



## Review

# Interleukin 1 $\alpha$ : a comprehensive review on the role of IL-1 $\alpha$ in the pathogenesis and treatment of autoimmune and inflammatory diseases

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## ABSTRACT

The interleukin (IL)-1 family member IL-1 $\alpha$  is a ubiquitous and pivotal pro-inflammatory cytokine. The IL-1 $\alpha$  precursor is constitutively present in nearly all cell types in health, but is released upon necrotic cell death as a bioactive mediator. IL-1 $\alpha$  is also expressed by infiltrating myeloid cells within injured tissues. The cytokine binds the IL-1 receptor 1 (IL-1R1), as does IL-1 $\beta$ , and induces the same pro-inflammatory effects. Being a bioactive precursor released upon tissue damage and necrotic cell death, IL-1 $\alpha$  is central to the pathogenesis of numerous conditions characterized by organ or tissue inflammation. These include conditions affecting the lung and respiratory tract, dermatoses and inflammatory skin disorders, systemic sclerosis, myocarditis, pericarditis, myocardial infarction, coronary artery disease, inflammatory thrombosis, as well as complex multifactorial conditions such as COVID-19, vasculitis and Kawasaki disease, Behçet's syndrome, Sjogren Syndrome, and cancer.

This review illustrates the clinical relevance of IL-1 $\alpha$  to the pathogenesis of inflammatory diseases, as well as the rationale for the targeted inhibition of this cytokine for treatment of these conditions. Three biologics are available to reduce the activities of IL-1 $\alpha$ : the monoclonal antibody bermekimab, the IL-1 soluble receptor rilonacept, and the IL-1 receptor antagonist anakinra. These advances in mechanistic understanding and therapeutic management make it incumbent on physicians to be aware of IL-1 $\alpha$  and of the opportunity for therapeutic inhibition of this cytokine in a broad spectrum of diseases.

## 1. Introduction

Members of the interleukin 1 (IL-1) family of cytokines are cardinal mediators of inflammation [1]. Within this family, IL-1 $\alpha$  and IL-1 $\beta$  are the archetypical pro-inflammatory cytokines. Following identification of these two cytokines in 1974, many studies explored the molecular biology and clinical effects of these molecules. However, IL-1 $\alpha$  and IL-1 $\beta$  are not equally established players in the body of clinical medicine. At present, the inflammatory properties of IL-1 $\beta$  are common knowledge in

the biomedical field, and many are familiar with molecular mechanisms of IL-1 $\beta$  secretion (i.e. processing by the inflammasome). Conversely, and perhaps surprisingly, the role of IL-1 $\alpha$  in the pathogenesis of autoimmune and inflammatory diseases has remained relatively overlooked, perhaps because IL-1 $\alpha$  is rarely observed in the circulation of patients with inflammatory diseases.

Excellent reviews on the biology of IL-1 $\alpha$  are available, and we refer the reader to these previous publications for the molecular features and pre-clinical studies of this cytokine [2–5]. While using these excellent

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works as a foundation, this review is primarily written for clinical audiences. Specifically, this review aims at illustrating the clinical relevance of IL-1 $\alpha$  to the pathogenesis of inflammatory and autoimmune diseases, as well as the rationale for the targeted inhibition of this cytokine for the clinical treatment of these conditions.

Several factors make this a timely and clinically relevant topic. On the one hand, the clinical arena has welcomed biologics inhibiting IL-1 $\alpha$  either selectively (monoclonal antibodies) or non-selectively (IL-1 receptor antagonist), which reveal the extent and relevance of IL-1 $\alpha$  in the pathogenesis of human disease. On the other, the recent outbreak of COVID-19, as well as advances in the understanding and therapeutic management of different diseases, make it incumbent on physicians to be aware of IL-1 $\alpha$  and of the opportunity for therapeutic inhibition of this cytokine.

## 2. Biology Of IL-1 $\alpha$

### 2.1. The IL-1 family of cytokines

Immune responses are orchestrated by cytokines, mediators produced by cells in order to induce a change in the function of different, target cells expressing specific receptors. The IL-1 family comprises 10 receptors and 11 cytokines, which can be classified into three subgroups based on the prevalent functional effect: I) secreted cytokines with agonistic activity (IL-1 $\alpha$ , IL-1 $\beta$ , IL-18, IL-33, IL-36 $\alpha$ , IL-36 $\beta$ , and IL-36 $\gamma$ ); II) receptor antagonists (IL-1Ra, IL-36Ra); III) anti-inflammatory cytokines (IL-37, IL-38) [1,6]. Interleukin 1 (IL-1) is the prototypical pro-inflammatory cytokine. Although the term IL-1, coined in 1979 [7], suggested a single molecule, previous studies on 'endogenous pyrogens' had already revealed the existence of two cytokines with different isoelectric points and molecular weight [8]. Afterwards, in the gene-cloning era, these two cytokines were unambiguously identified as two biological forms of IL-1 ( $\alpha$  and  $\beta$ ).

### 2.2. IL-1 $\alpha$ and IL-1 $\beta$ bind the same receptor and induce identical pro-inflammatory effects

Distinct genes encode IL-1 $\alpha$  and IL-1 $\beta$ , and the sequence homology is less than 26%, but the region of homology accounts for binding of both cytokines to the same IL-1 family receptor, namely IL-1R1 [4]. Since they bind the same receptor, IL-1 $\alpha$  and IL-1 $\beta$  induce the same pro-inflammatory effects. These include activation of key transcription factors associated with inflammatory and immune responses, such as nuclear factor- $\kappa$ B (NF- $\kappa$ B), activator protein-1 (AP-1), c-Jun N-terminal kinase (JNK), p38 and other mitogen-associated protein kinases (MAPKs), extracellular signal-regulated kinases (ERKs), and interferon-regulating genes [9]. Once activated, these signaling cascades lead to the expression of myriad mediators, which collectively orchestrate the development of an immune response. Chief mechanisms include the synthesis of other cytokines, such as IL-6, IL-2, interferons or chemokines; production of prostaglandins; vasodilation and expression of adhesion molecules by endothelial cells, which enable migration of immune cells into tissues; activation of T-helper cells and maturation and clonal expansion of B cells, which activate adaptive immunity [9]. In inducing these pro-inflammatory effects, IL-1 $\alpha$  and IL-1 $\beta$  act synergistically with other mediators such as TNF $\alpha$ , bradykinin, or growth factors. Activation of this interconnected network of soluble and cellular mediators has both local and systemic effects. For example, local effects are characterized by inflammation-mediated organ dysfunction and, eventually, damage. On the other hand, systemic effects include fever, vasodilation (rash), and musculoskeletal pain, as well as hypotension and shock for increasing concentrations.

### 2.3. IL-1 $\alpha$ and IL-1 $\beta$ : differences

Although the shared IL-1R1 receptor transduces identical pro-

inflammatory effects, there are key differences in the biology of IL-1 $\alpha$  and IL-1 $\beta$ , which account for the unique contribution of each cytokine to the orchestration of inflammatory responses (Table 1).

#### 2.3.1. Expression by different tissues and cell types

IL-1 $\alpha$  is constitutively present as a precursor in all healthy tissues of mesenchymal origin, in particular, cells rich in IL-1 $\alpha$  constitute tissues with a barrier function, such as keratinocytes in the skin, type 2 epithelial cells in the lung, the epithelium of the entire gastrointestinal tract, endothelial cells in blood vessels, and astrocytes in the brain [3]. In addition to constitutive presence in barrier epithelia, production of IL-1 $\alpha$  precursor can be induced in myeloid cells during inflammation. Conversely, IL-1 $\beta$  is not constitutively expressed in healthy states and is exclusively produced by myeloid cells during inflammation.

#### 2.3.2. Activity of the precursor molecule and need for processing by the NLRP3 inflammasome

Both IL-1 $\alpha$  and IL-1 $\beta$  are synthesized as intracellular precursors. However, the IL-1 $\alpha$  precursor is biologically active, whereas the IL-1 $\beta$  precursor is not [10]. Inside the cell, the activity of the IL-1 $\alpha$  precursor is kept in check by the type 2 IL-1R (IL-1R2), a decoy receptor which binds the cytokine but does not transduce inflammatory effects, thus functioning as a 'sink' [11,12]. However, IL-1 $\alpha$  exiting from the cell can directly bind the IL-1R1 and exert its biologic effects. Conversely, the IL-1 $\beta$  precursor must undergo intracellular processing and activating cleavage by the NLRP3 inflammasome in order to generate biologically active IL-1 $\beta$  [13].

