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Tuning inflammation and immunity by the negative regulators IL-1R2 and IL-1R8

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Abstract

Interleukin-1 receptor family members (ILRs) and Toll Like Receptors (TLRs) are key players in immunity and inflammation and are tightly regulated at different levels. Most cell types, including cells of the innate and adaptive immune system express ILRs and TLRs. In addition, IL-1 family members are emerging as key players in the differentiation and function of innate and adaptive lymphoid cells. IL-1R2 and IL-1R8 (also known as TIR8 or 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 and can be released as a soluble form (sIL-1R2), thus modulating IL-1 availability for the signaling receptor. IL-1R8 dampens ILR- and TLR-mediated cell activation and it is a component of the receptor recognizing human IL-37.

Here, we summarize our current understanding of the structure and function of IL-1R2 and IL-1R8, focusing on their role in different pathological conditions, ranging from infectious and sterile inflammation, to autoimmunity and cancer-related inflammation. We also address the emerging evidence regarding the role of IL-1R8 as a crucial checkpoint molecule in NK cells in anticancer and antiviral activity and the potential therapeutic implications of IL-1R8 blockade in specific pathological contexts.

Keywords

interleukin-1; inflammation; infection; inflammation-associated cancer

Introduction

The IL-1 system is involved in host responses in infections and inflammation, as well as in the activation of innate and adaptive lymphoid cells (1, 2). The system consists in receptors

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and accessory proteins (AcP) and their ligands (IL-1 α and IL-1 β , IL-18, IL-33, IL-36 α , IL-36 β and IL-36 γ) (Fig.1). Interleukin-1 receptor family members (collectively called ILRs) are characterized by the presence of a common intracellular signaling domain, called Toll-IL-1 resistance (TIR) domain, and Ig-like domains in their extracellular part (3). The nomenclature of ILRs has recently been revised (2) and will be used here: IL-1R1 (IL-1RI), IL-1R2 (IL-1RII), IL-1R3 (IL-1RAcP), IL-1R4 (ST2), IL-1R5 (IL-18R α), IL-1R6 (IL-1Rrp2, IL-36R), IL-1R7 (IL-18R β), IL-1R8 (also known as TIR8 or SIGIRR), IL-1R9 (TIGIRR- 2), IL-1R10 (TIGIRR-1) (Fig.1).

Upon ligand binding, ILRs dimerize through their TIR domains, leading to the recruitment of TIR domain containing adapter proteins, in particular MyD88, MAL, TRIF, TRAM and SARM, which activate downstream protein kinases (e.g. IL-1R associated kinases (IRAKs), and tumor necrosis factor receptor-associated factor 6 (TRAF6)). ILR-induced signaling leads to the activation of key transcription factors associated with inflammatory and immune responses, such as nuclear factor- κ B (NF κ B), 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 members of the interferon (IFN)-regulatory factor (IRF) (4–6). Through complex gene transcription activation, the IL-1 system has a primary role in the initiation of an amplification cascade of inflammation and innate responses that contribute to the activation and orientation of adaptive immunity (7–9).

The IL-1 system also comprises a long list of negative regulators, which include ligands with anti-inflammatory activity (IL-37, IL-38), receptor antagonists (IL-1Ra, IL-36Ra, IL-38), decoy receptors (e.g. IL-1R2), scavengers (e.g. IL-1R2 and IL-18BP), dominant negative molecules (IL-1R2) (Fig.1), miRNAs that post-transcriptionally regulate signaling proteins or transcription factors of the IL-1 system (10), signaling molecules (e.g. IRAK-M and MyD88s) and other mechanisms, acting extracellularly or intracellularly. The abundance of these regulatory mechanisms underlines the relevance of the negative regulation of the IL-1 system, which if uncontrolled, may activate detrimental inflammation, cause tissue damage and contribute to autoimmune or allergic responses. For instance, local and systemic inflammation induced by IL-1 are associated with a broad list of diseases, ranging from rheumatic diseases and autoinflammatory syndromes to cardiovascular diseases (e.g. ischemia and reperfusion, atherosclerosis), graft rejection, cancer and infections and sepsis, and targeting of IL-1 family members or their receptors has relevant therapeutic implications (11–15).

Here, we will focus on the decoy receptor IL-1R2, the first decoy receptor identified that served to define the decoy paradigm, and on IL-1R8, a novel negative regulator of inflammatory and adaptive responses, discussing their relevance in different inflammatory or immune-mediated pathological disorders and emphasizing recent discoveries.

1 The decoy receptor IL-1R2

1.1 Gene and protein: structure and function

IL-1R2 gene is highly conserved from bony fish to mammals and is localized in the cluster of IL-1R family members in chromosome 2 (e.g. the receptors for IL-33, IL-18 and IL-36)

(16, 17). The IL-1R2 genomic structure is similar to that coding for the extracellular portion of IL-1R1. However, IL-1R2 differs from all other members of the family for the absence of a TIR domain and for the presence of only a short 29 amino acid-long cytoplasmic tail, and indeed, it does not signal (18, 19). The protein is glycosylated and consists of a 386 amino acid-long protein with a molecular mass of 68 kD and 28% amino acid homology with the extracellular portion of IL-1R1. IL-1R2 also exists as a soluble molecule, generated by enzymatic cleavage, in particular by the metalloproteinase ADAM17 (20–22), after cell stimulation with pro-inflammatory molecules, such as lipopolysaccharide (LPS), TNF α , leukotriene B₄, or fMLF (23–26) or by alternative splicing (27).

