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Review Article

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IL-1 Receptor Dynamics in Immune Cells: Orchestrating Immune Precision and Balance

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Conflict of Interest
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Abbreviations
DCs, dendritic cells; FDA, Food and Drug Administration; IL-1R, IL-1 receptor; IL-1Ra,

ABSTRACT

IL-1, a pleiotropic cytokine with profound effects on various cell types, particularly immune cells, plays a pivotal role in immune responses. The proinflammatory nature of IL-1 necessitates stringent control mechanisms of IL-1-mediated signaling at multiple levels, encompassing transcriptional and translational regulation, precursor processing, as well as the involvement of a receptor accessory protein, a decoy receptor, and a receptor antagonist. In T-cell immunity, IL-1 signaling is crucial during both the priming and effector phases of immune reactions. The fine-tuning of IL-1 signaling hinges upon two distinct receptor types; the functional IL-1 receptor (IL-1R) 1 and the decoy IL-1R2, accompanied by ancillary molecules such as the IL-1R accessory protein (IL-1R3) and IL-1R antagonist. IL-1R1 signaling by IL-1β is critical for the differentiation, expansion, and survival of Th17 cells, essential for defense against extracellular bacteria or fungi, yet implicated in autoimmune disease pathogenesis. Recent investigations emphasize the physiological importance of IL-1R2 expression, particularly in its capacity to modulate IL-1-dependent responses within Tregs. The precise regulation of IL-1R signaling is indispensable for orchestrating appropriate immune responses, as unchecked IL-1 signaling has been implicated in inflammatory disorders, including Th17-mediated autoimmunity. This review provides a thorough exploration of the IL-1R signaling complex and its pivotal roles in immune regulation. Additionally, it highlights recent advancements elucidating the mechanisms governing the expression of IL-1R1 and IL-1R2, underscoring their contributions to fine-tuning IL-1 signaling. Finally, the review briefly touches upon therapeutic strategies targeting IL-1R signaling, with potential clinical applications.

Keywords: Interleukin-1; Receptors, Interleukin-1; T cells; Autoimmunity; Regulatory T cells

INTRODUCTION

IL-1 is the prototype of a pleiotropic cytokine that affects nearly every type of cell, especially innate and adaptive immune cells (1-3). There are two distinct forms of IL-1, IL-1α and IL-1β.

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IL-1R antagonist; IRAK, IL-1R-activated protein kinase; MyD88, myeloid differentiation primary response gene 88; PGE2, prostaglandin E2; RA, rheumatoid arthritis; sIL-1R, IL-1R exists in a soluble form; TF, transcription factor; Tfr; follicular Tregs; TIR, Toll/IL-1R.

Author Contributions

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IL-1α is constitutively present in mesenchymal cells and its precursor form functions as an "alarmin" by rapidly mediating the early phases of sterile inflammation. On the other hand, IL-1β is mainly produced by hematopoietic cells, especially mononuclear phagocytes insulted by infectious stimuli such as TLR agonists or danger signals (4). IL-1α and IL-1β are expressed at low levels under normal conditions of cells and require induction at both the transcriptional and translational levels *via* appropriate stimulus (1). Unlike other cytokines, IL-1α/β is initially translated into a precursor protein. IL-1α precursor is biologically active, whereas IL-1β precursor is further processed and matured into a shorter active form *via* inflammasome-mediated cleavage with proteolytic enzyme caspase 1 (3-5). IL-1α and IL-1β have indistinguishable biological activities due to their shared signaling pathway with the same receptors (2,3). However, differences in cell sources and release mechanisms of IL-1α and IL-1β lead to differences between their functions, which impact immunity and inflammation (3). Given its potent proinflammatory effects, the activities of IL-1 have to be tightly controlled at different levels and by diverse mechanisms (3). Accumulating evidence suggests that the regulation of the expression of IL-1 receptors (IL-1Rs) on immune cells is one of the mechanisms controlling the activities of IL-1 during immune responses (6,7).

IL-1R complex is composed of two IL-1-binding receptors, such as IL-1R1 (also known as IL-1RI) and IL-1R2 (IL-1RII), and one accessory receptor, IL-1R3 (IL-1RAcP) (8). A functional IL-1R1 directly binds IL-1, followed by recruitment of IL-1R3 to assemble a heterotrimeric complex, thereby igniting IL-1-dependent signaling (9,10). On the contrary, IL-1R2 is a non-functional decoy receptor of IL-1 with a short cytoplasmic tail lacking the signal-transducing Toll/IL-1R (TIR) domain. The major role of IL-1R2 is to scavenge or neutralize exogenous IL-1 and to inhibit the IL-1 signaling in the responsive cells (2). Accumulating evidence has revealed that the expression of IL-1Rs is dynamically regulated by immune cells in response to diverse inflammatory contexts, such regulation influences immune responses by modulating IL-1β responsiveness.

The prevailing consensus acknowledges the predominant impact of IL-1α/β on non-immune cell populations. Specifically, the expression of IL-1R1 can be observed in fibroblasts, epithelial cells, and endothelial cells, while IL-1R2 exhibits primary expression within various hematopoietic cells. IL-1R3, serving as a co-receptor alongside IL-1R1, demonstrates ubiquitous expression across all cell types responsive to IL-1α/β (11,12). Recent findings indicate the presence of IL-1R1 in ventricular cells, astrocytes, and dentate gyrus neurons within the brain, in addition to endothelial cells. Notably, cell-specific IL-1R1 signaling within the brain governs distinct neuroimmune functions (13). Endothelial IL-1R1 plays a pivotal role in orchestrating endothelial activation during IL-1-driven brain inflammation by facilitating the upregulation of cell adhesion molecules and cytokines (14). Consequently, this regulatory mechanism modulates IL-1-induced microglial activation (13).

