IL-1 – Master mediator or initiator of inflammation

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Interleukin-1 (IL-1) lies at the center of the inflammatory response. This pro-inflammatory cytokine was first pinned down for its ability to induce fever, and was later assigned additional biological functions including neutrophil recruitment, lymphocyte activation and induction of inflammatory mediators[1]. Excessive production of IL-1β drives the recurrent episodes of fever and systemic inflammation in certain autoinflammatory diseases, linked to mutations in genes regulating innate immunity; such conditions include familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS)[2], as well as gout, a condition where IL-1β induced by monosodium urate crystals (MSU) causes inflammatory response in joints.

IL-1β, together with TNF-α and IL-6, IL-1β also plays a key role in the pathology of organ-specific autoimmune diseases, such as rheumatoid arthritis (RA) and multiple sclerosis (MS). These diseases are caused by uncontrolled pathogenic T cell and antibody responses to self antigens, resulting in organ specific inflammation and tissue damage. Although studies in mouse models have shown that IL-1 is a central mediator of pathology of such diseases, drugs that target IL-1 have not proved to be as effective against most autoimmune disease in humans.

Two recent clinical reports describe a new autoinflammatory syndrome where patients are hyper-responsive to IL-1β. These individuals have mutations in the gene encoding IL-1 receptor anatagonist (IL-1Ra, *IL1RN*)[3,4], a protein that antagonizes IL-1 signaling by inhibiting the occupancy of the IL-1 receptor by IL-1. Animal studies have highlighted a role for IL-1Ra in maintaining immune homeostasis, and the new studies provide unequivocal evidence in humans that IL-1Ra regulates IL-1β. In addition, the new studies provide evidence that IL-1 drives production of the T cell-derived inflammatory cytokine, IL-17. IL-17-secreting T cells are major mediators of inflammation in organ-specific autoimmune diseases, such as RA and MA, and chronic inflammatory disease, such as psoriasis and Crohn's disease. Autoinflammatory diseases appear to involve dysregulation or overactivation of innate immunity by endogenous stimuli in a process known as sterile inflammation, whereas autoimmune disease develop as a result of adaptive immune responses to self antigens, which may be precipitated by exogenous activators of innate immune responses, such as microbial molecules.

The IL-1 family includes 11 known members, the most prominent being IL-1α and IL-1β. These two cytokines operate through the IL-1 type I receptor (IL-1RI) on a variety of cell types inducing expression of an array of pro-inflammatory genes, such as IL-6, TNF-α, IL-8, IL-17 and IL-1 itself. The activity of IL-1β and IL-1α is controlled by IL-1RII, a decoy receptor, and IL-1Ra, a naturally expressed inhibitor of IL-1 receptor occupancy.

IL-1α is constitutively expressed and cleaved by calpain, whereas IL-1β is synthesized as pro-IL-1β and cleaved by caspase-1 to generate the biologically active cytokine. Caspase-1 itself is activated following assembly of the inflammasome

complex, which contains members of the NOD-like receptors (NLR) family, such as NALP3[5,6]. These receptors recognize conserved components of microbes and endogenous 'danger' signals that arise in response to injury. Recent studies show that mutations in NALP3 lead to dysregulation of IL-1β production and result in cryopyrin-associated periodic syndromes, including FCAS and MWS, rare autoinflammatory diseases affecting an array of tissues and organs, such as the lungs, gastrointestinal tract, skin and central nervous system[2 5].

In one of the new studies, Aksentijevich *et al*.[3] describe nine infants or children with clinical features of systemic inflammation, including pustular rash, joint swelling, bone abnormalities and respiratory distress. The patients responded poorly to antibiotics and steroids but their symptoms resolved dramatically with anakinra, a recombinant form of IL-1Ra approved by the US Food and Drug Administration. Subsequent genetic analysis revealed mutations in *IL1RN* that resulted in a nonfunctional form of IL-1Ra[3]. The authors also found that one patient was homozygous for a deletion encompassing several IL-1 family members, as well as IL1Ra itself. In a second study, Reddy *et al*[4] reported a similar case. The syndrome has been referred to as 'deficiency of the interleukin-1 receptor antagonist' (DIRA)[3].

As well as underscoring the importance of IL-1Ra in immune homeostasis, these studies also provide some clues on the variable efficacy of anakinra in treating autoimmune disorders. Clinical studies and studies in mice[7] show that IL-1 has a central role in T cell mediated autoimmune diseases. However, apart from systemic onset juvenile idiopathic arthritis, anakinra has not proved to be very effective against other autoimmune diseases, such as RA. In contrast, it is highly effective in autoinflammatory diseases, such as DIRA, MWS and gout. This difference may in part reflect the fact that autoinflammatory diseases result from hereditary defects in the regulation of innate immunity, whereas autoimmune diseases develop as a result of a more complex combination of hereditary and environmental factors that lead to a failure to regulate adaptive immune responses, in particular those mediated by IL-17-producing by T cells.

