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The IL-12 cytokine family in cardiovascular diseases

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ABSTRACT

Cytokines of the Interleukin (IL)-12 family, consisting of IL-12, IL-23, IL-27 and IL-35, are important regulators in (chronic) inflammatory disorders such as rheumatoid arthritis and multiple sclerosis, but also in cardiovascular diseases. Cytokines of the IL-12 family consist of two subunits and are known for their regulatory functions in the immunologic response, more specifically in the regulation and differentiation of T-helper (Th) cells such as Th1 and Th17 cells. Binding of these cytokines to its specific heterodimeric receptor results in the activation of the JAK-STAT signaling. Despite similarities in structure, the members of the IL-12 family have diverse, both pro- and anti-inflammatory, effects and functions. Because of the pro-inflammatory effects of IL-12 cytokine family members on immune responses, the IL-12 cytokines have been implicated in the development and progression of cardiovascular diseases such as atherosclerosis, but also in acute cardiovascular syndromes such as myocardial infarction and stroke. For example, patients suffering from cardiovascular disease display increased blood levels of IL-12, IL-23 and IL-27, while decreased IL-35 levels have been linked to a lower cardiovascular risk. In this review, we aim to highlight the current understandings of the IL-12 cytokine family and its specific family members to cardiovascular diseases, including both clinical and experimental studies. We will also discuss the potential of these cytokines as a biomarker in acute cardiovascular syndromes.

1. Introduction

The IL-12 cytokine family consists of four cytokines, which comprise IL-12, IL-23, IL-27 and IL-35 (Fig. 1) [1]. All members of the IL-12 cytokine family are dimeric proteins and consist of an alpha subunit (p19, p28 or p35) and a beta subunit (EBI3 or P40) [1]. The receptors interacting with the IL-12 family members are heterodimers and currently, there are several known combinations of subunits (IL-12Rβ1, IL-12Rβ2, IL-23R, IL-27Rα and gp130) of the IL-12 family receptors (Fig. 1) [2]. IL-12 cytokine family members have distinctive effects on the immunological response, which can act pro-inflammatory (IL-12 and IL-23) by regulating Th1 and Th17 cells. IL-27 can act pro- or anti-inflammatory by either inducing the transcription factor for Th1 subset or by inhibiting Th17 differentiation, respectively. IL-35 acts anti-inflammatory due to its effects on regulatory T cells (Tregs) and regulatory B cells (Bregs). During antigen presentation to naïve T cells IL-12, IL-23 and IL-27 can be secreted by antigen-presenting cells such as macrophages and dendritic cells [3–5]. IL-35, on the other hand, is secreted mainly by regulatory T and B cells [6,7].

Upon binding its receptor, the cytokines of the IL-12 family signal via the JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathway [8]. Activation of the STAT pathway through phosphorylation of STAT proteins leads to the induction of gene transcription and forms thereby a bridge for cytokine-induced gene transcription.

Members of the IL-12 cytokine family are involved in inflammatory responses and known to contribute to diseases such as rheumatoid arthritis (RA), inflammatory bowel disease and psoriasis [9–11]. In the last two decades, these cytokines have also been shown to participate in cardiovascular diseases. In previous studies, it was established that serum levels of IL-12 [12], IL-23 [13] and IL-27 [14] are increased, while IL-35 levels are decreased in patients suffering from cardiovascular diseases [15]. In this review, we will focus on current knowledge of the IL-12 family members in experimental models of cardiovascular disease and in CVD patients. We have also included IL-6, which receptor is very similar in structure to the IL-27 receptor by sharing the gp130 subunit, as an important cytokine in cardiovascular disease.

2. Structure and function of the IL-12 cytokine family and its receptors

2.1. Interleukin-12

IL-12 is the first cytokine of the IL-12 family that was discovered. This heterodimeric cytokine (p70) is composed of a 40 kDa heavy chain (p40 or IL-12β) and a 35 kDa light chain (p35 or IL-12α) subunit. In

