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Review

The Heterogeneity and Functional Roles of Dendritic Cells in Atherosclerosis: Origins, Subsets, and Therapeutic Implications

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Received: 19 July 2025; Accepted: 29 September 2025; Available online: 10 October 2025

ABSTRACT: Atherosclerosis, a chronic inflammatory disease of the arterial wall, is driven by dysregulated immune responses. Dendritic cells (DCs), as central orchestrators of innate and adaptive immunity, accumulate in atherosclerotic lesions and critically influence disease progression through their roles in lipid metabolism, antigen presentation, and cytokine signaling. Recent advances in single-cell omics and genetic lineage tracing have unveiled the functional diversity of DC subsets, including conventional DCs (cDC1, cDC2), plasmacytoid DCs (pDCs), and monocyte-derived DCs (Mo-DCs), in shaping plaque inflammation, immune tolerance, and tissue repair. However, the mechanisms underlying DC heterogeneity, recruitment, and crosstalk with other immune and vascular cells remain incompletely understood. This review summarizes current knowledge on DC ontogeny, subset-specific functions, and their interplay with T cells, B cells, endothelial cells (ECs), and smooth muscle cells in Atherosclerosis. We also critically evaluate transgenic models for DC research and emerging DC-targeted therapies, including tolerogenic vaccines and nanoparticle-based strategies. Unresolved questions about spatial distribution, functional duality, and ontogenetic pathways are discussed to guide future investigations.

Keywords: Dendritic cells; Atherosclerotic plaques; Vascular cells; Mouse models



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1. Introduction

Atherosclerosis, a chronic inflammatory arterial disease, represents the primary pathological basis for cardiovascular diseases (CVDs)—the leading global cause of mortality and morbidity [1,2]. While immune dysregulation has been well-established as a critical driver of atherosclerotic lesion development, progression, and plaque instability[3,4], the specific contributions of DCs within the complex immune microenvironment (comprising macrophages, T/B lymphocytes, NK/NKT cells, neutrophils, and mast cells) remain poorly characterized [5,6]. This knowledge gap persists despite compelling evidence of DC presence in both healthy arterial intima and atherosclerotic lesions across human carotid arteries and murine models [7–11], along with their demonstrated capacity to orchestrate dual atheroprotective and atherogenic immune responses [12–17].

Emerging clinical and preclinical data reveal that DC accumulation correlates with atherosclerotic progression in humans, rodents, and mice [18–21], with mechanistic studies implicating DCs in regulating tertiary lymphoid organ formation and lesion dynamics [22]. Although recent advances have identified distinct DC subsets with specialized roles in atherogenesis [23,24], the precise molecular mechanisms governing their context-dependent pro- and anti-inflammatory functions remain incompletely elucidated.

This review systematically examines: Functional heterogeneity of DC subsets in atherosclerosis pathogenesis, including subset-specific biomarkers; Crosstalk between DCs and key lesion cellular components (T cells, B cells, ECs, smooth muscle cells); Genetically engineered murine models for DC research; Emerging DC-targeted immunotherapeutic strategies. This comprehensive analysis aims to clarify DC biology in atherosclerotic progression and highlight translational opportunities in DC-based therapeutics.

https://doi.org/10.70322/immune.2025.10014

2. Origin and Development of DCs in Atherosclerosis

Since DCs discovery by Steinman et al. in 1973, their ontogeny has been extensively characterized [25]. DCs originate from hematopoietic stem cells (HSCs) in the bone marrow, progressing through a hierarchical differentiation pathway via common myeloid progenitor (CMP, $CD34^+$), granulocyte/macrophage progenitor (GMP, $CD34^+CD16/32^+$), macrophage-dendritic progenitor (MDP, $Lin^-c\text{-}kit^+CX_3CR1^+$), common DC precursors (CDP, $Lin^-c\text{-}kit^{int}Flt3^+Csf\text{-}1R^+$) [26]. The CDP bifurcates into two primary lineages, plasmacytoid DCs (pDCs) and conventional DCs (cDCs). The cDC lineage further diversifies into two major subsets: cDC1 and cDC2, each with distinct developmental dependencies (e.g., FLT3L, IRF8, BATF3 for cDC1; IRF4, ZEB2 for cDC2) and functional specializations [27]. Beyond this canonical pathway, DCs can also derive from monocytes under inflammatory conditions, highlighting their ontogenetic plasticity [28] (Figure 1).

In the context of Atherosclerosis, DCs are believed to originate from both the local activation of resident cells within the vessel wall [29,30] and the recruitment of circulating precursors (e.g., pre-DCs, monocytes) [31]. Damage-associated molecular patterns (DAMPs) released from injured ECs [32,33], necrotic smooth muscle cells [34], apoptotic macrophages [35], destabilized extracellular matrix components (e.g., fragmented collagen, oxidized LDL) [36], local cytokines and chemokines (e.g., CCL2, CCL20, GM-CSF, FLT3L, IFN-γ), orchestrate the homing and subsequent maturation of these cells within the atherosclerotic niche [37]. Mature DCs migrate to secondary lymphoid organs via CCR7 (C-C Motif Chemokine Receptor 7) to prime naive T cells, bridging innate and adaptive immunity [37]. The specific contributions of the different DC subsets, cDC1, cDC2, pDCs, and moDCs, to atherogenesis are complex and context-dependent. The subsequent sections discuss their detailed roles in modulating T cell responses (e.g., Th1, Th2, Th17, Treg) and overall plaque fate.

