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IL-1 family cytokines in cardiovascular disease

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ABSTRACT

The interleukin (IL)-1 family is a group of cytokines crucially involved in regulating immune responses to infectious challenges and sterile insults. The family consists of the eponymous pair IL-1α and IL-1β, IL-18, IL-33, IL-37, IL-38, and several isoforms of IL-36. In addition, two endogenous inhibitors of functional receptor binding, IL-1R antagonist (IL-1Ra) and IL-36Ra complete the family. To gain biological activity IL-1β and IL-18 require processing by the protease caspase-1 which is associated with the multi-protein complex inflammasome. Numerous clinical association studies and experimental approaches have implicated members of the IL-1 family, their receptors, or component of the processing machinery in underlying processes of cardiovascular diseases (CVDs). Here we summarize the current state of knowledge regarding the pro-inflammatory and disease-modulating role of the IL-1 family in atherosclerosis, myocardial infarction, aneurysm, stroke, and other CVDs. We discuss clinical evidence, experimental approaches and lastly lend a perspective on currently developing therapeutic strategies involving the IL-1 family in CVD.

1. The history of IL-1 family members

Among the broad range of cell signaling-inducing cytokines the interleukin 1 family represents a group of molecules principally targeting leukocytes. In the 1940 s discovery of cytokines began with the search of endogenous mediators of fever, yet until today the overall goal was and remains to clarify the axis of infection, fever, and inflammation. Indeed, Menkin and Bennett discovered fever-inducing factors in the supernatant of rabbit neutrophils unrelated to endotoxin involvement [1,2]. For the next two decades the characterization of the endogenous fever protein termed “Leukocytic Pyrogen” continued [3]. The examination of the unfractionated supernatant revealed involvement of the so called “Lymphocyte Activating Factor” in excessive proliferation of lymphocytes in response to antigen [4]. The characterization of the small, non-structural proteins was the challenging task for next decade. The reported successful purification of human Leukocyte Pyrogen in 1977 demonstrated its similarity with the Lymphocyte Activating Factor [5].

To unify the nomenclature of the broad range of terms used, the name interleukin (IL) was defined by a committee of the International Union of Immunological Societies (IUIS) for these 17–20 kDa evolutionarily ancient cytokines expressed by leukocytes [6]. With its currently 11 members, the IL-1 family (Table 1) is the largest family of interleukins and closely linked to innate inflammatory and immune responses, the major contributors to non-communicable diseases [7].

The cytokines IL-1α and IL-1β represent close homologues of IL-1 gene family-coded proteins. Neither contains a secretion sequence, however, both share a similar structures and are initial present as 30 kDa precursor forms [18]. They are converted to their bioactive 17.5 kDa forms by enzymatic cleavage [19]. In contrast to IL-1β, IL-1α shows biologically activity as intact, full-length form [20]. IL-1α and IL-1β bind to the same receptor and share similar functional characteristics as potent pro-inflammatory cytokines.

The IL-1 receptor type 1 (IL-1R1) is expressed by several cell types, including immune cells and non-hematopoietic cells (e.g. smooth muscle cells). The binding of the two distinct ligands IL-1α and IL-1β induces pro-inflammatory effects [19,21].

In contrast, the IL-1 receptor antagonist (IL-1Ra) acts as endogenous inhibitor blocking the binding of IL-1α and IL-1β to IL-1R1. IL-1Ra contains a signal peptide at the N-terminus for the effective secretion. Rare mutations associated with absence of IL-1Ra lead to uncontrolled activity of IL-1 and severe systemic inflammation [22,23]. Subtle changes in the carefully regulated IL-1/IL-1Ra system result in a broad range of chronic inflammatory conditions (e.g., type 2 diabetes mellitus, psoriasis, rheumatoid arthritis, inflammatory bowel disease) [24,25].

Engagement of the ligand (IL-1α or -β) with the heterodimeric receptor consisting of IL-1R1 and IL-1R-accessory protein (IL-1RAcP)

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Table 1
IL-1 family cytokines.

Name Synonym	Function	Gene (human/mouse) ID name location	Ref.
IL-1α IL-1F1, hematopoietin-1	Pro-inflammatory, Th17 cell response, tissue repair	3552/16175 *IL1A*/Il1a 2q14.1/2 F1; 2 62.9 cM	[8]
IL-1β IL-1F2, leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor	Pro-inflammatory, Th17 cell response, tissue repair	3553/16176 IL1B/Il1b 2q14.1/2 F1; 2 62.97 cM	[9]
IL-1Ra Interleukin-1 receptor antagonist, IL-1F3	Antagonist for IL-1α, IL-1β	3557/16181 IL1RN/Il1rn 2q14.1/2 A3; 2 16.36 cM	[10,11]
IL-18 IL-1F4, IFNγ-gamma inducing factor (IGIF)	Pro-inflammatory, Th1 polarization, IL-22 signaling	3606/16173 IL18/Il18 11q23.1/9 A5.3; 9 27.75 cM	[12]
IL-33 IL-1F11	Pro-inflammatory, Th2 polarization	90865/77125 IL33/Il33 9p24.1/19; 19 C1	[13]
IL-36Ra Interleukin 36 receptor antagonist, IL-1F5, FIL1(δ)	Antagonist for IL-36α, IL-36β, IL-36γ (NFkB induced IL-1 family members)	26525/54450 IL36RN/Il1f5 2q14.1/2 A3; 2 16.31 cM	[14]
IL-36α IL-1F6, FIL1(ε)	Pro-inflammatory	27179/54448 IL36A/Il1f6 2q14.1/2 A3; 2 16.26 cM	[15]
IL-36β IL-1F8, FIL1(η)	Pro-inflammatory	27177/69677 IL36B/Il1f8 2q14.1/2 A3; 2 16.21 cM	[15]
IL-36γ IL1-F9	Pro-inflammatory	56300/215257 IL36G/Il1f9 2q14.1/2 A3; 2 16.24 cM	[16]
IL-37 IL-1F7, FIL1(ζ)	Anti-inflammatory	27178/n/a *IL1F7*/n/a 2q14.1/n/a	[15]
IL-38 IL-1F10, FIL1(θ)	Anti-inflammatory	84639/215274 ILF10/Il1f10 2q14.1/2 A3; 2 16.32 cM	[17]

induces signal transduction leading to the synthesis of acute phase and pro-inflammatory proteins (Fig. 1) [26]. The highly-sensitive IL-1/IL-1R1/IL-1RAcP signaling complex is considered a major pathway to activate the inflammatory response during infection, tissue damage, or stress by only 10 activated receptors/cell or less [27].