The biology of IL-1 family cytokines and receptors on a variety of cell types has been extensively reviewed elsewhere (2,4,8). Therefore, this review will focus on the role of IL-1R signaling and the regulation mechanism of IL-1β in T cells and monocytes/macrophages, which are crucial for cell-mediated adaptive immunity. We mainly discuss recent advances in the understanding of the expression of the IL-1R1 and IL-1R2 on $CD4^+$ and $CD8^+$ T cells and how the cell actively regulates the IL-1R under their circumstances to fine-tune the IL-1 signaling.

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THE COMPONENTS OF IL-1R COMPLEX AND THEIR FUNCTIONS

IL-1α and IL-1β play a pivotal role in regulating local and systemic inflammation through the control of IL-1R1/3-mediated signaling in various immune cells. Given the potency and wide-ranging functions of the IL-1R1/3 signaling in the immune system, the biological activity of IL-1α/β is rigorously modulated by multiple mechanisms, such as functional and decoy receptors, receptor antagonists, and other negative regulators (3).

IL-1R1 is primarily responsible for initiating the cellular signaling that mediates the immune responses of IL-1 (15). Although IL-1R1 is ubiquitously expressed at low levels, its expression on immune cells is more dynamically up-regulated in response to environmental factors, and such regulation influences immune responses (6,7,16,17). The interaction between IL-1 and IL-1R1 induces a ligand-driven conformational alteration in the first extracellular domain of IL-1R1, which facilitates the recruitment of IL-1R3, ultimately resulting in the formation of a trimeric signaling complex (9,18-20). Cytoplasmic TIR domains of this trimeric complex rapidly bind to an adaptor protein, myeloid differentiation primary response gene 88 (MyD88), and recruit IL-1R-activated protein kinase (IRAK)-4 to death domains of MyD88. IL-1α/β, IL-1R1, IL-1R3, MyD88, and IRAK-4 are essential components to assemble a stable IL-1-induced first signaling module (21). Upon MyD88 binding, IRAK4 undergoes autophosphorylation, leading to the subsequent phosphorylation of IRAK1 and IRAK2. This event is followed by the recruitment and oligomerization of TNF-associated factor 6, which ultimately activates a diverse array of transcription factors (TFs), including NF-κB, IFN regulatory factor 5, activation protein 1, and cAMP response element binding protein (22,23). Consequently, numerous IL-1-responsive genes such as IκBα, IL-6, IL-8, MCP-1, and cyclooxygenase 2 are transcribed (18) (**Fig. 1**).

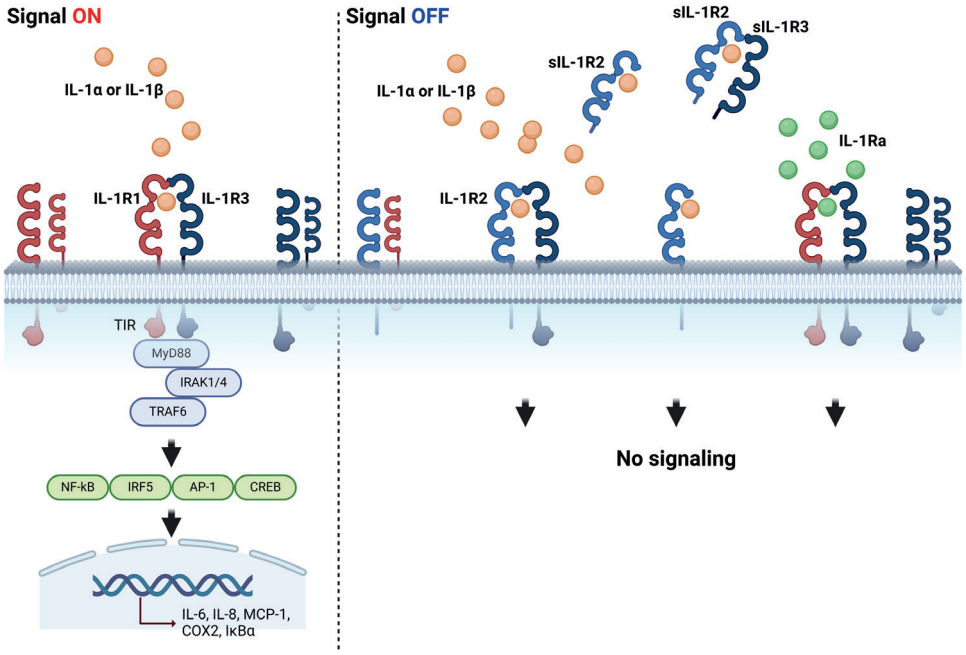

Figure 1. Role of IL-1R components in IL-1 signal transduction. A trimeric complex formation involving IL-1, IL-1R1, and IL-1R3 is imperative for the initiation of IL-1 signaling. MyD88 interacts with the TIR domain of the IL-1R complex, inducing the phosphorylation of IRAK4, subsequently activating transcription factors like NF-κB, IRF5, and AP-1. Furthermore, IL-1R2 functions as a decoy receptor, diminishing the availability of IL-1α/β and IL-1R3 in both membrane-bound and soluble form. The regulatory influence of IL-1Ra is evident through its competitive limitation of IL-1α/β within the IL-1 signaling system. Figure created with BioRender.com.

