Review
Combining Bibliometric Analysis to Uncover the Detrimental and Protective Roles of Various Dendritic Cell Types in Cardiovascular Arterial Diseases

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Abstract

Immune cell dysregulation is increasingly recognized as a pivotal pathological factor in cardiovascular disease. Over the past decade, a surge of research has focused on the role of immune cells such as dendritic cells (DCs), T cells, macrophages, and neutrophils in cardiovascular diseases, findings that are frequently featured in leading cardiology journals. This review provides a comprehensive synthesis of the roles that DCs play in common and potentially fatal arterial diseases, including hypertension, coronary artery atherosclerosis, acute coronary syndrome, pulmonary arterial hypertension, aortic aneurysm, aortic dissection, and vasculitis. Combining with bibliometric analysis, this review delves into the critical mechanisms by which DCs contribute to these diseases and reveals the shared mechanisms across diverse diseases. This review also offers new advances in clinical treatment strategies involving DCs.

Keywords: dendritic cells; chemokines; renin-angiotensin-aldosterone system; hypertension; acute coronary syndrome

1. Introduction

Hypertension is recognized as a critical factor in the onset of severe cardiovascular diseases, which are among the leading causes of mortality. Acute coronary syndrome (ACS) and aortic dissection are prevalent emergencies encountered in clinical practice. Pulmonary arterial hypertension (PAH), characterized by features of both the cardiovascular and respiratory systems, also has a high mortality rate. Vasculitis represents a group of diseases characterized by inflammation of the blood vessel walls, affecting vessels of various sizes and types, leading to organ damage and multiple systemic dysfunctions, posing a significant threat to patient health. Given these considerations, the exploration of potential therapeutic targets for these diseases is of great significance.

As key players in the immune system, dendritic cells (DCs) play a central role in antigen presentation and the regulation of immune cell activity. During inflammatory responses, DCs are activated by recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs) on their cell surface. Once activated, DCs promote inflammatory responses through three main mechanisms: Firstly, by expressing major histocompatibility complex (MHC) molecules and the costimulatory molecules B7 (CD80 and CD86), DCs activate T cells. The activated T cells can release perforin, express Fas ligand, and recruit and activate specific and non-specific immune cells to eliminate pathogens; Secondly, DCs directly secrete inflammatory mediators, such as interleukins (IL-1, IL-6, IL-12, IL-23) and tumor necrosis factor α (TNF-α), which enhance the inflammatory response, promote the activation and differentiation of T cells, increase vascular permeability, and recruit macrophages and neutrophils to the inflammatory site, further promoting inflammation and potentially leading to tissue damage; Lastly, guided by chemokines, DCs migrate to the lymph nodes, where they continue to activate T cells, including cytotoxic T cells and various helper T cells (e.g., Th1, Th2, Th17), which are crucial for defense against pathogens. Moreover, DCs indirectly assist in the activation and differentiation of B cells, promoting antibody production, through the activation of T cells [1–4]. However, in pathological states, abnormally activated DCs may cause auto-inflammatory conditions by expressing self-antigens, among other pathways.

Within cardiovascular research, the subtypes of DCs frequently discussed include conventional DCs (cDC1 and cDC2), plasmacytoid DCs (pDCs), monocyte-derived DCs (Mo-DCs), and tolerogenic DCs (tDCs). tDCs, in contrast to their pro-inflammatory counterparts, promote a protective effect against acute myocardial infarction in murine models. Their protective role is achieved by suppressing the development of inflammation through various means, such as increasing the number of regulatory T cells (Tregs), elevating IL-10 levels, and enhancing the activity of indoleamine 2,3-dioxygenase (IDO). Collectively, current re-
search demonstrates the critical involvement of DCs in various cardiovascular diseases, positioning them as potential targets for therapeutic strategies.

DCs have gained substantial attention as critical players in the pathophysiology of cardiovascular diseases, marking a new frontier in cardiac research. In 2007, research by Guzik et al. [5] unveiled the irreplaceable role of T cells in the progression of hypertension in a mouse model. Building on Guzik’s work, in 2010, Vinh and colleagues [6] further confirmed that blocking the activation of T cells by DCs could reduce blood pressure. This finding sparked widespread interest in the crucial functions of DCs in other cardiovascular diseases [7]. In recent years, cDCs have been implicated in the pathogenesis of a variety of cardiovascular diseases, including hypertension, heart failure, coronary artery disease, cardiomyopathy, and myocarditis, through extensive animal model research. While scholars have summarized the mechanisms of action of DCs in heart disease, their role in arterial diseases has been less discussed. This study provides a comprehensive review of the involvement and potential mechanisms of DCs in common and severe arterial conditions of the cardiovascular system such as hypertension, coronary artery atherosclerosis, ACS, PAH, aortic dissection, and vasculitis. It also employs bibliometric methodologies to discern the developmental trends in this area of research. The aim of this article is to furnish a valuable reference for cardiovascular disease research and to foster a deeper understanding of disease mechanisms, as well as the exploration of novel therapeutic strategies.

2. Bibliometric Analysis

Bibliometrics, a tool for analyzing and visualizing extensive volumes of scientific literature, provides a comprehensive frame of the developmental dynamics and research hotspots within a given field. CiteSpace and VOSviewer are the two most used software tools for bibliometric analysis. In this study, we employed CiteSpace (version 6.2.R2 Advanced, Chaomei Chen, Drexel University, Philadelphia, PA, USA) and VOSviewer (version 1.6.19, Nees Jan van Eck and Ludo Waltman, Leiden University, Leiden, NL, USA). These tools were instrumental in comprehensively summarizing publication trends, contributions by country and region, leading research institutions, influential research cohorts, prominent journals, and significant keywords in this domain.

