HHS Public Access

Author manuscript

Immunol Rev. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

Immunol Rev. 2018 January ; 281(1): 124–137. doi:10.1111/imr.12615.

Function and regulation of IL-1α in inflammatory diseases and cancer

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Summary

The interleukin (IL)-1 family of cytokines is currently comprised of 11 members that have pleiotropic functions in inflammation and cancer. IL-1α and IL-1β were the first members of the IL-1 family to be described, and both signal via the same receptor, IL-1R. Over the last decade, much progress has been made in our understanding of biogenesis of IL-1β and its functions in human diseases. Studies from our lab and others have highlighted the critical role of Nod-like receptors (NLRs) and multi-protein complexes known as inflammasomes in the regulation of IL-1β maturation. Recent studies have increased our appreciation of the role played by IL-1α in inflammatory diseases and cancer. However, the mechanisms that regulate the production of IL-1α and its bioavailability are relatively understudied. In this review, we summarize the distinctive roles played by IL-1α in inflammatory diseases and cancer. We also discuss our current knowledge about the mechanisms that control IL-1α biogenesis and activity, and the major unanswered questions in its biology.

Keywords

IL-1; cell death; autoinflammatory disorders; cancer

IL-1 cytokine and receptor family

Interleukins were first identified as pyrogenic molecules produced by leukocytes incubated with lipopolysaccharide (LPS) that also enhance the T cell response to lectins (1, 2). Dinarello et al., identified two distinct pyrogens produced by monocytes and neutrophils upon stimulation with heat-killed *Staphylococcus* (3, 4). With the advent of DNA sequencing strategies, these pyrogenic molecules were later described as IL-1α and IL-1β (5). The IL-1 family is now comprised of 11 members, (IL-1α, IL-1β, IL-18, IL- 33, IL-36α, IL-36β, IL-36γ, IL-1R antagonist (IL-1Ra), IL-36Ra, IL-37, and IL-38) which can have complimentary or distinct biological functions (6). Most of the genes encoding the members of the IL-1 cytokine family are located on human chromosome 2, except for IL-18 and IL-33 encoding genes that are located on chromosomes 11 and 9 respectively. Cytokines

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Conflict of Interest Statement: Authors have no conflict of interest

of the IL-1 family share a common structure at the C-terminus, which is comprised by of a typical β-trefoil fold consisting of 12-β-strands connected by 11 loops (7).

While IL-1 receptor antagonist (IL-1Ra) possesses a leader secretion sequence that targets it for secretion via the endoplasmic reticulum (ER)-golgi pathway, all other IL-1 cytokines require unconventional pathways of maturation and/or release from the cell. IL-1α, IL-33 and IL-36 possess a nuclear localization signal and localize to the nucleus under homeostatic conditions. However, the function of nuclear localization of these cytokines is unclear. IL-1β and IL-18 are expressed as inactive zymogens that are activated by cleavage in the N-terminal region by caspase-1, which is itself activated by formation of a multi-protein complex known as the inflammasome (8, 9). The release of other IL-1 cytokines in bio-active forms is also thought to require some form of inflammatory cell death (10). Therefore, the activity of IL-1 cytokines is tightly regulated not only at the level of expression, but also maturation by activated caspases and release from the cell by cell death pathways.

Binding of the cognate IL-1 agonist to the specific receptor leads to the recruitment of the co-receptor, followed by activation of intracellular signaling. Receptors of the IL-1 cytokines typically possess three immunoglobulin (Ig) domains and one Toll-like/IL-1R (TIR) domain (11, 12). Signaling downstream of the receptors can be further modulated by membrane-bound and soluble decoy receptors, accessory proteins and antagonists. The IL-1 receptor family is comprised of several members including IL-1R1 (commonly referred to as IL-1R), decoy receptor IL-1R2, IL-1R accessory protein (IL-1RaP or IL- 1R3), IL-1R4 (T1 or ST2), IL-18Rα (IL-1R5), IL-36R (IL-1R6), IL-18R accessory protein (IL-18Rβ or IL-1R7), IL-1R8 (TIR8), IL-1R9 (IL-1RAPL2), and IL-1R10 (TIGIRR) (11, 12). IL-1α and IL-1β are agonists of IL-1R, while IL-18 and IL-36 bind to IL-18Rα and IL-36R respectively to induce activation of downstream signaling in a MyD88-dependent manner. IL-1R1, IL-1R2, IL-1R4, and IL-36R share the co-receptor IL-1RaP, while IL- 18Rα utilizes IL-18Rβ as the accessory receptor (12). The decoy receptors are unable to initiate a signaling cascade as they lack the cytoplasmic TIR domains. IL-1Ra and IL- 36Ra are soluble receptor antagonists that preclude activation of the cognate receptors (11, 12). Furthermore, a secretory form of IL-1R1 (sIL-1R1) also inhibits IL-1α, IL-1β, and IL-1Ra (13). Furthermore, IL-1R2 can be cleaved and solubilized by matrix metalloproteases (MMPs) to act as an IL-1 antagonist (14). Unsurprisingly, a tight control of agonist and antagonist activity is required to mount an appropriate immune response, and mutations associated with dysregulated activity of IL-1 cytokines are frequently associated with autoinflammatory diseases and cancer. While the regulation and function of IL-1β and other IL-1 cytokines has been reviewed elsewhere (7, 15) here we will focus on our current understanding of regulation and function of IL-1α in inflammatory diseases and cancer.

IL-1α expression and sub-cellular localization

Both IL-1α and IL-1β signal via IL-1R. IL-1α is constitutively expressed in epithelial, endothelial and stromal cells and can be upregulated in hematopoietic and non-hematopoietic cells by a number of stimuli, including Toll-like receptor (TLR) agonists (6, 16), inflammatory cytokines (including IL-1α and IL-1β) (17, 18), oxidative stress (19–21), fatty acid induced mitochondrial uncoupling and hormones (18, 22, 23). *Il1a* promoter lacks

canonical TATA and CAAT box regulatory regions, but contains binding sites for the transcription factor Sp1 (24, 25) which mediates expression during homeostasis. *Il1a* promoter also contains binding sites for AP1 and NF-κB transcription factors (26–28) which up-regulate expression during inflammatory stimulation. In contrast, expression of IL-1β is largely restricted to immune cells, where it is induced by AP1 and NF-κB transcription factors. In myeloid cells, a long noncoding anti-sense *Il1a* transcript (AS-IL- 1α) is required for *Il1a* transcription (29). However, the mechanism by which AS-IL-1α promotes IL-1α expression is unknown.