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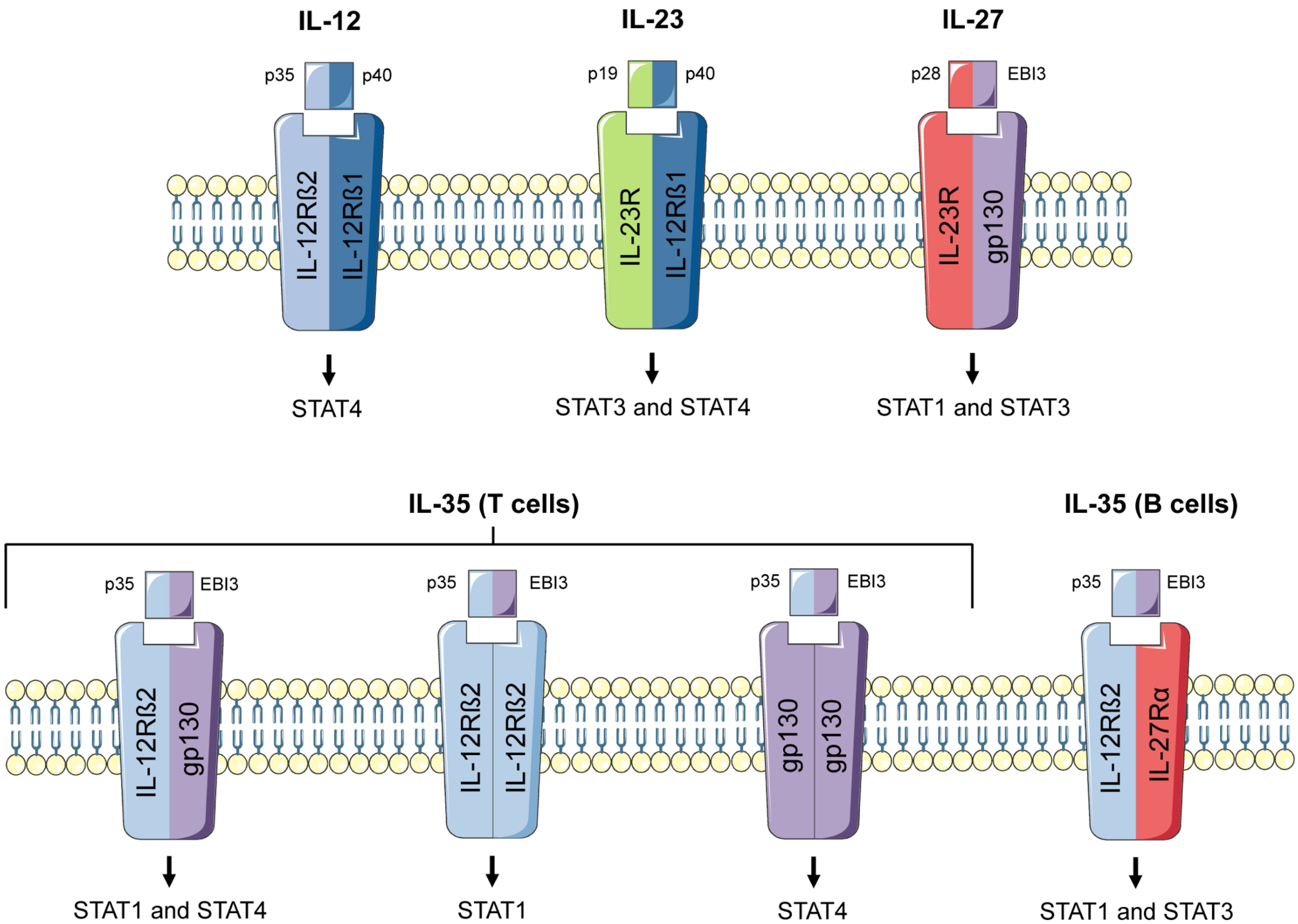

Fig. 1. Overview and composition of the IL-12 cytokine family and its receptors. All IL-12 cytokine family members are heterodimeric proteins consisting of an alpha subunit (p19, p28 or p35) and a beta subunit (EBI3 or P40). Receptors of the cytokines consist of 2 subunits (IL-12Rβ1, IL-12Rβ2, IL-23R, IL-27Rα and gp130) and are mainly heterodimers. Receptors belonging to IL-35 (IL-12Rβ2 and gp130) have been described to form homodimers. Binding of the IL-12 cytokine family to its receptor leads to activation of the STAT pathway and subsequent gene transcription.

1989, the heterodimeric structure and function of IL-12 were described for the first time [16]. After its discovery, a number of studies showed that IL-12 is a pro-inflammatory cytokine involved in T helper 1 (Th1) differentiation [17,18]. IL-12 is produced by various cell types among which monocytes, macrophages, dendritic cells and neutrophils [19]. IL-12 production by macrophages and dendritic cells results in Th1 activation and development [20,21]. This induces IFNγ production by T cells which favors Th1 differentiation [22]. Furthermore, it was shown that IFNγ is required for IL-12 induced Th1 development and the differentiation of activated $CD4^+$ T cells into Th1 cells leads to increased proliferation and secretion of IFNγ [23].

In addition to its function as a heterodimer, the p40 subunit of IL-12 can also function as a homodimer. By competing for its binding to IL-12Rβ1, homodimers of p40 acts as an IL-12 antagonist, both in vitro as well as *in vivo* [24–26].

The IL-12 receptor (IL-12R) consists of the two subunits IL-12Rβ1 and IL-12Rβ2 [27]. The IL-12R is mainly present on $CD4^+$ and $CD8^+$ T cells and NK cells while not detectable on resting T cells [28]. Upon mitogen stimulation, the expression of IL-12Rβ2 on resting T cells is upregulated [29]. Th1 cells express both IL-12R subunits while in Th2 cells only subunit IL-12Rβ1 is expressed [29,30]. Binding of IL-12 to its receptor is species specific and human IL-12 does not interact with the mouse IL-12R [27]. Upon binding of IL-12, signaling is mediated via the JAK-STAT family. IL-12-IL12R interaction can result in activation of STAT1, STAT3 and STAT4, but subsequent signaling is primarily mediated via STAT4 [27,31]. For IL-12-mediated IFNγ production, for example, both $CD4^+$ and $CD8^+$ T cell lineages require STAT4 signaling [32]. Only in Th1 cells, STAT4 can be phosphorylated by IL-12, because in Th2 cells the IL-12Rβ2 subunit is downregulated leading to IL-12 unresponsiveness [29,30].

