replenished from bone marrow-derived progenitors.^{58–63} Among the overall cell population, the largest cell populations are macrophages/monocytes and B cells, followed by Natural Killer cells (NK cells).¹²

Macrophages phagocytose bacteria, clear dead cells, and contribute to cardiac rhythm. They are abundant within cardiac tissue and serve various functions, including phagocytosing bacteria and clearing dead cells, which help prevent tissue inflammation and support cell turnover.^{8,48,64} Notably, macrophages form direct connections with cardiomyocytes via connexin 43 (Cx43) gap junctions, enabling electrical coupling that modulates cardiomyocyte activity and contributes to cardiac rhythm maintenance without promoting inflammation.^{65,66} Moreover, macrophages appear to play a role in cardiac renewal. Under normal conditions, macrophages remain in an anti-inflammatory state but can shift to a pro-inflammatory phenotype in¹² response to minor injuries, facilitating repair and clearance of damaged tissue without excessive inflammatory responses.⁶⁴

NK cells inhibit cardiac fibrosis and promote vessel remodeling. NK cells support immune regulation by controlling the extent of inflammation, preventing immune cell over-accumulation in cardiac tissue, and thus preserving cardiac stability.^{48,67} NK cells play a critical role in preventing cardiac fibrosis by directly limiting

collagen production in cardiac fibroblasts and curbing the buildup of specific inflammatory populations and profibrotic cell types, such as eosinophils, within cardiac tissue.⁶⁸ Upon activation through IL-2 administration, NK cells facilitate blood vessel remodeling via $\alpha 4 \beta 7$ integrin and killer lectin-like receptor subfamily G member 1 (KLRG1), independent of their involvement in initial vascular formation.⁶⁹ Activated NK cells initially adhere to cardiac epithelial cells (CECs) through $\alpha 4 \beta 7$ integrin and vascular cell adhesion molecule 1 (VCAM-1), disrupting N-cadherin bonds via KLRG1.⁶⁹ This interaction translocates β -catenin from the cytoplasm to the nucleus, alleviating contact inhibition and promoting cellular proliferation.⁶⁹

Neutrophils prevent chronic inflammation and infections. Neutrophils contribute to cardiovascular health by performing tissue surveillance, patrolling the vascular endothelium, and identifying potential pathogens or tissue damage, which helps maintain cardiac integrity and prevent infections.^{70,71} Under normal conditions, neutrophils produce reactive oxygen species (ROS) in controlled amounts, essential for pathogen defense and promoting cellular repair, with regulated ROS release avoiding oxidative stress.^{72,73} Additionally, neutrophils release proteolytic enzymes, including elastase and matrix metalloproteinases (MMPs), which facilitate extracellular matrix remodeling and vascular adaptability.⁷⁴ Through vascular endothelial growth factor (VEGF) release, neutrophils promote angiogenesis, supporting the formation and maintenance of blood vessels crucial for oxygen supply in metabolically active cardiac tissue.⁷⁵ By signaling macrophages to phagocytize apoptotic cells, neutrophils help reduce inflammation, prevent unnecessary immune activation, and maintain cardiac immune balance.⁷⁶ Overall, neutrophils play a supportive role in cardiac function by balancing immune responses, preventing chronic inflammation, and promoting tissue integrity.

DCs present antigens and enhance immune tolerance. DCs in cardiac tissue serve as antigen-sensing sentinels, continuously surveying for foreign antigens or cellular abnormalities, thus preventing infections while maintaining tolerance to self-antigens to avoid autoimmunity.⁷⁷ They regulate local inflammation by presenting antigens to T cells and activating anti-inflammatory pathways, which minimize immune activation that could harm cardiac tissue.⁷⁸ DCs also monitor endothelial health by detecting changes in the endothelial environment, supporting vascular integrity, and facilitating the clearance of apoptotic cells, thus preventing inflammatory responses caused by cellular debris and contributing to overall cardiac stability.⁷⁹

Regulatory T/B cells prevent excessive immune activation while effector T/B cells provide low-level surveillance. By secreting anti-inflammatory cytokines like IL-10, Regulatory T cells (Tregs) prevent excessive immune activation that could lead to inflammation in cardiac tissue. This helps prevent autoimmunity and chronic inflammation within the heart, maintaining a balanced immune environment.⁸⁰ While Tregs aid in immunosuppression, effector T cells provide low-level surveillance, ensuring any damaged or abnormal cells within the cardiovascular system are promptly recognized and, if necessary, cleared.⁸¹ B cells contribute to normal cardiac function by maintaining immune homeostasis within the cardiac environment. Bregs play a critical role in this process by producing anti-inflammatory cytokines, such as IL-10, which prevent excessive inflammation that could disrupt normal cardiac function.⁸² Furthermore, B cells produce antibodies that identify and neutralize pathogens in the bloodstream, helping to prevent infections that could indirectly affect the heart by triggering systemic immune responses.^{83,84} In addition, B cells regulate autoimmune responses by controlling antibody diversity, limiting self-reactive antibodies that could target cardiac tissue and ensuring cardiac stability.⁸⁵ Certain B cell subsets also release

factors that support tissue repair, which is beneficial for minor myocardial injuries, enhancing cardiac resilience and structural integrity.^{82,86,87} Moreover, B cells interact with macrophages and T cells in the cardiac environment to promote a balanced immune response, ensuring that immune reactions are proportional and supportive of cardiac health.⁸⁸ Collectively, these functions allow B cells to play a multifaceted role in preventing unnecessary inflammation, controlling autoimmunity, providing immune surveillance, and supporting tissue integrity in the heart.)

Innate and adaptive immune signaling pathways in cardiovascular homeostasis

Innate immune signaling pathways facilitate cell-to-cell communication, enhance efferocytosis, and prevent autoimmunity. Certain cells, such as resident macrophages and endocrine cells, respond to external stimuli or internal signals by producing and releasing chemokines, which act as messengers to convey information to neighboring cells. These bioactive mediators can orchestrate different cell types within a particular tissue, modulating a wide range of physiological processes, such as development, growth and renewal. Furthermore, nucleic acid-recognizing molecules, such as the DNA and RNA sensors are directly involved in regulating cardiovascular behaviors through interacting with other intracellular homeostatic processes, including apoptosis and autophagy, thereby regulating cardiometabolic health.⁸⁹ This biological process largely depends on their ability to discriminate self-DNA/RNA from non-self DNA/RNA, suppressing uncontrolled autoimmune response.⁹⁰ Importantly, incorrect self-DNA/RNA recognition could lead to the release of specific autoantibodies, indicating that DNA/RNA sensors serve as critical immune checkpoints and control the autoimmune responses.⁹¹ On the other hand, the activation of these immune pathways in phagocytes helps facilitate the resolution of apoptotic cells harboring damaged self-DNA/RNA following programmed cell death.^{92,93}

Adaptive immune signaling pathways contribute immunosuppression and prevent autoimmunity. Tregs exert an immunosuppressive function through the production of anti-inflammatory cytokines like TGF- β and IL-10, playing a role in maintaining peripheral tolerance.⁹⁴ However, they also limit sterilizing immunity against abnormal self, such as cancer cells and mutated cells.⁹⁵ Usually, these transformed target cells could be eliminated by cytotoxic T lymphocytes (CTLs).⁹⁶ In addition to the cell-mediated adaptive immune response, specific antibodies produced by B cells also play a role in maintaining the homeostasis of the cardiovascular system. For example, cardiovascular-reactive natural antibodies (NABs) can be produced in the absence of infection, even under homeostatic conditions. NABs interact with multiple self-derived antigens, providing benefits in autoimmunity prevention.⁹⁷

THE ENDOTYPES AND IMMUNO-FEATURES OF CVDs

CVDs encompass various endotypes such as hypertension, atherosclerosis, ischemic heart disease, cardiac remodeling, chronic heart failure, metabolic cardiomyopathy, diabetic cardiomyopathy, aortic disease, cardiac aging, arrhythmia, inflammatory and infectious cardiomyopathy, cardiotoxicity of antitumor drugs, and thrombotic disease. Traditionally, CVDs were understood through their pathophysiological aspects, like plaque buildup and heart muscle failure. However, recent advancements have revealed the immuno-features in the pathogenesis and progression of these diseases (Fig. 3).

Hypertension and immuno-dysregulation

Hypertension is a global health challenge, impacting over 1.3 billion people worldwide, with an increasing prevalence among

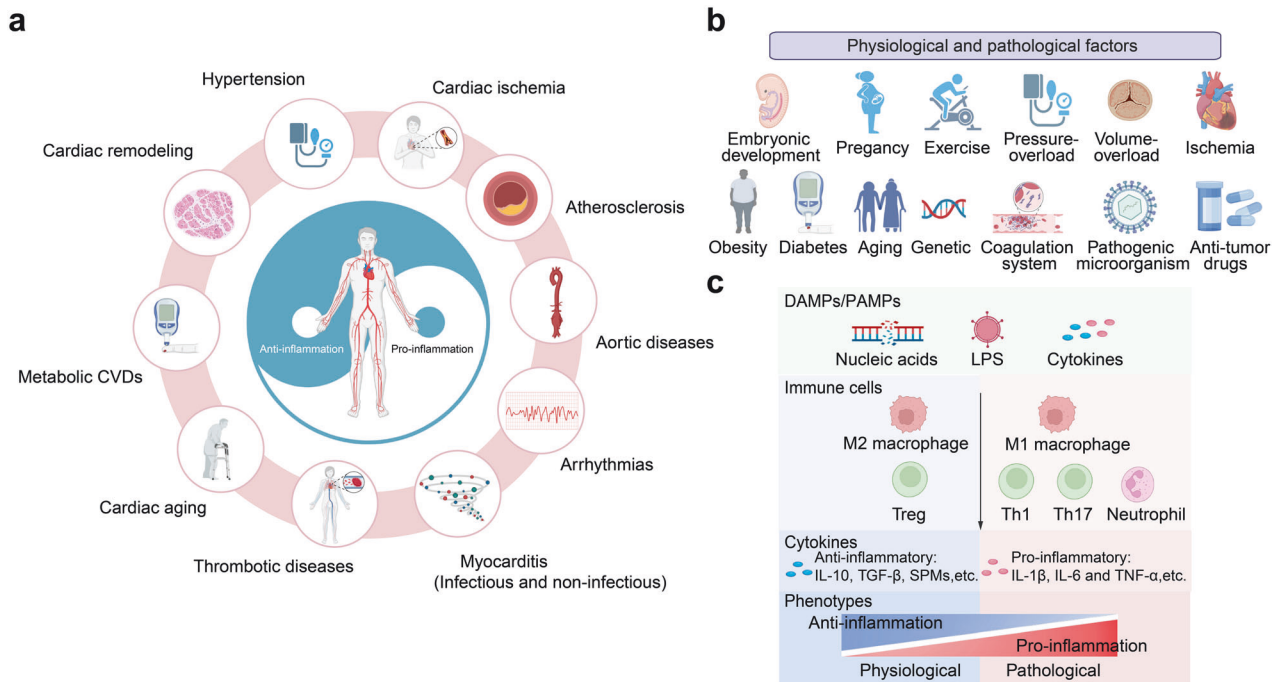


Fig. 3 Mechanisms of Immune Regulation in Physiological and Pathological Processes of CVDs. **a** Immune regulation in various kinds of CVDs. **b** Physiological and pathological factors in CVDs. **c** Physiological and pathological immune regulation in CVDs. CVDs cardiovascular diseases, PAMPs Pathogen-Associated Molecular Patterns, DAMPs Damage-Associated Molecular Patterns, LPS Lipopolysaccharide, Tregs Regulatory T cells, Th1 cell T helper 1 cell, Th17 cell T helper 17 cell, IL-10 Interleukin-10, TGF- β Transforming Growth Factor-beta, SPMs Specialized Pro-resolving Mediators, IL-6 Interleukin-6, TNF- α Tumor Necrosis Factor- α (Created with BioRender.com, <https://BioRender.com/r16i827>)

younger individuals.^{98,99} Emerging evidence suggests that the development of hypertension is closely linked to immune dysregulation.^{100,101} Genetic and integrative network analysis showed that some single-nucleotide polymorphisms (SNPs) or genes related to immune response have been implicated in hypertension.¹⁰² In individuals with immune-mediated diseases, the risk of developing hypertension increases by 22% to 90%.^{103–106}

Immune regulation in normal blood pressure. Normal blood pressure regulation is based on a delicate balance between pro-inflammatory and anti-inflammatory responses. Tregs are vital for vascular homeostasis under physiological conditions, as they suppress excessive inflammation and oxidative stress by producing anti-inflammatory cytokines like IL-10 and TGF- β , thereby maintaining normal endothelial function and vascular tone.^{107,108} Also, resident macrophages in the vessel wall and perivascular adipose tissue contribute to blood pressure regulation by modulating vascular reactivity and NO production.⁸ DCs maintain a tolerogenic state under normal conditions, preventing over-activated immune response that could lead to hypertension.^{109–111} Moreover, renal DCs interact with tubular cells to maintain normal renal sodium handling and blood pressure by regulating local inflammation.¹¹² Additionally, the immune system closely interacts with the nervous system to regulate blood pressure. Vagus nerve activation reduces excessive inflammation by releasing acetylcholine to lower pro-inflammatory cytokines production, while the sympathetic nervous system regulates immune cell function and trafficking, maintaining balanced blood pressure.^{113,114}

Immune dysregulation in hypertension. Hypertension often results from chronic, dysregulated inflammation driven by various immune and non-immune cells, including T cells and endothelial cells (ECs).¹¹⁵ Its onset can be triggered by factors like renin-angiotensin-aldosterone system activation, the sympathetic

nervous system (SNS) stimulation, high salt intake, stress, eicosanoid changes, mechanical forces, or proteasome inhibitors treatment.^{109,116} These pro-hypertensive stimuli drive the release of upstream inflammatory regulators, leading to local inflammation and mechanical and oxidative damage.^{109,116,117}

T cells play a vital role in the development of hypertension. The increase in CD3+CD45RO+ memory T cells, especially CD8+ effector memory T cells, which exhibit upregulation of pathways related to mitochondrial oxidative metabolism and inflammatory activation, is also associated with hypertension.^{118,119} Moreover, activated DCs produce IL-6, IL-23, and IL-1 β , which drive T cell polarization and the production of effector cytokines.¹⁰⁹ In addition to immune cells, non-immune cells such as endothelial cells can also affect the progression of hypertension.^{109,120} For example, IL-10 deficiency aggravates angiotensin II-induced endothelial dysfunction and superoxide production, which contribute to hypertension.¹²¹ This immune-endothelial crosstalk illustrates the complex interactions that drive hypertension.

Atherosclerosis and immuno-dysregulation

Atherosclerosis, the primary underlying pathology of coronary artery disease (CAD), is characterized by the chronic accumulation or acute rupture of vessel-occluding plaques in the subendothelial intimal layer of large and medium-sized arteries.¹²² This process ultimately leads to significant stenosis, restricting blood flow and causing critical tissue hypoxia.

Immune regulation in vascular homeostasis. Under physiological conditions, the immune system plays a critical role in maintaining vascular health through balanced inflammatory and anti-inflammatory responses. ECs are central to this process, as they maintain vascular tone, support hemostasis, and regulate thrombosis.^{123,124} ECs respond to inflammatory signals by secreting mediators that initiate both innate and adaptive immune responses.¹²⁵

In normal inflammation, immune cells like neutrophils and macrophages produce cytokines and chemokines to amplify the

localized immune response. These molecules recruit additional immune cells, creating a balance between pro-inflammatory cytokines such as TNF- α , IL-6, and IL-1, and anti-inflammatory mediators like IL-10 and TGF- β , which are essential for vascular stability and function.¹²⁶ Tregs further aid in this process by modulating inflammatory responses and preventing excessive vascular inflammation.^{107,108}

Immune dysregulation in atherosclerosis development. The initiation of atherosclerosis is driven by immune dysregulation triggered by hemodynamic forces, particularly in regions of low shear stress. This hemodynamic environment contributes to endothelial dysfunction, allowing the infiltration of apolipoprotein B (ApoB)-containing lipoproteins into the subendothelial space.¹²⁷ Upon activation, endothelial cells secrete chemokines that recruit monocytes, which differentiate into macrophages within the vascular wall. These macrophages, upon taking up lipoproteins, transform into lipid-laden foam cells, marking the onset of plaque formation.¹²⁷

Additionally, antigen-presenting cells (APCs) such as macrophages and DCs present lipid and peptide antigens to invariant natural killer T (iNKT) cells and T cells. This interaction triggers adaptive immune responses that contribute to plaque progression.¹²⁸ Single-cell transcriptomics have shown that VSMC-derived foam cells constitute a significant portion of foam cells, with these cells demonstrating phenotypic plasticity.¹²⁸ They can adopt macrophage-like characteristics that exacerbate lesion growth or fibroblast-like traits that stabilize plaques.^{129–131} Collectively, these processes worsen endothelial dysfunction and drive additional inflammation through continued monocyte recruitment, increased lipoprotein uptake (which adds to the plaque's lipid load), VSMC activation and proliferation, and fibroblast migration, which aids in forming the fibrous cap.

Immune crosstalk and plaque progression. The progression of atherosclerosis involves continuous immune cell recruitment and inflammation. Monocytes migrate to the subendothelial layer, where they differentiate into macrophages, perpetuating inflammatory responses through cytokine production and further lipoprotein uptake, which contributes to plaque lipid accumulation.¹²⁶ VSMC activation and proliferation add to the plaque mass, while fibroblast migration contributes to the formation of a fibrous cap that stabilizes the plaque but can also increase the risk of rupture in vulnerable plaques.¹²⁶

The crosstalk between immune cells in atherosclerosis highlights the intricate interactions at play, involving not only the innate immune system but also adaptive immune responses that drive disease progression. This cross-talk between immune cells and vascular structures reinforces inflammation, fostering an environment conducive to plaque buildup and instability, which underpins the pathology of atherosclerosis and its progression to CAD.

Ischemia heart disease and immuno-dysregulation
Ischemia heart disease occurs when blood flow to the heart muscle is reduced, usually due to partial or complete blockage of coronary arteries. The most common cause is atherosclerosis—the buildup of plaque in the coronary arteries.¹³² Other causes can include coronary artery spasm, thrombosis, and coronary artery dissection.^{133,134} Ischemic heart disease has the highest global age-standardized DALY at 2275.9 per 100,000.¹³⁵ It occurs when blood flow to the heart muscle is reduced, usually due to partial or complete blockage of coronary arteries.

Immune dysregulation in ischemia heart disease. The immune response plays a complex and stage-specific role in myocardial ischemia, encompassing both inflammatory and reparative processes. Within hours following ischemic injury, CD4 + T helper

cells, particularly Th1 and Th17 subsets, are recruited to the myocardium,¹³⁶ where they produce pro-inflammatory cytokines, such as IFN- γ and IL-17, which escalate inflammation and attract additional immune cells to the site.¹³⁷ This early influx of pro-inflammatory cells establishes a highly reactive environment that can lead to exacerbated injury if unchecked. Tregs are also quickly activated during the early stages of the ischemic response, playing a protective role by modulating inflammation and promoting tissue repair. They secrete anti-inflammatory cytokines like IL-10 and TGF- β , which help to control excessive inflammation and support the resolution phase.¹³⁸ This dual response highlights the immune system's dynamic involvement, with both pro-inflammatory and anti-inflammatory pathways engaged in managing ischemic damage.

B lymphocytes are activated within the first 24–48 h post-ischemia, contributing to the early immune response through antigen presentation and production of auto-antibodies against cardiac antigens exposed during tissue damage.¹³⁹ Some subsets of B cells, particularly regulatory B cells, may have a protective role by producing IL-10 and modulating T cell responses.¹⁴⁰ Thus, modulating the activity of lymphocytes may offer promising approaches to mitigate ischemic injury and improve cardiac outcomes.

Crosstalk and therapeutic implications in immune response to ischemia. Crosstalk among immune cells in ischemic heart disease is critical, as it shapes the progression and resolution of inflammation in myocardial tissue. For instance, interactions between Tregs and Th17 cells modulate the intensity and duration of the inflammatory response, with an overactive Th17 response potentially leading to prolonged inflammation and myocardial damage, while Tregs help suppress excessive immune activation.^{80,141} This balance is essential for tissue recovery, and dysregulation at any stage can exacerbate ischemic injury or hinder repair mechanisms.

B cells also interact with T cells in the ischemic heart, influencing the overall immune response; while effector B cells promote inflammation through antigen presentation and antibody production, regulatory B cells help mitigate immune activation.^{84,142} Understanding these interactions provides insights into potential therapeutic approaches to limit ischemic injury, highlighting the value of targeting specific immune cell types or pathways to enhance cardiac recovery and prevent further ischemic damage.

Cardiac remodeling and immuno-dysregulation

Cardiac remodeling involves structural and functional changes in the heart due to hemodynamic overload and/or cardiac injury.¹⁴³ Changes in the heart's size, shape, and function are clinically observed and detected through echocardiography, magnetic resonance imaging (MRI), positron emission tomography (PET) scans, ventriculography, and tomography.^{144–146} Remodeling can be either physiological or pathological, classified as adaptive or maladaptive.¹⁴³ Physiological hypertrophy, occurring during development, pregnancy, or endurance training, is fully reversible.^{147–149} It features mild heart growth (10–20% larger than normal), no reactivation of fetal genes, increased cardiomyocyte growth in both length and width, angiogenesis, and lack of apoptosis and interstitial fibrosis.¹⁴³ However, pathological remodeling occurs in acute and chronic phase of MI, pressure-overloaded conditions, volume-overloaded conditions, or genetic changes.

Immune regulation in physiological cardiac remodeling. The immune system plays a critical role in modulating physiological cardiac remodeling during both development and in adulthood.¹⁵⁰ In normal conditions, cardiac-resident macrophages, derived from embryonic origins, predominate and are maintained

through local proliferation. These macrophages support homeostasis by modulating local inflammation and promoting angiogenesis without triggering adverse remodeling.^{55,151,152} Additionally, circulating CCR2+ monocytes contribute minimally to the cardiac macrophage population under these conditions, highlighting the importance of resident macrophages in maintaining physiological homeostasis.^{55,151}

Physical exercise has been shown to modulate macrophage function by promoting a shift from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages. This transition helps enhance cardiac function and minimize interstitial fibrosis, suggesting that lifestyle interventions could modulate immune responses favorably.¹⁵³ Exercise also activates cardiac-resident stem cells, contributing to cardiac repair and regeneration through immune modulation.¹⁵⁴

Immune regulation in pathological cardiac remodeling. Pathological cardiac remodeling occurs following cardiac injury or sustained mechanical stress. This process involves significant changes in the immune system, with infiltrating monocytes and macrophages exacerbating adverse remodeling.¹⁵⁵ In this context, mechanical stress activates innate immune responses, leading to the recruitment of neutrophils and macrophages to the myocardium. These cells release pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, which contribute to cardiomyocyte hypertrophy, fibrosis, and tissue damage.