Both IL-1α and IL-1β are translated into 31 kDa pro-forms. However, unlike pro-IL-1β, pro-IL-1α has a functional nuclear localization signal (NLS) in the N-terminal domain (30, 31). In epithelial cells, myeloid cells, and keratinocytes, pro-IL-1α is shuttled to the nucleus upon translation. In contrast, in vascular smooth muscle cells, NLS of pro-IL-1α is masked by interaction with intracellular form of IL-1R2 that leads to its cytosolic retention (32). The mechanisms that regulate sub-cellular targeting of IL-1α in different cell types and under different stimulation conditions are largely unknown. HS-1- associated protein X (HAX)-1 is a protein associated with mitochondrial, endoplasmic reticulum and the nuclear membranes, and can bind to pro-IL-1α and promote its nuclear localization (33, 34). Using over-expression systems, pro-IL-1α has been suggested to interact with histone acetyltransferases p300, P300/CBP-associated factor (PCAF) and GCN5 in the nucleus (35, 36) and modulate gene expression independently of IL-1R (37, 38). Furthermore, pro-IL-1α is post-transnationally modified, including myristoylation or acetylation on Lys82 (39, 40) and phosphorylation at Ser90 (41, 42). The functions of these modifications are also largely unknown (Figure 1).

Like pro-IL-1β, pro-IL-1α is also cleaved by proteases, including caspase-1, to yield the bioactive 17 kDa form and the 16 kDa N-terminal cleavage product termed as the pro- piece (43). Pro-IL-1α can also be cleaved by calpain, chymase, elastase and granzyme B in the intracellular or extracellular space to yield mature IL-1α (44–47). While cleavage of pro-IL-1β by caspase-1 is required to generate bioactive IL-1β, both pro-IL-1α and mature IL-1α bind to IL-1R with similar kinetics (48) and have similar biological activity on epithelial and hematopoietic cells, as judged by their ability to induce secretion of IL-6 and TNF (49). Therefore, the biological role of proteolytic processing of IL-1α is currently unknown. Caspase-1 activation by inflammasomes does, however, facilitate secretion of IL-1α (and other inflammasome-associated cytokines) by inducing an inflammatory form of cell death termed as pyroptosis (43, 50). In addition to the cytokines (IL-1 and IL-18), active caspase-1 also cleaves the cell death executioner, Gasdermin D (GSDMD) (51- 54). Upon cleavage, the N-terminal fragment of GSDMD oligomerizes and inserts into the cell membrane, leading to loss of osmotic potential, cell swelling and eventual bursting that is accompanied by release of cytoplasmic contents, including IL-1α and IL- 1β, from the cell (51, 52, 54–60). Therefore, inflammasome activation and subsequent pyroptosis is a mechanism of release of IL-1α from the cell, even though the processing of IL-1α by caspase-1 is dispensable for its bioactivity. As they signal via the same receptor, release of IL-1α alongside IL-1β during inflammasome activation may supplement IL-1R activation by IL-1β. In certain cell types, binding of cytosolic IL-1R2 holds pro-IL-1α in an inactive state, as the pro-IL-1α-IL1R2 complex that is released upon necrotic death cannot signal via

IL-1R (32). This inhibition of IL-1α activity by IL- 1R2 can be relieved by active caspase-1, as it can cleave IL-1R2, which leads to its dissociation from pro-IL-1α (32). Therefore, inflammasome activation may indirectly promote IL-1α bioavailability by relieving IL-1R2 inhibition. However, proof of such inhibition of IL-1α, or the requirement of inflammasomes for its bioactivity has not been confirmed under *in vivo* settings.

A membrane-associated form of the full-length pro-IL-1α has also been observed. Exposure of innate immune cells or endothelial cells to inflammatory stimuli such as LPS or heat-killed *Mycobacterium tuberculosis* leads to up-regulation of IL-1α expression, and pro-IL-1α can be detected in the cytoplasm, the nucleus and the plasma membrane (61–63). This membrane-associated form of pro-IL-1α is also bioactive, as it can signal via IL-1R in a paracrine manner to promote T cell proliferation and chemokine secretion (64–67). This membrane-association property of IL-1α is unique in the IL-1 family, and simultaneous localization in the nucleus, cytoplasm and the plasma membrane is unique amongst all known cytokines. Membrane-bound pro-IL-1α is glycosylated (66) suggesting the involvement of a lectin in its membrane targeting or localization. Plasma- membrane-bound pro-IL-1α can also be cleaved by extracellular proteases to yield the mature form of IL-1α, or cause its inactivation (47, 67, 68). The mechanisms that regulate the cytosolic, cellular membrane, or nuclear trafficking of IL-1α, and their relative functions are major questions in the biology of IL-1α.

IL-1α as an apical instigator of inflammation

IL-1α is expressed under homeostatic conditions by multiple hematopoietic and non-hematopoietic cells, and can be upregulated by a diverse array of inflammatory stimuli. Furthermore, IL-1α does not depend on proteolytic processing for its bioactivity. Therefore, cell death caused by injury due to sterile or infectious insults leads to release of bioactive IL-1α that signals via IL-1R to induce inflammatory responses. IL-1R is expressed constitutively by a broad range of cell types and NF-κB and MAPK activation downstream of IL-1R induces production of pro-inflammatory mediators such as cyclooxygenase type-2 (COX-2), IL-6, tumor necrosis factor (TNF), that further promote production of IL-1α and IL-1β, amplifying the inflammatory stimuli provided by the initial release of IL-1α (16, 69, 70). Physiological manifestations of IL-1 signaling include fever, hypotension, vasodilation and increased sensitivity to pain (71).