Our analysis up to 2024 indicates a consistent upward trajectory in the volume of literature within this field (Fig. 1). Specifically, 8700 authors, 1943 research institutions, and 71 countries and regions have contributed to the authorship of 1651 reviews and research articles. Among these contributors, the United States leads in both the quantity of publications and citation frequency, followed closely by China and Germany. Institutions such as Harvard University, Massachusetts General Hospital, Duke University, and University of Washington stand out for their publication volume and collaborative endeavors. Furthermore, researchers like Kirabo Annet, Harrison David G., Xiao Liang, and Chen Wei are closely aligned with the research directions in this field and rank among the top in terms of the number of publications. The study covers 1651 articles published in 677 journals, with a particular focus on the top 10 journals by publication volume (Table 1). Most of these journals are situated in the first quartile of the Journal Citation Reports (JCR), with 5 out of these being leading journals in the cardiovascular domain, as detailed in the Average JIF Percentile data. The substantial volume of work published in these high-impact journals further corroborates
Table 1. Top 10 journals with the highest number of publications.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Journal</th>
<th>Documents</th>
<th>JIF (2022)</th>
<th>Average JIF percentile</th>
<th>JIF QUARTILE (2022)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Frontiers in Immunology</td>
<td>60</td>
<td>7.3</td>
<td>78.6</td>
<td>Q1</td>
</tr>
<tr>
<td>2</td>
<td>Hypertension</td>
<td>41</td>
<td>8.3</td>
<td>90.4</td>
<td>Q1</td>
</tr>
<tr>
<td>3</td>
<td>Circulation</td>
<td>41</td>
<td>37.8</td>
<td>98.8</td>
<td>Q1</td>
</tr>
<tr>
<td>4</td>
<td>Circulation Research</td>
<td>32</td>
<td>20.1</td>
<td>96.5</td>
<td>Q1</td>
</tr>
<tr>
<td>5</td>
<td>Arteriosclerosis Thrombosis and Vascular Biology</td>
<td>28</td>
<td>8.7</td>
<td>89.4</td>
<td>Q1</td>
</tr>
<tr>
<td>6</td>
<td>Journal of Immunology</td>
<td>26</td>
<td>4.4</td>
<td>52.5</td>
<td>Q2</td>
</tr>
<tr>
<td>7</td>
<td>Plos One</td>
<td>24</td>
<td>3.7</td>
<td>65.1</td>
<td>Q2</td>
</tr>
<tr>
<td>8</td>
<td>Cardiovascular Research</td>
<td>23</td>
<td>10.9</td>
<td>92.0</td>
<td>Q1</td>
</tr>
<tr>
<td>9</td>
<td>Scientific Reports</td>
<td>20</td>
<td>4.6</td>
<td>70.5</td>
<td>Q2</td>
</tr>
<tr>
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<td>International Journal of Molecular Sciences</td>
<td>20</td>
<td>5.6</td>
<td>74.1</td>
<td>Q1</td>
</tr>
</tbody>
</table>

JIF, Journal impact factor.

Fig. 2. Network map of journals using VOSviewer. In VOSviewer, a node’s size represents the quantity of articles, and the node’s color indicates different research areas. The connecting curves between nodes illustrate the interconnections among various journals, where the thickness of a line between any two nodes reflects the strength of their relationship. A node that establishes numerous connections with others demonstrates its greater influence within the network.

the popularity of this research area. To gain a deeper insight into the interconnections between academic journals, we constructed a Network map of journals (Fig. 2). This map not only showcases the interrelations among various journals but also indirectly maps the cross-disciplinary integration through these linkages. For instance, journals in the fields of cardiovascular, immunology, renal, and respiratory systems are the primary submission targets for articles in this research domain. This bibliometric analysis highlights an expanding interest in the symbiotic relationship between immunology and arterial diseases of the cardiovascular system, especially the pivotal role of DCs in this context.

3. Dendritic Cells and Hypertension

3.1 Dendritic Cells and Hypertension: Correlation and Bibliometric Analysis

Hypertension is one of the diseases that pose a significant threat to human health globally. Over the past decade, researchers have increasingly focused on the role of DCs in the development of hypertension. Stimulated by vari-
ous factors such as increased vascular endothelial pressure, elevated sodium levels, and an increase in Angiotensin II (ANG II), DCs in hypertension animal models are activated and release various inflammatory cytokines. They also activate T cells through the interaction of their surface MHC molecules and co-stimulatory molecule B7 with the TCR and CD28 on the surface of T cells. See Fig. 3 for the mechanism diagram. The activated T cells gradually invade the vascular adventitia, perivascular tissue, renal tissue, etc., and directly or indirectly lead to collagen deposition within the vessel and increased vascular resistance through the release of reactive oxygen species (ROS), IL-1, IL-21, interferon (IFN)-γ, and TNF-α, thereby causing arterial remodeling and hardening, ultimately promoting the progression of hypertension [8,9]. As antigen-presenting cells, DCs bridge innate and adaptive immunity, potentially amplifying vascular inflammation. Current research suggests that inhibiting the activity of DCs can reduce blood pressure; the following will detail the main mechanisms involved.

In the field of bibliometric analysis, the utilization of keyword visualization is instrumental in delineating key research directions and their temporal evolution. For example, within the purple cluster of Fig. 4A, research efforts are squarely focused on pertinent themes such as high-sodium intake, inflammatory pathways, salt-sensitive hypertension, and oxidative stress mechanisms. Fig. 4B augments the insights from Fig. 3 by tracking the developmental arc of these keywords. A noteworthy point of discussion within the high-sodium narrative is the role of sodium transport proteins, which emerged as an area of interest in 2017 and attained renewed prominence by 2022, highlighting their nascent significance in this field. By employing keyword mapping as a navigational tool, we have identified pivotal discussion vectors in the investigation of DCs in the context of hypertension, encompassing high-sodium intake, the renin-angiotensin-aldosterone system (RAAS), isolevuglandin (IsoLG)-protein adducts, chemotactic cytokines and their receptors, Toll-like receptors, and the complement receptors.
Fig. 4. Keyword visualization network of DCs and hypertension. (A) Network map of keywords using VOSviewer. Different colors represent distinct clusters, with each cluster representing a specific research theme. Within the same cluster, there are closely related research directions. (B) Keyword Timezone Visualization from 2012 to 2023 Using CiteSpace. Squares represent different keywords; the size of a square indicates the total number of articles related to that keyword; the time displayed below a square denotes when the keyword first appeared within a specific time segment; the colors within a square correspond to different years, and the width of the color indicates the volume of articles published that year. The Keyword Timezone Visualization reveals the time periods when each keyword first emerged and subsequently gained researchers’ attention, reflecting the dynamic trends in the research.
3.2 Heterogeneous Manifestations of Dendritic Cells in Hypertensive Populations and Their Potential Mechanisms

In diverse cohorts of hypertensive individuals, including adults, adolescents, and pregnant women, consistent findings have been reported regarding abnormalities in both the count and activity of DCs. In adult patients with primary hypertension, an elevation in total DC and cDC counts has been observed, accompanied by an increase in Mo-DCs, while pDCs numbers either remain stable or decrease. Among hypertensive adolescents, a decrease in the total DC count is reported, yet an augmented proportion of the cDC subset is evident, culminating in an increased cDC/pDC ratio, a pattern also prevalent in gestational hypertension [10–13]. Although discrepancies in DC counts are noted across different demographic groups with hypertension, an amplified activation state of DCs is broadly noted across the spectrum of the condition.

Animal studies have delved into the mechanistic role of DCs in the development of hypertension. Consistent with bibliometric studies, factors such as sodium, RAAS, and IsoLG-protein adducts have been identified as crucial mechanisms through which DCs influence hypertension. Analyzing these key mechanisms can enhance our comprehension of hypertension and aid in advancing therapeutic approaches.