2.2. Interleukin-23

In 2000, IL-23 was discovered by Oppmann and colleagues [33]. This cytokine shares the IL-12p40 subunit with IL-12 but is combined with the IL-23p19 subunit to form biologically active IL-23 [33]. IL-23 is produced by several innate and myeloid immune cells including macrophages and dendritic cells [34]. This cytokine has generally been shown to act pro-inflammatory and is involved in the differentiation and stabilization of Th17 cells by acting on memory T cells [35]. Furthermore, it promotes memory T cell activation and IL-17-mediated neutrophil recruitment [36].

The IL-23 receptor shares one of the subunits with IL-12 (IL-12Rβ1) but it does not bind to IL-12Rβ2 [33]. The other subunit is IL-23R, which is specific for IL-23 signaling [37]. The IL-23 receptor is expressed by Th17 cells, natural killer T (NKT) cells and activated T cells [34,37]. The effects of IL-23 are mediated via STAT3 and STAT4 signaling [33,37]. Previously it was shown that activation of STAT3 via IL-23 leads to binding of phosphorylated STAT3 to promoters of IL-17 thereby leading to increased generation of Th17 cells [38].

2.3. Interleukin-27

In 2002, IL-27 was identified for the first time [39]. IL-27 is composed of the EBI3 subunit (IL-12p40) and of p28 (IL-12p35) [40]. IL-27 is produced by antigen-presenting cells, such as macrophages and dendritic cells, and can have both pro- and anti-inflammatory effects as a regulator in the balance of pro- and anti-inflammatory responses. It can act pro-inflammatory by differentiating naïve $CD4^+$ T cells to a Th1 subset [39]. Furthermore, it supports IL-12-induced IFNγ production by these T cells and induces the expression of T-bet, the transcription factor of Th1 cells [41]. An example of the anti-inflammatory effect of IL-27 is that IL-27 can inhibit Th17 differentiation [42,43]. Furthermore, IL-27 can induce the conversion of naïve T cells into T regulatory type I-like (Tr1-like) cells, which secrete the anti-inflammatory cytokine IL-10 [44,45]. IL-27 has also been shown to suppress IL-2 production of $CD4^+$ T cells [46].

The IL-27 receptor consists of the subunits gp130 and the unique IL-27Rα (WSX-1) [47]. The IL-27R is mainly expressed by NK and naïve T cells, but also by several other immune cells including monocytes, mast cells and B cells. The IL-27 receptor is furthermore expressed by endothelial cells [47]. IL-27 mediates its effects via STAT1 and STAT3 after binding the IL-27R [41,48]. Subsequent phosphorylation of STAT1 and STAT3 leads to the induction of T-bet expression. Furthermore, it can induce IL-12Rβ2 on naïve T cells which may lead to more responsiveness to IL-12 and thereby differentiation to Th1 cells [41].

2.4. Interleukin-35

The last member of the IL-12 cytokine family that was discovered is IL-35 and this cytokine is composed of the subunits p35 and EBI3 [49]. In contrast to IL-12 and IL-23, IL-35 is an anti-inflammatory cytokine, which is mainly produced by regulatory T cells (Tregs) [6], and it has the capacity to suppress proliferation of T cells and their effector functions [49]. IL-35 can suppress the differentiation of Th17 cells and induce the expansion of Tregs [50]. Exogenous stimulation of naïve $CD4^+CD25^-$ T cells with IL-35 results in their differentiation into inducible regulatory T cells type 35 (iTr35), which induces T cell suppression via IL-35 production [51]. IL-35 also acts on B cells, mainly by inducing regulatory B cells (Bregs). Bregs are a regulator type of B cells [52] and represent a small population of B cells (1–2%), which participate in the suppression of immune responses by the production of IL-10 [53].

IL-35 can signal via three different IL-35 receptors on T cells. IL-35 can act via a heterodimeric receptor consisting of IL-12Rβ2 and gp130 [54]. Interestingly, in the absence of either one of the receptor chains, IL-35 has still suppressive capacity *in vivo*, possibly via homodimers of either IL-12Rβ2 or gp130 [54]. However, for maximal suppression, the complete heterodimeric receptor is required. Upon binding of IL-35 to its heterodimeric receptor, signaling is mediated via STAT1 and STAT4. Via gp130 IL-35 activates STAT1 signaling and via IL-12Rβ2 STAT4 signaling [54]. Binding of IL-35 to its receptor leads to the phosphorylation of the STAT proteins, which can then bind to specific sites in the promoter regions of IL-12a and EBI3 genes [54]. Thereby, IL-35 induces the expression of these genes, which lead to (enhanced) IL-35 production.

Besides affecting T cells, IL-35 has the capacity to inhibit proliferation of primary B cells and can expand IL-10 producing B cells [7]. In contrast to T cells, Wang and colleagues [7] showed that IL-35 signals via IL-12Rβ2 and IL-27Rα on B cells, although this study did not examine whether homodimers of one of these subunits are expressed by B cells. Binding of IL-35 to its receptor on B cells results in the activation of STAT1 and STAT3. Upon silencing of both these subunits, the inhibitory effect of IL-35 on B cell proliferation and IL-10 production was completely lost [7].

2.5. Interleukin-6

Due to its similarity in molecular structure, IL-6 and IL-12 cytokines are often called IL-6/IL-12 family cytokines. The α-subunits (p19, p28, and p35) of the IL-12 family members have a unique four-helix bundle conformation and are structurally homologous to that of IL-6 family cytokines [55]. This family includes IL-6, cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), IL-11, leukemia inhibitory factor (LIF) and oncostatin M (OSM) [56].

