Nakayama and Fujiu
Inflammation and Regeneration (2025) 45:17
https://doi.org/10.1186/s41232-025-00382-5

Inflammation and Regeneration

REVIEW

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Innate immune memory in macrophage differentiation and cardiovascular diseases

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Abstract

Innate immune memory (trained immunity) refers to the ability of innate immune cells, such as monocytes and macrophages, to retain a long-term imprint of a prior stimulus through epigenetic and metabolic adaptations, enabling amplified responses upon restimulation. Recent studies have classified innate immune memory into central and peripheral types. Central innate immune memory originates in hematopoietic stem cells (HSCs) within the bone marrow, where epigenetic reprogramming generates a sustained inflammatory bias, contributing to chronic diseases such as atherosclerosis, heart failure, and stroke. Peripheral innate immune memory occurs in monocytes or macrophages that acquire heightened responsiveness after repeated exposure to stimuli in peripheral tissues. This review explores the mechanisms underlying both central and peripheral innate immune memory, their roles in chronic inflammatory diseases, focusing on cardiovascular diseases, and potential strategies to target innate immune memory for therapeutic purposes. Advancing the understanding of these processes could facilitate the development of novel approaches to control inflammatory diseases and immune-related disorders.

Keywords Central innate immune memory, Peripheral innate immune memory, Macrophage, Heart failure

Concept and historical background of innate immune memory

For a long time, innate immunity was deemed to provide only "rapid, nonspecific, and short-lived" protection, whereas immunological memory was thought to be the exclusive province of T and B cells [1]. However, studies demonstrating nonspecific protective effects of BCG vaccination and β-glucans in monocytes and macrophages revealed that these innate immune cells can, in fact, record and recall a single stimulus over the long-term, mounting enhanced responses upon restimulation [2, 3]. This phenomenon led to the concept of "trained immunity," in which innate immunity acquires a form of "memory" through epigenetic and metabolic reprogramming [4, 5].

Recently, the field has further subdivided this phenomenon into "central innate immune memory" and "peripheral innate immune memory" [6–8] (Fig. 1). Central innate immune memory involves epigenetic reprogramming of hematopoietic stem cells (HSCs) in the bone marrow following exposure to stimuli such as BCG vaccines or β-glucans, endowing these HSCs with the capacity to persistently generate inflammatory monocytes and macrophages over the long term [6, 7]. In contrast, peripheral innate immune memory refers to the long-term memory-like adaptations arising in monocytes or macrophages once they have migrated to the periphery, where repeated recognition of factors such as oxidized LDL or microbial components drives them toward an augmented cytokine response upon subsequent challenges [3, 9].

For instance, in atherosclerotic lesions, macrophages repeatedly exposed to oxidized LDL can become "trained" in the periphery, sustaining chronically

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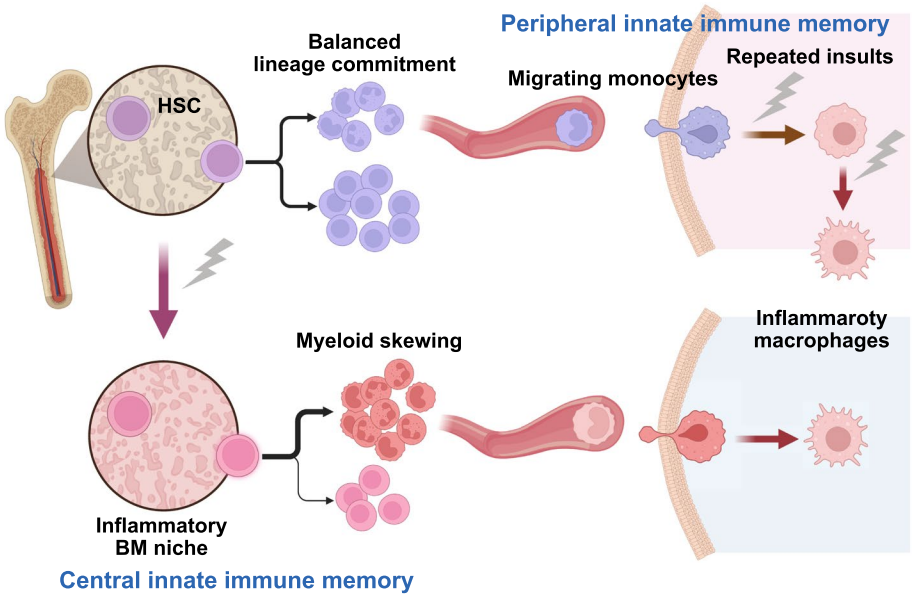

Fig. 1 Central or peripheral innate immune memory. In a peripheral organ, myeloid cells are repeatedly exposed to stimulation such as pathogen-associated molecular patterns. Once macrophages encounter microbial components, they augment cytokine expressions against subsequent challenges by "peripheral innate immune memory." HSCs are also trained in the inflammatory bone marrow niche. Macrophages derived from trained HSCs exhibit heightened responsiveness against challenges, which is referred to as "central innate immune memory"

heightened proinflammatory cytokine release [9, 10]. Meanwhile, HSCs in the bone marrow can undergo just one round of stimulation and remain primed to produce inflammatory clones for an extended period—an example of "central" trained immunity [6–8]. BCG or β-glucans reprogram HSCs in the bone marrow, and the traits of murine modulated HSCs are passed on after secondary transplantation for at least 1 year [11]. Human studies also confirm that the effect of BCG vaccination in HSCs persists for months or years [12, 13]. Furthermore, in mouse models of heart failure and stroke, epigenetic modifications at the HSC level have been reported to propagate a chronic proinflammatory macrophage phenotype, thereby hastening the decline in cardiac function [14, 15]. These findings collectively underscore how the innate immune memory concept extends beyond peripheral monocytes/macrophages to encompass a "central" niche in the bone marrow [8, 16]. Deciphering this two-tiered immune memory structure—central vs. peripheral—holds promise for devising innovative therapeutic strategies against chronic inflammatory diseases such as cardiovascular disorders and autoimmune conditions [10, 16]. Future interventions may aim to downregulate bone marrow–driven inflammatory bias while preserving peripheral infection-fighting capabilities.

Mechanisms: epigenetic regulation and cellular metabolism in central and peripheral innate immune memory

A central feature of trained immunity is the transcriptional reorganization of monocytes or macrophages after an initial stimulus, causing selective amplification of inflammatory gene expression upon restimulation [17]. This section details how epigenetic modifications and metabolic reprogramming intertwine to enable robust and long-lasting inflammatory responses. Innate immune memory can be broadly classified into two types: central innate immune memory and peripheral innate immune memory. Both mechanisms are driven by epigenetic reprogramming (e.g., histone modifications and DNA methylation) and alterations in cellular metabolism. This section focuses primarily on histone modifications, highlighting how epigenetic control shapes innate immune memory and influences disease progression.

Epigenetic regulation via histone modifications

Central innate immune memory

Central innate immune memory refers to the phenomenon whereby hematopoietic stem cells (HSCs) in the bone marrow acquire a long-term ability to produce inflammatory monocytes and macrophages following exposure to inflammatory stimuli. Histone modifications within HSCs play a critical role in this process.

For instance, the promoters of inflammatory genes (e.g., *CCR2*, *IL-1β*, and *TNF-α*) accumulate H3K4me3 (trimethylation), thereby enhancing transcriptional activity and promoting an inflammatory bias. This mechanism underlies the prolonged production of inflammatory cells associated with chronic inflammatory conditions such as heart failure and atherosclerosis [18]. Furthermore, H3K27ac (acetylation) at enhancer regions further augments the expression of proinflammatory cytokines (e.g., *IL-6* and *IL-1β*). Following BCG vaccination, these histone modifications are strengthened in HSCs, enabling broad immune responses against various pathogens [6].

In heart failure models, downregulation of TGF-β signaling induces chromatin closure centered around Smad3-binding sites, thereby suppressing the anti-inflammatory function of HSCs and expanding inflammatory clones. This phenomenon exacerbates heart failure by promoting the infiltration of inflammatory macrophages into cardiac tissue and worsening tissue remodeling for several months [14].