#### 2.3.3. Role as 'alarmin'

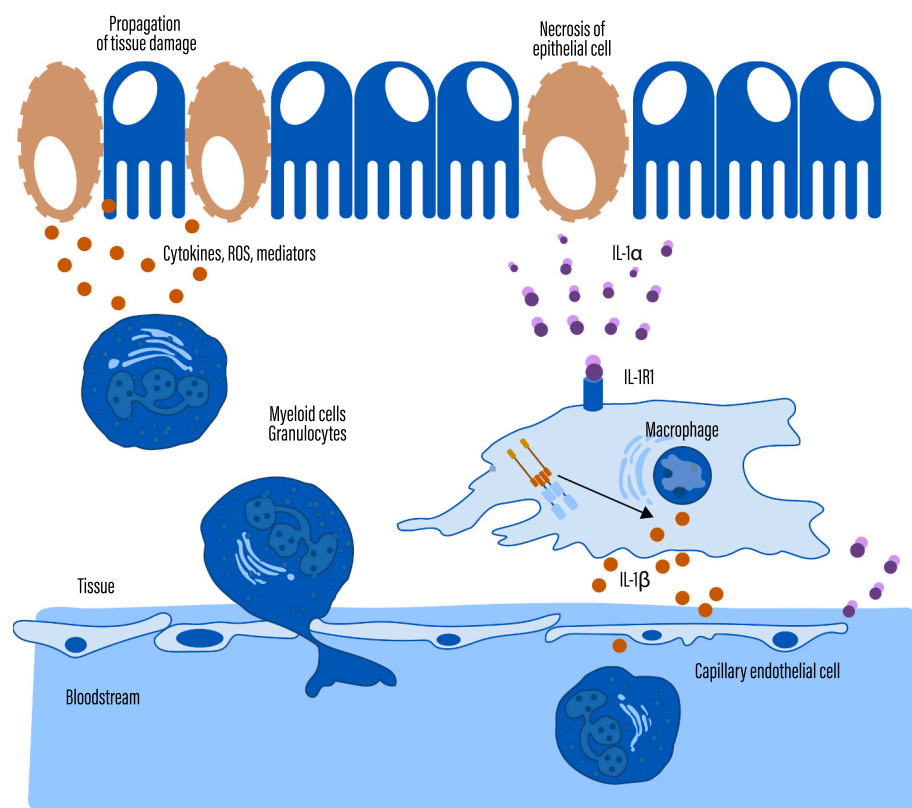
Alarmins are proteins or molecular components normally found inside the cell, whose presence in the extracellular compartment signals loss of membrane integrity to nearby cell [3]. Thus, alarmins function as *de facto* danger-associated molecular patterns (DAMPs), and trigger sterile inflammation. Notable examples include HMGB1 [14], as well as IL-1 $\alpha$  [10]. Since the IL-1 $\alpha$  precursor is constitutively present in a biologically active form in epithelial cells, necrosis (i.e. following trauma, ischemia or viral infection) results in the immediate release of IL-1 $\alpha$  in the extracellular space, and consequent engagement of IL-1R1 on adjacent live cells. This results in induction of tissue inflammation (Figure 1). Conversely, IL-1 $\beta$  is neither present in most cells nor biologically active as a precursor, and thereby does not function as an alarmin.

#### 2.3.4. Juxtacrine versus paracrine signaling

Both IL-1 $\alpha$  and IL-1 $\beta$  can be released into the extracellular space and bind IL-1R1 on nearby cells (paracrine signaling). However, IL-1 $\alpha$  also

**Table 1**  
Differences in biological properties and function of IL-1 $\alpha$  and IL-1 $\beta$

IL-1 $\alpha$	IL-1 $\beta$
IL-1 $\alpha$ is constitutively present in a wide variety of cells; expression can be induced in hematopoietic and nonhematopoietic cells in response to inflammatory stimuli.	IL-1 $\beta$ is absent in cells at homeostasis and is expressed upon stimulation only in myelomonocytic cells.
Both the precursor (pro-IL-1 $\alpha$ ) and the cleaved form of IL-1 $\alpha$ are biologically active IL-1R1 ligands. Caspase-1 and the inflammasome have no direct role in cleaving pro-IL-1 $\alpha$ .	Only the cleaved mature form of IL-1 $\beta$ is biologically active and a ligand for IL-1R1. Pro-IL-1 $\beta$ is cleaved by caspase-1 following activation of the inflammasome.
Preformed, biologically active IL-1 $\alpha$ is released by necrotic cells and acts as an alarmin.	Not being functionally active as a precursor, IL-1 $\beta$ does not function as an alarmin.
IL-1 $\alpha$ functions both as a soluble mediator and as a membrane-bound cytokine.	Mature IL-1 $\beta$ only functions as a soluble mediator.
Dual function: extracellular binding to the IL-1R1 and nuclear function as a transcription factor.	Extracellular binding to the IL-1R1 only.



**Fig. 1.** The IL-1-driven inflammatory loop. Tissue damage triggers release of intracellular IL-1 $\alpha$  from dying cells. This generates an IL-1 $\alpha$ -containing milieu, which is sensed by infiltrating myeloid cells (i.e. monocytes, macrophages) expressing the IL-1R1. These cells in turn activate inflammasome-dependent production of IL-1 $\beta$ , which initiates a cascade leading to the recruitment of inflammatory myeloid cells (i.e. granulocytes) to the site of tissue damage. Influx of inflammatory cells producing cytokines, reactive oxygen species, and effector mediators propagates tissue damage.

functions as an integral membrane protein, particularly on macrophages [15,16]. Membrane-bound IL-1 $\alpha$  exposed on the cell membrane by activated macrophages binds the IL-1R1 on adjacent cells (juxtacrine signaling) [17], a mechanism instrumental to the induction of local –or even focal– inflammation.

### 2.3.5. Dual function of IL-1 $\alpha$

Dual functions of proteins allow the relatively few human genes expressed in adult life to accomplish a multitude of functions. Unlike IL-1 $\beta$ , IL-1 $\alpha$  is a ‘dual function’ cytokine. In the extracellular space, released or membrane-bound IL-1 $\alpha$  binds to the IL-1R1 on the surface of the cells and triggers a pro-inflammatory cascade. Inside the cell, the IL-1 $\alpha$  precursor has its own function. In health, the IL-1 $\alpha$  precursor shuttles between the cytosol and the nucleus: due to a very strong nuclear localization sequence (KKRR) in the N terminus pro-piece, IL-1 $\alpha$  binds to DNA [18]. In cells undergoing non-inflammatory apoptosis, IL-1 $\alpha$  remains tightly bound to DNA and is not available to bind to IL-1R1 and trigger inflammation. In cells undergoing a necrotic cell death, the IL-1 $\alpha$  precursor remains in the cytosol and is released into the extracellular space and triggers inflammation [18]. In stimulated cells, for example skin keratinocytes exposed to ultraviolet light, the IL-1 $\alpha$  precursor functions as a nuclear transcription factor [9,18–20]. The ‘dual function’

of IL-1 $\alpha$  in the extracellular and cytosolic compartments is also found in IL-1 family member IL-33. In IL-33, a similar phenomenon occurs; failure of the IL-33 precursor to bind to DNA results in release of the IL-33 precursor into the extracellular space and marked systemic inflammation [21]. IL-1 family member IL-37 also has dual (intracellular and extracellular) functions. However, since IL-37 is an anti-inflammatory cytokine, failure to localize to the nucleus results in a loss of its anti-inflammatory properties [22,23].

### 2.4. Functional properties in inflammation: $\alpha$ is local, $\beta$ is systemic

The binding to the same receptor by IL-1 $\alpha$  and IL-1 $\beta$  raises the question as to why there are two IL-1s: either redundancy is needed for backup and robustness, or perhaps each cytokine has a specialized function [24]. The conundrum of an apparent functional excess and redundancy of IL-1 $\alpha$  and IL-1 $\beta$  production at sites of inflammation is explained by the ‘IL-1 $\alpha$ -driven inflammatory loop’ (Figure 1). In this model, IL-1 $\alpha$  is either released from dying cells, or exposed on the surface of cells undergoing oxidative or metabolic stress. This generates an IL-1 $\alpha$ -containing milieu, which is sensed by myeloid cells expressing the IL-1R1. These cells in turn activate IL-1 $\beta$  production downstream of IL-1R1, which initiates a cascade leading to recruitment of inflammatory

hematopoietic cells to the site of damage or stress.

Thus, *IL-1 $\alpha$*  is a *primum movens* of local inflammation, affecting the local microenvironment either through exposure on the membrane of stressed cells followed by juxtacrine binding of IL-1R1 on nearby cells, or through release upon cell death followed by paracrine binding of IL-1R1 on surrounding cells. Conversely, *IL-1 $\beta$*  acts as a master regulator of systemic inflammation, as production of IL-1 $\beta$  by infiltrating macrophages and circulating monocytes takes inflammation beyond the local level and causes widespread inflammation.