In 1986, IL-6 was identified as a B cell stimulatory factor inducing the maturation of B cells into antigen-producing plasma cells [57]. IL-6 is secreted by several immune cells including monocytes, macrophages but also by endothelial cells. Like the receptors for the IL-12 family members, the IL-6 receptor is a heterodimer and composed of gp130 and the IL-6R subunit [58]. The IL-6 receptor shares the gp130 subunit with the receptors for IL-12 family members IL-27 and IL-35 [56]. In contrast to cytokines of the IL-12 family, IL-6 can signal through both membrane-bound (classic signaling) and soluble IL-6 receptors (trans-signaling) [59]. Soluble IL-6R, which can still bind IL-6, is generated by proteolytic cleavage of the IL-6R [60]. Furthermore, cytokines of the IL-6 family can be secreted as monomers, while the IL-12 family cytokines form heterodimeric complexes [55]. For example, monomeric p28 can bind to the gp130 subunit and thereby inhibit IL-6 or IL-27 induced STAT signaling [61], while p28 dimerization with EBI3 leads to IL-27 secretion.

3. IL-12 family in human cardiovascular diseases

Cytokines of the IL-12 family have been shown to be important regulators in several inflammatory diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). RA is a chronic inflammatory disease in which disease severity score is correlated with increased levels of pro-inflammatory cytokines, including IL-12 [62]. Similarly, these cytokines have been implicated in cardiovascular diseases. Below, we have summarized the current knowledge regarding the IL-12 family members in cardiovascular diseases, including atherosclerosis and its subsequent acute cardiovascular syndromes (Table 1).

3.1. Interleukin-12

IL-12 has been shown to accumulate in human atherosclerotic plaques [63]. For example, by immunohistochemical staining with an antibody specific for IL-12p70, which comprises both subunits of IL-12, it was shown to be abundantly expressed in human advanced atherosclerotic lesion [63]. p40, one of the IL-12 subunits, was seen to be preferably expressed by monocytes rather than by $CD3^+$ T cells. It is however established that oxidized LDL can induce the release of IL-12p40 from PBMC isolated monocytes, showing that cells from the myeloid origin can express IL-12 in a hyperlipidemic setting [63]. However, the specificity of measuring only the p40 subunit of IL-12, which is also shared with IL-23, is obviously limited. Together, these data suggest that IL-12 is present in atherosclerotic lesions, and it would be of interest to determine its expression levels in different stages of atherosclerosis development.

Besides being present in the atherosclerotic plaque and thereby affecting the inflammatory status, circulating IL-12 may also be of interest as a biomarker for cardiovascular diseases. It was established in a cross-sectional study, investigating arterial stiffness and inflammatory markers, that circulating IL-12 levels associated with arterial stiffness as measured by pulse wave velocity [64]. In patients with acute coronary syndrome (ACS), the plasma levels of inflammatory markers were determined and compared between patients with events, such as acute myocardial infarction (AMI), unstable angina and death, and patients without these events [12]. IL-12 was shown to be increased in patients who developed events as compared to patients free of events [12]. Also, serum levels of IL-12 were increased in patients suffering from AMI when compared to patients with unstable angina pectoris or healthy controls [65].

Diabetes is a disease which is closely related to the incidence of atherosclerosis. Diabetic patients with cardiovascular complications

Table 1
The role of IL-12 family in human cardiovascular diseases.

Interleukin	Role in human cardiovascular disease	References
IL-12	Circulating serum levels associate with arterial stiffness	Yong et al. [64]
	Increased plasma levels in patients with acute coronary syndrome	Correia et al. [12]
	Increased serum levels in patients with acute myocardial infarction	Zhou et al. [65]
IL-23	Patients with lower extremity peripheral arterial diseases have increased serum levels compared to healthy controls	David et al. [71]
	Patients with carotid atherosclerosis have increased plasma levels compared to healthy control	Abbas et al. [13]
	High plasma levels associate with increased mortality and recent symptoms	Abbas et al. [13]
IL-27	Patients with coronary artery diseases have elevated serum levels compared to controls	Jin et al. [14]
	Patients with either acute myocardial infarction or unstable angina pectoris had higher serum levels compared to stable angina pectoris patients	Jin et al. [14]
IL-35	Patients with acute myocardial infarction, unstable angina, and stable angina have decreased plasma levels compared to patients with chest pain syndrome	Lin et al. [15]
IL-6	Unstable angina patients have increased plasma levels compared to stable angina patients	Biasucci et al. [79]
	Plasma levels are associated with acute coronary syndrome outcome	Biasucci et al. [79]
	In healthy men, increased risk of myocardial infarction associated with raised plasma levels	Ridker et al. [80]
	Elevated plasma levels increase the risk of death in unstable coronary artery disease patients after 6 and 12 months	Lindmark et al. [81]
	Elevated plasma levels in patients with acute myocardial infarction compared to healthy control	Miyao et al. [82]

have an altered lipid profile compared to diabetic patients without cardiovascular complications and healthy people [66]. The level of several pro-inflammatory cytokines, including IL-6, IL-12 and TNF-α, was shown to be increased in serum of diabetic patients with cardiovascular complications. Furthermore, this study showed that the increased serum IL-12 level correlated with increased levels of soluble VCAM-1, ICAM-1 and also increased levels of hs-CRP and LDL [66].

