

Review

The Role of Th17 Cells in Cardiovascular Diseases: From Pathogenic Mechanisms to Therapeutic Intervention

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Abstract

Cardiovascular diseases (CVDs) are a leading cause of morbidity and mortality worldwide and impose a substantial burden on physical and mental health. In recent years, the relationship between inflammation, immune dysregulation, and CVDs has received extensive attention. T helper 17 (Th17) cells represent a distinct CD4⁺ T-cell subset separate from Th1 and Th2 cells and play a crucial role in the inflammatory mechanisms underlying of CVDs, including atherosclerosis, coronary heart disease, hypertension, cardiomyopathy, and aortic dissection. In this review, we summarize the pathogenic mechanisms of Th17 cells in CVDs, and discuss related therapeutic strategies. By advancing understanding of the pathogenic roles of Th17 cells, we aim to provide insights into potential therapeutic strategies for CVDs.

Keywords: cardiovascular diseases; Th17 cells; Treg cells; ROR γ t; IL-17

1. Background

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide. Although the global, age-standardized mortality rate for CVDs declined by 34.9% between 1990 and 2022, the absolute number of CVD-related deaths has risen significantly [1,2]. Historically, the management of CVDs has focused on risk factors such as dyslipidemia, hypertension, diabetes, and smoking. However, in recent years, the role of immune mechanisms in CVD has attracted increasing attention. While conventional interventions remain effective, residual risks may persist. Inflammation has been identified as a central driver of disease pathogenesis, and multiple studies have demonstrated that targeted anti-inflammatory therapy can reduce the incidence of cardiovascular events. For instance, low-dose colchicine reduces ischemic cardiovascular events in patients with myocardial infarction (MI) by suppressing inflammation [3]. Similarly, colchicine lowered the risk of ischemic stroke and major adverse cardiovascular events (MACE) in patients with coronary heart disease [4]. Canakinumab, an interleukin-1 β inhibitor, reduces cardiovascular event rates by counteracting activation of the innate immune pathway [5]. Collectively, these findings underscore the importance of inflammation as a pivotal process in CVD progression and suggest that its suppression can effectively mitigate cardiovascular risk. The initiation and amplification of inflammatory responses are closely regulated by immune mechanisms. Among the key immune regulators, programmed cell death protein 1 (PD-1), expressed mainly on T cells and B cells, plays a critical

role. PD-1 blockade promotes T-cell and neutrophil infiltration, exacerbating inflammation in atherosclerotic plaques [6]. Monocyte and neutrophil recruitment accelerates the development of atherosclerosis [7].

Innate and adaptive immunity work in concert to maintain physiological homeostasis. Following injury to brain tissue, activation of the innate immune system triggers monocyte-driven responses that contribute to myocardial fibrosis and cardiac dysfunction [8]. In contrast, adaptive immunity exerts a more targeted influence on the onset, progression, and prognosis of diseases. Sustained activation of T cells and B cells underlies the pathogenesis of heart failure after myocardial infarction, leading to chronic inflammation and persistent immune responses [9]. Central to adaptive immune regulation is the control of T cell activity. T cells are activated in both cellular and humoral immunity, with different T cell subsets performing distinct functions [10]. For instance, Th17 cells drive mucosal and joint inflammation [11,12]. Similarly, gut microbial metabolites exacerbate psoriatic inflammation by modulating Th17 cells [13]. Together, these findings highlight the pivotal role of Th17 cells in the pathogenesis of multiple diseases. In the cardiovascular context, Th17 cells contribute to cardiovascular complications in ankylosing spondylitis and promote vascular remodeling and reorganization in primary hypertension [14,15]. Given the significant role of Th17 cells in the cardiovascular system, this review focuses on their involvement in CVDs—from pathogenic mechanisms to therapeutic strategies. We discuss several emerging approaches, including interleukin-17 (IL-17)-targeting mon-



oclonal antibodies, small-molecule inhibitors of the key transcription factor retinoic acid receptor-related orphan receptor γ (ROR γ t) for Th17 differentiation, modulation of the cytokine microenvironment, and indirect regulation of Th17 cells via the gut microbiota-immune axis.

2. Differentiation of Th17 Cells

T cells are broadly categorized into two major subsets: CD4-positive T helper cells (CD4⁺ T cells) and CD8-positive T cells (CD8⁺ T cells). Upon antigen presentation by dendritic cells (DCs), naïve CD4⁺ T cells differentiate into distinct lineages depending on the cytokine milieu. These include Th1, Th2, Th17, and regulatory T (Treg) cells, of which Th1 and Th2 cells represent the classical T helper subsets [16]. The differentiation of Th1 cells is primarily driven by interferon- γ (IFN- γ) and interleukin-12 (IL-12) [17], whereas Th2 cell differentiation is critically dependent on IL-4 and IL-2 [18,19,20]. In addition to these well-established subsets, Th17 cells have gained increasing attention in recent years. Their development is initiated by transforming growth factor- β (TGF- β) and IL-6, directed by the transcription factor ROR γ t, and characterized by the production of effector cytokines such as IL-17 and IL-22. While Th17 cells play an essential role in host defense against fungi, dysregulated expansion of these cells has been implicated in the pathogenesis of numerous inflammatory and autoimmune diseases.

The differentiation of naïve CD4⁺ T cells into pathogenic Th17 cells is primarily initiated by the synergistic action of IL-6 and TGF- β . During Th17 polarization, low concentrations of TGF- β induce expression of the key transcription factor ROR γ t [21], while IL-6 further upregulates ROR γ t via signal transducer and activator of transcription 3 (STAT3) activation, thereby promoting commitment to the Th17 lineage [22]. This process is tightly regulated, and under physiological conditions, the Treg-associated transcription factor Foxp3 inhibits ROR γ t function. However, in the presence of inflammatory cytokines such as IL-6, IL-21, and IL-23, this suppression is relieved, shifting the immune response toward a Th17 phenotype [21]. IL-6, IL-21, and IL-23 activate STAT3 in the development of Th17 cells, leading to expression of ROR γ t, ROR α , IL-17A, and IL-23R [23]. During Th17 expansion, IL-21 forms a positive feedback loop with STAT3 through autocrine signaling, amplifying the differentiation signal [24]. In the stabilization phase, IL-23 promotes phosphorylated STAT3 activation to maintain Th17 stability and pathogenicity [25], a mechanism that is further supported by recent findings [26]. Additionally, IL-1 β acts as a potent inducer of human Th17 differentiation and can drive a mixed Th17/Th1 phenotype that co-expresses ROR γ t and TGF- β [27]. ROR γ t serves as the master transcription factor for Th17 lineage commitment, directly regulating IL-17A and IL-17F expression along with its co-factor ROR α [28]. However, ROR γ t does not act alone. The basic helix-

loop-helix transcription factor BATF and interferon regulatory factor 4 (IRF4) cooperate to optimize the transcriptional landscape of IL-17-related genes [29,30,31]. Recent studies also show that the deacetylase SIRT6 interacts with ROR γ t and deacetylates specific lysine residues. This facilitates ROR γ t recruitment to the IL-17A promoter and enhances its transcription, uncovering a post-translational regulatory layer in Th17 differentiation [32]. Th17 cells can be functionally categorized into two distinct subsets [33]: non-pathogenic Th17 cells induced by TGF- β and IL-6, which exert protective roles [34]; and pathogenic Th17 cells generated in the presence of TGF- β , IL-6, and IL-23, which express high levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-22 and drive autoimmunity and chronic inflammation [35]. The fundamental distinction between the two Th17 cell subsets lies in their dependency on IL-23 [36].

Both Th17 cells and Treg cells are derived from a common TGF- β -mediated signaling pathway. Their differentiation fate is determined by the concentration of TGF- β : low concentrations of TGF- β , in synergy with IL-6 and IL-21, promote Th17 differentiation driven by the transcription factor ROR γ t; whereas high concentrations induce expression of the transcription factor Foxp3, leading to Treg cell differentiation [21,37,38]. Th17 cells produce cytokines such as IL-17, IL-22, and IL-23, which recruit neutrophils and promote inflammation at the site of infection. In contrast, Treg cells produce anti-inflammatory cytokines like IL-10 and TGF- β , which suppress the activity of various immune cells and inhibit immune responses [39]. Therefore, Th17 and Treg cells play opposing roles. Disruption of the Th17/Treg balance is commonly observed in CVDs such as hypertension, atherosclerosis, and MI. Specifically, an increase is observed in Th17 cells and associated factors, alongside a decrease in Treg cell numbers and function [40]. This imbalance promotes a pro-inflammatory response, accelerating vascular injury and plaque instability.

