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Interleukin 17A in atherosclerosis – Regulation and pathophysiologic effector function

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ABSTRACT

This review summarizes the current data on the interleukin (IL)-17A pathway in experimental atherosclerosis and clinical data.

IL-17A is a prominent cytokine for early T cell response produced by both innate and adaptive leukocytes. In atherosclerosis, increased total IL-17A levels and expression in CD4$^+$ T helper and γδ T cells have been demonstrated. Cytokines including IL-6 and TGFβ that increase IL-17A expression are elevated. Many other factors such as lipids, glucose and sodium chloride concentrations as well as vitamins and arylhydrocarbon receptor agonists that promote IL-17A expression are closely associated with cardiovascular risk in the human population. In acute inflammation models, IL-17A mediates innate leukocyte recruitment of both neutrophils and monocytes. In atherosclerosis, IL-17A increased aortic macrophage and T cell infiltration in most models. Secondary recruitment effects via the endothelium and according to recent data also pericytes have been demonstrated. IL-17 receptor A is highly expressed on monocytes and direct effects have been reported as well. Beyond leukocyte accumulation, IL-17A may affect other factors of plaque formation such as endothelial function, and according to some reports, fibrous cap formation and vascular relaxation with an increase in blood pressure. Anti-IL-17A agents are now available for clinical use. Cardiovascular side effect profiles are benign at this point.

IL-17A appears to be a differential regulator of atherosclerosis and its effects in mouse models suggest that its modulation may have contradictory effects on plaque size and possibly stability in different patient populations.

1. Introduction

The pro-inflammatory cytokine interleukin (IL)-17A has received major immunologic attention in the last years as a marker of a novel T helper cell lineage, TH17 cells. Its regulation and physiologic functions have been explored in a variety of disease models and its concentrations associated with human pathologies. By now, there is a sizeable number of murine and human studies investigating its role in atherosclerosis [1–4]. This review aims to summarize the current knowledge of factors that promote IL-17A expression in pro-atherogenic conditions and the available data on its role in plaque development and structure. Finally, cardiovascular data from current trials of IL-17A antagonists in humans provide an outlook to possible clinical applications.

2. The IL-17 cytokine family, regulation, producing cell types and receptors

The IL-17 family consists of six members in total, termed IL-17A to F, which signal through five heteromeric receptor subunits, termed A to E [5]. IL-17A is the best-investigated cytokine of this family and the topic of this review. However, there are reports of IL-17F regulation in hypertension and vascular injury [6,7]. This is interesting as IL-17F is the closest genetic and functional homologue of IL-17A and signals through the same main receptor unit, IL-17 receptor A (gene name: Il17ra). Among the other IL-17 family members, IL-17C [8] and IL-17E [9] have currently been investigated for a mechanistic role in atherosclerosis. IL-17 receptor A is the main IL-17A receptor subunit that is required for signaling [5,10]. It is expressed on endothelium, smooth muscle cells, pericytes, macrophages, and T cells [5,11,12]. In addition, IL-17 receptor C is required for IL-17A signaling [13].

3. Regulation of IL-17A production during atherosclerosis development in murine models

IL-17A is mainly produced by T helper cells that are termed TH17 according to this signature cytokine. Depending on health status and location, other cell types, most notably γδT cells and innate lymphocytes produce significant amounts of IL-17A as summarized elsewhere

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Table 1
Regulation of IL-17A and related T cell cytokines in atherosclerotic mouse models.