3.2. Interleukin-23

Pathology studies have shown that the expression of both IL-23 and IL-23R was increased in carotid atherosclerosis compared to non-atherosclerotic vessels [13]. However, there were no differences in the expression levels between asymptomatic and symptomatic patients [13].

Another study investigated the presence of IL-17A positive cells in human carotid artery plaques obtained from patients which underwent endarterectomy [67]. IL-17 is secreted by Th17 cells and proliferation of these Th17 cells can be induced by IL-23 [68]. Increased IL-17A expressing cells were found in plaques obtained from symptomatic patients (either stroke or transitory ischemic attack due to carotid stenosis) compared to asymptomatic patients [67]. IL-17 expression in human atherosclerotic lesions was however also associated with a decreased macrophage content and an enhanced smooth muscle cell content, which may be indicative of a more stable plaque phenotype [69]. Thus, studies establishing an association between IL17, Th17 cells and cardiovascular diseases (as recently reviewed by Nordlohne and von Vietinghoff [70]) seem to have rather diverse outcomes, which may be dependent on patient cohort and disease stage studied.

As a biomarker for cardiovascular diseases, IL-23 serum levels may be of interest. In patients suffering from lower extremity peripheral arterial diseases, serum IL-23 levels were increased compared to healthy controls, and these levels remained increased up to 5 days after lower extremity bypass surgery [71]. Interestingly, also patients with carotid atherosclerosis had increased plasma levels of IL-23 when compared to healthy controls [13]. Furthermore, high levels of IL-23 were associated with increased mortality and recent symptoms (e.g. transient ischemic attack, stroke within 2 months prior to clinical examination) [13].

3.3. Interleukin-27

The EBI3 subunit of IL-27, the subunit which is shared with IL-35, was shown to be expressed in advanced human atherosclerotic lesions obtained from patients with symptomatic stenosis of the carotid artery [72]. Immunohistochemical staining demonstrated that IL-27 was expressed by both $CD68^+$ macrophages and $CD31^+$ endothelial cells [72]. Recently, IL-27 was shown to enhance the upregulation of ICAM-1 and VCAM-1 on TNF-α-activated human endothelial cells [73], which suggests that IL-27 can contribute to vascular inflammation.

Serum levels of IL-27 were shown to be elevated in patients with coronary artery disease (CAD) compared to controls [14]. It was furthermore demonstrated that patients with either AMI or unstable angina pectoris had higher serum IL-27 levels compared to stable angina pectoris patients [14], establishing that IL-27 correlates with the severity of CAD.

3.4. Interleukin-35

Although being the last member of the IL-12 family that was discovered, data on IL-35 are rapidly accumulating. IL-35 increases the suppressive capacity of the anti-inflammatory regulatory T cells (Tregs) and thus suppresses the immune response. IL-35 plasma levels were shown to be decreased in patients suffering from AMI, unstable angina, and stable angina compared to patients with chest pain syndrome (chest pain with no signs of cardiovascular diseases) [15]. Also in type 1 diabetes (T1D) patients (both recent onset and longstanding), IL-35 levels were decreased in plasma when compared to age-matched healthy controls [74]. In RA patients levels of IL-35 were decreased compared to healthy controls [75]. Furthermore, IL-35 levels were lower in patients with active RA compared to inactive. These results suggest that there is an impaired IL-35 production in inflammatory disease, including RA and cardiovascular diseases, which may be associated with disease progression.

3.5. Interleukin-6

IL-6 was shown to be expressed in atherosclerotic arteries compared to non-atherosclerotic arteries [76]. More specifically, IL-6 was shown to be expressed in the shoulder region of coronary atherosclerotic lesions obtained from patients with unstable angina, and to co-localize with macrophages [77]. Quantitative analysis of IL-6 on protein and RNA level showed that IL-6 levels were increased in fibrous plaque compared to expression in intima and media tissue [78].

A number of studies showed that circulating IL-6 levels are associated with cardiovascular diseases. For example, increased plasma levels of IL-6 were found in patients with unstable angina compared to stable angina patients [79]. Furthermore, IL-6 plasma levels were associated with acute coronary syndrome outcome (either myocardial infarction or angina refractory) [79]. In healthy men, an increased risk of myocardial infarction was associated with raised IL-6 plasma levels [80]. In another study, elevated IL-6 plasma levels in unstable CAD patients were demonstrated to increase the risk of death in patients after 6 and 12 months [81]. In addition, patients suffering from AMI had elevated plasma IL-6 levels compared to healthy controls, from 6 h after symptom onset, which remained elevated over a time course of 4 weeks [82]. C-reactive protein, which is a marker of inflammation and cardiovascular risk in humans [83], correlates strongly with circulating IL-6 levels in both healthy men as well as patients with unstable angina [80,82].

Besides IL-6, also the association of its receptor with cardiovascular disease, IL-6R, has been investigated. In a meta-analysis, the IL-6R pathways and its relationship to coronary heart disease were assessed [84]. This study showed that a specific allel variant, which affects IL-6 signaling, is associated with decreased CRP levels and CAD. Furthermore, a Mendelian randomization analysis using single nucleotide polymorphisms in the IL-6R gene suggested that there was a strong evidence between IL-6R signaling and coronary heart disease [85]. IL-6R could, therefore, be a novel target to reduce the risk of CAD. Tocilizumab, which is an anti-human IL-6 receptor monoclonal antibody, reduces systemic and articular inflammation in rheumatoid arthritis patients [86]. This may thus also seem promising as a therapeutic to limit atherosclerosis, but this monoclonal antibody was shown to increase plasma total cholesterol, HDL and triglyceride levels in rheumatoid arthritis patients [84,86,87]. In a recent study however the increased lipid levels, caused by tocilizumab, were not associated with increased cardiovascular events, but nevertheless, treatment of cardiovascular patients with Tocilizumab seems unwanted [88].

