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REVIEW

Dendritic cells immunotargeted therapy for atherosclerosis

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Abstract Atherosclerosis, a chronic inflammatory disease, is markedly influenced by both immune and inflammatory reactions throughout its progression. Dendritic cells, as pivotal antigen-presenting entities, play a crucial role in the initiation of immune responses and the preservation of immunological homeostasis. Accumulating data indicates that dendritic cells are present in healthy arteries and accumulate significantly in atherosclerotic plaques. Novel immunotherapeutic approaches and vaccination protocols have yielded substantial clinical advancements in managing chronic inflammatory diseases, with dendritic cell-centric modalities emerging for atherosclerotic management. In this review, we delineate the essential functions and underlying mechanisms of dendritic cells and their subsets in the modulation of atherosclerotic inflammation and immune responses. We underscore the immense promise of dendritic cell-based immunotherapeutic strategies, including vaccines and innovative combinations with nanotechnological drug delivery platforms for atherosclerosis treatment. We also discuss the challenges associated with dendritic cell immunotherapy and provide perspectives on the future direction of this field.

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1. Introduction

Globally, atherosclerotic cardiovascular disease (ACVD) stands as a significant health concern, notorious for its high death and disease burden[1]. Each year sees the demise of around 17.6 million individuals due to ACVD[2]. Alarmingly, the prevalence of atherosclerosis is on the rise, increasingly affecting the younger population[3]. Known risk contributors to heart disease encompass aging, tobacco use, hypertension, diabetes, and elevated lipid levels in the blood[4]. Emerging risk factors also play a role, including biological sex, intestinal microflora, and their metabolic byproducts, which have been linked to a heightened risk of conditions such as atherosclerosis[5,6]. Present clinical practices prioritize the management of secondary complications, like heart attacks, with treatment strategies targeting cholesterol reduction through medications like statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Aspirin and other antiplatelet drugs are employed to thwart clot formation, while lifestyle modifications, including a balanced diet, regular exercise, and quitting smoking, are recommended[7-9]. Nonetheless, drug treatments grapple with issues like lack of targeted delivery, high dosage requirements, and notable adverse effects[10]. Statins, when used over long periods, can trigger muscle-related symptoms, including myalgia and even rhabdomyolysis[11]. The elderly, particularly those with various health issues and on multiple drugs, are more susceptible to negative drug interactions, and the criteria for halting treatment in these cases remain a subject of debate[12]. Despite these interventions, there has been no substantial improvement in ACVD outcomes, underscoring the persistent global impact of the disease and necessitating continued research into its underlying mechanisms, targeted management, and novel therapeutic approaches[13].

Immunotherapy has seen remarkable progress in recent times, especially in combating cancer. Various approaches, including oncolytic viruses, cancer vaccines, cytokine therapy, cell transfer, and checkpoint inhibitors, are clinically recognized[14]. For instance, herpes simplex virus-based oncolytic immunotherapy treats melanoma, Rituximab targets recurrent indolent lymphoma, and the PD-1 inhibitor nivolumab addresses metastatic renal cell carcinoma[15-17]. High-dose interferon is used for chronic myeloid leukemia and melanoma[18], with a multitude of treatment forms like oncolytic viruses, cancer vaccines, cytokine therapy, cell transfers, and checkpoint inhibitors gaining clinical acceptance[14]. For example, the herpes simplex virus-based oncolytic immunotherapy, talimogene laherparepvec, has shown significant success in melanoma treatment during phase III trials[15]. The targeted therapeutic Rituximab has been effective against recurrent indolent lymphoma, while the PD-1 checkpoint inhibitor Nivolumab has been utilized in the treatment of metastatic renal cell carcinoma, working to boost T-cell mediated tumor shrinkage[16,17]. High doses of interferon have been directly combating tumor cells and bolstering immune responses, aiding in the treatment of chronic myeloid leukemia and melanoma[18]. In the realm of cardiovascular ailments, particularly atherosclerosis, immunotherapy has considerable promise. Targeted treatments addressing specific inflammatory markers, such as Interleukin-1β (IL-1β), IL-6, tumor necrosis factor α (TNF-α), and C−C motif chemokine ligand 2 (CCL2), have yielded promising results in animal models and patient outcomes[14]. The Canakinumab Antiinflammatory Thrombosis Out-come Study (CANTOS) trial, for instance, has shown that targeting the IL-1β pathway with anti-inflammatory therapy can significantly cut down on recurrent cardiovascular events[15]. Further, the use of the costimulatory inhibitor abatacept has been effective in curbing T-cell activity, slowing heart failure progression, and enhancing heart function[16]. Moreover, in cases of ischemia−reperfusion injury, cell therapy has been instrumental in improving cardiac function by inducing an acute sterile immune response, characterized by the mobilization of CCR2 and CX3CR1 macrophages to the affected tissue[17].

Dendritic cells (DCs) are a distinct group of antigen-presenting cells within the immune system, noted for their potent activation of T lymphocytes. They play a pivotal role in sparking both the innate and adaptive immune responses, thereby forming an essential bridge in the defense against infectious agents and tumors[18]. As research advances, the significance of DCs in cardiovascular disorders, particularly atherosclerosis, has become increasingly apparent. They are implicated in various stages of atherosclerotic development, from lipid accumulation and foam cell formation to the presentation of antigens and the modulation of inflammatory responses through cytokines and chemokines. Additionally, DCs orchestrate the T-cell response in atherosclerosis through a range of pathways[19]. Britsch et al.[20] pointed out that DCs are considered as important coordinators of adaptive immunity in atherosclerosis. DCs play a dual role in atherosclerosis, and additionally, different subsets of DCs can exacerbate or alleviate the inflammatory response. Notably, recent strides have been made in immunotherapy that targets DC regulation to combat atherosclerosis, showing promising results.

This review compiles the latest findings regarding the role and therapeutic potential of DCs in atherosclerosis management. It elucidates the origins and functions of DCs, their interplay with atherosclerosis, and methods for leveraging their regulatory capacity to treat the condition. Emphasis is placed on emerging strategies that employ DCs as a therapeutic avenue for atherosclerosis. We also explore prospective therapeutic targets within this domain. The paper concludes by addressing the current obstacles in this area of research and proposes future directions for the advancement of atherosclerosis therapies.

2. Role of dendritic cells in atherosclerosis

2.1. Biological characteristics of dendritic cells

In 1973, Steinman's groundbreaking research led to the identification of a distinct cell type known as DCs within the peripheral lymphoid structures of mice, including the spleen, lymph nodes, and Peyer's patches[21]. Characterized by their irregularly shaped, large nuclei and star-like cellular extensions, these DCs are bone marrow-derived and produced by the lymphoid-myelopoietic system. The lineage of DCs has been controversial in the field of immunology: DCs are an independent hematopoietic lineage, distinct from other monocyte-derived cells. Contemporary research indicates that DCs develop from a chain of limited-potential precursors that branch into varied populations with distinct phenotypes present in both peripheral blood and bodily tissues[22].

In humans, DCs categorize into two primary types: the conventional dendritic cells (cDCs), which include cDC1 and cDC2 subsets, and the plasmacytoid dendritic cells (pDCs). Studies on hematopoietic progenitor and stem cells reveal that both pDCs and cDCs emerge from the same precursors, with their differentiation influenced by the fms-like tyrosine kinase 3 ligand (Flt3L)[23,24]. A Flt3-driven developmental route, unique from lymphogenesis,

guides the maturation of these cells, involving CX3CR1 progenitors that quickly differentiate into all dendritic cell subsets. While these progenitors are shared, the commitment to a specific dendritic cell subset is diverse and may take place at various stages of hematopoiesis[23].

The progression of DCs to maturity is intimately linked to their functionality and role in the immune system, forming a pivotal bridge between the innate and adaptive immune mechanisms[25,26]. The maturity of DCs is traditionally gauged by three characteristics: a decline in endocytic ability, heightened efficacy in prompting T cell proliferation, and an enhanced response to specific chemokines like CCL19 and CCL21, which direct their migration to lymph nodes[27,28]. DCs originate in the bone marrow and migrate to various tissues, remaining in the immature stage. However, when DCs are exposed to and absorb external antigens, they begin to mature and begin to migrate to the lymph nodes. In the lymph nodes, DCs present antigens to T lymphocytes (Fig. 1)[27,29]. The DCs maturation process encompasses three phases: precursor, immature, and mature DCs[30]. Initially, precursors travel through the bloodstream and transform into immature DCs in target tissues. These cells exhibit low levels of molecules required for antigen presentation and co-stimulation, hindering effective antigen display. However, upon antigen stimulation or arrival in lymphoid tissue, they evolve into mature DCs, which express high levels of the necessary molecules for efficient antigen presentation and T cell activation[31].

In humans, our understanding of DCs ontogenesis is mainly derived from individuals with DCs deficiency and dendritic cell-mediated immunodeficiency[32,33]. In summary, DCs are everywhere, and they are found in lymphoid organs and peripheral tissues throughout the body[34]. Proper positioning of DCs is essential for the regulation of immune function.