The balance between M1 and M2 macrophages influences the progression of pathological remodeling, where an excess of M1 macrophages can drive fibrosis and hypertrophy, while M2 macrophages attempt to counteract these effects.¹⁵⁶ Cardiac-resident macrophages exhibit a protective effect by regulating inflammation, whereas infiltrating monocyte-derived macrophages contribute to adverse outcomes. Additionally, T cells, particularly CD4+ T cells, infiltrate the myocardium, promoting fibrosis and inflammation, thereby contributing to ventricular stiffness and dysfunction.¹⁴²

Immune crosstalk and heart failure development. The development of heart failure involves intricate interactions between innate and adaptive immune responses. Initially, cardiac injury triggers the activation of innate immune cells, including macrophages and neutrophils, which release pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6.¹⁵⁷ These cytokines promote inflammation and cardiac remodeling by promoting hypertrophy and fibrosis.¹⁵⁷ As heart failure progresses, chronic immune activation becomes prominent, marked by the involvement of adaptive immune cells, particularly T lymphocytes. CD4+ and CD8+ T cells expand systemically and infiltrate the failing myocardium.¹⁵⁸ This persistent immune activation leads to a state of chronic low-grade inflammation that exacerbates cardiac dysfunction. Also, compensatory anti-inflammatory mechanisms are activated, including the production of IL-10 and TGF- β , in an attempt to resolve inflammation and promote tissue repair.¹⁵⁹ However, the balance between pro- and anti-inflammatory processes eventually becomes dysregulated, leading to maladaptive ventricular remodeling and the progression of heart failure.¹⁵⁹

The neurohumoral activation induced by mechanical stress also interacts with immune responses, enhancing inflammation and contributing to adverse remodeling.¹⁶⁰ Over time, compensatory anti-inflammatory mechanisms, such as the production of IL-10 and TGF- β , attempt to resolve inflammation and promote tissue repair. However, this balance between pro- and anti-inflammatory factors becomes dysregulated in chronic heart failure, leading to further deterioration.

Metabolic cardiomyopathy and immuno-dysregulation

Metabolic cardiomyopathy is a chronic metabolic disorder characterized by structural and functional cardiac changes,

occurring independently of hypertension and coronary artery disease. It involves interstitial fibrosis, diastolic and systolic dysfunction, and cardiomyocyte injury. In its early stages, metabolic disturbances may not significantly affect myocardial structure or cardiac function, but they induce low-grade inflammation in the heart, leading to impaired myocardial relaxation due to abnormalities in subcellular components, such as endoplasmic reticulum stress, oxidative stress, calcium handling, and impaired mitochondrial dysfunction. In the advanced stage, a vicious cycle of subcellular component abnormalities and immune cell infiltration leads to cardiomyocyte injury, death, and cardiac fibrosis, ultimately impairing both diastolic and systolic functions.¹⁶¹

Immune regulation in myocardial metabolism. Recent studies have highlighted the impact of cellular metabolism on immune activation, with coordinated regulation benefiting the organism by optimizing energy resources during immune or inflammatory responses.¹⁶² Nutrient-sensing pathways can trigger immune responses, while inflammatory or stress responses inhibit anabolic pathways like insulin/insulin-like growth factor (IGF) signaling, diverting energy metabolism from synthesis to catabolism.¹⁶³ A key concept in this context is “trained immunity,” which refers to the long-term functional reprogramming of innate immune cells, especially monocytes and macrophages, following metabolic stress or inflammatory stimuli. This adaptation can contribute to the sustained low-grade inflammation seen in cardiometabolic diseases.¹⁶⁴

Immune dysregulation in metabolic cardiomyopathy. Emerging clinical evidence indicates strong links between the immune system and the development of metabolic cardiomyopathy.¹⁶¹ Macrophages play a crucial role in the development of metabolic cardiomyopathy.⁸ M1 macrophages secrete inflammatory cytokines that impair systemic and cardiac insulin signaling, and their presence is associated with metabolic cardiomyopathy induced by a Western diet in mice.¹⁶⁵ Additionally, inflammation in β -cells leads to β -cell dysfunction, which combined with insulin resistance, exacerbates the condition.¹⁶⁶

Beyond immune cells, endothelial cells and myofibroblasts in metabolic cardiomyopathy contribute to dysregulated immune responses.^{167–169} For instance, in human epicardial adipose tissue treated for diabetes, pro-inflammatory cytokines like TNF- α and IL-1 β induce an inflammatory phenotype in human coronary endothelial cells, resulting in diminished vascular progenitor potential and promoting cardiomyopathy development.^{170,171} Furthermore, myofibroblasts activated by inflammatory mediators such as IL-13, IL-18, and MMPs play a significant role in initiating myocardial fibrosis. This process increases cardiac stiffness and impairs the heart's contractile and relaxation functions.¹⁷² The interplay between immune cells and these non-immune cells perpetuates a cycle of inflammation and fibrosis, which ultimately leads to metabolic cardiomyopathy progression.

Aortic diseases and immuno-dysregulation

Aortic diseases are a variety of conditions affecting the aorta, the main artery, including congenital or acquired diseases of the chest and abdomen. They can be divided into three categories, thoracic aortic aneurysm (TAA), abdominal aortic aneurysm (AAA) and acute aortic syndrome (AAS).¹⁷³ These conditions can result in life-threatening complications, such as aortic dissection, which carries a mortality rate exceeding 80 percent.¹⁷⁴

Immune regulation in the aorta under physiological conditions. In physiological states, the immune system plays a pivotal role in maintaining aortic homeostasis by preventing excessive inflammation and supporting vascular function.^{175,176}

At the forefront of this regulation are Tregs, which secrete anti-inflammatory cytokines such as IL-10 and TGF- β .¹⁷⁷ These

cytokines are crucial in mitigating inflammation and oxidative stress, thereby preserving endothelial cell function and reducing vascular stiffness to maintain aortic integrity. Resident macrophages within the aortic wall significantly contribute to vascular stability by producing NO and anti-inflammatory cytokines.⁸ These macrophages regulate vascular tone and prevent inflammation, thereby protecting endothelial health.⁸ Additionally, endothelial cells are key regulators within this network, producing NO and modulating cytokine levels to establish an anti-inflammatory environment.¹⁷⁸ This reduces immune cell adhesion to the aortic wall, thus preserving vascular integrity and preventing inflammation-induced injury.¹⁷⁸ DCs are another critical element in maintaining immune tolerance within the aortic tissue.¹⁷⁹ They help establish a regulatory environment that curtails excessive immune activation, thereby preventing potential inflammatory damage.

Mechanical forces, such as shear stress resulting from blood flow, also play an essential role in modulating immune responses within the aorta.¹⁸⁰ Macrophages and other immune cells can detect these forces and subsequently adjust their cytokine production to reduce inflammation, enabling them to respond to physiological changes in blood flow.¹⁸⁰ Furthermore, aortic smooth muscle cells contribute to immune regulation by interacting with macrophages and releasing anti-inflammatory mediators, thereby maintaining a stable aortic wall and preventing inflammatory cell infiltration.¹⁸¹ Moreover, the SNS interacts closely with immune cells in the aorta, modulating their trafficking and activation.¹⁸² This interaction is vital to preventing excessive immune infiltration and maintaining balanced vascular reactivity.¹⁸² This neural-immune interaction is essential for maintaining vascular health and controlling inflammation within the aorta. Collectively, these cellular and molecular mechanisms underscore the intricate yet essential role of immune regulation in preserving aortic homeostasis, providing valuable insights into how immune cells and signaling pathways work in concert to maintain a healthy vascular environment.

Immune dysregulation in aortic aneurysms. The underlying pathology of aortic aneurysms involves significant immune cell infiltration and activation within the aneurysmal regions. This immune response contributes to inflammation and progressive structural degradation of the aortic wall.¹⁸³ Macrophages, DCs, and T lymphocytes play central roles in maintaining aortic homeostasis and modulating inflammatory responses within the aorta. Macrophages are particularly abundant in aneurysmal tissue, where they accumulate and undergo local expansion through self-renewal.¹⁸⁴ This macrophage presence is critical to aneurysm progression; macrophage depletion has been shown to disrupt endothelial integrity, leading to fibrin accumulation and microthrombus formation.¹⁸⁵ DCs within the normal aorta have high antigen-presenting capacity and are essential in maintaining immune homeostasis by capturing and presenting antigens effectively.^{186,187} In aneurysmal tissues, however, DCs contribute to inflammation through the recruitment and activation of T cells, exacerbating tissue remodeling.¹⁸⁸

T lymphocytes play an instrumental role in regulating aortic tissue integrity by secreting cytokines and modulating apoptosis and extracellular matrix remodeling. Recent single-cell transcriptome analysis reveals that T lymphocytes are abundant in aneurysmal aortic tissue and exhibit clonal expansion, suggesting their active involvement in the pathogenesis of aortic aneurysms.^{176,189} These T cells can drive inflammation and matrix degradation, leading to compromised structural stability of the aortic wall, which increases the risk of dissection and rupture. In addition, Tregs may have a protective role in modulating excessive immune activation and tissue destruction.¹⁹⁰ Tregs can counterbalance pro-inflammatory responses by secreting anti-inflammatory cytokines, thereby promoting tissue stability

and potentially limiting aneurysm expansion. However, dysregulation in Treg activity or quantity may contribute to unchecked inflammation and accelerated aneurysm development.

Cardiac aging and immuno-dysregulation

Cardiac aging is a gradual process that diminishes cardiac structure and function due to the cumulative impact of internal and external stressors. With aging, the myocardium undergoes structural changes, including increased cardiomyocyte hypertrophy, interstitial fibrosis, and chronic inflammation, ultimately contributing to diastolic and systolic dysfunction.¹⁹¹

Immune dysregulation in cardiac aging. At the cellular level, various forms of cellular senescence contribute to cardiac aging. Immune cells, including T cells, mast cells, and macrophages, regulate tissue homeostasis and pathogenesis by modulating inflammatory responses and myocardial senescence in cardiac tissue.¹⁹¹ T cells can affect age-related diseases, including senescence, through several mechanisms, as outlined below: 1) Age-associated T cells continue to produce cytokines, such as IFN- γ and TNF- α , which leads to chronic inflammation and promotes senescence of neighboring cells¹⁹²; 2) T cells enhance senescence-associated secretory phenotypes (SASP), which further exacerbate inflammation and Th17/Th1 cell differentiation, leading to tissue damage¹⁹³; 3) Dysfunctional T cells fail to clear senescent cells, leading to the accumulation of these cells and exacerbating tissue damage¹⁹⁴; Senescent CD8 $^{+}$ and CD4 $^{+}$ T cells acquire cytotoxicity, which directly damages tissue cells.^{195,196}

Mast cells and macrophages also contribute to cardiac aging by promoting cardiomyocyte hypertrophy and cellular senescence. Mast cells release enzymes like chymotrypsin, which influence hypertrophy, while macrophages drive senescence through the activity of connexins and pro-inflammatory cytokines.^{197,198} Additionally, macrophages in the aging heart release cytokines, such as IL-6, TNF- α , and IL-1, which have been shown to induce an osteogenic phenotype in valvular interstitial cells (VICs).¹⁹⁹ This change promotes calcification and fibrosis within heart valves, impairing valve function and exacerbating age-related cardiac dysfunction.¹⁹⁹

Involvement of non-immune cells in cardiac aging. Non-immune cells, such as endothelial cells, VSMCs, and VICs, also play crucial roles in cardiac aging. Senescent endothelial cells release inflammatory chemokines and cytokines, with reduced levels of anti-inflammatory molecules, contributing to a pro-inflammatory environment.²⁰⁰ VSMCs display a SASP, characterized by the secretion of monocyte chemoattractant protein-1 (MCP-1), chemokine (C-C motif) ligand 3/4 (CCL3/4), and various interleukins (IL-1, IL-6, IL-8), further promoting inflammation and fibrosis.²⁰¹ VICs, as the primary cell type in heart valves, also undergo senescence, impairing their function and contributing to calcification and fibrosis. Pro-inflammatory cytokines released by macrophages in aging cardiac tissue further promote VIC senescence and functional decline.¹⁹¹

Arrhythmia and immuno-dysregulation

Arrhythmias, including atrial fibrillation (AF) and ventricular arrhythmias, arise from disruptions in cardiac electrical activity and conduction, which are influenced by the immune system.²⁰² Inflammatory cells, especially macrophages, are pivotal in maintaining cardiac electrical stability and have direct and indirect roles in modulating cardiac conduction.⁶⁵ These roles include influencing ion channel expression and promoting fibrotic changes that alter the electrical landscape of the myocardium.⁶⁵

Immune regulation in cardiac conduction. Macrophages in cardiac tissue interact with cardiomyocytes and influence electrical conduction through the modulation of ion channels. They express

conduction-related genes, including those encoding ion channels such as *Cacna1c* (Cav1.2), *Kcnj2* (Kir2.1), *Kcnc1* (Kv7.1), *Hcn2* (HCN2), and *Kcnh2* (Kv11.1).⁶⁵ Additionally, macrophages interact with cardiomyocytes through gap junctions formed by connexin 43 (Cx43), impacting both resting and action potentials in cardiomyocytes.⁶⁵ Through these mechanisms, macrophages contribute to arrhythmogenesis by altering the electrophysiological properties of the heart.

Immune regulation in arrhythmia. A strong link exists between inflammation and arrhythmias,²⁰² including ventricular tachyarrhythmias due to myocarditis.²⁰³ New-onset AF is common in acute sepsis.²⁰⁴ Existing studies suggest that inflammatory signaling in cardiomyocytes has a key role in the development of AF, and in particular, NLR family pyrin domain containing 3 (NLRP3) inflammatory vesicles are particularly associated with cardiomyocyte-mediated inflammatory signaling in AF.²⁰⁵ Autoantibodies contribute to the development of arrhythmias by modulating the function of cardiac ion channels and significantly affecting cardiac electrical activity.²⁰⁶ Bradyarrhythmias and conduction disorders: anti-Ro/SSA antibodies target L-type and T-type calcium channels, inhibit calcium currents, and affect sodium currents in the sinoatrial node (SA node) and atrioventricular node (AV node).^{207,208}

Autoantibodies have also been implicated in arrhythmia development by targeting cardiac ion channels, thereby altering cardiac electrical activity. For example, in bradyarrhythmias, anti-Ro/SSA antibodies target L-type and T-type calcium channels, inhibiting calcium currents and impacting the SA and AV nodes.²⁰⁹ In conditions such as Long QT syndrome (LQTS), anti-SSA antibodies targeting K11.1V11.1 K channels (hERG) inhibit potassium currents, resulting in delayed repolarization.²¹⁰ Autoantibodies targeting K1.4V1.4 K channels may inhibit transient outward potassium currents.^{211–213} Conversely, in Short QT syndrome (SQTS), autoantibodies targeting K7.1V7.1 potassium channels increase potassium currents, accelerating repolarization and predisposing the heart to arrhythmic episodes.²¹⁴

Myocarditis and immuno-dysregulation

Myocarditis is characterized by the infiltration of inflammatory cells into the myocardium, which increases the risk of cardiac dysfunction. It can be caused by a wide range of factors, classified into infectious and non-infectious types.²¹⁵ The immune system's role in myocarditis is complex, as immune regulation is crucial for both protecting cardiomyocytes from pathogens and managing inflammation to prevent further tissue damage.

Immune dysregulation in infectious myocarditis. Infectious myocarditis, commonly caused by viral infections, may also result from bacterial, protozoal, or fungal infections.²¹⁶ Immunoregulatory mechanisms play a vital role in the development and progression of cardiomyopathies in both physiological and pathological states. Under normal conditions, the heart maintains a balanced immune state to protect cardiomyocytes from pathogens while avoiding tissue damage from excessive immune response.²¹⁷ Following infection, immune cells in the myocardium initiate an inflammatory response upon recognizing pathogens, which is vital for controlling infections but can also damage myocardial tissue. For instance, tripartite motif-containing protein 18 (TRIM18) regulates viral myocarditis by modulating TBK1-mediated immune responses in macrophages, thereby limiting the extent of inflammation.²¹⁸ Additionally, TRIM29 has been shown to control viral myocarditis through the regulation of ER stress and ROS responses in macrophages.²¹⁹ Moreover, the heart-spleen axis is essential in managing the systemic inflammatory response; by preventing the recruitment of pro-inflammatory monocytes to the myocardium, this axis helps mitigate myocardial damage and chronic inflammation, emphasizing the importance of balanced immune signaling in limiting disease progression.²²⁰

Immune dysregulation in non-infectious myocarditis. Non-infectious myocarditis is often associated with immune-modulatory treatments, particularly immune checkpoint inhibitors (ICIs) and CAR T-cell therapy. In ICIs-induced myocarditis, CCR2+ macrophages are significantly recruited to the heart, creating a pro-inflammatory environment that accelerates myocardial damage.²²¹ T cells also contribute to this damage through clonal expansion and recognition of myocardial antigens, which exacerbates inflammation and can lead to further myocardial injury.^{222,223} Additionally, "epitope spreading" in this context may lead to tumor-specific T cells attacking cardiac tissue, expanding the scope of immune dysregulation.²²³

In CAR T cell therapy, myocarditis can arise through multiple mechanisms: 1) Cytokine Release Syndrome (CRS): The anti-tumor activity of CAR T cells often triggers CRS, a systemic inflammatory response associated with high circulating cytokine levels, which correlates with the severity of adverse cardiac events.^{224–226} 2) Cross-Reactivity with Myocardial Antigens: CAR T cells may inadvertently target myocardial proteins, as seen with melanoma-associated antigen-3 (MAGE-3), which cross-reacts with titin, a myocardial protein, leading to fulminant myocarditis²²⁷; 3) Off-Target Effects: Immune responses directed at non-tumor antigens unrelated to the intended targets of CAR T therapy can also result in cardiac injury, underscoring the broad impact of immune dysregulation on myocardial health.^{224,225}

Cardiotoxicity and immuno-dysregulation

Cardiotoxicity, a severe adverse effect of numerous drugs, particularly those used in cancer chemotherapy and anti-viral treatments, poses significant challenges in clinical applications and patient management. The immune system plays a crucial role in the cardiotoxicity caused by various anti-tumor and anti-viral drugs.

Many anti-tumor drugs, such as anthracyclines (doxorubicin and pirarubicin), triptolide, antibody-Drug Conjugates (ADCs) are widely associated with cardiotoxicity. Anthracyclines (doxorubicin and pirarubicin) are widely associated with cardiotoxicity due to its oxidative stress induction and DNA damage in cardiomyocytes.²²⁸ Studies indicate that doxorubicin activates an immune response, recruiting inflammatory cells to the heart and initiating pro-inflammatory cytokine release.²²⁹ This inflammation often leads to fibrosis and eventual heart failure. The presence of T cells, specifically CD8+ cytotoxic T cells, exacerbates this cardiac damage by promoting fibrosis and systolic dysfunction.²³⁰ Triptolide, derived from the herb *Tripterygium wilfordii*, is a highly potent anti-tumor agent but is limited by its cardiotoxicity.^{231,232} Triptolide induces mitochondrial damage in cardiac cells, leading to dysfunction in energy production and increased oxidative stress. It also triggers an immune response, with macrophages playing a key role in the resultant inflammation.²³¹ ADCs are engineered to target specific tumor cells, but their toxic payloads can lead to unintended cardiac toxicity.²³³ ADCs may cause off-target effects, where immune cells, particularly macrophages, respond to the cytotoxic payload released in cardiac tissue.²³⁴ This immune activation leads to the release of pro-inflammatory cytokines such as TNF- α and IL-6, which promote inflammation, oxidative stress, and endothelial damage, thereby exacerbating cardiac injury. Some ADCs can trigger delayed hypersensitivity reactions, where immune cells initiate a T-cell-mediated response.²³⁵ This response involves the release of cytotoxic mediators that target cardiac cells, leading to inflammation and subsequent myocardial fibrosis and heart failure.

Anti-viral treatments are associated with an increased risk of cardiotoxicity, which may involve immune activation. For example, abacavir induces pro-inflammatory cytokine release, promoting endothelial dysfunction and atherosclerosis, which increases cardiovascular risk.²³⁶ Ritonavir acts as a CYP3A inhibitor, affecting the metabolism of various cardiac medications and leading to

immune cell activation and oxidative stress.^{237,238} This immune reaction can increase pro-inflammatory cytokines, causing myocardial strain, especially in critical COVID-19 cases where the immune response is already heightened.

Thrombotic diseases and immuno-dysregulation

Thrombosis is the localized formation of blood clots that can affect arterial or venous circulation, potentially leading to severe conditions like myocardial infarction, pulmonary embolism, and thrombotic microangiopathy.²³⁹

Immune regulation in the blood coagulation system under physiological conditions. Under physiological conditions, immune regulation within the blood coagulation system is crucial for maintaining balance between coagulation and immune defense, ensuring that clot formation and inflammation are appropriately controlled.¹⁹⁹ The complement system, for example, directly influences coagulation through its interaction with fibrin clots, which can activate pathways that prevent excessive inflammation and regulate clot formation.¹⁹⁹ Factor H, a key regulator in this process, mitigates immune activation by binding to fibrin clots, thus ensuring a controlled immune response while supporting hemostasis.²⁴⁰

Interactions between the immune system and coagulation cascade are central to cardiovascular health.^{241,242} Pro-inflammatory cytokines, often released during immune responses, can trigger coagulation factors, which in turn help regulate inflammation and prevent infections.²⁴³ Immune cells like neutrophils and monocytes participate actively in the coagulation cascade by releasing factors that promote clotting when an immune response is necessary, thereby protecting tissue integrity and limiting pathogen spread.²⁴² However, their activity is tightly regulated to avoid excessive clot formation, which could otherwise lead to thrombosis.²⁴²

Additionally, the immune-coagulation interplay is critical for managing immune responses in aging population.^{244,245} With age, immune cells may exhibit changes that impact coagulation, as evidenced by single-cell analyses showing alterations in immune and hematopoietic cell function related to immune aging.^{244,245} This balance is particularly crucial in the aging population, where dysregulated coagulation can contribute to age-related diseases.

These findings underscore the complex, tightly regulated relationship between the immune and coagulation systems under physiological conditions, where immune and metabolic signals finely tune clot formation and inflammation to maintain overall homeostasis and vascular health.

Immune dysregulation in thrombotic diseases. The rupture of an atherosclerotic plaque exposes the subendothelial matrix and releases tissue factor (TF), activating the coagulation cascade and promoting leukocyte recruitment via platelet adhesion and activation.^{246–248} Platelets, in particular, play a pivotal role by releasing chemokines and cytokines, including CCL5 and chemokine (C-X-C motif) ligand 4 (CXCL4), which recruit bone marrow-derived progenitor cells and leukocytes to the plaque site.^{249–252} These cells aid in vascular repair and mediate inflammatory responses that can stabilize or destabilize the plaque, influencing thrombus formation.