3.3 Activation of Dendritic Cells in a High-Sodium Environment and Their Role in the Development of Hypertension

High-sodium intake exacerbates the progression of hypertension by influencing DCs. Under hypertremic conditions, sodium ions enter DCs through Amiloride-Sensitive Channels, leading to a series of intracellular events beginning with the activation of the sodium-calcium exchange mechanism, which elevates intracellular calcium levels. This calcium influx activates protein kinase C, subsequently enhancing the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and increasing the production of NADPH-oxidase-dependent superoxides, including isoketals (IsoLGs) [14]. IsoLGs, highly reactive ketoaldehyde compounds produced by superoxides, readily form adducts with proteins. These IsoLG-protein adducts contribute to the pathogenesis of hypertension by upregulating the inflammasome NLRP3 [15], which, upon activation, increases the secretion of pro-inflammatory cytokines and promotes T-cell differentiation, thereby elevating blood pressure. In addition, IsoLG-protein adducts increase the expression of co-stimulatory molecules B7 on the surface of DCs and promote the presentation of these IsoLG-modified antigens via MHC II molecules to T cells [14,16]. The overexpression of B7 and MHC II molecules leads to robust T-cell activation and subsequent hypertension [16,17]. Experimental studies demonstrate that the use of ENaC inhibitors and IsoLG adduct scavengers effectively reduces the expression of NLRP3 and IsoLG-protein adducts in DCs in hypertremic mice and ameliorates salt-induced hypertension [15]. Moreover, aberrantly activated DCs not only heighten sensitivity to the RAAS but also exacerbate fluid retention by affecting renal tubular sodium transport proteins and urinary sodium excretion, ultimately leading to increased blood pressure [18–20].

3.4 Interactions between Dendritic Cells and the Renin-Angiotensin-Aldosterone System in Blood Pressure Regulation

In recent years, the Interactions between DCs and the RAAS have emerged as a focal point of research within the field of hypertension pathology. The expression of RAAS-related genes in DCs was first reported in 2001 [21]. Subsequent studies have revealed that DCs harbor a complete angiotensin-converting enzyme (ACE)-angiotensin II (Ang II)-angiotensin II type 1 receptor (AT1R) axis, as well as an ACE2-angiotensin-(1-7)-Mas axis [22]. Alterations in the quantity of RAAS within or circulating through DCs can lead to functional abnormalities of these cells, thereby facilitating the progression of hypertension.

Ang II can activate DCs through multiple mechanisms. In Ang II-induced hypertension models, the pronounced activation of DCs and their release of inflammatory factors have been identified as critical elements in disease progression [23,24]. Inhibition of DC activity has been proven to effectively reduce blood pressure [6]. Moreover, in vitro experiments have demonstrated that Ang II can significantly enhance the differentiation, phagocytic function, and T-cell activation of human DCs. In contrast, AT2 receptor antagonists also enhance these functions, whereas AT1R antagonists have the opposite effect [25]. The mechanisms by which Ang II acts on DCs are complex. Firstly, Ang II can promote DC activation through the activation of signaling pathways such as ERK1/2, p65/NF-κB, and STAT1 [22,26], and the inhibition of these pathways can markedly attenuate DC activation [27]. Secondly, A20 is a zinc-finger protein and ubiquitin-editing enzyme. Under the influence of Ang II, mice lacking A20 exhibit more severe hypertension, cardiac dysfunction, and hyponatremia [28]. Additionally, Ang II can stimulate DCs to produce an increased amount of IsoLG-protein adducts and significantly upregulate the expression of CD70. IsoLG-protein adducts exacerbate the pathology of hypertension by activating CD8+ T cells [16,24,29]. Overexpression of CD70 on DCs can activate memory T cells, leading to increased blood pressure [30]. Furthermore, mechanical stretching of endothelial cells under hypertensive conditions, via the GAS6 and Axl signaling pathways, promotes the conversion of monocytes to atherogenic DCs (AS DCs), and the proliferation of AS DCs is closely associated with the pathological state of hypertensive patients. The use of Axl inhibitors can effectively reduce AS DC formation and Ang II-induced hypertension [12], suggesting a potential close
relationship between RAAS and the GAS6/Axl signaling pathway. Lastly, studies have found that angiotensin II can directly affect the paraventricular nucleus of the hypothalamus and the peripheral renal sympathetic nervous system, thereby driving the progression of hypertension [31,32]. A significant reduction in activated DCs and T cells, accompanied by a decrease in blood pressure, has been observed following renal sympathetic denervation [31].

Recent studies indicate that aldosterone can also contribute to the elevation of blood pressure by activating DCs. Under the influence of aldosterone, a standard mouse model demonstrated increased blood pressure and myocardial hypertrophy; these phenomena were significantly attenuated in DC-deficient DOG mice [33]. In vitro experiments have further elucidated the mechanism of aldosterone’s action: by binding to mineralocorticoid receptors on the surface of DCs, aldosterone activates the mitogen-activated protein kinase (MAPK) signaling pathway, leading to the secretion of pro-inflammatory cytokines such as IL-6 and TGF-β, while concurrently reducing the expression of PD-L1, an inhibitory ligand for T cell activity. This, in turn, activates T cells, including Th17 cells, which play a pivotal role in the development of hypertension [34]. Additionally, neutrophil gelatinase-associated lipocalin (NGAL), a target of mineralocorticoid receptor (MR), was found to be significantly upregulated in a cohort of 62 patients with primary hypertension and is currently considered to be closely associated with cardiovascular diseases [35]. Aldosterone stimulation significantly increases NGAL expression in DCs, and reducing NGAL levels in DCs and other immune cells can help alleviate myocardial damage induced by aldosterone [36]. However, research into the role of NGAL in regulating hypertension via DCs remains limited.

It is noteworthy that studies have reported an increase in the expression of angiotensin-converting enzyme during the activation of DCs, affecting the presentation of major histocompatibility complex II molecules. Yet, its specific role in hypertension has not been fully explored.

3.5 The Role of IsoLG-Protein Adducts in Dendritic Cell Activation and Blood Pressure Regulation Mechanisms

IsoLG-protein adducts are critical inflammatory mediators in DC activation and blood pressure regulation. These adducts are modulated by sodium and angiotensin II, yet they are also susceptible to alterations induced by factors such as gut microbiome imbalance, magnesium deficiency, and elevated levels of prostaglandin E2 (PGE2). The interplay between dysbiosis of gut microbiota and hypertension is garnering significant interest in cardiovascular research [37]. Studies in hypertensive rat models with high-salt-induced dysbiosis have shown that IsoLG-protein adducts increase within intestinal DCs and other antigen-presenting cells, precipitating a swift T-cell activation and escalating inflammatory responses [38,39]. Beyond sodium’s role, research by Ashley Pitzer Mutchler et al. [40] has linked magnesium deficiency with increased blood pressure and noted a concomitant rise in IsoLG-protein adducts and NLRP3 inflammasome levels within DCs under such conditions. Furthermore, PGE2 is confirmed to activate DCs [41,42], and antagonism of its receptors yields antihypertensive effects [43]. Liang Xiao and colleagues [44] have further elucidated this mechanism, demonstrating that PGE2, by interacting with its EP1 receptor, directly facilitates the formation of IsoLG in DCs and upregulates the expression of surface B7 ligands.

