Regulation of Immunity and Disease by the IL-1 Receptor Family Members IL-1R2 and IL-1R8

Martina Molgora, Domenico Supino, and Cecilia Garlanda

Abstract

Interleukin-1 and other IL-1 family members are key players in immunity and inflammation.

The activation of the IL-1 system is tightly regulated, through ligands with antagonistic or anti-inflammatory activity, or decoy and negative regulatory receptors. IL-1R2 and IL-1R8 (also known as SIGIRR) are members of the ILR family acting as negative regulators of the IL-1 system. IL-1R2 binds IL-1 and the accessory protein IL-1RAcP without activating signaling, thus modulating IL-1 availability for the signaling receptor. IL-1R8 dampens IL-1 receptor- and Toll Like Receptor-mediated cell activation and is a component of the receptor complex recognizing the anti-inflammatory cytokine IL-37.

The deregulated activation of the IL-1 system is the potential cause of detrimental local or systemic inflammatory reactions. Here, we summarize our current understanding of the function of IL-1R2 and IL-1R8, focusing on their role in pathological conditions, ranging from infectious and sterile inflammation, to cancer-related inflammation.

Keywords

Interleukin-1 · Inflammation · Infection · Inflammation-associated cancer

1 Introduction

Innate and adaptive immunity cells are tightly regulated by a plethora of cytokines and receptors. The Interleukin-1 system plays a crucial role in controlling immune responses and inflammatory processes [1, 2]. IL-1 family ligands include 7 molecules with agonist activity (IL-1α, IL-1β, IL-18, IL-33, IL-36α, β, and γ), three receptor antagonists (IL-1Ra, IL-36Ra and IL-38), and an anti-inflammatory cytokine (IL-37). The IL-1R family members include 11 molecules [IL-1R1, IL-1R2, IL-1R3 (IL-1RAcP), IL-1R4 (ST2), IL-1R5 (IL-18Rα), IL-1R6 (IL-1Rrp2, IL-36R), IL-1R7 (IL-18Rβ), IL-1R8 (TIR8, also known as SIGIRR), IL-1R9 (TIGIRR-2), IL-1R10 (TIGIRR-1)] (Fig. 1) [2].

ILRs are characterized by an evolutionarily conserved structure which consists of Ig-like

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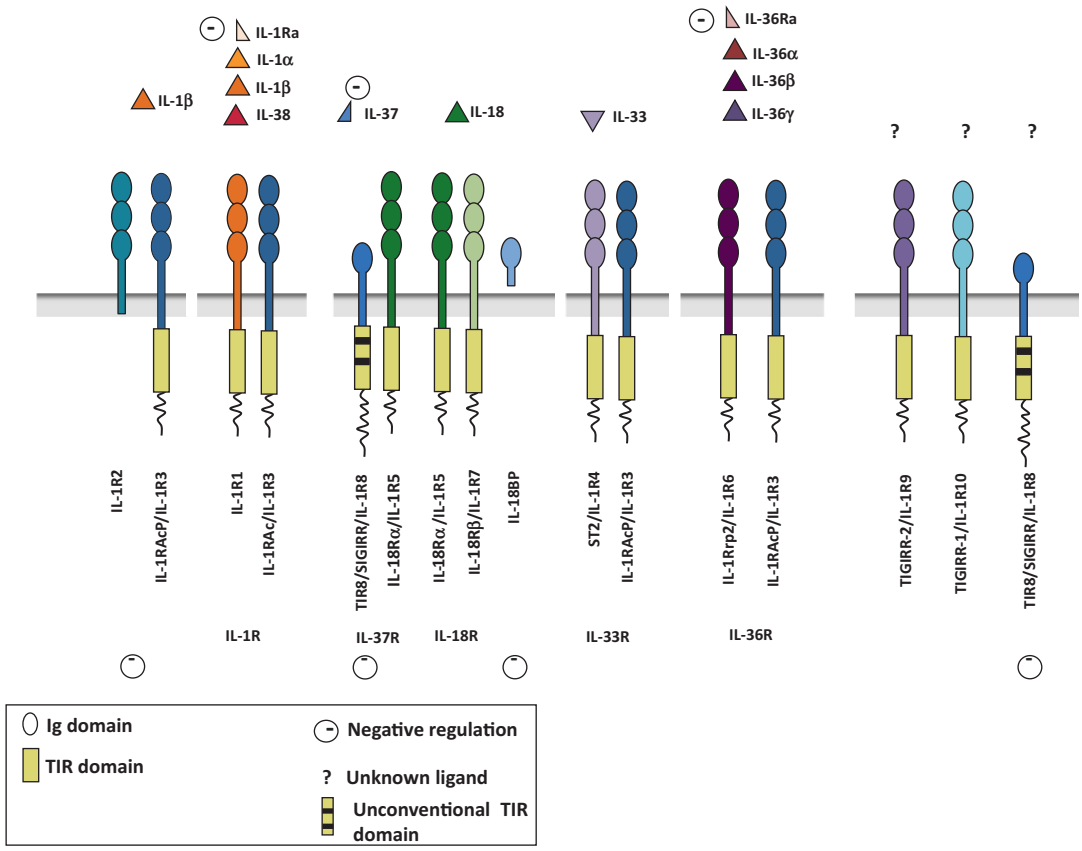

Fig. 1 The IL-1 system Ligands of the IL-1 receptor (ILR) family are shown (IL-1α, IL-1β, IL-38, IL-33, IL-36α, IL-36β, IL-36γ and IL-18). IL-1R, IL-33R, IL-36R and IL-18R complexes activate signal transduction. IL-R2, sIL-1R2, IL-1Ra, IL-36Ra IL-18BP and IL-1R8 are negative regulators acting with different mechanisms. IL-37 is an anti-inflammatory cytokine, signaling upon the formation of a tripartite complex (IL-37/IL-1R5/IL-1R8). IL-1R3 is an accessory protein for IL-R1, IL-1R2, IL-1R4 and IL-1R6. Ligands for IL-1R8, IL-1R9 and IL-1R10 are still partially defined

extracellular domains and an intracellular Toll-IL-1 resistance (TIR) domain, that is shared with Toll-like receptors (TLRs) [3]. Ligand binding induces the dimerization through the TIR domain of the specific receptor with a second receptor molecule, acting as an accessory protein and establishing an intracellular signaling platform, which recruits one of the adaptor proteins MyD88, MAL, TRIF, TRAM or SARM. In turn, these molecular complexes unleash protein kinases activation (e.g. Tumor necrosis factor receptor-associated factor 6 (TRAF6) and IL-1R associated kinases (IRAKs),) and trigger a cohort of downstream targets such as nuclear factor-κB (NFκB), activator protein-1 (AP-1), c-Jun N-terminal kinase (JNK), p38 mitogen-associated protein kinase, extracellular signal-regulated kinases (ERKs), mitogen-activated protein kinases (MAPKs), and interferon (IFN)-regulatory factors (IRF) [4–6]. The modulation of multiple Transcriptional Factors (TFs) orchestrates a robust pro-inflammatory reaction, enforcing both the innate and adaptive immunity [7–9].