The non-redundant functions of IL-1 $\alpha$  as an alarmin and mediator of local inflammation also emerge during highly conserved immune mechanisms against invading pathogens, such as granuloma formation and responses to immune-evasive viruses. Granulomas function as focal inflammatory lesions comprising both hematopoietic and non-hematopoietic cells, which typically surround poorly degradable particulate matter or microbial, viral, fungal, protozoan or helminthic pathogens [25]. Because granulomas are fundamentally a local inflammatory response, it is not surprising that IL-1 $\alpha$ , with its specific role in inducing an inflammatory milieu upon exposure on the cell membrane, is involved in granuloma formation. Exposure of macrophages as well as lung epithelial cells to *M. tuberculosis* results in rapid expression of biologically active membrane-bound IL-1 $\alpha$ ; in experimental models of *M. tuberculosis* infection, IL-1 $\alpha$ -deficient mice did not develop protective granuloma structures and succumbed to the infection earlier than wild-type mice [25]. An analogous role has emerged for IL-1 $\alpha$  in granulomas induced by *Cryptococcus neoformans* and *Leishmania major* infections [26,27]. Granuloma formation is thereby an example of an evolutionarily non-redundant role of IL-1 $\alpha$  in inflammatory responses. Indeed, the expression of membrane-bound IL-1 $\alpha$  by myeloid cells surrounding a pathogen flags a restricted, infected area within a tissue, thus fostering targeted accumulation of recruited immune cells on the circumferential borders of the forming granuloma. This process results in efficient confinement and trapping of the invading pathogen (or foreign body). This same result could not be achieved by production of soluble mediators, which would result in widespread tissue inflammation or even inappropriate and detrimental systemic inflammatory responses.

In addition, non-redundant functions of IL-1 $\alpha$  are important for protection against immune-evasive viruses, which are poorly immunogenic or actively suppress inflammatory gene expression. For example, vesicular stomatitis virus infects keratinocytes and prevents induction of interferon responses, thereby being immune-evasive. However, infection and virus-induced lysis of keratinocytes prompts the release of preformed IL-1 $\alpha$ , whose immunogenic function is similar to and vicariates that of interferons [28]. IL-1 $\alpha$  is most important to control immune-evasive virus replication in fibroblasts and other barrier cell types, and represents a functional backup antiviral system to ensure barrier defense. In addition, neutralization of IL-1 $\alpha$  inhibits the antiviral activity of IFN- $\gamma$  by 90%, whereas no inhibition of type I IFN activity was observed. Indeed, the antiviral activity of IFN- $\gamma$  depends largely on the basal level of NF- $\kappa$ B, which is maintained by constitutively expressed IL-1 $\alpha$  [29].

### 2.5. Evolutionary origin of IL-1 $\alpha$ accounts for intracellular localization and dual function

The IL-1 family of cytokines is evolutionarily ancient, and likely originated from duplications of a common ancestral gene related to fibroblast growth factors (FGFs) [30,31]. Indeed, a related IL-1-like molecule is found in the starfish and acts as a growth factor for the repair of severed limbs [32]. IL-1 $\alpha$  likely arose as a result of an ancestral gene duplication of IL-1 $\beta$  [33]. Within the IL-1 family, IL-1 $\alpha$  has the closest homology to FGF [34]. FGF proteins localize in the nucleus, and this nuclear localization of FGF progenitors provides an evolutionary explanation for the role of IL-1 $\alpha$ , as well as other IL-1 family members IL-33 and IL-37, as nuclear factors [35,36]. Later in evolution, appearance of surface receptors of the immunoglobulin family enabled extracellular signaling [37]. In parallel, molecular machinery evolved in order to

expose IL-1 $\alpha$  on the cell surface and initiate paracrine inflammation upon binding of IL-1R1 on nearby cells (juxtacrine signaling). On the cell surface, extracellular proteases cleave pro-IL-1 $\alpha$ , leading to its release as a soluble mediator. At the same time, cell death due to injury or infection results in a passive leakage of cytosolic pro-IL-1 $\alpha$  into the surrounding milieu and activation of inflammation in an IL-1R1-dependent manner.

### 2.6. Mechanisms for control of inflammation mediated by IL-1 $\alpha$

To accomplish the task of preventing unwanted activation and minimizing collateral damage of inflammation, the innate immune system relies on feedback regulatory circuits provided by suppressive mediators. Within the IL-1 family of cytokines, several inhibitory mechanisms are in place to prevent runaway inflammation induced by IL-1 $\alpha$  or IL-1 $\beta$ . The main mechanism is the IL-1 receptor antagonist (IL-1Ra), which blocks the IL-1R1 and prevents binding of IL-1 $\alpha$  and IL-1 $\beta$  [38].

In addition, the decoy receptor IL-1R2 binds to both IL-1 $\alpha$  and IL-1 $\beta$ , but does not induce cytoplasmic signaling, thus inhibiting inflammation by functioning as a 'sink' for these mediators [39]. Specifically, the IL-1R2 genomic structure is similar to that coding for the extracellular portion of IL-1R1; however, IL-1R2 lacks a TIR domain and only has a short 29 amino acid-long cytoplasmic tail, and indeed, it does not transduce an inflammatory signal upon binding of IL-1 $\alpha$  and IL-1 $\beta$ , thus acting as a molecular trap [40,41]. IL-1R2 is found both in the cytosol where it binds pro-IL-1 $\alpha$  and limits excessive IL-1 $\alpha$ -dependent sterile-inflammation during necrosis [11,12], as well as in the extracellular space and circulation, where it binds IL-1 $\beta$  and limits systemic inflammation [42,43].

An additional way of taming the inflammatory response is provided by regulatory cytokines [44], which orchestrate a complex network of mechanisms leading to resolution of inflammation, including reduced cell infiltration and suppression of pro-inflammatory mediators. Within the IL-1 family, regulatory cytokines involved in the regulation of IL-1-driven inflammation include IL-37 and IL-38 [1,45–47].

Finally, non-immunological mechanisms are also in place to prevent IL-1 $\alpha$  release and initiation of inflammatory responses during programmed, non-inflammatory cell death. Release of cytosolic pro-IL-1 $\alpha$  during apoptosis is prevented by sequestration into the nucleus, followed by inclusion into apoptotic bodies and clearance by scavenging phagocytes [18,48]. In addition, the decoy receptor IL-1R2 binds and sequesters cytosolic IL-1 $\alpha$ , thus preventing inflammatory signaling during programmed cell death [11].

## 3. Role of IL-1 $\alpha$ in the pathogenesis of autoimmune and inflammatory diseases

### 3.1. The role of IL-1 $\alpha$ in the pathogenesis of human diseases

Given its role as a bioactive precursor released upon tissue damage and cell death, IL-1 $\alpha$  is centrally involved in diseases primarily characterized by tissue or organ inflammation (i.e. pericarditis, myositis), by disruption of barrier epithelia (i.e. dermatoses, airway diseases such as COVID-19, colitis), and by endothelial damage or thromboembolic activation (i.e. Behçet's syndrome, vasculitides). There is an overlap in the effects of IL-1 $\alpha$  and IL-1 $\beta$  in many diseases, as local inflammation initiated by IL-1 $\alpha$  eventually triggers systemic inflammatory responses (see the IL-1 $\alpha$ -driven inflammatory loop in Figure 1). In this section, we describe the contribution of IL-1 $\alpha$  to the pathogenesis of different diseases, subdivided by tissue or organ system.

### 3.2. Skin

The skin is the prototypical IL-1 $\alpha$  'organ'. Skin keratinocytes contain abundant IL-1 $\alpha$ , which is released upon injury, trauma, or infection. Prompt release of IL-1 $\alpha$  ensures rapid induction of local inflammatory

responses, which are essential both to the maintenance of skin integrity (i.e. by inducing wound healing) and to the deployment of effective barrier functions (i.e. by enabling clearance of invading pathogens). Several human diseases illustrate the relevance of IL-1 $\alpha$  to skin inflammation.

### 3.2.1. Deficiency of IL-1Ra (DIRA)

DIRA is a rare, neonatal-onset monogenic disorder characterized by constitutive lack of IL-1Ra [49]. Newborns develop severe, multisystem inflammation due to the unopposed activity of both IL-1 $\alpha$  and IL-1 $\beta$ . A striking clinical manifestation of DIRA is severe, widespread neutrophilic dermatosis, which resembles pustular psoriasis. This manifestation is mediated by IL-1 $\alpha$ , as it is not observed in other auto-inflammatory conditions exclusively characterized by excessive release or activity of IL-1 $\beta$ , such as cryopyrin-associated periodic syndromes or familial Mediterranean fever [50]. These clinical observations pinpoint the role of IL-1 $\alpha$  in the development of neutrophilic dermatoses. Treatment with anakinra is rapidly effective and leads to a reversal of clinical manifestations.

