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Interleukin 1α and the inflammatory process

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Abstract

Inflammation occurs after disruption of tissue homeostasis by cell stress, injury or infection and ultimately involves the recruitment and retention of cells of hematopoietic origin, which arrive at the affected sites to resolve damage and initiate repair. Interleukin 1α (IL-1α) and IL-1β are equally potent inflammatory cytokines that activate the inflammatory process, and their deregulated signaling causes devastating diseases manifested by severe acute or chronic inflammation. Although much attention has been given to understanding the biogenesis of IL-1β, the biogenesis of IL-1α and its distinctive role in the inflammatory process remain poorly defined. In this review we examine key aspects of IL-1α biology and regulation and discuss its emerging importance in the initiation and maintenance of inflammation that underlie the pathology of many human diseases.

In 1974, Dinarello *et al.*[1] described acidic and neutral human pyrogens, which could be purified from monocytes and neutrophils, respectively, and showed that they have similar potencies in increasing body temperature in rabbits[1]. It was another ten years before the acidic and neutral pyrogens were identified as proteins that are distinct at the amino acid level, and the first described mouse acidic pyrogen and human neutral pyrogen were both called interleukine 1 (first reported in 1984)[2,3]. In 1985, amino acid sequences for both the acidic and neutral human pyrogens were reported, and these proteins were called interleukins IL-1α and IL-1β, respectively[4], a designation that is accepted today. Early research into the molecular properties of IL-1α and IL-1β revealed numerous similarities between these cytokines that appear to justify naming them as two forms of IL-1, a family of cytokines that has grown to 11 members[5]. Specifically, both IL-1α and IL-1β are synthesized as precursor (proform) proteins with molecular weights of about 31 kDa, can be cleaved to smaller mature forms of 17 kDa and bind the cell surface receptor IL-1R1, and they trigger identical biological responses. Despite these similarities, IL-1α and IL-1β have

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different amino acid sequences, and the factors that control their functional maturation and bioavailability are highly dissimilar. First, whereas only the cleaved mature form of IL-1β is a functional pyrogen and a ligand for IL-1R1, both the proform (pro-IL-1α) and the cleaved form of IL-1α are biologically active IL-1R1 ligands[6]. Second, although mature IL-1β is a released protein, IL-1α functions both as a secreted and as a membrane-bound cytokine[7]. Third, during the functional maturation process, pro-IL-1β is cleaved by an aspartic protease caspase-1 downstream of a multi-protein complex called the inflammasome[8–10], whereas capsase-1 and the inflammasome have no direct role in cleaving pro-IL-1α. Fourth, although IL-1α has higher affinity than IL-1β for IL-1R1, IL-1β has higher affinity for the decoy soluble receptor IL-1R2 (ref. 11). And fifth, although IL-1β is absent in cells at homeostasis and is expressed upon activation only in cells of hematopoietic origin, IL-1α is present in health in a wide variety of cells and expressed in hematopoietic and nonhematopoietic cells alike in response to appropriate stimuli[12]. These differences translate directly into the biological contexts in which IL-1α and IL-1β exert their functions. Remarkably, although IL-1β expression regulation, cleavage and release are relatively well understood, most aspects of IL-1α biogenesis and function and its role in the inflammatory process remain areas of active debate. The literature on IL-1β biology is abundant and has been reviewed in depth elsewhere[13,14]; here we will review the current understanding of the roles of IL-1α in initiating and sustaining the inflammatory processes that stem from the unique biochemical and functional properties of this pleiotropic cytokine and that may point to new opportunities for therapies of numerous human diseases and pathologies mechanistically linked to IL-1-driven inflammation.

Control of IL-1α expression

IL-1α is constitutively expressed in many cell types in healthy tissues at steady state, and its expression can be increased in response to growth factors and proinflammatory or stress-associated stimuli. Absolute amounts of IL-1α protein vary among cell types, but barrier cells—such as endothelial and epithelial cells—express substantial amounts of this cytokine at steady state[5,12,15]. The *Il1a* promoter lacks canonical TATA and CAAT box regulatory regions, containing instead a binding site for the Sp1 transcription factor[16] that is known to mediate expression of housekeeping genes at homeostasis[17]. The inducible expression of IL-1α depends on the presence of binding sites for AP1 and NF-κB transcription factors[18–20], which can upregulate IL-1α expression in a cell-type-specific manner. It has also been shown that the proximal *Il1a* promoter region contains a transcriptional-repressor-binding site that reduces its transcriptional activity[16], thus dissociation of a transcriptional repressor can be an additional mechanism to increase IL-1α expression upon stimulation. In human $CD4^+$ T cells, IL-1α expression is monoallelic and regulated via hyper- or hypomethylation of CpG nucleotides located in promoter regions proximal to the transcription initiation site[21]. Monocytes have a unique mechanism of inducible *Il1a* expression that involves upregulation of the long noncoding RNA AS-IL-1a, a natural antisense transcript that is partially complementary to IL-1α mRNA[22]. Although constitutive IL-1α expression is likely to be regulated by Sp1-family transcription factors in terminally differentiated cells, inducible IL-1α expression occurs rapidly in response to a variety of physiological stimuli, including oxidative stress[15,23,24], lipid overload[25,26], hormonal

stimulation[27], exposure to cytokines (including IL-1β and IL-1α itself)[28–30] and canonical proinflammatory mediators of microbial origin with Toll-like receptor (TLR) agonistic activities[29]. The responsiveness of the *Il1a* promoter to such a broad spectrum of stimuli, which trigger inducible expression of IL-1α in addition to its constitutive expression in both hematopoietic and nonhematopoietic cells, has important implications for IL-1α's ability to drive sterile and pathogen-induced inflammation.