The fundamental role of ILR family in inflammation is underlined by a broad spectrum of inflammatory, autoimmune and neoplastic diseases correlated to deregulation of the IL-1 system. For instance, several lines of evidence indicate that IL-1 and its regulation play a pivotal

role in cancer-related inflammation and progressive tissue damages in chronic inflammatory conditions. This link emphasizes the implications of ILR and cytokine targeting as therapeutic strategy in several pathological conditions associated with acute and chronic inflammation, ranging from cardiovascular and autoimmune diseases to cancer [10–16].

The IL-1 system includes several extracellular and intracellular endogenous regulators, which tune ILR signaling and are necessary to restore homeostatic conditions. These "caretakers" are anti-inflammatory cytokines (IL-37, IL-38), receptor antagonists (IL-1Ra, IL-36Ra, and IL-38), scavengers and/or decoy or negative regulatory receptors (e.g. IL-1R2, IL-1R8 and IL-18BP), and miRNAs [17] that tune ILR signaling at transcriptional and post-transcriptional level.

Here, we summarize our current understanding of the structure and function of IL-1R2 and IL-1R8, two negative regulators of inflammation and immune responses, describing their relevance in physiology and pathology.

2 The Decoy Receptor IL-1R2

2.1 IL-1R2 Protein and Function

Human *IL-1R2* is a highly conserved gene localized in chromosome 2, in a large cluster which includes several ILR members such as the receptors for IL-33, IL-18 and IL-36 [18, 19].

IL-1R2 gene encodes an extensively glycosylated 68 kDa protein composed of 386 amino acids. The IL-1R2 extracellular domain has the canonical ILR Ig-like-structure, and shares 28% amino acid homology with IL-1R1. In contrast, the IL-1R2 intracellular domain is peculiar for the absence of a functional TIR domain, which is substituted by a short 29 amino acid-long cytoplasmic tail [20, 21]. Several enzymes, in particular the metalloproteinase ADAM17, cleave the full-length receptor to generate an IL-1R2 soluble form with decoy activity [22–24]. Pro-inflammatory molecules (LPS, TNFα, leukotriene B4, or fMLF) trigger the enzymatic cleavage and the release of soluble IL-1R2 [25–28], which can be also generated by an alternative splicing isoform of the IL-1R2 transcript [29].

IL-1R2 exerts its decoy activity through different mechanisms. First, IL-1R2 sequesters IL-1R3 to generate a dominant negative receptor complex [30], which competes with IL-1R1 for the formation of a signaling receptor complex [31–33]. Second, the IL-1R2/IL-1R3 complex binds IL-1α and IL-1β, without activating the pro-inflammatory signaling cascade [20, 34]. In addition, the soluble form participates in reducing IL-1 availability for the signaling receptor, since soluble IL-1R2 and IL-1R3 are found at high concentration (in the order of ng/ml) in the blood, and their physical interaction increases the affinity for IL-1α and IL-1β [34, 35]. Finally, IL-1R2 is present in the cytoplasm and interacts with pro-IL-1α preventing cleavage and activation by different enzymes (calpain, granzyme B, chymase, and elastase) during necrosis [34–37].

2.2 IL-1R2 Expression and Regulation

IL-1R2 is the predominant IL-1 receptor in the myeloid compartment, in particular monocytes, macrophages and neutrophils, and it is overexpressed in M2 macrophages [20, 34, 38, 39]. In the lymphoid compartment, IL-1R2 shows a high expression level in B cells and in T regulatory cells (Treg) and it is up-regulated upon TCR stimulation [20, 34, 38, 39]. In colorectal and non-small-cell lung cancers, Treg express higher levels of IL-1R2 compared to Th1 and Th17 tumor infiltrating lymphocytes [40]. Similarly, breast cancer infiltrating Tregs express higher IL-1R2 levels compared to healthy breast resident Tregs and circulating Tregs [41]. The functional activity of IL-1R2 in tumor infiltrating Tregs and the molecular mechanisms regulating its expression are still unknown. Interestingly, IL-1β inhibition significantly reduced the risk of incident lung cancer and lung cancer mortality in a large cohort of atherosclerosis patients, suggesting the relevance of IL-1 regulation in cancer [16].

In the mouse, *Il1r2* is widely expressed in innate and adaptive immune cells of myeloid and lymphoid origin [25, 42–50], it is up-regulated by several anti-inflammatory stimuli (e.g. IL-4, IL-13, IL-27, IL-10, glucocorticoid hormones and prostaglandins) [20, 38, 51–56], and down-regulated by pro-inflammatory and chemotactic molecules (e.g. LPS, IFNγ, TNFα, reactive oxygen intermediates and phorbol myristate acetate) [22, 27, 28, 54, 57].

The regulation of IL-1R2 expression on the myeloid compartment has been associated with the pathogenesis of several inflammatory diseases. Atherosclerosis is associated with vessel wall inflammation and IL-1 has long been known to drive atherosclerosis and its complications. Interestingly, reduced expression of IL-1R2 was observed in atherosclerosis vascular lesions, which suggests defective tuning of IL-1 activity [48]. Based on the role of IL-1 in the pathogenesis of cardiovascular diseases, a large prospective study was conducted using anti-IL-1β (Canakinumab) in high-risk atherosclerosis patients, which showed that treatment led to a significantly lower rate of recurrent cardiovascular events [15].

Up-regulation of IL-1R2 in microglia represents a protective mechanism of the central nervous system suppressing IL-1β-mediated brain inflammation and neurotoxicity [45, 46, 58]. IL-1R2 down-regulation has been associated with type II osteoarthritis [59] and correlated to bone resorption upon IL-1 stimulation [47].