3.6 The Impact of Inflammatory Reflex Modulation on Dendritic Cells (DCs) in Hypertension

The inflammatory reflex is a neuroregulatory mechanism that plays a crucial role in modulating inflammation. The inhibitory effect on inflammation by the inflammatory reflex is mainly accomplished through the parasympathetic nervous system, also known as the vagus nerve. This mechanism involves the peripheral afferent vagus nerve sensing local inflammatory factors (such as IL-1) and transmitting this information to the central nervous system. Subsequently, the central system activates efferent vagus nerve fibers to release glucocorticoids and directly or indirectly release acetylcholine, suppressing the activation of immune cells via the cholinergic anti-inflammatory pathway, thus effectively alleviating inflammation [45–47].

In cardiovascular diseases, the regulatory role of the inflammatory reflex is particularly significant. Activation of the efferent fibers of the vagus nerve through low-intensity focused ultrasound stimulation has been proven to reduce blood pressure in hypertensive rats [48]. In abnormal psychophysiological stress conditions, where there is reduced excitability of the parasympathetic and increased excitability of the sympathetic nervous system, some patients may experience stress-related chronic resting hypertension [49]. Additionally, with aging, there is a decrease in parasympathetic excitability and an increase in sympathetic excitability, leading to a chronic inflammatory state [50]. In such an inflammatory state, endothelial dysfunction occurs, increasing the incidence and progression of diseases such as hypertension, coronary heart disease, and heart failure.

Immune cells, such as dendritic cells (DCs), macrophages, and T cells, all express α7-nicotinic ACh receptors (α7nAChR) [45]. The vagus nerve can inhibit the activation of these immune cells by directly or indirectly releasing substances like acetylcholine, which bind to α7nAChR. In models of sepsis, colitis, and rheumatoid arthritis, agonists of α7nAChR have been shown to reduce the number and activation of dendritic cells, improving the prognosis of these diseases [51–53]. In patients with hypertensive heart disease, postganglionic neurons of the cardiac vagus nerve become hypertrophied and less excitable [54]; and in heart failure patients, the heart often exhibits increased sympathetic excitability and substantial infiltration of DCs. These phenomena suggest...
a potential deficiency in parasympathetic inhibition of DCs in patients with hypertension and hypertensive heart failure. Reduced parasympathetic excitability is also present in pulmonary arterial hypertension and right heart failure due to pulmonary arterial hypertension. Enhancing parasympathetic excitability can improve survival rates, right ventricular function, and pulmonary vascular remodeling in experimental pulmonary arterial hypertension [55]. Overall, the role of dysregulation in the cholinergic anti-inflammatory pathway in cardiovascular diseases such as hypertension, pulmonary arterial hypertension, heart failure, and coronary artery disease warrants further study.

3.7 Chemokines, Toll-Like Receptors, and Complement Receptors: New Roles and Potential Therapeutic Targets in the Pathogenesis of Hypertension

In the current research milieu, the roles of newly identified molecules such as chemokines and their receptors, Toll-like receptors, and complement receptors are garnering increased attention. Studies have demonstrated that alterations in perivascular adipose tissue can accelerate the progression of hypertension. Under the influence of ANG II, a significant increase in DCs numbers within the perivascular adipose tissue of mice has been observed. Concurrently, inhibition of the chemokine RANTES markedly reduces T-cell infiltration into these tissues [56]. Although the direct link between DCs and chemokines was not the primary focus of this article, their pivotal role in diseases associated with adipose tissue, such as coronary artery disease and diabetes, suggests that DCs and chemokines also hold significant functions within perivascular adipose tissue related to hypertension. CCR7 is one of the well-characterized chemokine receptors. Recent research has revealed that CCR7-dependent T lymphocytes and DCs play critical roles in ANG II-induced hypertension [57]. Newly identified chemokine receptors, such as the fractalkine receptor expressed on DCs, have been shown to exert a protective effect against hypertensive nephropathy by regulating DC migration [58]. However, out of the 40 chemokines and 20 receptors identified, only a handful of receptors have been thoroughly investigated in the pathophysiology of hypertension [56,58], indicating that this research domain is poised for increased scientific scrutiny in the future.

Toll-like receptors are highly expressed in DCs and are responsible for the recognition of pathogen-associated molecular patterns or damage-associated molecular patterns, triggering DC activation and subsequent inflammatory responses. Existing studies have shown that inhibition of Toll-like receptors and their signaling adaptors can reduce blood pressure levels in rats [59,60]. Yet, to date, no studies have specifically addressed how the absence of Toll-like receptors and their signaling adaptors on the surface of DCs impacts the development of hypertension. The complement receptor C5aR1 is also highly expressed in DCs and has been suggested to have a potential protective role against cardiac fibrosis and hypertrophy in ANG II-induced hypertension [61]. This discovery offers a new perspective on the role of the complement system in the pathogenesis of hypertension.

4. Dendritic Cells in Coronary Atherosclerosis and Acute Coronary Syndromes

4.1 Dendritic Cells and Coronary Artery Disease: Correlation with Acute Coronary Syndrome and Bibliometric Analysis

Complications arising from coronary artery atherosclerosis, particularly coronary heart disease (CHD), are among the leading causes of global mortality, underscoring the imperative need for novel therapeutic targets. ACS, which includes unstable angina and acute myocardial infarction, is a focal point in the treatment of CHD. DCs play a crucial role in the formation and progression of CHD. This study focuses on the relationship between DCs and ACS. Fig. 5A categorizes the pertinent research into seven major clusters through a keyword co-occurrence map, while Fig. 5B’s keyword timezone visualization reveals the continuous emergence of new terms over the past five years, accentuating the sustained high interest in this domain among scientific investigators. Integrating the analyses of these two graphics, our research meticulously delineates the distribution, activation, and functional aberrations of DCs in CHD patients. Furthermore, we vigorously explore the critical mechanisms by which DCs influence the initiation and progression of ACS. These mechanisms predominantly involve chemokines and their receptors, exosomes, regulatory DCs, Indoleamine-2,3-Dioxygenase, P-selectin, as well as factors related to diabetes and dyslipidemia.