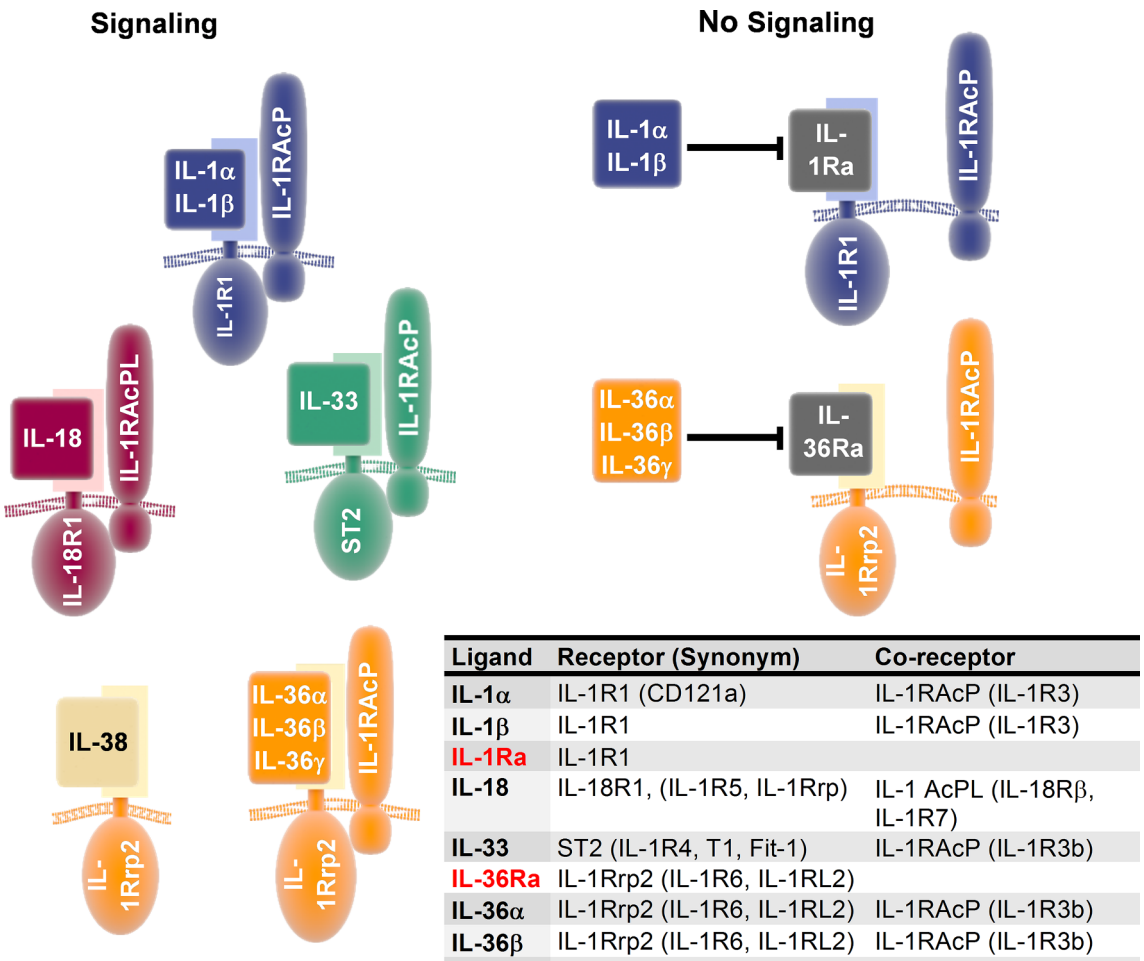
IL-1R2 (known as CD121b) provides negative regulation of the IL-1 pathway. This receptor lacks intracellular signaling capacity and acts as a decoy receptor competitively binding IL-1α and IL-1β thus inhibiting signal transduction through the IL-1R1 complex [28]. The receptor-based signal transduction initiation is further negatively controlled by the antagonists IL-1Ra and IL-36Ra, which represent an additional repressive chain to balance the inflammation response [28].

IL-1 family members are generally expressed as precursors that require specific proteolytic cleavage for the enhanced signal transduction. The preform of IL-1α is activated via calpain, a Ca-dependent cysteine-protease, whereas IL-1β and IL-18 precursors require proteolytic processing by the inflammasome, a complex of intracellular molecules containing the enzyme caspase-1 (see below) [29,30]. IL-33 and IL-36 require neutrophil proteinases (elastase, Proteinase-3 (PR3), and Cathepsin G) for their processing [31,32]. While the other members of the IL-1 family have relatively short pro-peptides (< 40 amino acid residues), the pro-peptides of IL-1α, IL-1β, and IL-33 comprise ≈ 110 amino acid residues at their N-terminus [30].