In addition to various positive regulators, Th17 cell differentiation is also subject to multiple negative controls. The master transcription factor for Treg cells, Foxp3, and the Th17 lineage-specifying factor ROR γ t mutually inhibit each other, thereby directing the polarization fate of CD4⁺ T cells [21]. Moreover, the signature cytokines of Th1 and Th2 cells, respectively IFN- γ and IL-4, also suppress Th17 differentiation [41]. While STAT3 serves as a central promoter of classical Th17 development, signal transducer and activator of transcription 5 (STAT5) acts as a potent inhibitor that can silence key Th17-associated genes such as ROR γ t and IL-17 [42]. C-Maf is a critical downstream node of TGF- β signaling that exhibits context-dependent functions. It promotes Th17 differentiation under strong IL-2 signaling, but drives T follicular helper (Tfh) cell development when IL-2 signaling is limited [43].

Th17 cells exert their pathogenic effects by secreting a range of pro-inflammatory cytokines, including

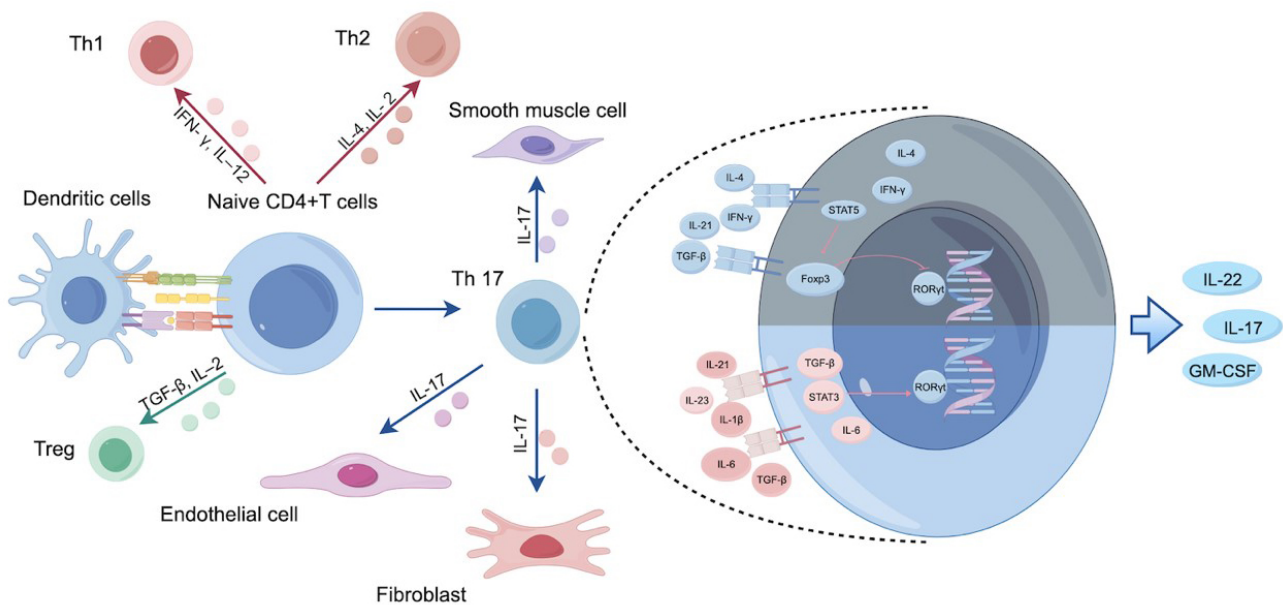


Fig. 1. Differentiation of Th17 Cells. IFN-γ, interferon-γ; IL, interleukin; CD4⁺, CD4-positive T helper cells; TGF-β, transforming growth factor-β; STAT5, signal transducer and activator of transcription 5; RORγt, retinoic acid receptor-related orphan receptor γt; GM-CSF, granulocyte-macrophage colony-stimulating factor. The figure was created by Figdraw (<https://www.figdraw.com/#/>).

IL-17A, IL-17F, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF), the neutrophil chemokines CCL20 and CXCL1, as well as matrix metalloproteinases (MMPs). In endothelial cells, IL-17 can synergize with pro-inflammatory cytokines such as TNF-α to activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and MAPK signaling pathways, and to upregulate the expression of adhesion molecules ICAM-1 and various pro-inflammatory and pro-angiogenic factors (including VEGF, IL-6, IL-8, and GM-CSF). This enhances leukocyte adhesion and transendothelial migration, promotes vascular inflammation, and contributes to the early development of atherosclerosis [44]. Under hyperlipidemic conditions, IL-17A can further promote the recruitment of monocytes and neutrophils to the vascular wall by upregulating the expression of IL-17 receptors in endothelial cells and activating the p38 MAPK signaling pathway, thereby inducing the secretion of chemokines such as CXCL1 and CXCL2 [45]. IL-17A activates downstream MAPK and NF-κB signaling pathways, inducing the synthesis of CXCL1 and CXCL2 in fibroblasts and other cells [46]. Although IL-17A does not directly activate fibroblasts in some cases, it can upregulate the expression of cell surface TGF-β receptors through the JNK signaling pathway, thus enhancing fibroblast sensitivity to TGF-β. This synergizes with TGF-β to promote fibroblast activation and the progression of fibrosis [46]. In vascular smooth muscle cells, IL-17 can stimulate the migration of carotid artery smooth muscle cells in an MMP-9-dependent manner through p38 MAPK- and ERK1/2-dependent activation of NF-κB and AP-1, suggesting a potential role for IL-17 in vascular remodeling and

plaque instability [47]. Furthermore, IL-17A can induce the phosphorylation and nuclear translocation of STAT3 through IL-17 receptor-associated signaling, thereby enhancing the expression of neutrophil chemokines (e.g., CXCL1 and CXCL8) and GM-CSF, which promotes neutrophil recruitment and sustains the inflammatory response [48]. IL-22 contributes to tissue repair and homeostasis, but also promotes the expression of inflammation-associated genes [49]. In addition, GM-CSF enhances the proliferation and activation of granulocytes and macrophages, exacerbating inflammatory infiltration [50]. These effector molecules represent key mechanisms through which Th17 cells mediate their functions. In summary, Th17-related cytokines, particularly IL-17A, participate in the occurrence and progression of atherosclerosis and coronary artery disease by inducing inflammation, remodeling, and fibrosis-related signaling pathways in endothelial cells, fibroblasts, and vascular smooth muscle cells (Fig. 1).

3. Th17 Cells and CVD

3.1 Th17 Cells in Atherosclerosis

Atherosclerosis is a chronic arterial wall disease and inflammatory disorder involving both innate and adaptive immune mechanisms. The plaque interior is not a static accumulation of lipids, but rather an active microenvironment rich in diverse immune cells. Adaptive immunity—particularly T cells—plays a critical role in this process. Numerous studies have established that Th17 cells and their signature cytokines are centrally involved in the initiation, progression, and plaque destabilization of atherosclerosis, with early research confirming the

pathogenic role of these cells. IL-17A exerts broad pro-inflammatory and pro-apoptotic effects on vascular cells, and blocking IL-17A effectively attenuates lesion progression and reduces plaque vulnerability [51] (Table 1, Ref. [51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75]). Subsequent studies further elucidated the upstream regulatory mechanisms, with the IL-1R–MyD88 signaling axis found to be a key pathway promoting Th17 cell differentiation and driving the development of atherosclerosis [76]. Allergic asthma exacerbates atherosclerosis by driving Th2/Th17 immune responses through the IgE/FcεRIα pathway. This not only increases plaque size, but also markedly reduces plaque stability via enhanced macrophage infiltration and reduced collagen content [77].

Th17 cells must be recruited to plaque sites to exert their pathological effects. Recent studies have elucidated specific homing mechanisms involved in this process. It has been reported that C-C motif chemokine ligand 18 (CCL18), produced by plaque macrophages, not only promotes Th17 cell differentiation but also drives their homing to plaques via binding to its receptor C-C chemokine receptor type 6 (CCR6), thereby exacerbating vascular inflammation [52] (Table 1). In a chronic kidney disease model, peritoneal dialysis-primed Th17 cells, which express high levels of C-X3-C motif chemokine receptor 1 (CX3CR1), respond to C-X3-C motif chemokine ligand 1 (CX3CL1) released from plaques and perivascular adipose tissue, leading to targeted infiltration and accelerated atherosclerosis [53] (Table 1). The pathogenicity of Th17 cells stems largely from the disruption of their balance with Treg cells. Studies indicate that atherosclerosis in systemic lupus erythematosus and cerebral infarction patients is influenced by an elevated Th17/Treg ratio [54,55] (Table 1). Molecules such as Cortistatin, vasoactive intestinal peptide (VIP), and IL-27 have been shown to ameliorate atherosclerosis by restraining Th17 activity while expanding the Treg population [78,79,80]. Interestingly, this imbalance has been linked to intestinal immunity. A high-fat diet induces gut microbiota dysbiosis, disrupts intestinal immune homeostasis, skews the Th17/Treg balance toward pro-inflammation, increases the atherosclerotic plaque area, and exacerbates perivascular inflammation [81]. Beyond these mechanisms, Th17 cells also have clinical relevance for guiding the management of atherosclerosis. Th17 profiles are a potential biomarker for subclinical coronary atherosclerosis in people living with HIV [82], thus highlighting their translational value.