The structure of the ligand-receptor complex of IL-1 β /IL-1R2/IL-1R3 is similar to that of the signaling complex (IL-1/IL-1R1/IL-1R3) (28). However, IL-1R2 associated with IL-1R3 binds IL-1 α and IL-1 β with high affinity but does not induce signaling, thus acting as a molecular trap for the agonists of the signaling IL-1R1 (18, 29). IL-1R2 also forms a complex with IL-1 and IL-1R3, exerting a dominant-negative effect by sequestering IL-1R3 (30–32). In addition, soluble IL-1R2, normally present in the circulation at high concentrations, in the order of ng/ml, binds pro-IL-1 β and blocks its processing by caspase-1 (33), as well as IL-1 α and IL-1 β (29, 34). The affinity of soluble IL-1R2 for IL-1 α and IL-1 β is dramatically increased by the soluble form of IL-1R3, which is found at high concentration in the circulation (300 ng/ml in humans) (29, 34). Finally, soluble IL-1R2 is found in the cytosol where it interacts with pro-IL-1 α , preventing its cleavage by different enzymes (calpain, granzyme B, chymase, and elastase), and tuning IL-1 α -dependent sterile-inflammation during necrosis (35, 36). Recent crystallography and small-angle X-ray-scattering studies revealed that there is no obvious charge complementarity at the binding interfaces of IL-1R1 and IL-1R2 in complex with IL-1 β and IL-1Ra, which would support ligand-binding promiscuity of IL-1R1 and IL-1R2 (37).

1.2 IL-1R2 expression

In contrast with IL-1R1 which is widely expressed, in humans IL-1R2 is expressed at very high levels by few cell types, including monocytes, macrophages (in particular IL-4 or IL-13 activated M2 macrophages), neutrophils and B cells, where it is the predominant IL-1 receptor (18, 29, 38, 39). IL-1R2 was shown to be rapidly upregulated in human regulatory T cells (Tregs) and preferentially expressed upon TCR-stimulation, in contrast with other T cell subsets. Accordingly, activated human Tregs displayed IL-1 β neutralizing activity, which suggests a physiological significance for the expression of IL-1R2 on Tregs (40). IL-1R2 expression by Tregs has recently been confirmed by two gene expression studies on tumor associated T lymphocytes. In a study on breast tumor, IL-1R2 was enriched in tumor infiltrating Tregs compared to normal breast parenchyma resident Tregs or peripheral blood Tregs (41). Along the same line, compared with Th1 and Th17 effector lymphocytes, Tregs from colorectal or non-small-cell lung cancers were shown to express high levels of IL-1R2 mRNA and protein, together with several molecules potentially involved in their immunosuppressive role (42). It is presently unknown which are the stimuli responsible for IL-1R2 upregulation and its functional relevance in cancer-associated Tregs.

In the mouse, IL-1R2 is expressed in DC (43), CD4⁺ T cells (44), T regulatory cells (45), monocytes (46), neutrophils (23), and different macrophagic cells, including M2-like macrophages (47), atherosclerosis-associated macrophages (48), microglial cells (49, 50), and osteoclasts (51).

IL-1R2 expression is upregulated by several anti-inflammatory mediators, such as glucocorticoid hormones, prostaglandins, aspirin, Th2 cytokines (IL-4 and IL-13), IL-10 and IL-27 (18, 38, 52–57). In contrast, pro-inflammatory and chemotactic molecules, such as bacterial LPS (58), interferon γ (IFN γ) (55), chemoattractants, reactive oxygen intermediates, TNF α and phorbol myristate acetate (20, 25, 26), inhibit IL-1R2 expression while increasing the expression of the signaling complex, thus preparing the cells to respond to IL-1.

The modulation of the expression of IL-1R2 in cells of the myelomonocytic cell lineage has been proposed to contribute to pathogenesis of several pathological conditions. Acetylated low density (ac-LDL) and very low density (VLDL) lipoproteins negatively regulate IL-1R2 expression in macrophages. In agreement, decreased expression of IL-1R2 was observed in atherosclerosis vascular lesions suggesting defective control of IL-1-dependent inflammation in this condition (48). IL-1R2 is upregulated in the brain by microglial cells in different pathological or inflammatory conditions of the central nervous system, including cerebral ischemia, kainic acid administration and central administration of IL-1 β (59), and has been shown to regulate IL-1 β -dependent brain inflammation and prevent IL-1 β -induced neurotoxicity (49, 50). In osteoclasts, IL-1R2 expression has been correlated to their resorptive activity in response to IL-1 (51). Defective expression of IL-1R2 and of IL-1Ra in osteoarthritic lesions has been associated with the development of the disease (60).

Upregulation of IL-1R2 and other negative regulators in monocytes upon *Listeria monocytogenes* infection has been associated with impaired anti-microbial activity of the infected cells (46). Recently, it was shown that *Staphylococcus aureus* induces IL-1R2 shedding by myeloid cells and that in monocytes the release of IL-1R2 was highly dependent on the expression of protein A, a complex virulence factor, contributing to evasion of immune clearance. *S. aureus* protein A rapidly activated ADAM17 in airway epithelial cells and macrophages, leading to IL-1R2 shedding and consequently reducing IL-1 β availability, therefore negatively modulating the subsequent inflammatory response critical for bacterial eradication during early systemic infection and contributing to the bacterial persistence in blood (61). Thus, IL-1R2 shedding by *S. aureus* would represent a novel mechanism of immune evasion by this microorganism.

After the discovery of IL-1R2 in the early 1990s showing that it acts as a molecular trap for IL-1R1 agonist ligands and the co-receptor IL-1R3, and the formulation of the decoy paradigm, decoy receptors for several cytokines and chemokines have been described, and are now recognized as a general strategy to tune the actions of primary inflammatory mediators. Decoy receptors also represent strategies of evasion from the immune system adopted by viruses. In particular, double strand DNA viruses such as Poxviruses and Herpesviruses have adopted strategies of evasion by acquiring key host genes through genetic recombination and several of these genes code for decoy receptors. For instance, poxviruses have acquired a soluble version of IL-1R, which by binding host IL-1 diminishes

the acute phase response and increases the survival rate of the host, leading to an evolutionary advantage for the virus (62).

