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Review

The Importance of Th17 Lymphocytes in the Pathogenesis of Atherosclerosis

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Abstract

Atherosclerosis is currently recognized as a chronic inflammatory disease of large arteries. In recent years, studies of the cellular and molecular biology of atherosclerosis have confirmed that its occurrence and development are associated with inflammation and autoimmunity. Various immune cells, cytokines, and transcription factors are involved in this process. Current studies have shown that T-helper 17 (Th17) cells and their cytokines play an important role in the development of atherosclerosis and the rupture of vulnerable plaques. This review presents current data on Th17 lymphocytes, their functions in the pathogenesis of atherosclerosis, and their use as therapeutic targets. This review provides comprehensive coverage of the functions and molecular pathways that Th17 exerts during atherosclerosis and provides potential strategies for the treatment of atherosclerosis targeting the Th17 axis.

Keywords: atherosclerosis; T-lymphocytes; interleukin-17; interleukin-22; interleukin-23; endothelial dysfunction; inflammation; helper-inducer

1. Introduction

About half of all fatalities in Western culture are caused by atherosclerosis, a chronic inflammatory disease of the arteries. It is thought to be the main cause of atherosclerotic cardiovascular disease (ASCVD), which can lead to peripheral artery disease, heart attacks, and strokes. It is essentially a lipid-mediated inflammatory reaction that is started by the buildup of low-density lipoproteins and residual lipoprotein droplets. It also involves an active process in focal parts of the arteries, especially in areas of decreased non-laminar flow near arterial branching sites [1].

Numerous variables, including genetic and environmental influences, are known to contribute to atherosclerosis. Male gender, age (male over 45, female over 55), cigarette smoking, diabetes mellitus, high blood pressure, high cholesterol, and a positive family history are the most prevalent risk factors. Furthermore, the risk is increased by sedentary lifestyles, obesity, diets heavy in trans and saturated fats, and certain genetic variations [2]. Preventing clinical outcomes by addressing incidence and reestablishing arterial blood flow using minimally invasive or surgical treatments is the gold standard of therapy for atherosclerosis. However, there is still a significant worldwide burden of cardiovascular disease (CVD), and the therapeutic efficacy of these methods on cardiovascular outcomes has plateaued [3].

Immune cells are crucial to the inflammatory process of atherosclerosis, a chronic inflammatory disease of the artery wall that affects the course and outcome of the illness. T cell infiltration occurs at every stage of atherosclerosis, and the immunoinflammatory reaction is brought on by the stimulation of both innate and adaptive immunity. Antigens stimulate $CD4^+$ T cells, which then develop into regulatory T cells (Tregs), Th-2, Th17, and helper T1 (Th-1) [4].

Th17 cells primarily generate the cytokine interleukin-17 (IL-17). Cytokines like IL-17A, IL-17F, IL-21, and IL-22 are also produced by it. Atherosclerosis progression can be controlled by the different cytokines secreted by these $CD4^+$ T cell subsets, which can either promote or inhibit the development of inflammation. The advancement of immunological inflammation involves all of these distinct subsets of $CD4^+$ T cells. The role of Th17 cells in atherogenesis and the development of atherosclerosis is becoming more definite, but there are still unanswered questions [5]. The role of Th17 cells in controlling atherosclerosis and potential treatment targets of molecular pathways depending on Th17 cells are the main topics of this review.

2. General Functions of Th17 Lymphocytes

2.1 Cytokines Produced by Th17 Cells

Cytokine secretion is one of the primary mechanisms by which T helper cells function, and the distinct cytokine profile generated by every subset is a key distinguishing trait utilized to characterize T cell populations [6]. Initially

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classified based on their production of IL-17A homodimers in response to IL-23, Th17 cells were the first fraction to be recognized as different from the traditional Th-1/Th-2 concept [7]. It was later shown that Th17 cells generate IL-17F, another homodimeric member of the IL-17 family, and IL-17A/F, a heterodimeric protein made up of one IL-17A and one IL-17F subunit [8]. Epithelial cells, endothelial cells, and fibroblasts are the most sensitive cells to IL-17-mediated responses. They produce tumor necrosis factor alpha (TNFα), IL-1β, IL-6, IL-8, C-X-C motif chemokine ligand 1 (CXCL1), CXCL8, and granulocyte colony-stimulating factor (G-CSF) in reaction to IL-17R signaling, which causes inflammation and the migration of neutrophils [9].

Though its induction is different from that of IL-17A, Th17 cells also release the cytokine IL-22, which belongs to the IL-10 family [10]. It is suggested that highly developed Th17 cells release IL-22 because its production is more reliant on IL-23 signaling pathway than on the Th17 differentiation cytokines TGFβ and IL-6 [11]. The majority of non-hematopoietic cells express its receptor, a heterodimeric complex of IL-22R1 and IL-10R2, and interactions between IL-22 and its target cells aid in tissue repair, antimicrobial compound production including β-defensins, and host defense against external pathogens [10].

Many $CD4^+$ T cells, including Th17 cells, produce the pleiotropic cytokine IL-21, which has also been demonstrated to be crucial for the growth and operation of these cells. Like IL-6, it can have an autocrine effect on Th17 cells by triggering RAR-related orphan receptor gamma t (RORγt) production through signal transducer and activator of transcription 3 (STAT3) signaling [12]. By improving the activity of Th-1 cells, $CD8^+$ cytotoxic T cells, and NK cells, IL-21 not only promotes Th17 responses but also cellular immunity. IL-21 signaling is also necessary for B cell development, terminal differentiation, and activity [13].

2.2 Th17 Cells in Disease

Th17 cells are essential for maintaining mucosal immunity, but the pathophysiology of autoimmune inflammation has been linked to their dysregulation. Their contribution to the emergence of this inflammation was the initial indication that a third $CD4^+$ T helper cell subset, apart from the classical Th-1/Th-2 paradigm, could exist. Although Th-1 cells were thought to be the main mediators of autoimmunity in the original model, it has been demonstrated that models of autoimmune inflammation, including experimental autoimmune encephalomyelitis, are made worse when their principal Th-1 effector cytokine, IFNγ, or their stimulating cytokine, IL-12, are absent [14]. Subsequent research described Th17 cells as a unique $CD4^+$ T helper cell subset linked to the IL-23/IL-17 axis, which was found to be the primary route driving this inflammation rather than IL-12/IFN-γ [15]. Since then, it has been demonstrated that Th17 cells contribute to the development of many autoimmune conditions, including psoriasis, multiple sclerosis, inflammatory bowel disease, and rheumatoid arthritis [14].