2.2. *Immune responses in atherosclerosis*

Atherosclerosis is a persistent condition marked by immune involvement and chronic inflammation that primarily targets the interior of both large and medium-sized elastic arteries, including the aorta and coronary arteries, within the vascular system[35]. The disease commences with damage to the vessel's inner lining, which sets the stage for low-density lipoprotein cholesterol to accumulate underneath. Once present, this cholesterol is prone to oxidation, leading to the creation of oxidized low-density lipoprotein (oxLDL), which prompts endothelial cells (ECs) to produce more adhesion molecules. The accumulation of white blood cells under the endothelial lining ensues, precipitating immune and inflammatory reactions that accelerate atherosclerosis[36]. Characteristic of this condition are the plaques that form within the arterial lining, which in severe instances, can coalesce or rupture, increasingly constricting or completely obstructing the artery. This can cause ischemia and deprive tissues of oxygen[37]. The intricate mechanisms at the heart of atherosclerosis remain

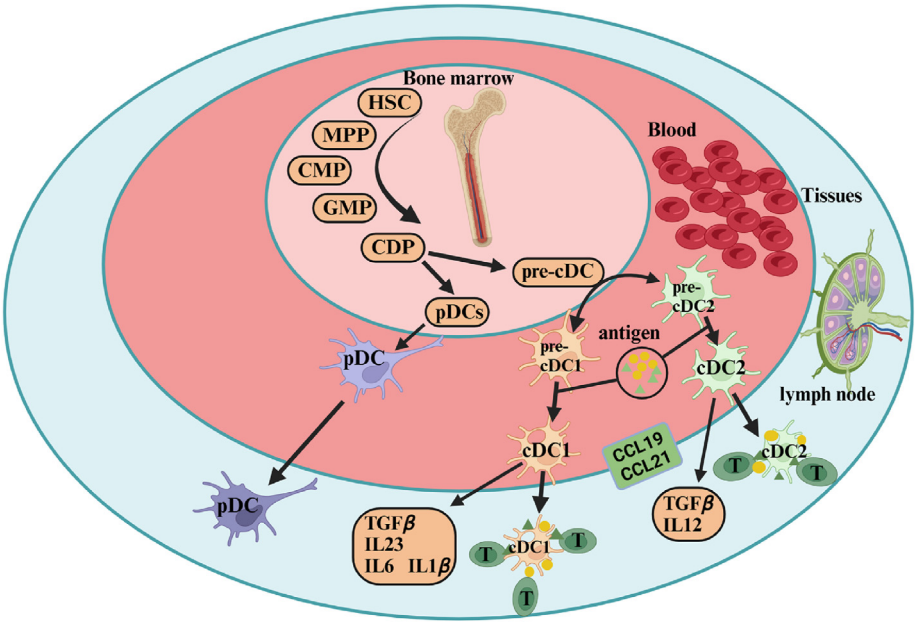

Figure 1 DC development and function in immune response. The maturation and dispersal of DCs is a complex process that originates in the human bone marrow. Here, HSCs, which possess the capacity for self-renewal, give rise to MPPs. These MPPs further branch into two pathways: the CMP and the common lymphoid progenitor cells. The CMP lineage progresses to form GMPs. Throughout the transition from HSCs to MPPs, CMPs, and GMPs, both monocytes and CDPs are produced. CDPs, having lost the ability to generate monocytes, are restricted to differentiating into three primary DC subpopulations. CDPs evolve to create pre-cDCs and pDCs. These precursors then relocate from the bone marrow into the bloodstream. Within this vascular system, pre-cDCs are further classified into two distinct subsets: pre-cDC1 and pre-cDC2. When exposed to antigens, pre-cDCs mature into cDCs in the bloodstream, where they exhibit enhanced capabilities for presenting antigens and eliciting T cell immune responses. The cDC1 subset predominantly secretes cytokines such as TGFβ, IL23, IL6, and IL1β, while the cDC2 subset principally produces TGFβ and IL12. Guided by chemokines CCL19 and CCL21, cDCs navigate to lymphoid tissues. In these locales, they fulfill their critical function in antigen presentation and the activation of T cells. DC, dendritic cell; HSC, hematopoietic stem cell; MPP, multipotent progenitor; CMP, common myeloid progenitor; GMP, granulocyte macrophage progenitor; CDP, common dendritic cell progenitor; pre-cDC, pre-classical dendritic cells; pDCs, plasmacytoid dendritic cells; cDCs, conventional dendritic cells.

elusive; however, the strong links among inflammation, immune responses, and the disease are the focus of this discussion.

The innate and adaptive immune systems are both implicated in the onset and progression of atherosclerosis, a chronic inflammatory condition[38]. Factors such as endothelial injury, abnormal lipid metabolism, and hemodynamic forces are instrumental in the early stages of lesion formation. ECs have been observed to mount an inflammatory response due to disturbed blood flow, with a variety of cells and cytokines, including macrophages, lymphocytes, DCs, vascular smooth muscle cells (SMCs), and TNF-α, playing a part in this process[39,40]. Within the vessel's intima, large quantities of low-density lipoprotein (LDL) undergo oxidation and accumulate, contributing to plaque formation. This oxidized form of LDL not only marks inflammation within the plaque but also binds to scavenger receptors on macrophages and DCs, facilitating the engulfment of oxLDL. DCs then convert into foam cells and present oxLDL-derived antigen fragments to T lymphocytes[41-43]. In the disease's advanced stages, the vessel wall is pervaded by an array of DCs and inflammatory cytokines, which secrete substances like matrix metalloproteinases that break down the collagen in the plaque matrix, potentially leading to plaque rupture and subsequently, bleeding and thrombosis[40].

Concerning atherosclerosis, both innate and adaptive immunities play critical roles in its development, with various lymphocyte types influencing the disease in different ways. For example, T lymphocytes have been found to exacerbate atherosclerosis in mice, while helper T cells 2 and regulatory T cells (Treg) seem to mitigate the process[44,45]. The complex participation of immune cells in atherosclerosis, akin to a "double-edged sword" presents opportunities for therapeutic intervention. B lymphocytes, similarly to T lymphocytes, exhibit both pro-atherogenic and anti-atherogenic capabilities, depending largely on the nature of the antibodies they produce[46].

To summarize, the intricate dance between inflammation and immune reactions is deeply entwined with the pathology of atherosclerosis. Exploring the detection of inflammatory biomarkers and strategic manipulation of immune cells and inflammatory pathways could offer promising avenues for treating this disease.

2.3. *Dendritic cells in atherosclerosis*

2.3.1. *Activation mechanism of dendritic cells in atherosclerosis*

In atherosclerosis, DCs play a critical role in the onset and progression of the disease through their activation and functional responses. DCs express Toll-like receptors (TLRs) and scavenger receptors, which, by binding to ligands such as oxLDL and heat shock proteins (HSP), initiate signal cascades that activate intracellular signaling pathways, including the NF-κB and MAPK pathways, thereby activating the DCs. This activation process involves the Myeloid differentiation factor 88 (MyD88)-dependent pathway, resulting in the nuclear translocation of the key transcription factor NF-κB. NF-κB upregulates pro-inflammatory cytokines, chemokines, and co-stimulatory molecules, enhancing the antigen-presenting capability of DCs[19,39,47]. Additionally, DCs express NOD-like receptors (NLRs) that recognize intracellular pathogen-associated molecular patterns and damage-associated molecular patterns, activating the NF-κB and MAPK signaling pathways, and through inflammasomes (such as NLRP3), activating caspase-1, promoting the maturation and release of IL-1β and IL-18, thereby activating and promoting DC maturation. DCs recognize carbohydrate structures through C-type lectin receptors (CLRs) and activate the NF-κB and CARD9/Bcl10/MALT1 complex *via* the Syk signaling pathway, promoting the secretion of pro-inflammatory cytokines[48]. When interacting with T cells, DCs enhance their activation and antigen-presenting functions through the signaling of co-stimulatory molecules (such as CD80/CD86 and CD40)[20,40].

The aforementioned signaling pathways work together to promote the maturation and activation of DCs, allowing them to play a critical role in atherosclerosis.

2.3.2. *The role of DCs in the inflammatory response of atherosclerosis*

DCs play multifaceted roles in the development of atherosclerosis, both as agents of disease and protectors against it. While these cells are sparsely distributed along the inner walls of healthy arteries, their numbers surge within the atherosclerotic areas, notably within the fatty streaks and fibrous plaques[49]. This increase in DC concentration within the arterial intima is driven by chemokines such as CCL2, CCL5, CX3CL1, and adhesion molecules that include P-selectin, E-selectin, and vascular cell adhesion molecule-1 (VCAM-1)[50]. Research using mouse models deficient in the CX3CL1 receptor, CX3CR1, has shown reduced DC presence in arterial walls, suggesting potential therapeutic avenues for atherosclerosis[51]. Furthermore, mature DCs dispatch CCL2 and CCL14 to draw in their immature counterparts to the plaque regions, where these cells mature amidst the inflammatory locale, exacerbating the inflammatory process. Experiments demonstrate that administering diphtheria toxin selectively diminishes DC populations, which in turn mitigates inflammation and plaque development[52].

DCs are pivotal antigen presenting cells integral to the immune system, responsible for modulating both inflammatory and tolerant responses[53]. Research has revealed that exosomes derived from DCs, harvested from bone marrow cultures, when introduced to human umbilical vein endothelial cells (HUVECs), elevate the inflammatory state *via* the NF-κB signaling pathway[54]. The presence of TNF-α on these exosomes ignites this pathway in HUVECs, hence promoting endothelial inflammation[55]. Therefore, DC derived exosomes can promote endothelial inflammation. Contrary to the longstanding notion that macrophages are the sole originators of foam cells in atherosclerosis, the past decade's studies have elucidated that various cell types within the arterial wall, including DCs, macrophages, SMCs, stem cells, and ECs, can engulf lipids to become foam cells[49]. The process by which DCs internalize lipoproteins to transform into foam cells, while not fully understood, is speculated to involve mechanisms such as receptor-mediated endocytosis, SR-B1-dependent uptake, direct cellular import from the bloodstream into the vascular lumen, and the release of cholesterol-rich particles[56-59]. These foam cells are identifiable by the DC marker CD11c. In CD11C-Dtr mice, which express the diphtheria toxin receptor, the injection of diphtheria toxin led to a reduction of DCs in the vascular wall and, subsequently, a lesser buildup of lipids in emerging lesions. This indicates that DCs are key players in the early stages of lipid accumulation in atherosclerotic lesions and present a target for therapeutic intervention[60]. Moreover, DCs are essential for antigen processing, with oxLDL and HSP 60/65 being the primary autoantigens linked to atherosclerosis. The uptake of oxLDL by DCs may not only enhance the presentation of antigens to natural killer (NK) cells and T cells, further fueling vascular inflammation, but also inflict damage on the vasculature through the dendritic cells' own inflammatory cytokine release triggered by oxLDL[19].