1.3 *In vivo* IL-1R2 functional role

The anti-inflammatory role of IL-1R2 was demonstrated in *in vivo* studies, including chronic skin inflammation (63), arthritis (60, 64, 65), endometriosis (66), and heart transplantation (67) or autoimmune myocarditis by blocking IL-1 and inhibiting polarization of Th17 cells (68). Recently, IL-1R2-deficient mice have been generated and the actual *in vivo* role of IL-1R2 was demonstrated in a model of collagen-induced arthritis (69). In mice, IL-1R2 was highly expressed in neutrophils, but no effects of IL-1R2-deficiency were observed in this cell type. In contrast, even if low expression was observed in monocytes and macrophages, the expression of inflammatory mediators in response to IL-1 was greatly enhanced in IL-1R2-deficient macrophages (69). A more recent study, confirmed a major role of IL-1R2 in arthritis, in the K/BxN serum transfer-induced arthritis model (70), in which immune complexes induce the release of IL-1 β from neutrophils. In this arthritis model, IL-1R2-deficiency was associated with a more severe clinical score and local inflammation and higher mRNA levels of the proinflammatory cytokines IL-6 and IL-1 β and chemokines CXCL1 and CXCL2 in the affected joints. In the joints of wild type mice, infiltrating neutrophils were the principal source of IL-1R2 expression. However, *in vitro* studies showed that IL-1R2-deficiency did not affect the functions of neutrophil, such as phagocytosis, ROS production, or cytokine response to IL-1 β , or of other cell types (macrophages, fibroblasts) indicating that the effects of IL-1R2 deficiency was not cell-autonomous. In contrast, 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-1 β treatment. Through this mechanism, IL-1R2 expressed by neutrophils recruited in tissues upon inflammatory stimulation could contribute to dampening and resolving acute inflammation (23).

IL-1R2-deficiency or overexpression were shown to be irrelevant in the control of systemic responses to acute administration of IL-1 β or LPS (63, 70), in contrast with IL-1Ra-deficiency (71, 72), thus indicating that IL-1R2 is mainly involved in regulating local inflammation and that these two negative IL-1 regulators have different roles.

1.5 IL-1R2 as biomarker

Modulation of IL-1R2 expression and release as soluble form has been proposed to reflect the activation of endogenous pathways of negative regulation of inflammation in several human pathological conditions. Plasma levels of soluble IL-1R2 are in the range of 5-10 ng/ml in healthy donors and increase in critically ill patients with infectious conditions such as sepsis, acute meningococcal infection, experimental endotoxemia, operative trauma, necrotizing enterocolitis in preterm infants, and acute respiratory distress syndrome (73), often correlating with the severity of the disease (57, 74, 75). Soluble IL-1R2 was shown to increase in multiple sclerosis patients (76), in the synovial fluid and plasma of rheumatoid arthritis patients, negatively correlating with the severity of disease (77, 78) or in the cerebrospinal fluid of patients with Alzheimer's disease (79). *In vitro* production of soluble IL-1R2 by monocytes was proposed to predict a good clinical response to TNF α blockade

with Etanercept (80). IL-1R2 was also included in a list of biomarkers reflecting islet transplantation outcome: higher levels of soluble IL-1R2 were observed in patients who reached insulin independence after islet transplantation (81).

IL-1R2 is expressed in the healthy skin by basal epithelial cells and is upregulated in psoriatic patients (82). Upregulation of IL-1R2 has been observed in different cancers, such as pancreatic ductal adenocarcinoma (83), prostatic cancer, benign prostatic hyperplasia (84) and ovarian cancer (85), but the functional consequence of IL-1R2 expression in cancer cells has not been addressed yet.

In inflammatory bowel disease, IL-1R2 was identified as one of the candidate genes potentially involved in the pathogenesis of the condition (86), and its expression was correlated to remission in ulcerative colitis (87) and to behave as steroid response biomarker (88).

2 IL-1R8 (TIR8/SIGIRR)

2.1 Gene and protein

IL-1R8 was identified by our group and called TIR8 in 1998 (Accession number: AF113795), and in parallel by John Sims' group in 1999 who called it Single Ig IL-1-related receptor (SIGIRR) (89). IL-1R8 is localized on human chromosome 11 and is composed by ten exons spanning about 11700 bp (89). The murine gene is localized on chromosome 7, and encompasses nine exons spanning about 4000 bp. The human protein is 410 aminoacid-long and is composed of a single extracellular Ig domain, in contrast with the other family members which have three, a transmembrane domain, a cytoplasmic TIR domain and an unusually 95 residues long tail. The lack of two conserved residues (Ser447 and Tyr536), which are replaced by Cys222 and Leu305 in IL-1R8 TIR domain suggests unconventional signaling.

IL-1R8 sequence and expression are highly conserved among vertebrates, from chicken to human (90). Human and murine protein sequences are 82% identical and share 23% overall identity with IL-1R1. The IL-1R8 extracellular domain is extensively N- and O-glycosylated. These post-transcriptional modifications are required for the functional activity of IL-1R8, since a IL-1R8 isoform generated by alternative splicing and lacking N-linked glycosylation was inactive (91).