Similarly, in stroke-induced central innate immune memory, epigenetic reprogramming of HSCs leads to the expansion of inflammatory clones. A study by Simats et al. demonstrated that post-stroke IL-1 stimulation triggers histone modifications in HSCs in a murine stroke model, driving the sustained production of inflammatory monocytes and macrophages [15]. Specifically, genes encoding inflammatory mediators (e.g., *IL-1β*, *TNF-α*) exhibit an accumulation of H3K4me3 at their promoter regions, enhancing their transcription and promoting the generation of inflammatory cells, including $CCR2^+$ monocyte/macrophages. These cells migrate to the heart and contribute to reduced cardiac function. Increased H3K27ac (acetylation) at enhancer regions further amplifies the expression of proinflammatory cytokines, whereas H3K27me3 (trimethylation) at anti-inflammatory gene promoters (e.g., *IL-10*) is reduced, dampening anti-inflammatory responses.

Peripheral innate immune memory

Peripheral innate immune memory is established when monocytes and macrophages repeatedly encounter stimuli in peripheral tissues. Histone modifications also play a pivotal role in this process. For instance, exposure to oxidized LDL or β-glucan induces sustained inflammatory gene expression (e.g., *IL-1β*, *TNF-α*) via increased H3K4me3 in macrophages. This effect is particularly important in the development and progression of atherosclerotic lesions [9]. In addition, macrophages exposed to β-glucan exhibit elevated H3K27ac at enhancer regions, leading to the broad upregulation of inflammatory cytokines [3].

Taken together, these findings underscore the critical roles of histone modifications in both central and peripheral innate immune memory, illuminating how epigenetic regulation and cellular metabolism cooperatively shape innate immune responses and drive disease pathogenesis.

Histone modifications and transcriptional regulation in innate immunity

Innate immune memory (trained immunity) is characterized by long-term functional reprogramming of monocytes and macrophages, allowing these cells to mount enhanced responses upon subsequent stimulation. This phenomenon is primarily driven by epigenetic modifications, particularly histone modifications, which regulate the accessibility of chromatin and influence the transcription of inflammatory and anti-inflammatory genes. This section explores how activating and repressive histone modifications dynamically interact to shape the transcriptional landscape of innate immune memory.

Activating histone modifications

Modifications such as H3K4me3 (trimethylation of lysine 4 on histone H3) and H3K27ac (acetylation of lysine 27 on histone H3) play pivotal roles in enhancing the transcription of inflammatory genes by promoting an open, transcriptionally active chromatin state [17]. H3K4me3 facilitates the recruitment of transcriptional machinery at gene promoters, whereas H3K27ac amplifies enhancer activity, coordinating a robust inflammatory response.

Repressive histone modifications

In contrast, repressive histone modifications, including H3K27me3 (trimethylation of lysine 27 on histone H3) and H3K9me3 (trimethylation of lysine 9 on histone H3), are essential for maintaining the balance of inflammatory responses. These modifications contribute to the compaction of chromatin and suppression of transcription at specific loci, preventing excessive activation of inflammatory genes.

For instance, H3K27me3 is enriched at promoters of anti-inflammatory genes such as IL-10 and Arg1 in resting macrophages, preserving their expression under homeostatic conditions. However, chronic inflammatory stimuli can lead to a reduction in H3K27me3 at these loci, impairing the negative feedback required to control inflammation. Simultaneously, the loss of H3K27me3 can exacerbate the activation of inflammatory genes, further propagating a chronic inflammatory state [19].

Dynamic interaction between activating and repressive modifications

The phenotype of innate immune memory arises from the dynamic interplay between activating and repressive

histone modifications. During inflammatory priming, activating marks such as H3K4me3 and H3K27ac dominate at inflammatory gene loci, promoting their sustained transcriptional activation. At the same time, repressive modifications, such as H3K27me3, serve as a counterbalance, limiting excessive inflammation and preventing tissue damage.

However, under conditions of chronic inflammation, the equilibrium between these modifications is disrupted. Activating histone modifications become predominant, whereas repressive marks are diminished. This imbalance leads to the persistent activation of inflammatory pathways, contributing to the pathogenesis of chronic inflammatory diseases, including atherosclerosis, heart failure, and stroke [15, 20].

DNA methylation and non-coding RNA in innate immune memory

Role of DNA methylation in innate immune memory

BCG vaccination has been shown to induce epigenetic reprogramming of bone marrow-derived hematopoietic stem cells (HSCs), leading to the formation of innate immune memory. This process involves significant changes in DNA methylation patterns that promote the selective expansion of inflammatory clones and sustained cytokine production. Importantly, these epigenetic changes are not confined to HSCs but are transmitted to their progeny, including monocytes and macrophages. Further analysis revealed that DNA methylation changes were targeted to specific clusters of immune regulatory genes, underscoring the precision of this epigenetic mechanism in modulating trained immunity [6].

In monocytes, β-glucan training reverses LPS-induced immune tolerance through dynamic changes in DNA methylation. This process reactivates inflammatory genes such as IL-6 and TNF-α while preserving the methylation patterns of anti-inflammatory genes, thereby balancing immune responses. This reprogramming is closely associated with histone modifications, including increased H3K4me3 and H3K27ac, which work in concert with DNA methylation to fine-tune transcriptional activity. These epigenetic changes ensure that monocytes exhibit a heightened yet controlled inflammatory response upon secondary stimulation [21].

Long non-coding RNAs and microRNAs in innate immune memory

Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are critical regulators of gene expression and play essential roles in shaping the transcriptional and functional landscape of innate immune memory. These non-coding RNAs modulate epigenetic processes and intracellular signaling pathways, influencing both the activation and resolution of inflammatory responses in monocytes and macrophages.

Long non-coding RNAs (lncRNAs) Recent evidence indicates that certain lncRNAs not only direct the recruitment of histone-modifying complexes to specific genomic loci but also modulate cellular metabolism to facilitate the resolution phase of inflammation. For instance, lncFAO in murine macrophages has been shown to promote inflammation resolution by reshaping metabolic pathways, thereby inducing epigenetic modifications that ultimately rewire transcriptional programs [22].

Additional examples underscore the broad scope of lncRNA-mediated immunomodulation. THRIL (TNF and hnRNPL-related immunoregulatory lincRNA) in human macrophages interacts with the RNA-binding protein hnRNPL to modulate the expression of pro-inflammatory mediators, including TNF-α, reinforcing the notion that lncRNAs act as key drivers in sustaining heightened inflammatory responses upon secondary stimulation [23]. Likewise, murine lincRNA-Cox2 participates in both transcriptional activation and repression of immune-related genes via its interactions with chromatin regulators, attesting to the bidirectional nature of lncRNA function in immune signaling [24].

In addition, mounting evidence suggests that lncRNAs can serve as molecular scaffolds, forming dynamic platforms that coordinate the recruitment of essential transcriptional co-regulators, such as histone acetyltransferases (HATs). By tethering these factors to enhancer or promoter regions, lncRNAs reinforce the magnitude and specificity of transcriptional responses upon restimulation [25].

MicroRNAs (miRNAs) MicroRNAs (miRNAs) are key regulators of immune responses, playing crucial roles in both the amplification and resolution of inflammation. Among them, miR-155 has been identified as a central player in enhancing inflammatory responses. As demonstrated by O'Connell et al., miR-155 amplifies the expression of pro-inflammatory cytokines such as TNF-α and IL-6, contributing to sustained activation of inflammatory genes in both murine and human macrophages [26]. β-glucan stimulation leads to an upregulation of miR-155 in macrophages, priming them for stronger immune responses upon subsequent stimulation, a hallmark of trained immunity [26].

Conversely, some miRNAs act as negative regulators to restrain excessive inflammation and maintain immune homeostasis. miR-146a, highlighted by Taganov et al.,

suppresses inflammatory gene expression through the NF-κB signaling pathway, functioning as a negative feedback mechanism in human macrophages [27]. During repeated immune stimulation, miR-146a helps to control inflammation, ensuring that the immune response remains balanced and prevents pathological overactivation [27]. This regulatory role suggests its involvement in modulating the balance required for effective trained immunity.

Novakovic et al. (Cell, 2016) demonstrated that specific changes in miRNA profiles accompany the epigenetic remodeling of inflammatory gene loci after β-glucan stimulation [21]. These changes enhance monocyte responsiveness to secondary stimulation, positioning miRNAs as critical components in the establishment and maintenance of trained immunity [21].

Additionally, miRNAs contribute to the resolution phase of inflammation, preventing prolonged immune activation and minimizing tissue damage. miR-21, as studied by Sheedy et al., plays a pivotal role in suppressing inflammatory cytokine expression in human monocytes during this phase, ensuring controlled resolution of immune responses [28].