The relevance of decoy receptors as fundamental brakes of the immune response is demonstrated by their exploitation by viruses and bacteria as pathogen evasion strategies. For instance, double strand DNA viruses (Poxviruses and Herpesviruses) have acquired decoy receptor genes through genetic recombination with the host genome [60]. In lethal *Listeria monocytogenes* infection, IL-1R2 expression is up-regulated in monocytes [42], and protein A of *Staphylococcus aureus* was shown to induce soluble IL-1R2 by stimulating ADAM17-mediated cleavage, resulting in IL-1β sequestration and decreased bacterial eradication [61].

2.3 IL-1R2 Functional Role In Vivo

Several studies have demonstrated the anti-inflammatory role of IL-1R2 *in vivo*. IL-1R2 deficiency exacerbates endometriosis [62], autoimmune myocarditis [63] and skin inflammation [64], through the inhibition of IL-1 signaling and therefore Th17 cell activation [65].

IL-1R2 deficient mice were also more susceptible to arthritis. In collagen-induced arthritis, IL-1R2-deficient macrophages increased their responsiveness to IL-1 and governed the pro-inflammatory response [59, 66, 67]. In contrast, in the K/BxN serum transfer-induced arthritis, increased joint degeneration has been attributed to neutrophils, through a not cell autonomous mechanism [68]. IL-1R2-deficiency on neutrophils increased the IL-1-induced response of fibroblasts, suggesting that IL-1R2 acts in trans, as soluble form shed upon IL-1β treatment. However, IL-1R2-deficiency did not affect the acute inflammation induced by systemic administration of IL-1β or LPS [64, 68], in contrast with pleiotropic effects of IL-1Ra-deficiency [69, 70].

Recently, it was shown that IL-1R2 was expressed together with the IL-1 receptor antagonist IL-1Ra, by follicular regulatory T (Tfr) cells, which are responsible for the modulation of follicular helper T (Tfh) cell effector functions and therefore B cell activation in the germinal center. IL-1 treatment induced IL-21 and IL-4 production by Tfh cells and this effect was inhibited in the presence of Tfr cells, possibly because of IL-1 capture by IL-1R2 [71].

2.4 IL-1R2 Like Prognostic and Diagnostic Marker

IL-1R2 shedding in pathological conditions has encouraged the studies of IL-1R2 soluble form as diagnostic and prognostic marker. IL-1R2 is released in plasma in physiological conditions (5–10 ng/ml), but its levels are proportionally increased upon infections (acute meningococcal infection, experimental endotoxemia, trauma, necrotizing enterocolitis, acute respiratory

distress syndrome, sepsis) [72]. IL-1R2 soluble form was suggested as biomarker in multiple sclerosis [73] and in Alzheimer's disease [74], whereas in the synovial fluid and plasma of rheumatoid arthritis patients IL-1R2 was correlated with symptom amelioration [75, 76]. Soluble IL-1R2 has been suggested as good prognostic biomarker in pancreas islet transplantation [77] and in inflammatory bowel disease [78] and as biomarker to monitor the clinical outcome of TNFα blockade with Etanercept [79] and in steroid treatment response [80].

Finally, IL-1R2 over-expression has been also observed in psoriatic patients [81] and in several solid tumors such as prostatic cancer, ductal adenocarcinoma [82], benign prostatic hyperplasia [83] and ovarian cancer [84], but the functional implication of IL-1R2 in neoplastic transformation is unknown. In ulcerative colitis, IL-1R2 expression was correlated to remission [78, 85] and to steroid response [80].

3 IL-1R8 (TIR8/SIGIRR)

3.1 IL-1R8 Gene and Protein

IL-1R8 is an antisense gene on human chromosome 11 [86], with three main isoforms that share a common coding DNA sequence. The murine locus is on chromosome 7. The gene is well conserved among vertebrates, and the human IL-1R8 protein has a primary sequence of 414 amino-acid with a high identity score (82%) between human and mouse species [87]. Despite the partial identity with IL-1R1 protein (23%), IL-1R8 has relevant structural differences: the extracellular region of IL-1R8 has only a single Ig domain and the intracellular TIR domain has a long tail of 95 residues. Compared to "canonical" TIR domains, IL-1R8 has two aminoacid substitutions in Ser447 and Tyr536 (switched to Cys222 and Leu305) and the lack of phosphorylation on these two residues influences IL-1R8 signaling activity.

Similarly to IL-1R2, IL-1R8 is N- and O-glycosylated on the extracellular domain, and these post-transcriptional modifications have been described as functionally relevant in a study performed in colon cancer patients (see below) [88].

IL-1R8 is expressed in the majority of epithelial tissues and it is particularly enriched in liver, in kidney and in lymphoid organs. The expression in leukocytes is ubiquitous, showing a higher expression level in NK cells and T lymphocytes, and it is also expressed in platelets [86, 89–91] (Fig. 2).

IL-1R8 was shown to be downregulated upon bacterial infections by *Pseudomonas aeruginosa* [92], or *Toxoplasma gondii* [93], in pyelonephritis induced by *E. coli* [94] and in necrotizing enterocolitis [95]. A reduced expression of IL-1R8 was also observed in acute inflammation, in psoriatic arthritis, in asymptomatic bacteriuria [96, 97], in colitis, and after stimulation with flagellin and LPS *in vivo* and *in vitro* [91, 98–100]. Treatment with LPS was shown to downregulate IL-1R8 in monocytes and neutrophils [98] through the inhibition of SP1 binding on IL-1R8 promoter [98, 101]. However, an increased expression of IL-1R8 was observed in monocytes in sepsis and sterile inflammation and this correlated with a tolerogenic phenotype after LPS and Pam_3CysSK_4 stimulation [102]. Moreover, amyloid β treatment has been proposed to downregulate IL-1R8 in microglia and hippocampal tissue through the transcription factor peroxisome proliferator-activated receptor (PPAR)γ [103]. Other stimuli involved in tuning IL-1R8 are the neuropeptide vasoactive intestinal peptide (VIP), *Lactobacillus jensenii* [104], and bacterial immunogenic molecules [105], which mainly affect myeloid derived cells (macrophages, DC, Langerhans cells).