Proinflammatory cytokines are produced in targeted cells by the Th17 cytokines IL-17A and IL-17F. These cytokines not only influence the inflammatory response by attracting innate immune cells like neutrophils, but they also encourage more Th17 activation in a positive feedback loop [15]. Because studies indicate that differentiation produced by high amounts of IL-6 and IL-1β leads to a more proinflammatory function, the specific environmental cues that lead to Th17 differentiation determine whether they progress towards a tissue-protective or pathogenic phenotype [16]. Research on Th17 cells and their cytokine products is still ongoing.

2.3 Structure and Function of IL-17

The IL-17 family comprises six members (IL-17A through IL-17F), of which IL-17A is the prototypical and best-characterized cytokine. Structurally, IL-17A is a disulfide-linked homodimeric glycoprotein belonging to the cystine-knot superfamily. Each monomer contains a conserved cysteine-knot motif—four conserved cysteines that form two disulfide bridges critical for maintaining the tertiary fold—and the two monomers are linked by an additional intermolecular disulfide bond, yielding a characteristic butterfly-shaped dimer. The mature secreted form of IL-17A is approximately 15 kDa per monomer (30 kDa as a dimer) and is encoded on chromosome 6p12 in humans. IL-17F shares approximately 50% amino acid sequence identity with IL-17A and can form either homodimers or IL-17A/F heterodimers, both of which signal through the same receptor complex [8].

IL-17A signals through a heterodimeric receptor complex composed of IL-17 receptor A (IL-17RA) and IL-17 receptor C (IL-17RC). IL-17RA is ubiquitously expressed, whereas IL-17RC expression is enriched on non-hematopoietic cells including epithelial cells, endothelial cells, fibroblasts, and smooth muscle cells. Upon ligand binding, the receptor complex recruits the adaptor protein Act1 (also known as CIKS), which in turn activates TRAF6 and subsequently multiple downstream pathways: the canonical nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (via IKKβ), the mitogen-activated protein kinase (MAPK) cascade (including ERK1/2, p38, and JNK), and CCAAT/enhancer-binding protein (C/EBP) transcription factors. These pathways converge to drive the transcription of pro-inflammatory mediators including cytokines (IL-1, IL-6, TNF-α), chemokines (CXCL1, CXCL8/IL-8, CCL2/MCP-1), and matrix metalloproteinases (MMPs) [9]. Functionally, IL-17A serves as a critical bridge between adaptive Th17 immunity and innate effector responses, with its principal physiological role being the mobilization and recruitment of neutrophils to sites of infection and tissue damage. However,

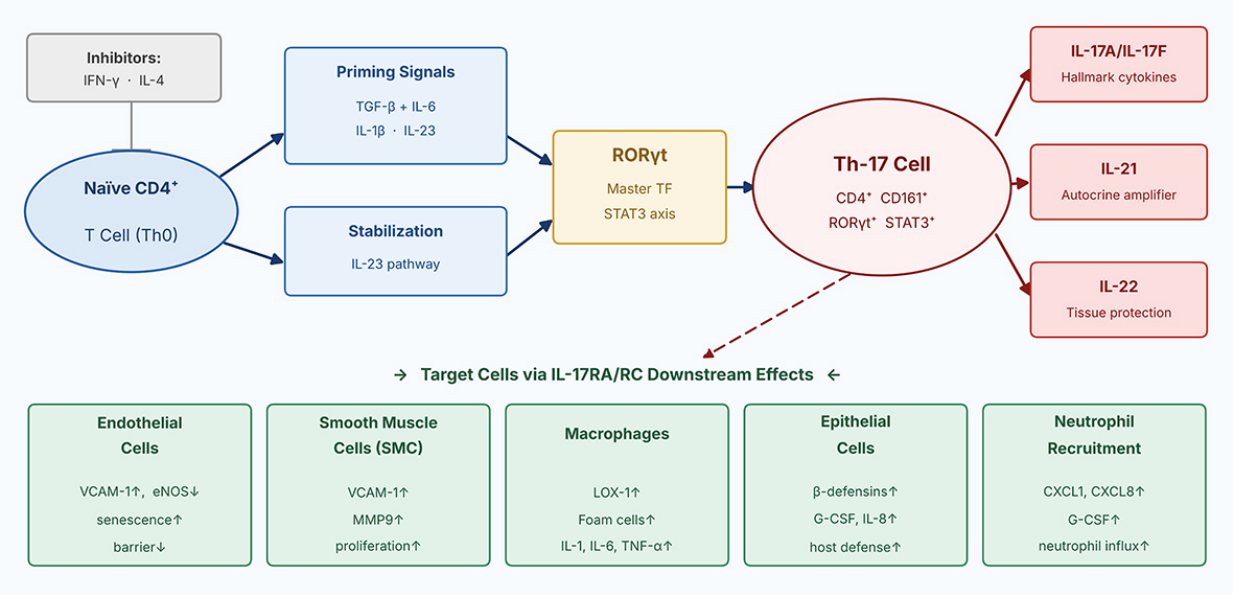


Fig. 1. Differentiation and cytokine profile of Th17 cells. Naive $CD4^+$ T cells differentiate into Th17 cells under the influence of transforming growth factor-β (TGF-β) + IL-6 (initial priming) and IL-23 (stabilization). Mature Th17 cells produce the key cytokines IL-17A, IL-17F, IL-21, and IL-22, which act on endothelial cells, smooth muscle cells, macrophages, and epithelial cells to drive pro-inflammatory signaling cascades. RORγt is the master transcription factor of Th17 lineage commitment. IFN-γ, interferon-gamma; IL, interleukin; TGF-β, transforming growth factor-beta; RORγt, retinoic acid receptor-related orphan receptor gamma t; TF, transcription factor; STAT3, signal transducer and activator of transcription 3; Th17, T helper 17; IL-17RA/RC, interleukin-17 receptor A/C; VCAM-1, vascular cell adhesion molecule-1; eNOS, endothelial nitric oxide synthase; MMP9, matrix metalloproteinase-9; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; TNF-α, tumor necrosis factor-alpha; G-CSF, granulocyte colony-stimulating factor; CXCL, C-X-C motif chemokine ligand.

when dysregulated—as occurs in autoimmune disease and chronic vascular inflammation—sustained IL-17A signaling perpetuates a destructive inflammatory milieu that contributes to tissue remodeling and endothelial dysfunction [12,17,18].