Model	IL-17A	IL-17A$^+$ cell type	Method of IL-17A identification	IFNγ	IL-6	TGFβ and TREG cells	Ref.
IL-17A regulation in atherosclerosis							
C57Bl/6 vs. *Apoe*$^{-/-}$	more	Aorta: CD3$^+$, CD4$^+$, αβTCR$^+$, γδTCR$^+$	Aorta mRNA, ELISA, Flow cytometry	n.d.	n.d.	n.d.	[7]
C57Bl/6 vs. *Apoe*$^{-/-}$	More	T cells	Spleen and aortic plaque mRNA and flow cytometry, serum ELISA, Western blot	n.d.	More	Less Less	[19]
C57Bl/6 vs. *Apoe*$^{-/-}$	More	γδT cells	Aorta and spleen flow cytometry	Unchanged in γδT cells	n.d.	n.d.	[20]
C57Bl/6 vs. *Apoe*$^{-/-}$	More	CD4$^+$ T cells	Aorta mRNA, spleen flow cytometry, ELISA	More	More	n.d.	[18]
Apoe$^{-/-}$ ctrl. vs WD	More	Splenocytes	ELISA supernatant	More	n.d.	n.d.	[6]
Apoe$^{-/-}$ ctrl. vs WD	More	CD4$^+$ splenocytes	ELISA supernatant	More	n.d.	n.d.	[105]
Regulation of mediators in IL-17A depletion or blockade							
Ldlr$^{-/-}$: wt vs. *Il17ra*$^{-/-}$ bone marrow	n.d.			n.d.	Less	More IL-10	[108]
Apoe$^{-/-}$ vs. *Il17a*$^{-/-}$*Apoe*$^{-/-}$	n.d.	Splenocytes	ELISA supernatant	Less (ELISA)	n.d.	n.d.	[6]
Apoe$^{-/-}$ vs. *Il17a*$^{-/-}$*Apoe*$^{-/-}$	n.d.			More after 8 weeks (ELISA)	n.d.	n.d.	[105]
Apoe$^{-/-}$ vs. *Il17a*$^{-/-}$*Apoe*$^{-/-}$	n.d.			Less (aortic mRNA)	Less	n.d.	[59]
Apoe$^{-/-}$ vs. *Il17a*$^{-/-}$*Apoe*$^{-/-}$ vs. *Il17ra*$^{-/-}$*Apoe*$^{-/-}$	same	CD3$^+$ T cells	Aorta mRNA and flow cytometry	Less (aortic mRNA and flow cytometry)	Less	n.d.	[104]
Apoe$^{-/-}$ Ad-Lu vs. *Apoe*$^{-/-}$ Ad-IL-17RA	n.d.			Same in plasma (ELISA)	Less	n.d.	[7]
Apoe$^{-/-}$ anti-IL-17A vs. IgG (rat)	Less	n.d.	ELISA serum	Less (splenocyte flow cytometry), same (thoracic aorta mRNA)	Less	n.d. less	[109]
Apoe$^{-/-}$ anti-IL-17A vs. IgG (mouse)	n.d.			Same (thoracic aorta mRNA)	Less	n.d.	[110]
Apoe$^{-/-}$ anti-IL-17A vs. IgG (rat or mouse) and *Ldlr*$^{-/-}$: wt vs. *Il17a*$^{-/-}$ bone marrow	Less (mouse)	Aorta (less with mouse antibody, same with rat)	Western blot	n.d.	Less: mouse same: *Il17a*$^{-/-}$	n.d.	[107]

Changes of parameters refer to the respective control model, or as stated. WD = Western diet, n.d: not determined, Ad: adenovirus, Lu: luciferase.

[2,5,14]. Production by other cells such as monocytic cells and neutrophils is controversial [15–17]. IL-17A measurements during atherosclerosis development are summarized in Table 1. IL-17A was elevated in *Apoe*$^{-/-}$ mice in comparison to wildtype C57/Bl6 mice, either on control or high fat diet. Levels increased with age and high fat "western diet" in *Apoe*$^{-/-}$ mice. In some instances, enhanced IL-17A expression decreased at late atherosclerosis stages, but it was still detected as late as after 20 weeks of high fat diet [18,19]. In addition to TH17 cells, aortic γδT cells upregulate L-17A production in hyperlipidemic *Apoe*$^{-/-}$ mice [7,20].

3. Molecular factors that regulate IL-17A production

3.1. Cytokines

Polarization to TH17 cells in mice is induced by combined action of transforming growth factor beta (TGFβ), IL-6 and IL-23, the latter being central for stabilization of the cell type and these relationships have been reviewed [21–25]. Among other cytokines that can further promote TH17 cells are IL-1, especially in human cells, and GM-CSF [26–28]. The TH17 defining transcription factors STAT3 and RORγt promote TH17 signature cytokines in response to these stimuli [29] (Fig. 1). This review addresses what has been investigated in atherosclerosis mouse models and proatherosclerotic conditions in vitro. In atherosclerosis, increased IL-17A production has been accompanied by increase of IL-6 in some reports [18,19,30]. IL-6, in addition to promoting TH17 cells, is itself directly induced by IL-17A, thus suggesting a positive feedback loop. There is currently no available experimental data on a mechanistic role of IL-23 for atherosclerotic lesion size. However, it appears to promote cell death in mature plaques [31]. TGFβ production is increased in atherosclerosis [32]. However, it has multiple functions other than promotion of TH17 cells, including profibrotic action that stabilizes plaques and as a main inducer of protective regulatory T cells [26–28]. Decreased aortic IL-17A expression has been reported in a neutrophil elastase (NE) and proteinase 3 (PR3) deficient atherosclerotic *Apoe*$^{-/-}$ mouse model with decreased IL-1 production and smaller atherosclerotic plaques [33]. These data collectively demonstrate that IL-17A-inducing cytokines are upregulated in atherosclerosis.

3.2. Low molecular weight molecules including vitamins

Aryl hydrocarbon receptor (AhR) activation induces a marked increase in TH17 cell proportion and cytokine production [34–36] (Fig. 1). AhR activation is a risk factor for cardiovascular events in humans [37] and mice [38]. Receptor agonists are common environmental toxins [39] and part of cigarette smoke [40]. Indeed, smoking increased TH17 polarization in a number of mouse models [41–43]. Retinol and vitamin A negatively regulate TH17 production in the gut [44], however its role in atherosclerosis is controversial [45,46]. Vitamin D suppresses TH17 differentiation [45,47,48]. Vitamin D levels negatively correlate with cardiovascular event rate [49–51].