2.3.3. Dendritic cells regulate T lymphocytes

DCs orchestrate a complex interplay of immune responses. Mature DCs adeptly present antigens, activating T lymphocytes which then trigger immune reactions. In contrast, immature DCs contribute to immune tolerance by effectively silencing T lymphocytes, thereby dampening immune responses and conferring vascular protection[61]. TLR4 is instrumental in the maturation of DCs in atherosclerotic patients, becoming a key player in both the disease's onset and progression[62]. Moreover, TLR4 offers a novel avenue for managing atherosclerosis. Amongst CD4 T cells that encounter antigens, a distinct subset does not prompt an immune response; instead, it suppresses the functioning of other T cells. These are the Tregs, which are pivotal in moderating a myriad of immune conditions such as allergies, infections, cancer, metabolic inflammation, and chronic diseases like atherosclerosis. The differentiation and operations of Tregs are under the tight control of the transcription factor FOXP3. The T cell receptor (TCR) signaling is critical for Treg differentiation and for FOXP3's gene regulatory activities. TCR signaling-induced transcription factors activate FOXP3 transcription. Upon expression, FOXP3 binds with other transcription factors, integrating TCR signaling pathways and shaping transcriptional and epigenetic profiles. These TCR-responsive genes are central to the immunosuppressive capacities of Tregs[63,64].

Tregs have been identified as inhibitors of atherosclerotic inflammation, offering a protective role. MyD88 is an essential mediator in TLR signaling, crucial for eliciting the proper immune response[65]. Recent studies pinpoint MyD88 as a vital component in the maturity of DCs and in the production of protective Tregs within atherosclerotic sites, though the precise mechanisms remain elusive[66,67]. At the cellular level, evidence is mounting that DCs can modulate T cells activation to combat atherosclerosis. Antigen-bearing DCs initiate T cells immune reactions, with the DC surface providing co-stimulatory signals that guide T cells responses towards either immunogenicity or tolerance as the disease progresses[19]. CD40 on DCs and T cells intensifies atherosclerosis by spurring helper T cell 1 (Th1) activity through the CD40−CD40 ligand interaction, while interference with this pathway can mitigate the disease[68]. CD80 and CD86 on DCs interact with the CD28 co-stimulatory receptor on T cells to activate them. Mice lacking these proteins exhibit disruptions in Tregs homeostasis[19,69]. pDCs facilitate T cells activation *in vivo* by presenting antigens through MHC-II. This is corroborated by the elevated antigen-presenting capability of pDCs in atherosclerotic ApoE$^{-/-}$ mice and the reduced T cells presence at lesions in mice deficient in pDCs[70]. Nonetheless, not every DC subset contributes to atherosclerosis progression. CD103CD11c DCs display an immunosuppressive effect, preserving Treg balance. The differentiation of these cells is propelled by Flt3L, and a deficiency in this growth factor leads to atherosclerosis[71,72].

In sum, DCs assume a myriad of roles in the pathogenesis of diseases, engaging in both direct and indirect mechanisms that culminate in the development of atherosclerosis (Fig. 2).

2.3.4. Association of DCs with macrophages, smooth muscle cells, and endothelial cells in atherosclerosis

DCs interact with various cell types within atherosclerotic plaques, including macrophages, SMCs, and ECs. These interactions contribute to the complex pathophysiology of atherosclerosis. DCs and macrophages engage in mutual communication through cytokine secretion. DCs release cytokines such as IL-12 and TNF-α, which activate macrophages. Conversely, macrophages produce IL-1β and IL-6, influencing the activation and maturation of DCs[73]. DCs secrete chemokines like CCL2, attracting SMCs to the plaque site. SMCs respond to signals from DCs and other inflammatory cells by proliferating and migrating from the media to the intima. Inflammatory cytokines from DCs, such as IL-1β and TNF-α, can induce SMCs to change from a contractile to a synthetic phenotype, producing extracellular matrix components that affect plaque stability[73,74]. DCs activate ECs through direct contact and the release of pro-inflammatory cytokines like TNF-α and IL-1β. Activated ECs express adhesion molecules such as ICAM-1 and VCAM-1, which recruit immune cells, including DCs, to the vessel wall. In addition, the inflammatory environment created by DCs contributes to endothelial dysfunction, an early event in atherosclerosis, by enhancing endothelial permeability and promoting the entry of lipoproteins and immune cells into the intima[39,73].

In summary, DCs interact with macrophages *via* cytokine exchange, antigen presentation, and shared roles in foam cell formation, thereby amplifying inflammation. DCs influence SMC migration, proliferation, and phenotype modulation, impacting plaque composition and stability. Additionally, DCs activate ECs, promote endothelial dysfunction, and facilitate immune cell recruitment, sustaining the inflammatory response.

2.4. The role of dendritic cell subpopulations in atherosclerosis

Previously established, DCs are a diverse group with multiple subpopulations. The existing classification system stratifies these subpopulations using a variety of factors, including phenotypic markers, pivotal gene signatures encompassing essential transcription factors, TLRs, and other molecules relevant to function, as referenced in studies[75]. This is a condensed overview of the latest findings concerning DC subsets in relation to atherosclerosis (Table 1)[76-85].

Flow cytometry and real-time qPCR analysis have revealed that CD11b DCs are the predominant subset in atherosclerotic plaques of both ApoE$^{-/-}$ mice and humans. There is an inverse relationship between CD11b DC prevalence in blood and C−C chemokine receptor-5/7 (CCR5/7) levels in aortic plaques[86]. CD11b DCs are linked to local T cell proliferation, suggesting a regulatory role on vascular T cell balance[76]. Research shows that CD11b DCs can detect inflammation sites and migrate to atherosclerotic regions from lymphoid and non-lymphoid tissues, where they enhance their antigen-presenting capabilities[87]. Excluding the thymus, CD11b DCs are the major subset near lymphatic vessels in all organs, with their proliferation dependent on Flt3L cytokine. Flt3 and Flt3L deficient mice show significant depletion of CD11b DCs, indicating Flt3's importance in maintaining DC subset balance[77]. CD11b DCs activate and expand CD4 T cells through MHC-II and TCR interactions and co-stimulatory signals[78]. Evidence suggests that increased activity of CD11b DCs worsens atherosclerosis. However, deletion of Atg16l1 induces tolerance in CD11b DCs, promoting Treg expansion, reducing effector T cells, and decreasing Th1 cytokine production in atherosclerotic sites[88].

Comprising 20%−30% of total cDCs, CD103 cDCs display CD8 and MHC-II markers but lack macrophage markers like CD11b, CD115, CD172a, F4/80, and CX3CR1[77]. They express higher Flt3 levels compared to CD11b DCs. In the intestines, CD103 cDCs promote immune tolerance by inducing Treg differentiation and inhibiting Th1 and Th17 cells through retinoic acid, indoleamine 2,3-dioxygenase, and transforming growth factor-β (TGF-β)[78,89]. Steinman's research showed an increase