Differentiation and cytokine profile of Th17 cells are depicted in Fig. 1.

3. Double Role of Th17 Lymphocytes in Atherosclerosis

The expression of IL-17A, IL-17F, IL-21, and IL-22 is characteristic of Th17 cells. Th17 cells are the primary source of IL-17, which is regarded as their characteristic cytokine. In addition to Th17 cells, other hematopoietic cell types, $CD8^+$ T cells, invariant natural killer T cells, and other immune cells can also generate IL-17. IL-17, the main cytokine released by Th17 cells, is crucial in controlling the development of atherosclerosis. Its pathway and cytokines engage in a complex interplay [5].

3.1 Atherogenic Role of IL-17 in Atherosclerosis

The function of IL-17 in the onset and advancement of atherosclerosis has been the subject of several investigations. Compared to wild-type (WT) mice, $ApoE^{-/-}$ mice exhibited a greater proportion of Th17 cells in atherosclerotic plaques, indicating that Th17 cells are linked to atherosclerosis [19]. A link between IL-17 and atherosclerosis was suggested by another study that discovered IL-17 in the blood of individuals with coronary atherosclerosis and documented significant levels of IL-17 production by Th17 cells invading arteries. Additionally, it was shown that IL-17A caused the elevation of pro-inflammatory mediator mRNA, such as plaque-degrading matrix metalloprotease 9 (MMP9) and chemokine monocyte chemoattractant protein-1 (MCP-1), when co-cultured with atheromatous plaques [20]. Additionally, it caused macrophages to express a pro-inflammatory transcriptome, which in turn caused pro-inflammatory intermediaries such as cytokines IL-1A and IL-6 or chemokines CC motif chemokine ligand (CCL) 2 and CCL8 to be upregulated. This, in turn, promoted the development of atherosclerotic plaque. Similarly, another study used IL-17A to stimulate human umbilical vein endothelial cells and found that it increased monocyte adherence to vascular endothelial cells and triggered the production of adhesion molecules [21].

Furthermore, by increasing expression of lectin-like oxidized low-density lipoprotein receptor 1 (LOX-1) in activated macrophages, IL-17A promoted the development of foam cells generated by oxidized low-density lipoprotein (oxLDL), contributing to the pathophysiology

of atherosclerosis. Additionally, IL-17 caused endothelial cells and vascular smooth muscle cells (SMCs) to generate chemical mediators such as CXCL1, CXCL2, and CXCL8, which in turn drew additional inflammatory cells to the site of inflammation and exacerbated atheromatous plaque inflammation [22]. By stimulating the nuclear factor kappa B (NF-κB)–p53–Rb signaling pathway, it has also been demonstrated that IL-17A may bind to IL-17RA on the endothelial cell membrane and accelerate endothelial cell aging, which is the main foundation of atherogenesis and one of the primary causes of morphological alterations and malfunction of veins and arteries [23].

IL-17 promotes atherosclerosis by causing vascular SMCs to express vascular cell adhesion molecule-1 (VCAM-1). Atherosclerosis is mostly caused by vascular SMCs. Leukocyte recruitment and vascular inflammation depend on VCAM-1, which is expressed in endothelial cells and intimal SMCs of atherosclerotic lesions. VCAM-1 is necessary for atherogenesis, as evidenced by the absence of atherosclerosis in VCAM-1$^{-/-}$ mice [16]. IL-17 promotes atherosclerosis by mediating VCAM-1 expression in SMCs via a variety of signaling mechanisms. The induction of VCAM-1 expression in SMCs has been shown to be dependent on NF-κB, and the knockdown of p65 by siRNA eliminated the production of VCAM-1 caused by IL-17, indicating that NF-κB is essential for this expression in SMCs [24].

Although TGF-β-activated kinase 1 (TAK1) is thought to be a significant signaling molecule induced by IL-17, it was demonstrated that TAK1 knockdown did not decrease NF-κB activation or IL-17-induced VCAM-1 expression in SMCs, indicating that NF-κB triggered by IL-17 is not dependent on the TAK1 pathway. It was also observed that the Akt1 pathway is not involved in the NF-κB activation brought on by IL-17. Additionally, the ERK1/2–MAPK signaling pathway was identified as one mechanism through which IL-17 increased VCAM-1 expression in SMCs. New treatments for vascular illnesses will thus be made possible by further research on these processes and, consequently, by focusing on the IL-17 signaling pathway [24].

At the molecular level, the atherogenic program driven by IL-17A integrates three major intracellular signaling axes. First, the canonical NF-κB pathway is activated upon IL-17RA engagement via Act1–TRAF6 signaling; nuclear translocation of p65/p50 heterodimers drives transcription of VCAM-1, intercellular adhesion molecule-1 (ICAM-1), MCP-1, IL-6, and IL-8, collectively promoting leukocyte adhesion and transmigration. Second, STAT3—activated both by IL-17-induced IL-6 secretion and by direct JAK signaling downstream of IL-21 co-stimulation—reinforces Th17 differentiation in a positive feed-forward loop (via sustained RORγt expression) while simultaneously upregulating pro-survival and pro-inflammatory gene programs in endothelial cells and macrophages. Third, the MAPK cascade (ERK1/2, p38, JNK) activated by IL-17A mediates post-transcriptional mRNA stabilization of cytokine and chemokine transcripts through AU-rich element-binding proteins, prolonging the inflammatory signal beyond the initial transcriptional burst. The interplay between these three pathways determines the amplitude and duration of IL-17-driven vascular inflammation and represents a multi-node target space for pharmacological intervention [25,26].