$CD4^+$ T cells that secrete IL-17 (Th17 cells) are now thought to mediate the inflammatory pathology in many autoimmune diseases[8]. There is growing evidence that IL-1α and IL-1β in combination with IL-23 promote differentiation and expansion of Th17 cells[7] and also promote IL-17 production by γδ T cells[9], major initiators of inflammation. Studies in IL-1RI defective mice provided definitive evidence that IL-1 is essential for promoting IL-17 production by T cells that mediate autoimmune disease[7]. The study of Aksentijevich *et al*.[3] dovetails with these findings in mice. The researchers observed a higher percentage of Th17 cells and enhanced IL-17 expression in biopsy samples from inflamed skin of DIRA patients compared with non-affected individuals[3]. This observation provides evidence that IL-1 drives IL-17 production in humans. Furthermore, recent studies in mice with targeted mutations in NALP3, identical to those in MWS, confirm that constitutive inflammasome activation leads to Th17-dominated immune responses[10,11].

There are several key questions for future studies. First, are autoinflammatory diseases are caused solely by an imbalance of IL-1β/IL-Ra? The relative contributions of IL-1α and IL-1β in various autoinflammatory and autoimmune diseases also need to be explored. Gain of function defects in NALP3 would enhance the activity of IL-1β, IL-18 and possibly other cytokines processed by caspase-1, but not IL-1α, whereas defects in IL-1Ra would result in uncontrolled activity of IL-1α as well as IL-1β.

Second, do autoinflammatory diseases require a trigger - endogenous or pathogen derived - of NLRs or the body's other key innate immune receptors, Toll-like receptors (TLRs)? In the absence of infection, sterile inflammation could conceivably be initiated by the release of danger-associated molecular patterns (DAMPs) or alarmins[12], such as IL-1α, from necrotic cells, although the precipitating factors for cell death are unclear.

Finally, researchers need to better understand where IL-1 is positioned in the cascade of inflammatory response. It is possible that IL-1 may directly mediate systemic inflammation in autoinflammatory diseases, but may function primarily upstream of T cells as an initiator of tissue-specific inflammation in autoimmune disease (**Fig. 1**). Recent research on the induction and function of T cells in autoimmunity provide support for this view.

Together, the findings in mice, and the recent clinical studies[3] suggest that drugs which target NALPs are likely to be effective in autoinflammatory diseases. But such drugs may be less effective against autoimmune disease, where both IL-1α and IL-1β may be a major initiator of the inflammatory process upstream of T cell activation. It appears that the critical role of IL-1 in autoimmune diseases may be in precipitating the disease by promoting the induction or expansion of Th17 and γδ T cells, rather than mediating the tissue pathology. Therefore treatment with IL-1 blocking drugs during active diseases may simply be too late. Conversely, drugs that target IL-1 or the inflammasome have considerable potential in other disease where IL-1-mediated innate immune responses have been implicated in pathology. Such conditions include type 2 diabetes, osteoarthritis and Alzheimer's disease.