Consistent with the hypothesis of IL-1α as an apical driver of inflammation during sterile injury, infiltration of neutrophils into the peritoneal cavity upon administration of necrotic cells was found to be dependent on the release of IL-1α from necrotic cells, and signaling via IL-1R in radio-resistant cells (68, 72, 73). These and subsequent studies have shown that release of IL-1α from dying cells is a major driver of many inflammatory processes (6, 73–75). IL-1α is therefore referred to as an “alarmin” and a critical danger- associated molecular pattern (DAMP) during sterile insults. Mechanisms are also in place to prevent IL-1α release and initiation of downstream inflammatory responses during regulated non-inflammatory cell death. During apoptosis, release of cytosolic pro- IL-1α is prevented by its sequestration into the nucleus, followed by clearance of the nuclei-containing apoptotic

bodies by scavenging phagocytes (76, 77). Binding of cytosolic IL-1α by IL-1R2 may also serve to sequester IL-1α during inflammatory signaling (32).

IL-1α and auto-inflammatory disorders

Auto-inflammatory disorders refer to the inflammatory diseases that are caused by in- born errors in the innate immune system and develop independently of involvement of T cells or B cells. Dysregulation of IL-1α or IL-1β production is associated with numerous auto-inflammatory disorders, and as they signal via the same receptor, they were initially thought to be functionally redundant. Studies in the last decade utilizing mouse models of auto-inflammatory diseases have helped determine specific roles of these cytokines, and the molecular mechanisms that control their production, bio-availability and downstream signaling events. Here, we will briefly discuss auto-inflammation induced by IL-1β (reviewed in (78)) and focus on complimentary and contrasting mechanisms by which IL-1α provokes autoinflammatory diseases.

Proline-serine-threonine phosphatase-interacting protein 2 (PSTPIP2) is a member of the Fes/CIP4 homology-bin/amphiphysin/rvs (F-BAR) family of proteins and interacts with protein tyrosine phosphatases of the PEST (a domain rich in proline, glutamic acid, serine, and threonine) family (79–81). Mice carrying a homozygous L98P missense mutation in *Pstpip2*, referred to as *Pstpip2*^{cmo} mice, develop a severe autoinflammatory disease affecting the bones that mimics chronic recurrent multifocal osteomyelitis (CRMO) in humans (82–84). Our group and others have shown that IL-1β, but not IL-1α, is required for disease development in *Pstpip2*^{cmo} mice (85, 86). Furthermore, caspase-1 functions redundantly with caspase-8 to induce IL-1β maturation in *Pstpip2*^{cmo} neutrophils, while elastase and neutrophil proteinase 3 are dispensable (85, 87, 88). Bone marrow chimera studies further reveal that IL-1β produced by hematopoietic cells signals via IL-1R on non-hematopoietic cells to mediate auto-inflammation (87).

Auto-inflammatory diseases familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID) are associated with mutations in NLRP3 (previously named as cryopyrin) and are collectively referred to as cryopyrin-associated periodic syndromes (CAPS) (89–94). Whole body or myeloid-cell specific knock-in (KI) mice expressing NLRP3 mutations associated with CAPS develop auto-inflammation that is associated with increased levels of circulating IL-1β (95, 96). Myeloid cells from human patients or mouse models of CAPS secrete IL-1β after TLR priming alone, and auto-inflammation in these mice is rescued by genetic deletion of ASC (97) or caspase-1 (98). However, IL-1β, IL-18 and IL-1R have a partial role, suggesting that other inflammasome-associated functions such as cell death can also contribute towards CAPS-pathology (95, 96, 98, 99). In contrast, in a mouse model of Familial Mediterranean Fever (FMF) wherein the auto-inflammation is caused by a gain-of-function mutation in the inflammasome sensor Pyrin (100–102), IL-1β, ASC and caspase-1 have a non-redundant role in mediating auto-inflammation, while IL-1α and caspase-8 are dispensable (103).

Inflammasomes and IL-1 cytokines can also promote auto-inflammation induced by other cytokines. *Sharpin*^{cpdm} mice are deficient in Shank-associated RH domain interacting protein (SHARPIN), a member of linear ubiquitin chain assembly complex (LUBAC), and develop severe dermatitis (104–108). Auto-inflammatory dermatitis in *Sharpin*^{cpdm} mice is completely rescued by genetic deletion of TNF (108), TNFR1 or downstream signaling molecules (109–111). However, deletion of IL-1β, IL-1R, NLRP3 or caspase-1 significantly delays dermatitis in *Sharpin*^{cpdm} mice (112, 113). In line with these findings, IL-1R signaling also upregulates the production of TNF (114). These studies show that concerted production of IL-1β and TNF can form an inflammatory loop, which is capable of causing destructive auto-inflammation, unless curtailed by negative regulators like IL-10 (115, 116).

In recent years, IL-1α has also emerged as an apical driver of cutaneous inflammation (117–119), colon inflammation and cancer (120), cardiovascular disease (121) and neural inflammation (122). We have shown that IL-1α has a non-redundant role in driving auto-inflammatory disease in a mouse model of neutrophilic dermatoses (119). Neutrophilic dermatoses are a heterogeneous group of autoinflammatory skin disorders that are associated with cutaneous inflammatory lesions and include Sweet's syndrome, pyoderma gangrenosum, subcorneal pustular dermatosis and hidradenitis suppurativa (123–125). Increased neutrophil infiltration at the affected sites is a defining clinical feature of neutrophilic dermatoses. A homozygous Tyr208Asn mutation in the *Ptpn6* gene (that encodes for the phosphatase SHP1) results in a severe form of autoinflammatory skin disease in mice (referred to as *Ptpn6*^{spin} mice) that mimics neutrophilic dermatoses in humans (119, 126–128). Furthermore, splice variants or mutations in *PTPN6* gene are associated with neutrophilic dermatoses such as Sweet's syndrome and pyoderma gangrenosum in humans (129). SHP-1 has a negative regulatory role in inflammatory signaling in immune cells, and modulation of SHP-1 expression is associated with skin inflammation, multiple sclerosis, psoriatic arthritis and cancer in humans (130–134). While SHP1-deficient mice have severe inflammation associated with early mortality, *Ptpn6*^{spin} mice retain approximately 30% of the SHP-1 phosphatase activity and present a milder phenotype with no disease-associated mortality (119). *Ptpn6*^{spin} mice develop footpad swelling at 8–16 weeks of age that is associated with marked neutrophilia, intraepidermal pustules and cutaneous tissue damage (119). The neutrophilic dermatoses in *Ptpn6*^{spin} mice is rescued by MyD88 or IL- 1R deficiency demonstrating a role for IL-1 signaling in provoking disease in these mice (135).