The balance between Th17 and regulatory T cells (Tregs) is a critical determinant of atherogenic inflammation. Th17 and Tregs share the common precursor cytokine TGF-β for their differentiation, but diverge depending on the cytokine milieu: TGF-β alone drives Foxp3^{+} Treg induction, while TGF-β combined with IL-6 (and further stabilized by IL-23) promotes RORγt^{+} Th17 fate. RORγt and Foxp3 are mutually antagonistic transcription factors: RORγt directly suppresses Foxp3 activity and vice versa. In atherosclerotic lesions, the local cytokine environment (enriched in IL-6, IL-1β, and oxidized lipids) favors Th17 expansion at the expense of Treg accumulation, tipping the Th17/Treg ratio toward a pro-inflammatory state. Restoring this balance—for example through IL-21R blockade (which reduces Th17 autocrine amplification and boosts Foxp3^{+} Tregs) or STAT3 inhibitors—is an emerging therapeutic strategy that addresses the upstream immunological imbalance rather than individual cytokine effectors [25,26].

3.2 Atheroprotective Role of IL-17 in Atherosclerosis

While several studies have indicated that IL-17 has proatherogenic effects, other studies have claimed that IL-17 inhibits the progression of atherosclerosis. By blocking the STAT3 signaling pathway and reducing proinflammatory reactions, the suppressor of cytokine signaling (SOCS) protein, which is regarded as a crucial physiological regulator of both innate and adaptive immunity, protects against atherosclerosis [27]. It was demonstrated that in T-cell-specific SOCS3-deficient mice, neutralization of IL-17 totally eliminated the atherosclerotic protective effect of T-cell-specific SOCS3 deletion and caused a notable development of atheromatous plaque.

In vitro, IL-17 was also shown to suppress the progression of atherosclerosis by drastically reducing the formation of atherosclerotic lesions and IL-1-induced endothelial VCAM-1 expression in mice. Later, it was discovered that IL-17A deficiency causes atherosclerotic lesions and unstable atherosclerotic plaques in ApoE$^{-/-}$, IL-17A$^{-/-}$ mice, whereas IL-17A therapy decreased the formation of atherosclerotic plaques in ApoE$^{-/-}$ and ApoE$^{-/-}$, IL-17A$^{-/-}$ animals [28].

The researchers have proposed that splenocytes' enhanced expression of interferon (IFN)-γ and decreased production of IL-5 may be the cause of IL-17A's lack of atheroprotective effects. Even though there are few studies on IL-17's anti-inflammatory properties, its significance cannot

be overlooked, and understanding its intricate mechanisms of action helps the immune system regulate atherosclerosis [28].

IL-17 functions as a cytokine with a variety of interactions and pathways. As a result, research using specific models, atherosclerosis stages, and IL-17 concentrations is anticipated to provide light on the protein's mechanism of activity in atherosclerosis and offer a viable and long-term therapy option for these conditions [29].

3.3 Effect of IL-17 on Endothelial Dysfunction as a Pathogenic Mechanism of Atherosclerosis

Endothelial dysfunction is widely recognized as a pivotal early event in atherogenesis, preceding and predisposing to the formation of atherosclerotic plaques. Healthy endothelium maintains vascular homeostasis through the production of nitric oxide (NO), prostacyclin, and other vasoprotective mediators that collectively suppress inflammation, inhibit leukocyte adhesion, and prevent thrombosis. IL-17A disrupts this balance through multiple interconnected mechanisms, positioning it as a key molecular link between adaptive Th17 immunity and vascular pathology [19].

IL-17A impairs endothelial function via several distinct pathways. First, IL-17A binding to IL-17RA on endothelial cells activates the NF-κB–p53–Rb signaling axis, which accelerates endothelial cell senescence. Senescent endothelial cells exhibit a pro-inflammatory secretory phenotype characterized by elevated expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin), reduced endothelial nitric oxide synthase (eNOS) activity, and impaired barrier integrity—all of which facilitate monocyte transmigration and early plaque formation [19]. Second, IL-17A directly upregulates VCAM-1 and ICAM-1 expression on endothelial cells, thereby increasing monocyte and leukocyte recruitment to sites of vascular injury, a key step in atherosclerotic lesion initiation [19]. Third, through induction of CXCL1, CXCL2, and CXCL8, IL-17A orchestrates a chemokine gradient that attracts additional inflammatory cells, amplifying and sustaining vascular inflammation [5].

The relationship between IL-17-mediated endothelial dysfunction and platelet activation further compounds vascular pathology. Dysfunctional endothelium loses its ability to suppress platelet aggregation (through reduced prostacyclin and NO) while simultaneously expressing von Willebrand factor and tissue factor that promote thrombotic responses. Recent molecular investigations highlight that IL-17-driven endothelial activation shares overlapping signaling nodes—particularly NF-κB and MAPK pathways—with platelet-endothelium crosstalk mechanisms implicated in atheroprogression. Meta-analytic data confirm that elevated IL-17 levels are significantly associated with ischemic cardiovascular disease, partly through IL-17-induced apoptosis of vascular endothelial cells and aggravation of endothelial dysfunction [28]. Moreover, IL-17D, another member of the IL-17 family, has recently been shown to accelerate atherosclerosis by promoting endothelial cell ferroptosis via CD93/miR-181a-5p/SLC7A11 signaling, with plasma IL-17D levels correlating with major adverse cardiovascular events in patients [30]. This underscores the need to consider IL-17 targeting not only as an anti-inflammatory but also as an antiplatelet and endothelium-stabilizing strategy in atherosclerosis management [5,19,30,31].

An important but underappreciated dimension of IL-17-mediated endothelial injury is its convergence with oxidative stress pathways. IL-17A stimulates endothelial NADPH oxidase (NOX) isoforms—particularly NOX2 and NOX4—to generate superoxide (O_2^-), which reacts rapidly with nitric oxide (NO) to form peroxynitrite ($ONOO^-$), a potent oxidant that nitrates tyrosine residues in eNOS and uncouples the enzyme, amplifying NO deficiency and endothelial dysfunction. Simultaneously, reactive oxygen species (ROS) produced downstream of IL-17A stabilize NF-κB and activate MAPK cascades, creating a feed-forward inflammatory loop that accelerates foam cell formation, smooth muscle cell proliferation, and matrix metalloproteinase (MMP)-dependent plaque destabilization. This redox–inflammatory crosstalk has been mechanistically characterized across cardiovascular and neurological models: NO bioavailability, eNOS coupling, and ROS-driven peroxynitrite formation jointly determine vascular and tissue fate in oxidative disease states [32]. In the context of atherosclerosis, this NO/ROS imbalance also impairs macrophage polarization, shifting the M1/M2 balance toward a pro-inflammatory M1 phenotype that further sustains plaque growth and vulnerability. Strategies that simultaneously target IL-17A and restore redox homeostasis—such as antioxidant supplementation, NADPH oxidase (NOX) inhibitors, or NO-donor compounds—may therefore provide synergistic atheroprotection beyond what cytokine blockade alone can achieve [32].