4. IL-12 family in experimental cardiovascular disease models

Preclinical studies have resulted in a better insight in how the members of the IL-12 cytokine family are involved in the complex processes affecting cardiovascular diseases. Here, we have summarized the experimental studies that have investigated the effects of IL-12 cytokine family members on cardiovascular diseases (Table 2).

4.1. Interleukin-12

A number of experimental studies have investigated the contribution of IL-12 to the development of atherosclerosis and mainly found it to be pro-atherogenic. IL-12p40$^{-/-}$apoE$^{-/-}$ mice showed, for example, a reduced lesion size compared to apoE$^{-/-}$ mice due to reduced macrophage accumulation in the aortic root after 30 weeks of chow diet [89]. Vaccination against IL-12 in LDLr$^{-/-}$ mice also resulted in reduced lesion development, with an increased collagen content in a carotid artery atherosclerosis model [90]. In addition, vaccination led to a decrease in serum IFNγ levels and resulted in a complete absence of IFNγ in the plaque itself [90]. In both studies, however, the authors made use of the IL-12p40 subunit thereby not excluding targeting IL-23 as well. In an EAE model, an experimental model for multiple sclerosis, deficiency of IL-12p40 (IL-12 and IL-23) resulted in resistance to EAE, while IL-12p35 (only IL-12) deficient mice were more susceptible to this disease. These data suggest that IL-12 and IL-23 can have differential effects on disease progression [91], and it is thus of importance to discriminate between these cytokines in disease models. The pro-atherogenic effects of IL-12 in the vaccination study were nevertheless substantiated by treatment of apoE$^{-/-}$ mice with recombinant IL-12 for 30 days, which increased atherosclerotic lesion development and the lesions contained more CD3^{+} cells [92]. Together, these pro-atherogenic effects of IL-12 illustrate that it may be a highly relevant therapeutic target to limit atherosclerosis.

4.2. Interleukin-23

IL-23 is involved in Th17 cell differentiation and stabilization, but the effects of IL-23 on atherosclerotic lesion development have up to date not been investigated. The contribution of IL-17, which is secreted primarily by Th17 cells, has been investigated in atherosclerosis. In apoE$^{-/-}$ mice, IL-17A serum levels were increased compared to that of C57Bl/6 mice and also, the mRNA expression levels were increased in several organs such as aorta and spleen [93]. IL-17$^{-/-}$apoE$^{-/-}$ mice showed reduced lesion formation in both the aortic root and the whole aorta after 12 weeks of Western-type diet [94]. Macrophage content was reduced, while there was no difference in vascular smooth muscle content. In line with these data, blockade of IL-17A reduced lesion development in the aorta of apoE$^{-/-}$ mice after 15 weeks of Western-Type diet feeding [95]. Furthermore, circulating IL-6 and G-CSF levels were reduced, while IFNγ levels remained unaffected. Neutralization of IL-17 by means of a monoclonal IL-17A neutralizing antibody in mice did, depending on the antibody used, reduce the size or did not affect atherosclerotic plaque development [96,97], whereas a soluble IL-17A receptor reduced lesion size [93]. Interestingly, administration of recombinant IL-17 to LDLr$^{-/-}$ mice on high-fat diet increases

Table 2
The role of IL-12 family in experimental cardiovascular diseases.

Interleukin	Mouse model	Diet	Role in experimental cardiovascular disease	References
IL-12	IL-12$^{-/-}$apoE$^{-/-}$	Chow	Reduced lesion size due to reduced macrophage accumulation in the aortic root after 30 weeks but after 45 weeks no differences	Davenport et al. [89]
	LDLr$^{-/-}$	Western-type	Vaccination against IL-12 reduced lesion development, with an increased collagen content	Hauer et al. [90]
	apoE$^{-/-}$	Chow	Treatment with recombinant IL-12 increased atherosclerotic lesion development	Lee et al. [92]
IL-23			Possibly pro-atherogenic effect but studies are still lacking	
IL-27	LDLr$^{-/-}$	Western-type	Transplantation with bone marrow lacking the IL-27 receptor increases lesion size	Koltsova et al. [100]
	LDLr$^{-/-}$	High-cholesterol	Recombinant IL-27 treatment inhibits atherosclerotic lesion development	Hirase et al. [101]
	LDLr$^{-/-}$	High-cholesterol	EBI3 deficiency increases atherosclerotic lesion development without affecting serum cholesterol levels	Hirase et al. [101]
	LDLr$^{-/-}$	Western-type	Overexpression of IL-27 using EBI3-p28 plasmid increased lesion formation	Unpublished
IL-35	apoE$^{-/-}$	High-fat	Decreased levels of IL-35 compared to C57BL/6 mice after 8 weeks of high-fat diet	Wang et al. [104]
IL-6	IL-6$^{-/-}$apoE$^{-/-}$	Chow	Increased lesion size and more calcified lesions compared to apoE$^{-/-}$ mice	Schieffer et al.[106] and Elhage et al. [107]
	apoE$^{-/-}$	Low-fat and high-fat	Weekly injection of recombinant IL-6 increased lesion size by 2-fold	Huber et al. [108]
	C57BL/6	High-fat	Lesion size was 5-fold increased by recombinant IL-6 treatment	Huber et al. [108]
	LDLr$^{-/-}$	High-fat, high-cholesterol	IL-6 trans-signaling reduces atherosclerotic lesion development	Schuett et al. [109]