In summary, miRNAs such as miR-155, miR-146a, and miR-21 demonstrate how these small non-coding RNAs intricately regulate trained immunity by balancing inflammatory gene expression, epigenetic changes, and immune homeostasis.

Interplay between lncRNAs and miRNAs in trained immunit Recent studies suggest that lncRNAs and miRNAs interact to fine-tune transcriptional programs underlying innate immune memory, including mechanisms related to trained immunity. Certain lncRNAs act as "sponges" for miRNAs, sequestering them and preventing their interaction with target mRNAs. For example, the lncRNA Malat1 has been shown to modulate macrophage polarization [29–33] by sponging miR-155, thereby influencing inflammatory gene expression and the balance between pro-inflammatory and anti-inflammatory pathways [26, 34]. Given the critical role of miR-155 in enhancing inflammatory responses and contributing to trained immunity, this interplay between lncRNA Malat1 and miR-155 may also influence the establishment and modulation of trained immunity.

Although the direct involvement of lncRNA-miRNA interactions in trained immunity requires further experimental evidence, these findings underscore the potential of such interactions to regulate innate immune memory. Future studies focusing on the role of these interactions in trained immunity could reveal novel mechanisms and therapeutic targets for immune modulation.

Cellular metabolic reprogramming and the inflammatory response

Acceleration of glycolysis and TCA intermediates

Another essential pillar of innate immune memory involves metabolic reprogramming. Upon an initial stimulus, macrophages or NK cells shift toward increased glycolysis [3, 35]. In parallel, intermediate metabolites accumulate and act as signaling molecules that modulate epigenetic enzymes and elevate the production of pro-inflammatory cytokines [36, 37]. For example, succinate stabilizes HIF-1α by inhibiting its degradation, thus promoting the transcription of inflammatory genes (IL-1β, TNF-α, etc.) [37, 38].

Itaconate and the control of inflammation

Itaconate has garnered particular interest as a novel metabolic regulator in immune responses. Itaconate impacts ROS and NO levels while also inhibiting certain microbial metabolic pathways [39, 40]. Furthermore, itaconate can activate the Nrf2 pathway, thus inducing an anti-inflammatory signal [38, 41]. Such feedback loops involving metabolic intermediates are thought to help trained cells avoid descending into pathological hyperinflammation.

The mTOR/HIF-1α Axis and Metabolic Switching

Upregulation of glycolysis in macrophages and NK cells is closely tied to mTOR/HIF-1α signaling [35]. mTOR, a nutrient-sensing kinase, regulates immune cell growth and metabolism [42, 43]. Activation of this axis promotes a shift from oxidative phosphorylation to glycolysis as the primary energy source, thereby providing TCA intermediates to epigenetic enzymes [3, 44]. Consequently, inflammatory genes are further upregulated, cementing the processes that define trained immunity [16, 17].

The interplay between metabolism and epigenetics

Cofactor requirements of epigenetic enzymes

Many epigenetic enzymes, including histone methyltransferases and demethylases, rely on cofactors such as S-adenosylmethionine (SAM) or α-ketoglutarate[45]. For instance, succinate and fumarate can inhibit certain histone demethylases, shifting the balance of histone marks [39, 46]. Thus, metabolic flux fundamentally supports the "memory imprint" established in trained innate cells [44].

Local metabolic remodeling at the immune synapse

Recent findings indicate that, upon encountering pathogens, macrophages or neutrophils locally rearrange key glycolytic enzymes near the immune synapse, altering the

epigenetic landscape that governs cytokine production [41]. Disruption of metabolic pathways can impair the supply of key metabolites to epigenetic enzymes, attenuating trained immune responses [38, 42]. Thus, the three-way interconnection among immunological synapse, cellular metabolism, and epigenetic regulation helps fine-tune the amplitude and duration of innate immune memory.

Bone marrow–level formation of innate immune memory and its implications

Innate immune memory is not solely confined to peripheral effector cells such as monocytes, macrophages, or neutrophils; increasing evidence suggests that it can also develop at the level of hematopoietic stem cells (HSCs) in the bone marrow [18, 47]. Chronic inflammatory settings or repeated pathogen-derived signals can reshape the entire bone marrow niche, leading to epigenetic reprogramming of HSCs, which preferentially produce inflammatory macrophages and neutrophils—an "inflammatory bias" that persists over time [10, 48].

The bone marrow niche and chronic inflammatory signals

Basic structure of the bone marrow niche

The bone marrow niche comprises osteoblasts, endothelial cells, mesenchymal stem cells (MSCs), and neural projections, which collectively regulate the proliferation and differentiation of hematopoietic stem cells (HSCs) and progenitor cells [49] (Fig. 2A). Under physiological conditions, signals such as CXCL12 and TGF-β help to maintain HSC quiescence and orderly differentiation, thereby preserving homeostasis[50]. However, in chronic inflammatory environments, proinflammatory cytokines—IL-1, TNF-α, IL-6—and damage-associated molecular patterns (DAMPs) can accumulate within the marrow, significantly altering the structural and cellular networks of this niche [18].

Impact of chronic inflammation on the bone marrow niche

When inflammatory signals act on osteoblasts and MSCs, they downregulate the production of key HSC regulators—such as CXCL12 and stem cell factor (SCF)—while preferentially secreting cytokines like GM-CSF and G-CSF, which promote the expansion of inflammatory macrophages and neutrophils [51] (Fig. 2B). As a result, the entire marrow niche shifts toward an "inflammatory phenotype," providing a powerful impetus for HSCs to favor the proinflammatory lineage [10].

Moreover, in chronic conditions such as heart failure or obesity, elevated levels of TNF-α and IL-6 are frequently observed [52, 53]. These cytokines can induce vascular disturbances within the marrow and disrupt local niche homeostasis, leading to excessive HSC activation [54, 55]. In such chronic inflammatory states, the stabilizing signals from endothelial cells or supporting cells—exemplified by CXCL12 or certain Notch ligands—are insufficiently sustained. Consequently, HSCs skew toward inflammatory differentiation, increasing the production of macrophages, neutrophils, and other myeloid cells prone to infiltrating tissues and exacerbating inflammatory pathology [8, 56].

Regulation by the nervous system

Recent evidence indicates that sympathetic innervation of the bone marrow niche also influences inflammatory responses. For instance, stress hormones and neurotransmitters within the marrow niche can alter HSC growth signals, tipping the balance in favor of inflammatory

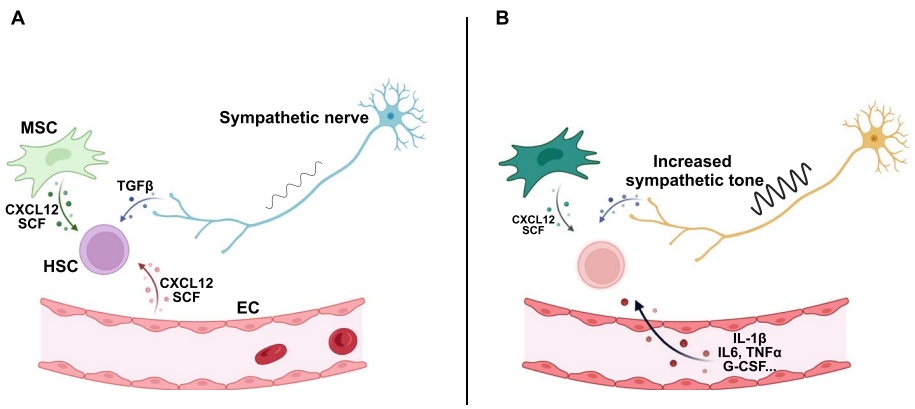

Fig. 2 Alterations of components in the BM niche. Bone marrow niche is composed of various types of cells including endothelial cells (EC), mesenchymal stem cells (MSCs), and neural projections. In unperturbed conditions (**A**), niche cells secrete retention factors like CXCL12, SCF, and TGF-β. However, in pathological conditions (**B**), proinflammatory cytokines like IL-1, TNF-α, and IL-6 or damage-associated molecular patterns (DAMPs) reach the bone marrow niche via the blood stream and secretion of the retention factors is repressed. Activity of sympathetic neurons also perturbs homeostatic status in the BM niche

clones [47]. These findings highlight a neuro-immune–endocrine axis that plays a pivotal role in shaping innate immune memory at the HSC level. When combined with prolonged inflammatory cues, sympathetic signals may further intensify or sustain the marrow's proinflammatory bias, with significant implications for chronic disease progression.