### 3.2.2. Hidradenitis suppurativa and other neutrophilic dermatoses

Neutrophilic dermatoses are a heterogeneous group of auto-inflammatory skin disorders, which are associated with cutaneous inflammatory lesions and rich infiltration with granulocytes at histology evaluation [51]. This group includes hidradenitis suppurativa (HS), pyoderma gangrenosum, Sweet's syndrome, and amicrobial pustulosis of the skinfolds. HS is a common, chronic disorder of skin areas rich in apocrine glands, characterized by formation of painful, pus-containing inflammatory nodules, followed by rupture and scarring. The causal role of IL-1 $\alpha$  in the pathogenesis of hidradenitis suppurativa is demonstrated by the clinical efficacy of anakinra [52], as well as by specific blockade of IL-1 $\alpha$  with monoclonal antibodies, which was associated with even more robust responses in clinical trials [53]. A central involvement of IL-1 $\alpha$  is also likely in the pathogenesis of pyoderma gangrenosum, yet evidence in this context is primarily derived from mouse models, in which caspase recruitment domain family member 9 (CARD9) signaling was identified as inducing IL-1 $\alpha$  [54]; however, reports on the efficacy of anakinra in patients with pyoderma gangrenosum are mixed [55,56]. Amicrobial pustulosis of the skinfolds is also characterized by elevated IL-1 $\alpha$  in skin biopsies and by response to treatment with anakinra [55,56].

### 3.2.3. Systemic sclerosis

Systemic sclerosis (SSc) is a severe autoimmune condition characterized by progressive vascular damage and fibrosis of tissues. Fibroblasts purified from lesional skin of patients with SSc express abundant amounts of IL-1 $\alpha$ , which is localized on the plasma membrane, in the cytosol, and in the nucleus [57]. Compared to fibroblasts from normal skin, SSc fibroblasts also express high amounts of IL-6, the growth factor PDGF- $\alpha$ , IL-1R1, and collagen [58]. Suppression of IL-1 $\alpha$  expression in SSc fibroblasts reduces amounts of secreted IL-6 and pro-collagen, whereas overexpression of pro-IL-1 $\alpha$  in normal fibroblasts increases IL-6 and pro-collagen production [57]. Moreover, IL-1-dependent PDGF- $\alpha$  production has direct mitogenic effects on fibroblasts and smooth muscle cells [59]. Collectively considered, these observations link excessive IL-1 $\alpha$  activity with a pathological tissue response leading to excessive deposition of collagen and fibrosis.

## 3.3. Lung and respiratory tract

IL-1 $\alpha$  is constitutively expressed in the lung epithelium [4], and is released upon cell death in conditions characterized by alveolar or airway epithelium inflammation. In addition, IL-1 $\alpha$  released by dying epithelial cells has a role in priming pro-inflammatory responses in fibroblasts, which leads to progressive fibrosis, maladaptive tissue remodeling, and damage.

### 3.3.1. Chronic obstructive pulmonary diseases (COPD)

COPD is a common disease characterized by chronic airway and alveolar inflammation, typically induced by cigarette smoking [60–62] and exacerbated by common viral infections [63,64]. COPD leads to maladaptive tissue remodeling, clinically manifested with emphysema and respiratory insufficiency. Overall, epithelial-derived IL-1 $\alpha$  mediates a pathologic cross talk between damaged lung epithelium and fibroblasts [65–67]. *In vitro* studies showed that IL-1 $\alpha$  released by damaged epithelium is both necessary and sufficient to promote a switch of primary human lung fibroblasts towards an inflammatory phenotype [65,68,69], with consequent up-regulation of IL-6, IL-8, monocyte chemoattractant protein-1, and GM-CSF. Interestingly, this effect is reduced with the administration of anti-IL-1 $\alpha$  or IL-1ra but not with anti-IL-1 $\beta$  antibodies, thus supporting the causal role of IL-1 $\alpha$  [65]. In addition, lung epithelial cells infected by human rhinovirus release IL-1 $\alpha$  upon death, thus prompting a pro-inflammatory response in fibroblasts [66,67]. Airway epithelial cells obtained from severe COPD patients co-cultured with fibroblasts induce production of the neutrophil recruiting factor IL-8/CXCL8 by fibroblasts. Neutralizing antibodies against IL-1 $\alpha$  but not IL-1 $\beta$  completely abrogated IL-8/CXCL8, suggesting a key role of IL-1 $\alpha$  in lung inflammation and tissue remodeling in COPD [68].

Altogether, these observations provided a biologic rationale for exploring the therapeutic potential of anti-IL-1 $\alpha$  agents in COPD, which remains a major public health problem due to disability and frequent virus-triggered exacerbations [63,64]. At present, experience with IL-1 $\alpha$  inhibition in COPD is limited. Treatment with MEDI8968, a fully human immunoglobulin G2 monoclonal antibody against the IL-1R1, did not yield statistically significant improvements in acute exacerbation rate, lung function and quality of life in a prospective trial of COPD patients [70].

### 3.3.2. Pulmonary fibrosis

Pulmonary fibrosis is the common end-stage of several inflammatory or autoimmune conditions characterized by progressive structural damage of the lungs [71,72]. Interstitial lung disease (ILD) is a form of pulmonary fibrosis that can be encountered in the context of systemic immune-mediated diseases such as connective tissue disease and rheumatoid arthritis [73]. In a study of 70 patients with rheumatoid arthritis, increased serum levels of naturally occurring antibodies against IL-1 $\alpha$  were detected in patients with ILD compared to patients without ILD. IL-1 $\alpha$  autoantibody positivity was also observed in a separate study of patients with rapidly progressive idiopathic pulmonary fibrosis [72]. Generation of autoantibodies against IL-1 $\alpha$  is indicative of the presence of extracellular IL-1 $\alpha$ , and may also represent a regulatory mechanism aimed at limiting IL-1 $\alpha$  bioactivity *in vivo*, in order to limit lung injury [74]. An open label extension of a randomized, double blind controlled study investigated the safety profile of anakinra compared to placebo in 1346 patients with rheumatoid arthritis. Only two patients developed interstitial lung disease, which indirectly suggest a protective effect of anakinra against the occurrence of ILD [75].

Lung involvement with fibrosis can occur in systemic sclerosis (SSc) and is associated with a poor prognosis [76]. The T-889C SNP in the promoter of the gene encoding IL-1 $\alpha$  is associated with pulmonary restrictive disease and with poor responses to cyclophosphamide in SSc-related lung fibrosis [77]. Studies investigating cytokine production in SSc patients revealed significantly increased IL-1 $\alpha$  plasma levels [78,79], which correlated with pulmonary impairment [80].

However, therapeutic inhibition of IL-1 yielded mixed results in pre-clinical models. IL-1Ra administration effectively antagonized activation of fibroblasts co-cultured with epidermal cells from SSc patients [81]. However, treatment with anakinra of mouse models of interstitial lung disease was associated with a worsening of pulmonary damage and with increased amounts of T cells, B cells and eosinophils in bronchoalveolar lavage fluid, possibly as a result of a polarization of the immune response towards a Th2 phenotype inducing pro-fibrotic alternatively activated macrophages [82]. Although management of

SSc-associated ILD still relies on non-selective immunosuppressants, targeted inhibition of cytokines remain an attractive therapeutic perspective and investigations in this field are ongoing [83].

### 3.3.3. Cystic fibrosis

Cystic fibrosis is characterized by thickening of secretions in the lungs, but also the pancreas, liver, kidneys, and intestine. Recurrent pulmonary infections result in progressive lung damage. Bronchoalveolar lavage fluid of patients with cystic fibrosis is rich in IL-1 $\alpha$ , IL-1 $\beta$ , and IL8, and is characterized by high neutrophil elastase activity [84]. Concentrations of these mediators, as well as neutrophil elastase activity, correlate with the extent of pulmonary structural damage on computed tomography; however, the association is strongest for IL-1 $\alpha$  [84]. These observations point at IL-1 $\alpha$  as a driver of neutrophilic inflammation, particularly in early stages of cystic fibrosis, even in germ-free conditions [84]. An interventional, Phase 2a trial evaluating safety and efficacy of anakinra in patients with cystic fibrosis is ongoing (NCT03925194).

### 3.3.4. Bronchopulmonary dysplasia

Bronchopulmonary dysplasia is one of the most common disorders associated with preterm birth. Experimental models show that the developing lung of mice subjected to endotoxemia exhibit a robust NF $\kappa$ B-dependent IL-1 $\alpha$  expression [85], and that the developing lung is susceptible to the downstream inflammatory effects of IL-1 $\alpha$ . In humans, evaluation of repeated tracheal aspirates of intubated, premature infants revealed a dramatic, sustained upregulation of IL-1 $\alpha$  mRNA (65-fold) and, to a lesser extent, of IL-1 $\beta$  and IL-1Ra. These findings indicate that, at least in intubated preterm infants, there is pulmonary IL-1-mediated inflammation [86]. Blockade of IL-1R1 may attenuate lung injury and subsequent abnormal development following neonatal inflammatory stress. However, this therapeutic opportunity presently remains unexplored.