In summary, Th17 cells have been demonstrated to actively drive the progression of atherosclerosis, which is a chronic inflammatory disease. Upon activation, Th17 cells exert pro-inflammatory effects and promote plaque destabilization. Consequently, targeting Th17 cells and their related pathways has emerged as a highly promising and novel therapeutic strategy for atherosclerosis.

3.2 Th17 Cells and Coronary Heart Disease

Coronary heart disease (CHD), a leading cause of morbidity and mortality worldwide, is pathologically rooted in atherosclerosis of the coronary arteries. Within this process, CD4⁺ T lymphocytes orchestrate local immune responses through dynamic interactions of their functional subsets. While the pro-atherogenic role of Th1 cells and their balance with Treg cells has been extensively investigated, other pathological mechanisms remain incompletely elucidated. As previously described, emerging evidence has established the contribution of Th17 cells within arterial plaques. Here, we focus specifically on the role of Th17 cells in the context of coronary atherosclerosis.

Numerous studies have established a direct pathogenic role for Th17 cells in CHD. Th17-derived IL-17 induces the production of IL-8, which recruits and activates neutrophils, thereby promoting atherosclerotic inflammation [83]. Furthermore, IL-17 can directly trigger vascular endothelial cell death—a process critical to plaque destabilization and the onset of acute coronary syndromes (ACS) [56] (Table 1). Significantly elevated levels of IL-17A and key Th17-sustaining cytokines (IL-6, IL-23, TGF-β) have been observed in the infarct zone of MI models, indicating their involvement in early inflammatory processes during cardiac remodeling [57] (Table 1). Disruption of the Th17/Treg balance is a key factor contributing to plaque vulnerability and the onset of ACS. Multiple studies have consistently demonstrated that compared to patients with stable angina (SA), those with ACS exhibit a marked Th17/Treg imbalance. This is characterized by elevated levels of Th17 cells, IL-17, IL-6, IL-23, and RORγt, along with reduced levels of Treg cells, IL-10, TGF-β1, and Foxp3 [84]. Th17/Treg imbalance partly stems from the heightened susceptibility of Treg cells to apoptosis via the Fas/FasL pathway, whereas Th17 cells remain relatively resistant, leading to their preferential accumulation. This shift in balance promotes plaque instability and ultimately leads to ACS [58] (Table 1). Furthermore, Fan et al. [85] suggested that activation of the NLRP3 inflammasome may disrupt the Th17/Treg equilibrium, thereby accelerating atherosclerotic progression.

Targeting the Th17 cell pathway has shown promising therapeutic potential. VEGF165 was found to restore the Th17/Treg balance by downregulating RORγt and upregulating Foxp3, thereby promoting cardiac recovery after myocardial infarction [86]. Additionally, IL-5 has been shown to exert protective effects in CHD by suppressing Th1/Th17 differentiation [87]. In terms of biomarkers, CDC42 and Lnc-NEAT1 show a negative correlation with both Th17 cell levels and the Th17/Treg ratio, while the expression of these biomarkers reflects the severity of coronary stenosis and the cholesterol level [88]. Furthermore, serum BDNF levels were inversely correlated with the Th17/Treg ratio and may predict a reduced risk of MACE [89]. A recent study in STEMI patients undergoing percutaneous coronary

Table 1. Th17 cells in cardiovascular diseases: their roles and mechanisms of action.

Disease type	Core mechanism of action	Key evidence/pathway
Atherosclerosis (AS)	<ol style="list-style-type: none"> 1. Drives Plaque Inflammation and Instability: <ul style="list-style-type: none"> - Secretion of IL-17A, inducing MMP-9 production and degrading the fibrous cap. - Recruitment of neutrophils, leading to microabscess formation. 2. Specific Homing: <ul style="list-style-type: none"> Targeted recruitment to plaques via the CCL18/CCR6 and CX3CL1/CX3CR1 axes. 3. Immune Imbalance: <ul style="list-style-type: none"> Increased Th17/Treg ratio, leading to a dominant pro-inflammatory response. 	<ul style="list-style-type: none"> • IL-17A exerts effects on vascular cells [51] • CCL18/CCR6 [52] • CX3CL1/CX3CR1 [53] • Th17/Treg Imbalance [54,55]
Coronary artery disease (CAD) / Acute coronary syndrome (ACS)	<ol style="list-style-type: none"> 1. Exacerbation of Plaque Vulnerability: <ul style="list-style-type: none"> - IL-17 directly induces vascular endothelial cell apoptosis. 2. Dominates Immune Imbalance: <ul style="list-style-type: none"> - Significant Th17/Treg imbalance is observed in ACS patients. 3. Participates in Cardiac Remodeling: <ul style="list-style-type: none"> - Tregs exhibit higher susceptibility to apoptosis, whereas Th17 cells remain relatively resistant. 3. Participates in Cardiac Remodeling: <ul style="list-style-type: none"> - During the early phase of myocardial infarction, the inflammatory cytokine milieu promotes Th17 differentiation and drives inflammatory processes. 	<ul style="list-style-type: none"> • IL-17 induces endothelial apoptosis [56] • Tregs are prone to apoptosis via the Fas/FasL pathway [58] • Levels of IL-6, IL-23, and TGF-β are elevated in the infarct zone [57]
Cardiomyopathy	<ol style="list-style-type: none"> 1. Drives Autoimmune Myocarditis: <ul style="list-style-type: none"> - Cardiac antigens (myosin) directly drive Th17 differentiation through TLR2 signaling. 2. Promotes Chronic Fibrotic Remodeling: <ul style="list-style-type: none"> - IL-17A serves as a key factor in the chronic progression from myocarditis to dilated cardiomyopathy (DCM). 3. Metabolic-Immune Regulation: <ul style="list-style-type: none"> - Metabolic enzymes including PGK1 promote Th17 differentiation by modulating mitochondrial ROS. 	<ul style="list-style-type: none"> • Cardiac myosin drives Th17 differentiation via TLR2 signaling [62] • IL-17A dictates the progression of DCM [61] • The PGK1 inhibitor NG52 alleviates myocarditis [60] • PGRN/JAK-STAT pathway [59]
Hypertension	<ol style="list-style-type: none"> 1. Central to Salt-Sensitive Hypertension: <ul style="list-style-type: none"> - High-salt diet alters gut microbiota, reduces Lactobacillus, and promotes Th17 differentiation. - SGK1-FoxO1 signaling axis serves as a key hub. 2. Causes Endothelial Dysfunction: <ul style="list-style-type: none"> - Th17 cells and their cytokines induce vascular inflammation and oxidative stress, impairing endothelial function. 3. Immune Imbalance: <ul style="list-style-type: none"> - A shift in Th17/Treg balance toward Th17 dominance is commonly observed. 	<ul style="list-style-type: none"> • A high-salt diet reduces Lactobacillus [66] • SGK1-FoxO1 axis [67] • Plcβ1/4-Stat5-NF-κB pathway [65] • Adoptive transfer of Th17 cells accelerates hypertension [64]
Aortic dissection (AD)	<ol style="list-style-type: none"> 1. Destabilizes Aortic Wall Structure: <ul style="list-style-type: none"> - Promotes vascular smooth muscle cell (VSMC) apoptosis. - Mediates extracellular matrix degradation. 2. Drives Acute Inflammation: <ul style="list-style-type: none"> - IL-6/STAT3 forms a positive feedback loop that amplifies inflammation. 3. Prognostic Biomarker: <ul style="list-style-type: none"> - Circulating Th17 cell levels show significant correlation with patient survival. 	<ul style="list-style-type: none"> • Promotes VSMC apoptosis [69] • IL-6/STAT3 positive feedback loop [70] • Th17 levels predict 30-day mortality [68]

Table 1. Continued.

Disease type	Core mechanism of action	Key evidence/pathway
Pulmonary arterial hypertension (PAH)	Promotes Pulmonary Vascular Remodeling: - IL-17A activates lung fibroblasts, driving inflammation and fibrosis. - Th17/Treg imbalance correlates with impaired pulmonary function.	<ul style="list-style-type: none"> • IL-17A activates fibroblasts [72] • The RORγt inhibitor SR1001 exhibits therapeutic efficacy [71] • JAK2-STAT3 pathway [72] • PI3K/AKT/mTOR pathway [73]
Aneurysm	Exacerbates Vascular Wall Destruction and Inflammation: - IL-17A promotes macrophage infiltration and compromises vascular wall integrity. - The IL-3/MDSCs/ICOSL axis positively regulates Th17 differentiation.	<ul style="list-style-type: none"> • IL-17A promotes macrophage infiltration [75] • IL-3/MDSCs/ICOSL [74] • PI3K/AKT • GSK3β pathway [63]

MMP-9, matrix metalloproteinase-9; CCL18, C-C motif chemokine ligand 18; CCR6, C-C chemokine receptor type 6; CX3CL1, C-X3-C motif chemokine ligand 1; CX3CR1, C-X3-C motif chemokine receptor 1; TLR2, Toll-like receptor 2; PGK1, phosphoglycerate kinase 1; ROS, reactive oxygen species; JAK/STAT, Janus kinase/signal transducer and activator of transcription; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K/AKT/mTOR, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; MDSCs, myeloid-derived suppressor cells; ICOSL, inducible T-cell costimulator ligand; GSK3 β , glycogen synthase kinase 3 beta.

intervention (PCI) found that an elevated Th17/Treg ratio was significantly associated with increased anxiety and depression, as well as reduced quality of life, suggesting it has potential as an integrative biomarker for psychosocial and cardiovascular management [90].