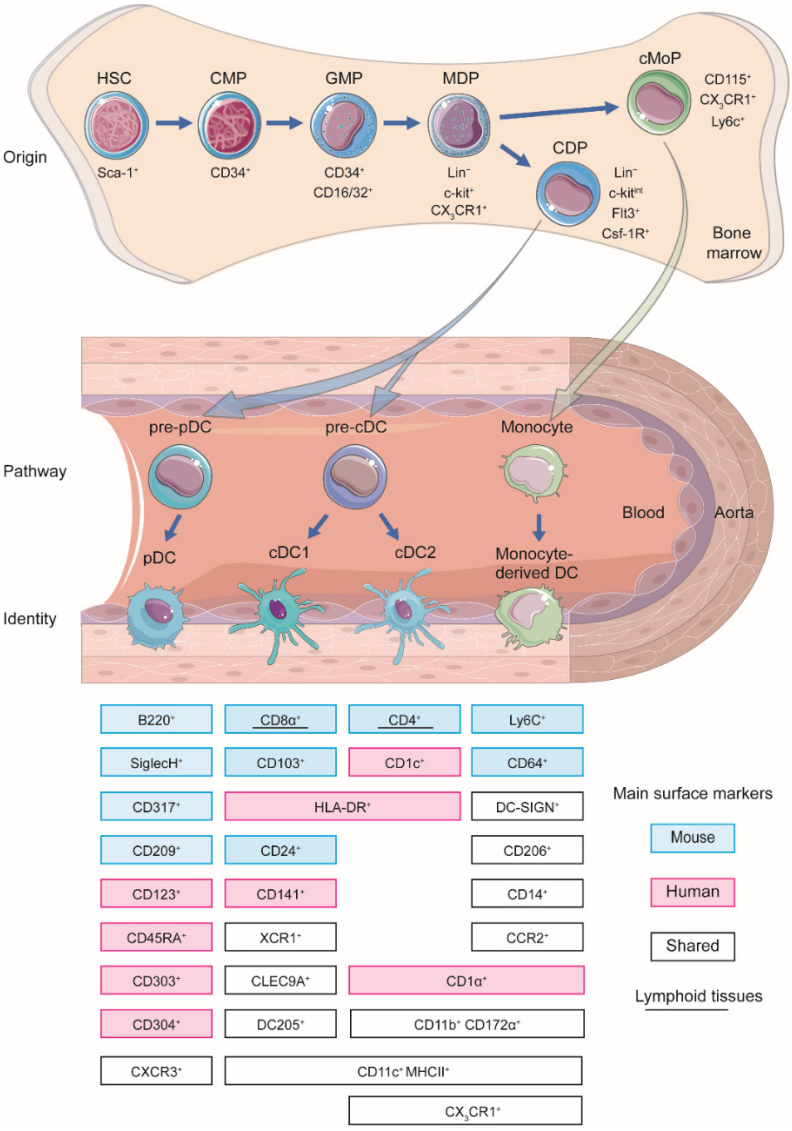


Figure 1. Differentiation of DC progenitor and origin of DC subsets.

3. Characterizing DC Subsets

In mice, DCs represent a functionally diverse population within the mononuclear phagocyte system. Vascular DCs uniformly express CD11c [12,24,38,39] and are identified through a combination of lineage-specific markers. As highly professional antigen-presenting cells (APCs), vascular DCs exhibit versatile antigen-presenting capabilities that support adaptive immune responses. They are proficient at priming naive $CD4^+$ T-cell activation and proliferation via strong MHC II–dependent interactions [40], and priming naive $CD8^+$ cytotoxic T-cell responses by loading exogenous antigens onto MHC I molecules [41]. Multiple phenotypically distinct vascular DC subsets have been mapped to the arterial intima in both healthy individuals and murine atherogenic hotspots, highlighting their spatial and functional diversity [7,8,12,17,21]. As summarized in Table 1, vascular DCs are broadly classified into three subsets based on ontogenetic origin and function: cDCs, pDCs, and Mo-DCs [12,24].

Table 1. Phenotype and ontogeny of mouse and human vascular DCs.

	Categories		Main Surface Markers	Main PRRs	Antigen Presentation	Cytokines
Mouse DC		Mo-DC	$CD11c^{++}$ $MHCII^{+++}$, CD11b, CD209, CD206, CD64, CD14, CD172a, DC-SIGN, CX3CR1, F4/80	Not well defined	Cross presentation to $CD8^+$ T cells, direct presentation to $CD4^+$ T cells	IL-12 IL-23 TNF iNOS
	cDC	cDC1	$CD11c^{+++}$ $MHCII^{+++}$, CD8a, CD103, CD24, CD205, XCR1, CLEC9A	TLR2-4, TLR11-13, RLR, STING, Clec12a	Cross presentation to $CD8^+$ T cells, direct presentation to $CD4^+$ T cells	IL-12 IFN-III
		cDC2	$CD11c^{+++}$ $MHCII^{+++}$, CD4, CD11b, CD172a,	TLR1-2, TLR4-9, TLR13, RLR, STING, CLEC4A, CLEC6A CLEC7A	Direct presentation to $CD4^+$ T cells	IL-6 IL-23 TNF
		pDC	$CD11c^{++}$ $MHCII^{+,}$ SiglecH, CD317, CCR9, B220, Ly49Q	TLR7, TLR9, TLR12, RLR, STING, CLEC12A	Limited antigen presentation ability	IFN-I IFN-III
Human DCs		Mo-DC	$CD11c^{++}$ $MHCII^{+++}$, CD11b, CD209, CD206, CD1a/b/c, CD14	Not well defined	Direct presentation to $CD4^+$ T cells, inducing Th1 and Th17 responses	IL-1β IL-6 IL-12 IL-23 IL-10, TNF iNOS
	cDC	cDC1	$CD11c^{+++}$ $MHCII^{+++}$, CD141, XCR1, CLEC9A	TLR1, TLR3, TLR6, TLR8, TLR10, STING, CLEC12A	Cross presentation to $CD8^+$ T cells, direct presentation to $CD4^+$ T cells, induction of Th1 responses	IL-12 TNF IL-6 IFN-I IFN-III
		cDC2	$CD11c^{+++}$ $MHCII^{+++}$, CD1c, CD172a, CD11b	TLR1-9, RLR, NLR, STING, CLEC4A, CLEC6A, CLEC7A,	Direct presentation to $CD4^+$ T cells, inducing Th2 and Th17 responses and Tregs	IL-1β IL-6 IL-12 IL-23 IL-10 TNF TGF-β