IL-1R8 is widely expressed in several epithelial tissues, in particular by epithelial cells of the kidney, digestive tract, liver, lung, and in lymphoid organs. Among leukocytes, it is expressed by monocytes, B and T lymphocytes, dendritic cells (DC) and natural killer (NK) cells (89, 92). IL-1R8 mRNA and protein expression are generally reduced in inflammatory conditions, such as ulcerative colitis in humans and colitis in the mouse, intestinal bacterial infections and exposure to flagellin (93, 94), psoriatic arthritis, asymptomatic bacteriuria (95, 96), necrotizing enterocolitis (97), acute lung infection by *Pseudomonas aeruginosa* in mice (98), intestinal infection by *Toxoplasma gondii* (99), in a model of pyelonephritis induced by *E. coli* (100) and *in vitro* stimulation with LPS of human bladder epithelial cells (101). IL-1R8 mRNA and protein were recently detected in platelets. Downregulation of

IL-1R8 protein was observed in platelets derived from septic patients and after *in vitro* stimulation with LPS (102).

In chronic lymphocytic leukemia (CLL), IL-1R8 mRNA and protein expression was reduced compared to B cells from peripheral blood of healthy individuals (103). Treatment of a CLL cell line with the hypomethylating drug 5-Azacytidine restored IL-1R8 mRNA expression, but similar methylation profiles were observed in CLL cases and healthy donors, suggesting that IL-1R8 downregulation might be caused by an aberrant epigenetic regulation in CLL, indirectly affecting IL-1R8 expression (103). Finally, colon tumorigenesis was associated with reduced expression of IL-1R8 on the intestinal cell surface, where an inactive mutant form of IL-1R8 was generated by alternative splicing (91). On the contrary, in breast cancer, IL-1R8 was identified as an upregulated gene in transformed cells compared to normal epithelial cells, in both cell lines and RNASeq data of primary breast tumors (104).

It has been proposed that the zinc finger protein SP1 normally binds to the proximal promoter of IL-1R8 inducing gene transcription in epithelial cells and human primary monocytes and neutrophils (93). Cell stimulation with LPS causes inhibition of SP1 binding to IL-1R8 promoter via activation of p38, which is downstream of TLR4 (93, 105). However, it has been reported that monocytes collected in sepsis and sterile systemic inflammatory conditions expressed enhanced level of IL-1R8 which correlated with reduced TNF α and enhanced IL-10 production in response to LPS and Pam₃CysSK₄ (106).

IL-1R8 was up-regulated in the cornea, macrophages and Langerhans cells of *P. aeruginosa* infected mice, by the neuropeptide vasoactive intestinal peptide (VIP) (107), in DCs of porcine Payer's patch by the probiotic microorganism *Lactobacillus jensenii*, (108), and in murine Payer's patch DCs by LPS (109). IL-1R8 is also expressed in T lymphocytes, with murine Th2 cells displayed higher levels of IL-1R8 compared with Th1 or naïve T cells (110).

Binding sites for the transcription factor peroxisome proliferator-activated receptor (PPAR) γ were identified in the IL-1R8 gene. This pathway was involved in the downregulation of IL-1R8 mRNA in microglia and hippocampal tissue in a model of neuroinflammation caused by amyloid β treatment (111).

Vilia et al. recently identified and cloned a novel long isoform of IL-1R8 (named IL-1R8L1), containing an additional in-frame sequence between the TIR domain and the cytoplasmic tail (112). IL-1R8L1 expression was detected in different leukemic cell lines of monocytic, T or B cell origin (e.g. Jurkat, MEC1, Ramos, Daudi, and THP1), in several tumor cell lines of epithelial origin (e.g. Hela, HT-29 and PC3) or in a neuroblastoma cell line (SK-N-HS) and human tissues (e.g. heart, small intestine, kidney, liver, lung, stomach, spleen, ovary, and testis). In monocytic leukemia cells (THP1) IL-1R8L1 was downregulated upon stimulation with LPS, similarly to the classic isoform, in line with the observations described above (112). The function of IL-1R8L1 is presently unknown.

2.2 Functional roles of IL-1R8

IL-1R8 gene targeting experiments showed that IL-1R8 negatively modulates the activation of IL-1R1, IL-1R5/IL-18R α , IL-1R4/ST2, TLR4, TLR7, TLR9, TLR3 and TLR1/2 leading to inhibition of NF κ B and JNK activation induced by TIR-containing ILRs or TLRs upon ligand binding (102, 110, 113–118) (Fig.2).

The molecular mechanisms underlying the negative regulation of TIR containing IL-1R and TLR family members reported until now include the recruitment of IL-1R8 at the signaling receptor complexes and dampening of signaling by competing with the formation of MyD88 dimers through the TIR domain and in particular its BB-loop, thus reducing the activation of downstream signaling molecules (IRAK and TRAF6) (89, 92, 113, 115, 119, 120). In addition, IL-1R8 extracellular domain was shown to block the dimerization between IL-1R1 and IL-1R3, and to be involved in the inhibition of IL-1R4/ST2 signaling (110, 115). Recent computational studies predicting the three-dimensional structures of TLRs suggested that IL-1R8 inhibits NF κ B activation by preventing the translocation of the signalosome from the receptor and not by blocking the formation of the MyD88-dependent signalosome (121), with a strategy similar to that used by IRAK-M (122). In addition to MyD88-dependent pathway, IL-1R8 was shown to target TRIF-dependent TLR3 signaling, probably by blocking TRAM homodimerization and TLR4-TRAM and TRIF-TRAM interactions (121, 123, 124).

IL-1R8 was also shown to regulate JNK and mTOR phosphorylation in Th17 cells (125) and NK cells (118), and mTOR phosphorylation driven by IL-1 or TLR agonists derived from commensal flora in intestinal epithelial cells (126) (Fig.2). In these cell types IL-1R8 is therefore crucial in the modulation of metabolism, differentiation, cell cycle and effector functions also in homeostatic conditions.