HSC clonal diversity and epigenetic reprogramming

Clonal heterogeneity of HSCs

HSCs are not a homogeneous population; individual clones differ in their proliferative capacity and lineage preferences [57]. Although one clone might favor lymphoid differentiation, another clone may predominantly give rise to neutrophils or macrophages [48]. Under chronic inflammatory conditions, clones susceptible to inflammatory priming may preferentially expand, thereby promoting the production of proinflammatory macrophages or $CCR2^{+}$ macrophages or $Ly6C^{high}$ monocytes [10]. As a result, even in the absence of overt infection or external triggers, systemic inflammatory activity can remain persistently elevated—an effect sometimes referred to as a "self-perpetuating" or "auto-propagating" loop.

Epigenetic modifications underlying HSC teprogramming

Epigenetic modifications are key to establishing innate immune memory at the HSC level. Chronic presence of IL-1 or TNF-α in the bone marrow niche, for instance, can induce changes in histone marks (H3K4me3) or DNA methylation patterns that increase the accessibility of inflammatory gene loci [18, 54]. Notably, studies have shown that BCG vaccination can trigger epigenetic remodeling in HSCs, conferring broad-spectrum protection against pathogens beyond Mycobacterium tuberculosis [6, 7]. Such findings lend robust support to the concept of bone marrow–derived innate immune memory and its capacity for long-term functional reprogramming.

Metabolic rewiring and the strengthening of HSC inflammatory bias

Changes in cellular metabolism likewise contribute to reinforcing an inflammatory bias in HSCs. Under chronic inflammatory conditions, HSC mitochondria often undergo structural and functional adaptations that favor a glycolysis-dominated metabolism, increasing the generation of TCA cycle intermediates and reactive oxygen species (ROS) [42, 47]. These metabolites modulate the activity of epigenetic enzymes, further amplifying the expression of inflammatory genes [10]. The outcome is a feed-forward loop wherein HSCs persistently generate proinflammatory cell types, fueling systemic inflammation.

Differences between mouse models and human studies

Human and mouse immunology are distinct. Although mouse models are valuable for studying the immune system, there are significant differences in their structure, function, and responses. Human HSCs in the bone marrow are identified as $CD34^{+}CD38^{-}$ cells, whereas murine long-term HSCs are found almost exclusively in the CD34low fraction. Microenvironments suitable for the growth of human HSCs, hematopoietic niche in the bone marrow, could be different from murine ones [58].

In terms of monocytes, human circulating monocytes are classified by the expression levels of CD14 and CD16, whereas murine monocytes are functionally divided between $Ly6C^{high}$ and $Ly6C^{low}$[55]. In contrast, functional analogous populations of $CCR2^{-}$ and $CCR2^{+}$ macrophages are identified in both human and murine myocardium [59]. Although most of the research about the bone marrow niche has been conducted in mouse models, the innate immune memory of HSCs primed by BCG and β-glucans shares the epigenetic features between human and mouse [12, 13]. Behavioral changes of HSCs after heart failure were also observed in human cases [60], and perturbations of murine HSCs in cardiovascular diseases could be applied to clinical research.

Systemic inflammation driven by bone marrow-derived cells and a negative feed-forward loop

Widespread effects of inflammatory bias

Once an inflammatory bias is established in the bone marrow, monocytes, and neutrophils released into the bloodstream can undergo significant functional changes. For example, $Ly6C^{high}$ monocytes can infiltrate lesions in atherosclerosis, failing myocardium, or tumor microenvironments in accordance with CCR2 levels, resulting in excessive inflammation and tissue damage [55, 61]. The proinflammatory mediators secreted by these cells may also affect distant organs such as the kidneys or liver, reinforcing organ-to-organ crosstalk that amplifies chronic inflammation [10, 62, 63].

Bone marrow–origin inflammation in chronic heart failure and kidney disease

In disease states like heart failure or chronic kidney failure, the bone marrow niche is subject to continuous sympathetic input and factors from the renin–angiotensin system, further accelerating the selection of proinflammatory HSC clones [64]. The proliferative monocytes and macrophages spawned by these clones home to the heart or kidneys, driving pathological tissue remodeling

and perpetuating what has been termed a negative feed-forward mechanism [10, 55]. Sustained over time, this mechanism may give rise to an intractable inflammatory state resistant to conventional pharmacological or surgical interventions.

Interplay among the nervous, hormonal, and immune systems

Not limited to heart or kidney disease, bone marrow-driven inflammatory bias is implicated in neurodegenerative and autoimmune disorders [47, 52]. Dysregulation of the autonomic nervous system or hormonal milieu can tip the scales toward more HSC-derived inflammatory cell production, whereas these cells in turn feed back on the central nervous or endocrine organs, aggravating disease progression [54, 55, 65]. Thus, far from being solely a rapid front-line defense, bone marrow-based innate immune memory can serve as a master regulator of systemic inflammation.

Innate immune memory in cardiovascular disease

Cardiovascular diseases rank among the top global causes of mortality and encompass a wide spectrum of conditions, including atherosclerosis, myocardial infarction, heart failure, and stroke. A persistent state of inflammation underlies many of these pathologies, and recent findings suggest that trained immunity (innate immune memory) may contribute to disease progression and severity [10, 66]. Once monocytes or macrophages have experienced an initial stimulus, they can undergo epigenetic and metabolic reprogramming that endows them with a heightened capacity to produce proinflammatory cytokines over the long term. This phenomenon has gained attention as a possible mechanism by which cardiovascular lesions become chronic or prone to recurrent flares [47, 55]. The following sections delve into the role of innate immune memory in atherosclerosis, myocardial infarction, heart failure, and stroke, examining the molecular underpinnings and potential clinical implications.

Atherosclerosis

Basic pathophysiology of atherosclerosis

Atherosclerosis is a pathological process in which cholesterol and lipids accumulate in the arterial wall, leading to foam cell formation in both smooth muscle cells and macrophages—thus generating an atheromatous plaque [67–69]. Oxidized low-density lipoprotein (oxLDL) is a key agent in this process: macrophages ingest oxLDL, become foam cells, and release proinflammatory cytokines and chemokines, in turn recruiting further leukocytes. Consequently, a self-sustaining inflammatory loop forms, reinforcing plaque growth and instability.

Epigenetic training of macrophages

Recent work has proposed that macrophages repeatedly exposed to oxLDL undergo epigenetic "training," thereby sustaining overproduction of proinflammatory cytokines such as IL-1β and TNF-α for weeks [9, 10]. This trained immunity contradicts the prior assumption that innate immunity is purely short-lived (for days) and nonspecific. It also highlights a potential novel driver of the chronic inflammation inherent in atherosclerosis. Notably, alterations in histone marks (e.g., H3K4me3) and DNA methylation are thought to amplify the transcription of genes promoting inflammation [5, 17].

Influence of the gut microbiota and microbial components

Further evidence indicates that microbial components from the gut microbiota, such as lipopolysaccharide (LPS), can enter circulation and reach atherosclerotic sites, enhancing the trained state of macrophages[35, 66]. Changes in the gut microbiota—commonly referred to as "dysbiosis"—may increase vascular permeability and augment the inflammatory activation of macrophages, thus exacerbating both plaque formation and the risk of plaque rupture [70, 71]. These insights have led to proposals for novel treatment concepts beyond lipid and blood pressure management, encompassing the "modulation of innate immune memory" and "normalization of the gut microbiota" to potentially revolutionize atherosclerosis therapy [10, 72].

Myocardial infarction

AMI and the significance of the inflammatory response

Acute myocardial infarction (AMI) occurs when coronary artery occlusion leads to ischemic necrosis of heart tissue, accompanied by a robust infiltration of neutrophils and macrophages into the infarct zone [73–75]. Although this inflammatory response is initially beneficial for clearing necrotic debris and facilitating tissue repair, prolonged or excessive inflammation can accelerate adverse ventricular remodeling and increase the risk of heart failure.

"Trained" inflammatory state and post-MI outcomes

In patients with underlying atherosclerosis or metabolic syndrome, bone marrow HSCs and peripheral macrophages may already be in a "trained" state, overproducing inflammatory cytokines [10, 55]. Such patients are more prone to an exaggerated post-AMI inflammatory response, heightening the risk of complications like no-reflow phenomena, ventricular aneurysm formation,

or progression to heart failure. Indeed, clinical studies indicate that the accumulation of specific inflammatory monocyte subsets (e.g., Ly6C^{high} monocytes) correlates with worse left ventricular remodeling after AMI [76, 77]. Consequently, the concept of trained immunity is gaining attention as a prognostic factor in myocardial infarction.