In acute conditions, such as COVID-19, immune dysregulation is evident in the form of neutrophil extracellular traps (NETs). Neutrophils interacting with platelets laden with pathogens release NETs that entrap pathogens and promote thrombosis.^{253,254} This process is intricately regulated by Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase and protein-arginine deiminase type 4 (PAD4), which are essential for modulating the immune response and preventing excessive thrombus formation.^{255,256} NETs play a dual role in immunity and thrombosis by targeting pathogens while inadvertently

promoting clot formation, which can lead to microvascular obstruction and tissue ischemia in severe infections.

Platelets act as critical mediators of the immune response in thrombotic diseases. They release high-mobility group box 1 (HMGB1), which binds to receptors such as receptor for advanced glycation endproducts (RAGE) and Toll-like receptors (TLR2) on monocytes.²⁵⁷ This interaction triggers NET release from neutrophils and amplifies the inflammatory and coagulation cascade, further intensifying thrombus formation. Additionally, monocytes release TF, which activates both the extrinsic and intrinsic coagulation pathways, reinforcing clot formation and sustaining the cycle of inflammation and coagulation.²⁴¹

THE IMMUNE SIGNALING PATHWAYS IN CVDS

Innate immune response

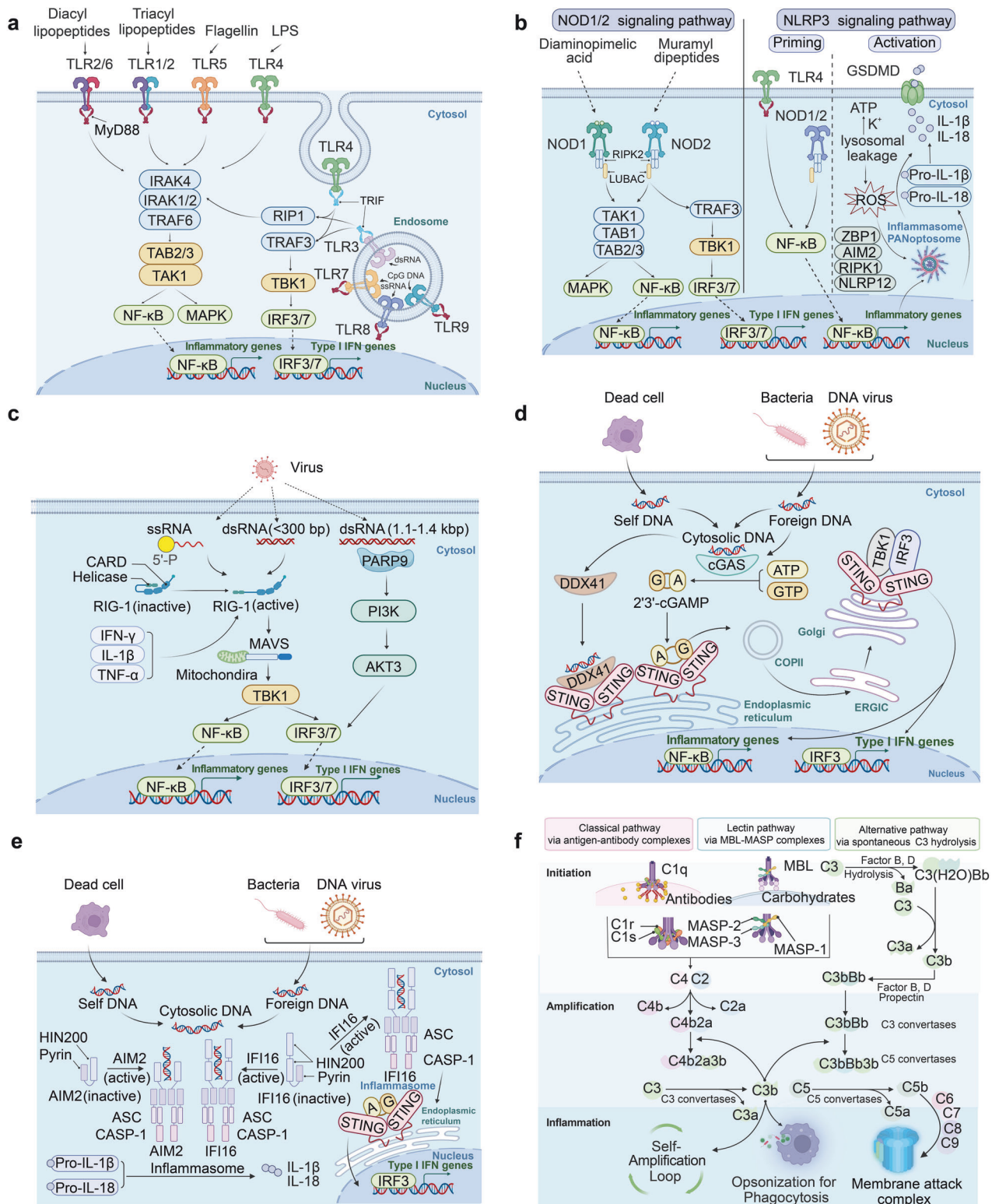
The innate immune system matters in CVDs.⁴ Pattern recognition receptors (PRRs), such as TLRs, are key components of the innate immune response that recognize damage-associated molecular patterns in cardiovascular tissues and initiate inflammatory cascades.²⁵⁸ Innate immune cells like macrophages and neutrophils contribute to both the progression and resolution of inflammation in CVDs, highlighting their dual role in tissue damage and repair.²⁵⁹ Sustained activation of innate immune signaling can lead to maladaptive inflammatory responses that promote cardiovascular dysfunction⁴ (Fig. 4).

TLRs-dependent innate immune response

TLRs: TLRs were the first family of PRRs discovered in the innate immune system.²⁶⁰ Ten TLRs (TLR1-10) have been identified in humans, each responsible for recognizing specific pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).²⁶¹ They are single-spanning receptors anchored in membrane structures, such as cell membranes, endosomes, and lysosomes. Leucine-rich repeats (LRRs), a conserved structural element in the extracellular region of TLRs, form the horseshoe-shaped ligand-binding domain responsible for binding a variety of PAMPs or DAMPs, such as lipopolysaccharides (LPS), peptidoglycans, flagellin, nucleic acids and oxidized low-density lipoprotein (ox-LDL).^{262,263} TLRs can be further categorized based on their cellular localization. For instance, TLR1, TLR2, TLR5, TLR6 and TLR10, are located on the plasma membrane to recognize extracellular pathogens. In contrast, endosomal TLRs such as TLR3, TLR7, TLR8, and TLR9 recognize nucleic acids from bacteria or viruses during endosomal or lysosomal degradation.⁴ TLR4 is unique in its localization, initially residing on the plasma membrane and later translocating to the endosomal membrane following endocytosis²⁶⁴ (Fig. 4a).

TLRs signaling pathways: Ligand binding initiates dimerization of TLR ectodomains, which in turn causes dimerization of the intracellular Toll/Interleukin-1 receptor (TIR) domains of each TLR, activating downstream pathways and triggering inflammatory responses. Generally, TLR signaling pathways primarily rely on two key protein adapters: myeloid differentiation factor 88 (MyD88) and TIR domain-containing adapter-inducing IFN- β factor (TRIF). These adapters are recruited to the cytoplasmic TIR domain of TLRs to initiate downstream signaling cascades.

MyD88 is utilized by all plasma membrane TLRs and most endosomal TLRs, with the exception of TLR3. Upon dimerization of TIR domains, MyD88 binds to these domains and recruits IL-1 receptor-associated kinases (IRAK), including IRAK4, IRAK1, IRAK2, and IRAK-M, to form a protein complex known as the myddosome.^{265,266} Subsequently, IRAK1 undergoes autophosphorylation and then phosphorylates tumor necrosis factor receptor-associated factor 6 (TRAF6), which serves as a scaffold for other components.^{267,268} The adapter proteins TAK1-binding proteins 2 and 3 (TAB2 and TAB3) bring transforming growth factor- β -activated kinase 1 (TAK1) into



proximity with IRAK1, activating TAK1 through close proximity-dependent transphosphorylation.²⁶⁹ Eventually, phosphorylated TAK1 activates the nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinases (MAPKs) pathways.

TRIF is specifically recruited to TLR3 and TLR4 when these receptors localize to endosomes. TRIF binds to and activates TRAF3, forming a complex known as the triffosome.²⁷⁰ TRAF3

activates the TBK1 and is an inhibitor of NF- κ B kinase (IKK) along with NF- κ B essential modulator (NEMO). Subsequently, TBK1 phosphorylates and activates IFN regulatory factor 3 and 7 (IRF3/7). Phosphorylation and dimerization of IRF3 and IRF7 facilitate their translocation into the nucleus, where they drive IFN production and subsequent IFN-stimulated genes (ISGs) expression²⁷¹⁻²⁷³ (Fig. 4a).

Fig. 4 Innate Immune Signaling pathway in CVDs. **a** TLRs-Dependent Innate Immune Signaling pathway; **b** NLRs-dependent innate immune signaling pathway; **c** cGAS-STING signaling pathway; **d** ALRs-dependent innate immune signaling; **e** RLRs-dependent innate immune signaling; **f** The complement system-dependent pathways. TLR Toll-like receptor, LPS Lipopolysaccharide, IRAK Interleukin-1 receptor-associated kinase, TRAF6 TNF receptor-associated factor 6, TAB2/3 TGF-beta activated kinase 1/MAP3K7 binding protein 2/3, TAK1 Transforming growth factor beta-activated kinase 1, MAPK Mitogen-activated protein kinase, NF- κ B Nuclear factor kappa-light-chain-enhancer of activated B cells, RIP1 Receptor-interacting serine/threonine-protein kinase 1, TRAF3 TNF receptor-associated factor 3, TBK1 TANK-binding kinase 1, IRF3/7 Interferon regulatory factor 3/7, NOD1/2 Nucleotide-binding oligomerization domain-containing protein 1/2, NLRP3 NLR family pyrin domain containing 3, GSDMD Gasdermin D, RIPK2 Receptor-interacting serine/threonine-protein kinase 2, LUBAC Linear ubiquitin chain assembly complex, ATP Adenosine triphosphate, ZBP1 Z-DNA binding protein 1, AIM2 Absent in melanoma 2, NLRP12 NLR family pyrin domain containing 12, IFN Interferon, cGAS Cyclic GMP-AMP synthase, STING Stimulator of interferon genes, GTP Guanosine triphosphate, 2'3'-cGAMP 2'3'-cyclic GMP-AMP, DDX41 DEAD-box helicase 41, HIN200 hematopoietic interferon-inducible nuclear proteins with a 200-amino-acid repeat, ASC Apoptosis-associated speck-like protein containing a CARD, CASP-1 Caspase-1, IFI16 Interferon-gamma inducible protein 16, MAVS Mitochondrial Antiviral Signaling Protein, pARP9 Poly(ADP-Ribose) Polymerase 9, AKT3 AKTserine/threonine kinase 3, IL Interleukin, TNF- α Tumor necrosis factor- α , RIG Retinoic acid-inducible gene, MASP Mannose-binding lectin-associated serine protease (Created with BioRender.com, <https://BioRender.com/e69d507>)

Role of TLRs signaling pathways in CVDs: TLR signaling pathways play crucial roles in cardiac ischemia. In myocardial ischemia (MI), endogenous DAMPs, such as heat shock proteins, HMGB1, and nucleic acids, are released from damaged myocardial cells. TLRs are activated upon binding to these DAMPs, promoting the expression of inflammatory cytokines. Of note, the mRNA levels of TLR2, 3, 4 are approximately 10-fold higher than that of TLR1, 5 - 10.²⁷⁴ The mRNA and protein levels of TLR4 were elevated in the infarct and remote area post-MI compared to sham mice.²⁷⁵ TLR4 deficiency resulted in smaller infarct areas and less inflammation in mice subjected to myocardial IRI compared with wild-type (WT) mice.²⁷⁶ Similarly, inhibition of TLR4 with eritoran significantly reduced MI/R injury and mitigated inflammatory responses.²⁷⁷ Aside from TLR4, mice with TLR2 gene knockout (KO) exhibited less myocardial fibrosis and a higher survival rate, despite having infarct sizes and inflammation levels comparable to WT mice.²⁷⁸ Also, increased expression and signaling by TLR2 and TLR4 could be observed in the hearts of patients with advanced heart failure, contributing to the sustained activation of innate immunity in the failing hearts.²⁷⁹ TLR2 or TLR4 induced cardiac hypertrophy and fibrosis in mice by regulating immune microenvironment.^{280,281} Additionally, activation of TLR7/8 leads to autoimmune vasculopathy and results in severe pulmonary arterial hypertension.²⁸²

Several factors act as pro-inflammatory stimuli in the vascular system, with ox-LDL being identified as one of the most potent DAMPs driving atherogenesis.²⁶³ Ox-LDL particles can be recognized by TLR ligands, inducing lipid-laden macrophages to release inflammatory cytokines.²⁸³ TLR2 and TLR4 are particularly important in vascular inflammatory responses due to their high abundance in atheromatous plaques.²⁸⁴ Loss-of-function studies have demonstrated the significant role of TLRs in the pathogenesis of atherosclerosis. Deficiency of TLR4 in macrophages protects them from transforming into foam cells, thereby mitigating the severity of atherosclerosis.²⁸⁵ In addition to affecting innate immune cells, lipid accumulation can induce non-immune cells to adopt a maladaptive phenotype in the vascular wall. Ox-LDL upregulates TLR2 and TLR4 expression in endothelial cells, concomitant with increased levels of adhesion molecules like VCAM-1, ICAM-1, and MCP-1.²⁸⁵ A recent study also demonstrated that a TLR2 agonist significantly promotes chondrogenic differentiation of VSMCs, an initial step towards arterial calcification.²⁸⁶ Overall, the role of TLRs signaling pathway has been well characterized and widely implicated in CVDs.

Nucleotide oligomerization domain (NOD)-like receptors (NLRs)-dependent innate immune response

NLRs: NLRs, a large family of cytosolic sensors, activate innate immune and inflammatory responses by recognizing intracellular PAMPs and DAMPs. Specific domains largely determine the distinct functions of NLR family proteins. Mammalian NLRs share a similar architecture, categorized into three core domains: (1) an

N-terminal variable domain for initiating downstream signaling; (2) a central nucleotide-binding domain (NBD) for oligomerization; and (3) a C-terminal horseshoe-shaped leucine-rich repeat (LRR) domain.²⁸⁷ Mammalian NLRs can be divided into four major subfamilies based on their different N-terminal domain structures: acidic transactivating domain-containing NLR (NLRA), baculovirus inhibitor of apoptosis protein repeat-containing NLR (NLRB), caspase activation and recruitment domain (CARD)-containing NLR (NLRD), and pyrin domain-containing NLR (NLRP).

NLR signaling pathways: NLR family members are crucial in regulating various innate immune pathways, including NF- κ B signaling, and cytokine and chemokine production. The functions of NLRs are diverse. Some modulate MHC class I or II genes and even Th2 response, while others form multi-protein complexes like inflammasomes or PANoptosomes.^{288–291} These complexes trigger caspase cleavage, leading to the maturation of IL-1 β and IL-18 and subsequent cell death. For instance, nucleotide-binding and oligomerization domain-like receptors 1 and 2 (NOD1 and NOD2) are prominent in NLR-mediated inflammation in CVDs.²⁹² NLRP3 is the most extensively studied NLR, recognized for its role in inflammasome or PANoptosome formation (Fig. 4b).

NOD1 and NOD2-dependent pathway: NOD1 and NOD2 are cytosolic sensors of bacterial peptidoglycans, essential for host defense and inflammation. Specifically, diaminopimelic acid binds to NOD1, and muramyl dipeptides bind to NOD2.^{293,294} NOD1 and NOD2 are associated with endosomal membranes, where they bind bacterial breakdown products transported through those membranes. Under steady-state conditions, NOD1 or NOD2 exists as an inactive monomer in the cytosol. Upon recognizing their specific ligands via the LRR regions, NOD1 and NOD2 self-oligomerize, undergoing a conformational change to recruit receptor-interacting serine/threonine kinase 2 (RIPK2) through homotypic CARD-CARD interactions.²⁹⁵ Subsequently, RIPK2 serves as a scaffolding protein that provides an organizing center for downstream signaling proteins.^{296,297} Further, the linear ubiquitin assembly complex (LUBAC) is recruited, mediating the recruitment of transforming growth factor β -activated kinase 1 (TAK1) and TAB1, TAB2 or TAB3, which forms a multi-protein complex termed as nodosome.²⁹⁸ Finally, these events contribute to the activation of MAPK pathways, NF- κ B signaling and even IL-13 effector response.^{299,300} Alternatively, studies have shown that NOD1 binding to its ligand activates the serine-threonine kinase RICK and the TRAF3 complex, resulting in the phosphorylation of IRF3 and IRF7, which induces expression of type-1 IFN genes³⁰¹ (Fig. 4b).

NLRP3-dependent inflammasomes and PANoptosomes: NLRP3 has recently garnered considerable attention due to its critical role in assembling inflammasomes. Mechanistically, the activation of NLRP3 inflammasome requires a 2-step process: priming (step 1)

and protein complex assembly (step 2). Studies have shown that upregulation of NLRP3, pro-caspase-1, pro-IL-1 β , and pro-IL-18 mRNA level via NF- κ B pathway, mediated by TLR4 and NOD1/2, primes the activation of NLRP3-dependent inflammasome.^{302,303} During priming, inflammasome formation can be fine-tuned by various posttranslational modifications of NLRP3, including phosphorylation, deubiquitination, and sumoylation.^{304–306} The subsequent activation process involves NLRP3 oligomerization via homotypic NACHT-NACHT interactions, leading to the binding of apoptosis-associated speck-like protein containing a CARD (ASC) to NLRP3 and the recruitment of pro-caspase-1.³⁰⁷ During this step, signals of cellular instability and damage - such as potassium ion efflux, adenosine triphosphate release, and/or leakage of lysosomal contents - are proposed to induce NLRP3 inflammasome activation.³⁰⁸ Recent studies suggest that these cellular indicators may function via ROS, which are crucial for the interaction between NIMA-related kinase (NEK7) and NLRP3, thereby inducing inflammasome formation and activation.^{309,310} Inflammasomes activate caspase-1, which cleaves IL-1 β and IL-18 precursors into their mature forms, thereby triggering and amplifying inflammatory responses that contribute to diseases such as chronic rhinosinuitis,²⁸⁹ very-early-onset inflammatory bowel disease,³¹¹ bronchiectasis and non-T2 asthma.^{312,313} In addition, NLRP3, functioning as a key component of the PANoptosome - a complex involved in pyroptosis, apoptosis, and necroptosis - interacts with various NLRs and non-NLR sensors to form multi-protein complexes essential for innate immune responses^{314–316} (Fig. 4b).

Role of NLRs signaling pathways in CVDs

Role of NOD1 and NOD2 signaling pathways in CVDs. The NOD1 and NOD2 signaling pathways have been associated with myocardial infarction, heart failure, and diabetic cardiomyopathy. Yang et al. first demonstrated that activating NOD1 with DAP (a synthetic activator) significantly worsened cardiac I/R injury and induced cardiomyocyte apoptosis in mice.³¹⁷ Specifically, NOD1 activation induced myocardial fibrosis in diabetic mouse hearts.³¹⁸ Similarly, Shen et al. reported NOD2 upregulation in diabetic cardiomyopathy in a mouse model of diabetes, and inhibiting NOD2 improved diabetes-induced myocardial fibrosis and cell apoptosis.³¹⁹ However, NOD2 deficiency exacerbated cardiac hypertrophy and fibrosis in mice with pressure-overload-induced heart failure, indicating a unique role of NOD2 in various CVDs.³²⁰ Except for myocardial infarction, Kanno et al. reported that oral administration of a NOD1 ligand accelerated the progression of atherosclerosis in *ApoE*^{-/-} mice by inducing vascular inflammation, whereas reduced development of atherosclerotic lesions was observed in *ApoE* and *Nod1* double-knockout mice.³²¹ Similarly, the NOD2 cognate ligand increased lesion burden and vascular inflammation in atherosclerotic cores in *Ldlr*^{-/-} mice.³²² Conversely, *ApoE* and *Nod2* double KO mice showed significant elevation in pro-inflammatory cytokines and atherosclerotic lesions.³²³ To investigate NOD2-mediated innate immune signaling in atherosclerosis, Liu et al. performed liquid chromatography coupled with tandem mass spectrometry to study the eicosanoid profiles after NOD2 activation. They discovered that NOD2 preferentially upregulated the prostaglandin E2 (PGE2) pathway. The role of PGE2 in atherosclerosis is complex, as it exhibits both pro-inflammatory and anti-inflammatory effects depending on cell types and PGE2 receptor subtypes, indicating a nuanced role for NOD2 in atherosclerosis.³²⁴ Intriguingly, a novel crosstalk between TLR4- and NOD2-mediated signaling was uncovered; NOD2 can sense the intensity of TLR4 signaling and modulate NF- κ B pathway activation.³²⁵ This finding suggests that NOD2 serves as an immune initiator and functions as an immune regulator.³²⁶

Role of NLRP3-dependent inflammasomes and PANoptosomes in CVDs. NLRP3 is a prominent research topic in CVDs due to its

involvement in myocardial infarction, cardiac hypertrophy, and atherosclerosis. In the ischemic heart of the mouse model, heightened inflammasome activation is evident from increased NLRP3 expression, elevated caspase-1 activity, and higher levels of IL-1 β and IL-18.³²⁷ Inhibition of NLRP3-dependent inflammasome reduced cardiac inflammation and MI/R injury in mouse models.³²⁷ Similarly, treatment with the selective NLRP3-inflammasome inhibitor, MCC950, reduced infarct size and improved cardiac function in a pig model of myocardial infarction.³²⁸ While ischemia-induced NLRP3 inflammasome activation primarily occurs in immune cells,³²⁹ it has also been observed in non-immune heart cells like fibroblasts and cardiomyocytes. In vivo study, NLRP3 inflammasome could be activated after hypoxia/reoxygenation in cardiac fibroblasts.³³⁰ Moreover, MCC950-mediated NLRP3 suppression attenuated Ang II-induced hypertrophy and pyroptosis in neonatal mouse ventricular myocytes.³³¹ Additionally, PANoptosis plays a role in the progression of various cardiovascular diseases, including heart failure,³³² and NLRP3-dependent PANoptosis exacerbates doxycycline-induced cardiotoxicity in cardiomyocyte.³³³ Of note, pro-atherogenic DAMPs, including oxidized low-density lipoprotein, free fatty acids, and cholesterol crystals, are potent triggers for NLRP3 inflammasome activation in macrophages, vascular smooth muscle cells or endothelial cells, driving the progression of atherosclerosis.^{334–338}

RNA sensor-dependent innate immune signaling

RNA sensors

Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs): The RLRs are RNA helicases, RIG-I, melanoma differentiation-associated factor 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) - that function as cytoplasmic sensors of PAMPs.²⁶¹ They recognize viral RNA and are involved in initiating and regulating innate immune response. RIG-I and MDA5 share similar structural features: an N-terminal region with tandem CARDs, a central DExD/H box RNA helicase domain capable of RNA binding, and a C-terminal repressor domain (RD) within the C-terminal domain (CTD) that autoregulates RIG-I.^{339,340} However, LGP2, a homolog of RIG-I and MDA5, competes with them for viral RNA binding, thereby inhibiting downstream signaling activation.^{261,341} (Fig. 4c).