Our studies show that IL-1α has a non-redundant role in driving SHP1-mediated neutrophilic dermatoses as genetic ablation of IL-1α, but not IL-1β protects the *Ptpn6*^{spin} mice from disease development (119). Transgenic mice that overexpress IL-1α in epidermal cells also develop an inflammatory skin disease, underscoring the pathogenic role of excess IL-1α production in skin inflammation (136). Bone marrow chimera studies further reveal that while *Ptpn6*^{spin} mutation in hematopoietic cells is required for disease development in these mice, the non-hematopoietic cells are the primary source of pathogenic IL-1α (137). Microabrasion injury in the footpads also accelerates disease progression and enhances severity in pre-diseased *Ptpn6*^{spin} mice, suggesting that passive release of IL-1α from epidermal cells during necrotic cell death is an instigator of disease (119). Microabrasion in the footpads of WT mice also leads to enhanced TNF-α, G-CSF and KC production in an

IL-1α-dependent manner (137). However, production of IL-1α, as well as G-CSF and KC is unaffected in the microabrated footpads of TNF-α- deficient mice (137). Furthermore, genetic deletion of TNF-α or TNFR adaptor tumor necrosis factor receptor type 1-associated death domain protein (TRADD) in *Ptpn6*^{spin} mice only partially protects mice from the disease (137). Taken together, these data show that IL-1α is the apical cytokine that induces production of other pro- inflammatory cytokines and ultimately recruits neutrophils to drive the autoinflammatory disease in *Ptpn6*^{spin} mice.

Unlike CAPS and FMF, the IL-1 driven cutaneous inflammation in *Ptpn6*^{spin} mice is independent of inflammasomes as genetic deletion of caspase-1, ASC or NLRP3 does not affect disease development (119). Instead, disease development depends on receptor-interacting protein kinase 1 (RIPK1) – a central hub in NF-κB signaling, apoptosis and necroptosis (138–140). Necroptosis is a regulated form of inflammatory cell death that depends on the kinase activity of RIPK1, which along with RIPK3 activates the cell death executioner mixed lineage kinase domain–like (MLKL) (138–140). MLKL is a pseudokinase that forms pores in the plasma membrane, leading to loss of osmolarity and eventual death of the cell (141). *Ptpn6*^{spin} mice that are also genetically deficient in RIPK3, MLKL or RIPK1 kinase activity develop the disease with the same severity as the *Ptpn6*^{spin} mice (137). While RIPK1-deficient mice die perinatally, fetal liver chimeras with *Ptpn6*^{spin} and RIPK1-deficient bone marrow donor cells are protected from disease development (119). Recent reports show that perinatal death of RIPK1-deficient mice can be rescued by simultaneous deletion of both RIPK3 and caspase-8 (142–144). In line with a critical role for RIPK1 in inducing disease in these mice, simultaneous germline deletion of caspase-8, RIPK3 and RIPK1, but not RIPK3 and/or caspase-8, protects *Ptpn6*^{spin} mice from disease (137). These studies demonstrate that IL-1α production from non-hematopoietic cells and scaffolding activity of RIPK1 is required for disease development in *Ptpn6*^{spin} mice, while RIPK3 and MLKL mediated necroptosis is dispensable. Ubiquitination of RIPK1 allows it to act as a scaffold to support transforming growth factor-β activated kinase 1 (TAK1) recruitment to the RIPK1 complex, which is central to signaling events downstream of both IL-1R and TLRs (145, 146). Our recent study shows that scaffolding activity of RIPK1 coordinates with TAK1 to provoke disease (137). We also show that SHP-1 controls activation of spleen tyrosine kinase (SYK), which further regulates MyD88 phosphorylation in myeloid cells (147). Consequently, *Ptpn6*^{spin} mice that are also deficient in TAK1 or SYK in myeloid cells are also protected from disease development. Overall, studies from the *Ptpn6*^{spin} mice demonstrate that IL- 1α production from non-hematopoietic cells acts on myeloid cells in a SYK, MyD88, RIPK1 and TAK1 dependent manner, and this pathway is negatively regulated by SHP-1 to restrain excessive IL-1R signaling and associated auto-inflammation (Figure 2) (142, 148–150).

Ptpn6^{spin} mouse model has therefore proved extremely useful in delineating cellular and molecular checkpoints that regulate the production of IL-1α, and its downstream signaling events. This model could also be useful in exploring mechanisms that control the bioavailability of IL-1α, and perhaps the function of IL-1α maturation and post-translational modifications. Interestingly, modulation of the gut microbiota by diet or antibiotic usage can affect the expression of IL-1α and IL-1β in the extra-intestinal sites, and development of the associated auto-inflammatory disorders (88, 119, 151). Therefore,

manipulation of gut microbiota, and specific blockade of IL-1α or IL-1β could be a potential therapeutic strategy for treatment of autoinflammatory disorders.

IL-1α is also suggested to promote inflammation in the skin in humans. Expression of IL-1α, IL-6, platelet-derived growth factor (PDGF)-α, collagen and IL-1R is increased in fibroblasts isolated from skin lesions of systemic sclerosis (SSc) patients (152–154). This IL-1α was localized primarily in the nucleus, but also detected in the cytoplasm and the cell membrane. Underscoring the importance of IL-1α as an apical driver of SSc, knock- down of IL-1α also reduced the proliferation, and levels of secreted IL-6, PDGF-α and pro-collagen in SSc-associated fibroblasts. On the other hand, levels of IL-6, PDGF-α and collagen are increased in normal fibroblasts when pro-IL-1α is over-expressed (152, 153). IL-1α has also been suggested to be a sensor of genotoxic stress (40). Upon induction of DNA-damage by exposure to UV or genotoxic agents, IL-1α co-localizes with gH2AX and HDAC-1 at the sites of DNA-damage. While the function of IL-1α nuclear localization is not known, acetylation of IL-1α within the NLS is required for this nuclear localization. Furthermore, secretion of IL-1α from the skin lesions, via unknown mechanisms, drives neutrophil-infiltration in the affected tissue (40).