As discussed above, the negative regulation of ILR and TLR signaling represents a strategy of immune evasion adopted by several pathogens, including bacteria (127). TIR-containing proteins (Tcps) able to interfere with TIR-TIR interactions have been found in several bacterial species, including *Brucella melitensis*, *E. coli*, *Salmonella enterica*, *Pseudomonas denitrificans* and *P. aeruginosa* (127–130). These molecules may be evolutionarily related to IL-1R8, sharing the ability to interfere with TIR-containing signaling receptors and adaptor molecules.

2.3 IL-1R8 as a coreceptor of IL-1R5/IL-18R α for IL-37

IL-37 is an anti-inflammatory cytokine that dampens the inflammatory response triggered by TLRs and cytokines in peripheral blood mononuclear cells (PBMCs), in macrophages and epithelial cells. In agreement, IL-37-transgenic mice (IL-37tg mice) are protected in different inflammatory pathological conditions (131). Recently, IL-37 was shown to interact with both IL-1R5/IL-18R α and IL-1R8 in human PBMCs and bone marrow-derived macrophages (BMDMs) of IL-37tg mice upon stimulation with LPS (132), and forming the tripartite complex IL-37/IL-1R5/IL-1R8 following a pro-inflammatory stimulus. This interaction was required for the anti-inflammatory activity of IL-37 both *in vitro* and *in vivo* and triggered multiple signaling events leading to anti-inflammatory responses, such as

inhibition of MAPK, NF κ B, mTOR, TAK1 and Fyn, and activation of STAT3, Mer, PTEN and p62(dok) (132, 133) (Fig.2). Indeed, IL-1R8-deficiency abolished the protection induced by IL-37 transgenic expression or treatment in LPS-induced endotoxemia, *A. fumigatus* pulmonary infection (132, 134), or OVA-induced asthma (135).

IL-37-overexpression is associated with improved response to insulin and glucose tolerance and protection from obesity. In addition, IL-37 activated AMPK in adipocytes and macrophages (136). Since the IL-37/IL-1R5/IL-1R8 axis inhibited mTOR signaling and activated AMPK, STAT6 and transcription factors of the Foxo family (132), these results indicate that IL-37 favors a pseudo-starvational state in macrophages and DCs thus regulating inflammation-dependent modification of cell metabolism through IL-1R8. Recently, Cavalli et al. showed that human IL-37 reversed the metabolic cost of inflammation and improved exercise performance, through the modulation of inflammation and metabolic reprogramming (137). In particular, IL-37 regulated cellular energy homeostasis and metabolism through the direct activation of AMPK in muscle cells, inducing increased mitochondrial respiration, changes in redox state, increased oxidative phosphorylation and reduction of proinflammatory mediators. Treatment with recombinant human IL-37 ameliorated exercise tolerance not only in mice subjected to systemic inflammation, induced by low dose-LPS administration, but also in healthy, unchallenged mice. IL-1R8-deficiency abolished the improvement due to IL-37 treatment, consistently with the requirement of IL-1R8 in IL-37 signaling (137). Given that inflammatory conditions are associated with fatigue and decreased physical activity, this study provides the rationale for targeting IL-37/IL-1R8 axis in patients with chronic inflammatory diseases, in which fatigue is often incapacitating (138).

2.4 IL-1R8 in infections and inflammation

IL-1R8-deficiency in mice was associated with exacerbated local and systemic inflammation and tissue damage in several infection models (Fig.3). In *Mycobacterium tuberculosis* infection, IL-1R8-deficient mice showed an overwhelming inflammatory response, characterized by enhanced macrophage and neutrophil lung infiltration and increased systemic levels of inflammatory cytokines. The increased mortality observed in IL-1R8-deficient mice was not due to enhanced mycobacteria overgrowth and was prevented by IL-1 and TNF α inhibition (139). In acute lung infections by *P. aeruginosa*, IL-1R8-deficiency was associated with increased susceptibility with higher mortality and bacterial load, and increased production of pro-inflammatory cytokines, due to deregulated IL-1 signaling (98). Also in a model of keratitis induced by *P. aeruginosa*, IL-1R8 was shown to regulate IL-1R1 and TLR4 signaling in Th1 cells, and prevent tissue damage (140). In *Candida albicans* or *Aspergillus fumigatus* infections, IL-1R8-deficiency was associated with increased susceptibility to mucosal and disseminated or lung infections, respectively, with increased mortality and fungal burden, enhanced activation of IL-1 signaling and Th17 cell response and reduced Treg activation (141). Increased susceptibility to LPS-induced mortality was described in IL-1R8-deficient mice on a BALB/c background (113), but not in a mixed C57BL/6 $\times$ 129/Sv background (114). In humans, 3 SNPs (rs10902158, rs7105848, rs7111432) in IL-1R8 gene correlated with the development of both pulmonary tuberculosis and tuberculous meningitis (142).

In contrast with these results, IL-1R8-deficiency caused reduced renal bacteria outgrowth and renal dysfunction in a model of experimental urinary tract infection (UTI) induced by uropathogenic *E. coli*. The initial recruitment of leukocytes in the kidney was increased, in agreement with increased production of TNF α and chemokines (CXCL1, CCL2 and CCL3) by tubular epithelial cells after stimulation with *E. coli* (100). Also in a human bladder epithelial cell line (BECs), IL-1R8 silencing caused increased LPS-induced JNK, p38 and ERK1/2 activation and IL-6 and IL-8 production (101). Similarly, in *Streptococcus pneumoniae* pneumonia and sepsis, IL-1R8-deficiency was associated with reduced mortality, bacterial load and dissemination (143).

In *Citrobacter rodentium* infection in mice, that resembles intestinal infections by enteric bacterial pathogens in humans, IL-1R8-deficiency induced an enhanced IL-1R1 and MyD88-dependent pro-inflammatory and anti-microbial response, that was however responsible of microbiota depletion and consequently favored pathogen colonization (144).