2. General role of IL-1 family members

2.1. IL-1α

IL-1α is constitutively expressed in the cytoplasm and nuclei of a range of non-hematopoietic cells in various tissues (e.g. lung, liver, and kidney) [33], but is also upregulated in immune cells [34]. Besides its classical function as cytokine via local contact-dependent cell surface receptor ligation, full-length pro-IL-1α can also directly regulate gene expression via an N-terminal amino acid sequence within its nuclear localization site [35]. The proteolytic cleavage of pro-IL-1α is driven by the membrane-associated calcium-dependent cysteine-protease calpain



Ligand	Receptor (Synonym)	Co-receptor
IL-1α	IL-1R1 (CD121a)	IL-1RAcP (IL-1R3)
IL-1β	IL-1R1	IL-1RAcP (IL-1R3)
IL-1Ra	IL-1R1	
IL-18	IL-18R1, (IL-1R5, IL-1Rrp)	IL-1 AcPL (IL-18Rβ, IL-1R7)
IL-33	ST2 (IL-1R4, T1, Fit-1)	IL-1RAcP (IL-1R3b)
IL-36Ra	IL-1Rrp2 (IL-1R6, IL-1RL2)	
IL-36α	IL-1Rrp2 (IL-1R6, IL-1RL2)	IL-1RAcP (IL-1R3b)
IL-36β	IL-1Rrp2 (IL-1R6, IL-1RL2)	IL-1RAcP (IL-1R3b)
IL-36γ	IL-1Rrp2 (IL-1R6, IL-1RL2)	IL-1RAcP (IL-1R3b)
IL-37	Unknown	Unknown
IL-38	IL-1Rrp2	Unknown

Fig. 1. The receptor complexes of IL-1 family member. The binding to their receptors and the generation of complexes with co-receptors, can activate signaling while antagonists like IL-1Ra and IL-36Ra (red) inhibit the inflammatory responses driven by IL-1 cytokines.

and through inflammasome activation [36]. While IL-1α is not commonly found in the circulation or body fluids, its presence strongly increases in inflammatory disease [37].

2.2. IL-1β

The mayor source of IL-1β secretion are monocytes and macrophages, dendritic cells (DC), neutrophils, B lymphocytes, and natural killer (NK) cells as well as non-immune cells such as keratinocytes [38]. The precursor form is rapidly induced and accumulates in cells by activation of pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) with pathogen-derived products or factors released by damaged cells [39]. Similar to IL-1α, the bioactivity of IL-1β is controlled through cleavage by a protease, in this case caspase-1, the effector molecule of the NLRP3 (nucleotide-binding leucine-rich repeat-containing pyrin receptor 3)-inflammasome [29,40]. However, activation of IL-1β that is either mediated by NLRP3-independent inflammasomes or entirely inflammasome-independent was reported in caspase-1-deficient mice involving neutrophil proteases [41]. Cells of the monocyte-macrophage lineage mediate a large part of their autocrine, paracrine, and endocrine effects via IL-1β. Thus, this cytokine is involved in a broad spectrum of inflammatory conditions involving pro-inflammatory processes on a variety of cell types that do, however, differ from auto-immune disorders driven by T cells [34,42].

2.3. IL-18

IL-18 was initially described as IFNγ-inducing factor isolated from endotoxin-treated mice [12]. Similar to IL-1β, IL-18 is synthesized as inactive precursor from and requires processing by caspase-1. The 24 kDa precursor is constitutively present in blood monocytes, peritoneal macrophages, endothelial cells, keratinocytes, and intestinal epithelial cells in the entire gastrointestinal tract [43]. Mature IL-18 forms a low-affinity signaling complex with its own receptor IL-18R1 [44], a homologue to IL-1R1. Without binding to the co-receptor IL-1RAcP-like (IL-1RAcPL, IL-18R beta chain; IL-18Rβ), there is no functional pro-inflammatory signal Fig. 1) [45]. Together with IL-12, IL-18 synergistically induces IFNγ production in T-helper type 1 (Th1) cells and promotes Th1 cell polarization [46]. In addition, IL-18 regulates IFNγ release by NK cells [47], cytotoxic T cells [48] and even smooth muscle cells [49]. Recently, Huber and colleagues showed a role for IL-18 in restricting expression of IL-22 binding protein (IL-22BP), the endogenous inhibitor of the tissue-protective cytokine IL-22 [50].

IL-18 binding protein (IL-18BP) belongs to a family of secreted proteins with structurally and functionally similarities to IL-1R2. This soluble decoy receptor, purified from blood of healthy individuals, has a high binding affinity to mature IL-18 [51]. IL-18BP inhibits binding of IL-18 to IL-18R1 thus decreasing Th1 polarization [52].

Recent findings suggest the complementary role of IL-18 and IL-1β in the pathogenesis of cutaneous and systemic manifestations of

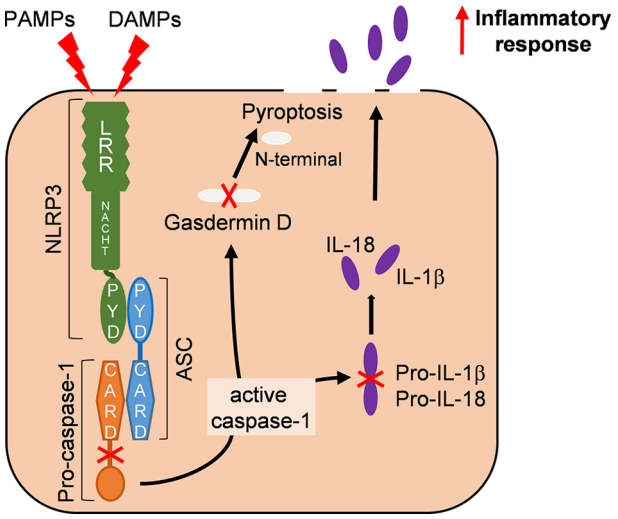


Fig. 2. Canonical NLRP3 inflammasome activation. The PAMPs- and DAMPs-stimulated NLRP3 inflammasome converts pro-caspase-1 to the active form. Caspase-1 further activates gasdermin D that disrupts the integrity of cell membrane by its N-terminal part and by that confers intrinsic pyroptosis-inducing activity. In addition, caspase-1 proteolytically converts the precursor of IL-1β and IL-18 to the bioactive form. The pyroptosis-driven release of the highly pro-inflammatory cytokines enhance the systemic immune response.

cryopyrin-associated periodic syndrome (CAPS) [53]. IL-18 expression is implicated in several autoimmune diseases, myocardial pathology, emphysema, metabolic syndrome, inflammatory bowel disease, macrophage activation syndrome, sepsis, inflammatory skin diseases, and metastasis formation [54,55].