3.3. Lipids and lipid metabolism

Lipid metabolism, especially intracellular cholesterol, centrally modulates TH17 pathogenicity [52,53]. De-novo lipid synthesis is important in this process [54]. The cholesterol derivate 7β, 27-dihydroxycholesterol activates the TH17 master transcription factor RORγt and thereby directly induces the production of IL-17 in CD4$^+$ T cells and γδT cells [55]. However, exogenous lipids also indirectly impact IL-17A production, mostly via activation of myeloid cells (Fig. 1). Especially modified low density lipoproteins (LDL), such as oxidized (ox)LDL, are potent activators of human [56] and murine [57–59] macrophages and dendritic cells. OxLDL enhances the production of IL-6 and IL-1β in monocyte-derived dendritic cells (DC) [2,60] and oxLDL treated human DC preferentially induce RORγt and IL-17A production in T cells, whereas DC pretreatment with atorvastatin resulted in anti-

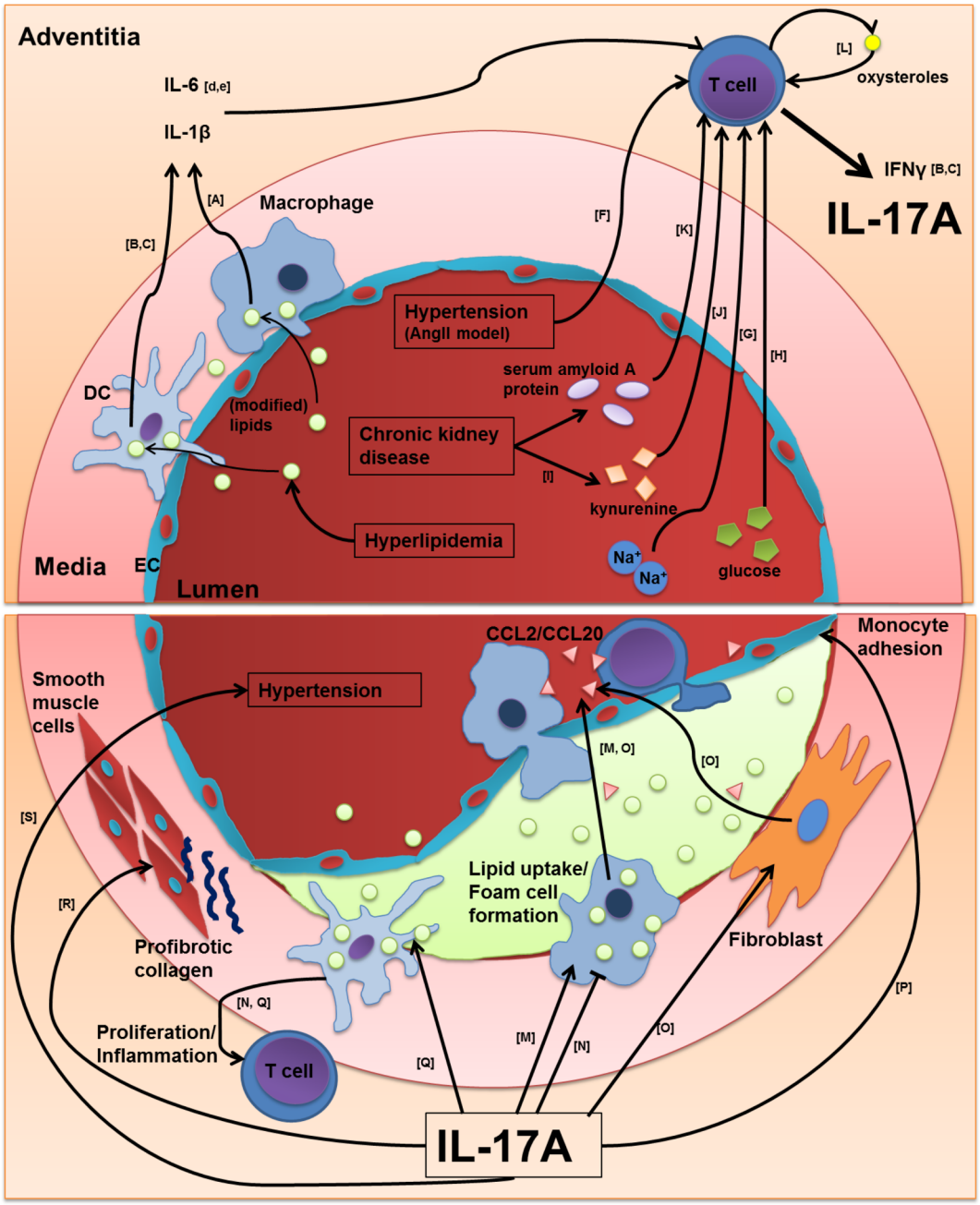

Fig. 1. Modulators of IL-17A expression and vascular IL-17A target cells in atherosclerosis. The aortic wall consists of an endothelial cell (EC) layer, a tunica media with large numbers of smooth muscle cells, and a fibroblast-rich tunica adventitia. Atherosclerotic plaques form a leukocyte–rich neointima, but macrophages, dendritic cells (DC) and lymphocytes are found in all layers of the wall. (A-L, upper panel): Factors that modulate IL-17A expression in atherosclerosis. Macrophages (A) [61] and dendritic cells (B) [56] (C) [58] produce pro-inflammatory cytokines such as IL-1β and IL-6 (D) [60] (E) [57] upon stimulation with modified lipids, leading to IL-17A but also IFNγ production (B, C). Cardiovascular risk factors such as hypertension (F) [74] and nutritional factors like high sodium (G) [64] or glucose (H) [65] promote IL-17A production. Chronic kidney disease induces kynurenines (I) [97] and serum amyloid A protein, which also contribute to TH17 response (J) [98] (K) [102]. T cell derived oxysterols also promote TH17 by directly activating transcription factor RORγt (L) [55]. (M-R, lower panel): Putative IL-17A target cells in the vascular wall. IL-17A may modify macrophage lipid uptake (M) [110] (N) [73]. It can induce chemoattractants CCL2 and CCL20 in macrophages (M) [110], fibroblasts (O) [127] and endothelial cells (P) [104]. Antigen presentation is enhanced by IL-17A (N, Q) [129]. Collagen production by smooth muscle cells (S) [113] and vascular tone (R) [74] are increased by IL-17A.

inflammatory IL-10 and TGFβ production [56]. Alternative modification of LDL by human group X-secreted phospholipase A2 also favors IL-17A or IFNγ production in T cells after DC stimulation [58]. In a murine model, oxLDL treatment of DCs resulted in increased IL-6 expression, and also enhanced polarization of T cells towards TH17 [57]. Beyond LDL, unsaturated fatty acids trigger the production of IL-1β via inflammasome activation in human macrophages [61], and free fatty acids also induced an array of TH17 promoting cytokines [62]. Thus, lipids are potent direct and indirect inducers of IL-17A in T cells.

3.4. Salt and glucose