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Table 1. List of human or mouse IL-1R components with their choromosome location, size of amino acids, Uniprot IDs, and GeneCards IDs

IL-1R component	Human				Mouse		
	Location*	Size (amino acids)	UniProt ID	GeneCards ID	Location*	Size (amino acids)	UniProt ID
IL-1R1	Chr 2: 102.06–102.18 Mb	569	P14778	GC02P102136	Chr 1: 40.23–40.32 Mb	576	P13504
IL-1R2	Chr 2: 101.99–102.03 Mb	398	P27930	GC02P101991	Chr 1: 40.11–40.16 Mb	410	P27931
IL-1R3	Chr 3: 190.51–190.66 Mb	570	Q9NPH3	GC03P190514	Chr 16: 26.4–26.55 Mb	570	Q61730
IL-1Ra	Chr 2: 113.10–113.13 Mb	177	P18510	GC02P128885	Chr 2: 24.23–24.24 Mb	178	P25085

*Information from UCSC Genome Brower (https://genome.ucsc.edu/).

IL-1R2 is also able to bind to IL-1α and IL-1β independently, followed by occurring structural changes to allow IL-1R2 to bind IL-1R3 (24). However, IL-1R2 cannot initiate further signal cascade due to the lack of intracellular TIR domain. Thus, IL-1R2 is considered a decoy receptor that can serve as a competitive inhibitor of IL-1 signaling (25). Unlike ubiquitously expressed IL-1R1, the expression of IL-1R2 is restricted to immune cells including monocytes, neutrophils, and B cells under steady-state conditions. Additionally, keratinocytes and endothelial cells can also induce IL-1R2 expression (17,26). Recent investigations have revealed that activated Tregs up-regulate IL-1R2 expression on the cells, which also express IL-1R1, thereby dampening their IL-1-dependent responses, implying a significant physiological role for IL-1R2 expression in immune regulation (6,7,27,28). The gene encoding IL-1R2 is located next to IL-1R1 gene on the same chromosome in humans and mice (3) (**Table 1**). Despite both IL-1R1 and IL-1R2 being membrane-bound receptors with a similar architecture, featuring an extracellular portion typically consisting of 3 Ig-like domains (D1, D2, and D3) responsible for ligand binding, their extracellular domains show a homology of only 28% in humans (10). While IL-1R1 binds IL-1α, IL-1β, and IL-1R antagonist (IL-1Ra) with approximately same high affinity (K_d=10^{-9} M), IL-1R2 demonstrates the strongest affinity for IL-1β at 2.2×10^{-9} M. Conversely, its affinity for IL-1Ra and IL-1α is reduced by 100 and 1,000 times, respectively (K_d=1.6×10^{-6} M and 1.4×10^{-8} M, respectively), compared to IL-1β (29). Furthermore, plasmon resonance analysis showed that IL-1β has a slow dissociation rate for IL-1R2 compared with IL-1α and IL-1Ra (30). These observations suggest that IL-1R2 efficiently acts as a molecular trap and competitive inhibitor for IL-1β, thereby inhibiting its activity during inflammation. In this regard, the spatiotemporal regulation of IL-1R2 expression becomes crucial for orchestrating an optimal IL-1-mediated immune response (**Fig. 1**).

In addition to its membrane-bound form, IL-1R2 also exists in a soluble form (sIL-1R2), released from cells by two mechanisms; alternative splicing and ectodomain shedding (17,31,32). The latter is the major mechanism responsible for the generation of sIL-1R2 via the proteolytical cleavage of the extracellular portion of membrane IL-1R2 by several enzymes, such as ADAM17, ARTS-1, α-, β- and γ-secretases (3,33). sIL-1R2 is abundantly present in normal blood at a relatively high concentration ranging from 5 to 10 ng/ml. Its levels escalate in patients with various infectious conditions and autoimmune disorders. Notably, the plasma concentrations of sIL-1R2 exhibit an inverse relationship with the severity of autoimmune arthritis (34). Additionally, sIL-1R2 demonstrates a higher binding affinity to IL-1β (K_d=1.9×10^{-7} M) compared to IL-1α and IL-1Ra (K_d=1.5×10^{-6} M and 2.5×10^{-5} M, respectively). Functionally, sIL-1R2 serves to sequester IL-1β in the extracellular milieu, thereby preventing it from interacting with IL-1R1 on target cells.

A recent study has proposed that a cytosolic IL-1R2 binds to pro-IL-1α and inhibits its cytokine activity by preventing enzyme-mediated cleavage and activation of pro-IL-1α. In infectious conditions, active caspase-1 cleaves IL-1R2, which causes dissociation from IL-1α, calpain processing, and complete restoration of IL-1α activity after necrosis (35).