2.4. IL-33

IL-33 is released by epithelial cells, endothelial cells, osteoblasts, fibroblasts, and immune cells (e.g. mast cells, DC, macrophages) in response to cell injury and necrosis but also less-fatal tissue imbalances such as adiposity or allergic challenges [56–58]. It acts as alarmin in the intestine in response to epithelial cell injury and initiates innate immune responses by binding to its unique receptor ST2 (suppression of tumorgenicity 2; IL-1R4) and the co-receptor IL-1RAcP [59,60]. Due to the epithelial expression of IL-33 and ST2 expression on Th2 cells, mast cells, and activated leukocytes the IL-33/ST2 signaling axis plays a key role in mucosal immunity [61]. The IL-33/ST2 axis was shown to primarily induce type 2 immune responses by Th2 and can drive the production of Th2-associated cytokines (e.g. IL-4). However, it can also active Th1 cells, group 2 innate lymphoid cells (ILC2s), regulatory T (T_{reg}) cells, $CD8^+$ T cells and NK cells [62].

2.5. IL-36

The IL-36 subfamily comprises 3 novel pro-inflammatory IL-1 family members, namely IL-36α, IL-36β, and IL-36γ (formerly known as IL-1F6, IL-1F8, and IL-1F9) [15]. They are primarily produced by innate immune cells, lymphocytes, and epithelial cells in the skin, lung, and brain [63]. Like other IL-1 family members, IL-36 cytokines require proteolytic processing. Removal of the N-terminus increases activity by 10000-fold, however, the involved proteases are currently unknown [64]. Alternative activation was shown by neutrophil derived proteases cathepsin G, elastase, and PR3 [31]. Mature IL-36α, -β, and -γ bind specifically to the IL-36 receptor (IL-1Rrp2) using the co-receptor IL-1RAcP [34]. IL-36 signaling is regulated by the IL-36 receptor antagonist (IL-36Ra), that shares 47% homology with IL-1Ra, but differs in its biological activity [65]. The pro-inflammatory effects of IL-36 are inhibited by the competetive binding of IL-36Ra to IL-1Rrp2 blocking the recruitment of the second receptor IL-1RAcP [64]. IL-36Ra is predominantly expressed in epithelial tissues and plays a role in skin diseases like psoriasiform dermatitis by controlling the IL-23/IL-17/IL-22 pathway [66]. IL-36 cytokines promote a number of factors that induce Th1 and Th17 polarization.

2.6. IL-37 and IL-38

Monocytes, macrophages, and epithelial cells express IL-37, that shares structural pattern with IL-1α, -β, and IL-18. The 5 known isoforms are expressed tissue-dependently and are regulated by LPS (Lipopolysaccharide S) and other TLR agonists [67]. Via binding to the extracellular binding domain of IL-18R1, IL-37 forms a complex with IL-18BP reducing IL-18 activity [68]. IL-37 acts during stress induction and has an inhibitory effect to excessive inflammatory responses by a negative feedback loop downregulating the secretion of pro-inflammatory cytokines such as TNFα, IL-1β, and IL-6 [69].

The other anti-inflammatory active IL-1 family member, IL-38, was first cloned in 2001 und shares some homology with IL-1Ra and IL-36Ra [17]. IL-38 exhibits a controversially discussed anti-inflammatory effect on peripheral blood mononuclear cells while acting pro-inflammatory on DCs [70]. Notably, these anti-inflammatory effects of IL-37 and IL-38 require further investigation and potential involved co-receptors are not identified yet. New insights about these cytokines and their crucial role in inflammatory responses may help to design new treatments of autoimmune diseases [71].

2.7. Inflammasome

Inflammation encompasses the immune response to exogenous or endogenous stimuli released during an initial cause of tissue trauma, infection or less harmful disruptions of tissue homeostasis (e.g., during chronic inflammatory responses, such as atherosclerosis) [72]. Molecules released from dying cells, altered or modified host cell products represent damage-associated molecular patterns (DAMPs; e.g. Heat shock proteins (HSPs), High-Mobility-Group-Protein B1 (HMGB1), uric acid or cholesterol crystals). Similar to pathogen-associated molecular patterns (PAMPs; e.g. LPS, viruses, dsRNA, extracellular ATP), they are detected by PRRs (e.g. TLRs) on immune cells and play a crucial role for the initial activation of innate immunity. Similar to classical PRRs, the inflammasome recognizes PAMPs or DAMPs and acts as signaling platform [73].

The central part of the most widely characterized intracellular inflammasome complex is the sensor protein NLRP3, a NLR family member [29] with 3 highly-conserved domains (a central NACHT nucleotide-binding domain, a C-terminal leucine-rich repeat (LRR), and a N-terminal death-fold pyrin domain (PYD) (Fig. 2) [74,75]. In addition, inflammasome formation requires apoptosis-associated speck-like protein (ASC) containing a caspase activation and recruitment domain (CARD) and the cysteine protease caspase-1 [76]. DAMPs recognition leads to an oligomerization of 7 NLRP3 monomers and triggers the helical fibrillar assembly of the adapter ASC via pyrin domain (PYD)–PYD interactions [76]. Recent work has also identified a critical role for microtubule-affinity regulating kinase 4 (MARK4) which binds NLRP3 and allocates it to the microtubule-organization center, a prerequisite for the formation of a large inflammasome speck complex [77]. Via these interactions, ASC recruits pro-caspase-1 via the CARD domain. The subsequent autocatalytic activation of caspase-1 is the molecular output of inflammasome assembly and represents the so called canonical inflammasome activation [29,78], that controls the maturation of IL-1β and IL-18 by proteolytic cleavage of their respective inactive precursor forms [76]. Caspase-1-triggered cleavage and activation of the pore-forming substrate gasdermin D initiates pyroptosis, a form of cell death [79] and the release of IL-1β and IL-18 (Fig. 2) [80]. Under certain circumstances, inflammasome activation can lead to the extracellular release of inflammasome components like

ASC, NLRP3 and pro-caspase-1. These can further augment the inflammatory cascade by activating interstitial cytokine precursors [81].