The deregulation of IL-1R8 has been associated with malignant transformation. In chronic lymphocytic leukemia (CLL), neoplastic B cells showed lower expression of IL-1R8 compared to B cells from healthy donors [106]. Several genes are downregulated through DNA hypermethylation in CLL, but no difference was observed in IL-1R8 methylation. However, treatment with the hypomethylating drug 5-Azacytidine led to IL-1R8 overexpression, suggesting an indirect regulation of IL-1R8 mediated by 5-Azacytidine [106]. IL-1R8 loss of

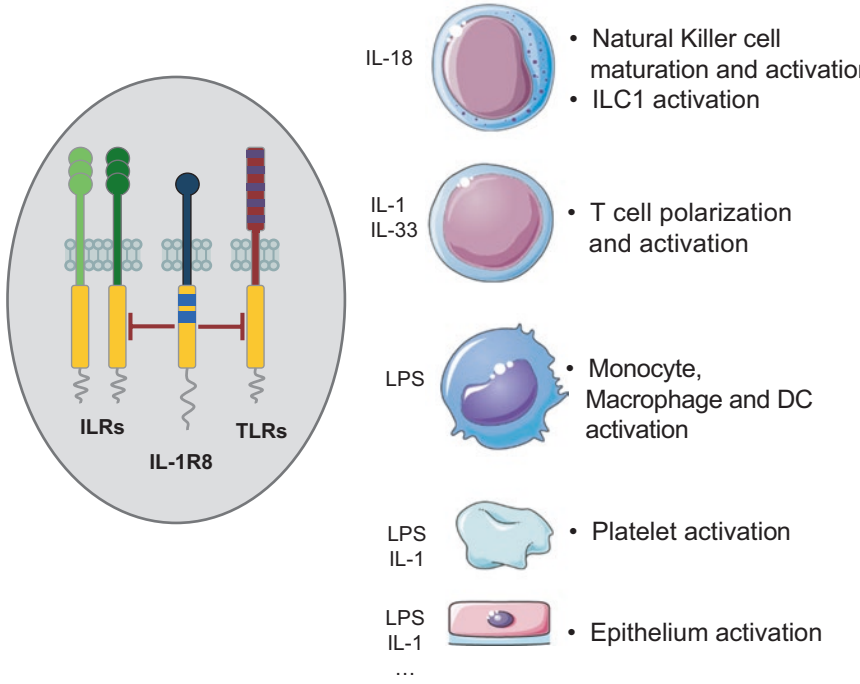

Fig. 2 IL-1R8 functions in different cell types IL-1R8 is widely express in both the hematopoietic and non-hematopoietic compartment and governs cell differentiation and activation. In particular, IL-1R8 modulates NK cell maturation and effector functions; ILC1 activation; T cell activation and polarization; monocyte, macrophage, DC, platelet and epithelium activation, through the negative regulation of IL-1 family members or microbial moieties acting on ILRs and TLRs, respectively

function has been described in colon tumorigenesis, which has been explained with the existence of a dominant negative isoform of IL-1R8, a truncated protein that was shown to trap the main IL-1R8 protein isoform in the endoplasmic reticulum [88]. Finally, RNAseq data and experiments on tumor cell lines showed that IL-1R8 was upregulated in breast cancer [107].

Other IL-1R8 isoforms are emerging, but their function is unknown. Recently a longer isoform called IL-1R8L1 was characterized in tumor epithelial cell lines (e.g. Hela, HT-29 and PC3), in a neuroblastoma cell line (SK-N-HS), in leukemic cell lines (e.g. Jurkat, MEC1, Ramos, Daudi, and THP1), and in human healthy tissues (e.g. hearth, small intestine, kidney, liver, lung, stomach, spleen, ovary, and testis) [108]. LPS stimulation was shown to downregulate IL-1R8L1 in THP1 cell lines, indicating a common regulatory mechanism shared by IL-1R8 isoforms [108].

3.2 Functional Roles of IL-1R8

IL-1R8-deficient mice have demonstrated the role of IL-1R8 in reducing NFκB and JNK activation, inhibiting ILRs and TLRs (e.g. IL-1R1, IL-1R5/IL-18Rα, IL-1R4/ST2, TLR1, TLR2, TLR4, TLR7, TLR9, TLR3) downstream signaling pathways [90, 91, 109–114].

IL-1R8 is recruited to the ligand-receptor complex, and the BB-loop structure of IL-1R8 TIR domain inhibits the dimerization of MyD88 [86, 89, 109, 111, 115, 116]. *In silico* studies of protein modeling have suggested a regulatory mechanism similar to IRAK-M, in which the Myddosome complex is retained on receptors and cannot drive the pro-inflammatory cascade [117]. Furthermore, IL-1R8 extracellular domain inhibits the reciprocal interaction between IL-1R1 and IL-1R3 [111]. The steric competition exerted by IL-1R8 has been also proposed to explain the IL-1R8-mediated regulation of TLR3

signaling, in which IL-1R8 blocks TRAM homodimerization and TLR4-TRAM and TRIF-TRAM interactions [117–119].

The decoy activity of IL-1R8 is also involved in the regulation of JNK and mTOR pathways in lymphoid and not lymphoid cells (e.g. Th17, NK cells and intestinal epithelium) [90, 120, 121].

The deregulation of the IL-1 system is part of pathogen evasion strategies, as mentioned in case of IL-1R2 [122]. Indeed, several bacteria (e.g. *Brucella melitensis*, *E. coli*, *Salmonella enterica*, *Pseudomonas denitrificans* and *P. aeruginosa*) [122–125] have evolved TIR-containing proteins (Tcps) that dampen TIR-related pathway, suggesting that Tcps might be evolutionary linked to IL-1R8.

3.3 IL-1R8 as a Coreceptor of IL-1R5/IL-18Rα for IL-37

In the last decade new anti-inflammatory interleukins involved in controlling TLR pro-inflammatory pathways were identified. In this regard, IL-37 has emerged as a bioactive molecule in leukocytes, in particular in macrophages, and epithelial cells, and IL-37-transgenic mice (IL-37tg mice) were reported to be refractory to inflammation [126]. Intriguingly, the formation of a tripartite complex composed by IL-37, IL-1R8 and IL-1R5 was demonstrated to be required for IL-37 signaling in human PBMCs and murine bone marrow-derived macrophages. This interaction induced an immunosuppressive pathway, inhibiting MAPK, NFκB, mTOR, TAK1 and Fyn, and activating STAT3, Mer, PTEN and p62(dok) signaling [127, 128]. IL-37 mediated protection was abolished by IL-1R8-deficiency in LPS-induced endotoxemia, *A. fumigatus* pulmonary infection [127, 129], and OVA-induced asthma [130].