atherosclerosis [69]. Confusingly, reconstitution of LDLr$^{-/-}$ mice with IL-17A deficient bone marrow did not alter lesion size, despite the significant reduction in serum IL-17A levels [95], while reconstitution with IL-17A receptor deficient bone marrow in LDLr$^{-/-}$ mice reduced lesion development [98]. This indicates the complexity of IL-17 and that of Th17 cells in atherosclerosis, as was also recently reviewed [70]. Further studies are required to determine the exact contribution of IL-17 to the development and progression of atherosclerosis, and how IL-23 may affect the Th17 cell population.

Recently, the role of GM-CSF, a cytokine which induces IL-23, in advanced atherosclerotic lesion development was investigated in Western-Type diet fed LDLr$^{-/-}$ mice [99]. In this study, it was shown that the atheroprotective effect of GM-CSF deficiency was abolished upon IL-23 administration. Furthermore, IL-23 increased the apoptosis sensitivity of cultured macrophages and dendritic cells by down-regulating the anti-apoptotic protein Bcl-2, [99]. Although this suggests a pro-atherogenic effect of IL-23, studies investigating the direct effect of IL-23 are still lacking.

4.3. Interleukin-27

LDLr$^{-/-}$ mice transplanted with bone marrow lacking the IL-27 receptor showed increased lesion size [100]. Furthermore, these lesions contained more CD45^{+} leukocytes and CD4^{+} T cells, which confirm the hypothesis that IL-27 acts anti-inflammatory. Hirase and colleagues [101] showed that recombinant IL-27 treatment inhibits atherosclerotic lesion development. In this study, recombinant IL-27 was injected intraperitoneally 3 times per week in LDLr$^{-/-}$ mice on a high-cholesterol diet for 16 weeks. IL-27 treatment reduced the amount of lipid accumulation and thereby the formation of foam cells in the plaque. Studies investigating the effect of EBI3 deficiency in LDLr$^{-/-}$ mice showed that this led to increased atherosclerotic lesion development without affecting serum cholesterol levels [101]. IL-27 is also investigated in mouse models for multiple sclerosis and rheumatoid arthritis [43,102]. In collagen-induced arthritis, mice treated with IL-27 had lower disease incidence and both IL-6 and IL-17 serum levels were reduced in these mice [102]. Also, mice deficient in the IL-27 receptor (IL-27RA$^{-/-}$ mice) developed more severe EAE. In cultured CD4^{+} T cells, IL-27 was shown to reduce Th17 differentiation [43]. In another study, it was shown that IL-27 induced the production of IL-10 from both CD4^{+} and CD8^{+} T cells [45].

Although these studies indicate an anti-atherogenic and anti-inflammatory role for IL-27, studies in humans show that circulating IL-27 levels correlate with coronary artery disease [103]. Unpublished data from our group show that overexpression of IL-27 using an EBI3-p28 plasmid increased lesion formation. In this study, LDLr$^{-/-}$ mice were injected intramuscularly with EBI3-p28 plasmid and fed a Western-type diet for 10 weeks. Within the plaque, the amount of intraplaque T cells was increased upon IL-27 treatment, and the collagen content was also higher compared to the controls. Combined, these data indicate that IL-27 can have both pro- and anti-atherogenic effects.

4.4. Interleukin-35

Stimulation of naïve T cells with IL-35 results into the differentiation into inducible regulatory T cells type 35 (iTr35) [51]. Upon treatment with iTr35, C57BL/6 mice were shown to be completely protected from EAE [51]. These iTr35 mediate their suppression via secretion of IL-35 [51]. Tregs (CD4^{+}CD25^{+}CD45RB^{lo}) isolated from mice which lack either the IL-12α or EBI3 subunits showed a reduced capacity to suppress T cell proliferation [6]. In an experimental autoimmune uveitis model, mice treated with IL-35 were protected from this disease, which was due to the induction of regulatory B cells that produce IL-35 [7]. Studies investigating the effects of IL-35 on atherosclerotic lesion development have up to date not been published. A recent study did show that apoE$^{-/-}$ mice have lower circulating levels of IL-35 compared to C57BL/6 mice after 8 weeks of a high-fat diet [104]. Furthermore, LDLr$^{-/-}$ mice transplanted with EBI3$^{-/-}$ bone marrow showed increased atherosclerotic lesion development [101]. As mentioned earlier, this subunit is shared with IL-27 and thus, the atheroprotective effects cannot solely be ascribed to IL-35 [101].

4.5. Interleukin-6

Also in experimental models of cardiovascular disease, IL-6 has been associated with disease progression. In isolated aortas of 20–24-week old apoE$^{-/-}$ mice, IL-6 mRNA expression could be measured, while this was not detectable in non-atherosclerotic C57Bl/6 mice [105]. In addition, using ex vivo aortic organ culture assays, IL-6 was secreted in 10-fold higher amounts from apoE$^{-/-}$ aortas as compared to C57Bl/6 aortas. Interestingly, the amount of IL-6 correlated with the total atherosclerotic lesion size [105].