IL-1R3 functions as a co-receptor for the ligand binding receptors of six distinct IL-1 family cytokines, such as IL-1α, IL-1β, IL-33, IL-36α, IL-36β, and IL-36γ. Upon the binding of cytokines to their respective receptors, a trimeric complex forms with IL-1R3. This complex facilitates the dimerization of cytoplasmic TIR domains, thereby initiating a unique response (36). Despite the absence of direct binding between IL-1R3 and IL-1α or IL-1β, IL-1R3 can associate with IL-1–IL-1R1 or IL-1–IL-1R2 complexes, resulting in the formation of high-affinity receptor complexes. Signaling is initiated by the approximation of the intracellular domains of IL-1R1 and IL-1R3 upon the formation of the IL-1–IL-1R1–IL-1R3 complex. Studies suggest that the extracellular portion of IL-1R3 interacts with IL-1β–IL-1R1 from the left side, engaging with domain 2 and 3. Conversely, in the interaction model of IL-1R3 with the IL-1Ra–IL-1R1 complex, only domain 2 of IL-1R3 establishes contact, resulting in an unstable interaction (24). IL-1R3 is expressed constitutively in all cell types responsive to IL-1α/β, albeit at relatively low levels (11,12).

Alternative mRNA splicing of the IL-1R3 transcript generates multiple isoforms, including a soluble variant consisting solely of the extracellular domain, which is presumed to be secreted into the blood and extracellular fluids (37). This soluble form, referred to as soluble IL-1R3 (sIL-1R3), augments the ability of sIL-1R2 to counteract the effects of IL-1β. Compared to sIL-1R2 alone, the interaction of IL-1α/β bound sIL-1R2 with sIL-1R3 markedly enhances the affinity for IL-1α (from 1.9×10^{-7} M to 2.3×10^{-9} M) and IL-1β (from 1.4×10^{-9} M to 1.8×10^{-11} M), while no notable change is observed for IL-1Ra (from 3.7×10^{-7} M to 3.2×10^{-7} M). This indicates that sIL-1R2 plays a crucial role as a negative modulator of IL-1α/β signaling within the immune system (37). Recent investigations have demonstrated that blocking IL-1R3 using its neutralizing Ab substantially reduces the activities of six IL-1 family members and associated disease manifestations, underscoring the pivotal function of IL-1R3 as a signaling regulator for IL-1R3-dependent cytokines that initiate inflammatory responses (36).

IL-1Ra is an endogenous inhibitor of IL-1α/β that exhibits full binding affinity to the IL-1R1. An isoform of IL-1Ra, characterized by the presence of a hydrophobic signal peptide at its N-terminus for efficient secretion, is primarily synthesized and secreted by myeloid cells including monocytes and macrophages. This isoform is predominantly found in extracellular compartments. Conversely, other IL-1Ra isoforms lacking the signal peptide are considered to locate intracellularly within epithelial cells and can be passively released by dying cells (38-43). The production of IL-1Ra is upregulated by several inflammatory stimuli, such as adherent IgG, cytokines, microbial components, and acute-phase proteins (39), suggesting its role as a negative regulator for IL-1-mediated response. A binding affinity of IL-1Ra to IL-1R1 is higher than that of either IL-1α or IL-1β. Furthermore, the formation of the IL-1Ra-IL-1R1 complex induces a distinct conformational change compared to that which occurs upon IL-1α/β binding. This disparity results in the failure to recruit IL-1R3 to the complex and initiate subsequent signal transduction (44,45). Considering the important role of endogenous IL-1Ra as a natural anti-inflammatory protein in a variety of disease conditions, a recombinant form of human IL-1Ra has been developed and used to inhibit inflammation mediated by both IL-1α and IL-1β in many inflammatory diseases (46).

IL-1R1 EXPRESSION AND ITS ROLE IN IMMUNE CELLS

T cells

IL-1R1/3 signaling by IL-1β is critical for the differentiation, expansion, and survival of IL-17-producing CD4⁺ T cells (known as Th17 cells). Th17 cells contribute to the defense against extracellular bacteria or fungi by promoting inflammation in local tissues (47). Naive CD4⁺ T cells differentiate into Th17 cells under the stimulation of a Th17-polarizing cytokine milieu, including IL-6, TGF-β, IL-23, and IL-1β (48). IL-1R1-deficient mice exhibit vulnerability to various infections such as *Staphylococcus aureus* and *Candida*, emphasizing the necessity of proper Th17-cell differentiation (48,49). Under certain conditions, Th17 cells are also implicated in the pathogenesis of autoimmune and inflammatory diseases (6,50). *Ex vivo* human CD4⁺ T cells expressing IL-1R1 display Th17 cell features, producing higher levels of IL-17 in response to TCR and IL-1β stimulation (6). A recent study indicates that IL-1R1 licenses TCR-independent IL-17A and IFN-γ production of memory CD4⁺ T cells in response to IL-1β and IL-23 (51,52).