Despite substantial evidence, the role of Th17 cells in coronary artery disease (CAD) presents considerable complexity. Some studies have reported no significant increase in the plasma IL-17A level in ACS patients, questioning its reliability as a stable diagnostic biomarker and underscoring the need for more research on its local expression and regulation within tissues [91]. Other work suggests the Th1/Th17 ratio may be an indicator of chronic atherosclerosis progression and lesion complexity, rather than a direct driver of acute plaque rupture [92]. In this review, we have summarized the differentiation of Th17 cells and their role in immune imbalance within the context of CAD. Th17 cells appear to exert stage-dependent effects throughout the disease course. Their levels correlate not only with the degree of vascular stenosis and lipid profiles, but also show predictive value for MACE, thus demonstrating high clinical relevance.

3.3 Th17 Cells and Cardiomyopathy

Cardiomyopathy represents a heterogeneous group of myocardial disorders that can ultimately lead to heart failure and malignant arrhythmias. Although cardiomyopathy has a diverse etiology, immune-mediated chronic inflammation has been recognized as a central driver in its pathogenesis and progression. In this section, we discuss the role of Th17 cells in relation to cardiomyopathy.

Th17 cells, and the immune imbalance they drive, play a central pathogenic role in the progression from myocarditis to cardiomyopathy. They are also critically involved in the pathogenesis of various secondary cardiomyopathies. Studies have shown that programulin (PGRN) exerts a pro-

TECTIVE effect by suppressing Th17 cells via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [59], while the NLRP3 inflammasome forms a positive feedback loop with Th17 cells, jointly exacerbating viral myocarditis [93] (Table 1). Recent research has highlighted the therapeutic potential of targeting upstream pathways of Th17 differentiation. The metabolic enzyme phosphoglycerate kinase 1 (PGK1) promotes Th17 differentiation and suppresses Treg cells by modulating PDHK1 phosphorylation and mitochondrial reactive oxygen species (ROS) balance. Moreover, its inhibitor NG52 effectively alleviated acute myocarditis and prevented its progression to dilated cardiomyopathy (DCM), thus identifying PGK1 as a potential metabolic-immunological therapeutic target [60] (Table 1). The critical role of IL-17A in disease chronicity has been clearly established. In a spontaneous myocarditis model, IL-17A had a limited impact on early inflammation, but was critical for progression to fatal DCM [61] (Table 1). Mechanistic studies have revealed how cardiac-specific antigens drive Th17 differentiation and subsequent cardiomyopathy via innate immune receptors. By analyzing patient samples, Myers et al. [62] (Table 1) found that cardiac myosin can directly promote Th17 cell differentiation via Toll-like receptor 2 (TLR2) signaling, thereby contributing to the development of DCM and heart failure. Using an experimental model, Machino-Ohtsuka et al. [94] showed that the extracellular matrix (ECM) protein Tenascin-C (TN-C)—an endogenous damage signal—activates DCs via TLR4, subsequently promoting Th17 cell differentiation and aggravating autoimmune myocarditis.

Although several early studies suggested a minimal role for Th17 cells in DCM [95,96], subsequent and more detailed mechanistic investigations have provided compelling evidence by demonstrating that the Th17/Treg imbalance is a common immunological hallmark in DCM

and other cardiomyopathies [97]. Bazedoxifene suppresses Th17 cell differentiation and restores Th17/Treg balance by inhibiting STAT3 phosphorylation and the expression of its downstream transcription factor ROR γ t, thereby ameliorating cardiac inflammation and fibrosis in experimental autoimmune myocarditis (EAM) [98]. In a related pathway, inhibition of PCSK9 was shown to reduce Th17 differentiation via the LDLR/STAT-3/ROR- γ t axis, leading to improvement in EAM [63] (Table 1). Furthermore, a non-pharmacological approach using low-intensity pulsed ultrasound was found to reverse Th17/Treg imbalance via the miR-99a-EV pathway, which dual-targets mTOR and TRIB2 in CD4⁺ T cells, offering a potential therapeutic strategy for inflammatory cardiomyopathy [99] (Table 2, Ref. [63,99,100,101,102,103,104,105,106,107,108,109,110,111]). These emerging immunomodulatory strategies—whether pharmacological or physical—converge on a common mechanism: the suppression of Th17 activity and restoration of immune homeostasis to improve cardiac function and attenuate fibrosis, thereby reaffirming the central role of Th17 cells in the pathogenesis of cardiomyopathy.

Beyond the contexts discussed previously, the pathogenic role of Th17 cells extends to a variety of cardiomyopathies through widespread immune dysregulation. In diabetic cardiomyopathy, a severe complication of type 1 diabetes (T1DM), metabolic crises such as ketoacidosis can strongly activate Th17 responses, leading to acute diastolic dysfunction [112]. Similarly, the microinflammatory environment in uremia promotes Th17 differentiation while suppressing Treg cells, collectively driving both atherosclerosis and myocardial injury [113]. Elevated Th17 frequency or functional imbalance has been closely associated with worsening cardiac function in peripartum cardiomyopathy, ischemic cardiomyopathy, septic cardiomyopathy, and Chagas cardiomyopathy [114,115,116,117].

Th17 cells serve as a critical immune nexus linking acute myocardial inflammation to chronic fibrotic remodeling. Targeting Th17 cells and their associated pathways has emerged as a highly promising strategy for preventing the progression from myocarditis to cardiomyopathy, as well as for treating various immune-related myocardial disorders. Th17 cells act as a central hub that connects diverse etiologies to the common final pathway of cardiomyopathy. They drive acute inflammatory responses, promote chronic fibrotic remodeling, and are key accelerators of disease progression toward heart failure. Consequently, immunomodulatory strategies aimed at Th17 cell differentiation represent a compelling therapeutic frontier in the management of cardiomyopathy.

3.4 Th17 Cells and Hypertension

Hypertension represents a major global health challenge. Its traditional pathogenesis involves activation of the

renin-angiotensin system (RAS), sympathetic nervous system excitation, sodium and water retention, and vascular endothelial dysfunction. However, a growing body of evidence indicates that immune inflammation plays a pivotal role in the development and progression of hypertension. Th17 cells and the immune imbalance they orchestrate have been established as a central pathway in the pathogenesis of hypertension, offering novel perspectives for its treatment. Both clinical and experimental studies have confirmed that Th17 cells act as key immune mediators driving hypertensive disease.

Patients with hypertension, particularly those with hypertension-mediated organ damage (HMOD) or resistant hypertension, have significantly elevated levels of peripheral Th17 cells, IL-17, and expression of the related transcription factors ROR γ t and STAT3 [118,119]. Animal studies have provided direct evidence by showing that adoptive transfer of Th17 cells into young, spontaneously hypertensive rats accelerates the progression of hypertension [64] (Table 1). In mice, DCs promote Th17 cell differentiation via the Plc β 1/4–STAT5–NF- κ B pathway, leading to increased blood pressure [65] (Table 1). Notably, certain dietary patterns have also been identified as hypertension risk factors through their influence on Th17 cells [120]. These cells play an especially critical role in salt-sensitive hypertension, a process closely linked to gut microbiota. A high-salt diet reduces intestinal *Lactobacillus* and its anti-inflammatory metabolite indole-3-lactic acid, thereby disrupting immune homeostasis by promoting Th17 differentiation and driving hypertension [66] (Table 1). High fructose intake, via IL-23-mediated activation of the SGK1–FOXO1/3 signaling axis, drives pathogenic Th17 cell activation in salt-sensitive (SS) rats to induce hypertension. This mechanism is absent in salt-resistant (SR) rats [121]. High salt promotes pro-inflammatory Th17 polarization in SS rats, causing hypertension and endothelial dysfunction, whereas it favors anti-inflammatory Treg differentiation in SR rats, conferring protection [122]. The imbalance between Th17 and Treg cells is widely recognized as a central immunological feature of hypertension. Restoration of this balance represents a promising therapeutic strategy. Impaired intestinal barrier function allows microbial products to translocate and systemically activate the immune system, thereby promoting Th17 differentiation and initiating or sustaining hypertension [123]. Using an Ang II-induced hypertension model, Du et al. [67] were the first to demonstrate that activation of the SGK1–FoxO1 axis relieves the suppression of ROR γ t, thus increasing Th17 differentiation and reducing Treg cells, identifying this as an upstream mechanism that drives imbalance (Table 1). Intervention studies further support this approach. Oh et al. [124] reported that Dieckol, a natural polyphenol from brown algae, restores Th17/Treg balance in the aorta and inhibits the downstream IL-17A/NF- κ B/IL-6 inflammatory axis, thereby improving vascular endothelial function and

Table 2. Therapeutic applications of Th17 cells in cardiovascular diseases.