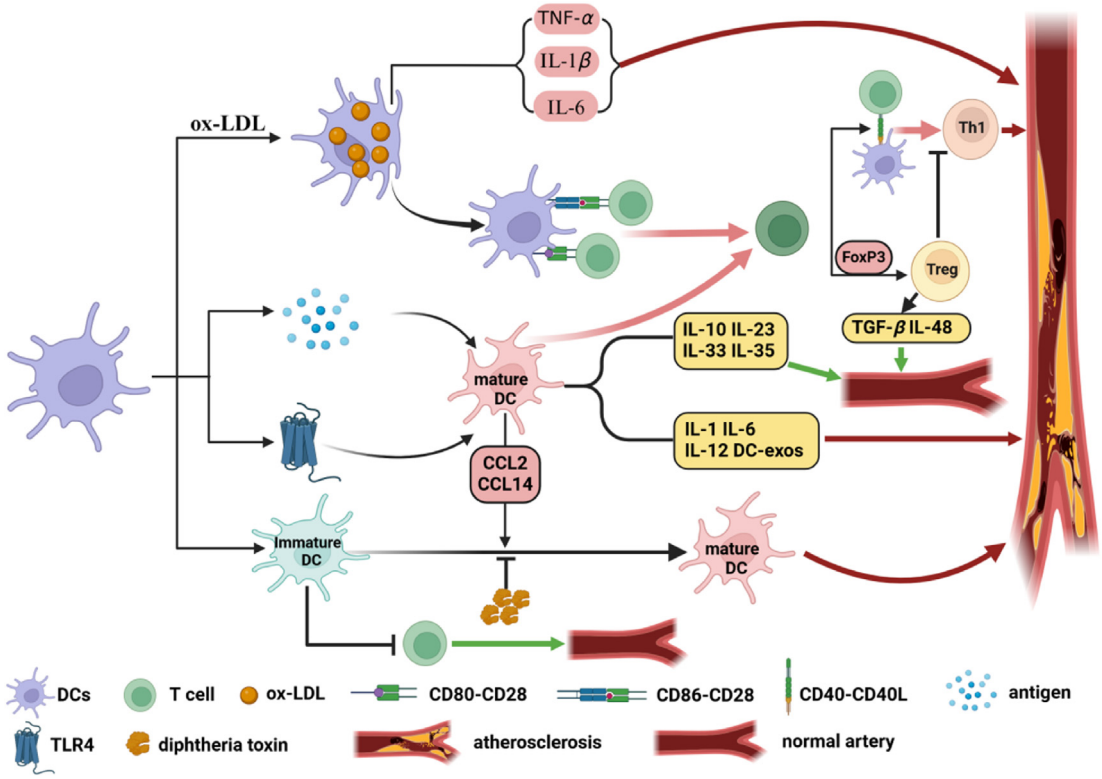

Figure 2 The dual role of DCs in atherosclerosis development. DCs play a multifaceted part in the progression of atherosclerosis, influencing the disease through both direct and indirect pathways. On one side, by absorbing oxidized LDL, DCs are key in antigen presentation to uninitiated T cells, setting off the transformation into Tregs and T helper 1 (Th1) cells. Conversely, oxLDL prompts dendritic cells to bind to their clearance receptors, which leads to the release of pro-inflammatory cytokines like TGF-β, IL-1β, and IL-6, thereby contributing to the progression of atherosclerosis. Tregs counter this by dampening the Th1 cell response that favors atherogenesis and by emitting anti-inflammatory cytokines, notably TGF-β and IL-48. Additionally, the maturation of DCs can be stimulated by various antigens and TLR4, resulting in T cell activation and a diverse cytokine response. This includes cytokines that both exacerbate atherosclerosis, such as IL-1, IL-6, IL-12, and DC-exos, and those that mitigate it, like IL-10, IL-23, IL-33, and IL-35. Mature DCs are also capable of promoting the maturation of their immature counterparts through the production of chemokines CCL2 and CCL14. In contrast, immature DCs play a protective role by inhibiting the activation of T cells. DC, dendritic cell; oxLDL, oxidized low-density lipoproteins; TLR4, toll-like receptor 4; DC-exos, dendritic cell exosomes.

Table 1 Function of dendritic cell subpopulations.

DCs subpopulation	Cytokine dependent	Relationship with plaque	Cell surface markers	The role of atherosclerosis	Ref.
CD11b DCs	Flt3L, CSF-1R	Positive correlation	MHC-II, CD45, CD11b, CD11c	Enhance the regulation of T cell morphology within blood vessels, facilitate the activation and proliferation of CD4T cells, and contribute to the exacerbation of atherosclerosis	76,77,78,79
CD103 cDCs	Flt3L	Negative correlation	CD8, MHC-II	Enhancing the differentiation and recruitment of Trey to alleviate the development of atherosclerosis	77,79, 80
CCL17 DCs	Flt3L	Positive correlation	MHC-II, CD40, CD80, CD86	Inhibiting the recruitment of Trey and exacerbating the progression of atherosclerosis	79,81
pDCs	Flt3L, GM-CSF	Positive/negative correlation	MHC-II, CD303, CD304, CD85g, CD85k, TLR7, TLR9	It exhibits both a pro-atherosclerosis effect and a protective effect	75,82, 83,84,85

in CD103 cDCs with Flt3L, while *Flt3*$^{-/-}$ mice lacked these cells in aorta tissue. CD103 DCs are primarily distributed in the atherosclerosis-prone regions, particularly the aortic sinus. During the process of atherosclerosis, the number of *Flt3*-dependent CD103 DCs significantly increases. Choi et al.[90] found an inverse relationship between CD103 cDCs and plaque size, suggesting that CD103 cDCs might protect against early atherosclerosis by promoting Treg differentiation and recruitment. Although CD103 cDCs appear to have a protective role in atherosclerosis, their exact mechanisms need further research.

In atherosclerotic lesions, CCL17 DC is abundantly recruited, but DCs in normal arteries do not express CCL17. Therefore, the study hypothesizes that CCL17 DC is directly recruited from the bone marrow during the progression of the lesion or originates from bone marrow-derived and matured resident DCs[80]. Recent findings show an increase in Tregs in mice lacking CCL17. CCL17 inhibits Tregs attraction by binding to the CCR4 receptor and activating Gq signaling pathways. While both CCL17 and CCL22 activate these pathways, CCL17 uniquely competes with CCL22, limiting its ability to induce β-arrestin signaling and Tregs migration[91]. The absence of CCL17-expressing DCs is associated with increased Tregs, providing protection against atherosclerosis progression in mice. The elevated Tregs levels in CCL17-deficient mice suggest that CCL17-expressing DCs restrict Tregs, promoting inflammation[81]. The exact mechanisms by which CCL17 DCs affect CD4 T cells need further study. However, current evidence highlights the crucial role of CCL17 DCs in atherosclerosis, with T cells guided by CCL17 DCs worsening the condition[80,81].

Plasmacytoid dendritic cells, predominantly found in the shoulder areas of plaques and near clusters of cDCs, have been identified in the atherosclerotic plaques of both humans and mice[92]. In healthy arteries, pDCs are in an immature state. When atherosclerosis occurs, the immature pDCs are activated into mature pDCs, thereby playing a role[93]. These cells are potent producers of type I interferon (IFN), which is integral to the body's defense against viruses. pDCs are distinct from bone marrow-derived cDCs, as they do not exhibit markers such as CD11c, CD33, CD11b, or CD13. Instead, they express an array of markers including CD303 (CLEC4C; BDCA-2), CD304 (neuropilin; BDCA-4), CD85k (ILT3), CD85g (ILT7), and other recently identified antigens like FcεR1, BTLA, DR6 (TNFRSF21/CD358), and CD300A[75,82]. IFN-α and IFN-β, produced by pDCs, are considered key contributors to atherosclerosis. There is a positive association between IFN-α levels and plaque presence in humans, with IFN-α also amplifying the sensitivity of DCs to TLR ligands and fostering the release of inflammatory cytokines[83]. Within the plaques, pDCs upregulate the expression of TLR-4, TNF-γ, and IL-12 in myeloid DCs, thus augmenting CD8T cell function[19]. Research by Sage et al.[84] has shown that by presenting antigens to MHC-II and activating CD4T cell immunity, pDCs exacerbate atherosclerosis in mice. Nevertheless, studies aiming to clarify the role of pDCs in atherosclerosis through antibody-mediated depletion have yielded inconsistent results. For instance, treating ApoE$^{-/-}$ mice with an anti-murine pDCs antigen 1 antibody led to a significant reduction in atherosclerosis by specifically eliminating pDCs within the aorta, suggesting their pro-atherosclerotic influence[93]. Conversely, another study found that removing pDCs in *Ldr*$^{-/-}$ mice increased T cell accumulation in the plaques, worsening the condition and indicating a potential protective role of pDCs[85]. Therefore, the precise function of pDCs in the context of atherosclerosis demands further investigation.

3. Dendritic cells immunotherapy for atherosclerosis

Presently, the treatment of atherosclerosis in medical practice predominantly involves systemic therapies, including lipid-modifying medications and agents that prevent platelet aggregation. Despite their widespread use, these strategies are not without limitations, potentially diminishing therapeutic efficacy and increasing the risk of adverse effects. Recent advances in clinical research have highlighted the effectiveness of incorporating immunological targets into cardiovascular disease treatments. As such, a multifaceted approach that integrates immune-targeted therapy is advocated for atherosclerotic lesions across various stages and cellular profiles, complementing conventional treatment modalities[94-96]. As research progresses, DCs have come to the fore as a pivotal focal point in atherosclerosis treatment strategies, drawing significant research interest (Table 2)[97-113].

3.1. DC vaccine strategies

The development of vaccines for chronic, non-infectious diseases is a promising intervention strategy that has recently gained traction due to its potential to require fewer doses, foster better patient adherence, and reduce costs. Specifically, vaccines targeting inflammatory agents linked to atherosclerosis, including ApoB-containing lipoproteins and heat shock proteins, have shown impressive efficacy in atherosclerotic mouse models. Vaccination using autoantigens associated with atherogenesis, such as oxLDL, HSP-60, and HSP-65, has demonstrated a capacity to curtail the progression of atherosclerosis in these models[114,115]. Protection was also observed in early immunizations with native LDL or oxLDL in rabbit models, a finding subsequently corroborated in ApoE$^{-/-}$ and low-density lipoprotein receptor$^{-/-}$ (*Ldlr*$^{-/-}$) mice[116-118]. Further research revealed that DCs pre-loaded with oxLDL *in vitro*, when reintroduced into *Ldlr*$^{-/-}$ mice on an atherogenic diet, resulted in the diminution of plaque size, enhanced plaque stability, and a decrease in T cell differentiation toward the Th1 phenotype[115,119,120]. These findings support the potential use of oxLDL-loaded DCs for *in vitro* atherosclerosis treatment. The success of an anti-oxLDL vaccine is hypothesized to rely on the DCs' ability to elicit protective Th2 and Treg responses and on the presence of phosphorylcholine to ApoB in LDL particles[114]. With the complexity of LDL particles in mind, identifying the minimal LDL-related epitopes for the creation of effective anti-atherosclerotic vaccines is the logical next step. In mouse models, Tregs and IL-10 are acknowledged for their anti-atherosclerotic effects by modulating vascular inflammation[121]. Moreover, the measles virus nucleoprotein has been shown to suppress immune responses by hindering DC activation, reducing IL-12 production, and curtailing the proliferation of effector Th cells. Extended administration of the measles virus riboprotein has been associated with a rise in IL-10 production by CD4T cells *in vitro* and a reduction in T cell proliferation with DCs present, significantly altering T-cell infiltration in plaques. Consequently, ApoE$^{-/-}$ mice treated with measles nucleoprotein exhibited substantial therapeutic benefits for atherosclerosis[122]. Similarly, extended administration of an inactivated bacillus Calmette-Guerin vaccine to ApoE$^{-/-}$ or *Ldlr*$^{-/-}$ mice provided atheroprotection through the induction of IL-10 and Treg expansion (Fig. 3)[121].