IL-1α is also associated with driving inflammation at mucosal barrier surfaces. IL-1α, but not IL-1β-deficient mice are protected from acute colitis induced by oral feeding of cytotoxic agent dextran sodium sulfate (DSS) (155, 156). Furthermore, epithelial cells are the primary source of this pathogenic IL-1α (155). We also demonstrated that another member of the IL-1 cytokine family, IL-33, promotes IgA production in the intestine, which in turn supports symbiotic gut microbiota (156). Consequently, IL-33- deficient mice have a dysbiotic microbiota characterized by increased levels of mucolytic and colitogenic bacteria. Upon cytotoxic stress induced by DSS administration, this dysbiotic microbial landscape promotes the release of IL-1α in the colon tissue, which acts as a critical driver of colitis. The increased susceptibility of IL-33-deficient mice to acute and chronic colitis can be ameliorated by genetic or biochemical ablation of IL-1α, underscoring the importance of IL-1α in driving colitis induced by exacerbated epithelial injury (156).

IL-1α also plays a significant role in the development of atherosclerotic lesions (157, 158). Fatty acids induce the expression of IL-1α in macrophages that accumulate in the atherosclerotic plaques. This macrophage-associated IL-1α drives vasculitis in an IL-1R-dependent manner (157, 158). IL-1α is also a critical driver of ischemia during myocardial infarction and brain injury (158, 159). It is unknown if a secreted or cell membrane-associated form mediates this function of IL-1α, or if proteolytic processing or post-translational modifications of IL-1α are required.

Overall, these studies indicate that IL-1α is an apical regulator of inflammation. Upon cellular injury, release of the pre-formed pool of IL-1α, or its shuttling to the plasma membrane can induce signaling via ubiquitously expressed IL-1R in an autocrine and paracrine manner. IL-1R signaling further leads to expression of cytokines and chemokines, including IL-1α and IL-1β that leads to recruitment of inflammatory cells to the site of damage. Therefore, the initial round of IL-1α–IL-1R1 signaling can lead to self-perpetuating inflammation until the anti-inflammatory mediators like IL-10 and IL- 1R2 suppress it.

IL-1α and microbial diseases

Consistent with its role as an alarmin, IL-1α also plays a non-redundant role in instigating host defense against multiple infectious agents. Exposure to *Mycobacterium tuberculosis* leads to upregulation of IL-1α and IL-1β expression in macrophages and epithelial cells (160). IL-1 signaling cooperates with TNF signaling to promote granuloma formation, which help sequester the bacteria. The absence of IL-1α, IL-1R or TNFR in the host leads to failure of granuloma formation, and increased mortality in the host (63, 160). The synergy between IL-1α and TNF signaling is also protective from gut-derived sepsis induced by *Pseudomonas aeruginosa* colonization and cyclophosphamide induced immune-suppression (161). IL-1α-induced chemokines IL-8, CXCL1, CXCL2 and G-CSF can further promote IL-1α expression, forming an inflammatory feedback loop that can exacerbate neutrophil infiltration following *Staphylococcus aureus* or *Chlamydia trachomatis* infection (162, 163). Therefore, IL-1α is also an apical instigator of inflammatory responses during bacterial infections and similar to cooperation between IL-1α and TNF in mediating auto-inflammation in *Ptpn6*^{spin} mice, cooperation between IL- 1α and TNF mediates host immune responses during infections. In contrast, inflammasomes and IL-1β play a major part in mediating host-defense to bacteria such as *Streptococcus pneumonia, Citrobacter rodentium* and *Francisella novicida* (164–169).

IL-1α is also the initiator of neutrophil influx in the lungs following infection with an intracellular bacterial pathogen *Legionella pneumophila,* the cause of severe pneumonia called Legionnaires' disease (170). IL-1α production in hematopoietic cells is necessary for neutrophil infiltration following *L. pneumophila* infection, while IL-1β has a relatively minor role. Furthermore, while inflammasome activation is necessary for IL-1β secretion, it is dispensable for IL-1α release following *L. pneumophila* infection (170). IL-1 also exacerbates neutrophilia in response to *Haemophilus influenzae* infection and cigarette smoke exposure, in a CXCR2-dependent manner (171). Specific IL-1α blockade also restricts intestinal inflammation induced by *Yersinia enterocolitica* (172) or cytotoxic agent DSS (156). In contrast, exogenous administration of IL-1α ameliorates intestinal ischemia and reperfusion injury by reducing intestinal permeability and bacterial translocation during thermal injury and endotoxemia (173). The mechanisms that control the bio-availability of IL-1α following these infections or treatments are not known. It is also unknown if specific sub-cellular localization, post-translational modification or proteolytic processing of IL-1α is required for these functions.

IL-1α also plays a role in neutrophil recruitment and host-defense following viral, fungal and protozoan infections. Interaction of adenovirus with β3 integrin on marginal zone macrophages leads to upregulation of IL-1α, which integrates with complement signaling to induce recruitment of neutrophils to the marginal zone of the spleen (174, 175). This IL-1α-dependent neutrophil recruitment is necessary for elimination of virus-containing cells (174, 175). IL-1α production from keratinocytes following *Candida albicans* infection also leads to G-CSF production from endothelial cells at the site of infection, which promotes neutrophil recruitment (176). IL-1α also boosts granulopoiesis in the bone marrow, increasing the number of circulating neutrophils (176). Therefore, IL-1α signaling in both hematopoietic and non-hematopoietic cells is required for neutrophil generation and

recruitment to the site of infection. These findings are similar to the concerted action of IL-1α in both hematopoietic and non-hematopoietic compartments for induction of auto-inflammatory disease in the *Ptpn6*^{spin} mice (137).