Level of action	Therapeutic strategies	Representative drugs/methods	Core mechanisms and effects
Directly targeting effector phase	Neutralizing Effector Cytokines	IL-17A monoclonal antibody (Secukinumab [100])	Directly blocks IL-17A signaling, alleviating tissue inflammation; however, it may increase infection risk, requiring evaluation of cardiovascular benefits versus risks.
Targeting differentiation and function	Inhibiting Key Transcription Factors	ROR γ t inhibitor (SR1001) [102] (Digoxin) [103]	Suppresses Th17 cell differentiation at the transcriptional level, effectively alleviating atherosclerosis and hypertension in animal models.
	Blocking Upstream Key Cytokines	Common p40 subunit of IL-12/IL-23 (Ustekinumab) [101]	Suppresses expansion and stabilization of pathogenic Th17 cells; however, its efficacy in atherosclerosis remains controversial.
	Modulating Key Signaling Pathways	STAT3 inhibition [63], SGK1 inhibition [108]	Interferes with Th17 differentiation signaling by inhibiting STAT3 phosphorylation or salt-sensing kinase SGK1.
Modulating immune balance	Restoring Th17/Treg Balance	Statins (Atorvastatin) [105], Angiotensin Receptor Blockers (Valsartan) [106]	Drug repurposing: Statins inhibit the STAT3/ROR γ t pathway, while ARBs suppress the NF- κ B/TSLP axis, achieving bidirectional immunomodulation to restore immune balance.
	Enhancing Treg Function	Rapamycin [107]	Indirectly suppresses Th17 responses by enhancing Treg cell function or inhibiting the mTOR pathway.
Intervening in migration and homing	Blocking Chemokine Axes	CCR6 antagonist (PF-07054894) [104]	Prevents recruitment and infiltration of Th17 cells into diseased sites such as vascular walls and cardiac tissue.
Modulating the upstream environment	Targeting the Gut Microbiota-Immune Axis	Yiai Kang Capsule [111]	Systemically suppresses Th17 differentiation by restoring gut microbiota homeostasis and increasing beneficial metabolites like short-chain fatty acids.
	Natural Products and Chinese Herbal Medicine	Acacetin [109], Geniposide [63], Buyang Huanwu Decoction [110]	Multi-target actions often involve concurrent inhibition of STAT3/ROR γ t pathways, metabolic regulation, and antioxidant effects to restore immune homeostasis.
Emerging technologies	Targeted Delivery and Physical Intervention	LIPUS [99]	Enhances drug targeting specificity while reducing systemic side effects; alternatively, employs physical stimulation to locally modulate pathways like mTOR for Th17 suppression.

ARBs, angiotensin receptor blockers; TSLP, thymic stromal lymphopoietin.

reducing blood pressure. Baranwal et al. [125] reported that indolepropionic acid, a gut microbiota metabolite, restores immune balance by suppressing Th17 cells and promoting Treg cells, while also enhancing urinary sodium excretion, ultimately ameliorating salt-sensitive hypertension.

In summary, Th17 cells and their associated immune imbalance represent a significant pathogenic mechanism in hypertension, particularly in salt-sensitive forms. Targeting Th17 differentiation pathways and their microenvironment offers a promising new direction for the immunomodulatory treatment of hypertension.

3.5 Th17 Cells and Aortic Dissection

Aortic dissection (AD) is one of the most critical cardiovascular emergencies, characterized by sudden onset, rapid progression, and high mortality. Recent studies

have revealed that immune-inflammatory responses, particularly those mediated by Th17 cells and their associated cytokines, play a central role in driving the pathogenesis of AD.

Multiple clinical studies have confirmed a close association between the level of Th17 cells and the prognosis of patients with AD. In a study on patients with Stanford type B AD, low Th17 cell levels were significantly correlated with higher survival rates, fewer complications, and more favorable cardiac and aortic remodeling, suggesting that circulating Th17 cells may be an important prognostic biomarker [126]. In Stanford type A AD, the proportion of Th17 cells was significantly correlated with inflammatory and injury markers such as CRP and D-dimer, and was independently predictive of 30-day mortality, highlighting its unique clinical value [68] (Table 1). Th17 cells con-

tribute to the destruction of the aortic wall and drive the initiation and progression of AD through multiple mechanisms [127]. A significant Th17/Treg imbalance (increased Th17, decreased Treg) in AD patients promotes the apoptosis of vascular smooth muscle cells and participates in AD pathogenesis [69]. Moreover, Th17 cells play a key role in the recruitment of inflammatory cells to the aorta. IL-6 is a critical cytokine that mediates recruitment of Th17 cells to the site of aortic injury and promotes Th17 differentiation and activation via the STAT3 signaling pathway, thereby establishing a pro-inflammatory positive-feedback loop [70] (Table 1). Single-cell RNA sequencing has directly validated that Th17 cells enhance inflammatory responses and contribute to ECM degradation in the aortic wall [128]. Under physiological conditions, CDC42 protein suppresses excessive Th17 activation. However, in AD patients, CDC42 levels are inversely correlated with Th17 cell frequency, and low CDC42 expression is an independent predictor of in-hospital mortality [129].

Th17 cells serve not only as a robust biomarker for assessing the prognosis of AD, but also as central immune effector cells that drive AD pathogenesis and progression. The targeting of Th17 cells and their related pathways represents a promising direction for future AD therapeutics.

3.6 Th17 Cells and Peripheral Vascular Disease

Vascular diseases are characterized by three principal types of pathological alteration: loss of vascular wall elasticity, leading to aneurysmal dilation or even rupture and hemorrhage; luminal narrowing due to pathological changes, causing ischemia or necrosis in dependent organs or limbs; and endothelial injury-induced intravascular coagulation and thrombosis, resulting in organ ischemia or distal embolism from detached thrombi [130,131]. Common clinical manifestations include pulmonary arterial hypertension (PAH), aneurysms, peripheral arterial disease (PAD), and aortic coarctation. Accumulating evidence indicates that Th17 cells actively contribute to the initiation and progression of these different types of vascular disorders.

PAH is a life-threatening, obstructive vasculopathy characterized by excessive pulmonary vascular proliferation, luminal obliteration, and vascular remodeling, ultimately leading to fatal right ventricular failure [132]. Growing evidence has established that Th17 cells and the immune-inflammatory responses they orchestrate are key drivers of PAH pathogenesis. Multiple clinical and experimental studies have confirmed the critical involvement of Th17 cells across various forms of PAH. In patients with connective tissue disease-associated PAH (CTD-PAH) and systemic sclerosis (SSc), Th17/Treg imbalance and elevated serum IL-17A levels correlate significantly with impaired pulmonary function and an increased prevalence of PAH, highlighting their value as disease markers and prognostic indicators [133,134]. Therapeutic targeting of Th17

pathways has shown promising results. The ROR γ t inhibitor SR1001, which potently suppresses Th17 differentiation, was found to attenuate the development of chronic hypoxia-induced PAH [71] (Table 1). Further mechanistic studies revealed that Th17-derived IL-17A activates lung fibroblasts, and that donepezil-mediated suppression of Th17 differentiation occurs via the α 7nAChR–JAK2–STAT3 pathway [72] (Table 1). PD-L1 exerts a protective effect in hypoxic PAH by restraining Th17 responses via inhibition of the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway [73] (Table 1), while serotonin limits PAH progression by modulating the Th17/Treg balance [135]. Moreover, ALK4 signaling promotes pathogenic Th17 responses and endothelial–mesenchymal transition in systemic lupus erythematosus-associated PAH [136].

Aneurysms, such as abdominal aortic aneurysm (AAA), represent a lethal vascular disorder characterized by permanent, pathological dilation of the arterial wall, with rupture being the most critical risk. Chronic inflammation plays a central role in driving the development and progression of AAA, with Th17 cells and their key effector cytokine IL-17A identified as critical pro-inflammatory mediators. The number of Th17 cells is significantly increased in patients with AAA, particularly in the mid-segment of the aneurysmal aorta, a response that may be mediated by miR-21-5p [137]. The differentiation of Th17 cells in the aneurysmal milieu is tightly regulated by a complex signaling network. Through the secretion of IL-17A, Th17 cells promote macrophage infiltration into the vascular wall and downregulate E-cadherin, thereby compromising vascular integrity and exacerbating aneurysm rupture [138]. In a study of AAA, Lu et al. [74] reported that IL-3 upregulates the expression of inducible T-cell costimulator ligand (ICOSL) on the surface of myeloid-derived suppressor cells (MDSCs) via suppression of the PI3K/AKT pathway. Elevated ICOSL then interacts with ICOS on Th17 cells, promoting their differentiation and ultimately amplifying vascular inflammation and aneurysm formation [74] (Table 1). Targeting Th17 cell differentiation or function has therefore emerged as a promising therapeutic strategy for AAA. The drug digoxin selectively inhibits ROR γ t, effectively curbing Th17 differentiation and preserving vascular wall structure, thereby reducing the incidence of AAA [75]. Similarly, the natural product geniposide mitigates vascular endothelial injury and suppresses Th17 polarization by modulating glycogen synthase kinase 3 beta (GSK3 β) signaling, offering a potential therapeutic avenue for intracranial aneurysms [139].