## 3.4. Gastrointestinal tract

The epithelial layers of the intestine contain abundant pro-IL-1 $\alpha$ . The role of IL-1 $\alpha$  as an alarmin is particularly relevant in the gut microenvironment, where constant exposure to pathogenic bacteria requires prompt induction of protective, host-defensive inflammatory responses. However, excessive epithelial cell injury and disruption of the mucosal barrier result in invasion of bacteria into the sub-epithelial *lamina propria* and in subsequent colon inflammation. These pathological features characterize chronic inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis.

### 3.4.1. Colitis

The expression of both IL-1 $\alpha$  by epithelial cells and IL-1 $\beta$  by myeloid cells in the intestinal mucosa correlates with the severity of inflammation in experimental models of IBD and in affected patients [87,88]. However, the two cytokines have different, non-redundant functions in intestinal inflammation: specifically, IL-1 $\alpha$  is released from damaged intestinal epithelial cells and functions as an alarmin by initiating and propagating inflammation, whereas IL-1 $\beta$  is primarily involved in repair and reconstitution of the epithelial barrier in the resolution phase of intestinal inflammation [89,90]. Consistent with this mechanistic model, mice lacking IL-1 $\alpha$  subjected to experimental colitis exhibit mild disease symptoms, whereas mice lacking IL-1 $\beta$  develop a more severe disease [89,90]. Neutralization of IL-1 $\alpha$  with monoclonal antibodies effectively reduced intestinal inflammation and damage in SAMP mice, which spontaneously develop a Crohn's-like ileitis, and in mice subjected to an established model of chemical (dextran sulfate sodium-induced) colitis [91]. In both models, the protective effects of IL-1 $\alpha$  neutralization were associated with taxonomic divergence of the fecal gut microbiome: most notably, a decreased ratio of *Proteobacteria* to *Bacteroidetes* heralds the anti-inflammatory effects of IL-1 $\alpha$

neutralization. These findings confirm the clinically relevant interconnectedness of IL-1-mediated inflammation and the microbiota in intestinal homeostasis. Despite strong conceptual and pre-clinical evidence, no clinical trials have tested the efficacy of anti-IL-1 strategies and of IL-1 $\alpha$  blockade in particular in patients with IBD.

## 3.5. Muscle tissue

### 3.5.1. Myositis

Inflammatory myopathies are a heterogeneous group of conditions including dermatomyositis, polymyositis and inclusion body myositis, collectively characterized by inflammation-mediated progressive muscle damage and loss of strength. Different pro-inflammatory mediators are involved in the pathogenesis [92], particularly Th1-related cytokines [93]. Muscle cells constitutively contain abundant IL-1 $\alpha$ . Accordingly, in patients with inflammatory myopathies (i.e. dermatomyositis and sarcoid myopathy granulomas) there is a marked release of IL-1 $\alpha$  [94]. This mediator is focally expressed by muscle fibres characterized by myosinolysis, atrophy, ischemia, or regeneration [95]. IL-1 $\alpha$  is also abundantly expressed by endothelial cells of capillaries and venules of muscle biopsies from patients with inflammatory myopathies [94]; of note, marked expression of IL-1 $\alpha$  on endothelial cells is found even in patients with symptomatic DM and PM without clear evidence of lymphocytic infiltrates. This finding indicates that IL-1 $\alpha$  is likely implicated in the development of clinically relevant inflammation independently of muscle infiltration [96]. Also consistent with these observations, some patients display high expression of IL-1 $\alpha$  on muscle fibers and persistent muscle weakness even following treatment with corticosteroids, which results in disappearance of lymphocytic infiltrates [97]. It is plausible that expression of IL-1 $\alpha$  results in low-grade, persistent, inflammation-mediated muscle weakness [98]. In turn, IL-1 $\alpha$  induces production of IL-1 $\beta$  by infiltrating myeloid cells: in line with the IL-1 $\alpha$ -driven inflammatory loop concept, IL-1 $\alpha$  is expressed on endothelial, muscle, and inflammatory cells, whereas expression of IL-1 $\beta$  is restricted to infiltrating immune cells [99].

At present, limited data is available supporting treatment of inflammatory myopathies with anakinra. In mouse models, muscle inflammation is prevented in mice lacking IL-1 $\alpha$  and IL-1 $\beta$  [100]; in a separate study, IL-1 $\alpha$  levels in muscle tissue correlated with disease severity and treatment with IL-1ra resulted in a significant suppression of muscle inflammation [101]. In humans, the efficacy of anakinra was evaluated in 15 patients with myositis refractory to conventional immunosuppressive therapies: seven out of 15 patients exhibited a clinical improvement [102]. In a separate study, anakinra was administered with benefit in a case of refractory of amyopathic dermatomyositis associated with anti-MDA5 antibodies [103]. In summary, inhibition of IL-1 $\alpha$  seems promising in difficult-to-treat inflammatory myopathies, or in patients with chronic muscle weakness and low-grade inflammation with mild or absent inflammatory infiltrates.

## 3.6. Cardiovascular system: heart and pericardium

### 3.6.1. Myocarditis

Myocarditis is an inflammatory disease affecting the myocardium, clinically manifested with heart failure and arrhythmia and diagnosed using imaging and/or histopathologic criteria. This condition can develop in isolated forms, or as part of infectious and autoimmune disorders [104]. Regardless of the initiating agent, the pathogenesis revolves around deregulated IL-1-mediated inflammation and innate immune system activation. During myocardial injury, dying myocytes release IL-1 $\alpha$ , together with several intracellular debris and other inflammatory proteins such as high-mobility group box 1 protein, IL-33 and the Ca<sup>2+</sup>-binding S100 proteins [105,106]. Following release of these alarmins, infiltrating immune cells are alerted of tissue damage and initiate local and systemic inflammatory responses. Binding of IL-1 $\alpha$  by IL-1R1 expressed on the cell membrane of immune cells results in

activation of nuclear factor- $\kappa$ B with subsequent transcription of several proinflammatory genes. These notably include the precursors of IL-1 $\beta$  and IL-18, as well as components of the NLRP3 inflammasome, which generates bioactive IL-1 $\beta$  and further enhances the inflammatory process [107]. The findings of exaggerated inflammasome activation were confirmed both in humans with acute myocarditis following a viral infection [107] and in murine models of coxsackievirus-induced myocarditis [108]. Further evidence was also found in the heart of patients with acute transplant rejection suggesting that inflammasome formation correlates with the severity of rejection and with heart failure [109]. This IL-1-rich milieu causes further apoptosis of cardiomyocytes, loss of contractile tissue, fibrosis, cardiomyopathy, heart failure, and arrhythmic outburst. A close relationship exists between IL-1 $\alpha$ , IL-1 $\beta$ , and heart function: both cytokines worsen contractile function by inhibiting L-type calcium channels, uncoupling  $\beta$ -adrenergic receptors from the adenylyl-cyclase [110] and causing transcriptional and post-translational changes in phospholamban and sarcoplasmic/endoplasmic reticulum calcium ATPase [111]. Moreover, effects of IL-1-mediated inflammation in the myocardium include disruption of calcium and  $\beta$ -adrenergic receptors signaling, mitochondrial dysfunction, and increased nitric oxide production [112].

Preliminary clinical experience with anakinra provided unequivocal proofs that IL-1 plays a pivotal role in both myocardial inflammation and systolic impairment. The effectiveness of IL-1 blockade was first shown in a randomized double-blind trial enrolling 23 rheumatoid arthritis patients with impaired vascular and left ventricular function: a prompt amelioration of cardiac function including myocardial contractility and relaxation, coronary flow reserve, and brachial artery flow-mediated dilatation was observed within 3 hours of anakinra administration [113]. More recently, a double-blind, placebo-controlled trial of anakinra in patients with diastolic heart failure and systemic inflammation confirmed beneficial effects of IL-1 inhibition; contractile function improved also in cases of life-threatening fulminant myocarditis or dilated cardiomyopathy [114–117]. The clinical trials ARAMIS and MYTH-1 are recruiting participants to assess superiority of add-on anakinra compared to conventional therapy in patients with acute and chronic myocarditis (NCT03018834 and EudraCT 2018-003472-13, respectively).

### 3.6.2. Myocardial infarction and ischemia-reperfusion injury

Acute myocardial infarction, characterized by myocardial ischemia followed by necrosis [118], is a common cardiac emergency and a leading cause of morbidity and mortality worldwide [119]. Following a myocardial infarction, a robust inflammatory response develops in the heart, which regulates infarct healing but may also promote maladaptive ventricular remodeling resulting in dilation and systolic dysfunction [120].