The bone marrow niche and autonomic regulation

Alterations in the bone marrow niche, including sympathetic signaling, have also been implicated in sustaining post-AMI hyperinflammation [76]. In animal models, sympathetic drive can activate HSCs toward a heightened proinflammatory phenotype, forming a pathological crosstalk between the heart and the marrow that perpetuates tissue damage [55]. This synergy between autonomic input and innate immune memory may be a key point of intervention to prevent progressive remodeling and chronic dysfunction following MI.

Heart failure

Chronic inflammation in HFrEF and HFpEF

Heart failure (HF) can arise from either systolic dysfunction (HFrEF) or diastolic dysfunction (HFpEF). In both cases, persistent inflammation is recognized as a substantial contributor to disease progression [73, 78]. Elevated levels of cytokines and chemokines in circulation are a hallmark of advanced HF, fostering detrimental remodeling of the left ventricle, systemic congestion, and metabolic imbalances that reinforce the heart failure state.

Expansion of inflammatory clones in the bone marrow

Recent investigations suggest that, within the bone marrow niche, certain "inflammatory clones" of HSCs expand under the influence of chronic sympathetic stimulation or proinflammatory cytokines, thus fueling HF progression. For instance, HSCs subjected to epigenetic reprogramming produce monocytes and macrophages primed toward an inflammatory phenotype—a process referred to as an "inflammatory bias." Over time, these cells can infiltrate the heart, aggravating pathological remodeling [66, 79].

Innate immune memory and heart failure

Although guideline-based therapies—such as RAS inhibitors, β-blockers, and diuretics—have become standard treatments for HF, they often offer only limited benefits in mitigating chronic inflammation [78]. As research unveils the central role of innate immune memory in sustaining the inflammatory underpinnings of heart failure, new therapeutic avenues have emerged. Trained immunity arises via epigenetic and metabolic transformations that program both bone marrow HSCs and peripheral macrophages to maintain a heightened inflammatory response [8, 16]. Potential future interventions include epigenetic enzyme inhibitors and metabolic reprogramming approaches aimed at alleviating the proinflammatory state, thereby enhancing HF management.

In the authors' own studies, cardiac macrophages have been shown to exert protective effects on the heart [80]. Moreover, these macrophages appear vital for preventing lethal arrhythmias by sustaining effective electrical conduction via gap junction protein connexin43 phosphorylation [81]. Specifically, amphiregulin (AREG) derived from murine cardiac macrophages has been identified as a major mediator in adaptive response to pressure overload [80] and improving cell–cell coupling under conditions of right ventricular pressure overload and β-adrenergic chronic or excessive β-adrenergic stimulation [81]. Paradoxically, bone marrow HSCs with accumulated innate immune memory can produce excessive inflammatory CCR2^{+} macrophages and disrupt cardiac macrophage homeostasis, which relatively reduces the number of CCR2^{-} macrophages and diminishes these protective effects, thereby exacerbating cardiac dysfunction [14] (Fig. 3).

Stroke and its cardiac consequences, including innate immune memory

Cerebrovascular occlusion and secondary inflammation

Stroke can be categorized as either ischemic or hemorrhagic, with ischemic stroke stemming from vascular occlusion that deprives regions of the brain of oxygen and nutrients, resulting in cell death [82, 83]. Subsequently, secondary inflammation arises, wherein immune cells inundate the ischemic region, releasing cytokines and chemokines that can expand the penumbra and hinder recovery.

The risk for patients with chronic inflammation

Patients with pre-existing chronic inflammatory conditions—such as atherosclerosis or heart failure—may harbor trained innate immunity at the bone marrow or peripheral macrophage level, amplifying inflammatory responses if a cerebrovascular event occurs [47, 55]. For instance, murine studies show that sympathetic signals triggered by ischemic stroke modulate myelopoiesis in the bone marrow, increasing the output of inflammatory monocytes [84]. Upon infiltrating the infarct zone, these primed cells mount a potent inflammatory assault that can impede neuroregeneration and hamper rehabilitative efforts [83, 85]. Indeed, clinical samples from stroke patients often exhibit heightened inflammatory mediators and activated immune cells, a phenomenon worsened by comorbid conditions like atherosclerosis or heart failure [83, 85].

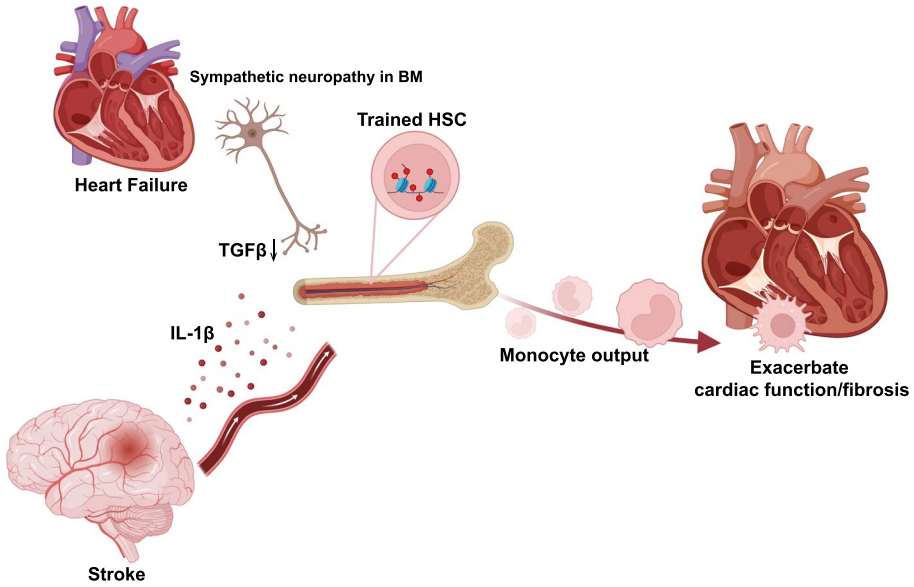

Fig. 3 Heart failure or stroke-induced central innate immune memory. In the setting of heart failure, sympathetic neuropathy in BM represses activation of TGF-β, which contributes to quiescence of HSCs. Epigenetic modulations of HSCs alter the pattern of monocyte output and the phenotype of cardiac macrophages, leading to exacerbation of cardiac function. In contrast, stroke raises circulating IL1-β levels, which leads to the training of HSCs. Trained HSC-derived monocytes and cardiac macrophages lead to cardiac fibrosis

Additionally, Simats et al. [15] have shown that stroke-induced immune memory in the bone marrow can precipitate myocardial fibrosis and HF progression [15]. Although the authors' heart failure research indicates that TGF-β signaling suppression can elicit epigenetic changes in HSCs and initiate an innate immune memory response [14], Simats and colleagues underscore the role of IL-1β in inducing proinflammatory memory at the HSC level [15]. Identifying key pathways in different disease contexts will be essential for developing targeted therapies. Altogether, these advances suggest that harnessing or modulating innate immune memory may open fresh opportunities for treating chronic inflammatory disorders such as HF and arrhythmias, offering new directions for future research.

Summary and future perspectives

Therapeutic and preventive strategies for controlling trained immunity

Harnessing or modulating trained immunity has emerged as a potential therapeutic or preventive strategy for various chronic inflammatory diseases, including atherosclerosis, heart failure, and autoimmune disorders [16, 66]. Specific approaches under investigation include the following:

Targeting the bone marrow HSC for therapeutic purposes

Epigenetic inhibitors or cytokine blockade directed at the bone marrow environment may help reverse the proinflammatory bias of hematopoietic stem cells (HSCs). Examples include histone acetyltransferase (HAT) inhibitors or DNA methyltransferase (DNMT) inhibitors aimed at selectively dampening the transcription of inflammatory genes. However, balancing immunosuppression with the preservation of host defenses remains a critical challenge [8, 10].

Potential of epigenetic inhibitors.

Potential of epigenetic inhibitors To curb excessive bone marrow inflammatory priming, epigenetic modifiers are a promising avenue. Inhibitors of histone acetyltransferases (HAT), DNA methyltransferases (DNMT), or histone demethylases, for instance, might selectively repress inflammatory gene expression in the marrow [46, 66]. However, because such interventions may affect global hematopoiesis and host defense, achieving specificity and safety remains a key challenge [8].