Th17 cells represent a central link connecting immune dysregulation to vascular pathological changes. Targeting the differentiation and functional pathways of Th17 cells has emerged as a promising and novel strategy for treating vascular diseases.

4. Pharmacology of Th17 Cells

4.1 Therapeutic Targeting of Th17 Cells in Cardiovascular Diseases

In the preceding sections, we delineated the developmental pathways of Th17 cells, described their characteristic cytokine profiles, and detailed the mechanisms by which they contribute to cardiovascular pathologies. Th17 cells play pivotal roles in driving vascular inflammation, endothelial dysfunction, and plaque destabilization. We will now discuss the diverse therapeutic strategies for targeting Th17 cells and their associated factors in cardiovascular contexts. The first of these strategies is the use of specific antibodies directed against cytokines. Our focus will center on interventions against IL-17, IL-23, and the master transcription factor ROR γ t.

Numerous studies have focused on therapeutic targeting at the cytokine level. Monoclonal antibodies against IL-17, such as secukinumab and ixekizumab, have been shown to alleviate inflammation by blocking IL-17 signaling in autoimmune diseases like psoriasis [140,141]. In the cardiovascular field, animal studies indicate that neutralization of IL-17 reduces inflammatory cell infiltration within atherosclerotic plaques and decreases the lesion size [142]. Knockdown of IL-17R significantly attenuates fibrosis and corrects the Th17/Treg imbalance, thereby ameliorating cardiac function in DCM [143]. Several anti-IL-17 antibodies are already approved for clinical use. Secukinumab, an antibody targeting IL-17, has been shown to improve endothelial function in patients with plaque psoriasis, suggesting potential cardiovascular benefits without promoting pro-atherogenic vascular changes [144]. Nevertheless, research in this area remains immature. Potential risks have been reported for secukinumab, including possible increases in the incidence of hypertension and infections. A meta-analysis associated secukinumab treatment with an elevated risk of hypertension in patients with autoimmune diseases [100] (Table 2). Long-term clinical observations have confirmed that mucocutaneous fungal infection represents a significant adverse event requiring management, and is a key reason for the discontinuation of treatment [145]. Among biologic agents targeting IL-17, secukinumab has been associated with the highest incidence of cardiovascular complications [146]. Therefore, although IL-17 inhibitors show clinical potential, their cardiotoxicity requires careful attention, and further investigation is warranted to establish their safety and efficacy profiles. Beyond anti-IL-17 agents, therapies targeting IL-23 have also been explored. IL-23 promotes the synthesis of cytokines such as IL-17A via the STAT3 signaling pathway. It also directly enhances the migration of activated CD4⁺ T cells to cardiac tissue by activating the RhoA GTPase pathway, thereby driving the progression of experimental autoimmune myocarditis (EAM) [147]. Koschitzky et al. [101] (Table 2) reported that 12 weeks of treatment with ustekinumab, an antibody targeting IL-12 and IL-23,

reduced the levels of inflammation and cardiovascular-risk-associated proteins in psoriasis patients. However, other studies have presented a more nuanced perspective. Research in ApoE^{-/-} mouse models showed that although neutralization of IL-23p19 significantly reduced the expression of pro-inflammatory factors (IL-17A, IL-6, TNF- α) in the aorta, it did not effectively suppress the progression of atherosclerotic plaques. No significant impact of this treatment was observed on plaque area, necrotic core size, or major inflammatory cell infiltration [148]. This suggests that merely blocking the IL-23/Th17 axis to reduce local inflammation may be insufficient to reverse or prevent the pathological process of atherosclerosis. Evidence in this area is still limited, and further research is needed to clarify the therapeutic potential of IL-23 targeting.

Direct inhibition of the master transcription factor ROR γ t is another key therapeutic strategy for modulating Th17 cell activity. The ROR γ t inhibitor SR1001 has been shown to significantly suppress Th17 cell differentiation, thereby attenuating the development of pulmonary hypertension and slowing the progression of atherosclerotic plaques [71,102] (Table 2). This class of agents represents a novel therapeutic modality with dual mechanisms of action, offering new hope for patients who are statin-intolerant or exhibit an inadequate response to conventional lipid-lowering therapy. Beyond such specific ROR γ t inhibitors, Yu et al. [103] (Table 2) recently demonstrated that digoxin reduces circulating IL-17A levels by inhibiting ROR γ t activity, consequently mitigating sympathetic overactivation and elevated blood pressure in angiotensin II-induced hypertensive rats. Interestingly, their work showed the ROR γ t/IL-17 axis is not uniformly detrimental, since ROR γ t-expressing $\gamma\delta$ T cells contribute to tissue repair and attenuate adverse remodeling through the secretion of IL-17A, IL-17F, and IL-23R. Heterozygous deletion of the ROR γ t gene was associated with exacerbated cardiac remodeling and reduced capillary density following MI, indicating that ROR γ t-expressing cells participate in the repair of infarcted myocardium in mice [149].

The STAT3/ROR γ t signaling axis serves as the central pathway governing Th17 cell differentiation. A variety of interventions exert their therapeutic effects by suppressing this pathway. For instance, IFN- γ reduces Th17 differentiation and ameliorates hypertensive remodeling in mice by inhibiting the expression of osteopontin (OPN), thereby downregulating ROR α and ROR γ t [150]. The acetylcholinesterase inhibitor donepezil suppresses Th17 differentiation in mice via the α 7nAChR–JAK2–STAT3 axis, resulting in attenuation of experimental pulmonary fibrosis and pulmonary hypertension [73]. Geniposide, a natural iridoid glycoside, modulates the GSK3 β /STAT3/ROR γ t pathway to inhibit Th17 polarization and reduce vascular endothelial injury in an animal model of intracranial aneurysm [139]. Additionally, inhibition of PCSK9 has been shown to attenuate Th17 cell differentiation through

the LDLR/STAT-3/ROR- γ t cascade, leading to improved outcomes in a mouse model of EAM [63] (Table 2).

Beyond the modulation of Th17 cell differentiation, targeting their migration has also emerged as a promising therapeutic strategy in CVDs. CCR6, a chemokine receptor highly expressed on Th17 cells, interacts with its ligand CCL20 to mediate the recruitment of pathogenic immune cells to inflammatory sites. The specific monoclonal antibody h6H12, which inhibits CCR6 function, has been shown to effectively block the migration of CCR6-expressing cells—including Th17 and $\gamma\delta$ T cells—thereby significantly ameliorating inflammatory diseases such as psoriasis in animal models [151]. Multiple studies support a pro-atherogenic role for CCR6 in CVDs. In Cocksackievirus B3 (CVB3)–induced acute viral myocarditis (AVMC), cardiac fibroblasts stimulated by TNF- α , IL-1 β , and IL-17 secrete high levels of CCL20, which recruits Th17 cells to the myocardium and exacerbates inflammatory injury [152]. However, contrasting findings have also been reported. Recent research indicates that CCR6 may exert a protective role in myocardial ischemia-reperfusion injury, since CCR6 deficiency was associated with increased infarct size following acute MI in mice [153]. A recent study found that the CCR6 antagonist PF-07054894 effectively prevents the homing and infiltration of Th17 cells into the vascular wall and cardiac tissue—presumably due to the high expression of CCR6 on Th17 cells—highlighting the translational potential of this agent [104] (Table 2).

Numerous studies have elucidated the immunomodulatory mechanisms of statins. Pitavastatin ameliorates EAM and reduces Th17 cell differentiation through a dual mechanism involving inhibition of both STAT3/STAT4 phosphorylation and the TGF- β /ROR γ t pathway [154]. The combination of telmisartan and rosuvastatin was shown to improve the Th17/Treg balance in hypertensive patients by modulating the expression of FoxP3 and ROR γ t [155]. Clinical research confirmed that atorvastatin rapidly restores the Th17/Treg immune imbalance in patients with non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) following PCI [156]. Amlodipine combined with atorvastatin can effectively reverse Th17/Treg imbalance by downregulating ROR γ t and upregulating Foxp3, thereby improving vascular endothelial function in patients with hypertension complicated by atherosclerosis [105] (Table 2). Collectively, these findings indicate that statins are not merely lipid-lowering agents, but also function as immunomodulators with the potential to restore immune homeostasis in CVDs.

Beyond conventional immunomodulators, a growing body of evidence highlights the close relationship between angiotensin inhibitors and Th17 cell regulation. Electrophoretic mobility shift assay (EMSA) was used to provide direct evidence that angiotensin II (Ang II) binds to the AT1 receptor on vascular smooth muscle cells (VSMCs) and activates NF- κ B, stimulating the production of thymic

stromal lymphopoietin (TSLP). This in turn promotes the maturation of DCs, ultimately driving Th17 cell differentiation and vascular inflammation, thereby accelerating the progression of atherosclerosis and hypertension in a rat model. The AT1 receptor antagonist valsartan has been shown to effectively counteract this pathological cascade, identifying it as a potential therapeutic target for these conditions [106] (Table 2). Furthermore, angiotensin receptor blockers (ARBs) significantly suppress Th17 cell hyperactivity in patients with type 2 diabetes complicated by carotid atherosclerosis [157].