The regulation of IL-1R1 expression during Th17 differentiation involves inducers, such as prostaglandin E2 (PGE_2), IL-6, and less potently IL-21 with TGF-β (6,53-56). PGE_2 enhances intracellular cAMP pathways by binding to prostaglandin receptor EP2 and EP4, whereas IL-6, IL-21, and TGFβ induce the TFs STAT3, IRF4, and RORα/γt, respectively, leading to the upregulation of IL-1R1 expression in CD4⁺ T cells (48) (**Fig. 2**). IL-1R1/3 signaling is crucial for early Th17 differentiation through the induction of IRF-4 and RORγt, as well as the upregulation of IL-23R expression (48). IL-1R1 is also expressed by a small population of naive CD4⁺ T cells, producing higher levels of IL-17 in response to a combination of IL-1β and TCR triggering. Despite the absence of IL-1R1 expression in CD4⁺ T cells from umbilical cord blood, a combination of IL-7, IL-15, and TGFβ upregulates IL-1R1 expression on naive CD4⁺

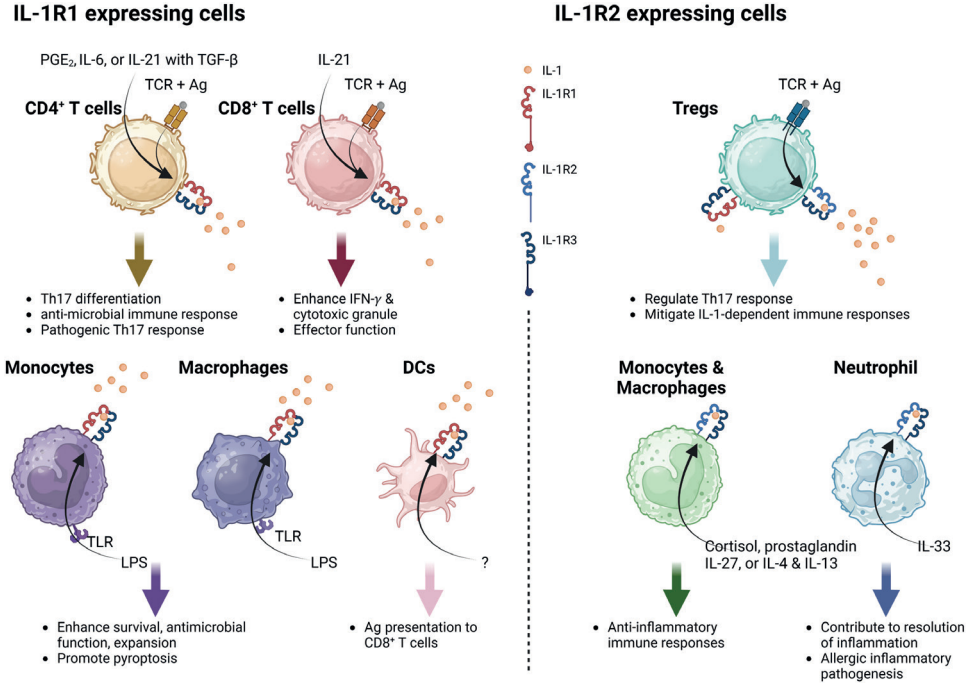

Figure 2. The induction of IL-1R1 and IL-1R2 in immune cells and their functions. Diverse stimuli elicit the expression of IL-1R1 (on the left) and IL-1R2 (on the right) in a manner specific to immune cells. The signaling mediated by IL-1Rs exerts a regulatory impact on the functions of these immune cells. Figure created with BioRender.com.

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T cells even without TCR stimulation (6). IL-1β is closely involved in generating pathogenic Th17 cells with pro-inflammatory features like expressing TF T-bet and co-expressing IFN-γ and GM-CSF, resembling Th1-like phenotype (57). Pathogenic Th17 cells contribute to various immunopathology, including autoimmune diseases (58). IL-1R1$^{-/-}$ mice do not develop experimental autoimmune encephalomyelitis due to the absence of pathogenic Th17 cells (59). The tight regulation of IL-1R1/3 signaling in CD4$^+$ T cells is crucial to induce appropriate Th17 responses against extracellular pathogens without causing autoimmune responses.

Limited studies have reported the importance of IL-1 signaling in the CD8$^+$ T-cell responses to viral infection or tumors compared to CD4$^+$ T cells. IL1R1$^{-/-}$ mice show impaired CD8$^+$ T-cell responses to various infections, including LCMV and influenza (60,61). IL-1 has been demonstrated to enhance *in vivo* expansion, differentiation, migration to the periphery, and memory response of Ag-specific CD8$^+$ T cells (62). Adoptively transferred WT OT-1 CD8$^+$ cells display increased cytotoxic granule production and IFN-γ secretion, as well as augmented memory recall with OVA Ag and IL-1β administration, whereas these effects are not observed in IL-1R1$^{-/-}$ OT-1 CD8$^+$ cells. IL-1β empowers the expansion of Ag-specific CD8$^+$ T cells, improving the protective capacity of weak immunization (62). A recent study highlights the critical role of the IL-1-MyD88-IRAK1/4 axis in programming the quantity and polyfunctionality of memory CD8$^+$ T-cell responses (63). IL-1β has been suggested as a vaccine adjuvant to boost cell-mediated immune responses to influenza virus and the formation of memory CD8$^+$ T cells (64,65). Despite the contribution of IL-1R1/3-mediated signaling to potent CD8$^+$ T-cell immune responses, the molecular mechanisms underlying IL-1R1 expression on CD8$^+$ T cells and IL-1R1/3 signaling-induced effector function remain poorly understood.