Poly (ADP-ribose) polymerase family member 19 (PARP9): Besides the canonical RNA sensors known as RLRs, PARP9 is an inactive mono-ADP-ribosyltransferase within the PARP family.^{342–344} Recent findings indicate that PARP9 preferentially recognizes and binds to viral double-stranded RNA ranging from 1.1 kb to 1.4 kb, acting as a noncanonical MAVS-independent RNA sensor during RNA virus infections³⁴⁵ (Fig. 4c).

RLRs signaling pathways: RIG-I signaling mechanisms are currently the most extensively studied among RLRs. Canonically, RIG-I can be activated by short double-stranded RNA (< 300 bp) and 5'-triphosphate single-stranded RNA.³⁴⁶ Upon binding to viral RNA at the CTD domain, RIG-I undergoes conformational changes that release the CARDs from RD repression, enabling interaction with its adaptor protein, mitochondrial antiviral-signaling protein (MAVS). This interaction activates the IRF3/7 and NF- κ B pathways, leading to the expression of type I IFN and other pro-inflammatory cytokines.^{340,347,348} Notably, Liu et al. identified a novel RNA sensor, Gasdermin B (GSDMB), which shares similar characteristics with RLRs in activating ISG expression and downstream inflammation, significantly expanding our understanding of RLRs-dependent innate immune signaling²⁷³ (Fig. 4c).

PARP9 signaling pathways: PARP9 identifies and binds to viral dsRNA from reovirus in the cytoplasm, which triggers the recruitment and activation of phosphoinositide 3-kinase (PI3K) and AKT3 pathway, which occurs independently of MAVS. This

activation of PI3K/AKT3 pathway subsequently phosphorylates IRF3/7, resulting in the production of type I interferon^{345,349} (Fig. 4c).

Role of RLRs signaling pathways in CVDs: RIG-I-mediated inflammation has recently garnered interest and is being actively investigated in cardiovascular diseases. Li et al. found that RLRs stimulation in human cardiac cells led to significant pro-inflammatory cytokines expression in fibroblasts, suggesting a pathogenic role for RIG-I in heart disease.³⁵⁰ Recent bioinformatics analysis identified RIG-I as a key gene in ischemic heart failure progression, with high RIG-I staining observed in human heart failure samples by immunohistochemistry.³⁵¹ Indeed, RIG-I is expressed in intimal macrophages in human atherosclerotic lesions, and IFN- γ enhances its expression in macrophages, highlighting its role in atherosclerosis.³⁵² In addition, RIG-I activation induced endothelial dysfunction by ROS accumulation and pro-inflammatory cytokines release during atherogenesis.³⁵³ Considering the critical role of innate immunity and inflammation in CVDs, along with RIG-I's established involvement in cardiac reprogramming, investigating RIG-I's function in the cardiovascular system warrants further study.

Role of PARP9 signaling pathways in CVDs: Bioinformatics analysis pinpointed PARP9 as a key gene with significant clinical diagnostic potential. Subsequent *in vivo* studies revealed that pirfenidone attenuated Ang II-induced myofibroblast differentiation and fibrosis by decreasing PARP9 expression triggered by Ang II.³⁵⁴ Consistently, PARP inhibition prevented the cardiac hypertrophy and contractile dysfunction in pressure overload-induced heart failure.³⁵⁵ Also, PARP inhibition could offer a promising new therapeutic approach to prevent postinfarction myocardial remodeling.³⁵⁶ However, the role of PARP9 in detecting cytoplasmic dsRNA and facilitating type I interferon production in relation to CVDs remains poorly understood.

PARP9 has been shown to be involved in atherogenesis. The PARP9 - PARP14 network, revealed through proteomics screening in cultured macrophages, demonstrated a notably stronger association with the human coronary artery disease gene module than with other cardio-metabolic diseases. Immunohistochemistry results confirmed that macrophages are a major source of PARP9 and PARP14 in human atherosclerotic lesions.³⁴⁴ Furthermore, inhibition of PARP with INO-1001 treatment markedly reduced atherosclerotic lesion development, as indicated by mitigated inflammatory reactions within the lesion.³⁵⁷ The molecular mechanisms underlying these effects of PARP9 on vascular inflammation have yet to be thoroughly investigated.

DNA sensor-dependent innate immune signaling

DNA sensors

cyclic GMP-AMP synthase (cGAS): cGAS belongs to the ancient cGAS/DncV-like nucleotidyltransferase (CD-NTase) protein family, which produces various cyclic oligonucleotide second messengers in response to DNA, whether exogenous (from bacteria and viruses) or endogenous (from dying cells and damaged mitochondria).^{358,359} Upon recognizing DNA, cGAS dimers form ladder-like networks and phase-separated structures.³⁶⁰ These spatially restricted higher-order assemblies of cGAS-DNA on longer DNA stretches are crucial for biological functions. This mechanism prevents erroneous activation of cGAS by short or limited dsDNA, serving as an effective built-in immune checkpoint.³⁶⁰ STING (also known as MITA), consists of a short cytosolic N-terminal segment, a four-span transmembrane domain, a connector region, and a cytosolic ligand-binding domain (LBD) with a C-terminal tail (CTT).^{360,361} It is capable of binding the second messenger 2'3' cyclic GMP-AMP (cGAMP), which is synthesized by cGAS.³⁶² Upon binding to cGAMP produced during cGAS activation, STING

undergoes conformational changes and forms a domain-swapped homodimer to initiate downstream signaling³⁶³ (Fig. 4d).

DEAD-box helicase 41(DDX41): DDX41 is part of the DEAD-box protein family which consists of ATP-dependent RNA helicases, characterized by the conserved motif Asp-Glu-Ala-Asp (DEAD). Despite of the DEAD motif, DDX41 also contains other conserved domains, such as a helicase C-terminal domain and sites for ATP binding and hydrolysis. It has been reported that the helicase DDX41 functions as a DNA sensor by recognizing viral DNA.³⁶⁴ Additionally, DDX41 recognizes bacterial secondary messengers, including cyclic di-GMP (c-di-GMP) or cyclic di-AMP (c-di-AMP), to activate innate immune response³⁶⁵ (Fig. 4d).

cGAS and stimulator of interferon genes (STING)-dependent pathway

cGAS and STING-dependent pathway: cGAS undergoes conformational changes and synthesizes cGAMP (2',5'-cyclic GMP-AMP dinucleotide) from guanosine 5'-triphosphate (GTP) and adenosine 5'-triphosphate (ATP) upon recognizing cytosolic dsDNA.³⁶² cGAMP binds to STING, prompting STING to move from the ER to the ER-Golgi intermediate compartment (ERGIC) and the Golgi apparatus through the canonical ER-to-Golgi transport via COPII vesicles. Once STING reaches the ERGIC and Golgi apparatus, it recruits TBK1, which then undergoes self-phosphorylation and activates the transcription factors IRF3 and NF- κ B pathways, thereby increasing the expression of type I IFN, ISGs expression and even IL-17 production.^{366,367} Notably, Liu et al. uncovered a crucial mechanism where GSDMB interacts with the C-terminus of STING, mediating STING's translocation to the Golgi, significantly promoting downstream cascade³⁶² (Fig. 4d).

DDX41-dependent pathway: DDX41 utilizes its DEAD domain to identify double-stranded DNA (dsDNA). Once the ligand is recognized, DDX41 associates with STING, which in turn activates the NF- κ B and IRF3, ultimately leading to the production of type I interferon and other inflammatory genes.^{368,369} Moreover, Bruton's tyrosine kinase (BTK) enhances DDX41 activation by phosphorylating the HELICc domain, thereby improving its binding to STING³⁷⁰ (Fig. 4d).

Role of cGAS and STING-dependent pathway in CVDs: The release of DAMPs, such as cytosolic DNA from necrotic tissue, following cardiac cell injury and death induced by MI, initiates the cGAS-STING pathway. Cao et al. observed MI-induced activation of the cGAS-STING pathway in mice, with significant upregulation of its transcriptional targets such as CXCL10, interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), IFIT3, and IRF7.³⁷¹ Inactivating cGAS signaling promoted myocardial repair by enhancing cardiac angiogenesis, reparative macrophage transformation, and myofibroblast transformation, and significantly reduced infarct size in mice with myocardial IRI.^{371,372} Pressure-overload induced HF, characterized by cardiac hypertrophy and fibrosis, was associated with elevated expressions of type I IFN and STING. Remarkably, mice deficient in STING exhibited improved cardiac function, with alleviated cardiac dysfunction and fibrosis, highlighting a direct role of cGAS-STING pathway in HF pathogenesis.³⁷³ Strikingly, Luo et al. found that doxorubicin-induced cardiac endothelial dysfunction via the cGAS-STING pathway modulated NAD homeostasis and mitochondrial bioenergetics in cardiomyocytes,³⁷⁴ indicating an intricate role of the cGAS-STING pathway in cell-cell crosstalk.

Cytosolic DNA from damaged cells and extracellular vesicles contributes to vascular inflammation, particularly in atherosclerosis.³⁷⁵ Activation of the cGAS-STING pathway in endothelial cells increases the expression of adhesion molecules, such as VCAM-1 and ICAM-1, aiding infiltration of innate immune cells into the arterial wall and contributing to the formation of early atherosclerotic lesions.^{376,377} However, activation of the cGAS-STING

pathway in macrophages specifically enhances lipid uptake and foam cell formation, which are critical factors driving atherosclerosis.³⁷⁷ Furthermore, genetic or pharmacological suppression of STING in macrophages downregulates inflammatory cytokine expression, thereby mitigating atherosclerosis progression in mice.³⁷⁸ Therefore, targeting this pathway may illuminate strategies to prevent the progression of atherosclerotic lesions.

Role of DDX41-dependent pathway in CVDs: While current studies have not widely investigated the direct role of DDX41 in CVDs, there is emerging evidence suggesting its potential significance.³⁷⁹ Mutations in DDX41 have been associated with CVDs.³⁸⁰ The DDX41/cGAS/STING-mediated interferon inflammation has been linked to an increased risk of adverse outcomes in coronary artery disease due to the deletion of myocyte enhancing factor 2 (MEF2).³⁸¹ These findings suggest that DDX41 may play a role in the regulation of cardiovascular conditions, highlighting the urgent need for further research into its clinical applications.

Absent in melanoma 2 (AIM2)-like receptors (ALRs) - dependent innate immune signaling

ALRs: ALRs are cytosolic and nuclear DNA sensors detecting bacterial and viral DNA, composed of an N-terminal PYD domain and one or two C-terminal hematopoietic expression, interferon inducibility, nuclear localization (HIN200) domain for DNA-binding.³⁸² Similar to NLRs, the PYD functions as the effector region, transmitting downstream signals to the cellular machinery. Several ALR family members, including the IFN-inducible protein 16 (IFI16), AIM2 and IFI207, have been well characterized and implicated in the pathogenesis of various innate immune-related diseases^{383–385} (Fig. 4e).

ALRs-dependent signaling pathways: AIM2, the first identified ALR family protein for innate immune signaling, detects long dsDNA via its hematopoietic interferon-inducible nuclear antigens with HIN200 domains.³⁸² Upon binding with a double-strand DNA (dsDNA), AIM2 interacts with the adapter protein ASC, whose CARD domain interacts with the CARD domain of pro-caspase-1 to form inflammasomes, leading to the release of mature IL-1 β and IL-18.^{386,387} Another ALR, IFI16, also functions as a dsDNA sensor, inducing type I IFN expression and activating inflammasomes in a similar manner.³⁸⁸ Additionally, IFI207 co-localizes with active RNA polymerase II (RNA Pol II) and IRF7 in the nucleus, enhancing the induction of IRF7-dependent gene expression³⁸³ (Fig. 4e).

ALRs-dependent signaling pathways in CVDs: Studies have shown that ALRs-dependent signaling pathways contributes to both cardiac and vascular inflammation.³⁸⁹ For instance, the AIM2 inflammasome contributed to chronic inflammation in human and murine failing hearts, and its inactivation by probenecid improved outcomes in pressure overload-induced HF in rats.³⁹⁰ Also, AIM2 inflammasome activation is implicated in the proliferation of cardiac M1 macrophages and the expansion of infarct areas post-MI.³⁹¹ In contrast, inactivation of the AIM2 inflammasome by Rg1 significantly reduced cardiac fibrosis and macrophage polarization, highlighting its potential as a crucial regulator of cardiac inflammation.³⁹² In vascular inflammation, the AIM2 inflammasome is constitutively expressed in the healthy arterial wall but can become over-activated under atherosclerosis conditions.³⁹³ Moreover, the injection of AIM2 inflammasome agonist in ApoE^{-/-} mice resulted in impaired endothelium-dependent vasodilation, increased endothelial cells apoptosis, enhanced endothelium permeability, and elevated adhesion molecule expression.³⁹⁴ Additionally, AIM2 inflammasomes promoted MMP2 expression through the TGF- β /Smad signaling pathway in VSMCs.³⁹⁵ Genetic or pharmacological inactivation of AIM2 reduced levels of IL-1 β and IL-18 in the necrotic core and destabilized atherosclerotic plaques.³⁹⁶ Apart from AIM2, IFI16 protein promotes inflammation in endothelial cells by activating of

p38 MAPK and NF- κ B p65, thereby contributing to vascular inflammation.³⁹⁶

The complement system-dependent pathways

Classical pathway: The classical pathway of the complement system is considered as the key bridge between the innate and adaptive immune systems. It is initiated by antigen-antibody complexes that involve IgM-class antibodies or specific IgG antibody sub-classes.¹³ This process begins when C1q, along with the serine proteases C1r and C1s, assembles into the macromolecular C1 complex, which then binds to the Fc region of complement-fixing antibodies.³⁹⁷ Notably, C1q can bind directly to various ligands - including C-reactive protein, DNA, annexins A2, and A5 - independently of IgM or IgG, thereby triggering the complement cascade.^{398,399} Upon binding antigen-antibody complexes, each C1 complex must bind to at least two constant regions of antibodies to establish a stable C1q-antibody interaction. This interaction induces a conformational change in one of the C1r proteins, activating and converting it into an active serine protease enzyme. Subsequently, the activated C1s cleaves C4 and C2 into larger fragments (C4b and C2a) and smaller fragments (C4a and C2b), respectively.^{400,401} The larger fragments associate with the formation of a C4bC2a complex on pathogenic surfaces, which acts as a C3 convertase, converting C3 into its enzymatically active forms: C3a and C3b. Specifically, the C3 convertase cleaves C3 into the anaphylatoxin C3a and the opsonin C3b⁴⁰² (Fig. 4f).

Lectin pathway: In contrast to the antigen-antibody complex dependency of the classical pathway, the lectin pathway utilizes lectins such as collectins and ficolins as PRRs to recognize specific carbohydrate components.⁴⁰³ The lectin pathway of complement activation activates a C3 convertase (4bC2a) like the classical pathway, despite differences in their initiation processes. Several PRRs, including mannose-binding lectin (MBL) in the collectin family (collectin-10 and collectin-11) and ficolins (ficolin-1, ficolin-2, and ficolin-3), have been identified as specific receptors of the lectin pathway.^{404,405} These proteins share a collagen-like triple helix linked to a carbohydrate recognition structure.^{403,406–408} MBL is constitutively expressed in the liver and secreted into the plasma to recognize carbohydrate PAMPs on bacteria, viruses, and parasites.^{409,410} It forms a complex with MASPs (MBL-associated serine proteases)-1, -2, and -3, which are functionally and structurally similar to C1s and C1r of the C1 complex in the classical pathway.^{411–413} Among these three MASP subtypes, MASP-2 is recognized as the primary initiator of the MBL pathway.^{414,415} When MBL binds to pathogenic surfaces, it activates the associated MASPs, leading to the cleavage of C2 and C4 and the formation of the C3 convertase C4bC2a⁴¹⁶ (Fig. 4f).

Alternative pathway: The alternative pathway of complement activation begins with the generation of C3(H₂O), facilitating rapid immune responses against exogenous pathogens or endogenous damaged cells, independently of antibody-antigen complexes.⁴¹⁷ After C3 undergoes spontaneous hydrolysis to form C3(H₂O), this molecule binds to factor B, allowing factor D to cleave factor B into Bb and Ba, thereby creating the initial C3 convertase, C3(H₂O) Bb.⁴¹⁸ This C3 convertase then cleaves C3 into C3b and C3a. C3b subsequently binds to factor B, which is then activated by factor D to form the main C3 convertase, C3bBb.⁴¹⁹ Properdin (Factor P) stabilizes this complex, amplifying the alternative pathway of complement activation.⁴²⁰ In addition to this "tickover" pathway, which involves the above four serum components—C3, factor B, factor D, and properdin—two other initiation modes have been identified. One of these is initiated by properdin, while the other is triggered by proteases such as thrombin and kallikrein⁴²¹ (Fig. 4f).

The complement system-dependent pathways in CVDs: The complement system is implicated in the pathogenesis and

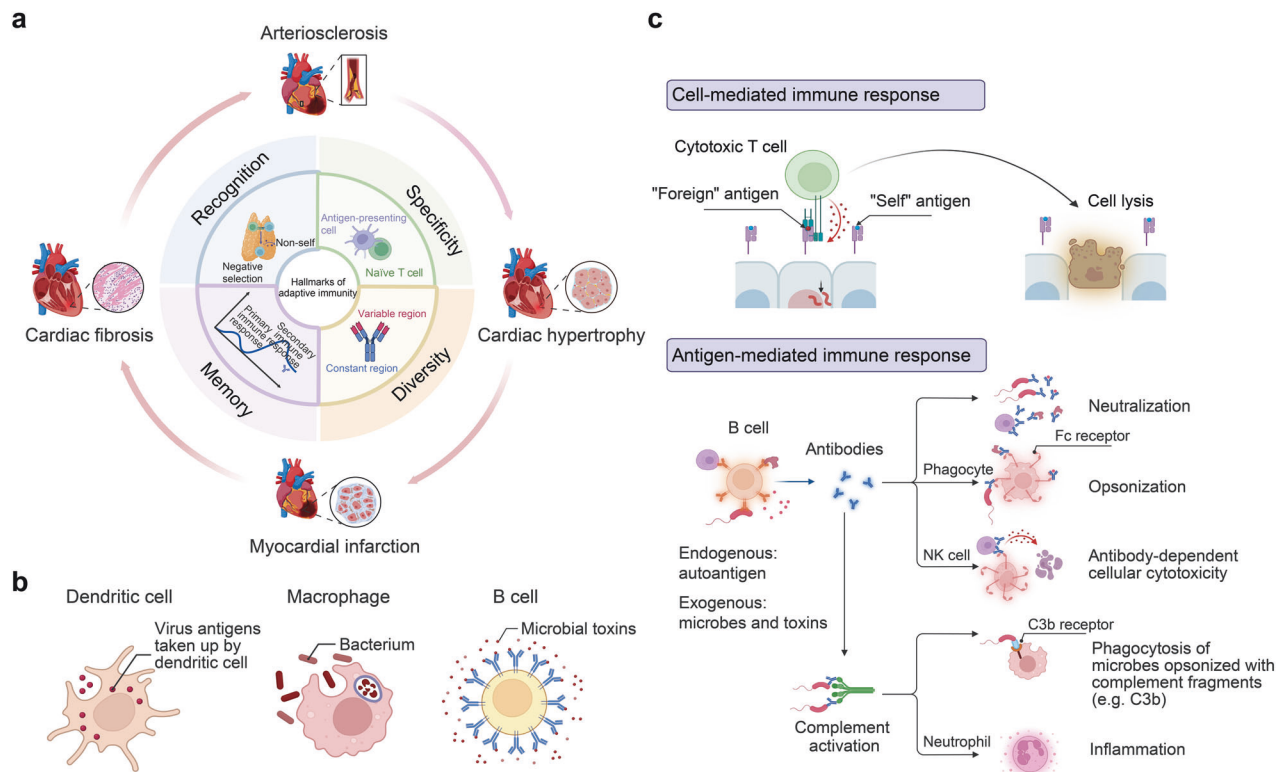


Fig. 5 Adaptive immune response in CVDs. **a** Hallmarks of adaptive immunity in CVDs; **b** antigen-presenting cells (APCs); **c** Function of T lymphocytes and B lymphocytes. (Created with BioRender.com, <https://BioRender.com/w51n151>)

development of various CVDs. Signs of complement activation are commonly observed in infarcted myocardium, failing hearts, and atherosclerotic arterial walls. For example, high-fat diet elevates plasma and local aortic complement expression levels, including C1q, C1s, C3, C4, and C9.^{422–424} C3-derived leukotactic fragments increased neutrophil infiltration in ischemic rat heart tissue and elevated plasma C3 levels correlate with the severity of atherosclerosis.^{425,426} Treatment with C3 inactivator reduced C3-derived leukotactic activity in the infarcted myocardium.⁴²⁷ Additionally, deposition of complement activation products C3d and C5b-9 was observed in ischemic human heart tissue, with more intense complement activation in patients who underwent reperfusion therapy or experienced reinfarction.⁴²⁸ Conversely, the absence of human complement components C1q in the classical pathway was associated with a higher incidence of cardiovascular events.⁴²⁹ Complement C1q reduces early atherosclerosis in *Ldlr*^{-/-} mice by clearing apoptotic cells.⁴³⁰ Also, lectin pathway is the key driver of tissue damage in CVDs.^{431–433} Mice lacking MBL or treated with an anti-MBL monoclonal antibody showed significantly reduced infarct size and cardiac inflammation.⁴³² Similarly, in thrombosis progression, the complement system acts as a central hub and can be activated through the classical, alternative, or lectin pathways, leading to the production of complement factors like C3a and C1q.⁴³⁴ Moreover, thrombin produced during coagulation not only promotes fibrin generation, but also directly activates components of the complement system, such as C3 and C5, enhancing the complement cascade reaction.⁴³⁵ Consequently, the interaction between the complement system and the coagulation cascade response amplifies inflammation, leading to thrombus formation and tissue damage.⁴³⁶

Adaptive immune response

The adaptive immune system consists mainly of T and B lymphocytes (T and B cells) and APCs. It works together with the innate immune system to collectively defend the organism

against foreign substances ("non-self").^{437,438} In detail, antigenic molecules (either protein- or lipid-based) are phagocytosed and processed.⁴³⁹ Professional APCs like DCs, macrophages, and B cells process exogenous antigens via MHC class II molecules, presenting epitopes to CD4⁺ Th cells. In contrast, all nucleated cells process peptide fragments of endogenous antigens via the MHC class I pathway, presenting epitopes to CD8⁺ CTLs.^{440,441} Of note, not all antigens will provoke a specific immune response. For instance, individuals are constantly exposed to harmless foreign antigens, such as food proteins and dust components, as well as "self" antigens. The immune response to these antigens is highly suppressed, preventing potentially harmful processes to the host, known as tolerance.⁴⁴² The adaptive immune system includes cell-mediated and antibody-mediated responses and is distinguished from the innate system by its specificity, diversity, memory, and self/non-self recognition (Fig. 5).