IL-1α biogenesis

IL-1α is translated as pro-IL-1α, and a number of studies have described post-translational modifications of this precursor form. Specifically, pro-IL-1α was shown to be phosphorylated at Ser90 (refs. 31,32), myristoylated on Lys82 (ref. 33) and acetylated on Lys82 (refs. 33,34). The functional significance of these modifications has not been formally established. Furthermore, it remains a matter of debate whether proteolytic cleavage of pro-IL-1α into the N-terminal IL-1α propiece (IL-1α-NTP) and a C-terminal mature IL-1α is a genuine functional maturation step that is necessary for efficient IL-1α-dependent biological responses. In early studies of human pyrogens it was established that human acidic pyrogen (corresponding to pro-IL-1α) is as potent at causing fever as human neutral pyrogen (corresponding to mature IL-1β)[1]. Subsequent analyses of the receptor binding kinetics of pro-IL-1α and mature IL-1α showed that the forms have similar receptor dissociation constants (K_d = 4.0 nM and 4.5 nM for pro-IL-1α and mature IL-1α, respectively)[35]. More recently, it was confirmed that recombinant pro-IL-1α and mature IL-1α have identical biological activities as measured by their ability to trigger secretion of the inflammatory cytokines IL-6 and TNF from epithelial and hematopoietic cells[6]. The mature IL-1α used in these studies was comprised of the C-terminal portion of IL-1α starting at Ser115. Cleavage of mouse pro-IL-1α at this site and of human pro-IL-1α at Phe118 (ref. 36) is mediated by the calcium-dependent neutral protease calpain. Calpain can cleave pro-IL-1α inside the cell or under cell-free conditions[36–38]. However, in the extracellular space, pro-IL-1α can also be cleaved at the evolutionary conserved Asp103 by granzyme B[39], and the C-terminal mature IL-1α generated via granzyme B cleavage is more biologically active than the pro-IL-1α form. This same study demonstrated that pro-IL-1α cleavage with elastase or chymase, as well as calpain, produces a mature IL-1α C-terminal piece that is more biologically active than the pro-IL-1α form[39]. Although it is plausible that pro-IL-1α cleavage at different sites may generate mature IL-1α forms that exhibit different biological activities, the reasons for different biological activity of pro-IL-1α form observed in different studies[6,35,39,40] require further clarification.

Pro-IL-1α has a functional nucleus localization signal (NLS) LKKRRL[41–43], which is retained in the IL-1α-NTP after pro-IL-1α cleavage with calpain or other proteases (Fig. 1). Pro-IL-1α and IL-1α-NTP can translocate into the nucleus; however, whether there is a single mechanism that regulates nuclear localization of pro-IL-1α and IL-1α-NTP in all cell types remain unknown. Genotoxic stress increases nuclear localization of pro-IL-1α, which in part depends on acetylation of Lys82 (ref. 34). Whereas macrophage pro-IL-1α is localized to the nucleus upon lipopolysaccharide (LPS) stimulation, in keratinocytes and fibroblasts, pro-IL-1α is localized to the nucleus at steady state without any cell stimulation[43]. One of the mechanisms that may control nuclear localization of pro-IL-1α is

its association with a repressor in the cytosol. In vascular smooth muscle cells, pro-IL-1α is bound to an intracellular form of inhibitory IL-1R2 (ref. 40) that may mask the NLS, leading to cytosolic retention of pro-IL-1α. Association of pro-IL-1α with IL-1R2 has also been shown in fibroblasts from systemic sclerosis patients[44]; however, in these cells, pro-IL-1α exhibits nuclear localization at steady state, which is regulated by HAX1, a ubiquitously expressed protein localized in mitochondria, endoplasmic reticulum and at the nuclear envelope[45]. HAX1 is able to bind both pro-IL-1α and IL-1α-NTP[44], and suppression of HAX1 abolishes nuclear localization of pro-IL-1α. Nuclear localization of pro-IL-1α and IL-1α-NTP is functionally important, as they are able to interact directly with histone acetyltransferases p300, PCAF and GCN5 (refs. 46,47) and stimulate transcription of genes, including those encoding proinflammatory chemokines, independently of IL-1R1 signaling[48,49]. Furthermore, pro-IL-1α can bind chromatin[50], and IL-1α-NTP localization to spliceosomes triggers apoptosis of numerous malignant cell types but not primary nontransformed cells[51].