		CLEC10A, CLEC12A,		
pDCs	$CD11c^{-}$ $MHCII^{+++}$, CD123, CD303, CD304, CD45RA,	TLR7, TLR9, RLR, STING, CLEC12A	Poor in antigen presentation	IFN-I IFN-III TNF

Notes: 1. DC-SIGN: DC-specific ICAM3-grabbing non-integrin; 2. TLR: Toll-like receptor; 3. IL: Interleukin; 4. TNF: Tumor necrosis factor; 5. IFN: Interferon; 6. CLEC9A/12A: C-type lectin domain containing 9A/12A; 7. RLR: RIG-I like receptors; 8. STING: Stimulator of interferon genes; 9: TGF-β: Transforming growth factor beta.

3.1. cDCs

cDCs derived from CDPs of the HSCs, which migrate into tissues via blood as pre-DCs, where they then locally differentiate into DCs [42]. cDCs are dedicated APCs and characteristiced by dendritic morphology and high expression of MHC class II molecules, and can proliferate in early lesions [29]. Based on phenotypic characteristics and ontogeny, cDCs can be broadly classified into two distinct main categories, cDC1 and cDC2, wherein subsets within each category share consistent similarities in development and function. Notably, a largely analogous classification system for cDCs exists in mice and humans[43,44]. In general, cDCs accumulate in mouse and human atherosclerotic lesions with a marked increase in advanced stages and in complicated plaques [45].

cDC1 subset expresses the transcription factor Batf3 and is specialized in presenting cell-associated antigens derived from intracellular pathogens. In preclinical models, a particular DC subset, cDC1 is shown to be specialized in cross-presenting extracellular antigens to $CD8^{+}$ T cells [46] and activating a type I immune response. The most commonly used marker to identify cDC1 is CD8α in mice and CD141 (also known as BDAC3) in humans. Other markers that can be used in combination with CD141 to identify cDC1 include CD103 [47], XCR1 [48], CLEC9A [49], and CADM1 [50].

cDC2 express the transcription factor IRF4 and are specialized in presenting antigens from extracellular pathogens [51], such as bacteria and parasites. They are present in atherosclerotic plaques and can promote the activation of $CD4^{+}$ T cells [52], which are important for coordinating the immune response against these pathogens. The characteristic markers for cDC2 are CD11b and CD172a (also known as SIRPα) in mice [53], and CD1c (also known as BDAC-1) in humans.

Based on tissue localization and migratory pathways, the cDCs can be divided into migratory DCs and lymphoid tissue-resident DCs [54,55]. Migratory DCs are a subset of DCs that have the ability to migrate from peripheral tissues to lymph nodes, where they interact with T cells to initiate an immune response [56]. These DCs are characterized by their expression of specific chemokine receptors, such as CCR7, which allows them to respond to chemotactic signals produced by lymphatic ECs [57]. Migratory DCs are important for the induction of adaptive immune responses against pathogens and tumors, and they play a critical role in immune surveillance and tolerance [58,59]. They are also involved in the pathogenesis of autoimmune diseases and allergy [60]. Lymphoid tissue resident DCs are a subset of DCs found in lymphoid tissues, such as lymph nodes, spleen, and Peyer's patches [61]. They play a critical role in maintaining immune homeostasis by regulating the activation and differentiation of T cells [62]. Lymphoid tissue-resident DCs are characterized by their expression of specific surface markers, such as CD8α in mice and CD141 in humans for cDC1s [63], and CD11b in mice and CD1c in humans for cDC2s [64]. They are also involved in initiating and regulating immune response against pathogens and tumors, and play a critical role in developing immune tolerance [65–67].

3.2. pDCs

pDCs are unique bone-marrow-derived cells, and have been found to reside primarily in the adventitia of arteries [13], and also identified in the shoulder regions of plaques in mice [45] and humans [8] in small numbers. Unlike cDCs, pDCs are a small subset of DCs and are poor in antigen presentation, and specialized in producing large amounts of type I interferons [68], which is dependent on the interferon response family transcription factors, including IRF7 [69]and IRF8 [70]. pDCs derive directly from CDPs in the bone marrow in a Flt3L-dependent manner, and the subsequent specification requires the E protein transcription factor TCF4 (also known as E2-2) [71,72]. pDCs are identified by expression of B220 (also known as CD45R), PDCA-1 (also known as blood pDC antigen 1 or CD317) and Siglec-H (sialic acid-bing immunoglobulin-like lectin H) in mouse lesions [73,74], and CD123 (also known as IL-3 receptor alpha chain), BDCA-2 and BDCA-4 (also known as blood DC antigen 2 and 4) in human plaques [75,76].