High dietary sodium chloride uptake is closely associated with cardiovascular events [63]. High salt has been linked to TH17 polarization in autoimmune disease. It induced IL-17 expression in $CD4^+$ T cells via the p38/MAPK pathway and downstream activation of NFAT5 and SGK1, which led to an exacerbated disease model in experimental autoimmune encephalomyelitis (EAE) [64]. However, a direct impact of sodium chloride on TH17 polarization in atherosclerosis has not been determined.

Table 2
Effects of IL-17A on atherosclerotic lesion size and structure.

Model	Diet (wk)	Diet	Other stressors	Lipids	Lesion size vs. ctrl.		Collagen or cap thickness	Leukocytes	Ref.
					En face	Aortic root			
Genetic models									
C57BL/6 and Il17a$^{-/-}$	12	Paigen	*C. pneumo-niae*	Chol: same Trig: n.d.	Less	Less	n.d.	Less CD3^{+} T cells, less Mph	[106]
Apoe$^{-/-}$ vs. Il17a$^{-/-}$Apoe$^{-/-}$	8, 16	Chow,WD		Chol: same Trig: same	More	More	less α-SMA	More Mph	[105]
Apoe$^{-/-}$ vs. Il17a$^{-/-}$Apoe$^{-/-}$	12	Chow, WD, Paigen		Chol: same	Less (WD),	Less (WD),	α-SMA same (WD, chow)	Less MPH in root (WD)	[59]
				Trig: same	Same (Paigen, chow)	Same (Paigen, chow)		Same (chow)	
Apoe$^{-/-}$ vs. Il17a$^{-/-}$Apoe$^{-/-}$	4, 12	Paigen, chow	± AngII	Chol: same Trig: same	Same (-AngII)	Same (-AngII)	n.d.	Less leukocytes in aorta (-AngII)	[6]
Apoe$^{-/-}$ vs. Il17a$^{-/-}$Apoe$^{-/-}$ vs. Il17ra$^{-/-}$Apoe$^{-/-}$	12, 15	WD		Chol: same Trig: same	Less	Less	Same (Apoe$^{-/-}$ vs. Il17ra$^{-/-}$Apoe$^{-/-}$)	Less leukocytes, incl. CD3^{+} T cells, Mph and neutrophils	[104]
Ldlr$^{-/-}$: wt vs. Il17ra$^{-/-}$ bone marrow	12	WD		Chol: same Trig: n.d.	n.d.	Less	Same collagen content	More Mph, less mast cells	[108]
Ldlr$^{-/-}$: wt vs. Il17a$^{-/-}$ bone marrow	6	WD		Chol: same Trig: same	n.d.	Same	n.d.	Unchanged (data not shown)	[107]
Ldlr$^{-/-}$: wt vs. Il17a$^{-/-}$ bone marrow	6, 12	WD	RI	Chol: same	n.d.	Same (ctrl),	Same	No change in control mice, less Mph in RI	[73]
				Trig: same		Less (RI)			
Anti-IL-17A intervention									
Apoe$^{-/-}$: IgG vs. anti-IL-17A (rat)	12	Chow		Chol: same Trig: same	n.d.	Less	More collagen	Less CD3^{+} T cells, less Mph in root	[109]
LDLr$^{-/-}$/SOCS3-wt and LDLr$^{-/-}$/SOCS3-cKO: IgG vs. anti-IL-17A (mouse)	6	WD		n.d	n.d.	Same in wt Increase in KO	n.d.	CD3^{+} T cells same in wt, more in KO	[112]
CD4Cre + Smad7$^{fl/fl}$/LDLr$^{-/-}$: IgG vs. anti-IL-17A (rat)	8	WD		Chol: same Trig: same	n.d.	Less	Less collagen and α-SMA	n.d.	[113]
Apoe$^{-/-}$: IgG vs. anti-IL-17A (rat)	4	WD		Chol: same Trig: same	n.d.	Less	n.d.	n.d.	[111]
Apoe$^{-/-}$: anti-IL-17A vs. IgG (rat or mouse)	12	Chow		Chol: same Trig: same	n.d.	Reduced for rat anti-IL-17A	n.d.	Same (data not shown)	[107]
Apoe$^{-/-}$: IgG vs. anti-IL-17A (mouse)	16	Chow		Chol: same Trig: same	n.d.	Less	Thicker cap and more collagen	Less CD3^{+} T cells and Mph	[110]
Apoe$^{-/-}$ Ad-Lu vs. Apoe$^{-/-}$ Ad-IL-17RA	15	WD		Chol: more in Ad-IL-17RA Trig: same	Less	Less	n.d.	Less Mph in root	[7]
Exogenous IL-17A									
Apoe$^{-/-}$: albumin vs. rIL-17A	5	WD		Chol: same Trig: same	n.d.	More	Less SMC	Mph same	[111]
LDLr$^{-/-}$: albumin vs. rIL-17A	5	WD		n.d	n.d.	less	n.d.	Less CD3^{+} T cells	[112]
Apoe$^{-/-}$, Il17a$^{-/-}$Apoe$^{-/}$: albumin vs. rIL-17A	12	WD		n.d.	Less	n.d.	n.d.	n.d.	[105]