IL-1α can function as a membrane-bound cytokine. A study using primary macrophage cultures stimulated with heat-killed *Listeria monocytogenes* found that IL-1 has biological activity at the plasma membrane of intact cells as well as in isolated plasma membrane preparations[7]. This finding was confirmed in many subsequent studies[52–55], which also demonstrated that the plasma membrane-associated IL-1α represents a full-length pro-IL-1α form that is fully biologically active. Plasma-membrane-bound IL-1α can be eluted from intact cells with D-mannose[56]. On the basis of this observation, it was proposed that pro-IL-1α is glycosylated and anchoring onto the membrane is mediated by a lectin-like interaction. Upon stimulation of cells with proinflammatory stimuli, the appearance of IL-1α on the plasma membrane occurs within hours on both hematopoietic and nonhematopoietic cells, such as fibroblasts and endothelial cells[57]. This implies the existence of a specialized molecular machinery that regulates translocation of pro-IL-1α from the cytosol to the outer side of the plasma membrane, thus allowing initiation of IL-1α– IL-1R1-mediated signaling in a paracrine manner. Over time, plasma-membrane-bound pro-IL-1α can be released via cleavage with extracellular proteases[39,54,57]. The excess of intracellular pro-IL-1α is subjected to proteosomal degradation through ubiquitin-dependent mechanisms[58].

Biological contexts of IL-1α signaling

Because pro-IL-1α is fully biologically active and because of its constitutive and induced expression in a wide variety of cell types, cell death due to injury or infection may result in a passive leakage of the cytosolic pro-IL-1α into the surrounding milieu and activation of inflammation in an IL-1R1-dependent manner. This assumption has been confirmed experimentally in several studies, where administration of necrotic cells to mice triggered neutrophilic inflammation that was completely dependent on the presence of IL-1α in necrotic cells and IL-1R1 signaling on stromal, nonhematopoietic cells[59,60]. These and subsequent studies[50,61] confirming the idea that the cytosolic pro-IL-1α is a principal inflammation-triggering moiety in necrotic cells have led to the designation of IL-1α as a key ‘alarmin’ in the cell[5,15,43,62] that alerts the host to injury or damage. Using the same experimental approach[59], it was also found that pro-IL-1α association with an inhibitory

IL-1R2 in the cytosol[44] is functionally important, as it can prevent or reduce the magnitude of inflammatory response to necrotic cells owing to sequestration of pro-IL-1α into cytosolic complexes with IL-1R2 (ref. 40) (Fig. 2). The importance of pro-IL-1α as a principal intracellular alarmin is underscored by findings that point to the existence of a machinery to sequester cytosolic pro-IL-1α during a physiologically regulated noninflammatory cell death routine, such as apoptosis. Upon induction of apoptosis, cytosolic pro-IL-1α is sequestered into the nucleus, preventing its inadvertent release and inflammation[48]. However, if not promptly phagocytosed, IL-1α-containing apoptotic bodies can trigger inflammation, as has been shown for apoptotic bodies produced by endothelial cells[63].

To execute its function as an extracellular alarmin, pro-IL-1α requires the loss of plasma membrane integrity, which is indicative of necrotic-type cell death[64], for passive release and activation of the inflammatory cascade. However, during normal responses to physiological stimuli, necrotic cell death is an unusual event; therefore, great effort has been put toward analyzing the biological contexts and molecular mechanisms that may control IL-1α-mediated signaling from living non-necrotic cells. These efforts have produced numerous findings[65–69], but their physiological relevance requires further clarification. Because pro-IL-1α lacks a signaling peptide to mediate its secretion from the cell, the most debated issue is whether caspase-1 and the inflammasome facilitate or are needed for pro-IL-1α proteolytic processing and release[70]. A study using LPS-stimulated monocytes from caspase-1-deficient mice showed that cells from these mice release significantly lower amounts of IL-1α than cells from wild-type mice[71]. The conclusion that caspase-1 and the inflammasome control release of IL-1α from hematopoietic cells such as macrophages and dendritic cells after their stimulation with LPS and ATP[65] can be explained by the induction of pyroptosis, a form of cell death that leads to plasma-membrane permeabilization[72], allowing release of intracellular pro-IL-1α and mature IL-1α forms without involvement of any specific secretory mechanism. A detailed analysis of IL-1α and IL-1β release from dendritic cells showed that LPS-stimulated cells treated with clostridium toxin B or alum, urea crystals or silica release mature IL-1α in a capsase-1- and NLRP3 inflammasome–independent manner, whereas the release of mature IL-1β in response to the same stimuli was completely dependent on caspase-1 and NLRP3 inflammasome components[73]. Because pro-IL-1α and pro-IL-1β are expressed in hematopoietic cells in response to the same stimuli, and because caspase-1 is targeted by many pathogens to suppress cell death and inflammation[74–76], release of IL-1α in an inflammasome-independent manner may provide an alternative pathway to trigger IL-1R1-dependent defense mechanisms and alert the host of an ongoing infection.

The ability of IL-1α to function as a plasma-membrane-bound cytokine is unique within the IL-1 family[5,77]. Indeed, exposure of hematopoietic cells to LPS or heat-killed bacteria such as *L. monocytogenes*[7,55] or *Mycobacterium tuberculosis*[78] stimulates intracellular expression of IL-1α as well as the rapid appearance of membrane-bound IL-1α that is fully biologically active, as shown by stimulation of T cell proliferation and production of chemokines. Similarly, exposure of endothelial cells to LPS or TNF also results in membrane IL-1α expression[52], providing important insight into biological contexts where IL-1α–IL-1R1 signaling can be triggered from living cells under stress or during infection

without necrotic cell death. The capacity of membrane-bound IL-1α to activate IL-1R1 signaling in an intracrine and paracrine manner on surrounding cells has important implications for the induction and maintenance of local inflammatory responses.