Recent findings reveal that IL-21 predominantly induces IL-1R1 expression on TCR-stimulated CD8$^+$ T cells, and their effector functions are augmented by additional IL-1β treatment (16) (**Fig. 2**). IL-21, mainly produced by NKT and CD4$^+$ T cells, has pleiotropic actions affecting the differentiation and effector functions of various immune cells (66,67). The CD8$^+$ T-cell lineage is the primary target of IL-21's immunomodulatory effects, enhancing proliferation, memory cell formation, and effector functions (67,68). IL-1R1 induced by IL-21 in TCR-stimulated CD8$^+$ T cells allows for IL-1β-mediated IL-1R1/3 signaling, enhancing IFN-γ production, cytotoxic granule release, and survival. Mechanistically, efficient and simultaneous activation of transcriptional factors STAT1, STAT3, and STAT5 is necessary for IL-1R1 induction on activated CD8$^+$ T cells. IL-21-IL-1R1/3-IL-1β axis directly augments the effector functions of CD8$^+$ T cells, providing a possible explanation for how CD4$^+$ T cells and Ag-presenting cells support CD8$^+$ T cells in robustly augmenting effector function.

Monocytes/macrophages and others

Mononuclear phagocytes play a crucial role in the production of IL-1β in response to various stimuli, including TLR activation, cytokine exposure, and IL-1α (1,69). Although their role as suppliers of IL-1β has been extensively studied, early investigations indicate that mononuclear phagocytes, comprising monocytes, macrophages, and dendritic cells (DCs), also express IL-1Rs. IL-1β-mediated IL-1R1/3 signaling in these cells enhances their survival, antimicrobial function, and expansion (3,70). Human CD14$^+$ monocytes express IL-1R1, with a substantial increase observed following stimulation by bacterial LPS (71-73) (**Fig. 2**). In alveolar macrophages, the signaling cascade initiated by LPS-triggered TLR4 activation not only facilitates the release of active IL-1β through Nlrp3 inflammasome activation but also increases the expression of IL-1R1 via MyD88- and NF-κB-dependent signaling pathways.

The upregulation of IL-1R1 in alveolar macrophages amplifies IL-1β signaling and promotes pyroptosis, which contributes to pulmonary inflammation and injury in response to LPS through an autocrine mechanism (74). Studies utilizing IL-1R1$^{-/-}$ mice have demonstrated that IL-1β directly stimulates an antimicrobial immune response against *Mycobacterium tuberculosis* within macrophages (70).

Recent investigations emphasize the pivotal role of IL-1β as a critical mediator of trained immunity, representing a form of innate immune memory, particularly pronounced in monocytes (75,76). This assertion is supported by earlier observations of IL-1β's protective effect against fatal bacterial and fungal sepsis in murine experiments involving pre-injection of IL-1β days or even weeks prior to infection (73). In the context of DCs, IL-1β plays a crucial role in facilitating proper Ag presentation to CD8$^+$ T cells. In the influenza A virus model, Pang et al. (77) have delineated that the priming of CD8$^+$ T cells critically depends on DCs activated by IL-1-mediated IL-1R1/3 signaling, which replaces signaling through the PRRs TLR7 and RIG-I (**Fig. 2**). Furthermore, a separate study has reported similar findings, demonstrating that IL-1R$^{-/-}$ DCs are compromised in their ability to induce adaptive immune responses and regulate viral infection, as demonstrated within the West Nile virus infection model (78).

IL-1R2 EXPRESSION AND ITS ROLE IN IMMUNE CELLS

T cells

In contrast to its critical role in Th17 cell function, IL-1R2 plays a regulatory role in Treg cells (7,27,28,79,80). Studies have demonstrated that human Treg cells, upon TCR stimulation, preferentially upregulate both IL-1R1 and IL-1R2 on their cell surface, with co-expression observed in a subset of these cells. IL-1R2-expressing Tregs exhibit potent suppressor activity, whereas resting IL-1R1-expressing Tregs lack suppressor activity. This underscores the physiological importance of IL-1R2 in mitigating IL-1-dependent immune responses (27,80). In addition to peripheral Treg cells, intra-thymic Tregs and tumor-infiltrating Tregs in colorectal and breast cancer patients also upregulate IL-1R2 expression (79,81,82), suggesting a crucial role for IL-1R2 in modulating IL-1 signaling within the local inflammatory microenvironment.

Lee et al. (6) reported an interesting observation where IL-1R2 mRNA is abundantly expressed in *ex vivo* IL-1R1$^+$ CD4 memory T cells compared to their IL-1R1$^-$ counterparts in humans. Furthermore, IL-1R2 directly diminishes the production of IL-17 in TCR-stimulated IL-1R1$^+$ CD4$^+$ memory T cells by limiting IL-1β responsiveness (6) (**Fig. 2**). Our recent study revealed that TCR triggering induces both IL-1R1 and IL-1R2 expression in memory CD4$^+$ T cells, even after depleting Tregs from CD4$^+$ T cells. However, the kinetics of IL-1R1 and IL-1R2 expression differ notably, with IL-1R2 lagging behind IL-1R1 expression by 24 hours, selectively observed in IL-1R1-expressing cells. IL-1R2 expression correlates with the strength of TCR stimulation, while IL-1R1 expression is induced by weak TCR triggering (7). Given that low-strength TCR stimulation favors Th17 responses in human CD4$^+$ T cells (83), these findings suggest that *cis*-regulation by IL-1R2 involves its competitive binding to IL-1β and IL-1R3 on CD4$^+$ T cells under inflammatory conditions. Consistent with previous reports (27,80), our study demonstrated that TCR triggering upregulates Foxp3 expression in memory CD4$^+$ T cells, and induction of IL-1R2 is preferentially observed in these Foxp3-expressing cells (7). Among IL-1R1-expressing CD4$^+$ T cells, IL-1R2$^+$ cells exhibit a higher expression of various Treg-related markers, such as CD39, CD73, and CTLA-4, compared to IL-1R2$^-$ cells (7). Reports exist on the existence of Foxp3$^+$Th17 cells or the trans-differentiation of Th17 into Treg cells under

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various inflammatory conditions in mouse models and disease patients. These Foxp3$^+$Th17 cells and transdifferentiated Tregs have a suppressive function similar to conventional Tregs (84,85). Due to their phenotype and potential modulatory function via IL-1R2, IL-1R1$^+$IL-1R2$^+$ cells may act as pivotal regulators of the Th17-cell-mediated inflammatory environment.

