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Survey

Structures and biological functions of IL-31 and IL-31 receptors

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Abstract

Interleukin-31, produced mainly by activated $CD4^+$ T cells, is a newly discovered member of the gp130/IL-6 cytokine family. Unlike all the other family members, IL-31 does not engage gp130. Its receptor heterodimer consists of a unique gp130-like receptor chain IL-31RA, and the receptor subunit OSMRβ that is shared with another family member oncostatin M (OSM). Binding of IL-31 to its receptor activates Jak/STAT, PI3K/AKT and MAPK pathways. IL-31 acts on a broad range of immune- and non-immune cells and therefore possesses potential pleiotropic physiological functions, including regulating hematopoiesis and immune response, causing inflammatory bowel disease, airway hypersensitivity and dermatitis. This review summarizes the recent findings on the biological characterization and physiological roles of IL-31 and its receptors.

Keywords: IL-31; Receptors; Biological function; Immunological regulation

Contents

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1. Introduction

IL-31 is a recently discovered helical cytokine [1], belonging to the gp130/IL-6 cytokine family that includes IL-6, viral IL-6, IL-11, IL-27 [2], leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC) [3,4] (also reported as neurotrophin-1 (NNT-1)/B cell-stimulating factor-3 (BSF-3) [5]), and neuropoietin (NP) [6]. All the members of this family share the common chain of glycoprotein 130 (gp130) in their multi-unit receptor complexes (except for IL-31 that uses gp130-like receptor [7]), and are involved in a variety of fundamental physiological processes, such as neuronal growth, bone metabolism, cardiac development, and immune regulation [8]. Members of this family share very low sequence homology, and consequently the identification of novel family members has proved challenging. The receptors for IL-6 family are type I receptors, and they share a number of common structural motifs, such as the cytokine-binding domain with two pairs of conserved cysteine residues and a WSXWS sequence motif in the extracellular domain. Novel receptors are therefore more readily identified and they have been utilized as a means to uncover new members of the gp130/IL-6 cytokine family. IL-31 was identified following the discovery of its receptor, IL-31RA [1] (also named as GLM-R [9] or GPL [7]). IL-31 is expressed preferentially by activated Th2 $CD4^+$ T cells, signaling through a heterodimeric receptor complex composed of IL-31RA and OSMRβ [1]. Its pleiotropic effects on the immune system are just beginning to be examined.

2. Discovery of IL-31 and IL-31 receptors

The gene encoding human IL-31 is located on chromosome 12q24.31 and the mouse ortholog is situated in a syntenic region of chromosome 5. The IL-31 cDNA is composed of an open reading frame encoding a 164 amino acid (aa) precursor and a predicted 141 aa mature polypeptide containing the four α-helix structure [1]. Based on overall length and secondary structure, IL-31 is suggested to belong to the short-chain cytokine group, although it has no apparent sequence homology to other known four helical-bundle cytokines [1,10]. At amino acid level, mature mouse IL-31 protein shares 31% identity with its human counterpart [1]. However, there is no cross-species activity, i.e., mouse IL-31 fails to interact with human IL-31 receptor and vice versa [11]. Dillon et al. cloned IL-31 gene using a functional cloning approach, based on the proliferation of cells bearing the novel IL-31RA and other known receptors of the gp130 family [1]. IL-31 mRNA is preferentially but not exclusively expressed by Th2 $CD4^+$ T cells after activation [1], and by skin-homing $CD45RO^+$ (memory) cutaneous lymphocyte-associated antigen (CLA)-positive T cells in patients with atopic dermatitis [12]. IL-31 mRNA was also found in testis, bone marrow, skeletal muscle, kidney, colon, thymus, small intestine, trachea [1] and dorsal root ganglia [13].

IL-31RA is a novel type I cytokine receptor that mediates IL-31 signaling when coupled with OSMR [1]. The IL-31R was discovered independently by three research groups using bioinformatic tools to search gene databases for novel cytokine receptors that share the conserved structural motifs of a type I cytokine receptor. Ghilardi et al. scanned the public database for putative cytokine receptors and a cDNA encoding full-length human gp130-like monocyte receptor (GLM-R) was subsequently cloned from a pooled tissue cDNA library. Murine GLM-R was obtained by a combination of cross-species library screening and PCR cloning from a murine spleen cDNA library [9].

Diveu et al. used gp130 cDNA sequence to screen the human genomic database at NCBI. cDNAs encoding a novel cytokine receptor were isolated from the U937 myelomonocytic and the GO-G-UVM glioblastoma cell lines. According to its homology to gp130, this novel cytokine receptor was named gp130-like receptor (GPL) [7].

When searching the translated human genomic sequence database with known cytokine receptor sequence, Dillon et al. identified an exon encoding part of a leukemia inhibitory factor receptor-like (LIFR-like) cytokine receptor. Subsequent cDNA cloning from activated peripheral blood mononuclear cells (PBMC) produced four splice variants of a type 1 cytokine receptor, which were later named as IL-31RAv1–v4. They also isolated two splice variants of mouse IL-31RA from a mouse testis cDNA library [1]. Next, Dillon et al. constructed a series of BaF3 cell lines expressing human IL-31RA alone or in combination with gp130, IL-12Rβ1, IL-12Rβ2, IL-27RA (WSX-1), IL-23R or OSMR. They assayed each cell line for proliferation in response to conditioned media from activated human peripheral T cells or from an activated T cell line CCRFCEM, and found that only the cells expressing GPL together with OSMR were able to proliferate in response to a soluble factor in the conditioned media, which was identified to be IL-31. Furthermore, the addition of an anti-OSMR antibody to the cultures abrogated the proliferation of BaF3 cells in response to IL-31 [1]. Hence, the functional receptor complex for IL-31 is composed of IL-31RA and OSMR.

3. Characterization of IL-31 receptors

IL-31RA belongs to the gp130-subfamily of type I cytokine receptors. It displays 28% amino acid identity with the common receptor component glycoprotein 130 (gp130) shared by the IL-6 family of cytokines, but lacks the Ig-like domain present at the N-terminus of gp130 [1,7,9]. Human IL-31RA gene is located on 5q11.2, only 24 kb downstream of gp130, with opposite transcriptional orientations to each other [7,9]. To date, IL-31 receptor exists in several different