IL-1α expression also precedes IL-1β expression in the brain after systemic infection with the fungal pathogen *Cryptococcus neoformans* (177) and supports neutrophil recruitment in the lung following *Apsergillus fumigatus* infection (178). IL-1α induced neutrophil recruitment can also be a driving factor for tissue damage during infections. In the genetically susceptible BALB/c mice, protozoan parasite *Leishmania major* induces pathology in an IL-1α-dependent manner (179). However, transient local administration of IL-1α during cutaneous leishmaniasis promotes IFN-γ production from T cells, which is protective for the host (180). IL-1α also drives neutrophil infiltration in lungs during RSV infection, in an IL-1R-dependent manner (181). Therefore, IL-1α can drive immunopathology or protective immune responses during infections, and IL-1α activity must be tightly controlled to protect from destructive inflammation while also boosting anti-microbial immunity.

IL-1α and cancer

Malignant cells, tumor-infiltrating immune cells and stromal cells can express IL-1α, IL- 1β and IL-1R. IL-1 signaling in the tumor tissue and its microenvironment can an affect tumor progression in different ways. IL-1R signaling leads to expression of inflammatory mediators, including IL-6 and COX2, which promote survival and proliferation of malignant cells. IL-1 derived from the tumor microenvironment can act on cancer stem cells to upregulate the expression of “stemness” associated genes, like Bmi1 and Nestin, promote proliferation and epithelial-mesenchymal transition (182–184). IL-1 cytokines can also induce production of pro-inflammatory cytokines, chemokines, prostaglandins and growth factors, which can, in turn, activate β-catenin signaling in proliferating cells (185–189). IL-1 signaling also promotes expression of chemokines and adhesion molecules that lead to recruitment of immune cells into the tumor tissue, and metalloproteases that promote tumor invasion and metastatic escape (190). IL-1 signaling also drives myelopoiesis in the bone marrow (191) and differentiation of monocytes into suppressor cells (referred to as myeloid-derived suppressor cells, MDSCs) that further promote production of pro-survival factors and suppress anti-tumor immune responses (184, 191–193). On the other hand, IL-1 signaling can also boost anti-tumor immunity. IL-1 signaling contributes to recruitment and activation of antigen presenting cells to the lymph nodes where they can induce activation, expansion and development of immunological memory in $CD4^+$ and $CD8^+$ T cells specific to tumor- associated antigens (194–197). Therefore, IL-1 signaling can both promote and regress cancer growth, probably depending on the characteristics of the tumor and its microenvironment (Figure 3).

IL-1α and IL-1β can have complimentary or contrasting functions in different types of cancers. Expression of both IL-1α and IL-1β is increased during genotoxic stress, and their secretion by necrosis or pyroptosis promotes the expression of vascular endothelial growth factor (VEGF) in the tumor tissue (198–200). 3-Methylcholanthrene (MCA) induced fibrosarcoma development requires IL-1β, but not IL-1α expression in the host (201).

However, IL-1α expression in the 3-MCA-induced fibrosarcoma cell line is required for tumor development upon implantation in a naïve host (202). 3-MCA-induced tumor cell lines from IL-1α-deficient mice have increased expression of MHCI, co-stimulatory and adhesion molecules, and this increased immunogenicity of IL-1α-deficient tumor cells is associated with increased activation of $CD8^+$ T cells and NK cells, which control tumor growth (202). Like IL-1α, IL-1β also promotes tumor growth and invasiveness. Fibrosarcoma cells that are genetically modified to express the mature form of IL-1β ligated to a signal peptide (ssIL-1β) constitutively secrete mature IL-1β via the canonical ER-golgi secretion pathway (192, 203). Upon implantation into a naïve host, these tumor cells demonstrate increased growth, angiogenesis and invasiveness (192, 203–206). Furthermore, both IL-1β and VEGF synergize to promote angiogenesis in the tumors (207). Increased IL-1α production is associated with distant metastases, and poor survival rate in head and neck squamous cell carcinoma and gastric carcinoma (208, 209). IL-1α is also a major driver of colon cancer that is associated with chronic inflammation in the colon (156). A single nucleotide polymorphism (SNP) in the *IL1a* gene that leads to A114S substitution is associated with increased risk of ovarian cancer (210). The A114S mutant form of pro-IL-1α form is more readily cleaved by inflammatory proteases, underscoring the idea of increased IL-1 secretion leading to increased tumorigenicity and metastasis (211).

In contrast with these observations, overexpression of cytosolic or membrane-bound forms of IL-1α lead to regression of fibrosarcoma (212, 213). The protection conferred by overexpression of IL-1α is associated with enhanced immune-surveillance mechanisms that depend on $CD8^+$ T cells, NK cells and M1-differentiated macrophages (214, 215). IL-1α-mediated anti-tumor immune response also leads to development of immunological memory that is protective from re-challenge with parental tumor cells (214, 215). Similarly, IL-1β (and IL-18) maturation by the NLRP3 inflammasome activated by chemotherapeutic drugs contributes towards activation of anti-tumor $CD8^+$ T cells (197). However, it was suggested that chemotherapy-enhanced production of pro- inflammatory mediators potentiate tumor invasiveness and metastasis (216, 217). Taken together, these studies suggest that while IL-1 signaling is inherently pro-tumorigenic, focused, local stimulation provided by membrane-bound or low levels of secreted of IL-1 can be beneficial by boosting anti-tumor immunity.

Clinical trials with an IL-1α-blocking monoclonal antibody has shown promising outcomes in patients with end-stage cancers (147, 218). MABp1 (XBiotech Inc.) is a naturally occurring human interleukin-1α neutralizing antibody. Monotherapy with MABp1 improved survival rate, increased lean body weight, normalized paraneoplastic thrombocytosis, decreased levels of serum IL-6 and associated systemic inflammation and cachexia without significant side-effects in patients with advanced non-small cell lung cancer, ovarian cancer and other refractory cancers (147, 219–221). MABp1 treatment also improved clinical parameters in patients with unresectable or metastatic colon cancer (222). Therefore, it is clear that IL-1α is a clinically significant driver of cancer and associated complications. Further clinical trials with these and other types of cancers, and in earlier stages of the disease, are warranted.