The ‘inflammatory loop’ model of IL-1α-driven inflammation

The diversity of stimuli that activate IL-1α expression in hematopoietic and nonhematopoietic cells and its capacity to activate IL-1R1 signaling from both living and necrotic cells provide the conceptual framework for understanding the role of IL-1α in inflammation and as a principal driver of pathologies that mechanistically depend on aberrant IL-1R1 signaling. Because IL-1α and IL-1β are equally potent activators of IL-1R1 signaling, the availability of mice deficient in either IL-1α or IL-1β provides an opportunity to analyze the contribution of each in the development of specific pathologies. Although the development of atherosclerotic lesions has an important IL-1R1 signaling component[79], evidence indicates that macrophage-derived IL-1α is a principal cytokine controlling the development of atherosclerotic plaques[26]. Mechanistically, the expression of IL-1α is induced in macrophages by fatty acids that accumulate in atherosclerotic plaques and leads to IL-1α-driven vasculitis under conditions where IL-1β activation is blocked via mitochondrial uncoupling[26]. IL-1α-deficient mice are resistant to ischemic injury in models of myocardial infarction[80] and ischemic brain injury[81]. Importantly, during ischemic brain injury, IL-1α expression in microglia precedes expression of IL-1β, providing conceptual insight into the role of IL-1α in the initiation of inflammation. In the model of spontaneous foot-pad inflammation in mice deficient in PTPN6 phosphatase, the development of neutrophilic inflammation in the foot pad is completely abrogated by the deletion of IL-1α in stromal, nonhematopoietic cells[82]. IL-1α produced by intestinal epithelial cells was found to be the principal driver of inflammation in a mouse model of colitis[12], where IL-1α-deficient mice showed improved survival after intestinal epithelial damage.

These findings can be conceptualized into an ‘inflammatory loop’ model, in which inflammation is initiated by stressed or damaged cells via IL-1α-dependent activation of chemokines that recruit inflammatory hematopoietic cells to the site of damage or stress (Fig. 3). These hematopoietic cells respond to the IL-1α-containing milieu, where pro-IL-1α can be either released from damaged cells or exposed as membrane-bound IL-1α on the surface of cells undergoing oxidative or metabolic stress, and in turn activate their own IL-1α and IL-1β production downstream of IL-1R1. The initial IL-1α–IL-1R1 signaling therefore initiates a loop of sustained and self-perpetuating inflammation that results in extensive tissue damage that occurs until IL-1R1 signaling is either exhausted or suppressed. This model is also supported by the role of IL-1α in host defense against viral and bacterial pathogens. IL-1α has a nonredundant role in initiating inflammatory responses to *Legionella pneumophila*[83] and *Yersinia enterocolitica*[84]. Splenic marginal zone macrophages sequester adenovirus from the blood and activate IL-1α-dependent chemokine production[85] and recruitment of polymorphonuclear cells to the spleen[86]. This IL-1α-dependent inflammation is critical for elimination of virus-containing cells from the host.

Because IL-1β is not known to be produced in a biologically active form in nonhematopoietic cells, the IL-1α-driven inflammatory loop model addresses the

conundrum of apparent functional excess and redundancy of IL-1α and IL-1β production at sites of inflammation. It is also consistent with abundant clinical data demonstrating the efficacy of IL-1β-targeted therapies at controlling autoinflammatory diseases[87], as the perpetuation of IL-1α-initiated inflammation into a clinically significant pathology is accomplished by the exuberant production of both IL-1α and IL-1β, despite their redundant functions or when pathology development depends largely on subsequent IL-1β production from activated hematopoietic cells.

IL-1α and autoinflammatory disease

IL-1α-mediated signaling initiates processes beyond recruitment of inflammatory hematopoietic cells. Although IL-1α–IL-1R1-dependent chemokine production leading to hematopoietic cell recruitment is a major component of numerous pathologies, autocrine and paracrine IL-1α signaling can also mediate activation of nonhematopoietic cells.

Fibroblasts purified from lesional skin of patients with systemic sclerosis (SSc) express abundant amounts of IL-1α, which is localized on the plasma membrane, in the cytosol and in the nucleus[88]. Compared to fibroblasts from normal skin, SSc fibroblasts express high amounts of IL-6, the growth factor PDGF-α[89], IL-1R1 (ref. 90) and collagen. Suppression of IL-1α expression in SSc fibroblasts reduces amounts of secreted IL-6 and pro-collagen, and overexpression of pro-IL-1α in normal fibroblasts increases IL-6 and pro-collagen production[88]. It has been demonstrated that IL-1-dependent PDGF-α production has direct mitogenic effects on fibroblasts and smooth muscle cells[91], mechanistically linking excessive IL-1α expression and signaling with a pathological tissue response that manifests in excessive deposition of collagen and fibrosis.