Changes of parameters refer to the respective control model, or as stated. WD: Western diet, Chow: control diet, wt: Wildtype, KO: knock-out, Chol: total cholesterol (serum), Trig: Triglycerides (serum), AngII: Angiotensin II, Mph: macrophages, RI: renal impairment, n.d.: not determined, Ad: adenovirus, Lu: luciferase.

Diabetes mellitus is one of the main cardiovascular risk factors in the western world and developing countries [63]. High glucose concentrations induced pro-inflammatory cytokines on Jurkat T-lymphocytes among them IL-6 and IL-17 [65]. TH17 frequency was also increased in peripheral blood lymphocytes from diabetic patients compared to controls [65].

4. Clinical risk factors for atherosclerosis and regulation of the IL-17A response

4.1. Hypertension

Immune mediators of hypertension and related end-organ damage including atherosclerosis include the IL-17A response [66,67]. In a number of small cohort studies, IL-17A serum levels were associated with refractory hypertension [68,69]. Inflammation-induced hypertension was promoted by IL-17A in a mouse model [70]. Angiotensin II, that is also a prominent hypertensive agent, induces IL-17A production in a variety of inflammatory conditions in vivo [71,72] and can enhance TH17 polarization in vitro [73]. Angiotensin induced enhanced aortic leukocyte infiltration and superoxide production depended on IL-17A in one [74] but not another [75] experimental setup of hypertension, leaving open questions [67].

4.2. Chronic inflammation and autoimmune disease

Chronically elevated markers of inflammation such as C-reactive protein (CPR) and white blood counts, in humans mostly caused by elevated concentrations of neutrophilic granulocytes, are significant risk factors for cardiovascular events, an association that has been recognized for many decades [76–79]. IL-17A is a potent inducer of G-CSF and thereby neutrophil counts [79].

Among chronic inflammatory conditions, psoriasis is one of the first for which IL-17A blockade was tested and approved [80]. It carries a significantly elevated cardiovascular risk [81]. However, a chemical psoriasis model did not increase atherosclerotic lesion size in a mouse model, which was not associated with increased IL-17A levels despite significant skin lesions [82]. Cardiovascular risk is much less evident in inflammatory bowel disease, another condition successfully treated with blockade of the IL-17A pathway [80].

In addition to chronic inflammation, cardiovascular risk is significantly elevated in a number of autoimmune diseases, many of which are closely linked to the IL-17A pathway [80]. It is highly elevated in systemic lupus erythematosus (SLE) [83]. Elevated numbers of TH17 cells have been described in this condition, however, their pathophysiologic role in SLE disease development at least in mouse models is still debated [84]. In contrast, multiple sclerosis, the mouse model of which has been closely linked to increase in the TH17 pathway in a large number of studies, does not consistently increase atherosclerotic event rate [85].

4.3. Chronic kidney disease

Renal impairment of any cause is a major risk factor for cardiovascular events and death at glomerular filtration rates of 60 ml/min or less [86,87], which increases vascular wall inflammation in humans [88,89] and mouse models [73,90]. An early study showed increased serum IL-6 in chronic kidney disease [91]. Both IL-17A producing T cells [92,93] and serum IL-17A levels [94] were elevated in small cohorts of patients with advanced CKD. Also in animal models with defined and more moderate reduction of renal function, others and we have found up-regulation of IL-17A in inflammation [73,95]. Uremic metabolites can also directly activate the AhR [96]. The tryptophan metabolite kynurenine is also elevated in chronic kidney disease and associated with cardiovascular risk [97]. In murine inflammation models and in vitro, kynurenine induced TH17 differentiation in some [98] (Fig. 1) but not other [99,100] experimental conditions. Also, indoleamine-dixoygenase that produces both kynurenine and anthranilic acid is protective in atherosclerosis [101]. Another possible mediator of TH17 induction in renal disease is the serum amyloid A protein, which can promote IL-17A production in vitro [102] (Fig. 1). It accumulates in HDL particles of patients with chronic kidney disease, possibly rendering HDL dysfunctional, enhancing the risk of cardiovascular disease [103].