Atherogenic mechanisms of IL-17 are depicted in Fig. 2.

4. Therapeutic Strategies Targeting Th17 Lymphocytes in Atherosclerosis

4.1 IL-17 Targeted Therapy

Anti-IL-17 antibody therapy may be a useful treatment approach for atherosclerosis because it is strongly linked to abnormalities in IL-17 levels in a number of autoimmune disorders [33,34]. Because anti-IL-17 antibody treatment is crucial for autoimmune illnesses, researchers have selected IL-17 for targeted therapy, with notable success [35]. The two primary strategies of anti-IL-17 antibody treatment are either directly decreasing inflammation by targeting the IL-17 pathway or indirectly restricting the inflammatory response mediated by IL-17 by controlling Th17 cell development [36]. Monoclonal antibodies that target the IL-17

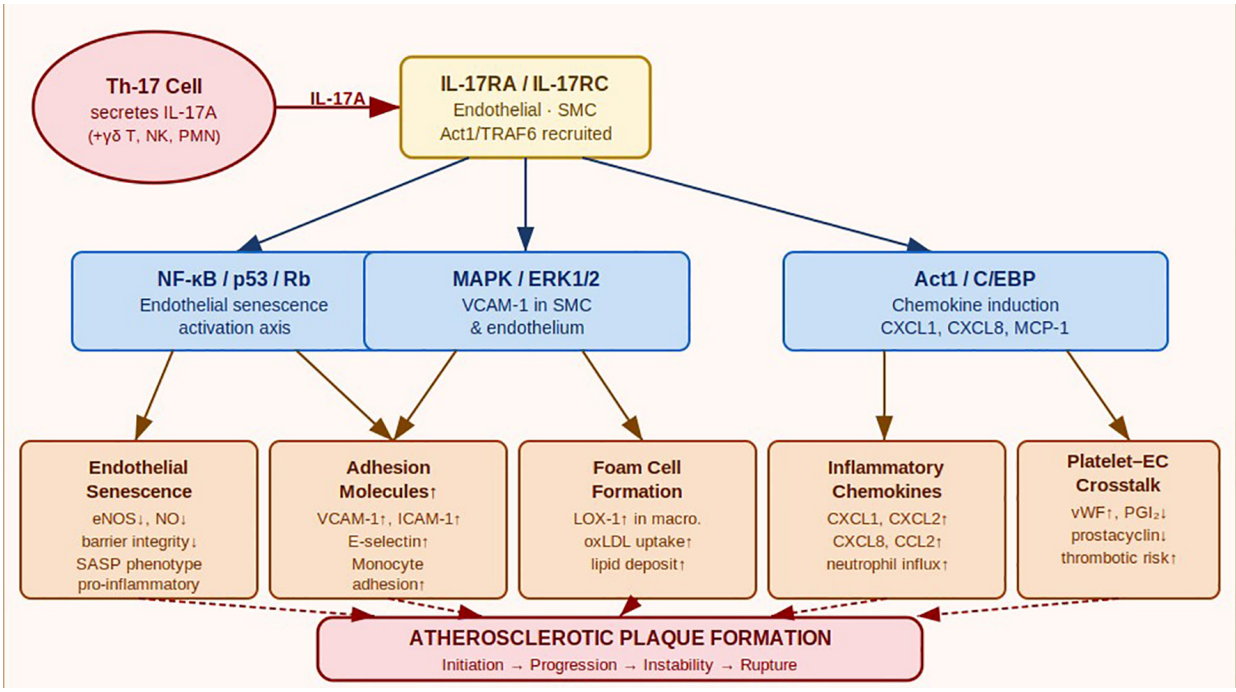


Fig. 2. IL-17-mediated mechanisms of endothelial dysfunction and atherogenesis. IL-17A binding to IL-17RA/RC activates NF-κB, MAPK/ERK1/2, and NF-κB–p53–Rb pathways in endothelial cells and SMCs. Downstream effects include VCAM-1/ICAM-1 upregulation, chemokine production (CXCL1, CXCL8, MCP-1), monocyte and neutrophil recruitment, accelerated endothelial senescence, LOX-1-dependent foam cell formation, and platelet–endothelium crosstalk, collectively driving atherosclerotic plaque progression. γδ T, gamma delta T cell; NK, natural killer cell; PMN, polymorphonuclear neutrophil; SMC, smooth muscle cell; Act1, adaptor protein Act1 (connection to IKK and SAPK/JNK); TRAF6, tumor necrosis factor receptor-associated factor 6; NF-κB, nuclear factor kappa B; p53, tumor protein p53; Rb, retinoblastoma protein; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated kinase 1/2; C/EBP, CCAAT/enhancer-binding protein; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; SASP, senescence-associated secretory phenotype; ICAM-1, intercellular adhesion molecule-1; E-selectin, endothelial selectin; oxLDL, oxidized low-density lipoprotein; CCL2, C-C motif chemokine ligand 2; vWF, von Willebrand factor; PGI_2, prostacyclin; EC, endothelial cell.

signaling pathway, such as secukinumab, ixekizumab, and brodalumab, have demonstrated encouraging efficacy in relation to their function in autoimmunity [37].

A human IgG1/kappa monoclonal antibody called secukinumab addresses IL-17A and stops it from attaching to and interacting with its receptor (IL-17R). Binding stops the subsequent synthesis of chemokines and proinflammatory cytokines, which are linked to a number of illnesses. For the treatment of moderate to severe plaque psoriasis, secukinumab was authorized [38]. Later on, it was given further permission to treat aggressive atherosclerosis. For patients who qualify for systemic treatment and/or phototherapy, secukinumab is advised. Upper respiratory tract infections (8.1–8.8%), headaches (10.4–11%), and nasopharyngitis (26.9–29.3%) are the most frequent side effects of secukinumab, followed by arthralgia, hypertension, diarrhea, back pain, pruritus, and cough [39].