IL-1α and cancer

Aging cells are known to acquire a ‘senescence-associated secretory phenotype’ characterized by production of IL-6 and other proinflammatory mediators that sustain the low-grade chronic inflammation underlying many age-related pathologies and cancer[92]. Normal human fibroblasts triggered to senesce by ionizing radiation show an increase in NF-κB activity, which stimulates production of proinflammatory mediators such as IL-6 and IL-8 (ref. 93). This NF-κB activity is due to an increase in IL-1α translation, leading to production of membrane-bound IL-1α that stimulates cells in an autocrine manner. Rapamycin treatment was found to repress IL-1α translation, resulting in suppression of production of senescence-associated factors. Senescent fibroblasts have also been shown to be pro-tumorigenic, as they promote growth of malignant epithelial cells and tumor formation in mice[93]. Therefore, this study[92] implicates IL-1α as a principal component in a feed-forward signaling amplification loop that leads to production of pro-tumorigenic factors by aged or senesced cells. There are many examples implicating an IL-1α-driven feed-forward amplification loop and even IL-1α itself in malignant transformation, tumor formation and support of tumor growth through stimulation of cell growth and production of vasculogenic factors[94–100]. Confirmation of the critical contribution of IL-1α to tumor development in humans comes from the field of clinical oncology. In patients with head and neck squamous cell carcinoma, IL-1α expression has been evaluated as a prognostic marker

of distant metastases[101]. IL-1α mRNA and protein expression were found to be higher in tumor samples from patients who later developed distant metastases than in tumors from patients who did not. Patients who had high IL-1α expression in tumors had significantly lower 5-year survival rates than patients with low IL-1α expression[101]. Analysis of genetic risk factors for the development of ovarian cancer in a large patient cohort (15,604 cases) showed a significant association between the *Il1a* single nucleotide polymorphism (SNP) rs17561 and reduced susceptibility to clear cell ovarian cancer type. rs17561 is a missense SNP that results in an alanine-to-serine substitution at residue 114 (A114S)[102]. The A114S substitution produces a pro-IL-1α form that is more readily cleaved by calpain[103]. Because the plasma-membrane-bound IL-1α form represents a full-length pro-IL-1α protein, enhanced cleavage by calpain may lead to reduced expression of membrane-bound IL-1α and, thus, tempering of IL-1α-driven autocrine pro-tumorigenic IL-1R1 signaling. Clinical trials with an IL-1α-blocking monoclonal antibody targeting this IL-1α-driven feed-forward signaling amplification loop as a cancer therapeutic have shown promising outcomes[104,105].

IL-1α and granulomatous diseases

Chronic granulomatous diseases manifest through the formation of focal inflammatory lesions, or granulomas, that consist of both hematopoietic and nonhematopoietic cells. Granulomas arise in response to poorly degradable particulate matter or can be induced by microbial, viral, fungal, protozoan or helminthic infections. Because granulomas are fundamentally a local inflammatory response, it is not surprising that IL-1α, with its capacity to produce proinflammatory signaling from the plasma membrane, is involved in granuloma formation. In a mouse model of pulmonary *M. tuberculosis* infection, IL-1α-deficient mice failed to establish protective granuloma structures and succumbed to infection sooner than did wild-type mice, even in the presence of functional *M. tuberculosis*–specific adaptive immunity[78]. Exposure of macrophages to heat-killed *M. tuberculosis* resulted in rapid expression of biologically active plasma-membrane-bound IL-1α, and lung epithelial cells treated with heat-killed *M. tuberculosis* and TNF upregulated IL-1α expression. Bone marrow transplantation studies further showed that an absence of IL-1R1 and TNF receptor TNF-R1 on stromal or hematopoietic cells compromised host resistance to *M. tuberculosis*, suggesting that TNF- and IL-1-driven cross-talk between monocytes and stromal cells is necessary for optimal control of this pathogen[78]. *Cryptococcus neoformans* infection causes severe meningoencephalitis in susceptible BALB/c mice. Cytokine profiling in the brain after systemic *C. neoformans* infection showed constitutive and induced IL-1α expression that preceded detectible expression of IL-1β by 7 d[106]. Although there is no consensus on whether granulomas arise as a host-protective response or are induced by pathogens to evade immunity, the potential pro-pathogenic role of IL-1α expression in response to pathogens that induce granuloma formation has also been noted. Specifically, IL-1α was found to promote pathogenesis during *Leishmania major* infection in susceptible BALB/c mice, and IL-1α-deficient mice are more resistant than wild-type mice to *L. major* infection[107]. Similarly, given that histologically confined granulomas do not form in the lungs of IL-1α-deficient mice after *M. tuberculosis* infection[78] and that granulomas are necessary for *M. tuberculosis* survival and spread, it is plausible that IL-1α induction in the context of tuberculosis may serve a pro-pathogenic function.

Conceptual perspective and remaining questions

IL-1α has a number of unique features, including its transcription in response to a wide range of stimuli, its widespread expression and its ability to activate IL-1R1 signaling from the plasma membrane or as an alarmin. Given these features, IL-1α emerges as a molecular decision-making nexus of the cell that gauges the magnitude of stress or damage or severity of infection to launch either the tissue or the whole body into action through initiation of inflammation or reparative fibrosis. Aberration of these sequelae can produce devastating disruption of tissue homeostasis and underlies the pathology of numerous human diseases. Because pro-IL-1α is present in healthy cells, it is likely that a number of specific mechanisms exist to tightly control and suppress aberrant IL-1α activity.