Considering the preferential expression of IL-1R2 by activated Foxp3$^+$ T cells, it is assumed that Treg-related TFs are involved in IL-1R2 gene expression. Ectopic overexpression of FOXP3 in effector CD4$^+$ T cells enhances IL-1R2 expression in response to TCR stimulation, while its expression is mildly diminished by silencing FOXP3 (80). Foxp3 forms a multiprotein complex with many protein partners related to the regulation of transcription (86). Among these Foxp3 partners, NFAT is essential for the regulation of major Treg-related molecules via direct binding of the NFAT/FOXP3 complex to the promotors of these genes (87). In our recent study, *in vitro* assays using peptide FOXP3 393-403, an inhibitor of NFAT/FOXP3 interaction, revealed that IL-1R2 expression is molecularly mediated by a cooperative complex comprised of NFAT and Foxp3. Reporter and ChIP assays confirmed that the NFAT/FOXP3 complex binds to the *IL-1R2* promoter and is critical for its transcription (7). CD4$^+$ T cells derived from synovial fluid of patients with rheumatoid arthritis (RA), a prototypic autoimmune disease, exhibit higher *de novo* expression of IL-1R1 and impaired TCR-mediated induction of IL-1R2 expression compared to counterpart peripheral cells derived from RA patients or healthy controls (7). Considering that the functional balance of Th17 versus Treg cells is critical for autoimmunity and tolerance, understanding the role of IL-1R2 as a novel regulator helps to comprehend the pathogenesis of Th17-related disorders, such as autoimmunity.

Recently, Ritvo et al. (28) demonstrated that foxp3-expressing follicular Tregs (Tfr) have a higher expression of IL-1R2 and IL-1Ra but a lower expression of IL-1R1 than follicular helper T cells (Tfh). Tfh cells are specialized helper cells for B-cell responses, such as germinal center formation, affinity maturation, and the development of most high-affinity antibodies and memory B cells (88). IL-1 markedly enhances the production of IL-4 and IL-21 by Tfh cells, suggesting a crucial role of IL-1 in T-cell help to B cells. Tfr cells dampen IL-1 signaling by capturing and controlling IL-1-mediated Tfh activation, resulting in the regulation of B-cell response and Ab production (28).

Monocytes/macrophages and others

IL-1R2 exhibits primary expression in specific innate cell types, including monocytes, M2-like macrophages, microglial cells, osteoclasts, and neutrophils. Resting monocytes prominently express IL-1R2 mRNA and its level is notably reduced upon LPS stimulation in a dose-dependent manner, unlike IL-1R1 (72). In patients with familial combined hyperlipidemia, monocytes/macrophages display reduced IL-1R2 expression, and low-density lipoproteins decrease IL-1R2 expression in human THP-1 macrophages (89). Down-regulated IL-1R2 expression in atherosclerosis vascular lesions may contribute to the impaired control of IL-1-mediated inflammation in patients. Conversely, anti-inflammatory signals, including glucocorticoid hormones, prostaglandins, Th2 cell-associated cytokines (IL-4 and IL-13), and IL-27, enhance IL-1R2 expression in human monocytes (90,91) (**Fig. 2**). This suggests that the induction of IL-1R2 contributes to the anti-inflammatory effect of these mediators by tightly and finely regulating IL-1 signaling. In macrophages, the M2 polarizing condition upregulates IL-1R2 expression (92), highlighting the importance of the regulation of IL-1 signal by IL-1R2 in macrophages for the pathogenesis of various inflammatory disorders. Shimizu et al. (93) identified that IL-1R2$^{-/-}$ mice exhibit high susceptibility to collagen-induced arthritis due to enhanced production of inflammatory mediators by IL-1R2$^{-/-}$ macrophages in response to IL-1β.

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Neutrophil abundantly expresses mRNA of IL-1R2 (94). In mice, *ex vivo* $CD11b^+Ly6G^+$ neutrophils and *in vitro*-differentiated $CD11b^+Ly6G^+$ bone marrow-derived granulocytes show higher IL-1R2 expression than other immune cell subsets, and hydrocortisone significantly upregulates its expression (94). Additionally, IL-1R2 expression is augmented by infiltrating neutrophils in *in vivo* models of inflammation, suggesting that neutrophils may contribute to the resolution of acute inflammation (94). A recent study demonstrated that IL-1R2 is specifically expressed on IL-33-induced neutrophils, contributing to allergic inflammatory pathogenesis (**Fig. 2**). Thus, IL-1R2 on the cell surface might serve as a biomarker for N (IL-33) cells, which selectively produce IL-4, IL-5, IL-9, and IL-13 (95).