4.2 The Role of Abnormal Dendritic Cell Distribution and Activation in Coronary Heart Disease and Acute Coronary Syndrome

In patients with CHD, peripheral blood DCs exhibit abnormal quantities, distribution, and activation states. Specifically, in patients with ACS, the numbers of total DCs, cDCs, pDCs, and their respective precursor cells (mDCPs, pDCPs) are reduced compared to those in a healthy population. Moreover, the activation levels of the majority of DCs are significantly heightened, as evidenced by increased expression of co-stimulatory molecules CD80 and CD86 [62–67]. Studies have also identified a negative correlation between the proportion of circulating cDC precursors in CHD patients and the severity and extent of coronary artery lesions [64]. Most scholars believe that the decrease in peripheral DC numbers is due to the recruitment of DCs to myocardial infarction sites to participate in the inflammatory response post-infarction.

Evidence suggests that DCs significantly impact the formation and progression of atherosclerotic plaques [68,
In mouse models deficient in apolipoprotein E and low-density lipoprotein receptor, a reduction in DC numbers effectively decreases the volume of atherosclerotic plaques [70,71]. Additionally, extensive infiltration of cDCs has been observed in myocardial infarction areas in mouse models and in post-mortem examinations of patients. Experimental evidence demonstrates that reducing the quantity of cDCs significantly improves cardiac function in mice [72,73]. Concurrently, the type I interferons released by pDCs exacerbate myocardial infarction injury [74].
The main pathological process in CHD involves the accumulation of atherosclerotic plaques within the coronary arteries, leading to insufficient blood supply to the heart and subsequently causing ischemia and necrosis of the myocardial cells. Recent studies have revealed that DCs can accelerate the formation of atherosclerotic plaques through the process of thrombo-inflammation. The core mechanisms of thrombo-inflammation involve the activation of platelets and immune cells, as well as the activation and dysfunction of endothelial cells, which collectively promote the formation of microvascular thrombi and damage organ function [75]. When the endothelial lining is damaged, platelets rapidly cover the injured area. In vitro experiments have shown that platelets express P-selectin on their surface, which binds to P-selectin glycoprotein ligand-1 (PSGL-1) on slowly moving cDCs, recruiting them to the site of injury [76]. Further interactions involve the junctional adhesion molecule-C (JAM-C) on the surface of platelets binding to Mac-1 (CD11b/CD18, a type of β2 integrin) on DCs, thus firmly anchoring the DCs to the platelets [76,77]. Additionally, platelets release various chemokines, such as CCL5, CXCL7, and HMGB1, which attract DCs and monocytes [78]. Platelets not only directly activate DCs to promote atherogenesis but also facilitate the transformation of peripheral blood monocytes into DCs and the transformation of monocytes within the plaque into foam cells [79]. In the injured area, the interactions between recruited monocytes, neutrophils, and platelets are crucial factors in the formation of atherosclerotic plaques. Moreover, monocytes entering the plaque transform into Mo-DCs and become activated by ingesting oxidized lipids; neutrophils release neutrophil extracellular traps (NETs), attracting monocytes to the endothelium of the coronary arteries, thus promoting plaque formation [80]. During these processes, DCs located on the surface of platelets or within the plaques become activated, secreting various pro-inflammatory factors and activating T cells, ultimately exacerbating vascular damage. See Fig. 6 for the mechanism diagram. Notably, pDCs can degrade NETs by secreting DNase [81]. However, in ACS, the number of circulating pDCs is significantly reduced [62]. In summary, under thrombo-inflammatory conditions, inflammation and thrombosis mutually promote each other, contributing to the formation of atherosclerotic plaques and ischemic damage to the coronary arteries, thereby making the suppression of monocytes and DCs inflammatory responses a potentially important research direction for improving the prognosis of CHD.

4.3 Chemokine Signaling in Dendritic Cell Regulation after Myocardial Infarction

In the pathophysiology of ACS, chemokines and their receptors are critically important in modulating the function of DCs. The chemokine receptor CCR7 regulates the migration of DCs following myocardial infarction. After an infarction, a persistent inflammatory response within the pericardial adipose tissue can exacerbate the damage. In this pathological context, B cells within the pericardial fat secrete large quantities of granulocyte-macrophage colony-stimulating factor (GM-CSF), which promotes DC activation and proliferation. Moreover, DCs, with increased CCR7 expression and under the influence of CCL21, migrate to the pericardium, where they persistently activate T cells [82].

CCL17 is implicated in exacerbating myocardial infarction. Studies using CCL17 knockout mouse models have shown that the absence of CCL17 can significantly improve cardiac function post-myocardial infarction. Following an infarction, GM-CSF upregulates the expression of CCL17 in cDCs by activating the NF-κB and STAT5 signaling pathways. CCL17 then binds to the CCR4 receptor and inhibits β-arrestin signaling, which weakens the chemotaxis of Tregs, ultimately exacerbating myocardial injury [83].

Finally, the CXCL12/CXCR4 axis is instrumental in regulating the migration of Tregs from hematopoietic tissues to regions of inflammatory injury. In mice with myocardial infarction, inhibition of CXCR4 has been observed to promote the migration of Tregs from the spleen to the infarcted area, thereby mitigating the extent of the infarction. In this dynamic interplay, DCs are essential facilitators in the activation of Treg cells [84].

4.4 The Role of Extracellular Vesicles in Immune Modulation after Myocardial Infarction

Researchers are increasingly focusing on the protective roles of extracellular vesicles, especially exosomes, in the aftermath of myocardial infarction. Studies have shown that post-myocardial infarction, DCs release a profusion of exosomes rich in CCR7. These exosomes, under the influence of CCR7 and its ligands, accumulate in the spleen of mice and facilitate the production of anti-inflammatory cytokines IL-4 and IL-10 by activating CD4+ T cells, thereby ameliorating post-infarction prognosis [85,86]. Notably, the CD4+ T cells referenced here pertain to Tregs [87].

Furthermore, as indicated in preceding studies, pericardial tissue is implicated in the inflammatory response following myocardial infarction. Intrapericardial injection of exosomes derived from mesenchymal stem cells significantly diminishes the area of myocardial damage caused by infarction. The mechanism underlying this effect involves the phagocytosis of exosomes by MHC-II positive antigen-presenting cells, such as DCs, which then activates the PP2A/p-Akt/Foxo3 signaling pathway within the APCs. This activation induces the formation of Tregs and establishes an immunosuppressive milieu [88].

Lastly, an increasing body of research is focusing on the role of extracellular vesicles, especially the contained circular RNAs (circRNAs) and microRNAs (miRNAs), in modulating the function of DCs after myocardial infarction. These studies highlight the critical role of extracellular vesi-
Fig. 6. The role of DCs in coronary artery atherosclerosis and acute coronary syndromes. In the event of coronary artery lesions, monocyte-derived DCs (Mo-DCs) within plaques are activated by engulfing oxidized low-density lipoprotein (LDL), thus promoting inflammation; platelets at the site of damaged coronary endothelium attract DCs by expressing P-selectin and junctional adhesion molecule-C (JAM-C) and releasing certain chemokines. DCs at the site of myocardial infarction migrate to the pericardial adipose tissue under the influence of chemokine (CCL21) and are proliferated and activated by granulocyte-macrophage colony-stimulating factor (GM-CSF), exacerbating myocardial injury. *Ex vivo* cultured tolerogenic DCs (tDCs) can alleviate myocardial injury by releasing anti-inflammatory factors. SMC, smooth muscle cells; NETs; neutrophil extracellular traps. This figure was created using BioRender.com (https://www.biorender.com/, Science Suite Inc., Toronto, Canada).