Even after more than 30 years of research, many critical questions related to IL-1α biology remain unanswered. Specifically, it is unclear what factors control pro-IL-1α translocation from the cytosol to the outer surface of the plasma membrane to allow it to signal as a membrane-bound cytokine. The functional significance of calpain-dependent cleavage of pro-IL-1α in the cell also remains unclear. Does calpain cleavage facilitate release of pro-IL-1α and mature IL-1 from living cells, or is it necessary only to induce IL-1α-NTP translocation into the nucleus? Which factors control the sequestration of IL-1α in the nucleus during apoptosis? The identity of factors that allow for IL-1α expression in aged and senescent cells also requires further investigation. As methodologies for quantitative genomics, proteomics and metabolomics continue to advance, it is likely that IL-1α will be implicated as a key driver in many human pathologies and diseases. The numerous unresolved questions related to this powerful yet understudied cytokine certainly warrant further investigation.

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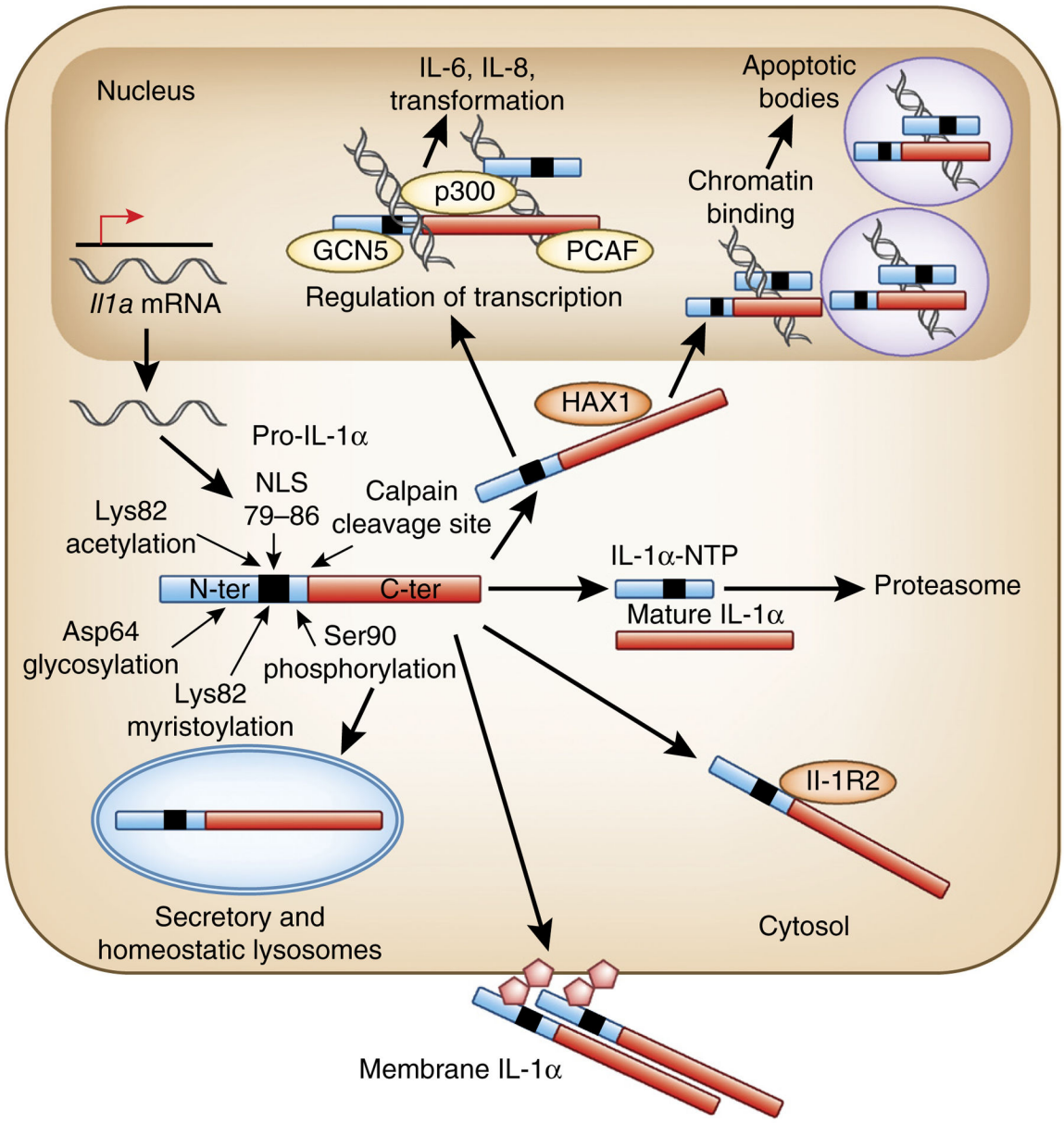

Figure 1.