Immunometabolic reprogramming One therapeutic approach to modulating trained immunity in hematopoietic stem cells (HSCs) involves reprogramming their metabolic activity. Research has demonstrated that targeting key metabolic pathways can mitigate excessive inflammation. For instance, the use of mTOR inhibitors or glutamine metabolism blockers has been shown to reduce glycolysis-driven inflammatory responses and partially restore immune homeostasis [7, 35]. These

findings highlight the potential of metabolic interventions in rebalancing the immune functions of HSCs.

Manipulating the gut microbiota

The gut microbiota exerts profound effects on both local and systemic immune responses. A balanced microbiota helps maintain intestinal homeostasis and overall health, whereas dysbiosis—an imbalance in microbial composition—has been linked to chronic inflammation, metabolic syndrome, and cardiovascular disease. In the context of innate immune memory, microbiota-derived metabolites such as short-chain fatty acids (SCFAs) play a pivotal role in the epigenetic and metabolic reprogramming of immune cells. These metabolites can modulate hematopoietic stem cell differentiation, macrophage activation states, and even peripheral immune responses, thereby influencing disease progression or resolution.

Adjusting the intestinal microbiome through probiotics or dietary regimens may alleviate inflammatory bias in the bone marrow or peripheral immune compartments. Changes in short-chain fatty acid (SCFA) production, for example, could recalibrate epigenetic states to lower chronic inflammation [8, 10].

Reprogramming macrophage metabolism

Strategies to inhibit excessive aerobic glycolysis—via mTOR inhibition, glutamine pathway blockade, or other metabolic interventions—can reduce the proinflammatory phenotype of trained macrophages [3, 8, 17, 48]. Restoring a more quiescent or balanced metabolic state may prevent persistent cytokine overproduction.

Purposeful induction of training to enhance anti-infective defense

Conversely, intentionally inducing trained immunity—for instance, using BCG-based or β-glucan-based vaccines—could bolster resistance to certain infections. Research aims to refine this concept to achieve strong anti-inflammatory benefits while minimizing chronic inflammation [16, 47, 56].

Integrating multi-omics

A systems immunology approach, employing technologies such as single-cell RNA sequencing, ATAC-seq, metabolomics, and even spatial imaging, is indispensable for a comprehensive understanding of innate immune memory [17, 48]. By mapping HSC clonal diversity, monitoring peripheral monocyte/macrophage functional states, and cataloging metabolite and epigenetic modifications under different stimuli, researchers can discern the fundamental question, "Which stimuli channel through which epigenetic pathways to establish a lasting memory?"[3, 8].

Systematically charting these processes holds promise not only for clarifying trained immunity's etiology in chronic inflammation but also for identifying precise molecular targets to prevent or reverse detrimental immune reprogramming.

Future perspectives: multi-omics and organ crosstalk

As single-cell and multi-omics technologies advance, bone marrow-based innate immune memory will likely be dissected in even greater detail. Elucidating HSC clonal dynamics, remodeling of the marrow niche, and metabolic-epigenetic coordination requires an integrated, systems immunology approach [7, 10, 18]. Moreover, the role of bone marrow–origin inflammation is becoming increasingly evident across a wide spectrum of chronic diseases—cardiovascular, renal, neurodegenerative, or oncological. Identifying how gut microbiota, neuroendocrine factors, and lifestyle determinants (diet, exercise, sleep) shape HSC behavior will be pivotal for designing holistic treatment guidelines [47, 77, 86].

HSC clonality, the gut microbiota, and neuroendocrine influences

The clonal characteristics of bone marrow HSCs are shaped by a variety of signals, from inflammatory cytokines to microbial metabolites (e.g., SCFAs) and neuroendocrine mediators such as catecholamines or cortisol [56]. Combining these findings into an integrated picture of the "bone marrow–gut–brain axis" may provide novel avenues for immune regulation. Emerging evidence suggests that such cross-disciplinary approaches could inform strategies spanning cardiovascular disease, oncology, chronic kidney disease, and neurodegenerative conditions [16, 47]. Ultimately, the aim is to transcend traditional disease boundaries and develop horizontal research that tackles the shared inflammatory roots of multiple pathologies.

Clinical perspectives

Despite the progress, several major challenges remain before innate immune memory can be widely applied in a clinical setting as follows:

Biomarker development

There is a pressing need for robust, specific, and quantitative biomarkers of trained innate immune cells to distinguish beneficial training from pathological hyperinflammation [8, 87]. Knowledge of the status of innate immune memory may help predict the risk of cardiovascular disease, even in the presymptomatic stage.

Risk of adverse effects

Although boosting trained immunity can offer enhanced protection against infections, it also poses the potential hazard of intensifying chronic inflammation. Stringent safety assessments will be critical [16].

Toward personalized medicine

The interplay between host genetics, gut microbiota, and environmental factors (nutrition, lifestyle) necessitates individualized treatment frameworks [16, 17, 48]. Understanding patients' unique immunometabolic profiles will be essential for designing effective interventions.

Bringing high-dimensional omics analyses and systems-biology approaches into the mainstream could bridge these gaps, offering innovative therapeutic paradigms centered on regulating trained immunity.

Conclusion

Trained immunity, or innate immune memory, represents a groundbreaking concept in which monocytes, macrophages, NK cells, and other innate immune effectors preserve a long-term imprint of an initial stimulus through epigenetic and metabolic reprogramming, thereby mounting an amplified response upon restimulation [2, 4]. This discovery has significant implications for chronic inflammatory conditions, where an "inflammatory bias" established in bone marrow hematopoietic stem cells (HSCs) and within the peripheral compartment could perpetuate or exacerbate disease processes such as atherosclerosis, heart failure, and stroke.

Recent progress has emphasized the distinction between central innate immune memory—in which bone marrow HSCs undergo epigenetic modifications that prime them to generate proinflammatory cell types for extended durations—and peripheral innate immune memory, wherein tissue-resident or circulating macrophages/monocytes acquire sustained hyperresponsiveness at the local level [6–8]. Moreover, in heart failure, recent studies have demonstrated that such central innate immune memory can be a critical factor in worsening cardiac dysfunction by continuously fueling inflammatory macrophage production [14, 15]. Collectively, these findings illustrate how trained immunity extends beyond T and B cells' classical antigen-specific memory, redefining our understanding of immune responses in both infection and sterile inflammation.

Looking ahead, multi-omics integration (single-cell RNA-seq, ATAC-seq, metabolomics, etc.) and systems immunology approaches will be vital for dissecting the precise pathways that impart this lasting "memory" to innate cells [16, 17, 48]. Identifying reliable biomarkers that distinguish beneficial from pathologic training, mitigating adverse effects of heightened inflammation, and moving toward tailored interventions that respect each patient's genetic and microbiome context will be of paramount importance [8, 87]. As our knowledge deepens, innate immune memory may pave the way for novel therapeutic targets that not only enhance host defense against infections but also attenuate chronic inflammation in conditions such as cardiovascular and neurodegenerative diseases, cancer, and autoimmune disorders. By manipulating the bone marrow "central" memory while judiciously steering "peripheral" immune responses, we may realize fundamentally new strategies to combat and prevent a broad spectrum of inflammatory pathologies.

Abbreviations

BCG	Bacillus Calmette-Guérin
LDL	Low-density lipoprotein
HSC	Hematopoietic stem cell
DNA	Deoxyribonucleic acid
IL	Interleukin
TNF	Tumor necrosis factor
TGF	Transforming growth factor
NF	Nuclear factor
TCA	Tricarboxylic acid
NK	Natural killer
HIF	Hypoxia-inducible factor
ROS	Reactive oxygen species
SCF	Stem cell factor
AMI	Acute myocardial infarction
HF	Heart failure
SCFA	Short-chain fatty acid
ATAC	Assay for transposase-accessible chromatin
EC	Endothelial cell

Acknowledgements

None.

Authors' contributions

Y.N. and K.F. wrote the first draft of the manuscript and designed the figures. K.F. critically reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by grants-in-aid for Scientific Research from the Japan Society for the Promotion of Science, the Japan Agency for Medical Research and Development, and the Japan Science and Technology Agency (24H00631, 23ek0210193h0001, 22gm6510010h0002, and JPMJMS2023) awarded to K.F. and by the grant (24gm7010008h0001) awarded to Y.N.

Data availability

Not applicable.