Thus, depending on the effect of inflammatory responses in specific infections, IL-1R8 may play beneficial or detrimental role in the innate resistance to pathogens, emerging as a key player in the maintenance of the equilibrium between protective immune responses and inflammation and host injury.

2.5 IL-1R8 in autoimmunity and allergy

ILRs and TLRs are involved in the pathogenesis of autoimmune disorders and allergy (Fig. 3). In this context, IL-1R8 was shown to control IL-1-dependent Th17 cell differentiation, expansion and effector functions. In particular, IL-1-induced mTOR pathway was critical for the IL-1R8-mediated modulation of Th17 response. In agreement, IL-1R8-deficient mice revealed higher susceptibility to experimental autoimmune encephalomyelitis (EAE), due to an increased Th17 infiltrate in the central nervous system (CNS) and enhanced Th17 polarization and pathogenic functions (125).

In two different models of arthritis, IL-1R8-deficient mice developed a more severe disease, which was associated with increased cellular infiltration into the affected joints (145). In agreement with this study, IL-1R8 expression was reduced in the peripheral blood of patients with psoriatic arthritis, compared with healthy donors (95). Moreover, IL-1R8-deficient mice showed enhanced susceptibility to psoriasis, increased infiltration and activation of $\gamma\delta$ T cells, and IL-1-driven IL-17A expression by $\gamma\delta$ T cells (146).

In C57BL/6^{lpr/lpr} mice, which develop delayed autoimmunity due to impaired Fas-induced apoptosis of autoreactive B and T cells, IL-1R8-deficiency caused massive lymphoproliferative disorder, enhanced 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 (147). IL-1R8 was also protective in a model of hydrocarbon oil-induced lupus, in which it modulated TLR7-mediated activation of DCs and expansion of autoreactive lymphocyte clones (148). In humans, reduced frequency of IL-1R8⁺ CD4⁺ T cells was reported in the peripheral blood of SLE patients in particular

those with nephritis, compared with healthy individuals (149). 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 (150), whereas the genetic variants of SNP rs7396562 correlated with the susceptibility to SLE in a Chinese population (151).

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* (110). In contrast with studies in mice, a genetic study on a cohort of Japanese asthma patients revealed that IL-1R8 alleles or haplotypes were not associated with asthma susceptibility or asthma-related conditions (152).

2.6 IL-1R8 in sterile inflammation

High expression of IL-1R8 in the kidney, in particular in tubular epithelial cells, DCs and macrophages (116) prompted studies on its function in this organ. In lupus nephritis, postischemic acute renal failure or kidney transplantation, IL-1R8 expressed by hematopoietic cells was shown to regulate TLR activation by nucleosomes and DAMPs, released during ischemic cell necrosis or associated with these conditions (147, 148, 153, 154). In a postischemic renal failure model, IL-1R8 deficiency was associated with increased renal injury, due to a massive activation of myeloid cells, increased intrarenal cytokine and chemokine production and increased leukocyte recruitment (153). In a mouse model of fully mismatched kidney allotransplantation, IL-1R8-deficient grafts were less tolerated compared with control grafts, showed enhanced ILR- and TLR-driven post transplant kidney inflammatory response, amplified allostimulatory activity of DCs and consequently allogeneic adaptive immune responses (154).

2.7 IL-1R8 in the brain

IL-1R8 is expressed in the brain by neurons, microglia and astrocytes (92, 155, 156) where it regulates LPS- or IL-1-induced inflammation (Fig.3). For instance, IL-1R8-deficiency was associated with a massive LPS-induced brain inflammation and in particular expression of CD40, ICAM, IL-6 and TNF α mRNA expression in microglia and inflammatory cytokine production in hippocampal tissue (157). 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 in IL-1R8-deficient mice. Higher expression of IL-1 α and high mobility group box 1 (HMGB1) and enhanced activation of IL-1R1 and TLR4 downstream signaling molecules (IRAK1, c-Jun, JNK and NF κ B) were responsible of the phenotype (158). In addition, the anti-inflammatory activity of IL-36Ra in glial cells was shown to be IL-1R8-dependent (155). A recent study showed that IL-1R8 acted as a negative regulator of β -amyloid (A β) 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 (111).

Recently, the molecular mechanisms underlying cognitive and synaptic function impairment were elucidated (117). It was shown that genetic hyperactivation of the IL-1R pathway due to IL-1R8-deficiency 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, indicating defective synapse plasticity and function. Hyperactivation of IL-1R1 activation in IL-1R8-deficient neurons was shown to impair spine morphogenesis and plasticity through the PI3K/AKT/mTOR pathway by increasing the expression of methyl-CpG-binding protein 2 (MeCP2), a synaptopathy protein involved in neurological diseases characterized by defective plasticity, impaired cognition and intellectual disability, such as Rett syndrome and MeCP2 duplication syndrome (159). Importantly, pharmacological inhibition of IL-1R1 with IL-1Ra (Anakinra) or IL-1R1 genetic silencing normalized MeCP2 expression and cognitive deficits in IL-1R8-deficient mice, indicating that physiological levels of IL-1R1 activation are required for correct long-term potentiation (117). Interestingly in this context, pharmacological inhibition of IL-1 in cryopyrin-associated periodic syndrome (CAPS) patients, in addition to reduce signs and symptoms of IL-1-dependent inflammation, reversed mental defects of these patients (160). These results thus identify IL-1R8 as a novel molecular player involved in synaptopathies acting by fine tuning IL-1 activity in neurons.