5. Mechanistic role of IL-17A for atherosclerotic plaque size in murine models

5.1. Genetic IL-17A and IL-17 receptor A deletion

A commonly used animal model for mechanistic atherosclerosis studies are Apoe$^{-/-}$ mice. Lesion formation is mainly driven by excessive blood lipid levels, both with normal “chow” and high fat “western type” diet. Lesion sizes in studies with in *Il17a*$^{-/-}$*Apoe*$^{-/-}$ mice in the aortic root and the whole aorta are summarized in Table 2. Results range from ameliorated [59,104], unchanged [6] to increased lesion size [105] compared to control mice. Most of these studies were conducted on a high fat diet. Paigen diet, which also contains sodium cholate and causes increased plaque inflammation, abolished the difference between *Apoe*$^{-/-}$ and *Il17a*$^{-/-}$*Apoe*$^{-/-}$ mice in one study [59]. This differs from protection of Paigen-diet-fed *Il17a*$^{-/-}$ compared to control wildtype C57BL/6 mice, where the absence of IL-17A decreased both total aortic en face and aortic root lesion size [106]. In the other most commonly studied murine atherosclerosis model, *LDLr*$^{-/-}$ mice, absence of IL-17A has been studied after reconstitution with deficient bone marrow, revealing no changes in lesion formation [73,107].

In addition to IL-17A itself, its main receptor subunit, IL-17 receptor A was studied in specifically gene deficient mouse models. Its deletion in *Il17ra*$^{-/-}$*Apoe*$^{-/-}$ mice led to a comparable decrease in lesion size as observed in *Il17a*$^{-/-}$*Apoe*$^{-/-}$ mice in the same study [104]. Similarly, in *LDLr*$^{-/-}$ mice IL-17 receptor A deficient bone marrow significantly reduced aortic root lesion size and also IL-6 levels [108].

5.2. Specific blockade or addition of IL-17A in atherosclerotic mouse models

Another way to inhibit IL-17A signaling is blockade of the cytokine with a specific neutralizing antibody. This approach has been used by different groups [107,109–112], also with varying results (Table 2). IL-17A blockade was protective on aortic root lesions in *Apoe*$^{-/-}$ mice in early (4 weeks [111]) as well as late (12–16 weeks [107,109,110]) atherosclerosis, but failed protection in another model [107,112]. As an alternative method, a soluble IL-17 decoy receptor A was expressed in *Apoe*$^{-/-}$ mice [7]. This reduced IL-6 levels and lesion size. On the other hand, exogenous recombinant IL-17A ameliorated disease in one bone-marrow transplanted *LDLr*$^{-/-}$ model and one set of *Apoe*$^{-/-}$ experiments [105,112], but aggravated atherosclerosis in another set of *Apoe*$^{-/-}$ mice [111]. Beyond possible non-specific effects of the employed proteins, there is no obvious explanation for these discrepancies to date.

5.3. IL-17A dysregulation in other genetic models of atherosclerosis with functional results

IL-17A expression is dysregulated and considered a pathophysiologic mediator also in a number of other specific gene deficient atherosclerotic mouse models. Increased IL-17A expression was observed in a transcription factor SOCS3-deficient *LDLr*$^{-/-}$ model. Treatment with anti-IL-17A antibody aggravated root lesions in the absence, but not in the presence of bone marrow SOCS3 [112]. IL-27 is a member of the IL-6/IL-12 family and absence of signaling skews the immune response

towards TH17. This resulted in an *LDLr*$^{-/-}$ model reconstituted with *Il27ra*$^{-/-}$ bone marrow in increased IL-17A production and inflammatory cell infiltration with enhanced plaque formation [30]. *CD4Cre*$^{+}$*Smad7*$^{fl/fl}$ bone marrow transplantation into *LDLr*$^{-/-}$ mice resulted in larger lesions than control bone marrow, together with increased IL-17A, but no change in IL-6 levels [113]. A rat anti-IL-17A antibody reduced lesion size in these mice (Table 2). These genetic models provide evidence of diverse impact of IL-17A on atherosclerotic plaque development.