IL-37 was also implicated in tuning metabolism and in AMPK activation in adipocytes and macrophages [131], with a significant effects on obesity, insulin response and glucose tolerance. In this context, IL-37 and IL-1R5/IL-1R8 receptor complex led to the inhibition of mTOR signaling and activation of STAT6 and Foxo TF family [127], which triggered a pseudo-starvational state in macrophages and DCs. Furthermore, IL-37 was described as a regulatory molecule in muscle cells, orchestrating AMPK pathway and improving exercise performance [132]. At the cellular level, IL-37 potentiated oxidative phosphorylation in mitochondria modulating redox state in the organelles [132]. Finally, recombinant human IL-37 increased muscular resistance in healthy mice and in models of systemic inflammation (upon LPS administration), and IL-1R8-deficiency abrogated IL-37 effects on fatigue tolerance [132]. These lines of experimental evidence support the potential targeting of IL-37/IL-1R8 axis in patients, in which chronic inflammation leaded muscle degeneration and impaired physical mobility [133].

3.4 IL-1R8 in Infections and Inflammation

IL-1R8-deficient mice exhibited an overwhelming local and systemic inflammation and tissue damage after infection with several pathogens (Fig. 3). In fungal infection models such as *Candida albicans* or *Aspergillus fumigatus*, the absence of IL-1R8 led to enhanced susceptibility to mucosal and disseminated or lung infection, respectively, with increased mortality and fungal burden, increased activation of IL-1 signaling and Th17 cell response and reduced Treg activation [134]. In *Mycobacterium tuberculosis* infection, IL-1R8-deficiency was associated with exacerbated inflammation, in terms of macrophage and neutrophil lung infiltration and increased systemic levels of inflammatory cytokines. The higher mortality observed in IL-1R8-deficient mice was prevented by IL-1 and TNFα inhibition and was not dependent on the increased mycobacteria load [135]. In acute lung infections with *P. aeruginosa*, IL-1R8-deficient mice showed deregulation of IL-1 signaling, leading to higher mortality and bacterial load, and increased production of pro-inflammatory cytokines [92]. Moreover, in a model of keratitis induced by *P. aeruginosa*, IL-1R8 was involved in preventing tissue damage, through the negative

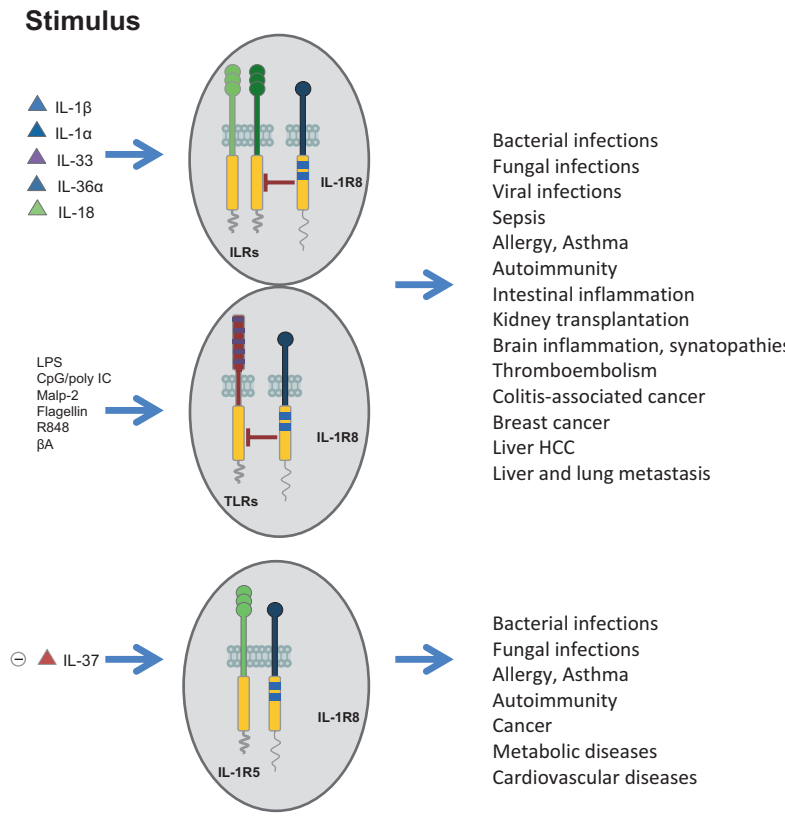

Fig. 3 Roles of IL-1R8 in pathology IL-1R8 emerged as a crucial modulator of inflammation, and innate and adaptive immune responses in several pathological contexts and it is also part of the tripartite complex necessary for IL-37 signaling. IL-1R8 plays a fundamental role in models of infections, autoimmunity, allergy, renal inflammation, platelet activation, brain inflammation and neuronal plasticity, intestinal inflammation and cancer (colorectal cancer, CLL and breast cancer). IL-1R8 acts as a checkpoint molecule regulating NK cell antitumor and antiviral activity

regulation of IL-1R1 and TLR4 signaling in Th1 cells [136]. In humans, 3 SNPs (rs10902158, rs7105848, rs7111432) were identified in the IL-1R8 gene, which correlated with the development of both pulmonary tuberculosis and tuberculous meningitis [137]. Increased susceptibility to LPS-induced mortality was described in IL-1R8-deficient mice on a BALB/c background [109], but not in a mixed C57BL/6 × 129/Sv background [110].

In contrast, IL-1R8-deficiency was protective in a model of experimental urinary tract infection (UTI) induced by uropathogenic *E. coli*, causing reduced renal bacteria outgrowth and renal dysfunction. The initial recruitment of leukocytes in the kidney was increased, in line with increased production of TNFα and chemokines (CXCL1, CCL2 and CCL3) by tubular epithelial cells after stimulation with *E. coli* [94]. In line with this, in a human bladder epithelial cell line (BECs), IL-1R8 silencing was associated with increased JNK, p38 and ERK1/2 activation and IL-6 and IL-8 production, after stimulation with LPS [100]. Similarly, in *Streptococcus pneumoniae* pneumonia and sepsis, IL-1R8-deficiency caused reduced mortality, bacterial outgrowth and dissemination [138].

In *Citrobacter rodentium* infection in mice, that mimics intestinal infections by enteric bacterial pathogens in humans, IL-1R8-deficiency was associated with microbiota depletion, due to enhanced IL-1R1 and MyD88-driven inflammatory and anti-microbial response, and therefore causing exacerbated pathogen colonization [139].

Thus, depending on the effect of inflammatory responses in specific infections, IL-1R8 may play a protective or detrimental role in the innate resistance to pathogens, emerging as a key player in the regulation of the complex and delicate balance between protective immune responses and inflammation and host tissue damage.

