CORRESPONDENCE

An immunopathogenic perspective of interleukin-1 signaling

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Interleukin-1 (IL-1), referred to as two distinct proteins, IL-1α and IL-1β, was first described almost 50 years ago.[1] IL-1α and IL-1β represent immediate early innate cytokines critically involved in alarming and activating the host defense system.[2] Therefore, any impairment of IL-1 signaling pathways often leads to devastating outcomes, such as autoimmunity and autoinflammation, dysmetabolism, cardiovascular disorders, and cancer.[2] Many advances in targeting IL-1 in immune therapies have been achieved; for example, the IL-1-blocking agents anakinra (IL-1 receptor antagonist, IL-1Ra), canakinumab (anti-IL-1β mAb), and MABp1 (anti-IL-1α mAb) have been approved for clinical use or are being evaluated.[2] Remarkably, the CANTOS study, which included over 10,000 patients, showed that blocking IL-1β not only reduced atherosclerosis-related cardiovascular mortality but was also effective in inflammatory diseases related to lung cancer, arthrosis, and gout.[3]

Nevertheless, because of the specific spatiotemporal expression pattern of IL-1 and the complex regulatory networks of IL-1-related pathways, it is still not fully understood how exactly IL-1 functions, and how to precisely rectify dysfunctional IL-1 signaling during diverse inflammatory conditions remains unknown.

For a long time, IL-1α and IL-1β, albeit sharing limited sequence homology, were considered redundant. They share similar three-dimensional structures and interact with the same receptor, a heterodimer composed of IL-1R1 and IL-1R accessory protein (IL-1Rap), to initiate the NF-κB signal transduction cascade. However, strong evidence is accumulating that IL-1α and IL-1β each play specific roles in different pathological conditions (Table 1). For example, it was reported that neutrophil recruitment induced by necrotic cells is likely dependent on IL-1α but not IL-1β.[4] The preferential usage of IL-1α over IL-1β for activating IL-1R1 has also been confirmed in other studies, including studies in drug-induced liver injury (DILI),[5] fatty acid-induced vascular response and atherosclerosis,[6] and autoimmune disease.[7] In a dextran sulfate sodium (DSS)-induced colitis mouse model, IL-1α from the intestinal epithelium drives intestinal inflammation, whereas IL-1β acts to heal the intestinal epithelial barrier.[8] Moreover, in murine neonatal sepsis, IL-1α but not IL-1β accounts for morbidity and mortality.[9] IL-1α signaling is also critical in leukocyte recruitment and pulmonary inflammation in response to *Aspergillus fumigatus*[10] and *Legionella pneumophila* infection.[11]

IL-1α and IL-1β differ from each other in gene expression and posttranslational modification. IL-1α precursor protein is expressed and preserved in a wild variety of mesenchymal cells, including keratinocytes, epithelial cells of the lung and entire gastrointestinal tract, and brain astrocytes.[12] In contrast, the IL-1β precursor is an inducible factor produced mainly by myeloid cells after TLR signaling is activated.[12] Furthermore, the IL-1α precursor is fully active, and upon direct release from damaged cells, it functions as an alarmin to initiate the inflammatory response. IL-1α precursor protein can also be cleaved by an array of different proteases, such as granzyme B, elastase, and calpain-1, leading to drastically enhanced bioactivity. The inactive IL-1β precursor, on the other hand, can be cleaved by inflammasome-activated caspase-1 and released via a tightly controlled GSDMD pore to the extracellular matrix.[13] It is worth noting that most studies on inflammasomes or IL-1β do not exclude the potential involvement of IL-1α, especially considering that inflammasomal activation also facilitates IL-1α secretion.[14]