3.3. Mo-DCs

In the steady state, Mo-DCs are scarcely identified in mucosal tissues in both mouse and human [77–79]. However, monocytes can give rise to cells with many of the phenotypic and functional features of DCs in an inflammatory status. Circulating monocytes from peripheral blood can rapidly mobilize and differentiate into Mo-DCs and acquire potent antigen-presenting capacity via upregulating CD11c and MHCII molecules [80]. Contrary to cDCs, Mo-DCs have a higher CX3CR1 and DC-specific ICAM3-grabbing non-integrin (DC-SIGN) expression [12], and they can be distinguished from resident CD11b+ DCs via Ly6c and Mac3 [81]. Mo-DCs express markers such as CD80, CD86, and HLA-DR [82], which are typical of mature DCS, and also express several DC-restricted markers [83], such as MIDC-8, CD172a, and CD209a [84–86]. In addition, a recent study identified other makers expressed in Mo-DCs, such as NAPSA, IFI30, and IFITM1, which play an essential role in the formation of functional blood vessels [87]. Like classical monocytes, Mo-DCs arise independently of FLT3 and instead are dependent on the cytokine macrophage clony-stimulating factor (M-CSF) [88]. They do not express the transcription factor ZBTB46 and depend on the chemokine receptor CC-chemokine receptor 2 (CCR2) for recruitment into inflammatory sites, a mechanism shared with classical monocytes and pre-cDCs [89,90].

4. Functional Role of Vascular DCs in Atherosclerosis

DCs, whether in lymphoid or nonlymphoid tissues, comprise only a minor portion of total cell population, and also scarce in human and mouse plaques, but they provide a unique role in the development and progression of atherosclerosis.

4.1. cDCs

cDCs are specialized in antigen presentation, with cDC1 excelling at cross-presenting exogenous antigens on MHC-I to activate naive $CD8^+$ T cells, and cDC2 primarily presenting antigens on MHC-II to activate naive $CD4^+$ T cells. Both subsets respond to antigens derived from oxLDL and are potent producers of pro-inflammatory cytokines, such as TNF-α [91], IL-6 [92], and IL-12 family [93], that promote Th1 and Th17 differentiation and activation [94]. Recent lineage-tracing studies underscore their subset-specific roles: cDC1s drive Th1 responses [95], while cDC2s promote Th2 [96], Th17 [97], and Treg responses [64], implicating DC heterogeneity as a critical determinant of plaque fate [27,28]. The ultimate role of cDCs in atherosclerosis is context-dependent. cDC1s typically promote pro-atherogenic immune responses through cross-presentation to $CD8^+$ T cells and interactions with NK cells and B cells [98]. However, they also exhibit functional plasticity and may contribute to tolerogenic responses in early disease stages or specific microenvironments. This duality is influenced by disease stage, tissue location, and local inflammatory signals. Meanwhile, cDC2 cells can promote the differentiation of naive T cells into various helper subsets—including Th1, Th2, Th17, Tfh, and Treg cells [99]. These subsets perform distinct functions: Th1, Th2, and Th17 cells produce pro-inflammatory cytokines such as IFN-γ, IL-4/IL-5/IL-13, and IL-17, respectively [100–102], whereas Treg cells exert immunosuppressive effects [103].

4.2. pDCs

Clinical studies have confirmed that pDCs exist in the shoulder region of human plaques, and the reduced number of pDCs is one predictor of cardiovascular events[104]. Due to low expression of MCH II and co-stimulatory molecules, pDCs are known as poor T cell activators. But the capacity of pDCs to phagocytose and prime antigen-specific T cell responses could be enhanced in mouse and human atherosclerotic lesions, when exposed to ox-LDL [105], and depletion of pDCs promotes plaque T cell accumulation and exacerbates lesion development and progression [68]. Further study suggested that pDCs may contribute to the progression of atherosclerosis by recruiting macrophages to the arterial wall [106] and stimulating cytotoxic T cell function in the lesions via producing type I interferons [107]. However, other studies have suggested that pDCs may also have a protective role in atherosclerosis by promoting Treg differentiation and dampening T cell proliferation and activity via the release of tolerogenic enzyme indoleamine 2,3-dioxygenase (IDO) in peripheral lymphoid tissue [68]. Another study indicated that pDCs may affect the development of atherosclerosis by inducing the maturation of cDCs and the recruitment of macrophages [106,108]. Overall, the role of pDCs in atherosclerosis is context-dependent. Within the inflammatory plaque, pDCs are activated by DAMPs (e.g., ox-LDL) via TLRs to produce type I IFNs, which exacerbate disease by recruiting macrophages and activating T-cells. Conversely, in lymphoid tissues, pDCs can exert a protective effect by producing IDO to suppress T-cell proliferation

and promote Treg differentiation. This functional duality explains apparent contradictions in the literature, which may also be influenced by factors such as disease stage and methodological approaches used to study pDCs.

4.3. Mo-DCs

Several studies proved that Mo-DCs are a crucial reservoir of APCs [109], and the major producer of pro-inflammatory cytokines, and can induce Th1 differentiation [110] and activate memory T cell [111]. Based on the intrinsic properties, Mo-DCs can differentiate into two distinct subsets: inflammatory DCs, which promote inflammation and immune cell activation by presenting antigens to T cells and secreting pro-inflammatory cytokines [112], and tolerogenic DCs, which induce immune tolerance by presenting antigens to regulatory T cells and secreting anti-inflammatory cytokines [113,114].

The accumulation and maturation of Mo-DCs in the arterial wall could be enhanced via interaction with platelets [115]. Mo-DCs can emigrate from the arterial wall and atherosclerotic lesions at the early stage of atherosclerosis [116]. Still, little emigration has been detected from progressive lesions, indicating that plaque progression may result not only from the robust monocyte recruitment into arterial walls but also from the reduced emigration of DCs from lesions [117]. Conversely, in some cases, egress of Mo-DCs from lesions with a fragile morphology may also contribute to plaque rupture or disruption rather than lead to an atheroprotective benefit [45,118]. Defective egress of DCs from the aorta and their altered trafficking toward lymph nodes can lead to excessive accumulation of Mo-DCs in the atherosclerotic lesions [14].