While recognizing the limitations of cultured DCs, the search continues for superior *in vivo* immunogenic cell sources and atherogenic autoantigens. Fortunately, Dr. Steinman and

Table 2 Strategies for dendritic cell-based immune targeting therapy of atherosclerosis.

Therapy	Method	Mechanism	Result	Ref.
DC vaccine	oxLDL-loaded DCs	Induce oxLDL-specific T cells, reduce Th1 response, increase oxLDL-specific antibody production increase	Reduction in the size of atherosclerotic plaques, enhanced stability, and decreased T-cell differentiation	98
	Measles virus nucleoprotein	Inhibit DC activation, reduce IL-12 production	Reduced T-cell infiltration in plaques	99
	Inactivated bacillus Calmette-Guerin vaccine	Induce IL-10, Treg expansion	Atherosclerosis protection effect	100
	DNA vaccine	Plasmid DNA binds to the DEC205 receptor specific to DCs, eliciting an anti-CX3XR1 antibody response	Reduce the accumulation of lipids and macrophages in plaques	101
"Tolerogenic" DCs	IL-10, ApoB100, IL-37, troponin I, R037	"Tolerogenic" DCs can limit effector T cell accumulation, reduce interferon-gamma production, and promote Treg proliferation.	Reduce the degree of atherosclerotic plaque	102,103,104
Suppress immune and inflammatory responses	DC exosomes carrying miR-203-3p	Inhibition of the lysosomal enzyme Ctss associated with inflammatory conditions	Slowing the progression of atherosclerosis	105
	Inclacumab	Inhibit the binding of P-selectin to its ligand PSGI-1, activating dendritic cells.		106,107
Inhibit DC maturation	IL-37	IL-37 inhibits the maturation of DCs through the IL-1R8-TLR4-NF-κB signaling pathway	Alleviate inflammatory response, exert atherosclerosis protective effects	108
	MCS-18	Inhibit DC migration and adhesion to the arterial wall		109,110
	Quercetin	Downregulation of CD80, CD86, MHC-II, IL-6, and IL-12 expression, while upregulation of Dabs, thereby inhibiting DC maturation.		111
	Dioscin	Reduce the expression of scavenger receptors on the surface of DCs and the uptake of oxidized low-density lipoprotein		112
	MALAT1	Inhibition of oxidized LDL-induced DC maturation through the miR-155-5P/NFIA pathway		113

Nussenzweig have introduced an innovative approach of directly targeting antigens to DCs *in vivo* using antibodies against highly expressed endocytic surface receptors specific to DC subpopulations. This method of targeting antigens with DC-specific antibodies, such as anti-CD207, anti-Clec9A, and anti-PDCA1/BST2/CD317, circumvents protracted *in vitro* procedures and is applicable in both humans and mice[123]. The ongoing task is to identify the most suitable atherosclerotic protein/peptide targets for this approach.

Inhibiting the CX3CL1 receptor, CX3CR1, in mice has demonstrated a reduction in atherosclerosis. However, adapting these methods for human clinical trials presents significant challenges[50]. A potential solution lies in DNA vaccination aimed at CX3CR1, which seems promising in bridging this gap. By attaching the plasmid DNA to the DEC205 receptor, which is specific to DCs, the potency of the DNA vaccine is enhanced. This vaccine has been shown to provoke an anti-CX3CR1 antibody reaction, reduce the accumulation of lipids and macrophages in arterial plaque, and decrease the prevalence of atherosclerotic plaque by 35%[124]. Consequently, DNA vaccines that target the chemokine pathway could be a viable treatment option for atherosclerosis. An additional study has found that a nasal DNA adjuvant system, specifically designed to target DCs and comprising DNA plasmids that express the Flt3 ligand and the CpG oligodeoxynucleotide 1826, can trigger the production of atheroprotective IgM antibodies within both mucosal and systemic lymphoid tissues. This response is facilitated by the interaction between DCs and CD5B220B cells[125]. It is anticipated that DNA vaccines focusing on CX3CR1 receptors may lessen atherosclerosis through stimulating an anti-CX3CR1 antibody response, reducing plaque invasion and formation. In parallel, DC-targeted nasal DNA adjuvant systems show promise in atherosclerosis prevention by generating protective antibodies. Both vaccine strategies offer optimistic prospects for atherosclerosis prophylaxis.

3.2. *Induction of "tolerogenic" DCs*

The process of tolerance is both dynamic and active, an intricate operation where the innate and adaptive elements of the immune system work in concert to rein in its activation and mitigate harm

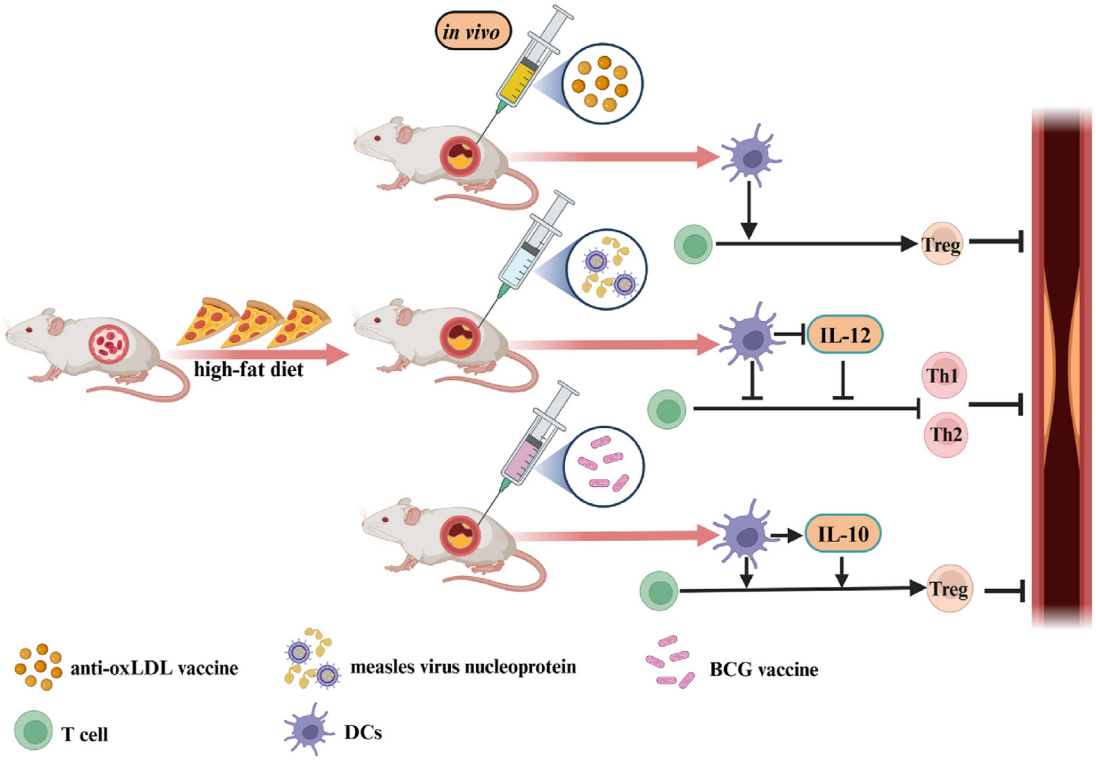

Figure 3 Dendritic cell vaccine immunotherapy for atherosclerosis. Dendritic cell vaccine immunotherapy has shown promising potential in the treatment of atherosclerosis. DCs have the ability to prevent infections, regulate diseases, eliminate tumors, and induce various immune responses when injected into experimental animals. By targeting atherosclerotic autoantigens like oxLDL, vaccines loaded with oxLDL can effectively hinder the progression of atherosclerosis. Injecting mice with a DC vaccine loaded with oxLDL enhances the DC's capacity to activate Treg, resulting in the inhibition of atherosclerosis. Moreover, immunization with ox-LDL-loaded DC vaccines generates "tolerant" DC, which further suppresses the development of atherosclerosis. When mice are injected with measles virus nucleoprotein, it can regulate the function of DC by reducing the production of cytokine IL-12, down-regulating Th1 and Th2, and inducing a tolerance phenotype in DC. Additionally, the BCG vaccine promotes the production of anti-inflammatory cytokine IL-10 and enhances the expansion of Treg in DC, thereby exerting anti-atherosclerotic effects when injected into mice. DC, dendritic cell; oxLDL, oxidized low-density lipoproteins; BCG, bacillus Calmette-Guerin.

to tissues[98]. Studies have unearthed that DCs, when primed with ApoB100 protein and modulated by the immunosuppressive cytokine IL-10, can evolve into "tolerogenic" DCs. These specialized cells play a pivotal role in dampening the progression of atherosclerosis by curtailing the expansion of effector T cells, diminishing the output of IFN-γ, and fostering the proliferation of Treg cells. Crucially, therapeutic approaches involving DCs do not compromise the immune system overall, positioning these methods as viable options for treatment in humans[49,114]. Experiments with hypercholesterolemic mice have demonstrated that administering DCs pre-treated with IL-10 and ApoB100 protein leads to a notable decrease in the extent of atherosclerotic plaques, a reduction in CD4T cell infiltration within arterial walls, and a lower incidence of systemic inflammation[126]. In parallel research, DCs conditioned with IL-37 and troponin I adopt a tolerogenic character, subsequently diminishing the severity of atherosclerosis and cardiac remodeling post-myocardial infarction. This suggests that the strategic delivery of IL-37 and troponin I-modulated "tolerogenic" DCs might offer a groundbreaking approach to atherosclerosis treatment[100]. Additionally, therapies that induce "tolerogenic" DCs and Tregs, such as glucocorticoids, IL-10, IL-27, oral anti-CD3 antibody, or calcitriol, the activated form of vitamin D3, have been shown to alleviate atherosclerosis in murine models[69,99,101,115,127].