Mutations altering the NLRP3 inflammasome can result in auto-inflammatory disorders, primarily observed in children and described as Cryopyrin-associated periodic syndrome (CAPS) based on an increased secretion of IL-1β [82]. Patients with the rare auto-inflammatory disorder Muckle Wells syndrome (MWS) carry a missense mutation of NLRP3 leading to its increased activity [83] and a subsequent increased caspase-1 triggered activation of IL-1β and IL-18 resulting in systemic inflammation [84]. The clinical features of CASPs (e.g. MWS; neonatal-onset multisystem inflammatory disease (NOMID)) and rheumatoid arthritis [85,86] are typically treated with canakinumab (human, monoclonal, neutralizing anti-IL-1β antibody), anakinra (recombinant version of IL-1Ra), and rilonacept (IL-1 trap/inhibitor), all of which successfully reduce associated inflammatory effects [87].

3. Diseases and experimental models

3.1. Atherosclerosis

Cardiovascular diseases (CVD) with atherosclerosis as the major underlying pathophysiological process, are the leading cause of death worldwide [88]. Atherosclerosis is a chronic inflammatory condition of medium- and large-sized arteries characterized by the generation of leukocyte-rich plaques elicited by hyperlipidemic conditions and dysfunctional clearance of lipoprotein particles from the vessel wall [89–91].

The chronic inflammatory response fosters leukocyte adhesion to the dysfunctional endothelium. A plethora of mediators involved in the processes of atherosclerosis are known to also play crucial roles in the biology of the IL-1 cytokine family. Indeed, oxidized low-density lipoprotein (oxLDL), considered a major plaque-borne immunogenic factor, can ligate TLRs or scavenger receptors such as CD36 thus leading to enhanced expression and/or activation of IL-1α [92], IL-1β [93–95], and IL-18 [96]. Of note, necrosis and apoptosis, which are frequent phenomena of atherosclerotic lesions, can also lead to activation of IL-1α and IL-1β [97]. More than two decades ago IL-1α and IL-1β expression in atheroma was reported [98]. Macrophages were identified as the predominant IL-1α and IL-1β sources within the lesion *in vivo* [98] and produced significantly more mRNA of these cytokines also *in vitro* when isolated from hyperlipidemic LDL receptor-deficient ($Ldlr^{-/-}$) mice [99].

Apolipoprotein E-deficient ($Apoe^{-/-}$) mice displayed reduced lesion burden when reconstituted with bone marrow from either IL-1α- or IL-1β-deficient donor mice compared to control mice receiving wild type bone marrow reconfirming the predominant role of hematopoietic cells in IL-1 family cytokine production [100]. Interestingly, in this study bone marrow-restricted deficiency in IL-1α conferred a higher degree of athero-protection corroborating a previous study using compound-deficient mice [101]. Using similar *in vivo* models and detailed *in vitro* experimentation, Freigang et al. could recently confirm the atherogenic function of both IL-1α and IL-1β, yet they also demonstrated that these two cytokines vary sharply in the factors regulating them and their mode of action [102]. Despite these differences, combined deficiency IL-1α and IL-1β does not confer additive protection in atherosclerosis [100] supporting reports of an intricate mechanism of counter regulation between these cytokines [102]. Others have also demonstrated reduced plaque formation in mice deficient in IL-1β [103] or injected with an IL-1β-antagonizing antibody [104].

In agreement with the pro-atherogenic function of its ligands deficiency of IL-1R alleviated plaque formation in models of hyperlipidemia [105] and bacteremia-accelerated atherosclerosis [106]. Of note, expression of IL-1R on vascular cells appears more relevant for its pro-atherogenic function than its presence on hematopoietic cells suggesting a directional pro-atherogenic pathway mediating signals from leukocytes to endothelial and smooth muscle cells within nascent plaques [107].

In line with its biological activity to block IL-1α and IL-1β-mediated activity, recombinant IL-1Ra [108] or endogenous overexpression [109] reduced lesion formation while heterozygous gene deficiency led to accelerated atherosclerosis [110].

Studies on carotid atherosclerotic plaques showed significant elevated levels of IL-18 mRNA in unstable compared to stable plaques [111]. Prompted by known elevated IFNγ expression during atherosclerotic plaque progression, further analysis proved the expression of functional IL-18 and IL-18R1 on human atheroma-associated cells and identified IL-18 as novel source to induce IFNγ on mononuclear phagocytes and surprisingly smooth muscle cells [49]. Corroborating these results and the critical role of IFNγ in atherosclerosis, lack of IL-18 led to increased levels of serum cholesterol and triglyceride, however, so to reduced lesion development in mouse model of atherosclerosis [112].

The application of recombinant IL-18 in T cell-deficient mice caused larger lesions and elevated IFNγ levels [113] implicating that IL-18 triggers IFNγ expression independently of T cells. Interestingly, IL-18 can affect atherosclerosis in $Apoe^{-/-}$ mice even in the absence of IL-18R1, as we recently discovered functional interaction of IL-18 with NaCl co-transporter (NCC) in atherosclerotic lesions [114]. Besides *in vitro* and animal studies clinical data confirmed the association of elevated IL-18 levels with CVD risk factors [115] complementing traditional cardiovascular biomarkers in the identification of patients at risk.

Enhanced expression of IL-33 in atherosclerotic tissue implicates an athero- protective function of this anti-inflammatory cytokine [116]. Indeed, when exogenous IL-33 was administered $Apoe^{-/-}$ mice developed less lesions while inhibiting the receptor ST2 aggravated disease. Of note, IL-33 promotes Th2-mediated immunity and increased protective oxLDL antibody level in serum [116]. Furthermore, *in vitro* studies identified IL-33 as key regulator of macrophage foam cell accumulation, the mayor cellular component of active atherosclerotic plaques. IL-33/ST2 signaling diminished acetylated LDL/oxLDL uptake as well as reduced intracellular total and esterified cholesterol levels. Confirming these findings, $Apoe^{-/-}$ mice treated with IL-33 showed markedly reduced levels of foam cell accumulation within atherosclerotic plaques *in vivo* [117].