IL-6 deficiency in apoE$^{-/-}$ mice resulted in increased lesion size compared to apoE$^{-/-}$ mice [106,107] and showed more calcified lesions [107]. Interestingly, serum IL-10 levels were reduced and this was associated with decreased macrophage and leukocyte content in the atherosclerotic lesion. Furthermore, total cholesterol levels were higher in apoE$^{-/-}$IL6$^{-/-}$ mice, which was shown to be caused by increased VLDL and LDL levels [106]. These data suggest that IL-6 can act as an anti-atherogenic cytokine.

In contrast to these studies, weekly injections of recombinant IL-6 increased lesion size by 2-fold in apoE$^{-/-}$ mice both on a low-fat and high-fat diet when compared to saline-treated mice [108]. In C57Bl/6 mice on a high-fat diet lesion size was increased 5-fold upon treatment with recombinant IL-6 [108]. In this study, no effect of IL-6 treatment was observed on total cholesterol levels.

In another study, the effect of inhibition of trans-signaling of IL-6 was investigated on atherosclerosis [109]. Trans-signaling is a process were IL-6 binds to the soluble IL-6 receptor (sIL-6R) instead of the membrane-bound receptor (classic signaling). By using sgp130Fc (a fusion protein of the natural sgp130 and IgG1-Fc) trans-signaling can be completely blocked while not affecting the classic signaling [110]. Using LDLr$^{-/-}$ mice on diet for 8 and 16 weeks, it was shown that inhibition of the soluble complex IL-6/sIL-6R reduced atherosclerotic lesion development [109]. In addition, these lesions contained fewer macrophages and there was a reduced expression of VCAM-1 and ICAM-1. Overall, these studies indicate that IL-6 signaling can have both pro- and anti-atherogenic effects.

5. IL-12 family – Targeted therapies in cardiovascular diseases

In the human atherosclerotic plaque, a variety of pro-inflammatory cytokines has been shown to be expressed and these cytokines may be of therapeutic interest in cardiovascular diseases [111]. Several studies show for example the potential of blocking IFNγ or TNF-α [112,113], and also, IL-1β levels were shown to be increased in human atherosclerotic coronary arteries [114]. Very recently, the effects of IL-1β inhibition on the cardiovascular outcome were described [115], which showed that the human monoclonal antibody canakinumab, that inhibits IL-1β, reduced the incidence of recurrent cardiovascular events (such as myocardial infarction) in stable patients with coronary artery disease [115].

Because of its pro-atherogenic role, IL-12 could be a pharmaceutical target for the treatment of inflammatory diseases including atherosclerosis. As discussed in this review, blockade of IL-12 has shown protective effects in atherosclerotic lesion development and resulted in increased plaque stability [90]. Less is known regarding IL-23 in inflammatory disorders and the effects of IL-23 in atherosclerosis still have to be determined.

For the treatment of other inflammatory diseases (psoriasis, psoriatic arthritis, Crohn's disease and multiple sclerosis), a monoclonal antibody named ustekinumab was developed. The interaction between

IL-12/IL-23 and their receptor is prevented by this antibody, which leads to blockade of the subsequent intracellular signaling and cytokine production [116]. However, for multiple sclerosis, ustekinumab was only effective in very early disease and not in patients with chronic disease, thus limiting the therapeutic use of this antibody [117]. Furthermore, a more recent study showed that treatment with ustekinumab could even increase the risk of major adverse cardiovascular events [118]. This suggests that although blocking pro-inflammatory cytokines seems promising, it could also have (severe) side effects. Another example of such a side effect was anti-TNF therapy, which altered the plasma lipid levels in rheumatoid arthritis patients to a more pro-atherogenic profile after 1 year of treatment [119]. There is thus an urgent need for new therapeutic targets. The EBI3 subunit of IL-35 was shown to be expressed in advanced human atherosclerotic lesions [72] and decreased IL-35 serum levels have been observed in several inflammatory diseases [15,74,75]. Based upon the experimental evidence in other disease models, IL-35 is thought to be potentially atheroprotective. Therefore, it could be of interest to use IL-35 as a therapeutic protein in atherosclerotic lesion development, however more experimental evidence establishing an atheroprotective effect of IL-35 needs to be provided. Furthermore, administration of anti-inflammatory cytokines may also not be as simple. For example, exogenous provision of IL-10, which is a potent anti-inflammatory cytokine, has been shown in several clinical trials not to be as efficient as predicted [120]. A more targeted delivery towards the atherosclerotic lesion could be a novel strategy although safety and efficacy should be determined before applied in human diseases [121].

6. Conclusion

The IL-12 cytokine family consists of pro- and anti-inflammatory cytokines, which can either induce or inhibit the progression of atherosclerosis. Subunits of the IL-12 family members and its receptors are locally expressed within the atherosclerotic plaque and increased serum levels of IL-12, IL-23 and IL-27, as well as reduced IL-35 levels, are associated with cardiovascular diseases. Experimental data have resulted in a better understanding of the contribution of IL-12 family members to immune-mediated disorders such as cardiovascular diseases, however, further research will shed more light on for example the therapeutic application of IL-35.

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Disclosures

None.

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