In the realm of cellular function regulation, autophagy has recently been recognized as a fundamental mechanism tied to the progression of atherosclerosis. It is deeply involved in a myriad of biological activities concerning DCs, including their maturation, Toll-like receptor responses, cytokine synthesis, antigen presentation, and T cell priming. A novel study has highlighted that nullifying autophagy in certain DC subsets, specifically by depleting the autophagy-related protein Atg16l1, can prompt tolerance in CD11b DCs. This leads to an expansion in Treg cells, a reduction in effector T cell accumulation, and a decline in Th1 cytokine production within atherosclerotic sites, effectively impeding the disease's progression[88]. Such findings propose that targeted manipulation of DC autophagy could serve as a compelling therapeutic avenue for atherosclerosis. Moreover, the intestinal microbiota has been identified as a significant contributor to atherosclerosis development. In studies utilizing ApoE$^{-/-}$ mouse models, the probiotic *Pediococcus acidilactici* R037 was scrutinized for its therapeutic potential. Compared to a control group over twelve weeks, mice administered with R037 displayed a substantial decrease in plaque size within the aortic root lesions[128]. The intake of R037 *via* the oral route has been demonstrated to suppress atherosclerosis by promoting the emergence of "tolerogenic" DCs, which in turn inhibit the inflammatory and pro-inflammatory cytokine responses driven by Th1 cells, such as

IFN-γ and IL-17 production. Given that statins are less effective in older patients, the inclusion of functional probiotics like R037 in the diet emerges as a promising alternative for atherosclerosis prevention. Collectively, these investigations underscore the potential of "tolerogenic" DCs as a therapeutic target for combatting atherosclerosis.

However, the effectiveness of inducing "tolerogenic" DCs in treating atherosclerosis still needs further investigation, as inducing DC tolerance may not completely eliminate inflammation, since other immune cells (such as macrophages and T cells) can still promote an inflammatory environment. Additionally, whether inducing DC tolerance may potentially suppress beneficial immune responses, increase the risk of infection, or reduce the ability to resist pathogens also needs further evaluation.

3.3. *Suppress immune and inflammatory responses*

It has been established that DCs release exosomes which play a role in encouraging inflammation within the endothelium, as indicated by references[53,54]. Research has shown that these exosomes facilitate the transfer of peptide-MHC complexes with functionality across DCs, which in turn significantly boosts the activation of CD4 T cells amid immune reactions in a living organism, as documented in study[129]. With their potential in cancer immunotherapy being validated in clinical trials, as seen in source[102], DC-derived exosomes (DC-exos) have garnered considerable interest for their use in combating cancer. The tactics employed in utilizing DCs for treating atherosclerosis might either align with or diverge from those currently applied in cancer immunotherapy, as suggested by study[103].

In human tissues affected by atherosclerosis and aneurysms, there's a notable presence of miR-203-3p, which specifically targets cathepsin S (Ctss), a lysosomal enzyme implicated in inflammatory conditions, according to research[130]. Given that Ctss is a direct target of miR-203-3p in the context of atherosclerosis, strategically inhibiting this protease presents a promising strategy for mitigating inflammation and thus a potential treatment for atherosclerosis. Evidence shows that DC-exos bearing miR-203-3p can decelerate atherosclerosis progression through the inhibition of Ctss. Moreover, DC-exos are characterized by their stable vesicular structures offering extended shelf life and their immune stimulatory properties which are amenable to manipulation. Consequently, DC-exos are emerging as a novel target for immunotherapeutic interventions.

Cell adhesion molecules such as L-, E-, and P-selectin are essential in driving the adherence of inflammatory cells to the vascular endothelium, as noted in source[131]. P-selectin, found on the surfaces of activated platelets and ECs, binds with its ligand, P-selectin glycoprotein ligand-1 (PSGL-1), on DCs, subsequently activating the DCs through the TLR4 signaling pathway and promoting atherosclerosis progression. Comparative studies involving $ApoE^{-/-}$ mice, $ApoE^{-/-}$ $P^{-/-}$, and $ApoE^{-/-}$ $PSGL\text{-}1^{-/-}$ mice have revealed that the latter two exhibit smaller atherosclerotic lesions in their arteries-this provides further evidence of the involvement of P-selectin and PSGL-1 in atherosclerosis as per reference[132]. In clinical settings, the P-selectin antagonist inclacumab has been associated with a significant reduction in myocardial damage in patients with ST-segment elevation myocardial infarction who underwent percutaneous coronary intervention, as outlined in studies[104,133]. Nonetheless, the detailed implications of inclacumab in the context of atherosclerosis are yet to be fully understood. P-selectin and PSGL-1 hold promise as potential targets in the treatment of atherosclerosis.

The innate immune receptor TLR features prominently in atherosclerosis, with DCs and macrophages being the primary expressers of these receptors. TLRs contribute to several processes in atherosclerosis, which include the recruitment and stimulation of leukocyte subsets, formation of foam cells, and activation of T cells. Recent studies have demonstrated that inhibiting TLR-2 signaling curtails the production of pro-inflammatory agents in human atherosclerotic conditions. Additionally, the interruption of TLR-2 signaling has been observed to mitigate injury by reducing inflammatory mechanisms in a mouse model of myocardial ischemia/reperfusion injury, as referenced in study[134]. These findings collectively endorse the blockade of TLR-2 signaling as a potentially therapeutic approach for cardiovascular ailments such as atherosclerosis.

Activation of T cells by DCs hinges on the presence of both a primary signal and a secondary, costimulatory signal. In the absence of the latter, DCs fail to activate naive T cells, leading instead to an immune tolerance or a state of non-responsiveness towards the antigen. The B7-CD28 superfamily represents the most extensively researched group of costimulatory molecules. Therapeutic approaches targeting these costimulatory pathways are considered crucial for the treatment of a variety of autoimmune and inflammatory conditions[135]. To induce immune tolerance towards atherosclerotic antigens and to curb the progression of atherosclerosis, DCs are cultured *in vitro* with extracts from atherosclerotic plaques and loaded with antigens. These cells are then modified by blocking the costimulatory signals before being reintroduced into the organism. Commonly, CTLA4Ig, a prominent inhibitor of the costimulatory signal that attaches to B7 molecules, is employed in this context[105,106].

Inflammation is at the heart of atherosclerosis, with numerous inflammatory mediators and pathways such as exosomes, Ctss, selectin, TCR, and costimulatory factors playing a role. Identifying and modulating the key targets within these inflammatory and immune responses represent the future direction in the management of atherosclerosis. Nevertheless, numerous aspects still demand deeper exploration. For example, exosomes are packed with a variety of proteins, lipids, and nucleic acids, making it challenging to identify precise therapeutic targets. Additionally, it remains to be determined whether altering cell adhesion molecules, TLRs, and co-stimulatory molecules will impact the body's normal immune functions, which requires further study.

3.4. *Inhibition of DC maturation*

DCs in their immature state contribute to T cell tolerance by eliminating activated T cells and fostering Tregs, while their mature counterparts stimulate Th1 polarization[123]. In atherosclerosis, mature DCs play a detrimental role, and strategies to inhibit their maturation offer a viable approach to mitigate the excessive inflammatory immune response and treat atherosclerosis effectively. Research has demonstrated that IL-37 hampers DC maturation *via* the IL-1R8−TLR4−NF-κB signaling pathway, which, in turn, diminishes atherosclerosis in $ApoE^{-/-}$ mice[107]. Furthermore, Monocyte chemotactic protein-1 specific 18-mer peptide (MCS-18), a natural compound known to impede DC maturation, has been observed to lower pro-atherogenic cytokines and chemokines in animal serum, suggesting its protective role against atherosclerosis[136]. In a model using $ApoE^{-/-}$ mice, MCS-18 injections resulted in smaller plaque formations compared to those

in untreated mice. Despite plaque sizes remaining unchanged after three months of MCS-18 administration, untreated plaques increased, indicating MCS-18's efficacy in preventing new plaque growth rather than reducing existing ones. Laboratory experiments have revealed that MCS-18 inhibits DC migration and adherence to the arterial wall, offering a protective effect against atherosclerosis. MCS-18's influence extends beyond its impact on DCs, as it significantly affects ECs, T cells, and their interactions. Consequently, MCS-18's therapeutic use, particularly when combined with other anti-atherosclerotic medications, appears promising, though its precise mechanisms warrant further exploration[137]. The LOX-1 critically influences the immune maturation of DCs, with oxLDL driving DC maturation through the LOX-1-mediated MAPK/NF-κB pathway. Upregulation of LOX-1 enhances oxLDL uptake and foam cell formation, whereas inhibiting the LOX-1 pathway reduces DC maturation, positioning LOX-1 as a viable therapeutic target for atherosclerosis and related conditions[138].