THERAPEUTICS TARGETING IL-1A/B SIGNALING

Due to its crucial involvement in inflammatory responses, the aberrant regulation of the IL-1/IL-1R complex axis is closely linked to the pathogenesis of numerous disorders, including autoinflammatory diseases like cryopyrin-associated periodic syndromes and familial Mediterranean fever, autoimmune diseases such as RA and ulcerative colitis, as well as other conditions like type 2 diabetes, cancer, and neuroinflammation-associated neurodegenerative diseases (4,46,96,97). Consequently, several therapeutic strategies aimed at modulating the IL-1 signaling by selectively targeting IL-1α, IL-1β, or IL-1R1 have been developed for the treatment of inflammatory diseases. Currently, there is only one Food and Drug Administration (FDA)-approved therapy, Anakinra, which is a recombinant IL-1Ra inhibiting IL-1R1-mediated signaling, and two approved therapeutics, Rilonacept and Canakinumab that neutralize IL-1α/β and IL-1β, respectively.

Anakinra, a recombinant and slightly modified form of IL-1Ra, is one of the earliest developed therapeutics. It competitively inhibits the binding of IL-1α and IL-1β and is the only FDA-approved blocker of IL-1R1-mediated signaling. While it has received FDA approval for the treatment of RA and several autoinflammatory diseases, it is frequently used off-label to manage various inflammatory disorders (4,39,46). Rilonacept, a soluble fusion protein composed of the extracellular domains of IL-1R1 and IL-1R3 linked to the Fc region of human IgG, can neutralize IL-1α/β signaling by acting as a decoy receptor. Its prolonged therapeutic half-life, due to the presence of an IgG Fc region, makes it effective in relieving symptoms of gout and autoinflammatory diseases (98,99). Canakinumab, a monoclonal Ab of the human IgGκ class, is approved for treating various autoinflammatory diseases by neutralizing IL-1β but not IL-1α (4,100). Conversely, Bermekimab (MABp1), a human $IgG_1\kappa$ monoclonal Ab, has recently developed as a novel therapeutic candidate aimed at IL-1α, currently in the phase of clinical evaluation (101,102).

AMG108 (now termed MEDI-78998) is a monoclonal Ab that binds to the extracellular domain of IL-1R1 to inhibit IL-1 binding and block IL-1-mediated signaling. Despite showing promise in preclinical studies for osteoarthritis, it did not demonstrate significant clinical benefits in phase II trials (97). EBI-005 (Isunakinra), a chimeric protein containing domains from IL-1β and IL-1Ra molecules, is a potent inhibitor that binds to IL-1R1 with higher affinity than IL-1β (103). However, phase III clinical trials were halted after EBI-005 failed to meet its primary endpoints. In addition to biological therapeutics, small peptides such as AF10847 and rytvela have been developed to bind to the extracellular region of IL-1R1, acting as allosteric negative modulators of IL-1R1 (96,104,105). Although both membrane-bound and soluble IL-1R2 play important roles in suppressing IL-1-mediated signaling in various inflammatory disorders, IL-1R2-based therapeutics have not yet been reported (97).

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CONCLUSION AND PERSPECTIVES

The IL-1/IL-1R axis stands out as a central player in immune system modulation, necessitating meticulous regulation across various stages, from production to receptor interactions. While considerable attention has been directed toward understanding IL-1α and β production in recent decades, the elucidation of molecular mechanisms governing IL-1R expression in target cells has progressed slowly. The immune system faces a crucial decision in regulating IL-1 signaling, which is pivotal in defending against both external pathogens and internal danger signals. Particularly noteworthy is the profound impact of IL-1β on T-cell immunity including differentiation, effector function, and survival, highlighting the essential need for precise IL-1R signaling regulation to establish an appropriate immune response, as unchecked IL-1 signaling is intricately linked to the development of various inflammatory diseases, including autoimmunity.

Consequently, fine-tuning IL-1R signals in T cells, adapted to specific timing and environmental demands, assumes paramount significance. Recent studies highlight distinct mechanisms employed by $CD4^+$ and $CD8^+$ T cells to dynamically adjust IL-1R1 and/or IL-1R2 levels in response to diverse inflammatory contexts. Various Treg cell types express decoy IL-1R2 to fine-tune IL-1R signaling, promoting appropriate immune responses or resolution of inflammation. Additionally, the upregulation of IL-1R1 in $CD8^+$ T cells, facilitated by cytokines like IL-21, holds promise for protection against viral infections by enhancing CTL effector function, suggesting the rationale for IL-1β-based vaccine adjuvants.

However, despite intensive efforts in developing therapeutic strategies targeting IL-1 directly, concerns persist regarding Ab therapeutics, particularly those aimed at IL-1β, due to significant adverse effects such as severe infections that impede clinical applications. Currently, much of our knowledge about the *in vivo* relevance of IL-1Rs is derived from traditional global gene knockout studies, limiting our comprehension of the precise mechanisms underlying IL-1R actions in disease models. Recently developed cell-specific conditional deletion mouse models for IL-1R1 and IL-1R2 present a new toolbox for exploring the roles of IL-1R in health and disease (106). Further research is imperative to unravel the molecular mechanisms governing cell-specific IL-1R expression in immune cells. Enhanced comprehension of the molecular and functional aspects of IL-1R expression holds promise for identifying potential intervention targets and advancing the development of biological therapeutics targeting IL-1Rs across a spectrum of inflammatory disorders.

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