Declarations

Ethics approval and consent to participate

No new studies with human participants or animals were performed in the course of writing this review, and thus, no specific ethical approval was required.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 24 January 2025 Accepted: 14 May 2025
Published online: 03 June 2025

References

1. Murphy K, Weaver C. Janeway's immunobiology: W.W. Norton; 2016.
2. Kleinnijenhuis J, Quintin J, Preijers F, Joosten LAB, Ifrim DC, Saeed S, et al. Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. Proc Natl Acad Sci. 2012;109(43):17537–42.
3. Arts RJW, Moorlag S, Novakovic B, Li Y, Wang SY, Oosting M, et al. BCG Vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. Cell Host Microbe. 2018;23(1):89-100.e5.
4. Netea MG, Quintin J, van der Meer JW. Trained immunity: a memory for innate host defense. Cell Host Microbe. 2011;9(5):355–61.
5. Netea MG, Joosten LA, Latz E, Mills KH, Natoli G, Stunnenberg HG, et al. Trained immunity: a program of innate immune memory in health and disease. Science (New York, NY). 2016;352(6284):aaf1098.
6. Kaufmann E, Sanz J, Dunn JL, Khan N, Mendonça LE, Pacis A, et al. BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis. Cell. 2018;172(1–2):176-90.e19.
7. Cirovic B, de Bree LCJ, Groh L, Blok BA, Chan J, van der Velden W, et al. BCG vaccination in humans elicits trained immunity via the hematopoietic progenitor compartment. Cell Host Microbe. 2020;28(2):322-34.e5.
8. Domínguez-Andrés J, Joosten LA, Netea MG. Induction of innate immune memory: the role of cellular metabolism. Curr Opin Immunol. 2019;56:10–6.
9. Bekkering S, Quintin J, Joosten LA, van der Meer JW, Netea MG, Riksen NP. Oxidized low-density lipoprotein induces long-term proinflammatory cytokine production and foam cell formation via epigenetic reprogramming of monocytes. Arterioscler Thromb Vasc Biol. 2014;34(8):1731–8.
10. Christ A, Günther P, Lauterbach MAR, Duewell P, Biswas D, Pelka K, et al. Western diet triggers NLRP3-dependent innate immune reprogramming. Cell. 2018;172(1–2):162-75.e14.
11. Khan N, Downey J, Sanz J, Kaufmann E, Blankenhaus B, Pacis A, et al. M. tuberculosis reprograms hematopoietic stem cells to limit myelopoiesis and impair trained immunity. Cell. 2020;183(3):752–70.e22.
12. Moorlag S, Folkman L, Ter Horst R, Krausgruber T, Barreca D, Schuster LC, et al. Multi-omics analysis of innate and adaptive responses to BCG vaccination reveals epigenetic cell states that predict trained immunity. Immunity. 2024;57(1):171-87.e14.
13. Sun SJ, Aguirre-Gamboa R, de Bree LCJ, Sanz J, Dumaine A, van der Velden W, et al. BCG vaccination alters the epigenetic landscape of progenitor cells in human bone marrow to influence innate immune responses. Immunity. 2024;57(9):2095-107.e8.
14. Nakayama Y, Fujiu K, Oshima T, Matsuda J, Sugita J, Matsubara TJ, et al. Heart failure promotes multimorbidity through innate immune memory. Science immunology. 2024;9(95):eade3814.
15. Simats A, Zhang S, Messerer D, Chong F, Beşkardeş S, Chivukula AS, et al. Innate immune memory after brain injury drives inflammatory cardiac dysfunction. Cell. 2024;187(17):4637-55.e26.
16. Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, et al. Defining trained immunity and its role in health and disease. Nat Rev Immunol. 2020;20(6):375–88.
17. Saeed S, Quintin J, Kerstens HH, Rao NA, Aghajanirefah A, Matarese F, et al. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. Science (New York, NY). 2014;345(6204):1251086.
18. Pietras EM, Mirantes-Barbeito C, Fong S, Loeffler D, Kovtonyuk LV, Zhang S, et al. Chronic interleukin-1 exposure drives haematopoietic stem cells towards precocious myeloid differentiation at the expense of self-renewal. Nat Cell Biol. 2016;18(6):607–18.
19. Ivanov AV, Bartosch B, Isaguliants MG. Oxidative stress in infection and consequent disease. Oxid Med Cell Longev. 2017;2017:3496043.
20. Barth TK, Imhof A. Fast signals and slow marks: the dynamics of histone modifications. Trends Biochem Sci. 2010;35(11):618–26.
21. Novakovic B, Habibi E, Wang SY, Arts RJW, Davar R, Megchelenbrink W, et al. β-Glucan reverses the epigenetic state of LPS-induced immunological tolerance. Cell. 2016;167(5):1354-68.e14.
22. Nakayama Y, Fujiu K, Yuki R, Oishi Y, Morioka MS, Isagawa T, et al. A long noncoding RNA regulates inflammation resolution by mouse macrophages through fatty acid oxidation activation. Proc Natl Acad Sci. 2020;117(25):14365–75.
23. Li Z, Chao TC, Chang KY, Lin N, Patil VS, Shimizu C, et al. The long noncoding RNA THRIL regulates TNFα expression through its interaction with hnRNPL. Proc Natl Acad Sci USA. 2014;111(3):1002–7.
24. Carpenter S, Aiello D, Atianand MK, Ricci EP, Gandhi P, Hall LL, et al. A long noncoding rna mediates both activation and repression of immune response genes. Science (New York, NY). 2013;341(6147):789–92.
25. Atianand MK, Hu W, Satpathy AT, Shen Y, Ricci EP, Alvarez-Dominguez JR, et al. A long noncoding RNA lincRNA-EPS acts as a transcriptional brake to restrain inflammation. Cell. 2016;165(7):1672–85.
26. O'Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. Proc Natl Acad Sci USA. 2007;104(5):1604–9.
27. Taganov KD, Boldin MP, Chang K-J, Baltimore D. NF-κB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci. 2006;103(33):12481–6.
28. Sheedy FJ, Palsson-McDermott E, Hennessy EJ, Martin C, O'Leary JJ, Ruan Q, et al. Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. Nat Immunol. 2010;11(2):141–7.
29. Ahmad I, Naqvi RA, Valverde A, Naqvi AR. LncRNA MALAT1/microRNA-30b axis regulates macrophage polarization and function. Front Immunol. 2023;14:1214810.
30. Cui H, Banerjee S, Guo S, Xie N, Ge J, Jiang D, et al. Long noncoding RNA Malat1 regulates differential activation of macrophages and response to lung injury. JCI insight. 2019;4(4):e124522.
31. Shin JJ, Park J, Shin HS, Arab I, Suk K, Lee WH. Roles of lncRNAs in NF-κB-mediated macrophage inflammation and their implications in the pathogenesis of human diseases. Int J Mol Sci. 2024;25(5):2670.
32. Masoumi F, Ghorbani S, Talebi F, Branton WG, Rajaei S, Power C, et al. Malat1 long noncoding RNA regulates inflammation and leukocyte differentiation in experimental autoimmune encephalomyelitis. J Neuroimmunol. 2019;328:50–9.
33. Ma Z, Zhang J, Xu X, Qu Y, Dong H, Dang J, et al. LncRNA expression profile during autophagy and Malat1 function in macrophages. PLoS ONE. 2019;14(8): e0221104.
34. Wu J, Zhang H, Zheng Y, Jin X, Liu M, Li S, et al. The long noncoding RNA MALAT1 induces tolerogenic dendritic cells and regulatory T cells via miR155/dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin/IL10 Axis. Front Immunol. 2018;9.
35. Cheng SC, Quintin J, Cramer RA, Shepardson KM, Saeed S, Kumar V, et al. mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. Science (New York, NY). 2014;345(6204):1250684.
36. Jha AK, Huang SC, Sergushichev A, Lampropoulou V, Ivanova Y, Loginicheva E, et al. Network integration of parallel metabolic and transcriptional data reveals metabolic modules that regulate macrophage polarization. Immunity. 2015;42(3):419–30.
37. Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, et al. Succinate is an inflammatory signal that induces IL-1β through HIF-1α. Nature. 2013;496(7444):238–42.
38. Mills EL, Kelly B, Logan A, Costa ASH, Varma M, Bryant CE, et al. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. Cell. 2016;167(2):457-70.e13.
39. Arts RJ, Novakovic B, Ter Horst R, Carvalho A, Bekkering S, Lachmandas E, et al. Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity. Cell Metab. 2016;24(6):807–19.
40. Lampropoulou V, Sergushichev A, Bambouskova M, Nair S, Vincent EE, Loginicheva E, et al. Itaconate links inhibition of succinate dehydrogenase with macrophage metabolic remodeling and regulation of inflammation. Cell Metab. 2016;24(1):158–66.
41. Bambouskova M, Potuckova L, Paulenda T, Kerndl M, Mogilenko DA, Lizotte K, et al. Itaconate confers tolerance to late NLRP3 inflammasome activation. Cell Rep. 2021;34(10): 108756.
42. Pålsson-McDermott EM, O'Neill LAJ. Targeting immunometabolism as an anti-inflammatory strategy. Cell Res. 2020;30(4):300–14.
43. Semenza GL. Hypoxia-inducible factors in physiology and medicine. Cell. 2012;148(3):399–408.