Consistent with the central role in maturation of IL-1β and IL-18 mice lacking caspase-1 developed less atherosclerosis and displayed a lesion phenotype with smaller inflammatory infiltrate [118,119]. Additional studies employing bone marrow transplantation revealed that caspase-1 is mainly active in hematopoietic cells to propagate IL-1β - and IL-18-mediated atherosclerosis [120]. Duewell et al. showed that mice lacking the inflammasome components NLRP3 or ASC had markedly less atherosclerosis, comparable to that of combined IL-1α/β deficiency [121]. Notably, they also identified cholesterol crystals as culprit activators of the inflammasome in experimental atherosclerotic lesions [121]. Concordantly, solubilizing these crystals using cyclodextrin can reduce atherosclerotic burden and alleviate vascular inflammation [122]. Recently, pharmacological inhibition of the NLPR3 inflammasome led to reduced disease progression in a collar-accelerated atherosclerosis model in $Apoe^{-/-}$ mice [123]. Yet, the unbid role of the inflammasome in experimental atherosclerosis was questioned recently in a study showing similar lesion progression in mice lacking NLRP3, ASC, or caspase-1 when compared to wild type [124]. The detailed role of the inflammasome in atherosclerosis was recently comprehensively discussed here [125,126].

3.2. Myocardial infarction and heart failure

The initial invasion of neutrophils as immediate reaction to infection or tissue injury is followed by an extended release of IL-1β, TNFα, and IL-6 by predominantly $Ly6C^{high}$ monocytes. These cellular responses are also observed in myocardial infarction and its experimental models [127]. The acute pro-inflammatory process is counteracted by the arrival of anti-inflammatory $Ly6C^{low}$ monocytes and tissue-intrinsic mechanisms which provide anti-inflammatory mediators and promote

healing processes such as fibrosis and angiogenesis [128].

The relevance of the IL-1 family to myocardial function was initially demonstrated by observing improved contractility in explanted myocardial tissue specimen upon inhibiting caspase-1, IL-1β, or IL-18 [129]. In addition, genetic ablation of IL-1R1 led to less severe tissue damage while deficiency in IL-1Ra exacerbated myocardial injury in a murine ischemia model [130,131]. Of note, IL-18 expression and abundance strongly increases in local heart tissue and in plasma upon experimental myocardial infarction in mice [132], a finding recapitulating data from patients with recent myocardial infarction [133]. In agreement, administration of recombinant IL-1Ra conferred a protective effect in similar models in mice and rats [134]. Lastly, pharmacological inhibition of IL-1β largely confirmed the detrimental role of IL-1β in processes instigated after myocardial injury [135,136].

Interestingly, a recent study reported a specific role for inflammasome activation and IL-18 but not IL-1β in β-adrenergic receptor-mediated insult to the myocardium [137]. Antibody-mediated inhibition of IL-18 and genetic deletion of IL-18 or NLRP3 markedly reduced inflammatory responses and cardiac injury upon isoproterenol stimulation [137]. However, less myocardial injury was observed when blocking IL-18 employing an antibody [138] or using recombinant IL-18BP [139] in more classical, ischemia-mediated insults to the myocardium. The role of IL-1β and IL-18 in acute myocardial injury and dysfunction was reviewed recently in more detail [140–142].

Again, in agreement with the phenotype of its substrates IL-1β and IL-18, caspase-1-deficiency led to improved survival following experimental myocardial infarction [143]. Furthermore, the authors noted improved function, less tissue production of IL-18 and a lower rate of myocardial apoptosis in the heart of mice deficient for caspase-1. This data was recently complemented by Kawaguchi et al. demonstrating inflammasome activation upon ischemia/reperfusion injury which was abrogated in ASC- or caspase-1-deficient mice [144]. In addition, the authors revealed a role for infiltrating leukocytes but also for resident fibroblasts in inflammasome-mediated immune processes. Moreover, inhibiting the inflammasome subunit NLRP3 by gene silencing [145] or pharmacological approaches using a small molecule inhibitor [146] also promoted post infarct tissue and functional preservation. Yet, using a similar experimental approach, Sandanger et al. could not confirm a protective role of inactivating the inflammasome components NLRP3 or ASC in myocardial ischemia/reperfusion injury indicating a protective role of the inflammasome [147]. Noteworthy, a recent study identified IL-1α as a crucial early danger messenger following experimental myocardial infarction [148]. Despite some disagreement, IL-1 family cytokines including their activating machinery appear highly activated following myocardial infarction and are considered to substantially contribute to acute post-ischemic tissue and functional deterioration [141].

In the view of potential long-term cardiac complications, increased expression of IL-18R1 in the myocardium as well as elevated levels of circulating IL-18 were found in patients with ischemic heart failure positively correlating with fatal outcome [149]. Another study revealed an intricate relationship of IL-1β and IL-18 in experimental heart failure with IL-1β promoting IL-18 expression, function of which has direct negative consequences on heart function [150]. Besides its immediate function in ischemia/reperfusion injury caspase-1 was also reported to promote long-term apoptosis of cardiomyocytes, thus facilitating heart failure [151].

3.3. Stroke

Ischemic stroke represents the thromboembolic blockage of cerebral arteries. The flow reduction and reduced oxygen supply triggers a wide range of systemic processes, which can further increase brain damage [152]. The occlusion of cerebral arteries and the resulting hypoxia during acute stroke leads to the release of DAMPs by necrotic cells thus inducing inflammation. Inflammatory processes can strongly influence the consequence in cerebral ischemia by causing brain damage due to the additional reduction of blood supply. In an experimental stroke model, where the injury is initiated by a middle cerebral artery occlusion (MCAo), elevated levels of IL-1α expression were detected in the ipsilateral and contralateral hemispheres during the first 4 h. In addition, IL-1α shows a strong association with infarct areas of focal blood brain barrier breakdown and neuronal death [153]. The early presence of IL-1α following MCAo is consistent with the temporal profile of IL-1 family member expression in sterile inflammation [34].