3.5 IL-1R8 in Autoimmunity and Allergy

IL-1 family and TLR signaling are involved in the pathogenesis of autoimmune diseases and allergy (Fig. 3). In two different models of arthritis, IL-1R8-deficient mice displayed an higher susceptibility, associated with increased cellular infiltration into the affected joints [140]. In line with this study, IL-1R8 expression was reduced in the peripheral blood of patients with psoriatic arthritis, compared with healthy donors [96]. Moreover, IL-1R8-deficient mice showed enhanced susceptibility to psoriasis, increased infiltration and activation of γδ T cells, and IL-1-driven IL-17A expression by γδ T cells [141]. In experimental autoimmune encephalomyelitis (EAE) IL-1R8-deficient mice developed a more severe disease, due to an increased Th17 infiltrate in the central nervous system (CNS) and enhanced Th17 polarization and pathogenic functions. IL-1R8 was shown to regulate IL-1-dependent Th17 cell differentiation, expansion and effector functions, by controlling IL-1-induced mTOR pathway [120].

In a model of hydrocarbon oil-induced lupus, IL-1R8-deficiency was associated with enhanced TLR7-mediated activation of DCs and expansion of autoreactive lymphocyte clones [142]. In SLE patients, in particular those with nephritis, reduced frequency of IL-1R8^{+} CD4^{+} T cells was reported in [143]. The analysis of IL-1R8 gene allelic variants of a single missense SNP (rs3210908) in a large European population showed no correlation between IL-1R8 polymorphisms and SLE [144], whereas the genetic variants of SNP rs7396562 correlated with the susceptibility to SLE in a Chinese population [145]. In C57BL/6$^{lpr/lpr}$ mice, which develop delayed autoimmunity due to impaired Fas-induced apoptosis of autoreactive B and T cells, the absence of IL-1R8 determined a massive lymphoproliferative disorder, increased autoimmune lung disease, lupus nephritis and hypergammaglobulinemia. The phenotype was associated with increased activation of DCs and B cells and production of proinflammatory cytokines (CCL2, IL-6, and IL-12p40) and B cell antiapoptotic mediators (Baff/BlyS and Bcl-2) in response to RNA and DNA immune complexes or other TLR agonists [146].

In the context of IL-33-dependent allergic responses, IL-1R8-deficient mice showed increased lung inflammation, splenomegaly and serum levels of IL-5 and IL-13 and enhanced production of type 2 cytokines *in vitro* [113]. In contrast, IL-1R8 alleles or haplotypes were not associated with asthma susceptibility or asthma-related conditions in a cohort of Japanese asthma patients [147].

3.6 IL-1R8 in Sterile Inflammation

IL-1R8 is expressed at high levels in the kidney, in particular in tubular epithelial cells, DCs and macrophages [112]. In a postischemic renal failure model, IL-1R8-deficient mice exhibit increased renal injury, caused by a massive activation of myeloid cells, increased intrarenal cytokine and chemokine production and increased leukocyte recruitment [148]. In lupus nephritis, postischemic acute renal failure or kidney transplantation, IL-1R8 expressed by hematopoietic cells was demonstrated to negatively modulate TLR activation by nucleosomes and DAMPs, released during cell necrosis associated with these conditions [142, 146, 148, 149]. In a model of fully mismatched kidney allotransplantation, IL-1R8-deficient grafts were less tolerated compared with control grafts. This phenotype was associated with enhanced allostimulatory activity of DCs and consequently allogeneic adaptive immune responses and increased post transplant kidney inflammatory response, driven by ILR and TLR signaling [149].

3.7 IL-1R8 in the Brain

IL-1R8 is expressed in the brain by neurons, microglia and astrocytes [89, 150, 151] and it regulates LPS- or IL-1-induced neuroinflammation (Fig. 3). IL-1R8-deficient mice exhibited a massive brain inflammation, in terms of CD40, ICAM, IL-6 and TNFα mRNA expres-

sion in microglia and inflammatory cytokine production in hippocampal tissue, upon treatment with LPS [152]. Even in the absence of external stimuli, cognitive and synaptic functions, such as novel object recognition, spatial reference memory, and long-term potentiation (LTP) were impaired. The phenotype was dependent on increased expression of IL-1α and high mobility group box 1 (HMGB1) and enhanced activation of IL-1R1 and TLR4 downstream signaling molecules (IRAK1, c-Jun, JNK and NFκB) [153]. Moreover, IL1R8 negatively regulated the anti-inflammatory activity of IL-36Ra in glial cells [150]. In addition, it was demonstrated that IL-1R8 regulated β-amyloid (Aβ) peptide-induced TLR2 signaling and inflammation in the brain, suggesting a potential role of IL-1R8 in Alzheimer's disease (AD) and AD-associated neuroinflammation [103].

A recent study elucidated the molecular mechanisms underlying cognitive and synaptic function impairment in absence of IL-1R8 [114]. It was shown that IL-1R8-deficiency and the consequent hyperactivation of the IL-1R pathway affected neuron synapse morphology, plasticity and function. Indeed, IL-1R8-deficient hippocampal neurons displayed an increased number of immature, thin spines and a decreased number of mature, mushroom spines along with a significant reduction of spine width, and reduced amplitude of miniature excitatory postsynaptic currents. Spine morphogenesis and plasticity impairment was caused by the IL-1R1-driven hyperactivation of the PI3K/AKT/mTOR pathway in IL-1R8-deficient neurons, leading to and increased expression of methyl-CpG-binding protein 2 (MeCP2), a synaptopathy protein involved in neurological diseases, such as Rett syndrome and MeCP2 duplication syndrome [154]. Pharmacological inhibition of IL-1R1 with IL-1Ra (Anakinra) or IL-1R1 genetic inactivation normalized MeCP2 expression and cognitive deficits in IL-1R8-deficient mice, revealing the key role of IL-1R8 in the fine tuning of IL-1R1 pathway, which is required for correct long-term potentiation [114]. Importantly, in cryopyrin-associated periodic syndrome (CAPS) patients, pharmacological inhibition of IL-1, reversed mental defects of the patients and reduced signs and symptoms of IL-1-dependent inflammation [155]. These results thus identify IL-1R8 as a key molecule involved in synaptopathies through the modulation of IL-1 activity in neurons.