IL-1 $\alpha$  is strongly expressed in cardiomyocytes. Similar to myositis and myocarditis, necrosis of cardiomyocytes results in the release of IL-1 $\alpha$  and other danger associated molecular patterns, including high mobility group box-1 (HMGB-1), heat shock proteins, myosin, hyaluronic acid, fibrinogen, fibronectin and nucleic acids. These are sensed by neighboring cells, such as infiltrating myeloid cells and cardiac fibroblasts, which differentiate into myofibroblasts. In these cells, IL-1 $\alpha$  induces different pro-inflammatory cytokines including IL-1 $\beta$ , TNF- $\alpha$  and IL-6 in a concentration-dependent manner by activation of different inflammatory pathways [121]. Upon sensing of IL-1 $\alpha$  and other DAMPs, myofibroblasts also initiate tissue repair and scar formation [122].

Various animal models showed that binding of either IL-1 $\alpha$  or IL-1 $\beta$  to the IL-1R1 receptor has detrimental consequences for ischemia-reperfusion injury and myocardial remodeling [123,124]. Following ischemia, mice lacking IL-1 $\alpha$  or IL-1 $\beta$  exhibit reduced tissue inflammation [125], whereas mice lacking IL-1Ra exhibit increased tissue inflammation [126]. Moreover, animals lacking the IL-1R1 or overexpressing IL-1Ra [124] exhibit reduced inflammation, neutrophil infiltration, and ventricular dilatation following myocardial infarction

[127].

There is also evidence for a specific, non-redundant effect of IL-1 $\alpha$ . Specifically, a study showed that treatment with anti-IL-1 $\alpha$  antibodies administered immediately after reperfusion resulted in reduced ischemic penumbra and in preservation of cardiac function [128]; notably, this study also revealed a decreased activity of caspase-1, thus substantiating the role of IL-1 $\alpha$  as an upstream and crucial danger signal triggering secretion of IL-1 $\beta$ . Conversely, in a different study from the same group, IL-1 $\beta$  inhibition alone neither prevented caspase-1 activation nor reduced the extent of the infarcted area [129]. Also of note, IL-1 $\alpha$  and IL-1R1, but not IL-1 $\beta$ , are required for neutrophilic influx [130].

In humans, there is clinical evidence that IL-1 inhibition is beneficial in ischemic heart disease. The efficacy of IL-1 inhibition with anakinra has been shown in 3 sequential studies enrolling patients with ST-segment-elevation myocardial infarction (STEMI) and elevated C-reactive protein. In these studies, patients treated with anakinra for two weeks experienced a significant reduction in C-reactive protein [131,132] as well as a lower incidence of new-onset heart failure and hospitalization for heart failure [131]. However, another randomized, placebo-controlled study enrolling patients with non-STEMI acute myocardial infarction failed to show an improvement in cardiac clinical outcomes despite a decrease in inflammatory markers with anakinra [133]. In the massive CANTOS trial, selective blockade of IL-1 $\beta$  prevented recurrent myocardial infarction in patients with previous ischemic events and systemic inflammation [134]. Overall, it appears that distinct roles of IL-1 $\alpha$  and IL-1 $\beta$  during myocardial infarction reflect different timing of activation, with IL-1 $\alpha$  found earlier and more upstream in the inflammatory process [128]. Altogether, these observations provide a conceptual framework for blocking IL-1 in patients with active acute myocardial infarction, also in order to prevent incident heart failure [135].

### 3.6.3. Pericarditis

Recurrent pericarditis affects 15-30% of patients after a first episode of acute pericarditis [136,137]. Treatment regimen consists of a combination of non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine, with the addition of corticosteroids in resistant or intolerant cases [136–139]. Patients often become corticosteroid-dependent and are unable to taper or discontinue steroids without experiencing a relapse. The necessity to avoid chronic corticosteroid treatment led to first evaluation of IL-1 receptor blockade in children with recurrent pericarditis [140]. Ever since, anakinra emerged as a safe and effective therapy to obtain or maintain remission while discontinuing corticosteroids, both in children and in adults [141]. On this basis, the European guidelines on the management of pericardial diseases gave a class IIb recommendation to administer anakinra to corticosteroid-dependent, colchicine-resistant patients with recurrent pericarditis [142].

The efficacy of anakinra for recurrent pericarditis was confirmed in a randomized clinical trial: the AIRTRIP study [140] evaluated 21 patients with recurrent pericarditis refractory to colchicine resistance and dependent on corticosteroids; anakinra was administered at a dose of 2 mg/kg/day (maximum 100 mg/day) for 2 months, then responders were randomized to continue anakinra ( $n = 11$ ) or switch to placebo ( $n = 10$ ) for 6 months or until a pericarditis recurrence. The primary outcomes were recurrent pericarditis and time to recurrence after randomization. Recurrent pericarditis occurred in 90% patients receiving placebo compared to 18% patients receiving anakinra; median time to recurrence was 72 days in patients receiving placebo, whereas this parameter could not be calculated due to too few events in the anakinra group [140]. A subsequent international multicenter registry of anakinra in recurrent pericarditis, the IRAP registry (International Registry of Anakinra for Pericarditis), confirmed the findings of the AIRTRIP trial in a real-world population [141]. On these bases, anakinra is currently the treatment of choice for recurrent pericarditis after failure of conventional anti-inflammatory therapies including non-steroidal anti-

inflammatory drugs, colchicine, and corticosteroids.

Recently, the efficacy of rilonacept, an interleukin-1 $\alpha$  and interleukin-1 $\beta$  cytokine trap, was also evaluated in the RHAPSODY study, a phase 3, randomized clinical trial of 61 patients with recurrent pericarditis. Patients presenting with pericarditis recurrence while receiving standard therapy were enrolled in a 12-week run-in period, during which rilonacept was administered subcutaneously once weekly and background medications were discontinued. Clinical responders were further randomly allocated to receive continued rilonacept monotherapy or placebo. The primary efficacy end point was the time to the first pericarditis recurrence. In this study, 2 of 30 patients (7%) in the rilonacept group had a pericarditis recurrence, compared to 23 of 31 patients (74%) in the placebo group. The median time to recurrence in the placebo group was 8.6 weeks, whereas in the rilonacept group recurrences were too few to allow for this outcome to be evaluated ([ClinicalTrials.gov NCT03737110](https://clinicaltrials.gov/ct2/show/study/NCT03737110)).

In recent reports, pediatric patients with refractory recurrent pericarditis, who were receiving treatment with anakinra with optimal disease control, were switched to canakinumab, a monoclonal antibody neutralizing IL-1 $\beta$ , and experienced disease relapses [143]. In these cases, treatment with anakinra was re-established and again led to disease control. These preliminary observations of differential efficacy of IL-1 $\beta$  and IL-1 receptor blockade support a central role of IL-1 $\alpha$  in the pathogenesis of pericarditis.

### 3.7. Vascular system and thrombosis

IL-1 $\alpha$  is expressed abundantly by endothelial cells, activated platelets, and circulating monocytes during inflammation [144,145]. Growing evidence suggests that IL-1 $\alpha$  acts as a link between inflammatory responses and the coagulation cascade. Mechanistically, during wounding or hemorrhage, surface pro-IL-1 $\alpha$  expressed on the surface of endothelial cells undergoes activating cleavage by thrombin [145]. Thrombin-cleaved IL-1 $\alpha$  is detectable in human conditions characterized by thrombo-inflammatory activation, such as sepsis [145]. Locally expressed IL-1 $\alpha$  promotes thrombosis by increasing platelet activity, time of clot lysis [146,147], and endothelial activation [148]; in addition, circulating IL-1 $\alpha$  induces thrombopoiesis and megakaryocyte fragmentation, thus increasing the number of circulating platelets [149]. In mice models of vascular inflammation, IL-1 $\alpha$  but not IL-1 $\beta$  expressed by platelets induces endothelial activation, with expression of adhesion molecules (ICAM-1 and VCAM-1), release of CXCL1, and production of tissue factor [150]. These effects promote recruitment of inflammatory cells (particularly neutrophils), endothelial cell dysfunction, and thrombosis, and are relevant to several human inflammatory diseases.

#### 3.7.1. Behçet's syndrome

Behçet's syndrome is a systemic vasculitis, clinically characterized by muco-cutaneous, ocular, vascular, neurological, pulmonary and gastrointestinal manifestations [151,152]. Inflammatory thrombosis is a hallmark of Behçet's syndrome, and up to 40% of patients develops vascular complications involving the venous or arterial vascular tree [153]. Superficial and deep venous thrombosis of the limbs is common, but thrombosis in atypical sites such as the vena cava, the hepatic veins with Budd-Chiari syndrome, the portal vein, the cerebral venous sinus, or the right ventricle, may also occur [151]. Arterial inflammation and thrombosis is not uncommon, which makes Behçet's syndrome one of the few disorders causing aneurysms both in the peripheral, visceral and pulmonary districts [154,155]. The term "angio-Behçet" identifies a specific group subtype of the disease characterized by recurrent thrombosis [156,157], often with concomitant arterial aneurysms and venous involvement [158].