44. Schultze JL, Mass E, Schlitzer A. Emerging principles in myelopoiesis at homeostasis and during infection and inflammation. Immunity. 2019;50(2):288–301.
45. Kaelin WG Jr, McKnight SL. Influence of metabolism on epigenetics and disease. Cell. 2013;153(1):56–69.
46. Rodriguez RM, Suarez-Alvarez B, Lopez-Larrea C. Therapeutic epigenetic reprogramming of trained immunity in myeloid cells. Trends Immunol. 2019;40(1):66–80.
47. Mitroulis I, Ruppova K, Wang B, Chen LS, Grzybek M, Grinenko T, et al. Modulation of myelopoiesis progenitors is an integral component of trained immunity. Cell. 2018;172(1–2):147-61.e12.
48. Paul F, Arkin Y, Giladi A, Jaitin DA, Kenigsberg E, Keren-Shaul H, et al. Transcriptional heterogeneity and lineage commitment in myeloid progenitors. Cell. 2015;163(7):1663–77.
49. Adams GB, Scadden DT. The hematopoietic stem cell in its place. Nat Immunol. 2006;7(4):333–7.
50. Morrison SJ, Scadden DT. The bone marrow niche for haematopoietic stem cells. Nature. 2014;505(7483):327–34.
51. Metcalf D. The granulocyte-macrophage colony-stimulating factors. Science (New York, NY). 1985;229(4708):16–22.
52. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177–85.
53. Birks EJ, Burton PBJ, Owen V, Mullen AJ, Hunt D, Banner NR, et al. Elevated tumor necrosis factor-α and interleukin-6 in myocardium and serum of malfunctioning donor hearts. Circulation. 2000;102(suppl_3):Iii-352-Iii-8.
54. King KY, Goodell MA. Inflammatory modulation of HSCs: viewing the HSC as a foundation for the immune response. Nat Rev Immunol. 2011;11(10):685–92.
55. Nahrendorf M, Swirski FK. Monocyte and macrophage heterogeneity in the heart. Circ Res. 2013;112(12):1624–33.
56. Brugman S, Ikeda-Ohtsubo W, Braber S, Folkerts G, Pieterse CMJ, Bakker P. A comparative review on microbiota manipulation: lessons from fish, plants, livestock, and human research. Front Nutr. 2018;5:80.
57. Notta F, Zandi S, Takayama N, Dobson S, Gan OI, Wilson G, et al. Distinct routes of lineage development reshape the human blood hierarchy across ontogeny. Science (New York, NY). 2016;351(6269):aab2116.
58. Sakurai M, Ishitsuka K, Ito R, Wilkinson AC, Kimura T, Mizutani E, et al. Chemically defined cytokine-free expansion of human haematopoietic stem cells. Nature. 2023;615(7950):127–33.
59. Bajpai G, Schneider C, Wong N, Bredemeyer A, Hulsmans M, Nahrendorf M, et al. The human heart contains distinct macrophage subsets with divergent origins and functions. Nat Med. 2018;24(8):1234–45.
60. Filipp M, Ge Z-D, DeBerge M, Lantz C, Glinton K, Gao P, et al. Myeloid fatty acid metabolism activates neighboring hematopoietic stem cells to promote heart failure with preserved ejection fraction. Circulation, 2025;151(20):1451–66.
61. Leuschner F, Dutta P, Gorbatov R, Novobrantseva TI, Donahoe JS, Courties G, et al. Therapeutic siRNA silencing in inflammatory monocytes in mice. Nat Biotechnol. 2011;29(11):1005–10.
62. Sookoian S, Pirola CJ. Systems biology elucidates common pathogenic mechanisms between nonalcoholic and alcoholic-fatty liver disease. PLoS ONE. 2013;8(3): e58895.
63. Sookoian S, Pirola CJ. Genetics in non-alcoholic fatty liver disease: the role of risk alleles through the lens of immune response. Clin Mol Hepatol. 2023;29(Suppl):S184–95.
64. Swirski FK, Nahrendorf M, Etzrodt M, Wildgruber M, Cortez-Retamozo V, Panizzi P, et al. Identification of splenic reservoir monocytes and their deployment to inflammatory sites. Science (New York, NY). 2009;325(5940):612–6.
65. Nahrendorf M, Swirski FK. Lifestyle effects on hematopoiesis and atherosclerosis. Circ Res. 2015;116(5):884–94.
66. Bekkering S, Joosten LA, van der Meer JW, Netea MG, Riksen NP. Trained innate immunity and atherosclerosis. Curr Opin Lipidol. 2013;24(6):487–92.
67. Libby P. Inflammation in atherosclerosis. Nature. 2002;420(6917):868–74.
68. Lusis AJ. Atherosclerosis Nature. 2000;407(6801):233–41.
69. Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med. 1999;340(2):115–26.
70. Gregory JC, Buffa JA, Org E, Wang Z, Levison BS, Zhu W, et al. Transmission of atherosclerosis susceptibility with gut microbial transplantation. J Biol Chem. 2015;290(9):5647–60.
71. Kelly B, O'Neill LAJ. Metabolic reprogramming in macrophages and dendritic cells in innate immunity. Cell Res. 2015;25(7):771–84.
72. Roy P, Orecchioni M, Ley K. How the immune system shapes atherosclerosis: roles of innate and adaptive immunity. Nat Rev Immunol. 2022;22(4):251–65.
73. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY, Cabrera-Fuentes HA, et al. Inflammation following acute myocardial infarction: multiple players, dynamic roles, and novel therapeutic opportunities. Pharmacol Ther. 2018;186:73–87.
74. Prabhu SD, Frangogiannis NG. The biological basis for cardiac repair after myocardial infarction: from inflammation to fibrosis. Circ Res. 2016;119(1):91–112.
75. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol. 2014;11(5):255–65.
76. Dutta P, Courties G, Wei Y, Leuschner F, Gorbatov R, Robbins CS, et al. Myocardial infarction accelerates atherosclerosis. Nature. 2012;487(7407):325–9.
77. Heidt T, Courties G, Dutta P, Sager HB, Sebas M, Iwamoto Y, et al. Differential contribution of monocytes to heart macrophages in steady-state and after myocardial infarction. Circ Res. 2014;115(2):284–95.
78. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res. 2015;116(7):1254–68.
79. Swirski FK, Hilgendorf I, Robbins CS. From proliferation to proliferation: monocyte lineage comes full circle. Seminars in immunopathology. 2014;36(2):137–48.
80. Fujiu K, Shibata M, Nakayama Y, Ogata F, Matsumoto S, Noshita K, et al. A heart-brain-kidney network controls adaptation to cardiac stress through tissue macrophage activation. Nat Med. 2017;23(5):611–22.
81. Sugita J, Fujiu K, Nakayama Y, Matsubara T, Matsuda J, Oshima T, et al. Cardiac macrophages prevent sudden death during heart stress. Nat Commun. 2021;12(1):1910.
82. Chamorro Á, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. Nat Rev Neurol. 2012;8(7):401–10.
83. Iadecola C, Anrather J. The immunology of stroke: from mechanisms to translation. Nat Med. 2011;17(7):796–808.
84. Courties G, Herisson F, Sager HB, Heidt T, Ye Y, Wei Y, et al. Ischemic stroke activates hematopoietic bone marrow stem cells. Circ Res. 2015;116(3):407–17.
85. Lin TY, Jiang D, Chen WR, Lin JS, Zhang XY, Chen CH, et al. Trained immunity induced by high-salt diet impedes stroke recovery. EMBO Rep. 2023;24(12): e57164.
86. Negi S, Das DK, Pahari S, Nadeem S, Agrewala JN. Potential role of gut microbiota in induction and regulation of innate immune memory. Front Immunol. 2019;10:2441.
87. Bekkering S, Arts RJW, Novakovic B, Kourtzelis I, van der Heijden C, Li Y, et al. Metabolic induction of trained immunity through the mevalonate pathway. Cell. 2018;172(1–2):135-46.e9.

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