3.8 IL-1R8 in Intestinal Inflammation and Intestinal Cancer

IL-1R8-deficiency is associated with uncontrolled inflammation in the intestine, leading to a reduced survival, weight loss, intestinal bleeding and local tissue injury in the model of dextran sodium sulfate (DSS)-induced colitis [110, 156] (Fig. 3). The phenotype was associated with increased local leukocyte infiltration and higher level of proinflammatory cytokines (TNFα, IL-6, IL-1β, IL-12p40, IL-17), chemokines (CXCL1, CCL2) and prostaglandins [110, 156], and demonstrated the regulatory function of IL-1R8 in epithelial cells.

IL-1R8 was also shown to inhibit the proliferation and survival signals for intestinal epithelial cells in colon crypts, through the regulation of microflora-induced ILR and TLR activation. Indeed, IL-1R8-deficiency was associated with constitutive NFκB and JNK activation and increased expression of Cyclin D1 and Bcl-xL [156]. This phenotype in healthy mice was not confirmed by other studies [110, 157], probably because of animal house-dependent variation of the microflora.

In agreement with the contribution of inflammation in increasing the risk of cancer, IL-1R8 was shown to act as a negative regulator of cancer-related inflammation and therefore cancer development and progression in different murine models of colon cancer. In a model induced by the procarcinogen Azoxymethane (AOM) followed by DSS, IL-1R8-deficiency was associated with increased susceptibility to cancer development, driven by exacerbated intestinal inflammation, as demonstrated by deregulated intestinal permeability, increased *in situ* production of proinflammatory cytokines, chemokines and prostaglandin

E_2 and expression of NFκB-induced genes involved in cell survival and proliferation (Bcl-xL and Cyclin D1) [156, 157]. IL-1R8 overexpression in gut epithelial cells rescued the susceptibility of IL-1R8-deficient mice to colitis-associated cancer development, suggesting that the regulatory activity of IL-1R8 in intestinal epithelial cells plays a central role in this model [156].

In the genetic $Apc^{min/+}$ model, which mimics the Familial Adenomatous Polyposis syndrome [158], IL-1R8 deficiency caused increased susceptibility to cancer development, due to a more sustained activation of the Akt/mTOR pathway, which is involved in cell cycle progression and consequent genetic instability [121].

Interestingly, in human colorectal cancer specimens, IL-1R8 expression was shown to be impaired compared with healthy tissues [88]. Zhao et al. identified a dominant negative isoform of IL-1R8 ($IL\text{-}1R8^{\Delta E8}$), derived from an alternative splicing causing the skipping of the exon 8. $IL\text{-}1R8^{\Delta E8}$ was retained in the cytoplasm, showed reduced N-linked glycosylation, and interacted with full-length IL-1R8, acting as an antagonist and suppressing its function. In agreement, gut epithelium-specific IL-1R8 transgenic mice expressing a mutant form of IL-1R8 ($IL\text{-}1R8^{N85/101S}$) that resembles $IL\text{-}1R8^{\Delta E8}$ isoform showed increased susceptibility to colon cancer. This indicates that IL-1R8 full functionality *in vivo* requires proper post-transcriptional modifications and cell membrane localization [88].

3.9 IL-1R8 in Chronic Lymphocytic Leukemia

TLR and ILR signaling are involved CLL development and progression, together with genetic defects and other microenvironmental contributions [159, 160]. IL-1R8-deficient mice exhibited an earlier and more severe appearance of monoclonal B cell expansion and an increased mortality, in the mouse model of CLL (TCL1), mimicking the aggressive variant of human CLL [161]. In line with these results, human malignant B cells expressed lower levels of IL-1R8 mRNA than normal B cells [160, 162, 163].

3.10 IL-1R8 in Platelets

In a recent study it was shown that both human and murine platelets and megakaryocytes expressed high levels of IL-1R8, which emerged as a key player in the regulation of platelet activation in inflammation and thromboembolism [91] (Fig. 3). Platelets express functional TLRs and IL-1 family receptors (e.g. IL-1R1 and IL-18Rα) [91, 164, 165] and interestingly, IL-1R8-deficiency caused increased platelet/neutrophil aggregate formation, induced by LPS, IL-1β or IL-18 *in vitro* and upon systemic treatment with LPS *in vivo* [91]. IL-1R8-deficient platelets displayed higher active α2bβ3 and P-selectin surface expression in basal conditions, suggesting a hyperactivated phenotype. After *in vitro* stimulation with pro-thrombotic stimuli, $Il1r8^{-/-}$ platelets showed enhanced aggregation amplitude and higher expression of α2bβ3 [91]. Moreover, IL-1R8-deficient mice were more susceptible to ADP-induced pulmonary thromboembolism, as shown by enhanced occlusion of vessels by fibrin clots and systemic levels of soluble P-selectin. IL-1R8-mediated regulation of IL-1 signaling was shown to be responsible for the hyperactivity of platelets in the absence of IL-1R8, since the phenotype was abrogated in $Il1r8^{-/-}/Il1r1^{-/-}$ mice, in line with the reported role of IL-1β in platelet activation [164]. In addition, commensal flora-derived TLR agonists were shown to be also involved in the phenotype, since microflora depletion abrogated the enhanced platelet activation in IL-1R8-deficient mice [91]. In agreement with these results in the mouse, in SIRS/sepsis patients, which exhibit platelet dysfunction [166], IL-1R8 surface expression was significantly downregulated compared to healthy controls and the downregulation correlated with the severity of the disease. Moreover, IL-1R8 expression was shown to be higher in microparticles released from LPS-stimulated platelets or collected from the serum of septic patients compared to controls, suggesting the shedding of the receptor in inflammatory conditions through microparticle release [91]. These results indicate that IL-1R8 contribute to the modulation of platelet activation, aggregation and hetero-aggregation,

both in physiological and pathological conditions *in vitro* and *in vivo*, and unveil a novel function of IL-1R8 in the regulation of thrombocyte function.