5.4. Role of IL-17A in models of atherosclerosis together with other disease

Il17a$^{-/-}$ mice on a C57/Bl6 background were protected from accelerated atherosclerosis in a model of Chlamydia infection and Paigen diet [106]. Also other pro-inflammatory cytokines such as IFNγ, CCL2 and IL-12 subunits were reduced. In *Apoe*$^{-/-}$ mice sensitized with collagen V, atherosclerotic lesion size increased. This was accompanied by an elevated number of aortic IL-17A producing T cells and macrophages [114]. However, a definite causal role for IL-17A signaling in plaque formation in this model was not tested. CD4^{+} T cells from C57/Bl6 mice on lupus-prone background increased atherosclerotic lesions in *LDLr*$^{-/-}$*RAG*$^{-/-}$ mice more than control cells. Reduced IL-10 receptor expression on TH17 cells was postulated as a mechanism [115]. *LDLr*$^{-/-}$ mice reconstituted with IL-17A deficient cells were protected from an increase in lesion size and lesional inflammation in renal impairment [73]. IL-17A in this model was derived from CX3CR1 expressing T cells [90]. Asthmatic chow-fed *Apoe*$^{-/-}$ mice benefit from IL-17A blockade with a reduction in aortic lesion size. More CD68^{+} macrophages and less collagen were observed in asthmatic versus non-asthmatic mice [116]. Thus, in these disease conditions with increased IL-17A and atherosclerosis, blockade of IL-17A appeared to be beneficial.

5.5. IL-17A in atherosclerotic models treated with clinically approved drugs

Digoxin is a direct antagonist of RORγt, the master transcription factor of IL-17A, and dose-dependently decreases circulating lipids, IL-17A, and concomitantly lesion size in *Apoe*$^{-/-}$ mice [117]. The immunosuppressive mycophenolate mofetil reduces expression of IL-17A in serum and aorta and decreases atherosclerotic lesion formation in *Apoe*$^{-/-}$ mice [118]. Pharmacologic angiotensin inhibition decreases vulnerable plaque phenotype and valsartan indeed also decreased aortic root lesion size, TH17 cells in spleens, serum IL-17A levels and aortic IL-17A mRNA in *Apoe*$^{-/-}$ mice [119]. These pharmacologic studies suggest that reduction of IL-17A may be beneficial, however, none of the employed agents is entirely specific for this cytokine.

5.6. Mechanistic effects of other IL-17 isoforms in atherosclerotic mouse models

Increased systemic IL-17F levels in a mouse model of dermatitis did not increase lesion size in *Apoe*$^{-/-}$ mice [82]. *Il17c*$^{-/-}$*Apoe*$^{-/-}$ mice displayed a decreased aortic lesion size and inflammatory cell content. IL-17C seems to promote the recruitment of adoptively transferred IL-17A producing splenocytes into atherosclerotic aortas [8], in line with a pro-atherogenic effect of IL-17A. Exogenous administration of IL-17E into *Apoe*$^{-/-}$ mice led to an expansion of the type 2 innate lymphoid cell population and decrease in lesion size [9]. This is in line with a possible atheroprotective role of a TH2 response [120].

6. Role of IL-17A in modulation of the atherosclerotic lesion structure

For the clinical outcome of atherosclerosis not only the size of the plaque is important but also factors that influence the structure, stability or inflammatory state. Unstable plaques are prone to rupture, leading to thrombosis and cardiovascular events including death [32,121]. Plaque instability is promoted by factors like decreased collagen deposition, increased matrix degradation by metalloproteinases, or imbalanced clearance of apoptotic cells. Deficiency of IL-17A had controversial effects on SMC content and fibrous cap thickness in mouse models (Table 2, Fig. 1). While few researchers found less αSMA or collagen content without IL-17A [105], the majority of studies suggest no significant differences [30,59,73,104,108,118] or even increased plaque stability and fibrous cap thickness without IL-17A [109,110,117]. Conversely, exogenous IL-17A disrupted the plaque structure [111]. However, in complex gene-deficient mice, opposite results have been observed (Table 2, [112,113]) Altered metalloproteinase expression was proposed as a possible mechanism of lesion destabilization by IL-17A [110,117]. Inflammatory cell infiltration also critically influences lesion stability and plaque rupture [32,78,122]. In most of the reports, there was an IL-17A-dependent increase in T cell or macrophage content in the aortic root (Table 2). Similar increases in aortic cells were found in hypertension [6,74], which required RORγt induced by gut microbiota [123]. Also in arterial dysfunction induced by a model of psoriasis, IL-17A was instrumental for aortic myeloid cell accumulation [70]. Collectively, these data suggest that IL-17A promotes arterial inflammation.

7. Possible IL-17A target cells in atherosclerosis

Inflammatory leukocytes are central in plaque development [32]. IL-17A and its main receptor subunit, IL-17 receptor A, regulate myeloid cells including granulocytic and monocytic response in infection and sterile inflammation [26]. Both, direct effects on myeloid leukocyte functions and actions via resident cell types in the vasculature have been reported [124].