Unlike secukinumab, which directly suppresses only the generation of IL-17A, brodalumab impedes all IL-17 cytokines by blocking their receptors. The human IgG2 monoclonal antibody brodalumab inhibits IL-17A, IL-17F, and IL-17-A/F heterodimer signaling through the IL-17RA/RC complex and IL-17E signaling through the IL-17RA/RB complex by binding to the IL-17 receptor A (IL-17RA). Proinflammatory chemokines and protein kinases are not released by IL-17 when IL-17RA is inhibited [40].

A humanized IgG4 monoclonal antibody called ixekizumab selectively binds to IL-17A and inhibits its interaction with IL-17R. It affects biological components by targeting cells and stopping the secretion of cytokines and chemokines. Ixekizumab has no effect on human complement system building blocks or Fc I, IIa, or IIIa receptors. In 2016, ixekizumab was approved by the FDA and EMA to treat moderate to severe plaque psoriasis [40].

Additionally, cytokines that stimulate Treg differentiation or restrict Th17 production can restore the Th17/Treg balance *in vivo*, indirectly regulating IL-17 production to provide therapeutic advantages [41].

Even though IL-17 blocking can be helpful in certain situations, the quantity of antibodies given must be carefully managed to prevent interfering with IL-17's regular bodily activities and raising the risk of opportunistic infections. Patients who received anti-IL-17 immunoglobulin experienced worsening symptoms in a study that used se-

cukinumab and brodalumab to treat Crohn's disease; as a result, the study was terminated early. As previously mentioned, IL-17 is also crucial for forming host barriers and preserving mucosal integrity [42]. The findings of that investigation confirmed the theory that excessive blockage of the IL-17 signaling pathway compromises intestinal barrier integrity, which is dependent on IL-17. Furthermore, additional research is required to determine the precise effects of various IL-17 inhibitors in people, even if some have shown promise in mouse models [43].

4.2 IL-21 Targeted Therapy

Elevated serum IL-21 levels have been detected in patients with coronary artery disease (CAD), but its exact role in atherosclerosis remains unknown. IL-21 is primarily secreted by T cells and binds to the IL-21 receptor (IL-21R), which is expressed on most lymphoid and myeloid cells. Therefore, IL-21/IL-21R signaling has pleiotropic effects and can induce immune cell activation but can also inhibit anti-inflammatory T regulatory cells. In a recent study, IL-21R blockade was shown to reduce atherosclerosis development by 38% [44]. This coincided with increased atheroprotective *Foxp3* expression in aortic $CD4^+$ T cells and an increased percentage of $CD4^+$ $Foxp3^+$ cells in lymphoid organs. Similarly, significant increases in anti-inflammatory IL-10 were observed in serum and splenocyte culture supernatant from αIL-21R-treated mice. Taken together, IL-21R blockade was shown to reduce atherosclerosis by stimulating atheroprotective regulatory T cell immunity and increasing anti-inflammatory IL-10 production, representing a promising new therapeutic strategy to extend healthy lifespan and combat cardiovascular disease [45].

4.3 IL-23/IL-22 Axis as a Therapeutic Target

The IL-23–IL-22 signaling module occupies a central regulatory position upstream of pathogenic Th17 responses and participates in cross-talk with the intestinal microbiota that can influence systemic inflammation and atherogenesis [43]. Genetic and pharmacological perturbation of IL-23 or IL-22 alters plaque burden in diet-induced models: IL-23 deficiency was associated with expansion of pro-atherogenic microbiota and accelerated atherosclerosis, whereas restoration of IL-22 signaling or microbiota modulation mitigated lesion formation [43]. Selective IL-23p19 inhibitors (*e.g.*, guselkumab, risankizumab) reduce downstream IL-17 production and have demonstrated potent anti-inflammatory effects in immune-mediated disease [46]; however, systemic blockade of IL-23/IL-17 pathways carries potential cardiovascular and microbiota-mediated consequences that require careful evaluation in atherosclerosis-focused studies. Thus, IL-23 (or modulation of IL-22 downstream effects) represents a plausible target to rebalance pathogenic Th17 activity while preserving protective mucosal functions—but clinical translation must consider microbiome and infection risks [43,46].

4.4 RORγt—Transcriptional Blockade of Th17 Differentiation

RORγt is the lineage-defining transcription factor for Th17 cells and controls the transcriptional program that drives IL-17 and allied pro-inflammatory mediators [47]. Pharmacologic inhibition of RORγt (inverse agonists/antagonists) suppresses Th17 differentiation and decreases IL-17 production in preclinical models [48], offering a strategy to blunt pathogenic Th17 responses at the transcriptional level rather than by neutralizing individual cytokines. Small-molecule RORγt inhibitors (*e.g.*, SR2211 and several clinical-stage inverse agonists such as VTP-series compounds) have shown efficacy in reducing Th17 signatures *in vitro* and in animal models [47,48]; their oral, small-molecule nature could enable titratable, possibly tissue-restricted exposure that mitigates some infection risks associated with full cytokine blockade. Nonetheless, clinical development has revealed safety and exposure-related challenges with systemic RORγt antagonists [48], arguing for refined chemistry (tissue-restricted exposure or partial/inverse agonism) and careful cardiovascular safety assessments in atherosclerosis contexts. Overall, RORγt inhibition is a rational complementary approach to antibody-based strategies, targeting Th17 cell development directly and potentially lowering IL-17-mediated vascular inflammation when appropriately optimized [47,48]. Potential anti-atherosclerotic therapy targeting Th17 pathways was summarized in Table 1.

Therapeutic targets along the Th17 axis in atherosclerosis are depicted in Fig. 3.

5. Concluding Remarks

Over the past 10 years, a subpopulation of $CD4^+$ T cells known as Th17 cells has drawn increasing attention. The third subset of Th cells, Th17, has been identified as a major regulator of inflammation and has been implicated in the development of autoimmune and allergic responses. As such, it may have a role in the immunopathogenesis of atherosclerosis. IL-17 is the primary cytokine released by Th17 cells, which are triggered by IL-23 [45].