2.8 IL-1R8 in intestinal inflammation and intestinal cancer

IL-1R8-deficiency is associated with exacerbated intestinal inflammation, leading to weight loss, intestinal bleeding, local tissue damage and a reduced survival in the model of dextran sodium sulfate (DSS)-induced colitis (114, 161) (Fig. 3). This phenotype was associated with increased local leukocyte infiltration and higher level of proinflammatory cytokines (TNF α , IL-6, IL-1 β , IL-12p40, IL-17), chemokines (CXCL1, CCL2) and prostaglandins, and was mainly due to the regulatory function of IL-1R8 in epithelial cells (114, 161).

IL-1R8 was also shown to regulate gut microflora-mediated activation of ILRs and TLRs which provides the proliferation and survival signals for intestinal epithelial cells in colon crypts. Indeed, IL-1R8-deficient mice displayed constitutive NF κ B and JNK activation and increased expression of Cyclin D1 and Bcl-xL (161). This phenotype in healthy mice was not confirmed by other studies (114, 162), probably because of the 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 play a protective role in the pathogenesis of cancer-related inflammation in different murine models of colon cancer. In the model induced by the procarcinogen Azoxymethane (AOM) followed by DSS, that mimics intestinal cancer developing in chronic IBD patients, in particular Ulcerative Colitis patients, IL-1R8-deficiency was associated with exacerbated intestinal inflammation and increased susceptibility to cancer development. IL-1R8 negatively regulated intestinal permeability, *in situ* production of proinflammatory cytokines and chemokines and prostaglandin E₂, and the expression of NF κ B-induced genes involved in cell survival and proliferation (Bcl-xL and Cyclin D1) (161, 162). IL-1R8 overexpression in gut epithelial cells abolished 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 (161).

In the genetic $Apc^{min/+}$ model, which mimics the Familial Adenomatous Polyposis syndrome (163), IL-1R8 deficiency led to 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 (126).

In human colorectal cancer, it was shown that IL-1R8 expression is impaired compared with healthy tissues (91). Zhao et al. identified a dominant negative isoform of IL-1R8 (IL-1R8^{E8}) originated from a transcript lacking the exon 8, which 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. Interestingly, gut epithelium-specific IL-1R8 transgenic mice expressing a mutant form of IL-1R8 (IL-1R8^{N85/101S}) that mimics IL-1R8^{E8} isoform were more susceptible to colon cancer, suggesting that complex glycan modifications and cell surface expression are necessary for IL-1R8 functional activity *in vivo* (91).

2.9 IL-1R8 in chronic lymphocytic leukemia

Both genetic defects and microenvironment stimuli, including endogenous TLR or ILR ligands, contribute to CLL development and progression (164, 165). In the mouse model of CLL (TCL1), IL-1R8-deficiency induced an earlier and more severe appearance of monoclonal B cell expansion and a reduced mouse life span, mimicking the aggressive variant of human CLL (166). In agreement with these results in mice, human malignant B cells were shown to express lower levels of IL-1R8 mRNA than normal B cells (165, 167, 168).

2.10 IL-1R8 in platelets

It was recently observed that IL-1R8 is highly expressed in both human and murine platelets and megakaryocytes and plays a key role in the regulation of platelet activation in inflammation and thromboembolism (102) (Fig. 3). In particular, IL-1R8-deficient platelets displayed a hyperactivated phenotype in basal conditions, showing higher active $\alpha 2b\beta 3$ and P-selectin surface expression. Upon *in vitro* stimulation with pro-thrombotic stimuli, $Il1r8^{-/-}$ platelets showed enhanced aggregation amplitude and higher expression of $\alpha 2b\beta 3$ (102). Platelets express functional TLRs and IL-1 family receptors (e.g. IL-1R1 and IL-18R α) (102, 169, 170) and interestingly, IL-1R8-deficiency in platelets was associated with increased platelet/neutrophil aggregate formation, induced by LPS, IL-1 β or IL-18 *in vitro* and in a systemic LPS-induced inflammation model *in vivo* (102). 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. Hyperactivity of platelets in the absence of IL-1R8 was dependent on IL-1 signaling, since the phenotype was abrogated in $Il1r8^{-/-}/Il1r1^{-/-}$ mice, in agreement with the reported role of IL-1 β in platelet activation (169). In addition, microflora depletion abrogated the enhanced platelet activation in IL-1R8-deficient mice, indicating that commensal flora-derived TLR agonists are also involved in the phenotype (102).

Importantly, in patients with SIRS/sepsis, which is associated with platelet dysfunction (171), IL-1R8 surface expression was significantly downregulated compared to healthy controls and the downregulation reflected the severity of the disease. Microparticles released from LPS-stimulated platelets or collected from the serum of septic patients expressed higher levels of IL-1R8 compared to controls, suggesting the shedding of the receptor in inflammatory conditions through microparticle release (102). These results indicate that IL-1R8 is involved in the modulation of platelet activation, aggregation and hetero-aggregation, both in physiological and pathological conditions *in vitro* and *in vivo*, and elucidate a novel function of IL-1R8 in the regulation of thrombocyte function.

2.11 IL-1R8 in breast tumors

Tumors develop various strategies to evade the recognition and eradication mediated by the immune system (172). Recently, we identified IL-1R8 in breast cancer as a crucial immunomodulatory molecule. IL-1R8 expression was upregulated in transformed breast epithelial cells and IL-1R8 upregulation was associated with impaired innate immune sensing and T cell response (104) (Fig. 3). Gene transfer experiments in breast tumor cell lines showed that IL-1R8 upregulation in transformed cells inhibits IL-1-dependent NF κ B activation and expression of pro-inflammatory molecules. IL-1R8-deficient mice were protected from the development of breast cancer in a genetic model (MMTV-neu) 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 (104). In line with this, RNAseq analysis in 1102 clinical samples of breast tumors revealed 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 expression in breast tumors represents a novel immunomodulatory mechanism, affecting the mobilization and activation of immune cells and therefore tumor growth and metastatization (104). These findings have important therapeutic implications, since the blockade of IL-1R8 in breast tumor cells may represent a way to restore the innate immune response and T cell trafficking and activation in the tumor microenvironment.