In *LDLr*$^{-/-}$ mice, IL-17 receptor A deficient bone marrow significantly reduced IL-6 levels and aortic root lesion size, indicating an important role of hematopoietic cells in IL-17A signaling in atherosclerosis [108]. IL-17ra is highly expressed on monocytes [124–126] and mediates their recruitment in a number of non-atherosclerotic inflammatory conditions [124,125,127]. Leukocytes also produce a set of other effector molecules such as GM-CSF, IL-6, IL-1β or TNFα in response to IL-17A [128]. IL-17A can also induce the IL-12 subunit IL-12p70 in macrophages [124]. Lipid uptake by myeloid cells was increased by IL-17A in some [110,129] but not other conditions [73], the latter with a coinciding decrease in scavenger receptor CD36 and lipid transporter ABCA1 (Fig. 1). IL-17A increased antigen-presenting cell marker expression on human and murine macrophages [73] and pretreatment of murine macrophages with an anti-IL-17A antibody ameliorated OVA-specific T cell response [124]. Recombinant IL-17A increased dendritic cells lipid accumulation and stimulation of T cell proliferation [129]. While some cell culture data have to be evaluated with caution due to lack of specificity controls, these results overall suggest a pro-inflammatory role for IL-17A in hyperlipidemia (Fig. 1).

Endothelial changes are critical for plaque formation in atherosclerosis. IL-17A induced IL-6 and CCL2 production in mouse aortic endothelial cells [106] and increased adhesion of the monocytic cell THP-1 to human aortic endothelial cells, possibly through increased expression of CXCL1, CXCL2, and ICAM-1 [130], monocyte adhesion to HUVEC monolayers [110] and explanted atherosclerotic *Apoe*$^{-/-}$ aortas [7,104] in vitro. *Il17ra*$^{-/-}$*Apoe*$^{-/-}$ aortas contained less CCL2 and CCL20. However, adhesion of wildtype monocytes was diminished, but still observed to IL-17A treated *Il17ra*$^{-/-}$*Apoe*$^{-/-}$ aortas [104]. A relatively recently defined resident vascular cell type are pericytes. In direct comparison with endothelium, a significantly stronger response to IL-17A was observed in this cell type [131]. IL-17A increased IL-6, IL-8, and CXCL5 expression that in turn prompted neutrophils to produce IL-1β and TNFα. Lastly, smooth muscle cell as a main component of the tunica media produced pro-fibrotic collagen I and pro-collagen 1A1 in response to IL-17A [113]. In combination, these results may indicate

that both hematopoietic and vascular resident cells are involved in IL-17A mediated cell recruitment.

In addition to local effects, systemic IL-17A may shape a pro-atherosclerotic environment. In angiotensin II-induced hypertension, IL-17A increased renal sodium reabsorption in the distal tubule cells by regulation of sodium transporters [132,133]. Systemic deletion of IL-17A protected from increased albuminuria in angiotensin II infusion [132]. A very recent report on a direct effect of IL-17A on the nervous system in the nematode *Caenorhabditis elegans* may open another systemic avenue how IL-17A modulates cardiovascular risk factors such as vascular tone [134].

8. Role of IL-17A in human atherosclerotic plaque structure

Immunohistological staining for IL-17A in human atherosclerotic plaques has been reported by a number of groups. While most detected an increase in unstable plaques [135–138], IL-17A according to immunohistochemisty and western blot was associated with fibrotic rather than macrophage rich plaque areas in another study [112]. Also, mRNA expression of the TH17 defining transcription factor RORγt was associated with pro-fibrotic gene expression in human endarterectomy specimens [113]. The fact that immunohistochemical staining in a number of studies was positive in a large range of cell types without detectable IL-17A production by other methods suggests that specificity needs to be closely monitored for this method.

Based on flow cytometric results, TH17 frequency in peripheral blood, either alone or in relation to T cell count, was elevated in unstable atherosclerosis [138–146]. However, most studies are small and IL-17A assessment by flow cytometry requires strict negative controls, thus larger and prospective studies should be awaited. Some studies also used serum IL-17A ELISA, detecting up-regulation in unstable plaques in some [140,147], but not all cohorts [148]. In this context it is of interest that a recent gene expression analysis, thus a non-hypothesis driven approach, demonstrated that sera from patients with acute myocardial infarction up-regulated IL-17A responsive genes in smooth muscle cells [149].

9. Effects of specific IL-17A antagonists on human atherosclerosis

Direct IL-17A blockade has now been used in a number of clinical trials, mostly psoriasis and inflammatory bowel disease [80]. There was no significant change in cardiovascular risk in recent metaanalyses for either psoriasis [150] or Crohn's disease [151]. Also for IL-23 antagonists, which appear to be more effective in psoriasis [80], meta-analyses did not detect a significantly altered rate of major adverse cardiovascular events [1,150,152]. However, effects in a broader population including patients with additional cardiovascular risk factors needs to be studied.

10. Conclusion

A large body of work conclusively shows IL-17A up-regulation in atherosclerosis. Its pathophysiologic role according to the majority of mechanistic studies in mouse models appears to be an increase in plaque size and aggravation of inflammation. However, there are contradictory findings. Possible reasons for this are different levels of inflammation and T cell polarization in the used mouse models. IL-17A actions on both leukocytes and resident vascular cells that may modulate plaque structure have been found. In addition, IL-17A can influence systemic factors relevant in atherosclerosis development such as renal salt excretion and neuronal activity. Clinical studies of IL-17A blockade in populations at low cardiovascular risk have not yet detected a signal regarding atherosclerotic events, however, experimental data propose diverse effects in different patient populations.

Disclosure

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