4.5 The Protective Roles of Tolerogenic Dendritic Cells and Indoleamine 2,3-Dioxygenase in Acute Coronary Syndrome

Unlike other arterial diseases, the protective roles of tDCs and IDO in ACS have captivated researchers’ attention. tDCs, a subset of immunosuppressive cells, promote immune tolerance in specific tissues or diseases by activating Tregs and releasing anti-inflammatory cytokines. tDCs have demonstrated their therapeutic potential in disease models such as atherosclerosis and asthma [89]. IDO is a pivotal immunoregulatory enzyme that inhibits T cell activation by degrading tryptophan and increasing the production of kynurenine metabolites.
In patients with non-ST-elevation myocardial infarction, there is a marked increase in Mo-DC activity, but a decrease in both the quantity and activity of secreted IDO, as well as a reduction in the systemic proportion of Treg cells [90]. In murine models of myocardial infarction, tDCs induced by myocardial lysates or serum have been utilized. Subcutaneous injection of tDCs near the inguinal lymph nodes in mice resulted in a significant reduction in infarct size and an increase in survival rates, mediated by mechanisms such as an increase in the quantity of Treg cells and IL-10 secretion, as well as enhanced expression levels of IDO mRNA [91]. Furthermore, after myocardial infarction, activated lymphatic endothelial cells, mediated by the chemokine CCL21 and the integrin ICAM-1, can penetrate the infarcted region, thereby augmenting the aggregation of tDCs [92]. In vitro experiments also demonstrated that DCs treated with IL-37 exhibit tolerogenic characteristics.

4.6 The Pathological Role of P-selectin, Diabetes, and Other Factors in Acute Coronary Syndrome

In this field, factors such as P-selectin, lipid metabolism, diabetes, RAAS overexpression, and pathogen infection also receive attention. P-selectin and its ligand PSGL-1 are key cell adhesion molecules that play a crucial role in the trafficking and activation of inflammatory cells within the context of ACS. Elevated P-selectin levels in patients with ACS correlate with increased DC maturation, adhesion, and migration, as demonstrated by in vitro studies. Animal models have provided further insight, demonstrating that the absence of P-selectin or PSGL-1 can lead to reduced DC activation in atherosclerotic plaques, lower DC numbers, and a slowdown in atherosclerosis progression, which in turn enhances plaque stability [93]. These interactions are mediated by MYD88-dependent Toll-like receptor 4 signaling pathways.

Lipoproteins have consistently been a focal point of clinical importance in the management of CHD. Studies reveal that oxidized low-density lipoprotein (ox-LDL) activates Mo-DCs, while high-density lipoprotein (HDL) has an inverse relationship with the activation level of Mo-DCs [65,94]. Low-density lipoprotein (LDL) penetrates atherosclerotic plaques through compromised endothelial barriers and undergoes oxidation to form ox-LDL. This ox-LDL is subsequently internalized by Mo-DCs, predominantly via scavenger receptors such as LOX-1, CD36, and CD205. This internalization activates the NF-κB signaling pathway, culminating in the activation of Mo-DCs. Activated Mo-DCs then release inflammatory cytokines and facilitate T cell activation, amplifying the inflammatory response [95,96]. Moreover, LDL modified by secretory phospholipase A2 group X (sPLA2-X) and heat shock proteins are also engulfed by Mo-DCs, eliciting a similar inflammatory response [95].

Additionally, in cases where unstable angina coexists with diabetes, the total number of DCs within the patient is significantly lower than in individuals with only one of these conditions. Concurrently, these patients’ DCs exhibit a higher activation status [97,98]. In vitro experiments demonstrate that both high concentrations of insulin and glucose can enhance the uptake of ox-LDL by Mo-DCs through the upregulation of scavenger receptors, ultimately activating Mo-DCs [99,100]. Similarly, an overactive RAAS affects DCs in coronary artery disease. Studies suggest that angiotensin-converting enzyme inhibitors can reduce DC activation and their migration from the spleen to peripheral tissues in myocardial infarction mouse models [101,102].

Lastly, the role of pathogen infection in the development of coronary artery disease should not be underestimated. Bacterial DNA has been detected in atherosclerotic plaques, and, for example, chronic infection with Porphyromonas gingivalis in periodontal disease may exacerbate plaque formation and rupture through interaction with DCs and migration to coronary arteries [103].

5. Dendritic Cells and Pulmonary Arterial Hypertension

PAH is another arterial vascular disease with a high mortality rate, and recent studies have shed light on the pivotal role DCs play in the progression of PAH [1,104]. In this section, we summarize the abnormalities of distribution and activation of DCs in PAH, as well as the underlying mechanisms of DC activation. Investigations indicate that while the number of DCs in the peripheral blood of PAH patients may remain stable or decrease, their activity and quantity are significantly elevated in the lungs and right heart [105–108]. This increase likely originates from the migration of DCs from peripheral blood to the lungs guided by chemokines, where they activate T cells, thereby promoting the progression of PAH. Additionally, utilizing the advanced Multi-isotope Imaging Mass Spectrometry-Time of Flight (MIBI-TOF) technology to quantitatively analyze immune cells in the pulmonary arteries of PAH patients, researchers have identified a congregation of Mo-DCs in the subendothelial and adventitial regions of pulmonary arteries. These cells contribute to the progression of PAH by promoting the proliferation of vascular smooth muscle cells and inhibiting the gene expression of endothelial cells [109].

In-depth research has explored the mechanisms of DC activation in PAH. For example, the ubiquitin-binding protein A20, which is encoded by the TNFAIP3 gene, is a key negative regulator in the NF-κB pathway during DCs activation. A research team led by Thomas Koudstaal has demonstrated through TNFAIP3 gene knockout experiments that the activation of the NF-κB pathway in cDCs can lead to the development of PAH in mice, reinforcing the concept that DCs play a crucial role in PAH [104]. His team also found that DCs and CD8+ T cells densely aggregate around the pulmonary vessels of patients with idio-
pathic pulmonary arterial hypertension (IPAH) and participate in the development of cardiac inflammation in PAH mice [1]. While different chemokines and their receptors have been shown to either promote or inhibit the development of PAH [110,111], the mechanisms involving DCs, chemokines, and their receptors in PAH warrant further investigation.