Senescence-associated secretory phenotype (SASP) is a phenomenon characterized by spontaneous production of low-levels IL-6, IL-8 and other inflammatory mediators by aged

cells undergoing senescence (223). Sustained production of inflammatory mediators at low levels leads to chronic systemic inflammation. This low-level chronic inflammation has been associated with age-related pathologies and cancer as IL-6 and other inflammatory mediators promote angiogenesis and proliferation of malignant cells (223). IL-1α expression after exposure to ionizing radiation enhances SASP, and inhibition of mTOR by rapamycin treatment represses IL-1α translation, resulting in suppression of SASP (223, 224). Initial IL-1α production results in amplification of production of pro-inflammatory and pro-tumorigenic factors, and consequently SASP in fibroblasts and epithelial cells is associated with worsening prognosis for cancer (194). Therefore, similar to auto-inflammatory disorders and infections, IL-1α can also be an apical driver of SASP.

Conclusions and future perspectives

New studies propose a paradigm of IL-1α-dependent pro-inflammatory priming as the initiator of several major human diseases. Certain unique properties of IL-1α support its critical function as an apical instigator of inflammation. First, IL-1α is ubiquitously expressed by both hematopoietic and non-hematopoietic cell *in vivo*, and its expression is rapidly upregulated by a wide variety of danger- and pathogen-associated molecular patterns. Second, IL-1α is very promiscuous in its sub-cellular localization, and can function as an IL-1R agonist upon secretion from the cell or as a cell membrane bound molecule. Third, IL-1α can translocate to the nucleus to modulate gene expression independently of IL-1R or as a sequestration mechanism during non-inflammatory cell death. Fourth, while the other IL-1R ligand, IL-1β, requires inflammasome activation for its maturation and pyroptosis for its secretion, IL-1α is bioavailable in a much wider set of cellular scenarios. IL-1α is bioactive in both the pro-form and mature form, and therefore both pyroptotic and necrotic cell death yields bioactive IL-1α. Despite increasing appreciation of the importance of IL-1α in the pathogenesis of human diseases, the factors that control its bioavailability remain poorly understood. The major unanswered questions in IL-1 biology include the mechanisms that control sub-cellular targeting of IL-1α, and their relative biological functions. Mechanisms that regulate IL-1α secretion from the cell, and the function of its cleavage by inflammatory proteases are also unknown. Due to its ubiquitous expression, potent activity and bioavailability, IL- 1α has emerged as a major player and drug target in many diseases. Further understanding of the regulation IL-1α will undoubtedly help develop novel therapeutics for the vast array of ailments associated with this cytokine.

Acknowledgments

Funding Statement: This work was supported by grants from the US National Institutes of Health (AI101935, AI124346, AR056296, and CA163507) and the ALSAC to T.-D.K.

We would like to thank Deepika Sharma and Subbarao Malireddi for helpful editing of the manuscript.

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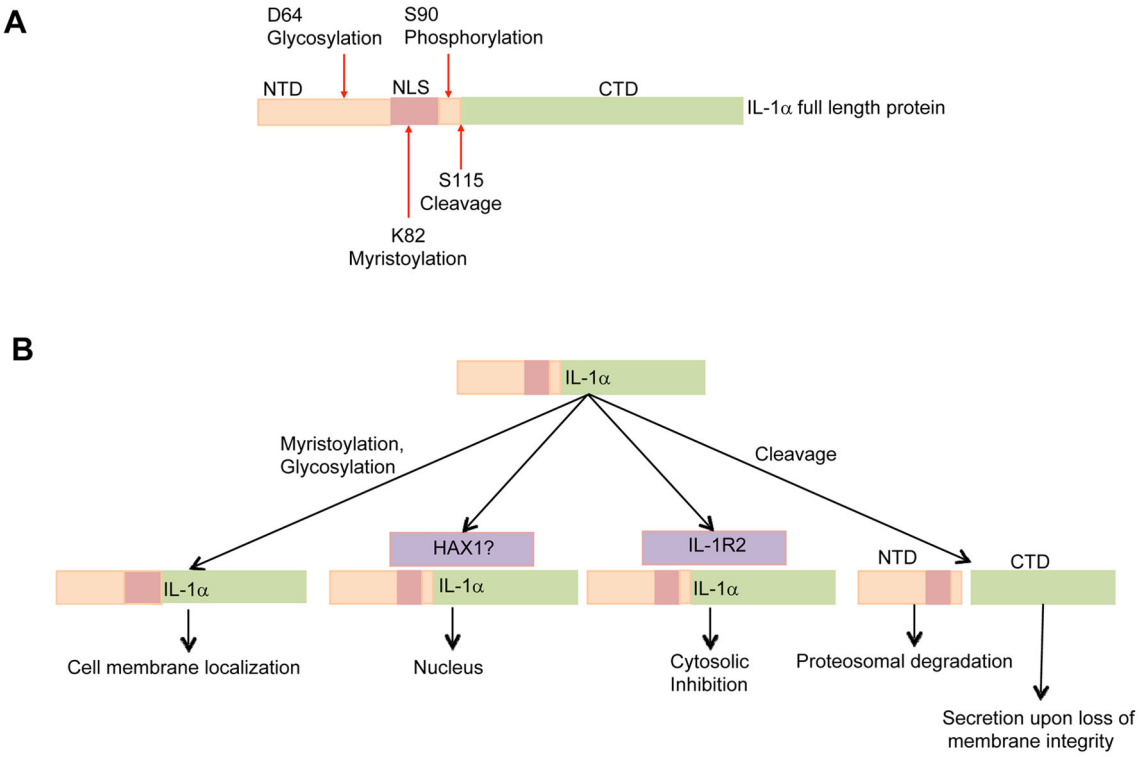

Figure 1. Post-translational modifications and sub-cellular localization of IL-1α

A) Pro-IL-1α is translated as a 31-kDa full-length protein and is composed of an N-terminal domain (NTD), nuclear localization signal (NLS) and C-terminal domain (CTD). NLS directs IL-1α translocation to the nucleus, while the CTD is the catalytically active domain capable of signaling via IL-1R. Pro-IL-1α is also modified post-translationally, including myristoylation on Lys82, phosphorylation at Ser90 and glycosylation at D64. The functions of these modifications are largely unknown. **B)** Upon translation, IL-1α can be targeted to the plasma membrane, nucleus or the cytosol. Myristoylation and glycosylation are associated with the membrane-bound form of IL-1α. Binding to HAX-1 promotes nuclear localization, while binding to IL-1R2 sequesters pro-IL-1α in an inactive form in the cytosol. Pro-IL-1α can also be cleaved by calpain and other inflammatory caspases to yield the inactive NTD and bioactive CTD. The CTD is released from the cell upon loss of membrane integrity, and can signal via IL-1R. Stimuli that control sub-cellular targeting of IL-1α, and their functions are relatively understudied.