The understanding of IL-1α and IL-1β is also complicated due to their shared usage of IL-1R1, which uses MyD88 as an adaptor in the pro-inflammatory NF-κB signaling pathway. IL-1R1 signal specificity may be based on the IL-1R1-expressing cell type and associated IL-1 stimulation from neighboring cells. In a mouse model of DILI, the expression of IL-1R1 is mainly restricted to myeloid cells among hepatic lymphocytes. In one study, IL-1α made by macrophages activated neutrophils via a paracrine loop and promoted hepatic injury during the early phase of DILI.[5] In another study, liver cells lacking IL-1R1 resisted cell death but were dependent on neighboring cells, arguing for the involvement of IL-1 from these cells.[15] The involvement of IL-1 in distinct immunological, neural, and physiological activities in the brain has recently been revealed in vivo, and it depended on different cell type-specific IL-1R1 signaling pathways. Liu et al. employed genetic knock-in reporter mice to track and reciprocally delete and/or express IL-1R1 in specific CNS cell types, including endothelial cells, ventricular cells, peripheral myeloid cells, microglia, astrocytes, and neurons. Particularly, they demonstrated that endothelial IL-1R1-driven leukocyte recruitment to the central nervous system accounted for impaired neurogenesis; ventricular IL-1R1 regulated monocyte recruitment; and noninflammatory ventricular, astrocyte, and neuronal IL-1R1-mediated neuromodulatory activities.[16,17] In addition, IL-1 is also a licensing signal to permit effector cytokine production by precommitted T helper lineage cells, including Th1, Th2, and Th17 cells. IL-1R signaling stabilizes cytokine transcripts to enable productive and rapid effector functions in CD4+ T cells.[18] Moreover, the pathogenetic roles of GM-CSF-secreting Th cells have been reported in central nervous system inflammation,[19] sepsis,[20] and the recently reported COVID-19.[21] IL-1R signaling is required for the maintenance and pathogenicity of GM-CSF-producing Th cells.[22] Specifying the cell sources and magnitude of IL-1α and IL-1β

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Table 1. Evidence for the nonredundant role of IL-1α in disease pathogenesis

References	Pathogenic conditions	Source of IL-1α	Description
Chen et al.[4]	Cell death induced inflammation	Macrophage	Cell death-triggered inflammation required IL-1α, and IL-1R function on non-bone marrow-derived cells was required.
Zhang et al.[5]	DILI	Macrophage	IL-1α, rather than IL-1β, was critically involved in the immunopathogenesis of AILI. Activation of IL-1α depended on Kupffer cells that sense and transduce DAMP signaling through the TLR4/MyD88 pathway.
Freigang et al.[6]	Atherosclerosis	Vascular cells	Fatty acids selectively stimulated the release of IL-1α but not of IL-1β by uncoupling mitochondrial respiration.
Lukens et al.[7]	Autoinflammation	Hematopoietic cells	IL-1α, but not IL-1β or RIP3-mediated necroptosis, was critical for exacerbated inflammatory responses and unremitting tissue damage upon footpad microabrasion of $Ptpn6^{spin}$ mice.
Bersudsky et al.[8]	DSS-induced colon inflammation	Intestinal epithelial cells (IECs)	The roles of IL-1α and IL-1β differed in DSS-induced colitis in that IL-1α, mainly expressed by colon epithelial cells, was inflammatory, whereas IL-1β, mainly of myeloid cell origin, promoted healing and repair.
Benjamin et al.[9]	Sepsis	NA	IL-1α, but not IL-1β, mediated the detrimental effects of IL-1R1 signaling on neonatal sepsis survival.
Caffrey et al.[10]	*Aspergillus fumigatus* infection	NA	IL-1α played an important role in orchestrating the optimal recruitment of neutrophils and monocytes, whereas IL-1β and the inflammasome were more important in the activation of the antifungal activity of monocytes.
Barry et al.[11]	*Legionella pneumophila* infection	Hematopoietic cells	IL-1α was a critical initiator of neutrophil recruitment to the lungs of *L. pneumophila*-infected mice.

signaling through the shared IL-1R1 is critical to understanding CD4+ T helper functions.

The therapeutic activities of anti-IL-1 antibodies across diseases argue for innate inflammatory response as a metanarrative in modern medicine. More efforts are needed to clarify the roles of IL-1/IL-1R1 signaling and effectors to better understand the immunopathogenesis of diseases and improve current targeted treatments.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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