Molecular modifications of IL-1α that regulate its intracellular distribution and bioavailability. Constitutive or inducible expression of IL-1α produces full-length pro-IL-1α. After synthesis, pro-IL-1α is localized into the nucleus, cytosol or lysosomal compartment or is displayed on the outer leaflet of the plasma membrane. Intracellular localization of pro-IL-1α can change in response to specific stimuli and pro-IL-1α can also be cleaved by calpain to generate IL-1α-NTP and a mature C-terminal IL-1α form. Both IL-1α-NTP and pro-IL-1α possess a functional NLS signal and bind HAX1 to allow translocation into the nucleus. In the nucleus, IL-1α-NTP binds transcription regulation factors and activates expression of proinflammatory cytokines and chemokines independently of IL-1R1 signaling. Pro-IL-1α can bind chromatin, which allows

sequestration of pro-IL-1α from the cytosol into the nucleus, thereby limiting aberrant IL-1α-dependent inflammation during apoptosis. In the cytosol, glycosylation of pro-IL-1α may allow pro-IL-1α translocation onto the outer surface of the cell. Plasma-membrane-bound pro-IL-1α can be released by mannose, suggesting a lectin-like mechanism of anchorage of pro-IL-1α to the outer leaflet of the plasma membrane. In the cytosol, pro-IL-1α can form a complex with inhibitory IL-1R2. Cytosolic pro-IL-1α can be polyubiquitinated, leading to its proteosomal degradation. Although several post-translational modifications of IL-1α-NTP and pro-IL-1α have been reported, formal confirmation of their functional importance is currently lacking.

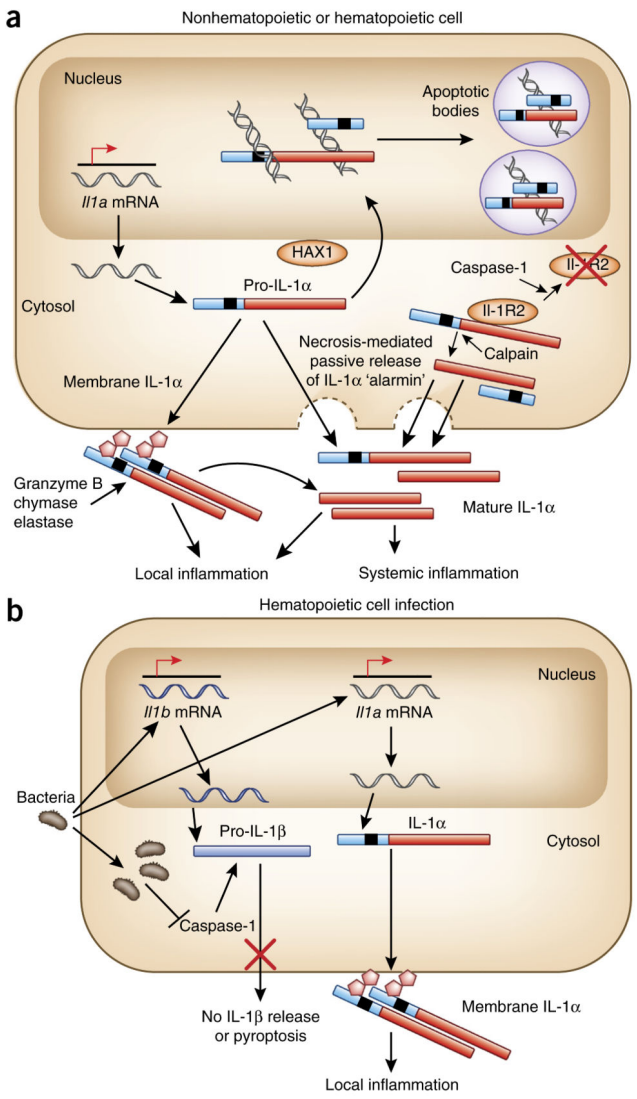

Figure 2.

Biological contexts of IL-1α-mediated signaling. (**a**) If a cell experiences supra-physiological stress that leads to necrosis, cytosolic pro-IL-1α is passively released through the ruptured plasma membrane and triggers the 'alarm' call, a functional IL-1R1-dependent proinflammatory response. Pro-IL-1α association with inhibitory IL-1R2 in the cytosol interferes with pro-IL-1 alarmin function. Inhibitory IL-1R2 association with pro-IL-1α can be relieved by capsase-1-dependent proteolysis of IL-1R2. In stimulated cells, pro-IL-1α is displayed on the cell surface. Plasma-membrane-bound pro-IL-1α is fully biologically active and can trigger local inflammatory responses from living cells. Membrane-bound pro-IL-1α can be cleaved extracellularly by granzyme B, chymase or elastase to produce a C-terminal mature IL-1α fragment that is also biologically active. (**b**) In hematopoietic cells, the proinflammatory stimuli that induce pro-IL-1β expression also activate expression of pro-IL-1α. However, pro-IL-1β is not biologically active and requires cleavage by capsase-1 in an inflammasome-dependent manner. This cleavage produces mature IL-1β and stimulates its secretion from the cell. Many pathogens express virulence factors that block caspase-1

activation and, therefore, maturation of pro-IL-1β and pyroptotic cell death. In these settings, pro-IL-1α can still be displayed at the cell surface and activate local IL-1R1-dependent inflammatory responses, thus bypassing blockade of IL-1β processing and release. Under the conditions of pyroptotic cell death, both pro-IL-1α and mature IL-1β are released to activate local and systemic inflammation.