6. Dendritic Cells in Aortic Aneurysms and Aortic Dissection

Similar to other arterial diseases, DCs have been implicated in the initiation and progression of aortic aneurysms in animal models [112–114]. In a mouse model of abdominal aortic aneurysms (AAA), depletion of DCs effectively slowed the development of experimental AAA, further emphasizing the facilitative role of DCs in AAA pathogenesis [115]. The immunosuppressive molecule CTLA-4 can inhibit T cell activation by binding to CD80 and CD86 on the surface of DCs. Overexpression of CTLA-4 on T cells markedly suppresses the activity of DCs in AAA, which significantly reduces the incidence, mortality, and adverse outcomes associated with AAA [116]. Additionally, group-2 innate lymphoid cells (ILC2s) play a protective role in AAA, functioning through mechanisms that include suppression of inflammatory cells like DCs or reduction in the apoptosis of vascular smooth muscle cells [117]. Lastly, extensive neutrophil extracellular traps (NETs) within the aortic aneurysm have been detected in AAA patients and animal models. These NETs recruit and activate pDCs through DNA-CRAMP complexes, leading to the induction of type I interferons and promoting AAA progression [118]. However, some studies have noted that a subset of pDCs within AAA can secrete the immunosuppressive enzyme IDO, which may confer a protective effect against AAA progression, indicating a potential dual nature of DCs in AAA [119].

Current research underscores the pivotal role of inflammation in the development of aortic dissection, particularly highlighted by recent histopathological examinations and single-cell sequencing revealing aggregations of DCs in aortic dissections [120,121]. This suggests that DCs may be potential contributors to the progression of aortic dissection.

7. Dendritic Cells and Vasculitis

Vasculitis is an immune system-mediated disease involving inflammation of the blood vessel walls. It can be triggered by primary or secondary factors within the body, leading to damage to the blood vessels by various inflammatory substances and immune cells. Based on the size of the affected vessels, vasculitis can be categorized into large-vessel vasculitis, medium-vessel vasculitis, small-vessel vasculitis, and various other specific types of vasculitis.

Large vessel vasculitis includes Giant Cell Arteritis (GCA) and Takayasu’s Arteritis (TAK). GCA primarily occurs in individuals over the age of 50, while TAK more commonly affects women aged 20–40. Most scholars currently believe that GCA and TAK have similar pathologies, although there are differences in the proportion of inflammatory cells within the vessel wall [122,123]. Specifically, no significant differences have been found in the role of dendritic cells (DCs) in promoting both diseases. In normal arterial walls, immune cells such as dendritic cells (DCs) and T cells are widely distributed [124]. Dendritic cells are primarily located in the outer membrane of the vascular wall and express high levels of PD-L1 molecules. PD-L1 interacts with PD-1 on the surface of T cells to inhibit their activity, thus maintaining immune balance within the vessel. However, under pathological conditions, DCs are activated by abnormal antigens through Toll-like receptors; these antigens may include certain bacteria and viruses [125–127]. At this time, DCs downregulate PD-L1 and upregulate costimulatory molecules to activate T cells, while also releasing inflammatory cytokines and chemokines to recruit more inflammatory cells to the affected area, and triggering full-layer vascular inflammation through the activation of antibodies and the complement system [123,128]. Therefore, T cells are considered key cells in causing vascular damage, but in recent years, the roles of neutrophils, B lymphocytes, and vascular endothelial cells have also increasingly come under scrutiny. In studies of the Giant Cell Arteritis (GCA) rat model, reducing DCs significantly ameliorated damage to the vascular wall, further proving that DCs are crucial antigen-presenting cells that initiate large vessel inflammation [129].

Medium vessel vasculitis primarily includes Kawasaki Disease (KD) and Polyarteritis Nodosa (PAN). Kawasaki Disease predominantly affects children under 5 years old, presenting as acute vasculitis, with serious complications such as coronary artery narrowing, aneurysms, and myocardial infarction. Researchers have confirmed the presence of numerous activated cDCs in the damaged coronary arteries, particularly in the adventitia, using methods such as RNA sequencing, immunohistochemical, and computer-assisted histomorphometric analyses [130]. The etiology of KD is still unclear but may be associated with factors such as infections and genetic susceptibility. Animal experiments have indicated that cell wall extracts from *Lactobacillus casei* (LCCWE) and the water-soluble fraction from *Candida albicans* (CAWS) can induce coronary artery inflammation in mice, with significant DC and T cell accumulation observed in the coronary vessels [131,132]. However, in mice with suppressed T cell maturation, LCCWE does not trigger coronary artery inflammation. Moreover, CAWS can induce coronary artery inflammation in mice, with significant DC and T cell accumulation observed in the coronary vessels [131,132]. However, in mice with suppressed T cell maturation, LCCWE does not trigger coronary artery inflammation. Moreover, CAWS can induce the activation of the Dectin-2/Syk/JNK/NF-κB signaling pathway in cDCs, leading to increased production of NLRP3 and pro-IL-1β, thus promoting inflammation [132]. In another animal study, inhibiting IL-1 significantly reduced lesions in KD rats [133]. Intravenous immunoglobulin (IVIG)
is one of the main treatments for KD. Post-treatment, the number and activation level of cDCs in the patient’s blood decrease with IVIG treatment [134]. However, the most recent clinical trial results are not consistent with this, possibly due to differences in sample sizes and inclusion criteria [135]. The impact of IVIG on DCs is multifaceted. tDCs and cDC2 internalize the heavy constant region of immunoglobulins (Fc) through Fcγ receptors (R) II and FcγRIII and present processed Fc peptides to Treg, activating Treg and ultimately exerting an anti-inflammatory effect. Simultaneously, tDCs and cDC2 secrete IL-10 to inhibit the activity of other inflammatory cells [136,137]. In addition, under the stimulation of Fc, tDCs highly express the adenosine A2A receptor (A2AR), which inhibits the release of pro-inflammatory cytokines by immune cells when activated by adenosine [138]. Polyarteritis Nodosa, a rare necrotizing vasculitis, has been found to have DCs in the damaged vessels, but the detailed mechanisms still require further exploration.