Brain injuries and the experimental injection of recombinant IL-1β into mammalian brains induced astrogliosis and angiogenesis [154]. Furthermore, IL-1α- and IL-1β-deficient mice showed a significant reduction of damaged areal after MCAo [155]. In other experiments, the application of anti-IL-1β antibody during reperfusion led to a reduction of ischemic brain injury. These studies suggest, that the outcome is due to the neutralization of low levels of IL-1β in cerebrospinal fluid rather an effect on parenchymal IL-1β processed by caspase-1 [156].

Clinical studies addressed the reduction of mircoglia activation, neutrophil migration, and the inhibition of IL-1 as possible treatment for reduction of cerebral ischemia. Intravenous application of recombinant human IL-1Ra (anakinra) can positively effect the pathophysiology and clinical outcome of acute stroke as shown in a small phase II clinical trial [157]. Of note, genetic variants within the IL-1 gene cluster were associated with incidence of ischemic stroke [158,159] although these findings have been debated controversially [160].

3.4. Aneurism/Vasculitis

Kawasaki disease (KD) affect manly children under the age of 5 and is characterized by systemic vasculitis of unknown cause. Treatment with immunoglobulins can reduce coronary artery aneurysms and abrogate the acquired heart diseases in affected children [161]. The treatment is limited by the increased resistance of patients to the immunoglobulin dose [162]. KD mouse models could demonstrate the importance of IL-1β for inducing coronary artery inflammation [163]. Similar to the animal model, increased expression levels of IL-1β are detected in human abdominal aortic aneurysm (AAA). IL-1-related gene upregulation in addition to inflammatory cell accumulation underline the similarities between human and mouse AAA lesions [164] and represent critical mediators of AAA formation. Lee et al. implicate both IL-1α and IL-1β in vasculitis and formation of AAA in a murine model of KD using gene-deficient mice [165]. Interestingly, IL-1 signaling in non-hematopoietic cells appeared critical for the disease process. In addition, lack of the receptor as well as pharmacological inhibition using anakinra confirmed the crucial involvement of the IL-1 cascade and identified a new treatment option [164].

Studies on thoracic aortic aneurysms (TAAs) confirm the upregulation of IL-1β and binding to its receptor (IL-1R1) leading to progressive inflammation characterized by the release of additional pro-inflammatory cytokines [166,167]. The pharmacological treatment with anakinra in an experimental TAA model led to decreased TAA formation and progression, confirmed by similar results in IL-1β deficient mice. Hence, IL-1β was proposed as potential target for the treatment of diseases driven by systemic artery inflammation [168].

3.5. Diabetes mellitus

The epidemic of cardio-metabolic disease affects millions of people worldwide and is characterized by a low-grade chronic inflammatory condition including an enhanced secretion of IL-1β [169]. The juvenile form diabetes mellitus (type 1 diabetes mellitus; T1DM) is characterized by a suddenly occurring immune cell-mediated loss of β-cells in the pancreatic isle. In contrast, the adult form (type 2 diabetes mellitus; T2DM) is frequently paralleled by overweight and metabolic dysregulation including peripheral insulin resistance while the β-cells

progressively lose their function [170]. During obesity adipose tissue is subjected to a chronic, low-grade inflammatory condition contributing to insulin resistance and eventually T2DM [171]. As a consequence, peripheral tissues lose their ability for insulin-mediated glucose uptake leading to chronically elevated blood glucose concentrations [172]. Macrophages infiltrating adipose tissue trigger local inflammation leading to reduced insulin sensitivity [171]. The activation of adipose tissue macrophages leads to an increase release of pro-inflammatory cytokines. Elevated levels of IL-18 were found in overweight adolescents. Together with IL-1Ra, they correlate with the body mass index (BMI) in adolescents while IL-1β was not detectable [173]. However, enhanced IL-1β mRNA expression induced by increased blood glucose could be measured in patients with T2DM [174]. Recent phase II trial data of T2DM patients treated with the IL-1β antagonist canakinumab displayed a dose-dependent, significant reduction of circulating levels of IL-6 and hsCRP, two prominent indicators of a systemic inflammatory state [175].

The inhibition of IL-1 family members could also provide an interesting pharmacologic target to reduce the outcome of global pandemics like obesity [176].

3.6. Clinical studies/treatments

As mentioned above canakinumab was used to target IL-1 expression in CASPs combined auto-inflammatory diseases (e.g. MWS, FCAS and NOMID) and rheumatoid arthritis [177]. Over years, treatments reducing atherosclerosis and CVD mainly focused on targeting established risk factors such as cholesterol, blood pressure, and smoking. A successful standard therapy for patients with high LDL cholesterol represents treatment with statins, which leads to a reduction of cardiovascular events by 25 to 50%. Next to the cholesterol lowering effect, the anti-inflammatory property of statins opened up new perspectives and gained further support for development of new treatments [178].

