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Cytokine decoy and scavenger receptors as key regulators of immunity and inflammation

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ABSTRACT

IL-1R2 was the first decoy receptor to be described. Subsequently receptors which act as pure decoys or scavengers or trigger dampening of cytokine signaling have been described for cytokines and chemokines. Here we review the current understanding of the mode of action and significance in pathology of the chemokine atypical receptor ACKR2, the IL-1 decoy receptor IL-1R2 and the atypical IL-1 receptor family IL-1R8. Decoy and scavenger receptors with no or atypical signaling have emerged as a general strategy conserved in evolution to tune the action of cytokines, chemokines and growth factors.

1. Introduction

Cytokines are the key mediators of the inflammatory response being responsible for the recruitment to the inflammatory site and immune cell activation. Cytokines are also orchestrating the correct development of the adaptive immune response determining immune response polarization, tolerance and memory [1].

Cytokine activity need to be tight regulated for the correct development of the immune response. Indeed the robust responses necessary to fight pathogens need to be controlled for the termination of immune responses to avoid inflammation-induced tissue damage and autoimmunity. Several mechanisms of negative regulation of the cytokine system have been described acting both at transcriptional and post transcriptional levels. One of these latter mechanism of regulation is represented by cytokine receptors that have been called decoys. The concept of a "receptor" was originally formulated by Langley in the '20 s. It includes ligand recognition with high specificity and signaling, or being part of a recognition and signaling concept. Decoy receptors are able to recognize certain inflammatory cytokines with high affinity and specificity, but are structurally incapable of signaling or they signal through pathways different to the canonical receptors with whom they share ligands. They are negative regulators because they act as molecular traps for the agonist and for signaling receptor components or they function as scavenger receptor driving cytokines to intracellular degradative compartments [2].

The first decoy receptor identified was the interleukin-1 type II receptor (IL-1RII or IL-1R2) [3] and subsequently decoy receptors have been identified in many cytokine receptor families such as the tumor necrosis factor receptor (TNFR), IL-1R, IL-10R and IL-6R families. Moreover, atypical receptors with scavenger function have been identified in the chemokine system. Therefore, the use of decoy and scavenger receptors is a general strategy of regulation of primary pro-inflammatory cytokines and chemokines to fine-tune and regulate innate and adaptive immunity [4].

2. Decoy and scavenger receptors in the chemokine system

Chemokines are cytokines mainly involved in leukocyte chemoattraction acting through a distinct family of G protein coupled receptors (GPCR) [5]. Among chemokine receptors both functional and structural decoy receptors that negatively regulate chemokine function have been identified.

Under exposure to pro- and anti-inflammatory stimuli, inflammatory chemokine receptors (such as CCR2) can become functional decoy receptors meaning that they are unable to elicit migration while they are still able to sequester and scavenge inflammatory chemokines. These functional decoy receptors are uncoupled from

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G proteins while maintain the ability to internalize and degrade the ligand promoting the resolution of the inflammation [6]. The precise mechanism by which this uncoupling is happening was not fully investigated, but several negative regulators of G protein signaling have been found [7].

Soluble and seven-transmembrane domain chemokine decoy receptors have been found in virus and parasites and represent an important strategy to modulate leukocyte recruitment and subvert the immune response of the host [4].

In addition a subgroup of structural decoy chemokine receptors called atypical chemokine receptors (ACKRs) have been identified in vertebrate genomes [8]. They are supposed to be evolved from canonical chemokine receptors from which they differ especially in the aminoacid composition of intracellular motifs relevant for signal transduction [9].

ACKRs, upon ligand engagement, do not elicit migration or conventional signaling responses. Indeed they are unable to couple to G proteins while they are still able to activate other intracellular pathways such as β-arrestin dependent ones. ACKRs regulate inflammatory and immune reactions in several ways, including by acting as decoy receptors and scavenger receptors that modulate chemokine bioavailability by transporting chemokines to intracellular degradative compartments or, in the case of polarized cells, to the opposite side of the cell monolayer. ACKRs can also modulate the chemokine system by regulating the expression or signaling of other canonical chemokine receptors [10]. These receptors are now officially nomenclated and the ACKR subfamily includes: ACKR1, previously called Duffy Antigen Receptor for Chemokines (DARC); ACKR2, also known as D6 or CCBP2; ACKR3, also called CXC-chemokine receptor 7 (CXCR7) or RDC1; ACKR4, previously called CC-chemokine receptor-like 1 (CCRL1) and also known as CCX-CKR. Two other molecules (CCRL2 and PITPNM3) could be included in the ACKR family with the names 'ACKR5' and 'ACKR6' [11].

In the last years we have focused our attention on one of these receptors, ACKR2, and we have contributed in the characterization of its function as a negative regulator of inflammation. Here we will describe in details ACKR2 structure and function.