Monoclonal antibodies are currently the only licensed treatments that target the IL-17–IL-17R pathway. Negative side effects including depression and an increase in the inflammatory response of the immune system are linked to some of them. Orally accessible small molecule drugs (SMDs) have the advantages of being easier to administer, having lower production costs, and potentially having fewer adverse effects associated with infections. While biologics frequently permanently block IL-17 production, SMDs can only do so transiently. This could aid in halting the cycle of inflammation without sacrificing IL-17's anti-infection properties. On the other hand, some SMDs could be harmful off-target [45]. A more specialized approach should be used to safeguard the host's own immunoregulatory mechanisms because IL-17 has both beneficial and detrimental ef-

Table 1. Potential anti-atherosclerotic therapies targeting Th17 pathways.

Target	Mechanism of action	Potential therapeutic agents	Expected effect on atherosclerosis	Key limitations/concerns
IL-17A	Neutralization of IL-17A cytokine to reduce vascular inflammation	Secukinumab, Ixekizumab	Reduced plaque inflammation, Reduced immune cell recruitment	Risk of infections, possible impairment of host defense
IL-21	Blockade of IL-21 receptor (IL-21R) to enhance Treg function and increase anti-inflammatory IL-10	αIL-21R antibodies (experimental)	Reduced atherosclerosis (~38% reduction in animal models), increased Foxp3+ Treg cells, increased IL-10	Limited clinical data, potential immune suppression, off-target effects
IL-23/IL-22 axis	Inhibition of IL-23p19 or modulation of IL-22 downstream effects to reduce Th17 activation and microbiota-mediated inflammation	Guselkumab, Risankizumab	Reduced Th17-mediated vascular inflammation, modulation of microbiota	Microbiome disruption, infection risk, incomplete preservation of mucosal immunity
RORγt	Transcriptional blockade of Th17 differentiation to reduce IL-17 production	SR2211, VTP-series inverse agonists	Reduced Th17 cell numbers and cytokine output, potential reduction in plaque inflammation	Safety/tolerability issues, need for tissue-restricted action, unknown long-term cardiovascular effects

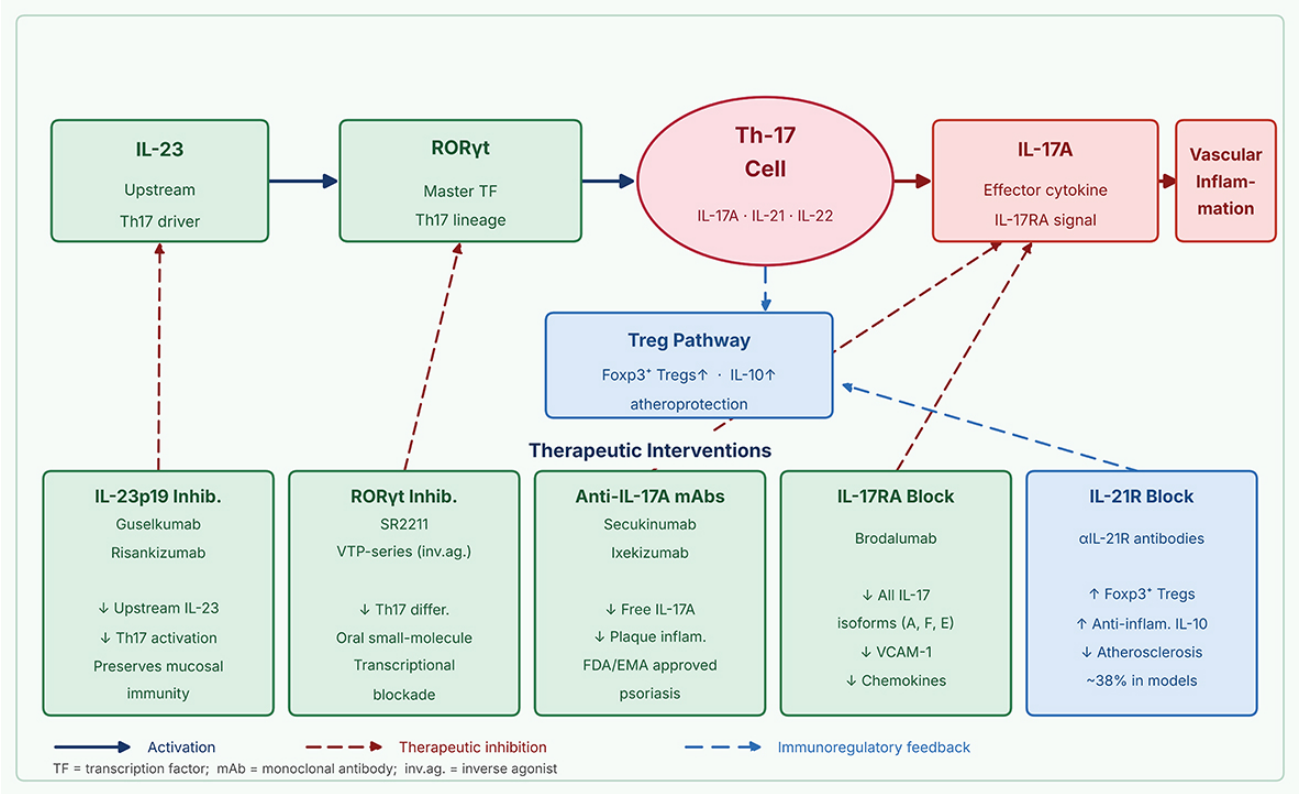


Fig. 3. Therapeutic targets along the Th17 axis in atherosclerosis. Five intervention points are highlighted: (1) IL-23p19 inhibitors (guselkumab, risankizumab) suppress upstream Th17 activation; (2) RORγt inverse agonists (SR2211, VTP-series) block Th17 differentiation transcriptionally; (3) anti-IL-17A monoclonal antibodies (secukinumab, ixekizumab) neutralize the effector cytokine; (4) IL-17RA blockade (brodalumab) prevents signaling of all IL-17 family members; and (5) IL-21R blockade enhances Foxp3^{+} Treg immunity and anti-inflammatory IL-10 production. FDA, Food and Drug Administration; Foxp3, forkhead box P3; IL, interleukin; IL-10, interleukin-10; IL-17A, interleukin-17A; IL-17RA, interleukin-17 receptor A; IL-21R, interleukin-21 receptor; IL-23, interleukin-23; IL-23p19, interleukin-23 p19 subunit; mAb, monoclonal antibody; RORγt, retinoic acid receptor-related orphan receptor gamma t; TF, transcription factor; Th17, T helper 17 cell; Treg, regulatory T cell; inv. ag., investigational agent.

fects on inflammation. Further detailed and comprehensive studies of IL-17-mediated signaling pathways under physiological and pathological conditions may provide prospects for the treatment of atherosclerosis.