Behçet's syndrome is considered a model of inflammation-induced thrombosis [159–161], and indeed few conventional thrombogenic risk factors have been described in Behçet's syndrome patients. IL-1

gene cluster polymorphisms (IL-1A 2889C and IL-1B +5887T haplotype) are associated with increased susceptibility to vascular inflammation and Behçet's syndrome [162,163]. Moreover, IL-1 $\alpha$  is highly expressed in neutrophils, lymphocytes and endothelial cells in the *vasa vasorum* of patients with Behçet's syndrome [163], and serum levels of IL-1 $\alpha$  are significantly higher in patients with Behçet's syndrome compared to healthy individuals [164]. The IL-1 $\alpha$ -rich milieu of inflamed blood vessels in Behçet's syndrome also promotes neutrophil recruitment, whose aberrant activation is followed by programmed cell death and release of structures containing condensed chromatin (Neutrophils Extracellular Traps, NETs) [165,166]. NETs contain proteases such as cathepsin G and elastase, which promote vascular inflammation and damage [167] while also serving as extracellular platforms for the processing and activation of IL-1 family cytokines, thus fostering inflammation [168]. Activated neutrophils also release abundant reactive oxygen species (ROS), which are responsible for post-translational modifications of fibrinogen leading to generation of more resistant clots [169]. Overall, these studies indicate that IL-1 $\alpha$  represents a potential therapeutic target for the treatment of arterial inflammation in vasculitis associated with Behçet's syndrome [170]. Factors suggesting the suitability of IL-1 $\alpha$  inhibition specifically in Behçet's syndrome include concomitant venous and arterial inflammation, as well as other clinical manifestations typically mediated by IL-1 $\alpha$  (i.e. pustular skin or mucosal involvement).

#### 3.7.2. Arterial aneurysms and Kawasaki disease

Besides inflammatory thrombosis, IL-1 $\alpha$  is involved in aneurysm formation. In a study evaluating changes in the concentration of serum cytokines following repair of abdominal aortic aneurysm, only IL-1 $\alpha$  was significantly reduced, which likely implicates this cytokine in the molecular pathogenesis of aneurysms [171].

In addition, IL-1 $\alpha$  is involved in the formation of arterial lesions associated with Kawasaki disease (KD), the main cause of acquired heart disease in childhood [172,173]. KD is a systemic vasculitis of medium-sized arteries, characterized by fever, rash, conjunctival injection, cervical lymphadenopathy, and inflammation of the coronary arteries. In 40-80% of children, KD leads to persistent coronary artery inflammation, aneurysmal dilation of coronary arteries, or myocarditis. The cause of KD remains undefined, but several infectious triggers (i.e. *Retroviruses*, *Coronaviruses*, *Epstein-Barr virus*, *Staphylococcal superantigen*) have been postulated to act on a predisposing genetic background [174,175]. Notable polymorphisms include Inositol 1,4,5- trisphosphate 3- kinase C (ITPKC) [176], which leads to persistent intracellular increase of Ca<sup>2+</sup>, and hence to enhanced activation of NLRP3 inflammasome.

Mouse models of Kawasaki disease showed that both IL-1 $\alpha$  and IL-1 $\beta$  play a non-dispensable role in the development of coronary arteritis [170], and that inhibition of either mediator by gene deletion or pharmacological blockade can prevent aneurysm formation. IL-1 $\alpha$ , released as an alarmin in the microenvironment or expressed by neighbouring fibroblasts, triggers the inflammatory response in the initial phase of KD and likely regulate IL-1 $\beta$  secretion, whose role prevails in later phases of KD [170]. Both IL-1 $\alpha$  and IL-1 $\beta$  trigger vasodilatation and promote the influx of myeloid cells to affected tissues. Genetic and transcriptomic data in humans confirmed the role of IL-1 $\alpha$  and IL-1 $\beta$  in the pathogenesis of KD vasculitis [177,178].

Treatment of KD is currently based on corticosteroids and intravenous immunoglobulins (IVIG). High-dose IVIG significantly inhibits coronary arterial endothelial cells and macrophage activation [179]. The mechanisms underlying the therapeutic efficacy of IVIG in KD remain undetermined [180]. Of note, previous study indicated that IVIG treatment suppresses IL-1 $\alpha$  and IL-1 $\beta$  and stimulates IL-1Ra production, both *in vitro* and *in vivo* [181]; decreased levels of IL-1 receptor antagonist (IL-1Ra) are documented in IVIG-resistant KD patients [182].

Treatment with anti-IL-1 $\alpha$  or IL-1 $\beta$  mAb alone protects mice against KD vasculitis and myocarditis, but the protection is partial unless the



two mAbs are used together or unless both cytokines are inhibited via receptor blockade [170]. In humans, treatment of KD with anakinra is under consideration in clinical trials [183,] and showed efficacy in case series [184]. In these studies, IL-1 receptor blockade led to the resolution of the clinical manifestations in difficult-to-treat patients [175,184,185].

#### 4. COVID-19

In 2020, a new infectious disease denominated coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in an unprecedented pandemic outbreak [186]. SARS-CoV-2 is an airborne pathogen, which infects lung epithelial cells as well as endothelial cells causing inflammation of the airway tract and thrombotic microangiopathy. Since COVID-19 is a new disease, limited mechanistic data is available on the pathogenesis. However, IL-1 $\alpha$  is constitutively present in epithelial cells, endothelial cells, and infiltrating myeloid cells in the lung. This implies a massive release of IL-1 $\alpha$  upon the lytic death of these cells due to the viral infection, with subsequent sensing by alveolar macrophages [187]. In some patients, a life-threatening hyper-inflammatory reaction ensues, which resembles a macrophage activation syndrome (MAS) or a cytokine storm [188] and culminates in acute respiratory distress syndrome (ARDS) [189]. Inflammatory thrombosis also typically occurs in the lung of COVID-19 patients [190]. Advanced stages of COVID-19 ARDS are characterized by diffuse lung damage (with both alveolar epithelial and endothelial injury), accumulation of inflammatory exudate fluid in alveolar spaces, extensive thrombosis, and maladaptive tissue repair with fibrotic changes [191].

Overall, the pathogenesis of COVID-19 seems to recapitulate several key steps of IL-1 $\alpha$ -mediated inflammation. Specifically, release of IL-1 $\alpha$  as an alarmin by epithelial cells is followed by sensing by inflammatory myeloid cells and activation of the inflammasome, which results in amplification of the inflammatory cascade; at the same time, expression of IL-1 $\alpha$  by endothelial cells results in granulocyte recruitment and inflammatory thrombosis.

Production of IL-1Ra is a physiologic mechanism to limit excess inflammation and tissue damage in ARDS. IL-1Ra is elevated in the broncho-alveolar fluid of ARDS patients, particularly in the resolution phase [192]. Moreover, IL-1Ra serum levels are also associated with disease severity in pediatric ARDS [193]; in patients with community-acquired pneumonia, polymorphisms are associated with adverse outcomes [194].

Given these evidences, as well as similarities between severe COVID-19 and hyper-inflammation in the context of IL-1-mediated autoimmune or autoinflammatory conditions, IL-1-blockade was evaluated for the treatment of COVID-19 [195]. In a landmark study, high-dose intravenous anakinra (5 mg/kg twice a day) reduced mortality and ameliorated systemic inflammation and respiratory function in 29 patients with ARDS and on non-invasive ventilation, compared to standard management [196]. Subsequent studies independently reported comparable reductions in mortality and/or need for invasive mechanical ventilation [197–204]. To date, 14 and 3 different clinical trials are evaluating treatment of COVID-19 patients with anakinra and canakinumab, respectively (<https://clinicaltrials.gov/>). Meanwhile, studies evaluating monoclonal antibodies blocking IL-6 yielded more conflicting results [205–209].

Given the bi-directional relationship between IL-1-mediated inflammation and coagulation, blockade of IL-1 $\alpha$  and IL-1 $\beta$  might also reduce inflammatory thrombosis and thromboembolic complications in COVID-19. In previous studies of disseminated intravascular coagulation during sepsis or MAS, anakinra treatment was associated with survival benefits [210,211]. However, this opportunity remains to be evaluated in COVID-19.

#### 4.1. Pediatric inflammatory multisystem syndrome temporarily associated to SARS-CoV-2 infection

During the COVID-19 pandemic, a severe pediatric inflammatory multisystem syndrome temporarily associated to SARS-CoV-2 infection (PIMS-TS) was described. Specifically, some children and adolescents with confirmed COVID-19 or close contact with affected relatives developed predominantly gastrointestinal symptoms followed by an acute hyper-inflammatory disease and myocardial insufficiency, mimicking acute KD [212,213].