T lymphocytes. T cells are produced in the bone marrow and then travel through the bloodstream to the thymus, where they mature and acquire the "T" designation. There are three primary types of T cells: cytotoxic, helper, and suppressor T cells.^{443,444} Cytotoxic T cells destroy virally infected, damaged, and cancerous cells through cell-mediated immune responses and release cytokines to activate other immune cells.⁴⁴⁵ Helper T cells activate both cell-mediated and antibody-mediated immune responses by recognizing antigens bound to class II MHC molecules and initiating adaptive immune responses.⁴⁴⁶ Some helper T cells also differentiate into memory T cells after clearing an antigen, retaining antigen-specific characteristics to rapidly activate the adaptive immune system upon re-exposure.^{447,448}

T lymphocyte-mediated adaptive immune response: Naïve T cells express either CD4 or CD8 molecules on their surface, classifying them as CD4⁺ or CD8⁺ T cells.^{449,450} They are

activated into Th lymphocytes when they encounter APCs displaying antigens on MHC II molecules. Once activated, Th cells stimulate other immune cells and secrete cytokines to alert additional effector cells to the pathogenic threat. There are two primary subtypes of Th cells: Th1 and Th2. Th1 cells activate cytotoxic T cells through cytokine secretion, while Th2 cells stimulate naïve B cells to produce specific antibodies that target and eliminate pathogenic antigens.^{451–453} Unlike CD4 + T cells, CD8 + T cells are directly activated into cytotoxic T lymphocytes (CTLs) when interacting with antigens presented on MHC I molecules by APCs. These T cells, with diverse T cell receptors, achieve specificity through precise antigen-MHC recognition. After clonal selection, CD8 + T cells proliferate and target specific cells, inducing apoptosis.^{454–456} Additionally, CTLs can recognize and destroy infected cells before intracellular pathogens replicate and escape, thereby preventing further infection.^{457,458}

T lymphocyte-mediated adaptive immune response in CVDs: T lymphocytes of adaptive immunity play significant roles in myocardial IRI mechanisms CVDs. Lymphopenia observed after primary percutaneous coronary intervention is linked to poor patient prognosis, possibly due to lymphocyte recruitment to ischemic myocardium.^{459,460} CD8 + T cells increase in aneurysmal aortic walls, promoting apoptosis and matrix remodeling by releasing IFN- γ .⁴⁶¹ CD8-deficient mice exhibited reduced cardiomyocyte injury but had impaired necrotic tissue clearance, leading to inadequate scar formation and a higher risk of cardiac rupture.⁴⁶⁰ Furthermore, a non-cytotoxic CD8 + AT2R + T cell subset recruited to rat infarct areas post-MI, which produces IL-10 upon angiotensin II stimulation and promotes cardiac repair.⁴⁶² In atherosclerosis development, *ApoE*^{-/-} *Cd8*^{-/-} mice showed no difference in plaque size compared to *ApoE*^{-/-} controls. However, *ApoE*^{-/-} *Cd4*^{-/-} mice had significantly increased early lesions, and early depletion of CD4 + T cells accelerated atherosclerosis, indicating that early CD4 + T cell-mediated responses are largely protective against the disease.^{6,463–465} In addition, CD4 + T cells activate macrophages and induce smooth muscle cell apoptosis by secreting Th1 cytokines and Th2 cytokines.⁴⁶¹ Tregs are also crucial for myocardial repair. Their depletion resulted in larger infarcts, increased local inflammation, reduced collagen deposition, and impaired survival.^{466–468} These effects may be due to Treg-derived cytokines like IL-10 and TGF- β .^{469,470}

B lymphocytes. B cells originate in the bone marrow, naming them “B”. Subsequently, they mature into specialized adaptive immune cells. Upon stimulation by Th2 cells, naïve B cells differentiate into antibody-secreting plasma cells.^{471,472} Generally, antibodies produced by activated B cells perform six functions: 1) Neutralizing pathogens or toxins; 2) Agglutinating pathogens to aid in clearance; 3) Opsonizing pathogens to attract phagocytic cells; 4) Activating complement by binding to pathogens, which starts the complement cascade; 5) Enhancing cell-mediated immune responses by recruiting cytotoxic cells, leading to antibody-dependent cell-mediated cytotoxicity (ADCC); 6) Inducing degranulation in granulocytes.^{473,474}

B lymphocyte-mediated adaptive immune response: Naïve B cells form a diverse population with numerous B cell receptors (BCRs) that bind and internalize foreign antigens.⁴⁷⁵ After processing the antigens, B cells present them on MHC II molecules to be recognized by Th2 cells. Plasma cells then rapidly produce and release significant quantities of antibodies that match the antigen recognition pattern of the BCRs into the bloodstream.^{476,477} Some activated B cells develop into memory cells to respond if the same antigen reappears. Antibody binding marks invading pathogens for destruction, primarily by facilitating their uptake by phagocytic cells.⁴⁷¹

B lymphocyte-mediated adaptive immune response in CVDs: Studies in mice have shown that B cell accumulation occurs in the infarcted myocardium following myocardial infarction.¹³⁹ Typically, B cells produce natural IgM antibodies against non-myosin heavy chain II, which can damage the heart because their response in generating specific antibodies is delayed.¹³⁹ Furthermore, mature B lymphocytes selectively produced Ccl7 and induce the mobilization and recruitment of Ly6C^{hi} monocyte to the heart after myocardial infarction, leading to decreased myocardial function.⁴⁷⁸ It's important to note that not all B cells are harmful. A subset of B cells that produce IL-10 may aid in resolving inflammation and promoting heart recovery after myocardial infarction.⁴⁷⁹ During arrhythmia development, autoantibodies alter the function of cardiac ion channels, significantly impacting cardiac electrical activity.²⁰⁶ For example, anti-Ro/SSA antibodies target L-type and T-type calcium channels, inhibit calcium currents, and affect sodium currents in the sinoatrial node and atrioventricular node.^{207,208} Anti-SSA antibodies also target K11.1V11.1 K channels (hERG), inhibiting potassium currents involved in rapid repolarization.^{211,213}

Other signaling pathways in immune response

Hippo/YAP pathway. The Hippo-YAP signaling pathway is highly conserved among various species.⁴⁸⁰ Recent findings have revealed that components of the Hippo-YAP pathway, including MST1/2 (mammalian Ste20-like kinases 1/2), MAP4Ks, LATS1/2, NDR1/2, and YAP/TAZ are crucial regulators of innate immune responses.⁴⁸¹ YAP has been shown to suppress interferon response by targeting TBK1 and disrupting its interaction with IRF3.⁴⁸² Furthermore, Wang et al. showed that YAP can interact with IRF3, preventing its dimerization and nuclear translocation, thereby reducing IFN- β and ISG production.⁴⁸³ However, the Hippo/YAP pathway can be activated downstream of TLRs, ultimately amplifying the NF- κ B signaling.⁴⁸⁴ This indicates that the Hippo/YAP pathway has a complex role in modulating innate immune response (Fig. 6a).

Role of Hippo/YAP pathway-mediated immune response in CVDs: The involvement of the Hippo/YAP pathway in modulating inflammation and immune responses in CVDs has gained significant attention recently.^{485,486} Emerging studies indicate that MI triggered the activation of Hippo pathway kinases, leading to enhanced caspase activation and elevated levels of phosphorylated YAP, which subsequently caused cardiomyocyte apoptosis.^{487,488} Importantly, the YAP/TEAD1 complex in cardiomyocytes modulated the expression of TLR genes during MI.^{489,490} The cardiomyocyte-specific overexpression of YAP has been shown to improve cardiac function and survival after MI in mice.⁴⁹¹ Meanwhile, this process was accompanied by the reduced expression of TLRs, particularly TLR2 and TLR4, suggesting the upstream regulation of Hippo-YAP pathway in TLRs-dependent immune response.^{489,492} Furthermore, activation of YAP in tissue samples from hypertrophic cardiomyopathy and in TAC-induced failing hearts from mice, suggesting that the Hippo/YAP signaling pathway plays a role in the development of cardiac hypertrophy and HF.⁴⁹³ Cardiomyocyte-specific inhibition of MST1 reduced neutrophil and macrophage infiltration in the heart and suppressed the release of inflammatory cytokines in the progression of diabetic cardiomyopathy.⁴⁹⁴

The inflammatory response regulated by the Hippo/YAP pathway has been linked to the process of vascular remodeling. In the atherosclerotic arteries, prominent YAP/TAZ staining was observed in the endothelium, media layer, and intimal hyperplastic plaque.⁴⁹⁵ Activation of YAP/TAZ triggered the expression of pro-inflammatory mediators, including IL-6, IL-8, and CCL2, and enhanced monocyte adhesion to endothelial cells, implying that endothelial YAP/TAZ activation plays a role in the early stages of atherosclerosis.^{495,496} Moreover, in the aortas of hypertensive mice

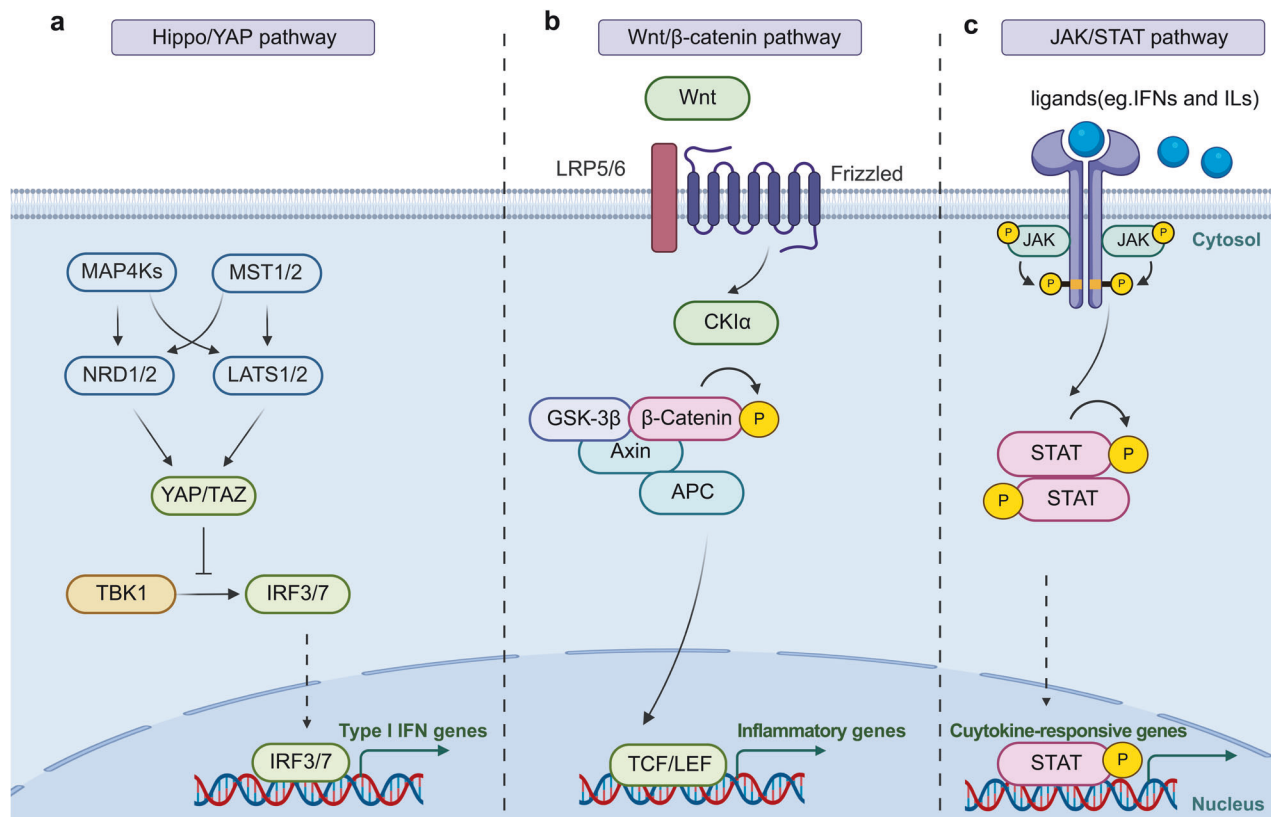


Fig. 6 Other immune signaling pathways in CVDs. **a** Hippo/YAP pathway, **b** Wnt/β-catenin pathway, **c** JAK/STAT pathway. MAP4Ks Mitogen-Activated Protein Kinase Kinase Kinase, MST1/2 Mammalian Sterile 20-like kinases 1/2, LATS1/2 Large Tumor Suppressor Kinase 1/2, NRD1 Nuclear pre-mRNA Down-regulation 1, YAP/TAZ Yes-Associated Protein/Transcriptional coActivator with PDZ-binding motif, IRF3/7 Interferon Regulatory Factor 3/7, LRP5/6 Low-density lipoprotein Receptor-related Protein 5/6, GSK-3β Glycogen Synthase Kinase 3 beta, JAK Janus Kinase, STAT Signal Transducer and Activator of Transcription, IFN Interferon, IL Interleukin, TBK1 TANK Binding Kinase 1, CK1α Casein Kinase I alpha (Created with BioRender.com, <https://BioRender.com/k49g175>)

induced by Angiotensin II, treatment with the YAP/TAZ inhibitor decreased the infiltration of inflammatory cells and the production of pro-inflammatory cytokines.⁴⁹⁷

Wnt/β-catenin pathway. The Wnt signaling pathways consist of both canonical and noncanonical routes. The canonical Wnt/β-catenin pathway is characterized by the translocation of β-catenin to the nucleus, where it activates target genes through T-cell factor/lymphoid enhancer-binding factor (TCF/LEF).⁴⁹⁸ This pathway is structured into four main components: the extracellular, membrane, cytoplasmic, and nuclear segments. Extracellular signals are primarily mediated by Wnt ligands, such as Wnt3a, Wnt1, and Wnt5a. The membrane segment mainly includes Wnt receptors, including Frizzled (a seven-transmembrane receptor) and lipoprotein receptor-related protein (LRP) 5/6. The cytoplasmic segment encompasses key proteins like β-catenin, glycogen synthase kinase-3β (GSK-3β), and casein kinase I (CK1). In the nuclear segment, β-catenin translocates into the nucleus, where it interacts with TCF/LEF family members to regulate the expression of downstream target genes.^{499,500} Recent studies reveal that the WNT/β-catenin pathway and TLR-mediated NF-κB signaling pathways interact, influencing each other's functions.⁵⁰¹ The Wnt/β-catenin pathway plays a dual role, exhibiting both pro-inflammatory and anti-inflammatory effects, which are partly due to its modulation of the NF-κB pathway. Similarly, the TLR signaling pathway also serves as a either positive or negative regulator of Wnt/β-catenin signaling^{501,502} (Fig. 6b).

Role of Wnt/β-catenin pathway-mediated immune response in CVDs: Growing evidence suggests that Wnt signaling is

activated during the pathological progression of MI injury, as evidenced by elevated expressions of Wnt ligands, including *Wnt2*, *Wnt4*, *Wnt10b*, and *Wnt11* after MI.⁵⁰³ Wnt5a has been identified as specifically expressed in cardiomyocytes, where it plays a key role in triggering the release of pro-inflammatory cytokines after MI.^{504,505} Endogenous Wnt pathway inhibitors, such as SFRPs, have been shown to protect against MI by preventing leukocyte activation and cytokine production.⁵⁰⁶ The activation of β-catenin in cardiomyocytes led to increased levels of inflammatory markers such as TNF-α, p-NF-κB, and IL-8, and enhanced the nuclear accumulation of NF-κB. This indicates that β-catenin contributes to post-MI inflammation by activating the NF-κB pathway.⁵⁰⁷ Dysregulated Wnt/β-catenin activation has also been observed in the pathogenesis of pressure overload-induced cardiac hypertrophy in mice, while interruption of Wnt signaling was found to attenuate cardiac dysfunction.⁵⁰⁸

Canonical Wnt/β-catenin signaling has been implicated in the pathogenesis of atherosclerosis. The transcriptional level of Wnt5a has been reported to be induced by oxLDL in macrophage-rich areas of human atherosclerotic plaques, where Frizzled 5 and Wnt5a cooperated to promote the expressions of pro-inflammatory markers to further amplify the local inflammation.^{509,510} Additionally, Wnt5a has been shown to exert a relatively long-lasting and sustained impact on the NF-κB pathway, thereby enhancing the innate immune response in the atherosclerotic plaques.⁵¹¹ Consistently, the Wnt receptor LRP5 expression was elevated in macrophages within advanced plaques compared to early ones, suggesting a crucial role of Wnt-mediated regulation of macrophages in the pathophysiology of atherosclerosis.⁵¹² Furthermore, myeloid β-catenin deficiency could

exacerbate atherosclerosis in mice.⁵¹³ These evidence demonstrate that targeting Wnt/ β -catenin pathway in macrophages within plaques could offer a promising strategy for treating atherosclerosis.

JAK/STAT pathway. The JAK/STAT pathway includes four JAK proteins - JAK1, JAK2, JAK3, and TYK2 - and seven STATs proteins - STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6.⁵¹⁴ The canonical signaling pathway is initiated when cytokines interact with their specific receptors, which consist of different chains that undergo oligomerization. This oligomerization of the cytokine receptor leads to the separation of the intracellular segments, distancing the receptor-bound JAKs from one another.^{515,516} This process removes the constitutive inhibition, resulting in JAK activation. The activated JAKs then phosphorylate the intracellular domain of cytokine receptors, creating selective binding site for STAT proteins.⁵¹⁷ STATs are subsequently phosphorylated on tyrosine residues by JAKs, leading inactive STAT monomers to undergo conformational changes, enabling them to form active homodimers, heterodimers, or tetramers. These activated STAT complexes then translocate to the nucleus, where they act as transcription factors to regulate downstream target gene expression.⁵¹⁸ The JAK/STAT signaling pathway is essential for coordinating immune and inflammatory responses, as numerous inflammatory cytokines, such as IFN α / β / γ and IL-4/6/11, activate this pathway⁵¹⁹ (Fig. 6c).

Role of JAK/STAT pathway-mediated immune response in CVDs: The involvement of the JAK/STAT pathway in IR injury has been well investigated. McCormick et al. found that myocardial ischemia triggered enhanced STAT3 phosphorylation, which further augmented following reperfusion in rat.⁵²⁰ Using JAK2 inhibitor AG490, increased apoptosis and caspase-3 activity were observed in rat following I/R injury.⁵²¹ Furthermore, overexpression of STAT3 protected mice against doxorubicin-induced cardiomyopathy.⁵²² Similarly, cardiac-specific STAT3-deficient mice were more vulnerable to I/R-induced cardiac injury, as indicated by larger infarct areas and increased apoptosis after reperfusion, compared to wild-type controls.⁵²³ Furthermore, IL-6 and NF- κ B activity are necessary for ischemic preconditioning and may act synergistically with the JAK/STAT pathway.^{524,525}

The JAK/STAT pathway regulates the inflammatory processes in vascular cells, contributing to the development of atherosclerosis. JAK2/STAT3 pathway modulates arterial adventitia inflammation via crosstalk with NF- κ B pathway. Dotan et al. demonstrated that *Apoe*^{-/-} mice deficient in macrophage *Jak2* developed accelerated atherosclerosis.⁵²⁶ Additionally, An et al. found that STAT3/NF- κ B decoy oligodeoxynucleotides (ODNs) reduced atherosclerosis by modulating the STAT/NF- κ B signaling pathway in mice.⁵²⁷

MULTI-LEVEL REGULATORY SIGNALING PATHWAYS/ CROSSTALKS IN CVDs

Epigenetic, post-transcriptional, post-translational modification regulatory mechanisms of immune response in CVDs. Epigenetic processes, including DNA methylation, histone modifications, non-coding RNA, RNA modifications, and post-translational modifications, mediate the diversity of gene expression patterns across different cells and tissues. These modifications establish a molecular framework through which environmental factors can impact gene expression. They play a crucial role in the activation and functional differentiation of immune cells and cardiomyocytes, thereby significantly influencing the development of CVDs (Fig. 7).

DNA methylation. DNA methylation acts as an annotation system for the genetic code, delivering essential instructions on when and how to read genetic information and control transcription. Unlike

inherited genetic sequences, methylation patterns are formed through a programmed process that persists throughout development, leading to stable gene expression profiles.⁵²⁸ In terms of mechanism, DNA methyltransferases (DNMTs) covalently transfer a methyl group from S-adenosyl methionine to the C-5 position of cytosine, forming 5-methylcytosine (5mC).⁵²⁹

Emerging evidences has highlighted the role of DNA methylation in regulating immune cell functions,⁵³⁰⁻⁵³² providing comprehensive insights into how DNA methylation affects immune cell behavior and contributes to CVDs. The CARDIA study discovered that the methylation risk score significantly improved the discrimination capacity for coronary artery calcification status compared to the cardiovascular health (CVH) score alone, and it was associated with the risk of incident coronary artery calcification 5-10 years later, independent of the cumulative CVH score.⁵³³ Shifting macrophage polarization from a pro-inflammatory (M1) to an anti-inflammatory (M2) state through epigenetic modifications could be a potential therapeutic strategy for conditions like atherosclerosis.^{534,535} In addition, DNMT1 regulates macrophage motility and mechanical properties by controlling cellular cholesterol accumulation and lipid homeostasis, affecting wound healing and macrophage chemotactic migration⁵³⁶ (Fig. 7a).

Histone modification. Histone modifications regulate chromatin structure and gene expression by chemically altering amino acids on histone tails, including acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. These changes influence chromatin openness, controlling gene activation or silencing, and impacting cell differentiation, development, stress responses, and disease progression.⁵³⁷⁻⁵⁴⁰

Histone modifications significantly impact the occurrence and progression of CVDs by mediating immune regulation through mechanisms such as inflammation response, immune cell function, cardiac remodeling, and vascular function. Histone lactylation in monocytes promotes early activation of reparative gene expression, crucial for immune homeostasis and cardiac repair post-myocardial infarction, by regulating anti-inflammatory and pro-angiogenic activities.⁵⁴¹ Inhibition of DYRK1A via histone modification, promotes cardiomyocyte cell cycle activation and cardiac repair after MI.⁵⁴² Also, nucleophosmin1 recruits histone demethylase KDM5b to the TSC1 promoter, reducing H3K4me3 and TSC1 expression. This enhances mTOR-related inflammatory glycolysis and abolishes macrophage repair.⁵⁴³ Similarly, HDAC3 controls macrophage polarization and inflammation, with its deficiency leading to increased IL-4-induced polarization and atherosclerotic plaque size. Upregulated in ruptured plaques, HDAC3 inversely correlates with TGF- β 1, and its knockdown reduces macrophage inflammation and pro-inflammatory mediators.⁵⁴⁴ Additionally, histone acetyltransferase pathways upregulate NADPH oxidase 5 in human macrophages during inflammation, potentially leading to excessive ROS production in atherosclerosis⁵⁴⁵ (Fig. 7b).