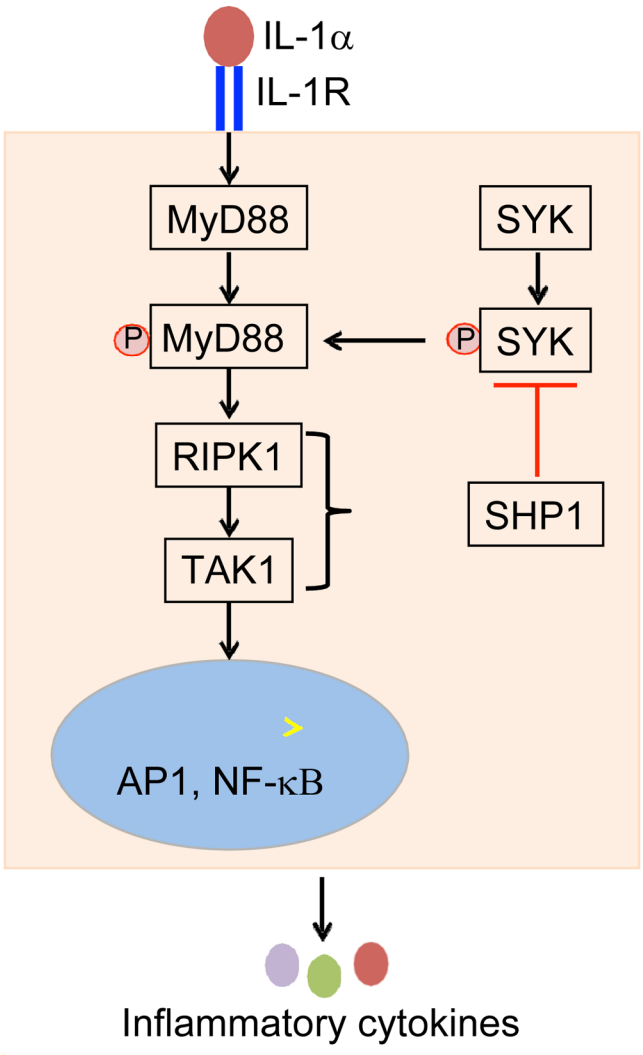

Figure 2. SHP-1 negatively regulates autoinflammation induced by IL-1α

IL-1α from non-hematopoietic cells signals via IL-1R on myeloid cells in a MyD88, receptor- interacting protein kinase 1 (RIPK1) and transforming growth factor-β activated kinase 1 (TAK1)-dependent manner to induce expression of pro-inflammatory cytokines. Src homology region 2 domain-containing phosphatase 1 (SHP1) controls phosphorylation of spleen tyrosine kinase (SYK), which further regulates MyD88 phosphorylation in myeloid cells, leading to restrained IL-1R signaling. Mice that express a mutant form of SHP1 (*Ptpn6*^{spin} mice) that has reduced SHP1 activity develop an auto-inflammatory disease that are is dependent on IL-1α production from non-hematopoietic cells, and SYK, MyD88, RIPK1 and TAK1 mediated signaling in myeloid cells.

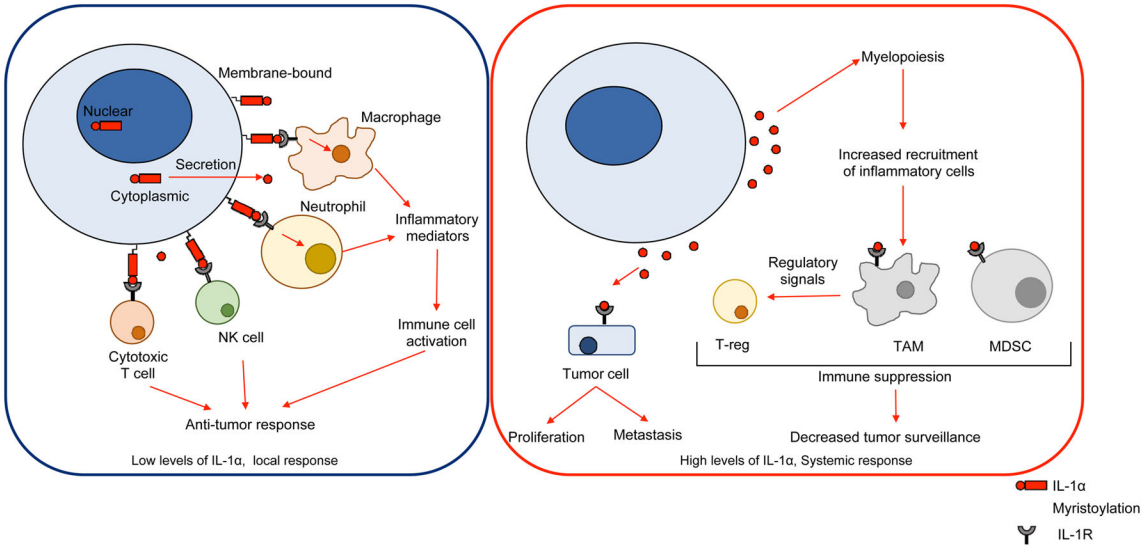

Figure 3. Functions of IL-1α in cancer

In the tumor microenvironment, low levels of cell-surface or secreted form of IL-1α are associated with anti-tumor responses. Activation of macrophages and neutrophils through IL-1R signaling promotes inflammatory responses and T cell activation through antigen presentation. Furthermore, IL-1R signaling promotes tumor killing through activation of cytotoxic T cells and natural killer (NK) cells. On the other hand, increased release of IL-1α is associated with pro- tumorigenic responses. IL-1α signaling increases myelopoiesis and accumulation of tumor associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) within the tumor microenvironment, which in turn promotes differentiation of regulatory T cells (Tregs). Together, these cell types suppress immune cell activation and reduce tumor surveillance. Furthermore, IL-1α can signal via IL-1R on tumor cells to promote proliferation and invasiveness.