Quercetin, a well-known flavonol, suppresses DC maturation both phenotypically and functionally by downregulating CD80, CD86, MHC-II, IL-6, and IL-12, and also by upregulating Dabs[139]. Dioscin, another agent, has shown promise in decreasing scavenger receptor expression and the assimilation of oxLDL, alongside reverting the DC production of IL-6 and IL-12 induced by high glucose levels. By impeding DC maturation and increasing IL-10 production in DCs, dioscin emerges as a potential atherosclerosis treatment[140]. *Ginseng*'s major active components, the total saponins of *ginseng* (TSPG), have been found to enhance vascular endothelial function through the promotion of nitric oxide synthesis. TSPG treatment markedly decreases the expression of DC maturation markers such as CD40, CD86, human leukocyte antigen (HLA)-DR, and CD1a, boosts endocytosis, and diminishes cytokine release, thereby dampening harmful immune responses in atherosclerosis and aiding its treatment[141].

MALAT1, a pivotal long non-coding RNA, is integral to several biological mechanisms, targeting nuclear factor I/A (NFIA)-a protein that binds DNA and modulates gene expression. MALAT1 has been found to regulate miR-155-5P, which in turn influences the 3′ untranslated region of NFIA. Recent research indicates that suppressing miR-155-5P hampers the maturation of DCs induced by oxidized LDL in a living organism. Moreover, an increase in NFIA levels also impedes the ox-LDL-induced maturation of DCs, and a deficiency in miR-155-5P results in heightened NFIA levels. These discoveries point to the possibility that by suppressing ox-LDL-induced DC maturation through the miR-155-5P/NFIA pathway, an overexpression of MALAT1 may help mitigate atherosclerosis. Consequently, the MALAT1/miR-155-5P/NFIA pathway presents a promising target for therapeutic strategies aimed at preventing the maturation of DCs[108].

However, treating atherosclerosis by inhibiting DC maturation still requires further evaluation in future preclinical studies. As mentioned above, DCs are present in lymphoid and non-lymphoid tissues throughout the body and play an important role in immune responses. Therefore, how to achieve targeted action on specific atherosclerotic lesion areas is a major challenge currently faced.

3.5. *DCs targeted delivery*

Nanotechnology's rapid progression has cast the spotlight on nanocarrier-based drug delivery systems, which promise to transcend the inherent drawbacks of conventional medications, including brief duration of action, instability, poor absorption, and heightened toxic responses. These innovative systems employ nanoscale materials to enable precise targeting and controlled release of drugs, markedly enhancing therapeutic outcomes. Nanocarriers also shield medications from enzymatic breakdown, prolonging their efficacy[109]. In the quest to combat atherosclerosis, scientists have explored the potential of directing endothelial-protective drugs straight to the affected blood vessels, a strategy that may surpass traditional systemic anti-inflammatory therapies. By fine-tuning the dimensions, form, and surface properties of nanocarriers, the nanomaterial-based approach promises to bolster local treatments and diminish adverse effects on non-target organs in atherosclerosis management. For instance, altering the shape of polymeric carriers has been proven to improve their interaction with DCs in mice with atherosclerosis[110]. An active immunization approach using the ApoB-100-derived peptide P210, carried by nanomaterial particles, has shown promise in reducing atherosclerosis. P210, incorporated into self-assembling peptide amphiphilic micelles (P210-PAMs), demonstrated an impressive ability to engage MHC-I molecules and regulate T cells, culminating in a substantial decrease in atherosclerotic lesions. Immunization with P210-PAMs was associated with an average 42% reduction in atherosclerosis, highlighting a potential therapeutic avenue for humans[142]. Moreover, DNA-coated superparamagnetic iron oxide nanoparticles (DNA-SPIONs), created by conjugating DNA oligonucleotides to PEG-coated SPIONs, have proven their efficacy in homing to DCs within atherosclerotic plaques. This was evidenced following their intravenous administration in an ApoE$^{-/-}$ mouse model, thereby endorsing the use of DNA-coated nanoparticles to enhance systemic delivery to atherosclerotic sites[111]. Future therapeutic strategies for atherosclerosis are likely to involve the integration of DNA-coated nanomaterials with established drugs such as statins and PCSK9 inhibitors, aiming for a targeted approach. Notably, disk-shaped nanoparticles showed a preference for areas of disturbed blood flow in both *in vitro* and *in vivo* shear loading models, outperforming their spherical counterparts. When these nanoparticles were loaded with the DNA methyltransferase inhibitor decitabine, they delivered localized anti-inflammatory and anti-atherosclerotic effects while reducing the drug's toxic side effects. This indicates that disk-shaped nanoparticles could represent an innovative method for refining systemic atherosclerosis treatments (Fig. 4)[112]. Collectively, these findings underscore the potential of nanomaterial drug delivery systems to revolutionize the treatment of atherosclerosis when combined with current medical therapies.

3.6. *Other treatments and targets*

A breakthrough approach for locally triggering anti-inflammatory mechanisms by removing apoptotic cells has shown promise in counteracting atherosclerosis. Evidence from mouse studies, where intravenous administration of apoptotic DCs stimulated with oxidized LDL (termed apo(ox)-DCs) was used, has shown a slowdown in the formation of atherosclerotic plaques and an improvement in plaque stability. This strategy's remarkable aspect lies in its employment of autologous LDL, which is oxidized and reintroduced into patient-derived DCs. This process fosters immune tolerance through the recognition of LDL-related peptides specific to the patient, eliminating the need to identify suitable agonistic peptides. It's evident that stimulating apoptotic DCs offers a highly specific and potent therapeutic option for combating atherosclerosis[143]. Alisol B 23-acetate (23B), a distinctive triterpenoid extracted from *Alisma* plant rhizomes, traditionally used in Chinese medicine, has been found to

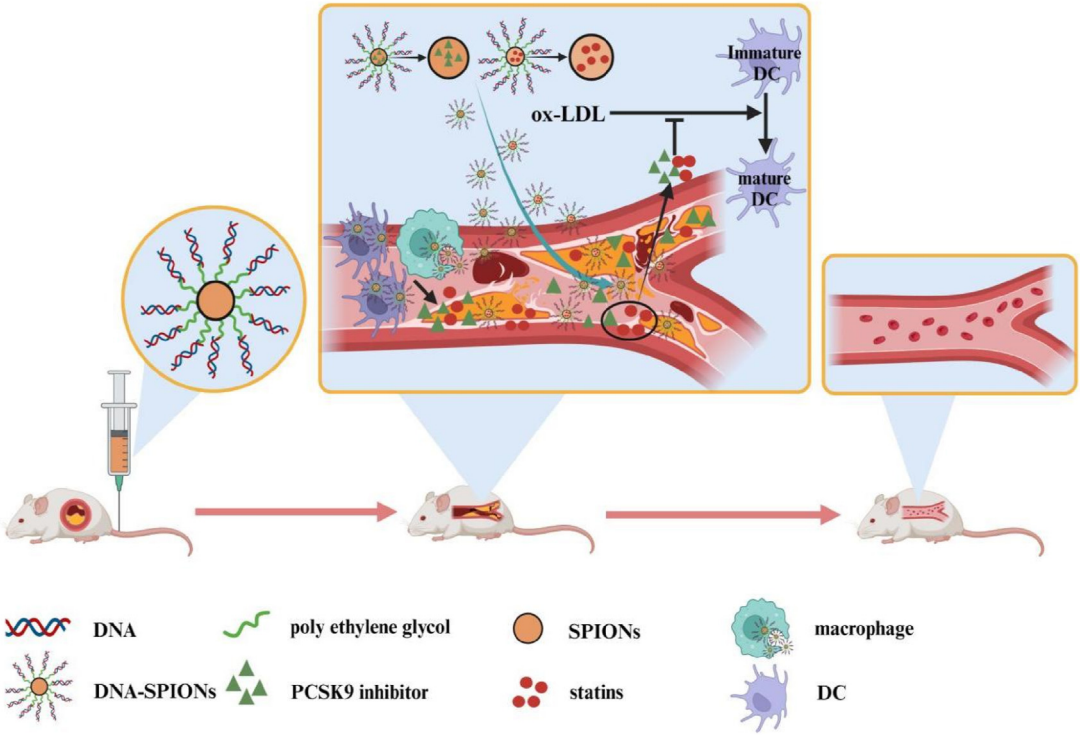

Figure 4 Advanced targeted nanotherapy for atherosclerosis. Harnessing the synergistic power of conventional pharmaceuticals and nanotechnology-based drug carriers holds considerable promise for atherosclerosis treatment. The pathological hallmarks of atherosclerotic plaques include an abundance of macrophages and dendritic cells, which are capable of ingesting foreign entities, such as nanoparticles. The strategic modification of PEG-SPIONs by attaching DNA oligonucleotides to their exterior enables these nanocarriers to efficiently target and penetrate atherosclerotic lesions. Upon intravenous administration in atherosclerotic mice, these DNA-SPIONs, when cloaked with lipid-modifying agents like statins and PCSK9 inhibitors, swiftly home in on the plaques. There, they are ingested by resident macrophages and dendritic cells, triggering the release of the therapeutic agents they bear. Once localized at the plaque, these medications mitigate the atherosclerotic process by halting the maturation of dendritic cells induced by oxLDL, dampening the production of inflammatory cytokines, and curtailing T cell proliferation. This targeted delivery system accentuates the precision of the treatment while minimizing adverse effects, thus offering a strategic advance in atherosclerotic therapy. DCs, dendritic cell; DNA-SPIONs, DNA coated superparamagnetic iron oxide nanoparticles; PEG-SPIONs, poly(ethylene glycol)-coated SPIONs; oxLDL, oxidized low-density lipoproteins.

influence antigen processing and manage cholesterol metabolism in cholesterol-engorged DCs. Laboratory studies confirm that 23B promotes cholesterol removal, downregulates the expression of MHC class II, CD80, and CD86 on these cells, and inhibits CD4 T helper cell activation. It also reduces the production of the inflammatory cytokines IL-12 and IFN-γ in DCs from ApoE$^{-/-}$ mice. Additionally, 23B has shown the ability to decrease triacylglycerol levels and increase high density lipoprotein in the bloodstream, as well as the upregulation of genes involved in cholesterol efflux in mice with severe atherosclerosis. Therefore, 23B modifies the immunological inflammatory response and serves as a beneficial tool in atherosclerosis management[113].