Beyond direct Th17 modulation, extensive research has revealed that multi-faceted regulation of the Th17/Treg balance confers significant cardioprotective effects. The targeting of key signaling molecules represents a core strategy. For instance, HMGB1 blockade and the cytokine IL-38 have been shown to suppress Th17 proliferation and ameliorate cardiovascular pathology [158,159]. By inhibiting mTORC1, rapamycin can effectively curb the aberrant differentiation of Th1 and Th17 cells and improve vasculitis in patients with Takayasu arteritis. RNA interference-mediated suppression of mTORC1 was sufficient to reduce Th17 frequency and limit disease progression *in vivo* [107] (Table 2). Furthermore, dietary and pharmacological interventions can also exert an immunomodulatory influence. High salt intake activates the salt-sensing kinase SGK1 in T cells and upregulates the NKCC cotransporter on Th17 cells, promoting the activation of these cells and contributing to hypertension. This effect can be partially reversed by SGK1 knockout [108] (Table 2). Repurposed drugs also demonstrate immunomodulatory potential. For example, aspirin modulates the gut microbiota and improves the Th17/Treg balance to attenuate atherosclerosis in mice [160]. Metformin suppresses Th1/Th17 responses while promoting Treg generation, alleviating autoimmune inflammation in mice [161]. Finally, clinical studies have shown that nebivolol, a β_2 -adrenergic partial agonist, inhibits Th17 differentiation in an NF- κ B-dependent manner [162]. Innovative approaches are also emerging. Low-intensity pulsed ultrasound (LIPUS) has been used to deliver miR-99a and inhibit mTOR and Th17 differentiation, effectively mitigating inflammatory DCM in mice [99]. Clinical research has developed a silicon-calcium microneedle-based SiO₃²⁻ delivery system that can effectively suppress Th17 cells and alleviate myocardial pathology by regulating the FOXO signaling pathway [163].

Interestingly, Huang et al. [164] reported that interleukin-12p35 deficiency exacerbates the Th17/Treg imbalance, yet paradoxically attenuates atherosclerosis in ApoE^{-/-} mice. In contrast, Zhang et al. [165] found that deletion of interleukin-12p40 suppresses Th17 differentiation and IL-17A production, thereby inhibiting the TRAF6/MAPK/p53 pathway and alleviating doxorubicin-induced ferroptosis in a mouse model of chronic cardiomyopathy. Collectively, these findings suggest that distinct

subunits of IL-12 exert divergent effects on Th17 cell biology, highlighting the existence of a complex and nuanced regulatory network that warrants further investigation.

Therapeutic strategies targeting Th17 cells operate at multiple levels, including direct neutralization of their effector cytokines, inhibition of key transcription factors and signaling pathways governing their differentiation, regulation of their migration and homing, as well as repurposing existing drugs and developing novel technologies to restore immune balance. Although some of these approaches remain investigational and are challenged by biological complexity, it is clear that targeting of Th17 cells opens promising new avenues for the immunomodulatory treatment of CVDs. However, clinical studies in this area are still relatively limited, and further research is needed.

4.2 Chinese Herbal Medicine in Cardiovascular Therapeutics: Targeting Th17-Cell-Mediated Pathways

In recent years, botanical therapeutics have attracted increasing attention. As a vital component of traditional medicine, Chinese herbal medicine has demonstrated significant potential in modern pharmacological research. This review systematically summarizes how small bioactive molecules derived from Chinese herbs can regulate Th17 cell differentiation and Th17/Treg balance, highlighting their considerable promise for immune intervention in CVDs. The findings provide a theoretical foundation and novel research directions for the treatment of Th17-driven pathologies.

Numerous studies have elucidated the direct mechanisms of natural small molecules at the metabolic and signaling levels. Acacetin is a naturally occurring flavonoid compound that binds to and inhibits mitochondrial complex II. By reducing T-cell energy metabolism and ROS levels, acacetin directly suppresses Th17 cell differentiation, thereby alleviating cardiac inflammation, fibrosis, and functional impairment in mouse models of EAM as well as *in vitro* systems [109] (Table 2). Tanshinone IIA has been shown to attenuate myocardial ischemia/reperfusion injury in rats by modulating activation of the NLRP3 inflammasome and Th17 cell differentiation [166]. Several classic herbal formulations confer cardiovascular protection through systemic regulation of Th17/Treg balance and inflammatory networks. Buyang Huanwu Decoction (BYHWD) suppresses inflammatory responses and slows plaque progression *in vitro* by reducing interleukin-17A and other pro-inflammatory cytokines [110]. Banxia Baizhu Tianma Decoction (BBTD) upregulates alpha-linolenic acid metabolism, inhibits NF- κ B and other inflammatory pathways, reduces Th17 differentiation, and decreases inflammation of perivascular adipose tissue (PVAT), thereby improving vascular function and enhancing aortic plaque stability to alleviate atherosclerosis in mice [167]. Qishen Yiqi Pills (QYP) mitigate atherosclerosis in mice by pro-

moting Treg cells, suppressing Th17 cells, and accelerating the excretion of cholesterol [168]. Angong Niu Huang Pill (ANP), a renowned traditional medicine used for millennia in treating central nervous and cardiovascular diseases, downregulates IL-6 mRNA and upregulates TGF- β 1 mRNA in the spleen and aorta. This modulates the Th17/Treg balance to effectively delay the progression of early atherosclerosis in mice, highlighting its potential as a multi-target anti-inflammatory agent [169]. Bu-Shen-He-Mai Granules (BSHM) ameliorate hypertensive renal injury through immunomodulation of the Th17/Treg balance [170]. Together, these studies indicate that inhibition of Th17 differentiation and reduction of IL-17 levels confer cardioprotective effects. Beyond CVDs, immunomodulation also extends to cardiovascular risk associated with chronic infection. The traditional Chinese medicine compound Yiaikang Capsules confer cardiovascular benefits in the SIVmac239-infected rhesus macaque AIDS model and in HIV/AIDS patients by regulating Th17/Treg imbalance. Specifically, this compound increases the proportion of Th17 cells and the level of ROR γ t mRNA expression, while reducing Treg cells and Foxp3 mRNA expression [111] (Table 2). From natural small molecules to complex formulations, Chinese herbal medicines demonstrate unique, multi-target, and holistic regulatory advantages in CVD prevention and treatment by targeting Th17 cell differentiation and immune balance. This provides a robust scientific basis for developing novel immunomodulatory strategies against CVDs.

Chinese herbal medicine has also demonstrated therapeutic potential in multiple disorders beyond CVDs by targeting Th17 cells and related immune pathways. Sanhuang Xiaoyan Formula significantly accelerates the healing of diabetic ulcers by selectively inhibiting Th17 cell differentiation, reducing IL-17A and other pro-inflammatory factors, and simultaneously promoting collagen deposition and angiogenesis. This effect is mediated through the suppression of STAT3 activation and downregulation of NF- κ B and p38 MAPK protein levels, without impairing Treg or Th1 cell function, reflecting its precise immunomodulatory properties [171]. In a non-obese diabetic (NOD) model, Zhang et al. [172] utilized metabolomics to demonstrate that Maidong Dishao Decoction modulates the gut microbiota, increases intestinal short-chain fatty acids (particularly butyrate), restores systemic and splenic Th17/Treg balance, alleviates submandibular gland inflammatory injury, and ameliorates the symptoms of Sjögren's syndrome. In a mouse model of type 1 diabetes, ursolic acid was shown to rebalance the Th17/Treg axis by downregulating ROR γ t and upregulating Foxp3 expression, leading to lower serum levels of IL-17A and TNF- α , elevated IL-10 levels, attenuated pancreatic inflammation and β -cell damage, and improved glycemic control [173]. Collectively, these studies demonstrate that Th17 cells are a key target of Chinese herbal medicine, highlighting the broad therapeutic value

of Th17-focused immunomodulation across a spectrum of immune-related diseases.

5. Discussion

The role of Th17 cells in lipid metabolism has attracted growing research interest in recent years. Nicholas et al. [174] proposed that disordered lipid metabolism driven by the accumulation of long-chain fatty acid metabolites activates the inflammatory response of Th17 cells. In contrast, aerobic exercise was shown to suppress Th17 cell differentiation by downregulating the p-STAT3/ROR γ t signaling pathway and reducing IL-17A levels, thereby improving vascular endothelial diastolic function and alleviating cardiovascular complications in diabetic mice [175]. This suggests that Th17 cells may be at the intersection of metabolic disease and cardiovascular pathology, underscoring their significant potential as a therapeutic target. Furthermore, Shang et al. [176] reported that specific antibodies targeting cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), while providing long-term benefits in cancer immunotherapy, may also induce severe adverse cardiac effects. Treatment with anti-CTLA-4 antibody was found to promote pressure overload-induced heart failure by activating Th17 cells. These findings indicate that Th17 cells can be activated by diverse stimuli, highlighting the need to anticipate and manage drug-related adverse effects, even while pursuing therapeutic benefits.