Beyond lesion initiation and progression, Th17 cytokines play an underappreciated role in plaque destabilization and vascular remodeling that predisposes to acute cardiovascular events. IL-17A and IL-21 synergistically upregulate MMP-1, MMP-3, and MMP-9 in plaque macrophages and vascular smooth muscle cells (VSMCs) via NF-κB and AP-1-dependent gene programs. These matrix metalloproteinases degrade fibrillar collagen in the fibrous cap and impair VSMC-mediated cap repair, thinning the protective barrier between the necrotic core and the arterial lumen. Concurrently, IL-17A suppresses collagen synthesis in VSMCs by inhibiting TGF-β-driven SMAD3 signaling, further compromising cap integrity. In parallel, IL-17A promotes tissue factor (TF) expression on macrophages and endothelial cells, increasing the thrombogenic potential of the plaque surface. Vascular remodeling is also influenced by IL-17-driven adventitial fibroblast activation and neovascularization of the plaque, both of which facilitate intraplaque hemorrhage and lesion expansion. Collectively, these mechanisms establish Th17 effectors as critical determinants not only of plaque growth, but of plaque vulnerability and rupture risk, suggesting that Th17-targeted therapies may reduce acute coronary syndrome incidence beyond what is explained by simple lipid-lowering or anti-inflammatory effects [31,46,49].

6. Future Perspectives

Despite significant advances in understanding the Th17 axis in atherosclerosis, several critical questions remain unresolved and warrant dedicated investigation. First, the context-dependency of IL-17's role—pro-atherogenic in established lesions yet potentially atheroprotective in early disease stages—demands longitudinal studies that precisely delineate the temporal window during which IL-17 blockade is beneficial versus harmful. Human biomarker studies correlating circulating IL-17A, IL-23, and soluble IL-17RA levels with plaque imaging endpoints (coronary CT angiography, carotid intima-media thickness) and cardiovascular events would provide mechanistic anchoring for clinical trials [30,31].

Second, the interaction between Th17-driven inflammation and oxidative stress represents a largely untapped therapeutic opportunity. As discussed in Section 3.3, IL-17A activates endothelial NOX isoforms and drives eNOS uncoupling, producing a NO/ROS imbalance that amplifies both vascular inflammation and plaque instability [32]. Future preclinical and clinical studies should evaluate combination regimens targeting both the IL-17 cytokine axis and redox imbalance—for example, pairing IL-17RA blockade with NOX2 inhibitors or mitochondria-targeted antioxidants. The therapeutic relevance of this approach is supported by emerging evidence that restoration of NO bioavailability and suppression of peroxynitrite-mediated nitrosative stress can independently reduce atherogenic endothelial activation [32].

Third, macrophage polarization downstream of Th17 cytokines deserves more detailed mechanistic dissection. IL-17A promotes the M1 pro-inflammatory phenotype via NF-κB and STAT1 activation, while suppressing M2 polarization mediated by IL-4/IL-13/STAT6 signaling. Whether selective modulation of the Th17/Treg balance—for instance, via IL-21R blockade or RORγt inhibitors—can simultaneously rebalance macrophage phenotypes in atherosclerotic lesions remains to be formally tested *in vivo*. Single-cell RNA sequencing of plaques from anti-IL-17-treated patients and atherosclerotic mouse models could resolve macrophage heterogeneity at the lesion level and identify transcriptional signatures predicting therapeutic response [26,50].

Fourth, metabolic reprogramming of Th17 cells—which rely heavily on glycolysis and fatty acid synthesis for their differentiation and function—offers a novel angle for therapeutic intervention. Targeting HIF-1α, mechanistic target of rapamycin complex 1(mTORC1), or fatty acid synthase (FASN) in Th17 cells could attenuate their atherogenic activity while exploiting metabolic differences between Th17 and Treg cells (the latter preferentially use oxidative phosphorylation). Integration of metabolomic profiling and immune phenotyping in cardiovascular cohorts would help identify metabolic-inflammatory interaction nodes relevant to Th17-mediated atherogenesis [26].

Finally, the plaque destabilization mechanisms downstream of Th17 effectors require greater attention. IL-17A and IL-21 upregulate matrix metalloproteinases (MMP-1, MMP-3, MMP-9) in plaque-resident macrophages and SMCs, weakening the fibrous cap and promoting rupture. Future studies should examine whether Th17-targeted therapies can reduce MMP activity, stabilize the fibrous cap architecture, and decrease the incidence of acute coronary syndromes in patients with established atherosclerosis. Imaging-based surrogate endpoints combined with histological plaque characterization in clinical trials would be particularly informative in this regard.

7. Conclusions

Th17 cells and their effector cytokines occupy a complex, context-dependent role in atherogenesis: while IL-17 and related pathways can promote vascular inflammation, leukocyte recruitment and plaque instability, upstream nodes such as IL-23/IL-22 and the transcription factor RORγt also modulate Th17 differentiation and systemic effects (including microbiota-driven influences). Therapeutic targeting of the Th17 axis therefore offers promise but requires precision—selective IL-23/IL-22 modulation or transcriptional suppression via RORγt inhibitors may attenuate pathogenic Th17 activity while minimizing loss of

mucosal host defense. Translation to clinical atherosclerosis will demand strategies that balance anti-inflammatory efficacy with preservation of barrier immunity, careful cardiovascular safety assessment, and consideration of microbiome effects. Future work should prioritize mechanism-driven trials that evaluate tissue-restricted or titratable interventions and use integrated immunologic and microbiome endpoints to clarify benefit–risk for cardiovascular indications.

Author Contributions

ANO, AVB and VAO designed the review plan. VAO, UVR and SAA performed the data analyses. All authors wrote the manuscript. 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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