4.4. DCs Engulf Lipids and Control Cholesterol Homeostasis

Although macrophages are the main participants in lipid take and foam cell formation, resident intimal DCs could also rapidly engulf lipid and become the first foam cells in nascent lesions [119]. However, the percentage of DC-derived foam cells in atherosclerotic lesions is unclear. Several studies point toward a role of DCs in cholesterol metabolism. $CD11c^+$ DCs enhance lipid uptake and clearance in circulation to lower LDL levels, but CD11c is also expressed by certain macrophages and other immune cells [120]. Thus, depletion of $CD11c^+$ cells (which may include non-DCs) increases the plasma cholesterol level [98]. However, the depletion of Flt3-dependent DCs in $Flt3^{-/-}Ldlr^{-/-}$ mice did not change lipid levels [12]. Further lineage-tracking systems may be an excellent method to solve this question.

DC-derived foam cell could precede endothelial cell activation and increased monocyte recruitment and enhance the presentation of lipid and peptide antigens to NKT and T cells [14]. Ox-LDL uptake by DCs induces upregulation of scavenger-receptors, maturation and differentiation via LOX1-mediated MAPK/NF-kappaB pathway [121], which promotes the initiation and progression of immune cell activation in atherosclerotic lesions [122]. Another study suggested enhanced cytokine production was observed in ox-LDL stimulated DCs, which are activated through binding of CD36 and TLR4 [123]. Future studies aiming at enhancing the lipid-lowering potential of DC could be a potential strategy for the treatment of atherosclerosis.

4.5. DCs Initiate of Native T Cell and T Cell Differentiation and Development

Several lines of evidence illustrate that the interaction of DCs and T cells causally contributes to atherogenesis. For example, a deficiency of the invariant chain of MHCII could reduce atherosclerosis in $Ldlr^{-/-}$ mice [124], and abrogating transforming growth factor beta receptor II signaling in DCs promotes immune reactivity of T cells resulting in enhanced atherosclerosis [125]. Recent studies have further linked DCs with Treg responses in atherosclerosis. CCL17-expressing cDC1 drives atherosclerosis via constraining Treg-maintenance [126], deficiency of aortic cDC1 diminishes Treg in the aorta of $Ldlr^{-/-}$ mice [12], and dysfunctional DCs lead to a loss in Tregs. Further clinical studies confirmed that peripheral Treg numbers were reduced and CCL17 serum levels were increased in CAD patients, which may be in line with the expansion of CCL17+ DCs in atherosclerosis [127,128]. While DCs can emigrate from atherosclerotic lesions after antigen uptake and home to lymphatic tissue in a CCR7-dependent manner, they may also recruit T cells to the inflamed vessel wall via secretion of CCL17, CCL19, or CCL20 [129]. They can activate T cells and induce their proliferation and differentiation into effector T cells, leading to the promotion of inflammation and immune cell activation in the arterial wall [125]. The differentiation of T cells into different subsets, such as Th1, Th2, Th17, and Treg cells, can also be influenced by the cytokine milieu and other signals provided by the DCs [94].

4.6. DCs Induce Immune Tolerance

DCs play a critical role in the maintenance of immune tolerance, which is the process by which the immune system is trained to recognize and tolerate self-antigens while mounting effective responses against foreign antigens [130]. The role of DCs in the induction of immune tolerance in atherosclerosis is an area of ongoing research. Recent studies have proved that DCs can induce the differentiation of Tregs, which play a protective role in atherosclerosis by suppressing immune response and preventing autoimmunity [131]. Vaccination of LDL receptor deficient mice with DCs transfected with foxp3 encoding mRNA reduced Tregs and aggravated atherosclerosis [132]. Some studies found that injection of DCs loaded with oxLDL or ApoB100 into atherosclerotic mice reduced atherosclerotic lesions and increased Tregs [133,134].

4.7. DCs Regulate B Cell Development, Differentiation and Activation

B cells were rarely found in atherosclerotic plaques, but vascular DCs were found to form direct contact with them [135]. DCs can present antigens to B cells, activating and differentiating them into antibody-secreting plasma cells. DCs can also secrete cytokines, such as IL-6 and IL-10, which can influence B cell differentiation and activation [136]. On the other hand, B cells can modulate the function of DCs by producing cytokines, such as BAFF and APRIL, which can promote the survival and maturation of DCs [137]. B cells can also present antigens to DCs, leading to their activation and the promotion of immune responses. The interaction between DCs and B cells in atherosclerotic lesions can contribute to the development of immune responses against modified lipoproteins and other antigens present in the arterial wall, promoting inflammation and the progression of atherosclerosis [138].

More recently, a proatherogenic role has been attributed to the newly identified innate response activator B cells by promoting the expansion of cDCs and polarization [139].

4.8. The Relationship between DCs and ECs in Atherosclerotic Lesions

ECs line the inner surface of blood vessels and act as a barrier between the bloodstream and underlying tissues, regulating the passage of substances and immune cells [140]. This endothelial dysfunction is characterized by the increased expression of adhesion molecules, the secretion of pro-inflammatory cytokines, and altered permeability, which together create a conducive environment for leukocyte recruitment and retention. The basic aspect of DC function is its capacity to adhere and migrate through ECs [141]. The interplay between these two cell types is crucial for the pathophysiology of atherosclerotic lesions, influencing both inflammation and immune responses in the arterial environment. During the development of atherosclerosis, ECs become activated and produce adhesion molecules and chemokines that promote the recruitment of immune cells, including DCs, to the site of the developing plaque [142,143].

DCs need to tether and adhere to ECs to exit from peripheral blood for antigen acquisition, then infiltrate into the subendothelial space [144,145]. Various mechanisms mediate the interaction of DCs and ECs, including adhesion molecules and chemokine receptors [146,147]. Chemotactic stimuli and the involvement of adhesion molecules are necessary to invade DCs into the intima [141]. For example, mature DCs express the chemokine receptor CCR7, which interacts with its ligands CCL19 and CCL21 produced by activated ECs, allowing DCs to migrate to the lymph nodes where they can initiate an immune response [148,149]. And the multiple factors which accelerate atherogenesis could also enhance the DCs binding to and transmigration through the endothelial cell layer, such like TNF-α, ox-LDL, hypoxia and inhibition of NO synthesis [141]. In addition, DCs can promote endothelial cell dysfunction and inflammation by producing pro-inflammatory cytokines and chemokines, such as TNF-α and IL-6 [150], which can activate ECs and promote the expression of adhesion molecules and chemokines [145].

