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. IL-1α and IL-1β represent immediate early innate cytokines critically involved in alarming and activating the host defense system. Therefore, any impairment of IL-1 signaling pathways often leads to devastating outcomes, such as autoimmunity and autoinflammation, dysmetabolism, cardiovascular disorders, and cancer. 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-1 β mAb), and MABp1 (anti-IL-1α mAb) have been approved for clinical use or are being evaluated. 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, arthritis, and gout.

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. 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), fatty acid-induced vascular response and atherosclerosis, and autoimmune disease. 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. Moreover, in murine neonatal sepsis, IL-1α but not IL-1β accounts for morbidity and mortality. IL-1α signaling is also critical in leukocyte recruitment and pulmonary inflammation in response to Aspergillus fumigatus and Legionella pneumophila infection.

IL-1α and IL-1β differ from each other in gene expression and posttranscriptional 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. In contrast, the IL-1β precursor is an inducible factor produced mainly by myeloid cells after TLR signaling is activated. Furthermore, the IL-1α precursor is fully active, and upon direct release from damaged cells, it functions as an alarm 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. It is worth noting that most studies on inflammammasomes or IL-1β do not exclude the potential involvement of IL-1α, especially considering that inflammasomal activation also facilitates IL-1α secretion.

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. 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. 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.

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-1R1 signaling stabilizes cytokine transcripts to enable productive and rapid effector functions in CD4+ T cells. Moreover, the pathogenetic roles of GM-CSF-secreting Th cells have been reported in central nervous system inflammation, sepsis, and the recently reported COVID-19. IL-1R1 signaling is required for the maintenance and pathogenicity of GM-CSF-producing Th cells. Specifying the cell sources and magnitude of IL-1α and IL-1β
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 metamnarrative 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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