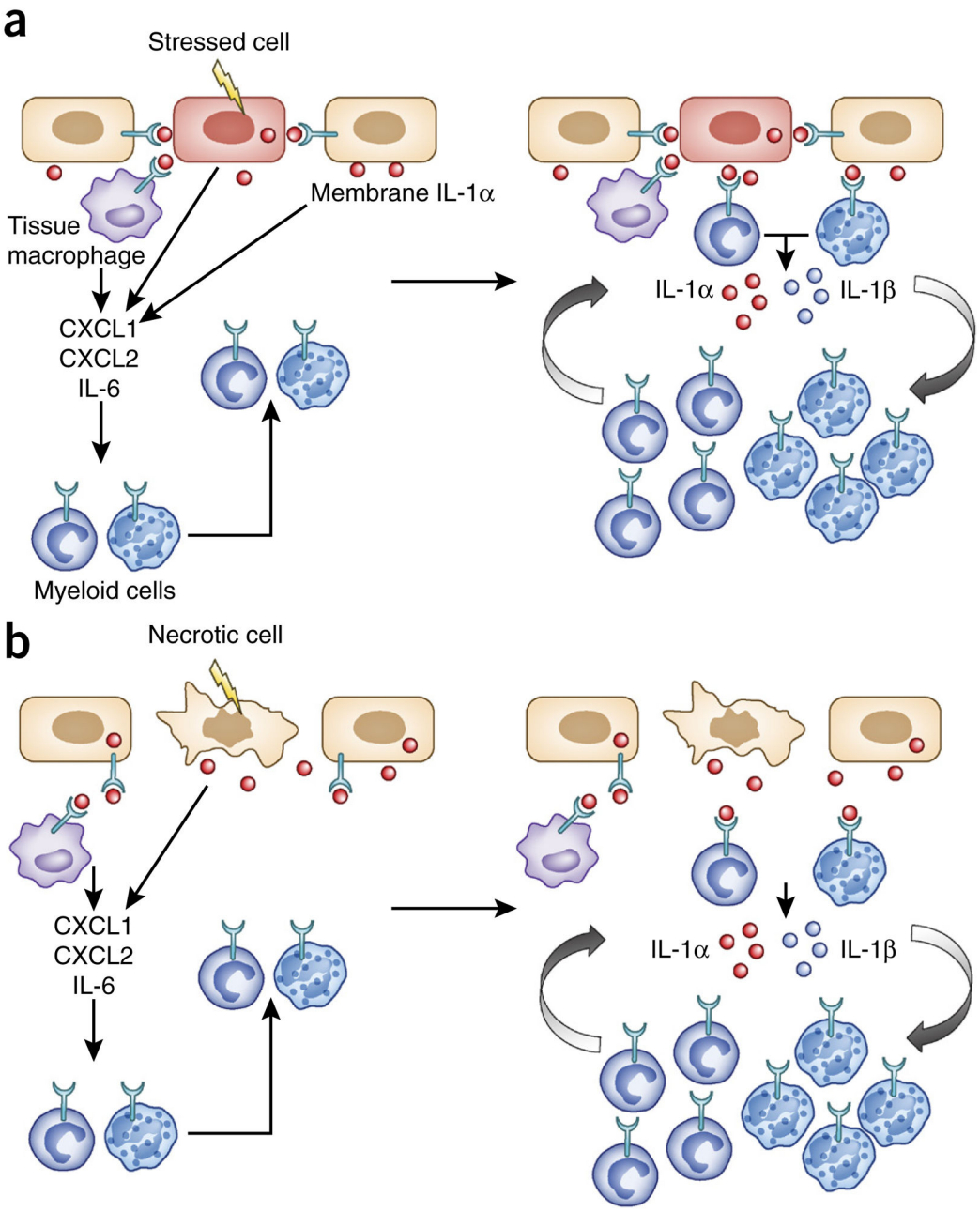

Figure 3.

IL-1α-driven inflammatory loop model. (**a**) IL-1α expression is induced in response to oxidative, genotoxic and metabolic stressors; hormonal stimulation; proinflammatory mediators that activate TNF-R1, IL-1R1 or TLR signaling; or infection. Without cell death, these stimuli trigger translocation of pro-IL-1α onto a plasma membrane and the appearance of membrane-bound pro-IL-1α, which activates IL-1R1-dependent chemokine and cytokine production from neighboring nonhematopoietic cells or tissue-resident macrophages. This initial IL-1α-dependent chemokine production leads to a recruitment of myeloid cells to the site of stress. Upon arrival, myeloid cells receive IL-1α-dependent IL-1R1 stimulation,

which leads to the expression of pro-IL-1α and pro-IL-1β. Therefore, in the context of alive nonhematopoietic or residential hematopoietic cells under stress, IL-1α-initiated signaling triggers the recruitment of cells from hematopoietic compartment, which can amplify and sustain IL-1R1-dependent inflammation through the new round of IL-1α and IL-1β production, thus closing an inflammatory loop of IL-1-IL-1RI-signaling-dependent chemokine production and recruitment of inflammatory cells to the site of stress that now can be sustained only by cells of hematopoietic origin. (**b**) Upon necrotic cell death due to damage, stress or infection, the IL-1α-driven induction of the inflammatory loop is triggered by the passive release of pro-IL-1α into the surrounding milieu, where IL-1α functions as an alarmin. The pro-IL-1α released from necrotic cells activates IL-1R1 signaling on neighboring cells, leading to the recruitment of hematopoietic cells that can further sustain inflammation as in **a**.