4.9. The Relationship between DCs and Vascular Smooth Muscle Cells (VSMCs) in Atherosclerotic Lesions

VSMCs are the predominant cell type in the arterial wall and responsible for maintaining the structural integrity and contractile function of blood vessels[151]. During atherosclerosis development, the interaction between DCs and SMCs may contribute to the progression of plaque inflammation, remodeling, and stability[152]. DCs can promote the activation of SMCs by producing pro-inflammatory cytokines and chemokines, such as IL-6 and MCP-1, which can induce SMCs migration and proliferation [153]. Moreover, DCs can also induce SMC apoptosis, which can contribute to the destabilization of the plaque and the rupture of the fibrous cap [154], and partially explained the phenomenon that up to 70% of DCs were accumulated in the shoulders of vulnerable plaques [45], On the other hand, SMCs can modulate the function of DCs by producing cytokines and growth factors that can influence DC maturation and

activation. For example, SMCs can produce TGF-β, which can promote the differentiation of tolerogenic DCs that induce immune tolerance.

In addition, one study has observed Lag-antibody positive cells in the aortic wall [155], and another study demonstrated that epidermal Langerhans cells could prevent UVB (ultraviolet radiation B) exposure-inhibited atherosclerosis development via suppression of proatherogenic T cell responses [156]. These data suggested that the close relationship between vascular DCs and Langerhans cells may also be involved in atherosclerosis.

5. Clinical Application

As DCs play a crucial role in the immune system by initiating and directing immune response, previous studies manifested that DCs have the potential to be used as a therapeutic toll in various diseases, including cancer [157–159], autoimmune disorders [160–162], and infectious diseases [163–167]. While the clinical application of DCs in atherosclerosis is still under investigation, several approaches have been explored.

5.1. DC-Based Vaccine

Induced tolerogenic DCs are a powerful immunotherapy for autoimmune disease, which have shown promise in clinical trials [168–170]. One of the approaches used to design DC-based vaccines for atherosclerosis is to load DCs isolated from patients and loaded with self-antigens, such as ox-LDL [171–174], heat shock proteins [175–177], apoB100 [133,178–180]and other plaque-associated antigens [181,182], can lead to a reduction of lesion size via dampening T cell activation and pro-inflammatory cytokine production, or inducing the differentiation of regulatory T cells, which can suppress immune responses against the arterial wall and reduce inflammation [133,183]. The activated DCs can then be delivered back to mouse or patient to decrease Th1 response and increase specific antibodies against these antigens, potentially reducing plaque formation and inflammation [134,184].

Another approach is to modify DCs to induce immune tolerance towards atherosclerosis. This can be achieved by using cytokines or factors to induce a regulatory DC phenotype that produces anti-inflammatory cytokines such as IL-10 [185]and TGF-β [186] via inducing regulatory T cells. This type of DC has been shown to reduce atherosclerotic lesion size and stabilize plaques in animal models.

Moreover, a DC-targeting nasal double DNA adjuvant system could be an effective nasal immunization strategy for preventing atherosclerotic lesion accumulation in the aortic sinus, mediated by inducing atheroprotective IgM antibodies via DC-B-1a B cell interactions [187]. In addition, DC-based vaccines have been combined with other approaches, such as statin therapy or adoptive transfer of regulatory T cells, to enhance their therapeutic effect further.

5.2. Therapeutic Modulation of Dendritic Cell Function and Signaling

Therapeutic strategies aimed at modulating dendritic cell (DC) function represent a promising approach to dampen inflammation and curb the progression of atherosclerosis. This can be achieved through several mechanisms, including the use of pharmacological agents to influence DC activation state or by targeting specific signaling pathways and receptors critical for their pro-inflammatory functions.

A broad range of conventional drugs has been shown to attenuate atherosclerosis, in part by indirectly modulating dendritic cell (DC) activation and maturation. It is important to note that the effects of these agents, which include conventional lipid-lowering drugs [188–191], HMG-CoA reductase inhibitors [188], PPAR agonists [192,193], and traditional Chinese medicines [194–197], and vitamin D receptor agonists [198], are pleiotropic. They exert their benefits by systemically altering the metabolic and inflammatory milieu (e.g., reducing hypercholesterolemia and oxidative stress), which in turn influences the function of multiple immune cell types, including monocytes, macrophages, T cells, and DCs. Consequently, while observed changes in DC phenotype following such treatments (e.g., suppressed maturation or a shift towards tolerance) are functionally important, they may often represent an indirect effect secondary to global changes in the immune environment rather than direct DC-specific targeting.

In contrast to these broad-acting therapies, a more precise strategy involves the direct targeting of specific molecules or receptors on DCs that are central to the inflammatory response. DCs express a repertoire of pattern-recognition and signaling receptors, including TLRs [199–201], TREM-1 [202,203], DC-SIGN [204–206], and TGFβRII [125], that recognize danger signals and orchestrate immune activation. Consequently, selectively modulating signaling through these receptors, such as by inhibiting specific TLR or TREM-1 pathways, may help regulate the immune response and reduce plaque inflammation in a more targeted manner [207]. Furthermore, selective modulation of autophagy in DCs has been identified as an intriguing therapeutic target [154,174]. Future efforts to develop truly

DC-specific therapies, such as nanocarriers for subset-specific delivery or antibodies against unique surface receptors, offer a promising path toward precise immunomodulation with reduced systemic effects. Beyond small molecules, biologic agents such as exogenous IL-37 can inhibit DC maturation, induce regulatory immune responses, and attenuate disease in *Apoe*$^{-/-}$ mice via the IL-1R8-TLR4-NF-κB pathway [208].