3.11 IL-1R8 in Breast Tumors

Tumor recognition and eradication mediated by the immune system can be escaped through various strategies developed by tumors [167]. Recently, we characterize IL-1R8 in breast cancer as a crucial immunomodulatory molecule. Transformed breast epithelial cells upregulated IL-1R8 expression, which was associated with impaired innate immune and T cell response [107] (Fig. 3). IL-1R8 upregulation in breast tumor cell lines led to the inhibition of IL-1-dependent NFκB activation and expression of pro-inflammatory molecules. In agreement, in a genetic model of breast cancer (MMTV-neu), IL-1R8-deficiency was associated with protection from the development of breast lesions and the number of lung metastasis was reduced. *In vitro* and *in vivo* evidences demonstrated that IL-1R8 in tumor cells was responsible for shaping the tumor microenvironment and IL-1R8-deficiency was associated with higher frequency of DCs, NK cells and $CD8^+$ T cells and lower frequency of TAMs [107]. Importantly, RNA sequencing in 1102 clinical samples of breast cancer patients showed that high IL-1R8 expression was associated with a non-T cell inflamed molecular signature, lower expression level of pro-inflammatory cytokines and chemokines, DC and NK cell metagenes, components of the peptide-presenting machinery, cytolytic enzymes and type I IFN-induced genes. Collectively, these data indicate that IL-1R8 emerges as a novel immunomodulatory molecule in breast tumors, affecting the mobilization and activation of immune cells and therefore tumor growth and metastatization [107]. These findings have important therapeutic implications, since the inhibition of IL-1R8 in this context may represent a way to restore the innate immune response and T cell trafficking and activation in the tumor microenvironment.

3.12 IL-1R8 as a Novel Checkpoint in NK Cells

Our group has recently described that IL-1R8 is expressed at high levels in murine and human NK cells and that IL-1R8 expression level increased during NK cell maturation, both in terms of mRNA and protein [90]. IL-1R8-deficient mice displayed a higher frequency and absolute number of NK cells in peripheral blood, higher frequency of mature NK cells ($CD11b^+CD27^-$ and $KLRG1^+$) in blood, spleen, bone marrow and liver. Moreover, IL-1R8-deficient NK cells showed a more active phenotype, in terms of activating receptor expression (NKG2D, DNAM-1, Ly49H), interferon-γ (IFNγ) and granzyme B production, Fas ligand expression and degranulation [90]. Bone marrow chimeric mice and IL-18 depletion experiments demonstrated that IL-1R8 directly acts on NK cells regulating IL-18, which is a key cytokine involved in NK cell activation [168, 169]. RNASeq and protein phosphorylation analysis showed that IL-18 responsiveness was dramatically different in IL-1R8-deficient NK cells, affecting pathways involved in NK cell activation, degranulation, cytokine production and anti-viral response. Moreover, IL-18-dependent activation of mTOR and JNK pathways was enhanced in IL-1R8-deficient NK cells. In contrast, other candidate pathways (i.e. IL-1 and microflora-driven TLR activation) potentially regulated by IL-1R8 in NK cells were not involved in the IL-1R8-deficient NK cell phenotype. In models of DEN-induced hepatocellular carcinoma, MCA-induced lung metastasis and colon cancer-derived liver metastasis, the disease severity and the number and dimension of metastasis were significantly reduced in $Il1r8^{-/-}$ mice. The protection was dependent on IL-1R8-mediated regulation of IL-18 in NK cells, since depletion of NK cells or IL-18-deficiency totally abrogated the phenotype. Finally, in a model of MCMV infection, $Il1r8^{-/-}$ mice controlled the virus more efficiently and the protection was dependent on enhanced NK cell degranulation and IFNγ production. Importantly, the adoptive transfer of $Il1r8^{-/-}$ NK cells was protective in the metastasis and viral infection models, compared to the treatment with $Il1r8^{+/+}$ NK cells. Partial silencing of the molecule

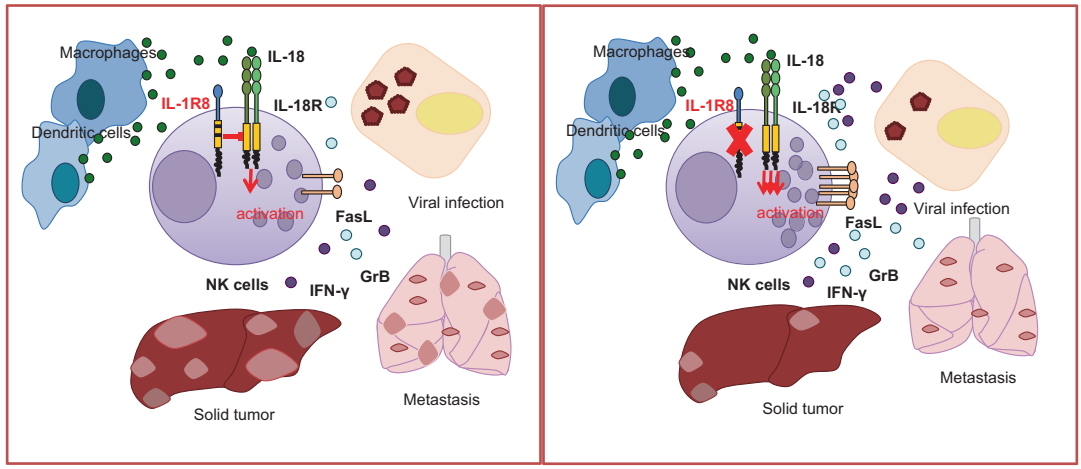

Fig. 4 IL-1R8 as a novel checkpoint of NK cell anti-tumor and anti-viral activity IL-1R8 plays a key role in the regulation of NK cell maturation and effector functions, through the modulation of IL-18-induced signaling pathway. IL-1R8 genetic blockade leads to enhanced NK cell anti-tumor, anti-metastatic and anti-viral activity

demonstrated that also in human IL-1R8 regulates NK cell activation, in terms of IFNγ production and CD69 expression [90].

NK cells are generally not credited to play a major role in the control of solid tumors, whereas evidences suggest that they are involved in the control of metastasis [170–172]. These results indicate that in addition to metastasis, NK cells have the potential to restrain solid tumors upon checkpoint blockade and in NK cell-enriched sites, such as the liver. Thus, IL-1R8 plays a non-redundant role in the regulation of NK cell development and effector functions, by tuning IL-18 signaling and emerges as a novel checkpoint molecule of NK cell antitumoral and antiviral potential [90] (Fig. 4).

4 Concluding Remarks

IL-1 family members are central mediators of the inflammatory process and play a key role in both homeostatic differentiation and activation of immune cells. ILR and TLR pathway activation is crucial for the immune surveillance against infectious agents and sterile damages, but given its broad inflammatory potential it needs to be tightly regulated at different levels. Indeed, the balance of positive and negative regulators, accelerators and brakes is a fundamental concept that governs the delicate equilibrium between host defense and detrimental inflammation leading to tissue damage.

IL-1R8 and IL-1R2 emerge as important regulators in various physiological and pathological conditions and the impairment of their function is an escape mechanism developed by pathogens and tumors. Dissecting their cell-specific and context-specific role is essential for the development and improvement of therapeutic strategies.

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