Considering the inflammatory component of CVD and in particular atherosclerosis the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS) was initiated in 2011 [25]. Goal was to assess whether an IL-1β inhibition therapy could reduce the rates of recurrent myocardial infarction, stroke, and cardiovascular death in post-myocardial infarction patients [179]. Over a median follow-up of 3.7 years, CANTOS randomly allocated 10,061 stable patients who remain at high inflammatory risk due to a persistent elevation of hsCRP (≥2 mg/L) to receive subcutaneous injections of either placebo or 3 different doses (50 mg, 150 mg and 300 mg) of the IL-1β-inhibiting antibody canakinumab every 3 months. The human monoclonal antibody canakinumab selectively neutralizes IL-1β without an alteration of IL-1α abundance. Blockage of the interaction of IL-1β with its type I and type II receptors leads to a reduction of IL-6 and hsCRP, common surrogates of systemic inflammation. Such an effect by canakinumab was already observed in several rare heritable pediatric conditions associated with enhanced IL-1β secretion [180]. One aim of the study was to clarify whether IL-1β-based therapy is effective for the secondary prevention of cardiovascular disease in high risk patients post AMI already on guideline-directed lipid lowering and antiplatelet therapy, but at increased residual inflammatory risk, indexed by an elevated baseline hsCRP (> 2 mg/l). Over 4 years of continuous IL-1β inhibition by canakinumab application, Ridker et al. observed a dose-dependent median reduction of hsCRP from 26 to 41 percentage points compared to the placebo group, while the lipid levels remained unaffected compared to the baseline [181]. Only the 150 mg dose met the pre-specified multiplicity-adjusted threshold for statistical significance for the primary end point (3.86 events per 100 person-years compared with 4.50 events in the placebo group) [181]. Adverse effects of the canakinumab were infrequent and consisted mainly of fatal infection. Here an increase from 0.18 events per 100 person/years in the placebo group to 0.31 (all doses) after canakinumab treatment was observed. Certainly, this issue requires intensive surveillance in upcoming trials of anti-inflammatory treatments in CVD. Of note, an additional effect of IL-1β inhibition with canakinumab was noted in CVD patients prone to lung cancer, as the 300 mg dose of canakinumab led to significantly reduced incidence of lung (hazard ratio [HR] 0.49 [95% CI 0.31–0.75]; p = 0.0009) compared to the placebo group. Prevalence of lung cancer (total n = 129) was less frequent in the 150 mg (HR 0.61 [95% CI 0.39–0.97]; p = 0.034) and 300 mg groups (HR 0.33 [95% CI 0.18–0.59]; p < 0.0001) [182]. Overall there was no significant difference in all-cause mortality (hazard ratio for all doses vs. placebo, 0.94; 95% CI, 0.83 to 1.06; P = 0.31) potentially mirroring balance of the beneficial effect on CVD and neoplastic disorder on one side and the higher risk of acquiring fatal infections. However, reducing total mortality in already guideline-treated study populations is a challenging task as also observed in the recent trial of potent lipid-lowering PCSK9 inhibitors [183]. Finally, this first long-term study could show a significantly lower rate of recurrent cardiovascular events due to anti-inflammatory therapy targeting IL-1β-triggered innate immune pathways without alteration of lipid-levels. The full extent of cardiovascular protection by IL-1β inhibition requires further evaluation also considering that this trial studied a cohort with > 90% of the patients already receiving lipid-lowering medication. Thus, anti-inflammatory therapy may show even greater atheroprotection in individuals not receiving a statin. Lastly, the CANTOS trial can be considered a landmark, however, preclinical data indicate that a plethora of inflammatory mediators is participating in the pathophysiological cascade of atherosclerosis. Thus, this trial may only resemble a proof-of-concept while future efforts will aim to refine anti-inflammatory treatment by optimizing anti-atherosclerotic potential and reducing harmful side effects such as higher incidence of infection.

An additional subject of recent investigation is the identification of a reliable biomarker for CVD prediction. In contrast to extremely low levels of cytokines measurement of IL-1Ra is a more reliable and workable indicator of cardiometabolic risk [34]. It is known that IL-1Ra concentration is increased in individuals with obesity or T2DM, known cardiometabolic risk factors [184]. Recent meta-analysis based on data of the MONICA/KORA Augsburg case–cohort study identified a positive correlation of circulating IL-1Ra levels with the risk of developing CVD, showing that IL-1 induces subclinical inflammation, oxidative stress, and endothelial activation that may play a crucial role in CVD [185].

Occlusive and atherosclerotic diseases in arteries of lower extremities are strongly correlated with a future progression of arterial diseases in coronary and cerebral vasculature [186]. In cases of superficial femoral artery (SFA) occlusion different endovascular treatments like angioplasty, atherectomy, and stenting are available. The most common complication after the intervention is restenosis as result of inflammatory processes. Recent studies targeted IL-1α with Xilonix, a specific human monoclonal antibody [187]. The intravenous dosing with Xilonix resulted in reduced rates of restenosis and supported use of Xilonix as safe and tolerate treatment to reduce inflammatory vascular processes leading to arteriosclerosis [188].

Lastly, the treatment with anakinra to block IL-1 immediately after acute ST-segment elevation myocardial infarction (STEMI) shows favorable effects leading to reduced incidence of heart failure [189].

4. Concluding remarks and future perspective

Research over the past three decades has generated substantial evidence for a functional role of members of the IL-1 family in cellular pathways underlying CVD. In fact, most members of this family, including the most prominent IL-1α, IL-1 β, and IL-18 confer a disease-aggravating function in experimental settings of atherosclerosis, myocardial infarction, or stroke. In addition, a plethora of clinical studies reporting association of plasma levels or genetic variants of the IL-1 family members or related molecules have supported the assumption of an intricate involvement of this cytokine family in CVD. Profound successes of pharmacologic modification of IL-1 family cytokine system

of in preclinical models have prompted considerable interest in applying such therapeutic strategies also in patients with CVD. In fact, several trials are currently under way and results may provide a proof of concept for the causal involvement of the immune system in CVDs, such as vasculitis, reperfusion injury, and atherosclerosis including its clinical precipitations such as myocardial infarction and stroke.

Yet, numerous questions remain unanswered. For example, it has to be clarified whether specific inhibition of single cytokines (e.g. IL-1β by canakinumab) or common receptors (e.g., IL-1R1 by anakinra; inhibiting both IL-1α, and IL-1β) represent appropriate therapies in CVD. Lastly, the IL-1 cytokine family is critically involved in host defense which must not be compromised by prolonged antagonistic therapy. Nonetheless, the data summarized here highlight the central role and hence great therapeutic potential of the IL-1 family in several cardiovascular diseases.

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Conflicts of interest

None declared.

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