Looking ahead, DC-based vaccines show promise for atherosclerosis treatment [209], and inhibiting the recruitment of pathogenic DC subsets may help limit lesion growth and local inflammation. As atherosclerosis is multifactorial, further research is needed to characterize DC subsets, optimize intervention design and delivery of vaccines, evaluate safety, and ultimately assess efficacy in clinical trials. Combination therapies incorporating DC-targeted strategies with other treatments may yield optimal outcomes. Ultimately, targeted modulation of DC function remains an active research area with significant potential for advancing therapeutic options against atherosclerosis.

5.3. Emerging Insights from Human Studies and Translational Challenges

Advancements in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics refine our understanding of human atherosclerotic plaques, providing unprecedented resolution of cellular heterogeneity and revealing rupture-prone microenvironments [210–212]. These technologies offer critical insights into human-specific DC involvement and potential therapeutic targets, helping to bridge the gap between animal models and human disease.

DC-based vaccines and targeted DC modulation hold translational potential, yet considerable challenges remain. Tolerogenic DC vaccines loaded with atherosclerosis-relevant antigens have shown promise in preclinical models by expanding regulatory T cells and reducing plaque inflammation [133,172,174,178–180]. Similarly, specific pharmacological agents or biologics can modulate DC function toward anti-inflammatory phenotypes [154,174,208]. A primary challenge involves the identification of human-specific therapeutic targets and biomarkers through deep molecular profiling of plaques across disease stages. Furthermore, manufacturing clinical-grade cell products or targeted therapies remains complex and costly, demanding rigorous standardization. Safety concerns, particularly the risk of disrupting broader immune function, also necessitate careful evaluation. Future progress will likely depend on integrating multi-omics data from human studies, developing standardized protocols for therapeutic development, and designing innovative clinical trials that can effectively evaluate both immunological and clinical outcomes in appropriate patient populations.

6. Animal Models Used for DC Research

A variety of animal models are used in atherosclerosis research, including non-human primates [213,214], pigs [215,216], rabbits [217], zebrafish [218,219], rats [220], and mice [221]. Among these, mice have become the predominant model organism due to their lower cost and superior genetic tractability. The two most widely used hypercholesterolemic mouse models are *Apoe*$^{-/-}$ and *Ldlr*$^{-/-}$ mice [222]. *Apoe*$^{-/-}$ mice develop spontaneous plaques on a chow diet, while *Ldlr*$^{-/-}$ mice typically require a high-fat diet to induce significant hyperlipidemia and lesion formation. Crossing gene-modified mice with these models has proven highly valuable for elucidating the roles of specific dendritic cell (DC) subsets in atherosclerosis.

Early studies predominantly utilized conventional knockout mice, including Batf3, Flt3L, IRF8, CCR2, CCR7, Clec9a and Clec4a4, CD40 and CD11c-DTR mice (Table 2). A major limitation of these models is that systemic gene deletion affects multiple cell types, making it difficult to attribute phenotypic changes exclusively to DCs. Despite this constraint, these foundational studies revealed essential and non-redundant roles for DCs by targeting specific biological processes, including development (e.g., *Batf3*, *Flt3L*, *IRF8*) [41,223–229], migration (e.g., *CCR2*, *CCR7*) [230–234], and immunogenic function (e.g., *CD40*, *Clec9a*) [98,134]. For instance, *Batf3*$^{-/-}$ mice underscores the complex role of cDC1s, which can be either pro-atherogenic by promoting Th1 responses or neutral, highlighting the importance of disease stage and metabolic environment. Conversely, deficiency in *IRF8* or *Clec9a* (DNGR-1) attenuates disease, revealing the critical role of cDC1s in bridging innate cell death to adaptive Th1 immunity. The atheroprotective effect of *Clec4a4* (a cDC2-specific receptor) deletion further demonstrates functional specialization within the DC lineage, suggesting subset-specific pathways that could be therapeutically targeted. The profound atherosclerosis exacerbation upon broad ablation of CD11c^{+} cells in CD11c-DTR model, despite the concomitant loss of some macrophages, unequivocally established the net protective role of the CD11c^{+} compartment, likely through immune-regulatory mechanisms. Recent advances in genetic tools have enabled more precise targeting of DC subsets. The identification of specific DC markers has facilitated the development of conditional transgenic strains using CRISPR/Cas9 technology,

such as CD11c-Cre, Zbtb46-Cre, Clec9a-Cre, and Xcr1-Cre (Table 3), offering improved specificity in interrogating DC functions.

Table 2. Summary of DC deficient mouse models for AS research.