As discussed above, Th17 cells are widely regarded as pro-inflammatory mediators in various diseases. However, it is noteworthy that while Th17 cells typically have a detrimental, pro-inflammatory role in chronic cardiovascular conditions, they undergo a form of immune paralysis during acute systemic infections such as sepsis. Suppression of their protective host defense functions—although potentially a compensatory mechanism to limit inflammatory damage—markedly increases susceptibility to secondary infections by opportunistic pathogens such as *Candida* species [177]. This phenomenon underscores the dual nature of Th17 cells in pathophysiology and highlights the need to carefully evaluate the complex immune status when managing critically ill cardiovascular patients with concurrent infections. Th17 cells are generally pathogenic in chronic CVD, and their overactivation drives inflammation and disease progression. In contrast, during acute systemic inflammation (e.g., endotoxemia/sepsis), Th17 function is rapidly suppressed, which may lead to immunodeficiency and elevate the risk of secondary infections [178]. Therefore, in complex microenvironments, Th17 cells can enter a paralyzed state, highlighting that indiscriminate anti-inflammatory strategies could be detrimental to the host. The role of Th17 cells in plaque formation and progression remains an area of ongoing debate. Numerous studies have posited IL-17 as a pro-inflammatory cytokine that promotes atherosclerotic plaque development. For example, IL-17A stimulates macrophages to produce

matrix metalloproteinase-9 (MMP-9), which is associated with vulnerable plaques [179]. However, other evidence suggests a more nuanced view. Mice treated with IL-17A antibody showed a shift in T-cell polarization toward a Th2 response, accompanied by reduced Th1 cytokine expression, partly explaining the attenuation of atherosclerosis in these models [51]. Consistent with this, Wu et al. [180] demonstrated that a high-fat diet promotes the production of thymic stromal lymphopoietin (TSLP) by vascular smooth muscle cells. After binding to TSLPR on hematopoietic cells, TSLP drives CD4⁺ T cell differentiation toward pro-inflammatory Th17 cells while suppressing anti-inflammatory Tregs. This leads to a Th17/Treg imbalance that exacerbates vascular inflammation and plaque progression, thereby accelerating atherosclerosis. Th17-derived IL-17A can induce the expression of metalloproteinases, which then degrade collagen in the fibrous cap, contributing to plaque vulnerability and instability [180].

A growing body of evidence suggests that Th17 cells and IL-17 do not exert pro-inflammatory effects in a uniform manner. Soraya Taleb et al. [181] reported that IL-17 can reduce the expression of vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, and administration of IL-17 significantly reduced the size of atherosclerotic lesions in mice. Analysis of human carotid plaques revealed that higher levels of IL-17 and phosphorylated STAT3 (p-STAT3) were associated with a more stable plaque phenotype. Enhancing IL-17A production, particularly under conditions of reduced Th1 bias, was shown to significantly slow disease progression. Conversely, in Th1-biased ApoE^{-/-} C57BL/6 mice with inherently low IL-17A production, inhibiting IL-17A signaling did not alter lesion development [182]. Furthermore, Gisterå et al. [183] reported that under certain conditions, IL-17 may enhance plaque stability by promoting collagen synthesis and strengthening the fibrous cap. Lee et al. [184] highlighted the context-dependent function of Th17 cells, showing that IL-17A-dependent regulation of the tight junction protein occludin helps to limit excessive vascular permeability and maintain integrity of the endothelial barrier. Other studies indicate the Mincle-Syk axis in DCs senses mucosal-resident bacteria, induces IL-6 and IL-23 p19 production, and subsequently stimulates intestinal Th17 cells to produce IL-17, thereby reinforcing gut barrier immunity [185]. Currently, research in this area is still quite limited, warranting further exploration. Future studies should comprehensively evaluate the dual roles of Th17/IL-17, and carefully weigh the beneficial versus detrimental effects of their modulation in a context-specific manner.

It is also worth noting that Th17 cells are not the sole source of IL-17. $\gamma\delta$ T cells, which exhibit features of both innate and adaptive immunity, have been identified as major IL-17-producing cells in vascular lesions. Upon IL-23 stimulation, IL-23R⁺ $\gamma\delta$ T cells were found to produce IL-17 and GM-CSF, thereby promoting plaque progression

and necrotic core formation [186]. We hypothesize that $\gamma\delta$ T cells—being innate-like lymphocytes—could begin IL-17 production within hours, whereas conventional Th17 cells are activated over several days. These responses are not mutually exclusive; rather, they may engage in positive feedback regulation, collectively driving vascular inflammation. The predictive value of Th17 cells in CVDs is also becoming increasingly recognized. The percentage of Th17 cells serves as an independent predictor of left ventricular diastolic function (LVDF) and shows significant correlation with fibrosis markers. Patients with lower Th17 differentiation levels tend to have better clinical outcomes, suggesting that Th17 cell activity may be a potential inflammatory biomarker for prognostic assessment in hypertension [15]. Additionally, the Treg/Th17 ratio and MIP-3 α /CCL20 level have been proposed as novel biomarkers for evaluating cardiovascular risk in patients undergoing maintenance hemodialysis (MHD) [187]. In people living with HIV-1 and receiving antiretroviral therapy, alterations in Th17 cells and non-classical monocytes have been associated with subclinical coronary atherosclerosis [82]. Together, these findings highlight the clinical relevance of Th17 cells as predictive indicators, suggesting a potential role in guiding future risk stratification and therapeutic strategies. Further research in this direction is highly anticipated.

6. Limitations and Future Perspectives

Substantial gaps remain in our understanding of the intercellular communication and regulatory mechanisms governing Th17 cells. The specific factors that influence Th17 cell behavior within complex pathophysiological milieus require further systematic investigation. Given their established significance in the initiation and progression of CVDs, the elucidation of these mechanisms has considerable clinical importance. A major limitation lies in the heavy reliance on rodent models. Due to interspecies differences, findings from these studies cannot be directly extrapolated to humans. For instance, Jiang et al. [188] revealed that the heterogeneity of Th17 cells in human pathological states far exceeds that observed in mice. Human pathogenic Th17 cells may possess unique surface markers, such as IL-17RE, that are not present in standard mouse models. Furthermore, while murine Th17 differentiation classically depends on TGF- β and IL-6, their human counterparts appear to rely more on IL-1 β and IL-23 for differentiation and pathogenicity [188]. Future research would therefore benefit from more optimized assays and experiments using human-derived cells. From a therapeutic perspective, the long-term use of targeted monoclonal antibodies against Th17-related cytokines increases the risk of infections. For patients with pre-existing immune dysregulation, such biologics or small-molecule inhibitors may introduce unintended side effects, underscoring the need for thorough safety evaluations of prolonged treatments. A significant

future challenge is the development of delivery systems that can precisely target diseased vascular segments or local immune responses. The emerging field of nanomedicine holds promise for enabling such targeted drug delivery. In summary, Th17 cells are a key orchestrator of immune balance and play a pivotal role in cardiovascular pathology. Further research into the precise mechanisms of action of these cells should enhance our understanding of CVDs, as well as provide critical insights for the development of more precise and safer therapeutic strategies.

7. Conclusion

Epidemiological data clearly show that CVDs are a severe threat to human health and quality of life. Inflammation plays a key role in driving the initiation and progression of CVDs, with the disruption of immune homeostasis serving as a cornerstone of this inflammatory process. Among the various immune players, Th17 cells have emerged as critical contributors to the pathogenesis of various cardiovascular conditions. As a distinct subset of T helper cells, Th17 cells have been extensively implicated in the development of multiple CVDs. They exert a strong influence on immune balance, and their regulatory mechanisms within the cardiovascular system are notably complex. The differentiation of Th17 cells is altered to varying degrees in atherosclerosis, coronary artery disease, cardiomyopathy, hypertension, and aortic dissection. Importantly, therapeutic interventions targeting the initiators of Th17 differentiation, their migration, or their effector cytokines have underscored the central role of Th17 cells in CVD treatment strategies. Furthermore, the therapeutic actions of Chinese herbal medicines in CVDs are closely linked to the modulation of Th17 cells, highlighting their considerable potential for clinical application in this field. Consequently, we anticipate further pharmacological research in this area, with the aim of improving both the prognosis and quality of life for patients with CVDs.

Author Contributions

YS: Conceptualization, Writing—originaldraft, Writing—review & editing. CL: The conception and structural design. JJ: Writing—originaldraft. YL: Literature retrieval and data interpretation. SL: Literature analysis and created tables. LN: Conceptualization, Drafting sections of the manuscript and critical revision. JY: Conceptualization, Writing—review & editing. All authors contributed to editorial changes in the manuscript. 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

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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