Non-coding RNA. Non-coding RNA (ncRNA) comprises RNA molecules that do not encode proteins but are essential for gene expression regulation, genome stability, post-transcriptional modification, and translation control.^{546,547} Present in eukaryotes, prokaryotes, and viruses, ncRNAs include microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNA), Piwi-interacting RNAs (piRNAs), and ribosomal RNAs.^{548,549} These molecules modulate gene function and cellular processes by interacting with DNA, RNA, and proteins.⁵⁵⁰

lncRNA has gained increased interest in the cardiovascular community for their ability to modulate cellular responses.⁵⁵¹ For example, lncRNA-H19 regulates lipid metabolism and inflammation in ox-LDL-treated Raw264.7 cells via the H19-miR130b pathway, decreasing lipid accumulation and pro-inflammatory factors while increasing anti-inflammatory factors.⁵⁵² The lncRNA

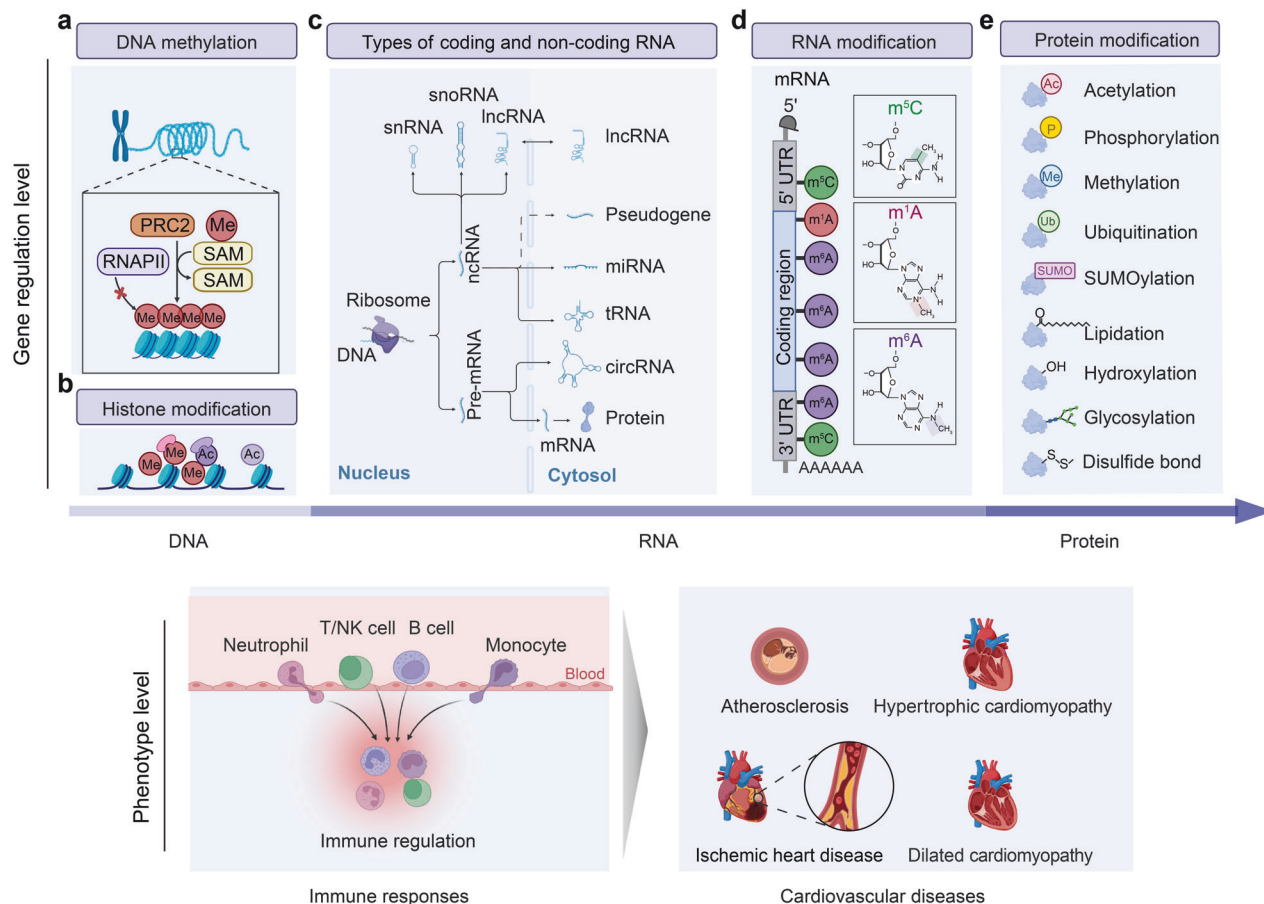


Fig. 7 Epigenetic, post-transcriptional, post-translational modification regulatory mechanisms of immune response in CVDs. **a** DNA methylation; **b** Histone modification; **c** Types of coding or non-coding RNA; **d** mRNA modification; **e** Protein modification. NK cell Natural Killer cell, UTR Untranslated Region (Created with BioRender.com, <https://BioRender.com/i78n158>)

MIAT is a newly identified regulator of cellular processes in advanced atherosclerosis, influencing the proliferation, apoptosis, and phenotypic transition of SMCs, as well as the pro-inflammatory characteristics of macrophages.^{553,554} The lncRNA SIMALR, suppresses inflammatory macrophage apoptosis via NTN1 (Netrin-1).⁵⁵⁵ lncRNA CCR reduced infarct size and improved cardiac function by inhibiting the secretion of proinflammatory factors through the suppression of TLR2 and TLR4.⁵⁵⁶ miRNAs also play a role in the progression of CVDs. Overloaded hearts in mice revealed that miR-21 is crucial for macrophage polarization towards an M1-like phenotype, miR-21 primarily determined macrophage-fibroblast communication, promoting the transition from quiescent fibroblasts to myofibroblasts.⁵⁵⁷ miR-214 shows the highest induction in response to Ang II-mediated hypertension. Global deletion of miR-214 prevents Ang II-induced periaortic fibrosis, vascular stiffening, and T-cell recruitment. Thus, *miR-214*^{-/-} mice are shielded from endothelial dysfunction and oxidative stress, underscoring miR-214's involvement in pathological perivascular fibrosis through T cell recruitment and the release of pro-fibrotic cytokines.⁵⁵⁸ Moreover, circRNA_002581 can sponge miR-122, a micRNA that targets genes involved in inflammation. By sponging miR-122, circRNA_002581 promotes a pro-inflammatory macrophage phenotype, which contributes to vascular inflammation and cardiac hypertrophy.⁵⁵⁹ circRNA_010567 promotes the activation of the NF- κ B pathway by sponging miR-141, which targets a key inhibitor of NF- κ B. In M2 macrophage-derived small extracellular vesicles (SEVs), circUbe3a promotes myocardial fibrosis by targeting the microRNA-138-5p/RhoC axis, driving cardiac fibroblast proliferation, migration, and phenotypic

transformation, thereby worsening myocardial fibrosis after MI⁵⁶⁰ (Fig. 7c).

RNA modification. RNA modification is essential for cellular function by regulating gene expression.^{561,562} Key modifications include m6A (N6-Methyladenosine), which methylates adenine residues and is added by the methyltransferase Like 3 METTL3-METTL14 complex and removed by demethylases like fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5); m5C (5-Methylcytosine), which methylates the fifth carbon of cytosine and is added by methyltransferases such as DNA methyltransferase 2 (DNMT2) or NOP2/Sun RNA methyltransferase family member 2 (NSUN2); and m7G (7-Methylguanylate), which is capped at the 5' end of mRNA by capping enzymes. These modifications influence various aspects of gene expression, including splicing, maturation, transport, stability, and translation.^{563,564}

Dynamic alterations in RNA modifications across different types of RNA are crucial for the development and functioning of the immune system.⁵⁶⁵ METTL3-deficient dendritic cells display immature characteristics and extend allograft survival.^{566,567} Also, METTL3-dependent N6-methyladenosine modification of Braf mRNA amplifies the macrophage inflammatory response and accelerates atherosclerosis in mice.⁵⁶⁸ Similarly, METTL14 exacerbates endothelial inflammation and atherosclerosis by increasing N6-methyladenosine modifications on FOXO1 and mediates the inflammatory response of macrophages through the NF- κ B/IL-6 signaling pathway.^{569,570} Seven key m6A regulators - Wilms tumor 1 associated protein (WTAP), Zinc Finger CCH-Type Containing

13 (ZCH3H13), YTH domain-containing protein 1 (YTHDC1), Fragile X Messenger Ribonucleoprotein 1 (FMR1), FTO, RNA Binding Motif Protein 15 (RBM15), and YTH N6-methyladenosine RNA Binding Protein 3 (YTHDF3)—could serve as novel biomarkers for the precise diagnosis of ischemic cardiomyopathy (ICM).⁵⁷¹ In addition, Kun Wang et al. reveal that piRNA-mediated m5C methylation is involved in the regulation of cardiomyocyte necroptosis. Heart necroptosis-associated piRNA (HNEAP) regulates cardiomyocyte necroptosis by inhibiting the m5C methylation of Atf7 mRNA⁵⁷² (Fig. 7d).

Post-translational modification. Post-translational modification (PTM) involves the covalent and enzymatic alteration of proteins after biosynthesis, impacting their function, localization, and cellular interactions.^{573,574} Key PTMs include phosphorylation, ubiquitination, and methylation.

Post-translational modifications like phosphorylation and poly-ubiquitination strongly regulate innate inflammatory responses by affecting the activation, translocation, and interaction of innate receptors and signaling molecules in response to harmful signals.^{575–577} In atherosclerosis, IL-8 binds to CXC motif chemokine receptor 2 (CXCR2) on neutrophils, promoting NET formation through Src, extracellular signal-regulated kinases (ERK), and p38 MAPK phosphorylation. This activates the TLR9/NF- κ B pathway in macrophages, increasing IL-8 release and worsening disease, highlighting NETs as a therapeutic target.⁵⁷⁸ In obesity-induced cardiomyopathy, deleting or inhibiting doublecortin-like kinase 1 (DCLK1) in macrophages protects against high-fat diet-induced heart dysfunction, hypertrophy, and fibrosis by suppressing receptor-interacting serine/threonine-protein kinase 2 (RIP2) phosphorylation and inhibiting RIP2/TAK1-mediated inflammation.⁵⁷⁹ Also, TRAF6, downstream of IL-1 β , ubiquitinates YAP at K252, enhancing its nuclear translocation and disrupting interaction with angiomin, leading to increased macrophage infiltration and atherosclerotic lesions.⁵⁸⁰ WWP2, an E3 ubiquitin ligase, regulates cardiac fibrosis in non-ischemic cardiomyopathy by

modulating the CCL5/Ly6chigh monocyte axis. WWP2 affects Ly6c high monocytes, promoting IRF7 mono-ubiquitination, nuclear translocation, and transcriptional activity, leading to CCL5 upregulation and reduced myofibroblast trans-differentiation.⁵⁸¹ RNF5 inhibits cardiac hypertrophy by promoting STING degradation via K48-linked polyubiquitination, thereby reducing inflammation and immune responses.⁵⁸² Additionally, interferon-stimulated gene 15 (ISG15) induces vascular damage in hypertension by promoting oxidative stress and inflammation, leading to endothelial dysfunction and vascular remodeling through post-translational modification (ISGylation) of macrophages.⁵⁸³ In ischemic myocardium, pharmacologically-induced hyper-O-GlcNAcylation enhances M2-like macrophage reparative activation. Myeloid knockdown of O-GlcNAcase, leading to hyper-O-GlcNAcylation, positively regulates M2-like activation and reduces post-MI hyper-inflammation.⁵⁸⁴

The regulatory mechanisms of epigenetic, post-transcriptional, and post-translational modifications are crucial for understanding immune responses in CVDs. These modifications—including DNA methylation, histone alterations, non-coding RNAs, and protein modifications—interact in complex ways to influence gene expression patterns that are vital for immune cell function and the progression of CVDs. Investigating these processes not only reveals the underlying biological mechanisms of CVDs but also opens innovative pathways for therapeutic interventions aimed at modulating these modifications to improve patient outcomes (Fig. 7e).

Integration of key signaling pathway in CVDs with immune response

Key signaling pathways in CVDs interplay with immune responses, which matters in CVDs. The crosstalk among those pathways highlights the importance of immune responses in CVDs (Fig. 8).

G protein-coupled receptor (GPCR)-signaling pathway. GPCR signaling pathways are intricate signaling processes initiated by GPCRs, a vast and diverse group of membrane receptors. Upon

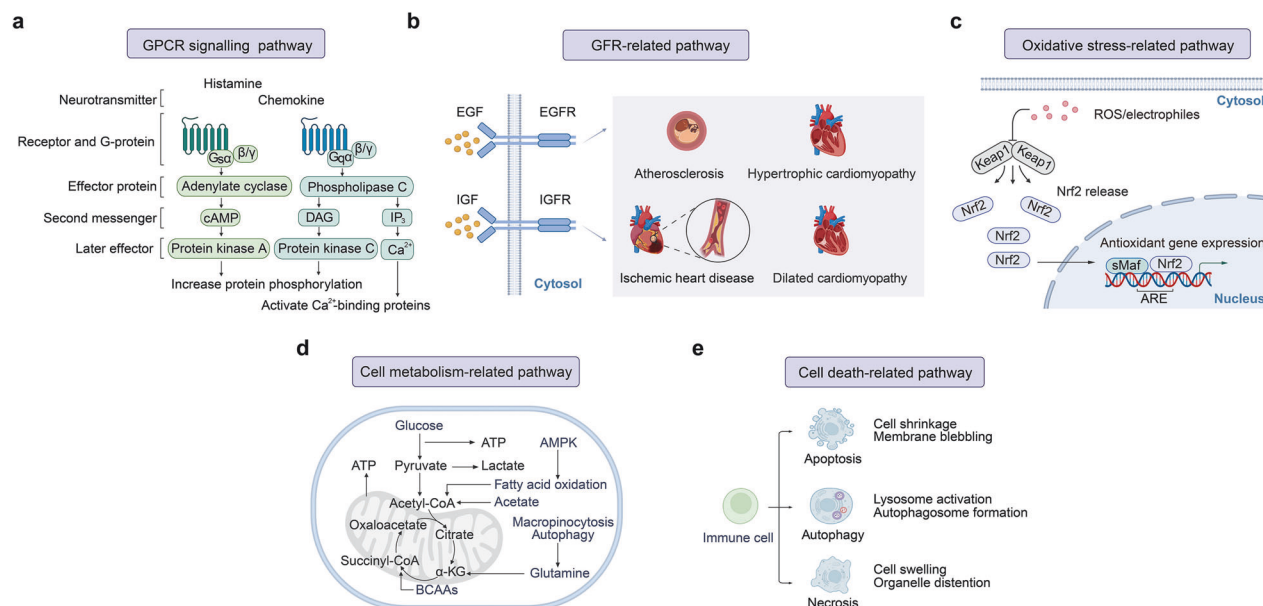


Fig. 8 Integration of key signaling pathway in CVDs with immune response. **a** G protein-coupled receptor (GPCR) signaling pathway; **b** GFR-related pathway; **c** Oxidative stress-related pathway; **d** Cell metabolism-related pathway; **e** Cell death-related pathway. GPCR G Protein-Coupled Receptor, DAG Diacylglycerol, cAMP Cyclic Adenosine Monophosphate, IP3 Inositol Trisphosphate, GFR Growth factor receptor, EGF Epidermal growth factors, IGF Insulin-like growth factors, EGFR Epidermal growth factor receptors, IGFR Insulin-like growth factor receptors, sMaf Small Musculoaponeurotic Fibrosarcoma, Nrf2 Nuclear Factor Erythroid 2-Related Factor 2, ARE Antioxidant Response Element, ATP Adenosine Triphosphate, TCA Tricarboxylic Acid cycle, BCAAs Branched-Chain Amino Acids, TLR Toll-Like Receptor, I κ B Inhibitor of kappa B, NF- κ B Nuclear Factor Kappa-light-chain-enhancer of activated B cells, P50 Nuclear Factor NF-kappa-B p50 subunit, P65 Nuclear Factor NF-kappa-B p65 subunit (Created with BioRender.com, <https://BioRender.com/p48m296>)

ligand binding to a GPCR, a conformational change occurs, which in turn activates an associated G protein by facilitating the exchange of GDP for GTP on the G α subunit. This activation causes the G protein to dissociate into G α and G $\beta\gamma$ subunits, both of which interact with various downstream effectors. These interactions produce second messengers, such as cyclic AMP (cAMP) or inositol triphosphate (IP $_3$), which further propagate the signal. The signaling cascade ultimately leads to a wide range of cellular responses. GPCR pathways are fundamental for numerous physiological functions, including sensory perception, immune response, mood regulation, and metabolism.⁵⁸⁵

The GPCR signaling pathway modulates immune cell behavior and the expression of inflammatory mediators, playing a crucial role in maintaining immune system balance and ensuring appropriate inflammatory responses. This regulation is essential for orchestrating an effective immune response while preventing excessive inflammation that could lead to tissue damage.⁵⁸⁶ Chemokine receptors (CCR) are a large family of seven transmembrane domain GPCRs that are differentially expressed across various cell types.⁵⁸⁷ Single-cell RNA sequencing reveals that tissue-resident cardiac macrophages guide monocyte fate differently. Selective depletion of CCR2- or CCR2+ macrophages before myocardial infarction has distinct effects on left ventricular function, myocardial remodeling, and monocyte recruitment.⁵⁸⁸ Mechanistically, these CCR2- macrophages communicated with adjacent cardiomyocytes through focal adhesion complexes and were activated by mechanical stretch via a transient receptor potential cation channel subfamily V member 4 (TRPV4)-dependent pathway, regulating growth factor expression.⁵⁸⁹ Furthermore, CXCR7 meticulously regulates the dosage and signaling of adrenomedullin, a mitogenic peptide hormone essential for cardiovascular development. The loss of this decoy receptor leads to postnatal lethality due to abnormal cardiac development⁵⁹⁰ (Fig. 8a).

Growth factor receptor (GFR)-related pathway. GFR-related pathway involves cellular signaling processes that start with growth factors binding to their receptors on the cell surface. This binding triggers a cascade of intracellular events leading to various cellular responses, including proliferation, differentiation, migration, and survival. Growth factors, such as the epidermal growth factors (EGF) and the insulin-like growth factors (IGF), are proteins that interact with specific transmembrane receptors possessing intrinsic tyrosine kinase activity.⁵⁹¹

The EGFR pathway mediates macrophage responsiveness to specific diseases, impacting cardiac function and remodeling after acute ischemic injury. Myeloid cell-specific EGFR deletion leads to increased cardiomyocyte hypertrophy and worsened cardiac function and repair after acute myocardial infarction, with decreased levels of pro-reparative mediators such as Vegfa and Il10, and reduced capillary density.⁵⁹² In addition to EGFR, inflammatory cells secrete myeloid-derived growth factor (MYDGF) to aid tissue repair and regeneration following acute myocardial infarction. MYDGF levels rise in the left ventricular myocardium and blood plasma of pressure-overloaded mice, which enhances sarcoplasmic/endoplasmic reticulum Ca $^{2+}$ -ATPase 2a (SERCA2a) expression, reduces hypertrophy and dysfunction, and improves survival rates in both mice and patients with severe aortic stenosis.⁵⁹³ Furthermore, EGFR blockade in CD4 + T cells induces T cell anergy and reduces the development of atherosclerosis. EGFR inhibition decreases T cell proliferation, activation, and cytokine production, leading to reduced T cell infiltration in atherosclerotic lesions.⁵⁹⁴ Additionally, IL-35 promotes the survival of reparative CX3CR1+Ly6Clow macrophages, which in turn reduces cardiac rupture, improves wound healing, and attenuates cardiac remodeling after MI by enhancing α -SMA and collagen expression.⁵⁹⁵ Thrombospondin-1 (TSP1), a well-known inhibitor of angiogenesis, exerts its effects by interacting with cell surface receptors such as CD36 and CD47.

TSP1 suppressed lymphangiogenesis and inhibited VEGF-C-induced AKT and eNOS activation in lymphatic endothelial cells (LEC). CD47 silencing in LEC prevented these effects, and Cd47 knockout mice showed reduced atherosclerosis and higher lymphatic vessel density.⁵⁹⁶ Insulin-like growth factor-1 (IGF1R) signaling in macrophages suppresses foam cell accumulation and reduces plaque vulnerability in atherosclerotic lesions. IGF1R-deficient macrophages showed enhanced pro-inflammatory responses and reduced lipid efflux, increasing atherosclerosis and plaque instability.⁵⁹⁷ Eosinophils and eosinophil cationic protein (ECP) promote SMC calcification and atherogenesis via the BMPR-1A/1B-Smad-1/5/8-Runx2 signaling pathway. Eosinophil deficiency in Δ dblGATA mice slowed atherogenesis, increased SMC content, and reduced calcification.⁵⁹⁸ TGF(transforming growth factor)- β activates Smad3 in macrophages, enhancing phagocytosis and anti-inflammatory transition. Smad3 knockout in macrophages leads to increased mortality, adverse remodeling, and impaired anti-inflammatory responses post-myocardial infarction.⁵⁹⁹ Fibroblast growth factor 10 (FGF10) coacervate injection significantly attenuated MI injury by preserving cardiac function, reducing inflammation and fibrosis, improving vascular stabilization, and activating phosphorylated fibroblast growth factor receptor (p-FGFR), PI3K/AKT, and ERK1/2 pathways more effectively than free FGF10 or heparin united FGF10⁶⁰⁰ (Fig. 8b).

Oxidative stress-related pathway. Oxidative stress-related pathways refer to the cellular signaling processes triggered by an imbalance between the production of ROS, reactive nitrogen species (RNS) and the cell's antioxidant defenses. This imbalance leads to oxidative damage to proteins, lipids, and DNA, which can disrupt normal cellular function.⁶⁰¹

In MI, mitochondria-targeted ROS scavenging mitigated impairments, enhanced myofibroblast function in vivo, and decreased mortality in mKO mice. These results underscore the crucial role of mitochondria in resolving inflammation and facilitating tissue repair through the modulation of efferocytosis and interaction with fibroblasts, holding significant potential for improving post-MI recovery and addressing other inflammatory conditions.⁶⁰² The mitochondrial deacetylase Sirtuin3 (Sirt3) plays a crucial role in regulating metabolic and antioxidant functions linked to hypertension. Sirt3 depletion in hypertension leads to endothelial dysfunction, vascular hypertrophy, inflammation, and end-organ damage. Targeting Sirt3 expression has therapeutic potential for vascular dysfunction and hypertension⁶⁰³ (Fig. 8c).