Inflammatory reaction markers known as inflammation response aggregates are made up of protein complexes found in the cytoplasm. Of particular note is the NLRP3 inflammasome, a component of the inflammation response that's overproduced in various immune cells, including DCs. This molecular complex activates caspase 1, which then converts IL-1β to its active form. Clinical and experimental studies indicate that IL-1β contributes to atherosclerosis. Investigations have shown that the use of the NLRP3 inhibitor MCC950 or lentiviral-based NLRP3 suppression therapy leads to a reduction in the size of atherosclerotic plaques, making the NLRP3 inflammasome a promising target for treatment. Small-molecule drugs like HCC950, CY-09, and OLT1177, aimed at the NLRP3 pathway, have already proven effective in curbing cardiovascular inflammation in preclinical trials[144].

Currently, clinicians commonly prescribe statins, like atorvastatin and simvastatin, which exert their cholesterol-lowering actions by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coA reductase. Beyond their lipid-lowering properties, these drugs also exhibit anti-atherosclerotic qualities, such as impeding the differentiation of DCs triggered by oxLDL, diminishing the release of inflammatory cytokines, and curtailing T cell proliferation[145]. For patients intolerant to statins, Bempedoic acid, as a novel lipid regulator, reduces low-density lipoprotein cholesterol (LDL-C) levels by inhibiting the early steps of cholesterol synthesis. Studies have shown that Bempedoic acid further reduces LDL-C levels in patients who have already been treated with statins but still have not achieved their target LDL-C levels, demonstrating a better therapeutic effect[146].

The latest research indicates that oxLDL promotes the production of PCSK9 in DCs, thus upregulating scavenger receptor A, CD36, and lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1), which in turn fosters the maturation of DCs. In contrast, the silencing of PCSK9 can mitigate oxLDL's impact on DCs[147]. Inclisiran is a novel small interfering RNA (siRNA) drug

that inhibits the expression of the PCSK9 gene in the liver, thereby reducing plasma LDL-C levels[148]. In recent years, the PCSK9 inhibitors employed in clinical settings owe their anti-atherosclerotic action to the suppression of DC maturation.

4. Conclusions and future prospects

In the realm of cardiovascular research, significant insights into the biology and pathophysiology of DCs have been amassed since their initial discovery, particularly regarding their association with atherosclerosis[149]. The evidence increasingly suggests a robust connection between DCs and the progression of atherosclerotic disease. This review spotlights the diverse functions that DCs and their various subsets play in atherosclerosis and underscores the substantial promise held by approaches such as DC-based vaccines, the generation of "tolerogenic" DCs, and the suppression of DC-related immune and inflammatory activities, as well as the prevention of DC maturation in the targeted immunotherapy against atherosclerosis. Research into the interplay between DCs and atherosclerosis is still nascent, and the specific roles of different DC subsets in the disease require further clarification. Compared to other recent reviews, they all elaborate in detail the central role of DC in the immune response and inflammatory response of atherosclerosis and the potential therapeutic directions based on DC. This review highlights various DC-based immunotherapeutic approaches for atherosclerosis[20,67,69,75]. The review also surveys the application of nanotechnology for targeted drug delivery, which may inform the future deployment of nanoparticle-mediated drug delivery systems in treating atherosclerosis. Moreover, several traditional medicines and phytochemicals have demonstrated significant effects on atherosclerosis, positioning them as promising subjects for subsequent investigations.

In the context of secondary prevention strategies for coronary heart disease, while the principal risk factors including LDL and inflammatory agents are well-considered, the achievement of optimal clinical outcomes remains elusive[150,151]. The development and worsening of atherosclerosis are intricately tied to inflammatory and immune mechanisms. The functionalities of DCs, such as lipid processing and antigen presentation, are pivotal in modulating inflammation and immune tolerance. The spotlight in cardiovascular disease research has increasingly been on immune cells, especially DCs. Recent therapeutic endeavors in atherosclerosis have prioritized vaccine-based interventions, fostering of immune tolerance, and mitigation of immune-driven inflammation, which are recognized as defining features of the condition. For instance, experiments in mice have demonstrated that atherosclerosis can be reduced and plaque stability can be enhanced through the intravenous introduction of exogenous oxLDL-bearing DCs. Furthermore, DCs carrying the ApoB100 protein, alongside the cytokine IL-10, have yielded success in promoting immune tolerance. However, the precise mechanisms and epitopes implicated in these responses remain to be fully elucidated. A promising method for epitope identification involves analyzing the atherosclerotic plaques themselves as manifestations of the illness. Due to the molecular complexity of LDL, which includes a mix of apolipoproteins, cholesteryl esters, triglycerides, and phospholipids, employing native LDL as an antigen in vaccine formulations is impracticable. On the contrary, a preclinical prototype of an atherosclerosis vaccine has been advanced using a relatively well-defined ApoB100 peptide as the antigen[79]. Consequently, future investigations should concentrate on pinpointing the specific antigens involved in the formation of atherosclerosis and determining the critical epitopes to facilitate the clinical application of these immunotherapeutic strategies.

Within the intricate environment of atherosclerotic lesions, a myriad of DC subsets display a remarkable range of diversity and functional disparity, with some yet to be fully delineated among the affected cohorts. This heterogeneity, coupled with the dynamic nature of DCs, introduces challenges in murine models that claim DC specificity, thereby obscuring our understanding of their role in atherosclerosis development. Moreover, the dearth of human samples impedes the extrapolation of mouse-derived insights to human conditions. Establishing the human equivalents of murine DC subsets would be a pivotal move to overcome this barrier. On a cellular scale, deploying high-throughput omics techniques could spotlight particular DC subsets within arterial lesions and their role in antigen presentation, facilitating targeted vaccine delivery through monoclonal antibodies to optimally modulate localized inflammation[152]. While our knowledge of arterial DC subsets and their functions has grown, we must delve deeper and refine our strategies to harness their therapeutic potential. It is through this dedicated approach that we stand to significantly enhance immunosuppressive outcomes and pioneer new avenues for clinical treatments.

Despite advances in the comprehension of atherosclerosis and the role of DCs, research still faces critical inquiries. These encompass: (1) the intricate dynamics between DCs, their effector cells, and the influence on atherosclerosis; (2) the definitive actions of DC subgroups. Variations within DC subpopulations in atherosclerosis are notable, with diverse subsets exerting distinct or contradictory effects on its evolution. A single subset may produce varying outcomes depending on the internal milieu and external factors. Hence, fine-tuning DC subset functions is vital for targeted immunotherapy against atherosclerosis. Investigating these subgroup mechanisms is key to this end; (3) the assurance of safety and consistency in DC-based vaccines. Animal studies have validated the efficacy of oxLDL-loaded DC vaccines against atherosclerosis, yet human trials lack data on their distribution, operational process, safe dosing, and interaction with other medications; (4) the longevity and sustained efficacy of DC vaccines; (5) the identification of specific epitopes for DC-targeted immunotherapy. OxLDL, being a composite entity, may harbor detrimental antigens. Isolating precise epitopes within oxLDL is crucial for the vaccine's clinical development. Additionally, patient-specific HLA genotyping might be necessary for personalized vaccines. Addressing these issues is pivotal for propelling future research in this field.

The confirmed effectiveness of the anti-oxLDL vaccine in mouse models has sparked optimism for its rapid integration into clinical therapies. DNA vaccines tailored to specific targets are proving to be a solution to the hurdles faced in human trials, boasting both high specificity and feasibility. Such strategies are crucial for future research and bear considerable significance for clinical applications. Essential to the success of targeted therapy for atherosclerosis is the research into "tolerant" DCs, the dampening of immune and inflammatory reactions, and the inhibition of factors involved in DC maturation. These areas demand further study. Remarkable successes in employing nano drug delivery systems for the management of conditions like cancer and inflammation have been observed recently[153]. Merging these current treatments with nanomaterial-based drug delivery systems, particularly for DC immunotherapy, promises precise interventions with reduced adverse effects. This innovative

combination therapy could be transformative for clinical practices. The promise of DC immunotargeted therapy for atherosclerosis is undeniable, as highlighted in this discussion. With a plethora of vaccine and target options on hand for the immunotherapy of atherosclerosis, we anticipate that continuous research and a deeper comprehension will soon bring these strategies into clinical use. Such advancements hold the key to confronting the persistent global challenge of atherosclerosis with effective treatments.

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Author contributions

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Conflicts of interest

The authors declare that they have no competing interests.

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