Model	Core Function	Atherosclerosis Phenotype & Mechanism	References
Batf3	Essential transcription factor for cDC1 development	• Apoe$^{-/-}$ background: ↑ Lesions (↓ splenic CD8$^+$ DCs/aortic CD103$^+$ cDC1, ↓ Th1) • Ldlr$^{-/-}$ background: no effect on lesion size	[41,223–225]
Flt3L	Critical cytokine for DC development	↓ cDC1/cDC2/pDCs (lymphoid/non-lymphoid tissues), progenitors (CDP/CLP)	[227–229]
IRF8	Transcription factor regulating DC subset differentiation	↓ Aortic CD103$^+$ cDC1 → Altered T-cell accumulation/differentiation (↓ Th1/Tfh, ↑ Treg)	[226]
CCR2	Chemokine receptor for monocyte/DC migration	• DCs: ↓ MHC-II/CD40 expression • Lymph nodes: ↓ IFN-γ$^+$ cells	[230–233]
CCR7	Key receptor for DC migration to lymph nodes	Blocks DC trafficking to LNs → Inhibits adaptive immunity initiation	[234]
Clec9a	cDC1 receptor for dead-cell antigens (DNGR-1)	Impaired cDC1-mediated CD4$^+$ T-cell regulation → ↑ Systemic IL-10 (atheroprotective)	[146]
Clec4a4	Pro-inflammatory CLR on cDC2s	↓ Aortic sinus plaque/necrotic core ↑ Lipid profile improvement	[235]
CD40	Co-stimulatory molecule for DC-T cell interaction	↓ Disease progression: Impaired DC-mediated T-cell activation → ↓ IFN-γ$^+$ Th1 cells, ↑ IL-10$^+$ Treg, reduced plaque necrosis	[134]
CD11c-DTR	Diphtheria toxin receptor under CD11c promoter	↑ Lesion severity: DT-mediated ablation of CD11c$^+$ cells (DCs + macrophages) → ↑ Plasma cholesterol, ↓ Treg, ↑ Inflammatory cytokines	[98]

Notes: ↑: Increase; ↓: Decrease.

Table 3. Commonly used Cre mouse models for DC research.

Model	Target Cells	Specificity	Application	References
CD11c-Cre	cDCs, pDCs, macrophages	Moderate	DC/macrophage depletion studies Hypercholesterolemia mechanisms Pan-DC functional screening	[236–238]
Zbtb46-Cre	cDC1, cDC2	High	cDC-specific gene ablation T-cell priming in plaques Plaque inflammation regulation	[239]
Clec9a-Cre	cDC1 (Clec9a$^+$)	Very high	Dead-cell antigen cross-presentation IL-10/Treg axis regulation Necrotic core dynamics	[240]
Xcr1-Cre	cDC1 (Xcr1$^+$)	Very high	cDC1 migration tracking CD8$^+$ T-cell activation Batf3-dependent pathway analysis	[241]

Translating insights from mouse models to human diseases requires a precise understanding of DC heterogeneity and spatial positioning in human plaques. Emerging scRNA-seq and spatial transcriptomic datasets from human atherosclerotic arteries are now validating and refining these concepts [242,243]. These studies consistently identify human orthologs of mouse DC subsets and reveal their distinct transcriptional states associated with inflammation, lipid handling, and interferon response. Spatial omics further maps these DCs within the plaque microenvironment, positioning DCs in close proximity to T cells in areas of neovascularization and the shoulder region, thus directly visualizing the "immunological synapse" in situ [244,245]. This interaction network is pivotal for local T cell activation and polarization. Therefore, integrating functional genetics from mouse models with human multi-omics data provides a powerful framework for identifying novel therapeutic targets. Future strategies may aim to selectively inhibit pro-inflammatory DC subsets while leveraging regulatory DC functions to promote immune tolerance in atherosclerosis.

7. Remaining Questions and Future Directions

Although numerous studies have established the crucial role of DCs in atherosclerosis development, a deeper mechanistic understanding of DC heterogeneity and function within atherosclerotic lesions remains essential for designing effective targeted therapies. Key unresolved questions include: spatial distribution, functional duality, and ontogenetic pathways. Specifically, it remains unclear whether all DC subpopulations identified in secondary lymphoid organs reside in the arterial intima or adventitia; DCs' capacity to drive disease progression via inflammation/immune activation, or confer protection through immune tolerance [246]; and the origins of vascular DCs, including recruitment of circulating precursors versus local proliferation, and factors regulating their plaque abundance.

In particular, several critical mechanistic questions highlighted by recent research deserve further investigation: While macrophages are the primary foam cells in atherosclerotic plaques, emerging evidence suggests that DCs also contribute to lipid accumulation and foam cell formation. The extent to which different DC subsets act as foam cell precursors, the specific receptors and metabolic pathways involved in DC lipid handling, and the functional consequences of lipid loading on DC immunogenicity or tolerance remain poorly defined. Second, the crosstalk between DCs and stromal cells within the plaque microenvironment remains poorly understood. Elucidating the bidirectional signals that dictate whether these interactions promote inflammation, fibrosis, or resolution is crucial for understanding plaque stability. Third, although migratory pathways for DC subsets have been delineated in other contexts, their relevance in atherosclerosis is underexplored. Defining the subset-specific routes and chemokine cues that govern DC recruitment to plaques, their navigation within the lesion, and their egress to draining lymph nodes will be vital for developing strategies to modulate local and systemic immune responses.

The complexity of DC roles in atherosclerosis manifests in their ability to mature and accumulate with T/B cells in plaques while simultaneously migrating to lymphoid organs. Resolving DC subset-specific migration patterns and precursor dynamics during atherogenesis is critical for identifying regulators of plaque DC accumulation, balancing their pro-inflammatory and tolerogenic functions, and developing immunotherapeutic strategies.

Furthermore, targeting DC recruitment, maturation, or functional polarization represents a promising frontier for modulating immune-driven vascular remodeling. Success requires balancing DC pro-inflammatory and tolerogenic functions and developing subset-specific interventions.

Acknowledgments

We thank all the members of GRIS in Xinxiang Medical University.

Author Contributions

Conceptualization, T.L. and Y.L.; Methodology, T.L.; Software, T.L.; Validation, L.L.; Investigation, J.Q. and D.L.; Writing—Original Draft Preparation, T.L.; Writing—Review & Editing, L.Z. and Y.L.; Visualization, T.L.; Funding Acquisition, Y.L. and T.L.

Ethics Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were generated or analyzed in support of this review. All data discussed or cited are available from the original publications provided in the reference list.

Funding

This work was supported by National Natural Science Foundation of China (82301972), Science and Technology Department of Henan Province (242102310030) and 111 program (No. D20036).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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