Cell metabolism-related pathway. Cell metabolism-related pathways encompass biochemical processes that convert nutrients into energy and essential building blocks for cellular functions. Key pathways include glycolysis, the citric acid cycle, and oxidative phosphorylation, all of which generate ATP. The pentose phosphate pathway produces NADPH and ribose-5-phosphate for biosynthesis. Lipid metabolism processes fatty acids for energy storage and membrane synthesis. AMPK and mTOR signaling are among the best-understood metabolite-sensing and signaling pathways. These pathways regulate cellular energy balance, growth, and responses to environmental changes, supporting vital functions such as cell proliferation, differentiation, and survival.⁶⁰⁴

Dysregulation of cell metabolism can lead to diseases like cancer, CVDs, and metabolic disorders.^{605,606} In CAD patients' monocytes and macrophages, excessive glucose metabolism enhances IL-6 and IL-1 β production through mitochondrial ROS and nuclear PKM2, driving systemic inflammation. Targeting glycolysis, superoxide, and PKM2 tetramerization could potentially correct this pro-inflammatory phenotype.⁶⁰⁷ Macrophages from CAD patients are prolific producers of T cell chemo attractants (CXCL9, CXCL10), pro-inflammatory cytokines (IL-1 β , IL-6), and the immunosuppressive ligand PD-L1, highlighting their significant

role in exacerbating the inflammatory environment.⁶⁰⁸ NPM1 recruits histone demethylase KDM5b to the Tsc1 promoter, erasing H3K4me3 marks, inhibiting TSC1 expression, and enhancing mTOR signaling. Deficiency of NPM1 in macrophages mitigates myocardial ischemic injury, improves cardiac function, and promotes tissue repair after myocardial infarction by shifting cardiac macrophages towards oxidative phosphorylation metabolism and a reparative phenotype⁵⁴³ (Fig. 8d).

Cell death-related pathway. Cell death-related pathways regulate programmed cell death mechanisms such as apoptosis, necroptosis, and autophagy. Apoptosis involves caspase activation triggered by intrinsic (mitochondrial) or extrinsic (death receptor) pathways, leading to DNA fragmentation and cell dismantling. Necroptosis, a form of regulated necrosis, is mediated by RIPK1, RIPK3, and MLKL, causing cell membrane rupture. Autophagy involves the formation of autophagosomes that enclose cellular components, which are subsequently degraded by lysosomes, playing a crucial role in regulating the immune system⁶⁰⁹ (Fig. 8e).

The roles of immunogenic cell death in cardiac disease have yet to be fully defined, and biology-based strategies to inhibit cell death in various cardiac syndromes are also explored.⁶¹⁰ In macrophages, ER stress activates the UPR, leading to apoptosis, with the PI3K/Akt pathway providing anti-apoptotic protection; JNK1 opposes Akt signaling, affecting atherosclerosis progression and plaque stability.⁶¹¹ CD47, an anti-phagocytic molecule that makes cells resistant to efferocytosis, is associated with atherosclerosis. CD47-blocking antibodies reverse this defect, normalize the clearance of diseased vascular tissue, and ameliorate atherosclerosis.⁶¹² Efferocytosis-derived nucleotides activate a DNA-PKcs-mTORC2/Rictor pathway, promoting non-inflammatory macrophage proliferation, apoptotic cell clearance, and tissue resolution, aiding in atherosclerosis regression and plaque stabilization.⁶¹³ Myeloid CD147 promotes atherosclerosis by enhancing inflammation via the TRAF6-IKK-IRF5 pathway and inhibiting efferocytosis by suppressing GAS6. Anti-human CD147 antibodies reduce atherosclerosis, suggesting a new therapeutic approach.⁶¹⁴ Serum immunity-related GTPase family M protein (IRGM) is linked to plaque rupture in STEMI patients. IRGM/Irgm1 deficiency increases plaque stability and suppresses macrophage apoptosis by inhibiting ROS production and MAPK signaling.⁶¹⁵ Solute Carrier Family 26 Member 4 (SLC26A4), identified as a potential asthma target,⁶¹⁶ also contributes to cardiac hypertrophy by promoting autophagy and inducing apoptosis in cardiomyocytes.⁶¹⁷ In an *in vitro* starvation model, neonatal mouse cardiomyocytes from WT mice and those with macrophage migration inhibitory factor (MIF) depletion showed a significant reduction in starvation-induced autophagic vacuole formation and an increase in starvation-induced cell death in H9C2 cells. These results suggest that MIF plays a supportive role in maintaining cardiac contractile function during starvation by regulating autophagy.^{618,619} SIRT1 levels are repressed, and acetylated p53 levels are enhanced in CAD patient monocytes, increasing pro-apoptotic events and pro-inflammatory responses, contributing to vessel damage and long-term recurrent ischemic events.⁶²⁰

By integrating multi-disciplinary efforts that include genomic, epigenetic, and immune response studies, we can identify novel biomarkers and therapeutic targets. This can facilitate the development of personalized treatments that modulate immune responses and key signaling pathways involved in CVD progression. Additionally, adopting flexible clinical trial designs, akin to those used in cancer research, will allow for rapid validation of new therapies and improved patient outcomes. Ultimately, these innovations promise to advance the clinical translation of cardiovascular research, offering new hope for better management of heart diseases.

The integration of key signaling pathways in CVDs highlights the complex interplay between immune responses and

cardiovascular mechanisms. This intricate crosstalk, involving pathways such as GPCR, growth factor receptors, oxidative stress, and cell metabolism, underscores the importance of understanding how these processes influence immune regulation in CVDs. By investigating these connections through multidisciplinary efforts—including genomic, epigenetic, and immune response studies—researchers can uncover novel biomarkers and therapeutic targets that facilitate the development of personalized treatments. Such approaches aim to modulate immune responses and regulate key signaling pathways, enhancing cardiac repair, reducing inflammation, and ultimately improving patient outcomes. Adopting flexible clinical trial designs, similar to those used in oncology, will further accelerate the validation of new therapies and support the clinical translation of cardiovascular research, offering renewed hope for advancing CVDs management.

IMMUNE-BASED THERAPEUTIC STRATEGIES FOR TARGETING CVDs

Immune-based therapeutic strategies for targeting CVDs represent a growing field aimed at modulating the immune system to prevent and treat these conditions. This approach categorizes potential therapeutic agents into three main groups: biologics, gene and molecular therapies, and chemical Drugs, based on existing preclinical studies. Given the current landscape, there is a pressing need to identify new targets and develop innovative treatment strategies for effective cardiovascular disease management (Table 1).

Biologics

Biologics, as defined by the FDA, are products made of sugars, proteins, nucleic acids, or their combinations, including live cells and tissues, and encompass vaccines, blood components, allergenic drugs, somatic cells, gene therapies, tissues, and recombinant proteins.⁶²¹ Relevant biologics for CVDs treatment include key subcategories such as fusion proteins, monoclonal antibodies, antibody peptides, CAR-T cell therapy, and peptidomimetic. Notably, fusion proteins like HCW-9302 and peptide-fusion proteins such as RBB-004 have shown promise in preclinical models. HCW-9302 targets IL-2R to promote the expansion of regulatory T cells for treating atherosclerosis in mice.⁶²² RBB-004 targets HSP70 in myocardial infarction, where extracellular HSP70 enhances the innate immune response as an immunomodulator.^{623,624} Also, monoclonal antibodies and humanized monoclonal antibodies are essential for modulating immune responses in CVDs. VSB-16 targets CCL4L1 to stabilize atherosclerotic plaques and reduce inflammation by inhibiting metalloproteinases, decreasing pro-inflammatory cytokine production, and suppressing the NF-κB signaling pathway.⁶²⁵ TNAX-103A targets CD300A in myocardial infarction, enhancing efferocytosis by infiltrating myeloid cells.⁶²⁶ Antibody peptides and antibody-drug conjugates further broaden the range of therapeutic options. CD40L/Mac-1 interaction inhibitors prevent the recruitment of inflammatory leukocytes and reduce inflammation in atherosclerosis by targeting CD11b, CD40LG, and integrin subunit beta 2 (ITGB2).^{625,627} The novel anti-CD45 ADC, initially used for anti-tumor therapy, is now being used to treat atherosclerosis by reducing the atherosclerotic plaque burden.⁶²⁸ Moreover, CAR-T cell therapy is currently under development. Antigen-specific CD8 T cells are used for adoptive transfer to effectively target and ablate cardiac fibroblast proteins, thereby reducing cardiac fibrosis.⁴⁵ Additionally, peptidomimetics and peptide-conjugated drugs such as NWL-283 and SIM-339 target Caspase3 and c-Jun NH2-terminal Kinase (JNK), respectively, to reduce apoptosis and inflammatory responses in myocardial infarction and cerebral hemorrhage.^{629–631} Galectin-3 (Gal-3) inhibitors, which target the protein involved in collagen synthesis, macrophage infiltration, and interstitial fibrosis, are being explored to treat myocardial infarction.^{632–634}

Table 1. Selected published articles on immune-regulating therapeutic agents in preclinical development

Drugs	Indication	Therapeutic agents	Targets
HCW-9302 ⁶²²	Atherosclerosis	Peptide-fusion proteins	IL-2R Factor VIII
Anti-CD45 antibody-drug conjugate ⁶²⁸	Atherosclerosis	Antibody-drug conjugates	CD45
APTA-5278 ^{635,636}	Atherosclerosis	Chemical drugs	NOX
AZ-6983 ⁶³⁷	Atherosclerosis	Small molecule drugs	$\alpha 7$ nAChR
VSB-16 ⁶²⁵	Atherosclerosis	Monoclonal antibody	CCL4L1
CD40L/Mac-1 interaction inhibitors ⁶²⁷	Atherosclerosis	Antibody peptide	CD11b CD40LG ITGB2
BRP-187 ⁶³⁸	Atherosclerosis	Chemical drugs	LOX5 FLAP
Endothelial lipase inhibitors ⁶³⁹	Atherosclerosis	Chemical drugs	LIPG
NLRP3 inflammasome inhibitor ⁶⁴⁷	Myocardial infarction	Chemical drugs	NLRP3
NH2-terminally truncated galectin-3 ^{632,634}	Myocardial infarction	Recombinant peptide	LGALS3
SIM-339 ⁶³⁹	Cerebral hemorrhage Myocardial infarction	Peptide-coupled drug	JNK
RBB-004 ⁶²⁴	Myocardial infarction	Antibody-fusion proteins	HSP70
TNAX-103A ⁶²⁶	Myocardial infarction	Humanized monoclonal antibodies	CD300A
NWL-283 ⁶³¹	Myocardial infarction	Peptidomimetic drug	CASP3
APD-588 ^{643,644}	Heart failure	Chemical drugs	S1PR
SR-9009 ⁶⁴⁵	Myocardial infarction Heart failure	Chemical drugs	REV-ERB
SA-12 ⁶⁴¹	Heart failure	Chemical drugs	MPO
GDF15 modulator ⁶⁴⁶	Congestive heart failure	Chemical drugs	GDF15
CAR-T cells ⁴⁵	Cardiac fibrosis	Adoptive T cell transfer	FAP
In vivo-generated CAR T cells ¹⁵	Cardiac fibrosis	LNP-encapsulated modified mRNA	FAP

IL-2R Interleukin-2 Receptor, *CD45* Cluster of Differentiation 45, *NOX* NADPH Oxidase, $\alpha 7$ nAChR Alpha-7 Nicotinic Acetylcholine Receptor, *MPO* Myeloperoxidase, *CCL4L1* C-C Motif Chemokine Ligand 4-Like 1, *CD11b* Cluster of Differentiation 11b, *CD40LG* CD40 Ligand, *ITGB2* Integrin Beta-2, *LOX5* 5-Lipoxygenase, *FLAP* 5-Lipoxygenase Activating Protein, *LIPG* Endothelial Lipase (LIPG), *HDAC6* Histone Deacetylase 6, *NLRP3* NOD-like Receptor Pyrin Domain Containing 3, *LGALS3* Galectin-3, *JNK* c-Jun N-terminal Kinase, *HSP70* Heat Shock Protein 70, *CD300A* Cluster of Differentiation 300a, *CASP3* Caspase-3, *S1PR* Sphingosine-1-Phosphate Receptor, *REV-ERB* REV-ERB Nuclear Receptors (including REV-ERB α and REV-ERB β), *GDF15* Growth Differentiation Factor 15, *FAP* Fibroblast Activation Protein

Gene and molecular therapies

Gene and molecular therapies involve the manipulation of genetic material to treat diseases. This category includes viral gene delivery systems and LNP-encapsulated modified mRNA. A notable approach includes generating antifibrotic CAR T cells in vivo by delivering modified mRNA via T cell-targeted LNPs. These cells have shown promise in mice, effectively reducing fibrosis and restoring cardiac function.¹⁵

Chemical drugs

Chemical drugs encompass a wide range of compounds with diverse mechanisms of action. For atherosclerosis, several targets have been identified to reduce inflammatory responses and arterial plaque formation. APTA-5278, an inhibitor targeting NADPH oxidase-dependent ROS formation, reduces oxidative stress and inflammation.^{635,636} AZ6983 activates $\alpha 7$ nAChR to inhibit atherosclerosis and enhance phagocytosis in myeloid cells.⁶³⁷ BRP-187 is a leukotriene synthesis inhibitor that prevents the assembly of the FLAP complex, reducing the production of pro-inflammatory leukotrienes.⁶³⁸ Endothelial lipase inhibitors target LIPG to reduce pro-inflammatory effects and improve high-density lipoprotein levels.^{639,640} For heart failure, myeloperoxidase (MPO) inhibitors such as SA-12 significantly improve cardiac function and inhibit myocardial structural changes in non-ischemic heart failure mouse models.⁶⁴¹ APD588, a selective S1P receptor modulator, regulates inflammatory responses and improves cardiac functional recovery following myocardial infarction.⁶⁴²⁻⁶⁴⁴ SR9009, a synthetic compound activating REV-ERB receptors, aids in long-term cardiac repair following myocardial ischemia-reperfusion.⁶⁴⁵ GDF-15 modulators are used to treat congestive heart failure by mitigating inflammation and tissue damage.⁶⁴⁶ In myocardial infarction, early inhibition of NLRP3

activation can reduce infarct size and protect cardiac function, making inflammasome inhibitors a promising treatment for acute myocardial infarction.⁶⁴⁷ Additionally, DNMT inhibitors and other epigenetic therapies might help modulate macrophage functions to prevent or treat CVDs. Indeed, inhibition of DNMT3b has been found to increase the expression of Tregs while decreasing the levels of pro-inflammatory cytokines such as IL-1 β and IFN- γ , thereby regulating the inflammatory response and the development of atherosclerosis.⁶⁴⁸⁻⁶⁵⁰ In heart transplantation, FNVs@RAPA utilize a ROS-responsive bio-orthogonal chemistry approach for active targeting delivery to the heart graft site, effectively alleviating IRI and promoting the polarization of Ly6C + Ly6G-inflammatory macrophages towards an anti-inflammatory phenotype.⁶⁵¹ The MNPs/Alg hydrogel, composed of melanin nanoparticles and alginate, eliminates ROS, promotes macrophage polarization to regenerative M2 macrophages, and provides antioxidant, anti-inflammatory, and proangiogenesis effects, showing great potential for myocardial infarction treatment and cardiac repair.⁶⁵²

CLINICAL TRIALS

Current clinical trials on immunomodulation in CVDs encompass broad-spectrum immunosuppressants, target-inflammatory treatments, cell therapies, and novel immunomodulatory targets, primarily targeting atherosclerosis and acute myocardial infarction (Table 2).

Broad-spectrum immunosuppressants

The efficacy of broad-spectrum immunosuppressants like Ciclosporin, sirolimus, rapamycin, and everolimus in CVD has been limited. The CIRT study (NCT01594333) revealed that methotrexate

Table 2. Clinical trials with immunomodulatory therapeutics for cardiovascular diseases

Study names	Drugs	Mechanism of action	Targets	Phase	Patient cohort	Primary endpoints	Main outcomes	NCT number
Lodoco2 (2020) ⁶⁹⁰	Colchicine	Microtubule inhibitor	TUBB	Phase3	Patients with CAD	MACE	Low-dose colchicine significantly reduced cardiovascular events.	ACTRN12614000093684
COLCOT (2019) ⁴⁷	Colchicine	Microtubule inhibitor	TUBB	Phase3	Patients with MI	MACE	0.5 mg daily colchicine significantly reduced ischemic cardiovascular risk	NCT02551094
NA	Colchicine	Microtubule inhibitor	TUBB	Phase 2	Patients with HFpEF	Change in hs-CRP	NA	NCT04857931
NA	Colchicine	Microtubule inhibitor	TUBB	NA	Patients with AAA	Changes in maximum diameter of AAA	NA	NCT05361772
NA	Colchicine	Microtubule inhibitor	TUBB	Phase 3	Patients with CHD requiring PCI	MACE	NA	NCT06472908
COCS (2024)	Colchicine	Microtubule inhibitor	TUBB	Phase4	Patients awaiting elective cardiac surgery (CABG/AVR)	Postoperative atrial fibrillation incidence	NA	NCT04224545
CIRT (2018) ⁶⁵³	Methotrexate	Broad immuno—suppression dihydrofolate reductase inhibitor	A2AR	Phase3	Patients with prior MI or multivessel CAD by angiography	MACE	Methotrexate didn't reduce IL-1 β , IL-6, CRP, or cardiovascular events	NCT01594333
NA	Methotrexate	Broad immuno—suppression dihydrofolate reductase inhibitor	A2AR	Phase4	Patients with RA	Change in peripheral SBP	NA	NCT03254589
CAPRI (2020) ⁶⁵⁴	Ciclosporin	Broad immuno—suppression Calcineurin inhibitors	MPTP	Phase2	Patients with STEMI and undergoing PCI	Change in infarct size	Single ciclosporin bolus had no effect on infarct size or LV remodeling	NCT02390674
Mohd Ali et al. (2018) ⁶⁵⁵	Sitrolimus	Broad immuno—suppression mTOR inhibitors	FKBP 12	Phase1	Patients with coronary DES restenosis	Late lumen loss	Novel SCB vs. proven PCB for coronary DES ISR shows similar angiographic outcomes	NCT02996318
ORAR ⁶⁵⁶	Rapamycin	mTOR inhibitor	mTOR	Phase3	Patients with BMS implantation	Cost differences in revascularization for de novo lesions	No outcome difference between oral rapamycin + BMS and DES for de novo lesions	NCT00552669
CLEVER-ACS ⁶⁵⁷	Everolimus	mTOR inhibitor	mTOR	Phase1/2	Patients with STEMI	MI size measured by MRI	Treatment didn't reduce MI size or MVO at 30 days	NCT01529554
CANTOS (2017) ⁴⁶	Canakinumab	Anti-interleukin-1 β antibodies	IL-1 β	Phase 3	Patients with MI	MACE	150 mg canakinumab every 3 months significantly lowered recurrent cardiovascular events versus placebo	NCT01327846
VCUART3 (2020) ⁶⁵⁹	Anakinra	IL-1 receptor antagonist	IL-1Ra	Phase 2	Patients with STEMI	The AUC for hsCRP	Compared to placebo, it significantly reduces the systemic inflammatory response	NCT01950299
MAGIC-ART(2020)	Anakinra	IL-1 receptor antagonist	IL-1Ra	Phase 2	Patients with cardiac sarcoidosis	Change in inflammation marker	NA	NCT04017936
Myachikova et al. ⁶⁶⁰	Goflikicept	IL-1 inhibitor	IL-1 β	Phase 2/3	Patients with idiopathic recurrent pericarditis	Time to first pericarditis recurrence was evaluated	Goflikicept reduced recurrence risk vs. placebo	NCT04692766
Sayed et al. ⁶⁵⁸	Xilonix	IL-1 α inhibitor	IL-1 α	Phase 2	Patients after PCI	Target vessel restenosis, time to restenosis, and MACE incidence	At 12 months, no significant difference in MACE or target vessel restenosis between groups	NCT01270945
RESCUE ⁶⁶¹	Ziltivekimab	IL-6-targeting monoclonal antibody	IL-6	Phase 2	Patients with moderate to severe CKD	12-week change in hs-CRP	Ziltivekimab markedly reduced atherosclerosis-related inflammation and thrombosis biomarkers	NCT03926117
ARTEMIS (2024)	Ziltivekimab		IL-6	Phase3	Patients with AMI		NA	NCT06118281

Table 2. continued

Study names	Drugs	Mechanism of action	Targets	Phase	Patient cohort	Primary endpoints	Main outcomes	NCT number
ATHENA (2024)	Ziltivekimab	IL-6-targeting monoclonal antibody	IL-6	Phase3	Patients with HF	Time to first 3-component MACE Change in KCCQ-CSS	NA	NCT06200207
ASSAIL-MI (2021) ⁶⁶³	Tocilizumab	IL-6-targeting monoclonal antibody	IL-6	Phase 2	Patients with STEMI within 6 h undergoing PCI	Myocardial salvage index (%)	Tocilizumab increased myocardial salvage in patients with acute STEMI	NCT03004703
Kleveland. et al. ⁶⁶²	Tocilizumab	IL-6-targeting monoclonal antibody	IL-6	Phase 2	Patients with NSTEMI	Between-group AUC difference for hs-CRP (days 1–3)	Tocilizumab attenuated the inflammatory response	NCT01491074
IMICA (2021) ⁶⁶⁴	Tocilizumab	IL-6-targeting monoclonal antibody	IL-6	Phase2	Patients with out-of-hospital cardiac arrest	Reduction in CRP levels at 72 h	Tocilizumab reduced systemic inflammation and myocardial injury in comatose patients post-cardiac arrest.	NCT03863015
NA	NT-0796	NLRP3 inhibitor	NLRP3	Phase 2	Patients with BMI ≥ 30 and ≤40 kg/m ²	Change in hsCRP levels	NA	NCT06129409
NA	DFV890	NLRP3 inhibitor	NLRP3	Phase 2	Patients with MI (ages 18–85, BMI 18–45 kg/m ² , hsCRP ≥ 2 mg/L)	Serum levels of IL-6 and IL-18	NA	NCT06031844
Wohlford et al. ⁶⁶⁷	Dapansutril	Selective NLRP3 Inflamma--some Inhibitor	NLRP3	Phase 1b	Patients with stable systolic HF, LVEF ≤ 40%, NYHA II-III symptoms	AEs	14-day dapansutril treatment was safe and well-tolerated in stable HFpEF patients	NCT03534297
CATCH-AMI (2013)	Balixafortide (POL6326)	CXCR4 antagonist	CXCR4	Phase 1a	Patients with reperfused STEMI	Change in LVEF determined by MRI	NA	NCT01905475
NA	Etanercept	TNF-α inhibitor	TNF-α	Phase4	Patients with AMI	MACE	NA	NCT01372930
Colombo et al. ⁶⁶⁹	Bindarit	Selective inhibitor of monocyte chemotactic protein-1 (MCP-1/CCL2)	MCP-1/CCL2	Phase 1a	Patients with coronary BMS	In-segment late loss	Bindarit significantly reduced in-segment late loss, indicating potential vessel wall benefits post-angioplasty	NCT01269242
NA	BRB-002	Novel Anti-CD47 Molecule	CD47	Phase 1	Healthy male volunteers	To evaluate the safety and tolerability of BRB-002	NA	ACTRN1262400405516
NA	Atibudlimab	Chimeric monoclonal antibody targeting CD14	CD14	Phase 1b	Patients with ACM	Safety and efficacy of the drug	NA	NCT06275893
Chen et al. ⁶⁷⁵	RTP-026	Annexin-A1 analog	FPR2	Phase2	Patients with STEMI undergoing PCI, chest pain <12 h, NLR 7–17	cTNT/CK-MB at 24 hours	NA	NCT06465303
Hernández-Jiménez et al. ⁶⁷¹	ApTOLL	Toll-like receptor 4 antagonist	TLR4	Phase1	Health male volunteers	Assess safety and pharmacokinetics of 30-min IV ApTOLL infusion	No ApTOLL accumulation, confirming safety and supporting clinical trials	NCT04742062
SATELLITE (2023) ⁶⁷⁰	AZD4831	Myelo--peroxidase inhibitor	Mpo	Phase2	Patients with HFpEF	Myeloperoxidase specific activity	AZD4831 was safe and effectively inhibited myeloperoxidase.	NCT03756285
RESTORE (2022)	OPL-0301	ST1PR1 agonist	ST1PR1	Phase 2	Patients with acute STEMI	Infarct size by CMR at Day 90	NA	NCT05327855
HUCV002-01 (2022) ⁶⁸⁴	αGCDC	α-galactosylceramide-pulsed dendritic cells (αGCDCs)	INKT cell	Phase 2	Patients with CHF	Change in LVEF from baseline to 24 weeks	NA	JRCT2073210116
Hare et al. (2005) ⁶⁸⁰	Adult hMSCs	Cell-based immuno--modulators	DMMI	Phase1	Patients with MI	AEs rates in 0.5, 1.6, and 5.0 million MSC/kg dose cohorts vs. placebo	Similar adverse event rates between hMSC and placebo groups	NCT00114452
Lee et al. ⁶⁸¹	SEED-MSC (BM-MSCs)	Cell-based immuno--modulators	DMAMI	Phase2/3	Patients with AMI	Absolute changes in global LVEF by SPECT	NA	NCT01392105