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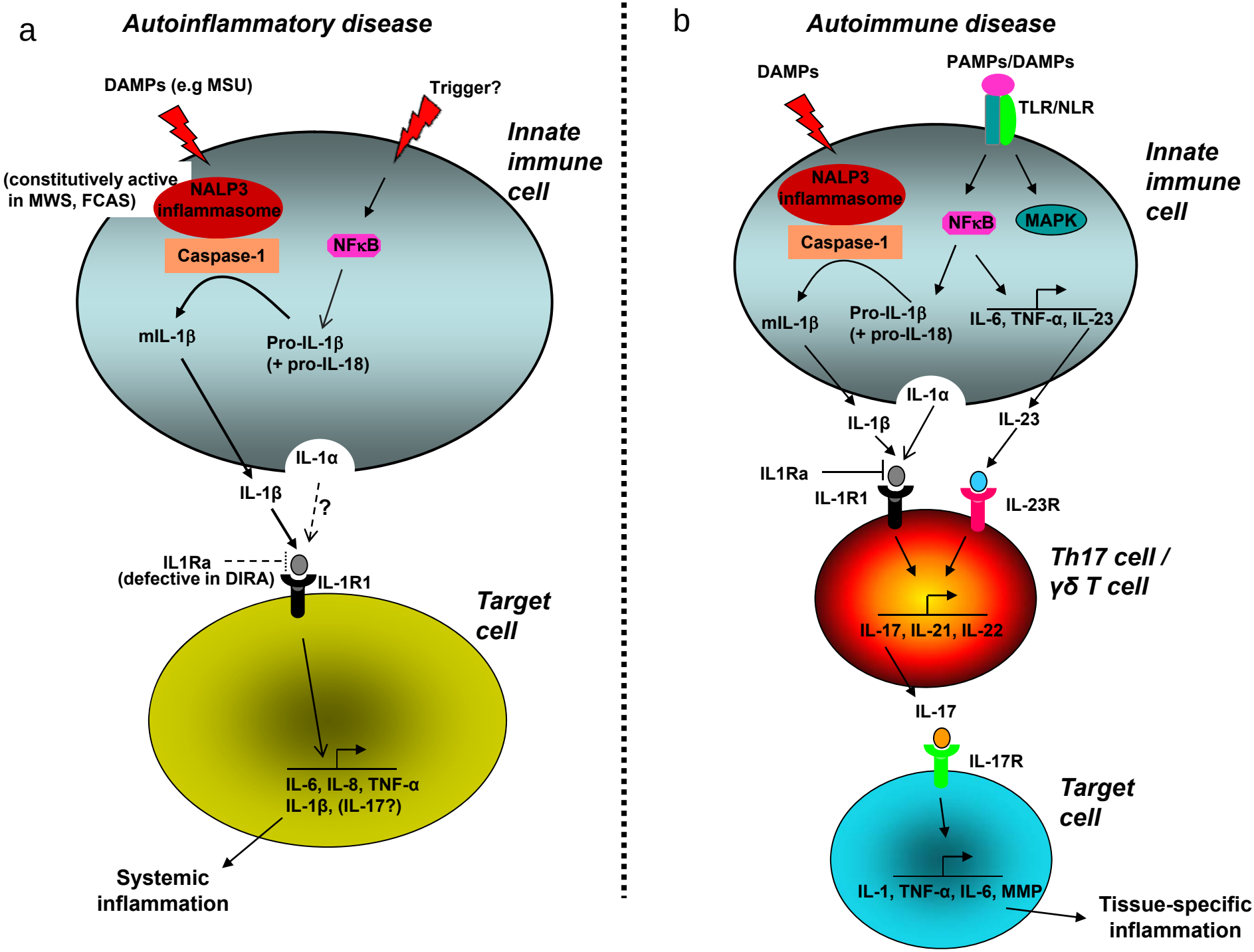
Figure legend

Figure 1. IL-1 in autoinflammatory and autoimmune diseases. (a) Autoinflammatory diseases are characterized by excessive or uncontrolled IL-1β production. The NALP3 inflammasome is activated in innate immune cells by endogenous DAMPs, such as monosodium urate (MSU) crystals, or is constitutively active, as in MWS or familial cold autoinflammatory syndrome (FCAS). Pro-IL-1β is produced following activation of NFκB by un-identified trigger, possibly through a TLR. NALP3 recruits and activates caspase-1, which processes pro-IL-1β into biologically active mature IL-1β (mIL-1β). Caspase-1 also processes IL-18 and possibly other inflammatory mediators. IL-1β binds to the IL-1RI expressed on a variety of cell types and triggers activation of a range of pro-inflammatory cytokines, including IL-6, IL-8, TNF-α, IL-1β itself. With the appropriate co-stimulus, IL-1β may also promote IL-17 production. IL-1β is regulated by IL-1Ra, which is defective in DIRA patients, as shown by a recent clinical study[3]. Excess or uncontrolled IL-1Ra activity causes systemic inflammation. However, IL-1Ra also regulates IL-1α, which could be released by necrotic cells during sterile inflammation. (b) In autoimmune diseases pro-IL-1β is induced via activation of TLR or NLR signalling pathways and processed by caspase-1 following activation of the NALP3 inflammasome with endogenous DAMPs and possibly exogenous PAMPs or bacterial toxins. Activation of the TLR and NLR pathways also leads to the production of pro-inflammatory cytokines, including IL-23. IL-1 and IL-23 bind to their respective receptors on Th17 and γδ T cells and induce production of IL-17, IL-21 and IL-22. IL-17 binds to receptors expressed on a variety of cells type and promotes production of inflammatory cytokines and matrix metalloproteinases (MMPS) that mediate tissue-specific autoimmune inflammation.


a
Autoinflammatory disease
DAMPs (e.g MSU)
Trigger?
Innate immune cell
(constitutively active in MWS, FCAS)
NALP3 inflammasome
Caspase-1
NFκB
mIL-1β
Pro-IL-1β (+ pro-IL-18)
IL-1α
IL-1β
?
IL1Ra (defective in DIRA)
IL-1R1
Target cell
IL-6, IL-8, TNF-α IL-1β, (IL-17?)
Systemic inflammation
b
Autoimmune disease
DAMPs
PAMPs/DAMPs
TLR/NLR
Innate immune cell
NALP3 inflammasome
Caspase-1
NFκB
MAPK
mIL-1β
Pro-IL-1β (+ pro-IL-18)
IL-6, TNF-α, IL-23
IL-1α
IL-1β
IL-23
IL1Ra
IL-1R1
IL-23R
Th17 cell / γδ T cell
IL-17, IL-21, IL-22
IL-17
IL-17R
Target cell
IL-1, TNF-α, IL-6, MMP
Tissue-specific inflammation