The clinical overlap between PIMS-TS and KD was first proposed by Jones *et al.*, who described a patient with classical KD, who had a positive nasopharyngeal swab for SARS-CoV-2 [214]. Children with PIMS-TS have more often antibodies against SARS-CoV-2 rather than a positive nasopharyngeal swab. This finding suggests a latency (up to one month) between COVID-19 infection and the development of PIMS-TS, which is consistent with a maladaptive immune response rather than a direct causative role of the virus. Given pathogenic and clinical similarities with both KD and COVID-19 hyper-inflammation, IL-1 $\alpha$  is plausibly implicated in the pathogenesis of PIMS-TS. In analogy with KD, the proposed first-line treatment for PIMS-TS was IVIG or corticosteroids. In non-responders or in patients with hyper-inflammation resembling macrophage activation syndrome, high-dose intravenous anakinra can be effective, consistent with use in KD and COVID-19 hyper-inflammation.

#### 5. Sjögren's syndrome

Sjögren's Syndrome (SS) is an autoimmune condition characterized by chronic inflammation of exocrine glands leading to sicca symptoms [215,216]. Epithelial cells of lacrimal and salivary glands are both the target and the instigator of inflammation in SS [217,218]. Indeed, epithelial cell activation and death result in the release of pro-inflammatory mediators, including IL-1 $\alpha$  as well as other IL-1 family members, which prompt recruitment of immune cells [219–221] and activation of the inflammasome [222]. In this IL-1-rich milieu, innate inflammation leads to progressive tissue damage and exocrine gland dysfunction in the early phases of the disease, whereas lymphocytic infiltrates are the hallmark of established SS [223].

Evidence for a role of IL-1 $\alpha$  in SS comes from pre-clinical and clinical studies. In experimental animals, direct instillation of IL-1 $\alpha$  in salivary [224] or lacrimal glands [225] causes inflammation, dysfunction, and loss of acinar epithelial cells. Consistently, deficiency of IL-1R1 prevents eye keratinization and epitheliopathy [226], without affecting lymphocytic infiltration of glands. The conjunctival epithelium of patients with SS exhibits high concentrations of IL-1 $\alpha$  as well as other cytokines [227]. In dry-eye disease, tear fluids display an increase in IL-1 $\alpha$  and mature IL-1 $\beta$  and a decrease in the biologically inactive precursor of IL-1 $\beta$  [228]. High levels of IL-1Ra are also observed in tears of patients with SS, which likely represents an insufficient attempt at curbing excess inflammation [229]. Indeed, an imbalance in the IL-1/IL-1Ra ratio is observed in the saliva of patients with SS compared to controls [230]. Exogenous administration of anakinra is clinically effective in dry-eye syndrome, both in experimental models [231] and humans receiving topical treatment [232]. A randomized, double-blind, placebo-controlled study evaluated systemic administration of anakinra in 26 patients with SS. Unfortunately, this study did not evaluate sicca symptoms, yet a decrease in inflammation-mediated fatigue was reported [233], which substantiates a systemic role of IL-1 in SS. Given the central role of epithelial inflammation and damage, leading to release of IL-1 $\alpha$  followed by active production of IL-1 $\beta$  in affected glands, IL-1 inhibition deserves consideration as a therapeutic strategy in SS, particularly in light of the lack of effective therapies for sicca symptoms.

## 6. Erdheim-Chester disease

Erdheim-Chester disease is a rare inflammatory neoplasm characterized by infiltration of multiple tissues by foamy macrophages [234]. These cells bear activating mutations along the MAPK pathway (most commonly BRAFV600E) and produce abundant cytokines [235–238]. Clinical manifestations are protean, and are caused both by the development of mass-like lesions as well as by systemic inflammation and fibrosis [239,240]. Mutated macrophages infiltrating tissues in ECD express abundant membrane-bound IL-1 $\alpha$ , which is likely instrumental to local recruitment and activation of inflammatory cells and progressive lesion growth [241]. Indeed, treatment with anakinra can be effective both in suppressing systemic inflammation and in reducing lesion size in ECD [242–244].

## 7. Cancer

Since IL-1 $\alpha$  is constitutively expressed in mesenchymal cells, malignant transformed cells of mesenchymal origin contain the IL-1 $\alpha$  precursor. IL-1 $\alpha$  is also observed within the nuclei of cancer cell lines, as a result of the nuclear localization sequence. However, whether IL-1 $\alpha$  in the nucleus has the potential to contribute to malignant transformation is unknown [245]. The current understanding of the role of IL-1 $\alpha$  in cancer development is more complex. In the early phases of carcinogenesis, IL-1 $\alpha$  expressed on the cell membrane of dendritic cells promotes the development of an immune response aimed at halting tumor formation by facilitating neoantigen recognition in the context of MHC [4]: for example, initial carcinogenesis induced by cigarette tars in the lung is often halted by neoantigen recognition and immune elimination. However, once tumors escape immune surveillance and a mass develops, high rates of cellular turnover result in abundant release of IL-1 $\alpha$  and in the development of chronic inflammation in the tumor microenvironment [4]. Additional sources of secreted IL-1 $\alpha$  found in the extracellular compartment include tumor-associated macrophages and plasmacytoid dendritic cells [246,247]. This IL-1 $\alpha$ -rich milieu has detrimental, clinically relevant consequences both at the local and systemic level. Locally, a pro-inflammatory tumor microenvironment promotes inflammation-mediated immunosuppression, cancer cell survival, and tumor progression [24,248]. Systemically, IL-1 $\alpha$ -driven inflammation mediates muscle loss and cachexia, clinically manifested as the loss of lean body mass and wasting syndrome typical of end-stage cancer patients [249].

Based on these observations, inhibition of IL-1 $\alpha$  was evaluated as a therapeutic strategy to reduce cancer growth and improve patients' clinical status. The first trials were proof-of-concept studies that evaluated the efficacy of bermekimab, a monoclonal neutralizing antibody targeting IL-1 $\alpha$  for the treatment of patients with advanced cancers of various origins [250,251]. Bermekimab was evaluated in an open label, Phase 1 dose escalation and expansion cohort study in patients with advanced NSCLC cancer refractory to standard therapies. Despite the small sample size limiting the statistical power, self-reported outcomes revealed pain and fatigue reduction as well as improvement in appetite, reduction in resting energy expenditure, and increase in lean body mass [250]. Following these encouraging observations, a randomized, placebo-controlled study evaluated the efficacy of this treatment in 333 patients with advanced, metastatic colorectal cancer [252]. The study met its primary and secondary endpoints, following an 8-week monotherapy course of the IL-1 $\alpha$  neutralizing human antibody, which resulted in increased lean body mass, decreased constitutional symptoms, decreased pain, improved quality of life, and lower circulating IL-6 and platelet counts in treated patients. Increased survival was also observed in responders compared with non-responders.

The role of IL-1 $\alpha$  is also likely relevant to the cytotoxic effects of chemotherapy, which can result in additional and accelerated release of IL-1 $\alpha$  by dying cells. Anakinra, which blocks IL-1 $\alpha$  binding to IL-1R1, was evaluated in patients with advanced metastatic colorectal cancer

[253] and resulted in improved survival. In addition, anakinra was administered to patients with hormone negative, metastatic breast cancer [254]. Anakinra also emerged as a suitable option for the treatment patients with advanced pancreatic cancer receiving the highly toxic FOLFIRINOX therapy [255]. Specifically, anakinra added to treatment with gemcitabine, nab-paclitaxel and cisplatin in patients with non-metastatic pancreatic ductal adenocarcinoma prior to resection resulted in reduced local cancer spread compared to historical controls receiving gemcitabine, nab-paclitaxel and cisplatin alone (NCT 0255037).

## 8. Conclusions

The IL-1 family member IL-1 $\alpha$  is a ubiquitous and pivotal pro-inflammatory cytokine. It is constitutively present in nearly all cell types as a bioactive mediator, and is released upon cell death or expressed by infiltrating myeloid cells within injured tissues. It binds the IL-1R1 receptor, shared with IL-1 $\beta$ , and induces identical pro-inflammatory effects. However, IL-1 $\alpha$  and IL-1 $\beta$  maintain non-redundant inflammatory functions. IL-1 $\alpha$  triggers local inflammation, which rapidly escalates into an IL-1-mediated pro-inflammatory loop characterized by secretion of IL-1 $\beta$  by nearby myeloid cells.

Given its role as a bioactive precursor released upon tissue damage and cell death, IL-1 $\alpha$  is central to the pathogenesis of numerous conditions characterized by organ or tissue inflammation. These include disorders of the skin, lung and respiratory tract, heart and pericardium, and blood vessels, but also complex multifactorial conditions, such as COVID-19, Behcet's syndrome, or Sjogren Syndrome. Among available therapies, anakinra and riloncept target IL-1 $\alpha$  but also reduce IL-1 $\beta$  activities; only bermekimab specifically targets IL-1 $\alpha$ . Unlike emerging oral NLRP3 inhibitors for reducing the activities of IL-1 $\beta$  and IL-18, presently there are no oral therapies to treat IL-1 $\alpha$ -mediated diseases. Targeting cytosolic IL-1 $\alpha$  with orally active synthetic molecules could also be used to suppress inflammation.

## Declaration of Competing Interest

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