Table 2. continued

Study names	Drugs	Mechanism of action	Targets	Phase	Patient cohort	Primary endpoints	Main outcomes	NCT number
Chullikana et al. ⁶⁸⁵	Stempeuce (BM-MSCs)	Cell-based immuno-modulators	DMAMI	Phase1/2	Patients with STEMI	AEs and ECG parameters	Safe and tolerable, showing modest LVEF improvement at 6 months by SPECT	NCT00883727
Butler (2016) ⁶⁸⁶	aMBMC	Cell-based immuno-modulators	NICM	Phase 2a	Patients with non-ischemic Heart Failure	Safety by number of AEs	Safe and well-tolerated IV in AMI patients 2 days post-PCI	NCT02467387
NA	BM-MSCs	Cell-based immuno-modulators	DMAMI	Phase3	Patients with AMI	Change in LVEF	Safe, immunomodulatory effects, with improved health status and functional capacity	NCT01652209
TRIDENT (2017) ⁶⁸⁷	hMSC	Cell-based immuno-modulators	ICM	Phase 2	Patients with ischemic cardiomyopathy	Number of Participants With TE-SAEs	100 million dose increased ejection fraction; both doses reduced scar size	NCT02013674
TAC-HFT-II (2020)	hmsc/hCSC	Cell-based immuno-modulators	DMMI	Phase1/2	Patients with chronic ischemic LV dysfunction and HF post-MI	Incidence of any TE-SAEs	NA	NCT02503280
WJ-MSC-AMI (2015) ⁶⁸²	WJMSCs	Cell-based immuno-modulators	DMSTEMI	Phase2	Patients with AMI	Myocardium metabolic and perfusion measurements, global LVEF by echocardiography	Intracoronary WJMSCs safe and effective in AMI, clinically relevant therapy	NCT01291329
RIMECARD (2016) ⁶⁸⁸	UC-MSC	Cell-based immuno-modulators	LV function in HFrEF	Phase1/2	Patients with compensated HF (dilated phase)	Change in global LVEF	IV UC-MSCs safe in stable HF with reduced LVEF	NCT01739777
HUC-HEART Trial ⁶⁸⁹	HUC-MSCs	Cell-based immuno-modulators	ICM	Phase1/2	Patients with chronic ischemic CM	Ventricular remodeling	Intramycardial HUC-MSCs effective in CIC	NCT02323477
NA	UC-MSCs	Cell-based immuno-modulators	DMMI	Phase1	Patients with MI	MACE	NA	NCT03902067
NA	Clinical-grade WJ-MSCs	Cell-based immuno-modulators	DMSTEMI	Phase1/2	Patients with STEMI	MI size	NA	NCT03533153
Qayyum et al. ⁶⁸³	ADSCs	Cell-based immuno-modulators	LV function in HFrEF	Phase2	Patients with HFrEF	Change in LVESV	Safe but no improvement in myocardial function or symptoms	NCT03092284

CAD Coronary Artery Disease, MACE Major Adverse Cardiovascular Events, MI Myocardial Infarction, HFrEF Heart Failure with Preserved Ejection Fraction, hs-CRP High-Sensitivity C-Reactive Protein, AEs Adverse event, TE-SAEs Treatment emergent serious adverse events, AAA Abdominal Aortic Aneurysm, CHD Coronary Heart Disease, PCI Percutaneous Coronary Intervention, CABG Coronary Artery Bypass Grafting, AVR Aortic Valve Replacement, RA Rheumatoid Arthritis, DES Drug-Eluting Stent, BMS Bare Metal Stent, NSTEMI Non-ST-Elevation Myocardial Infarction, CKD Chronic Kidney Disease, KCCQ-CSS Kansas City Cardiomyopathy Questionnaire Clinical Summary Score, AUC Area Under the Curve, CRP C-Reactive Protein, IL-6 Interleukin-6, IL-18 Interleukin-18, LVEF Left Ventricular Ejection Fraction, NLR Neutrophil-to-Lymphocyte Ratio, SPECT Single Photon Emission Computed Tomography, CMR Cardiac Magnetic Resonance, cTNT Cardiac Troponin T, CK-MB Creatine Kinase-MB, UC-MSC Umbilical Cord Mesenchymal Stem Cells, HUC-MSC Human Umbilical Cord Mesenchymal Stem Cells, ACM Arrhythmogenic Cardiomyopathy, CHF Congestive Heart Failure, LVESV Left Ventricular End-Systolic Volume, MVO Myocardial Viability Outcome, CM Cardiomyopathy, AMI Acute Myocardial Infarction, AE Adverse Event, STEMI ST-Elevation Myocardial Infarction, *Tubb* Tubulin Beta Chain, A2AR Adenosine A2A Receptor, *MPTP* Mitochondrial Permeability Transition Pore, *FKBP12* FK506 Binding Protein 12, *mTOR* Serine/Threonine-Protein Kinase mTOR, *FFR2* N-Formyl Peptide Receptor 2, *TLR4* Toll-Like Receptor 4, *DMMI* Damaged Myocardium in Myocardial Infarction, *DMAMI* Damaged Myocardium in Acute Myocardial Infarction, *NICM* Myocardium in Nonischemic Cardiomyopathy, *ICM* Myocardium in Ischemic Cardiomyopathy, *DMSTEMI* Damaged Myocardium in ST-Elevation Myocardial Infarction, *HFrEF* Heart Failure with Reduced Ejection Fraction

did not reduce inflammation markers or major adverse cardiovascular events (MACE) in coronary artery disease patients.⁶⁵³ Ciclosporin (NCT02390674) did not significantly impact infarct size or left ventricular remodeling in acute myocardial infarction patients.⁶⁵⁴ Studies on sirolimus (NCT02996318) and rapamycin (NCT00552669) for drug-eluting stents (DES) to inhibit restenosis also reported negative outcomes.^{655,656} Everolimus (NCT01529554) failed to reduce myocardial infarction size in acute ST-elevation myocardial infarction patients.⁶⁵⁷ These findings suggest that while these immunosuppressants hold potential in other diseases, their effectiveness in CVDs, particularly in acute myocardial infarction and stent-related treatments, is limited.

Target-inflammatory treatments

IL-1 and IL-6 are central to the inflammatory response, with varying outcomes in related studies. El Sayed et al. found no significant differences in MACE and target vessel restenosis rates between groups using the IL-1 α inhibitor Xilonix after percutaneous coronary intervention.⁶⁵⁸ The CANTOS study (NCT01327846) on 10,061 post-myocardial infarction patients showed that quarterly administration of 150 mg canakinumab significantly reduced recurrent cardiovascular events.⁴⁶ The VCUART3 study demonstrated that anakinra (an IL-1 receptor antagonist) significantly reduced systemic inflammation in 99 ST-elevation myocardial infarction patients.⁶⁵⁹ Studies have shown that IL-1 α and IL-1 β are key cytokines in the pathophysiology of acute pericarditis and its recurrence, with rilonacept preventing recurrences and maintaining remission in idiopathic recurrent pericarditis (IRP).⁶⁶⁰

IL-6, as a downstream inflammatory marker of IL-1, has also been a focus of research. The RESCUE study (NCT02660034) showed that ziltivekimab, an IL-6 targeting monoclonal antibody, significantly reduced atherosclerotic inflammation markers like high-sensitivity CRP and thrombosis markers in patients with moderate to severe chronic kidney disease.⁶⁶¹ Cleveland et al. (2016) found that tocilizumab, an IL-6 monoclonal antibody, reduced inflammation in patients with acute non-ST-elevation myocardial infarction.⁶⁶² The ASSAIL-MI study (NCT03004703) indicated that tocilizumab improved the myocardial salvage index in acute ST-elevation myocardial infarction patients undergoing PCI.⁶⁶³ The IMICA study (NCT03640180) demonstrated that tocilizumab significantly reduced systemic inflammation and myocardial injury in out-of-hospital cardiac arrest patients.⁶⁶⁴

The NLRP3 inflammasome, an upstream activator of IL-1 β and IL-18, plays a crucial role in the strong inflammatory response during myocardial ischemic and non-ischemic injury.³²⁹ The non-selective NLRP3 inflammasome inhibitor colchicine has been shown to reduce cardiovascular events in coronary artery disease patients over the long term in the Lodoco2 (NCT02285360) and COLCOT (NCT02551094) trials, leading to FDA approval for cardiovascular anti-inflammatory treatment.⁶⁶⁵ Selective NLRP3 inflammasome inhibitors like dapansutride have shown good safety and tolerability in HFrEF patients, warranting further research on their efficacy.^{666,667} NT0796 and DFV890, also selective NLRP3 inflammasome inhibitors, are currently in phase 2 clinical trials for coronary artery disease patients (NCT06129409, NCT06031844).

In addition to classical targeted therapies for inflammation, several non-classical inflammatory-targeted treatments have also emerged. Although, some clinical trials have yet to achieve their primary endpoints or disclose conclusive results. For instance, etanercept (NCT01372930), a TNF- α inhibitor, reduces inflammation by blocking TNF- α produced by macrophages,⁶⁶⁸ though clinical trial results are yet to be revealed. Bindarit (NCT01269242), selectively inhibiting monocyte chemoattractant protein-1 (MCP-1/CCL2), reduces monocyte chemotaxis and infiltration, significantly lowering late lumen loss in coronary bare-metal stent patients, despite not meeting primary endpoints.⁶⁶⁹ AZD4831 (NCT03756285), a myeloperoxidase (MPO) inhibitor, reduces

inflammation and improves microvascular function, showing good tolerability in heart failure patients.⁶⁷⁰ ApTOLL (NCT04742062), a TLR4 antagonist, reduces inflammation following acute ischemic stroke and acute myocardial infarction by blocking TLR4 signaling, with good safety and pharmacokinetic profiles.⁶⁷¹

Novel immunomodulatory targets

There also strategies focused on precisely modulating immune responses involved in tissue repair, immune cell migration, and receptor signaling. Notably, BRB-002 (ACTRN12624000405516) enhances macrophage phagocytosis and modulates atherosclerotic immune responses by blocking CD47-SIRP α interaction.⁶⁷² RTP-026 (NCT06465303), an Annexin-A1 analog, reduces myocardial injury by regulating immune cell migration and reactivity in acute and chronic cardiovascular disease models.^{673–675} Atibucimab (NCT06275893) targets CD14, regulating inflammation, apoptosis, and tissue injury responses, with ongoing evaluations of its safety and efficacy.⁶⁷⁶ POL6326 (NCT01905475), a CXCR4 antagonist, mediates angiogenesis and tissue repair through splenic Foxp3 regulatory T cells, improving cardiac function post-myocardial infarction.⁶⁷⁷ S1P receptors regulate cardiac fibroblast remodeling, proliferation, and differentiation, mediating peripheral vascular tone and endothelial responses.⁶⁷⁸ An ongoing clinical trial (NCT05327855) is held to evaluate the efficacy of OPL-0301, a S1PR1 agonist, for myocardial injury in acute myocardial infarction patients.

Cell therapy

It is widely acknowledged that Mesenchymal stem cells (MSCs) are highly immunomodulatory. MSCs have demonstrated promising potential in myocardial protection, mainly through their abilities to reduce inflammation, promote cardiomyocyte differentiation, enhance angiogenesis, increase anti-apoptotic capacity, and inhibit fibrosis.⁶⁷⁹

The first clinical trial involving adult MSCs in acute myocardial infarction patients, conducted by Joshua Hare et al. (2005), confirmed their safety.⁶⁸⁰ Since then, MSCs derived from various sources, such as bone marrow, umbilical cord, and adipose tissue, have been shown to be safe and well-tolerated in clinical trials for acute myocardial infarction and heart failure patients.^{681–683} In addition to MSC-based therapies, other immunomodulatory cell therapies, such as α -galactosylceramide-pulsed dendritic cells (α GDC), have shown potential for chronic heart failure, with research still ongoing (JRCT2073210116).⁶⁸⁴

Several recent studies have focused on MSCs specifically for cardiovascular applications. In a Phase 1/2 trial (NCT00883727), Chullikana et al. demonstrated that intravenous administration of Stempeuce (BM-MSCs) was safe and well-tolerated in STEMI patients, with no significant adverse effects reported 2 days post-PCI.⁶⁸⁵ Similarly, Butler et al. conducted a Phase 2a trial (NCT02467387) using autologous bone marrow MSCs (aBMBC) in non-ischemic heart failure patients, showing that the treatment was not only safe but also had potential immunomodulatory benefits, with improved health status and functional capacity.⁶⁸⁶ Furthermore, a Phase 3 trial (NCT01652209) using BM-MSCs in AMI patients assessed changes in left ventricular ejection fraction (LVEF), although detailed efficacy results were not disclosed. The TRIDENT study (2017) (NCT02013674) extended these findings by demonstrating that a high dose of hMSCs improved ejection fraction and reduced scar size in patients with ischemic cardiomyopathy.⁶⁸⁷ Similarly, the TAC-HFT-II trial (2020) (NCT02503280) investigated a combination of hMSC/hCSC in patients with chronic ischemic LV dysfunction and heart failure post-MI, focusing on treatment-emergent serious adverse events.

Research on MSCs from other sources, such as umbilical cord MSCs (UC-MSCs), has also progressed. The RIMECARD study (2016) (NCT01739777) found that intravenous UC-MSCs were safe in stable heart failure patients with reduced LVEF.⁶⁸⁸ Additionally, the HUC-HEART Trial (2020) (NCT02323477) demonstrated that

intramyocardial HUC-MSCs effectively promoted ventricular remodeling in patients with chronic ischemic cardiomyopathy.⁶⁸⁹ Further studies included a Phase 1 trial (NCT0390206) investigating UC-MSCs in MI patients, with MACE as the primary outcome, and a separate trial (NCT03533153) examining clinical-grade WJ-MSCs in STEMI patients, with a focus on reducing myocardial infarct size.

In brief, these studies highlight the safety and therapeutic potential of MSC-based therapies for improving cardiac function and remodeling across various cardiovascular conditions. However, to confirm these benefits and optimize the most effective MSC sources and delivery methods, further large-scale studies are essential.

Future strategies for immunomodulation in CVDs

In contemporary clinical research addressing CVDs, these conditions are increasingly recognized as being intricately linked to immune responses. Early clinical investigations utilized traditional broad-spectrum immunosuppressive agents, such as methotrexate, cyclosporine, sirolimus, rapamycin, and everolimus, to evaluate their efficacy in the treatment of cardiovascular diseases.⁶⁸¹ However, these studies did not yield significant reductions in the incidence of MACE, nor did they effectively decrease inflammatory markers or ameliorate myocardial damage following acute myocardial infarction.

The emergence of cell therapies, particularly MSCs treatments, has offered new avenues for managing cardiovascular disease. MSCs have demonstrated potential in modulating immune mechanisms, downregulating immune cell activity, and mitigating inflammatory responses. Despite the promising safety and tolerability observed in clinical trials involving MSCs derived from bone marrow, umbilical cord, and adipose tissue in patients with acute myocardial infarction and heart failure,^{681–683} the long-term benefits of these therapies for cardiovascular patients remain to be fully elucidated.

While the disappointing outcomes associated with broad-spectrum immunosuppressive drugs have prompted a shift in focus, targeted anti-inflammatory medications are gaining prominence. Notably, drugs aimed at IL-1, IL-6, and NLRP3 are under active investigation.^{658–663} Colchicine, a microtubule inhibitor and non-selective NLRP3 inhibitor, has demonstrated significant efficacy in reducing the incidence of MACE in patients with coronary artery disease and myocardial infarction, as evidenced by the results of two large-scale clinical trials, Lodoco2 and COLCOT.^{47,690} Following these findings, the FDA approved colchicine as an anti-inflammatory treatment for cardiovascular disease, marking a significant advancement in targeted anti-inflammatory strategies.

Moreover, clinical research targeting various immune modulation pathways is continuously evolving, with ongoing studies exploring novel targets such as CXCR4, MCP-1/CCL2,⁶⁶⁹ CD14, and CD47. Currently, targeted anti-inflammatory therapy represents a crucial strategy in the immunotherapeutic approach to cardiovascular diseases; however, the number of confirmed effective targets in clinical research remains relatively limited. In the pursuit of targeted anti-inflammatory therapies, it is essential to avoid pro-inflammatory responses that may lead to detrimental effects on the body, underscoring the need to maintain a delicate balance between anti-inflammatory and immunosuppressive mechanisms. Furthermore, the development of effective targeted drug delivery systems aimed at the heart will be a vital direction for future research, enabling more precise anti-inflammatory interventions in the treatment of cardiovascular diseases.

CONCLUSION AND PERSPECTIVE

This article provides a comprehensive overview of the research history and key milestones in the immunology and immunotherapy of CVDs. It offers a broad perspective on the activation and

regulation of the immune response and details the multi-level regulatory signaling pathways and their crosstalk in CVDs. We also described the mechanisms of immune regulation in physiological and pathological processes of CVDs, as well as the advancements in targeted immune response therapy both in preclinical strategies and clinical trials.

Although the immune system plays a crucial role in CVDs, the complexity and variability of inflammatory processes across patients make it difficult to develop universally effective immune-targeted strategies. Several areas with significant gaps in mechanistic research need to be further explored: 1) There is a huge shortfall in characterizing cell-specific mechanistic pathways in CVDs. Meanwhile, understanding the complex network of interactions among various cell types is crucial for regulating CVDs. Utilize state-of-the-art techniques such as advanced *in vivo* imaging, genome-wide association studies, transgenic lineage tracing mice, making it possible to gain a deeper understanding of the immune landscape in CVDs; 2) The human body is an intricately regulated system of multiple interconnected systems. Therefore, it's of great importance to explore the circuit among cardiovascular system-immune system-other system; 3) Given the dynamic changes in immune cell populations during CVDs, providing comprehensive information on these shifts, including multi-level regulation and the roles of anti-inflammatory and pro-inflammatory responses, is crucial for developing personalized treatments tailored to different disease stages; 4) Incomplete understanding of sex-specific CVDs mechanisms, especially conditions unique to women, underscores the need for targeted research. Moreover, large-scale studies should be designed separately for men and women to address these distinct pathophysiologies and develop gender-focused research systems; 5) Since morphological and molecular changes in diseases often occur asynchronously, disease phenotyping should incorporate both morphological and molecular classifications. Integrating these classifications is crucial for a comprehensive understanding of CVDs and for advancing clinical applications. Overall, these gaps will be resolved by the continuous development of single-cell technologies and computational analysis, coupled with powerful artificial intelligence-based histology, allowing for mapping disease-specific immune profiles.

From the perspective of cardiovascular immuno-modulatory therapies, the promising research directions are listed as follows: 1) Personalized inflammatory therapies are urgently needed for CVD treatment. Future research should focus on cell-specific mechanisms, intercellular interactions, dynamic immune changes across disease stages, and gender-specific immune regulations to translate immunological advances into clinical precision medicine; 2) Combination therapies targeting multiple immune pathways or combining immunotherapy with conventional treatments show promise in CVDs management. Moreover, considering holistic medicine, immune therapies targeted at other systems may benefit CVDs, making it possible to apply conventional medicine into new use. 3) While current research often emphasizes anti-inflammatory strategies, activating immune repair programs, such as stimulating Treg cells, could complement these therapies and help address their limitations in regulating CVDs; 4) Development of novel biomarker panels is essential to enhance cardiovascular risk prediction and guide treatment decisions. Machine learning and Mendelian randomization can enhance risk stratification and treatment selection using large-scale inflammatory biomarker data.

Overall, the ongoing development of basic and translational researches on immunotherapy in cardiovascular medicine may pave the way for more targeted and efficacious treatments, potentially reducing the burden of CVDs on global health. However, it is imperative to approach this promising field with caution, ensuring that rigorous scientific standards are maintained and patient safety remains paramount. As our understanding of the complex interplay between the immune system and

cardiovascular health deepens, we may witness a paradigm shift in how CVDs are treated and managed in the future.

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AUTHOR CONTRIBUTIONS

Yunzeng Zou, Xiaoyan Wang and Tao Liu contributed to conception and manuscript design. Xiaoyan Wang, Liming Chen, Jianming Wei, Hao Zheng, Ning Zhou drafted the manuscript. Xiaoyan Wang, Liming Chen, Jianming Wei, Hao Zheng, Ning Zhou prepared the tables and figures. Xiaoyan Wang, Liming Chen, Jianming Wei, Hao Zheng, Ning Zhou collected the related references. All authors participated in the revision of the manuscript. Yunzeng Zou, Xiaoyan Wang were involved in funding acquisition. All authors have read and approved the article.

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