In small vessel vasculitis, ANCA-associated vasculitis (AAV) is a group of specific necrotizing inflammatory diseases that includes Microscopic Polyangiitis (MPA), Granulomatosis with Polyangiitis (GPA), and Eosinophilic Granulomatosis with Polyangiitis (EGPA). In AAV, Anti-Neutrophil Cytoplasmic Antibodies (ANCAs) targeting myeloperoxidase (MPO) and proteinase 3 (PR3) within the neutrophil cytoplasm play a pivotal role. Patients with AAV exhibit a generalized reduction in circulating dendritic cells (including cDCs and pDCs) during both acute and remission phases, with numbers rebounding during remission [139,140]. Moreover, the pro-inflammatory capabilities of cDCs and pDCs are diminished in the acute phase, evidenced by decreased secretion of interferon-alpha, tumor necrosis factor, IL-12, and IL-23, potentially increasing infection risk [140,141]. Normally, dendritic cells engulf foreign pathogens and present their specific antigens to T cells or B cells, while also releasing inflammatory factors to attract neutrophils to damaged tissues. Studies have highlighted that Neutrophil Extracellular Traps (NETs) released by neutrophils, containing components such as DNA, histones, MPO, and PR3, can neutralize pathogens. Pathologically, MPO and PR3 within NETs can be captured by dendritic cells as antigens and presented to B cells, leading to ANCA production and consequent vascular damage. Researchers have extensively investigated the origins of these abnormal antigens. Polymorphonuclear Leukocytes can release intact NETs through a process known as NETosis, termed NETotic PMNs. When NETotic PMNs are co-cultured with cDCs, the cDCs can detect NET components including DNA, PR3, and MPO. Injection of these co-cultured cDCs into mice can induce an increase in PR3-ANCA and MPO-ANCA levels and the development of AAV-like disease. Similarly, the interaction between DCs and NETotic PMNs has been observed in human vasculitis studies [142,143]. Recent research has discovered that CpG DNA within NETs can be internalized by DCs expressing MPO antigens through the DEC205 receptor and bind to its TLR9 ligand, further activating DCs and exacerbating vascular damage [144]. Additionally, co-cultured cDCs can promote the development of AAV by secreting CCL18 [144].

8. Dendritic Cells: Shared Pathological Mechanisms and New Advances in Clinical Treatment Strategies for Arterial Diseases of the Cardiovascular System

8.1 Shared Pathological Mechanisms

The mechanisms by which DCs operate within various cardiovascular conditions are intricate and numerous. While the extent and depth of attention they receive vary across different diseases, their underlying mechanisms of action share commonalities. The exploration of these mechanisms offers a valuable frame of reference for research across various arterial diseases.

DCs-related studies are particularly rich in the context of hypertension and coronary artery atherosclerosis. In hypertension, research on DCs encompasses a range of topics, including high sodium intake, IsoLGs, the RAAS, chemokines and their receptors, and perivascular adipose tissue. In the field of coronary artery atherosclerosis, the research focus has shifted to chemokines and their receptors, extracellular vesicles, the immunosuppressive enzyme IDO, tDCs, RAAS, and epicardial adipose tissue. It is particularly noteworthy that the interactions between DCs and perivascular as well as epicardial adipose tissues have been published in leading cardiovascular journals yet remain underexplored in other disease contexts. The relationship between DCs and RAAS has been extensively studied in hypertension, less so in atherosclerosis.

Furthermore, the regulatory molecule A20 has drawn significant attention in the studies of hypertension and PAH. Additionally, the role of DCs in relation to chemokines and their receptors has been implicated in a variety of cardiovascular diseases, including hypertension, coronary artery atherosclerosis, PAH, and aortic aneurysms. With over 40 known chemokines and their 20 plus receptors, the potential roles in cardiovascular diseases are spurring researchers to delve deeper.

Finally, in the field of immune modulation, the significance of tDCs and the immunosuppressive enzyme IDO has been especially noted in the context of coronary artery atherosclerosis and aortic aneurysms. Moreover, the relationship between DCs and NETs has been prominently emphasized in studies on aortic aneurysms and vasculitis, while it has been less explored in the context of coronary artery atherosclerosis.

8.2 New Advances in Clinical Treatment Strategies

In the investigation of the link between inflammation and cardiovascular disease, a consensus has formed...
among academic authorities that research should now pivot towards clinical application. This shift has been partly enabled by the successful completion of several large-scale clinical trials that have yielded preliminary results [145, 146]. Against this backdrop, the present article focuses on the potential role of DCs in clinical therapy for cardiovascular disease.

First, a range of widely prescribed medications, such as statins, are primarily known for their cholesterol-lowering effects, but recent studies have unveiled new mechanisms of action. For instance, research has shown that atorvastatin can decelerate the progression of AAA by inhibiting DCs [112]. Similarly, pravastatin and dimethyl fumarate have been found to improve the prognosis of coronary heart disease by suppressing the activation of DCs [147,148]. Cilostazol, an antiplatelet drug used in coronary heart disease, has been demonstrated in vitro to inhibit the activation and antigen-presenting capabilities of pDCs [149].

Furthermore, researchers have utilized nanocarriers to deliver anti-inflammatory drugs that specifically target DCs, a strategy that has proven to slow down the progression of atherosclerosis in mice [4]. Novel vaccines modulating the interaction between DCs and other immune cells have shown significant cardiovascular protective effects in animal models [150]. Lastly, preclinical studies targeting cardiovascular diseases suggest that antagonizing chemokines and their receptors may become an important research direction [146]. Considering these developments, the interactions between DCs and chemokines are expected to become a focal point of interest for researchers.

9. Conclusions

This article reviews the role of DCs in the development of arterial diseases, particularly emphasizing the protective effects of tDCs and the pathological impacts of other types of DCs. It also discusses the shared mechanisms and latest therapeutic strategies involving DCs across various arterial diseases. DCs and the vagus nerve have shown potential anti-inflammatory effects in multiple systemic diseases; however, the specific role of the \(\alpha 7\) nicotinic acetylcholine receptor on the surface of DCs in arterial diseases has not been fully elucidated. Furthermore, the pro-inflammatory actions of DCs, abnormally activated in adipose tissues surrounding blood vessels and the pericardium, have become a focus of research. Their potential impacts on conditions such as pulmonary arterial hypertension and vasculitis also merit deeper investigation. With ongoing research into the anti-inflammatory mechanisms of DCs, their role in arterial diseases is expected to receive more attention. Clinically, the discovery of new drug mechanisms for inhibiting the activation of DCs, as well as the development of nano-carriers specifically targeting DCs and immunological vaccines, highlights the potential of DCs as therapeutic targets for cardiovascular diseases. These advances represent a significant step from scientific research to clinical application.

Abbreviations

DCs, Dendritic Cells; tDCs, tolerogenic DCs; pDCs, plasmacytoid DCs; cDCs, conventional DCs; Tregs, regulatory T cells; ACS, Acute Coronary Syndrome; IDO, Indoleamine 2,3-Dioxygenase; PAH, Pulmonary Arterial Hypertension; AAA, abdominal aortic aneurysms; RAAS, Renin-Angiotensin-Aldosterone System.

Author Contributions

WXL, LL, YF, XLL, QFJ and YJ conceived the study topic and the manuscript design. WXL, LL, and YF contributed to figure preparation and making the table. WXL QFJ and YJ made significant revisions and proofread the manuscript. LL, YF, and XLL contributed to editorial changes. All authors performed the literature search and manuscript writing and made substantial contributions to the interpretation of the literature. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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