2.12 IL-1R8 as novel checkpoint in NK cells

Our group has recently described that murine and human NK cells express very high levels of IL-1R8 and that IL-1R8 is acquired during NK cell differentiation, both in terms of mRNA and protein (118). IL-1R8 deficiency was associated with higher frequency and absolute number of mature NK cells in blood, spleen, bone-marrow and liver, higher levels of activating NK cell receptors and increased interferon- γ (IFN γ), granzyme B, Fas ligand expression and degranulation (118). Bone marrow chimeric and mixed chimeric mice experiments demonstrated that IL-1R8 directly acts on NK cells regulating IL-18, which is a key cytokine involved in NK cell activation (173). Indeed, the enhanced NK cell differentiation and activation observed in the absence of IL-1R8 was abrogated upon depletion of IL-18 or in IL-1R8/IL-18 double deficient mice. RNASeq and protein phosphorylation analysis showed that IL-18 responsiveness in NK cells was dramatically

different in IL-1R8-deficient cells, affecting pathways involved in NK cell activation, degranulation, cytokine production and antiviral response. Moreover, IL-18-dependent activation of mTOR and JNK pathways was enhanced in IL-1R8-deficient NK cells (118). To assess the role of IL-1R8 in NK cells in pathology, we examined the anticancer and antiviral resistance. In models of DEN-induced hepatocellular carcinoma, MCA-induced lung metastasis and colon cancer-derived liver metastasis, the liver disease severity and the number and dimension of lung and liver metastasis were significantly reduced in *Il1r8*^{-/-} mice. The protection observed in the absence of IL-1R8 was dependent on IL-1R8-mediated regulation of IL-18 in NK cells, since depletion of NK cells or IL-18 or IL-1R8/IL-18 double deficiency in these models totally abrogated the phenotype (118). Finally, in a model of MCMV infection, *Il1r8*^{-/-} mice controlled the virus more efficiently in liver and the protection was dependent on enhanced NK cell degranulation and IFN γ production (118). 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, suggesting that IL-1R8 blockade in NK cells may represent a novel therapeutic approach to unleash NK cell activity and potentiate antitumor and antiviral resistance (118). In human primary NK cells, we observed an inverse correlation between IL-1R8 expression level and IFN γ production. In addition, partial silencing of the molecule in human primary NK cells demonstrated that IL-1R8 regulates NK cell activation, in terms of IFN γ production and CD69 expression (118).

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 (174–176). These results indicate that 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 (118) (Fig. 3).

Concluding Remarks

Cytokines of the IL-1 family are the key mediators of the inflammatory and innate immune responses and of the orchestration of the development, differentiation and function of innate and adaptive lymphoid cells. However, the members of the IL-1 family are also mediators of immunopathology, including autoimmunity and cancer and their activity need to be tightly regulated. Negative regulatory receptors are indeed essential components for balanced responses to IL-1 family members.

In the case of IL-1R2, its actual relevance *in vivo* has been supported by genetic evidence only in arthritis, and the pharmacological targeting of IL-1R2 has not been developed in the clinic. However, the recent demonstration of its expression by cancer associated Tregs suggests new areas of investigation in the context of cancer immunosuppression.

IL-1R8 acts as an atypical receptor, which negatively modulates ILRs- or TLRs-dependent signaling. Its function has been demonstrated by strong genetic evidence in the mouse in different conditions, and data supporting its relevance in human disease are emerging in the

context of cancer. Pharmacological targeting of IL-1R8 has not been developed yet, however it holds promise of innovative therapies in several pathological conditions.

The IL-1 system and TLR ligands affect all cells of the immune system, as well as epithelial, endothelial and stromal cells. IL-1R8 is expressed by most cell types and recent studies discussed here have elucidated its role in platelet activation, NK cell-dependent anti-tumoral and anti-viral activity and neuronal synapsis plasticity and function, thus further underlying the relevance of fine tuning of the IL-1 system in a multitude of cell types and functions, in homeostasis and disease. In particular, IL-1 family agonists are key molecules in the development and polarization of innate and adaptive lymphoid cells. The recent elucidation of the role of IL-1R8 in tuning IL-18-dependent NK cell maturation and function represents the identification of this molecule as a novel potential checkpoint molecule in innate lymphoid cells.

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Figure 1. The IL-1 system and Toll Like Receptors

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). Microbial compounds (LPS, CpG, poly IC, Flagellin and others), β-amyloid and danger signals are ligands for Toll Like Receptors (TLRs). IL-1R, IL-33R, IL-36R and IL-18R complexes activate signal transduction.

IL-R2, sIL-1R1, 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.

Regulatory function of IL-1R8

Figure 2. Negative regulation exerted by IL-1R8

IL-1R8 comprises a single extracellular domain, a transmembrane domain, a cytoplasmic TIR domain and an unusually long tail (95 residues). The IL-1R8 TIR domain lacks two conserved residues (Ser447 and Tyr536), which are replaced by Cys222 and Leu305 suggesting unconventional signaling. IL-1R8 acts as a negative regulator of ILR and TLR signaling, inhibiting TIR containing receptors and adaptor proteins and thus blocking Akt, JNK, MAPKs, TAK1 and consequently mTOR and NFκB activation.

Figure 3. Roles of IL-1R8 in pathology

IL-1R8 emerged as a key modulator of inflammation, and innate and adaptive immune responses in several pathological contexts. IL-1R8 plays a non-redundant role in models of bacterial and fungal infections, autoimmune diseases, 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.