2.1. ACKR2 (D6 or CCBP2)

ACKR2 was cloned in 1997 by two groups [12,13]. ACKR2 is able to bind almost all inflammatory CC chemokines, ligands of the canonical chemokine receptors from CCR1 to CCR5 [14]. In humans the ACKR2 gene is located on chromosome 3p21.3, a region that includes a cluster of chemokine receptor genes. It shares high homology sequence with CC chemokine receptors but having selected mutations in the intracellular motifs important for signal transduction [9]. In particular both murine and human D6 lacked the canonical DRYLAIV motif, which was found in all other cloned chemokine receptors and is important for G protein signaling and migration. We therefore to set out to test the hypothesis that ACKR2/D6 was a decoy receptor [15].

ACKR2 is a constitutively internalizing receptor and in steady state most of the molecules are present in intracellular recycling compartment. After ligand binding ACKR2 does not induce leukocyte migration while it activates a β arrestin-dependent pathway that increases the number of receptors on the cell surface to optimize chemokine uptake and delivery to lysosomal compartments [16,17] (Fig. 1). For this reason ACKR2 is not a pure decoy receptor because it is able to drive an intracellular signaling that is devoted to the optimization of its scavenger function. This property appear to be shared by the 4 ACKRs.

ACKR2 is expressed by lymphatic endothelial cell [18], by trophoblasts in the placenta [19] and by some leukocytes such as alveolar macrophages [20] and innate-like B cells [21].

ACKR2 KO mice have increased number of circulating inflammatory monocytes [22] and defects in lymphatic vessel density and function [23] compared to WT mice. When challenged with inflammatory stimuli ACKR2 KO exhibit exacerbated inflammatory reactions in barrier tissues such as the skin, lung, gut and placenta that result in worse pathology [10]. ACKR2 KO have also defect in cardiac remodelling after myocardial infarction [24] and are not able to control infectious diseases such as Mycobacterium tuberculosis [25]. All these phenotypes found in ACKR2 KO mice are mainly reconducted to lack of chemokine clearance, increased infiltration of inflammatory cells and lack of inflammation resolution. In addition it was found that ACKR2 expressed by leukocytes restrict their inflammatory phenotype by inhibiting neutrophil migration [26,27] and regulating macrophage cytokine production and efferocytosis [28].

Finally, in the cancer context ACKR2 acts as a tumor suppressor gene inhibiting inflammation that fuel cancer in mouse models of chemically induced skin tumors [29] and in colon cancer [30]. In Kaposi sarcoma ACKR2 is expressed by tumor spindle cells and is downregulated in more advanced states by the oncogenic pathway KRas/Braf/MEK/ERK [31].

Unexpectedly it was found that ACKR2 deletion can be protective in several disease models that often involve adaptive immunity: ACKR2 KO mice are resistant to experimental autoimmune encephalomyelitis ([32]), have reduced graft versus host disease (GVHD) [22] and reduced renal inflammation in a model of diabetic nephropathy [33]. This protection to autoimmune or immune mediated diseases was explained by a defect in dendritic cell migration or increased myeloid derived suppressor cells. It has to be underlined that Hansell et al. have recently reported that in four models of autoimmune diseases ACKR2 KO mice are not protected by disease development, not confirming previously published papers. They have also found that lack of ACKR2 is not affecting T cell priming while increased interleukin-17 (IL-17) production [27].

All these data indicate that considering ACKR2 only as an anti-inflammatory molecule can be overly simplistic. Indeed ACKR2 is able to scavenge CC chemokines such as CCL17 and CCL22 that are able to recruit Th2 and Treg cells and are important in the generation of chronic immune responses [14]. For this reason, ACKR2 deletion or inhibition could produce complex results depending on the pathological context.

Few data are available on the expression and regulation of ACKR2 in humans. In the preeclampatic placentas ACKR2 expression is lower than in normal placentas [34]. Elevated ACKR2 expression was found in skin of psoriatic patients around psoriatic plaques and in patients' peripheral blood leukocytes [35]. ACKR2 was also expressed by human vascular tumors and in Kaposi sarcoma were a negative correlation was found with disease progression rate [31]. Finally ACKR2 is expressed by human colon carcinomas and its downregulation correlates to more invasive tumors [36].

3. Decoy receptors of the IL-1 system

The IL-1 system is involved in protective host responses in infections and inflammation, as well as in the activation of innate and adaptive lymphoid cells [37,38]. The deregulated or excessive activation of these receptors is the potential cause of dangerous and detrimental local or systemic inflammatory reactions, as well as autoimmune or allergic responses. The system consists in receptors (collectively called ILR) and accessory proteins (AcP) and their ligands (IL-1α and IL-1β, IL-18, IL-33, IL-36α, IL-36β and IL-36γ), as well as negative regulators, which include antagonists (IL-1Ra, IL-36Ra), decoy receptors (e.g. IL-1R2), scavengers (e.g. IL-1R2

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