IL21R (interleukin 21 receptor)

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Identity

Other names: IL-21R, MGC10967, NILR
HGNC (Hugo): IL21R
Location: 16p12.1
Local order: The human IL21R gene maps on 16p11 between the IL4R and the GTF3C1 loci.
Note: The gene for interleukin 21 receptor is the partner of BCL6 in t(3;16)(q27;p11) translocation, which is recurrently observed in diffuse large B-cell lymphoma (Ueda, 2002).

DNA/RNA

Description
The IL21R gene is comprised of 9 exons (+2 alternative first exons), spanning 48.4kb on chromosome 16p11 (Parrish-Novak, 2000).

The human IL21R promoter region, contained within nucleotides -789 to +195 (relative to the start of exon 1a) induces the high levels of transcription in reporter assays (Ueda, 2002). A critical SP1 binding site is contained in the region from -80 to -20 and is essential for gene expression in human T cells (Wu, 2005). The DNA region (12MB) containing the IL21R gene contains multiple copies of large, duplicated segments (duplicons) originating in other regions of the genome (Loftus, 1999), which may predispose to additional duplications or deletions.

Transcription
Three alternatively spliced transcript variants of 3248, 3361 and 3263 bp, each comprising 9 exons, have been described. They differ only for the alternative usage of a different first exon, which is contained within the 5' UTR region. Therefore these transcript variants encode for the same protein.

Diagram of IL21R gene organization and of the encoded transcripts. The IL21R gene is comprised of 11 exons and encodes for three alternatively spliced transcript variants that use a different first exon. As the first exon is contained within the 5' UTR region the three transcripts encode for the same protein.
**Protein**

The IL21R complex

The IL21R requires interaction with the common-gamma chain (γc) for mediating signal transduction upon IL21 binding. The tyrosine kinases JAK1 and JAK3 associate with the receptor complex and mediate receptor chain phosphorylation, recruitment and activation of downstream STAT1 and STAT3 molecules.

**Description**

The IL21R gene encodes for a 538 aminoacid precursor protein with a 19 aminoacid signal peptide. The mature IL21R protein is a transmembrane glycoprotein with a molecular mass of approximately 75 kDa. IL21R is a type I cytokine receptor with an extracellular domain involved in cytokine binding, which contains one copy of the conserved WSXWS (Trp-Ser-X-Trp-Ser) motif, two fibronectin type-III domains of about 100 amino acids each, and conserved cysteine residues (Parrish-Novak, 2000). IL21R has a transmembrane domain followed by a large intracellular domain that contains the Box 1 and Box 2 elements shown to be important in signal transduction, and six tyrosine residues. The IL-21R also displays a consensus motif for STAT3 binding in its C-terminal tail. IL21R forms a heterodimeric receptor complex with the common gamma-chain (CD132) (Asao, 2001), which is also shared as subunit by the receptors for interleukin 2, interleukin 4, interleukin 7, interleukin 9, and interleukin 15.

**Expression**

IL21R is expressed on normal B, T and NK lymphoid cells and also on monocyte/macrophages and dendritic cells. It is of note that also certain lymphoid neoplasias, such as multiple myeloma, Hodgkin's and non-Hodgkin's lymphomas, B-chronic lymphocytic leukemia and acute T cell leukemia express IL21R.

IL21R expression has been reported on other non-immune cell types such as intestinal epithelium in inflammatory bowel disease (Caruso, 2007a), gastric epithelium in Helicobacter pylori infection (Caruso 2007b) and rheumatoid synovium (Junge, 2004).

**Localisation**

IL21R protein is localized at the cell membrane.

**Function**

The IL21R mediates the pleiotropic biological activities of IL21, the lastly identified member of the IL2 family (Parrish-Novak, 2000). IL21 co-stimulates mature T and B cell proliferation and differentiation and also potentiate NK cytolytic functions, inducing NK terminal differentiation (Kasaian, 2002). IL21 also promotes proliferation, cytotoxic function and IFN-gamma production by murine and human CD8+ effector T cells (Parrish-Novak, 2000; Strengell, 2003; Di Carlo 2004). IL21R signaling may mediate B cell proliferation and survival or B-cell apoptosis, in relationship to the activation status of the B cells (Ozaki, 2004; Metha, 2003; Jiu, 2004). Mice deficient of IL21R (IL21R -/-) show defects in antibody production (in particular decreased IgG1 and increased IgE production in response to antigen stimulation) and reduced CTL responses, although their CD8+ T cell numbers are normal (Ozaki, 2002). The IL21R system is also a regulator of Th17 development and activity (Wei, 2007).

The IL21R/common gamma chain complex, upon engagement of its specific ligand IL21, mediates signal transduction through the activation of downstream signaling molecules. These include the tyrosine kinases JAK1 and JAK3, which phosphorylate STAT1 and STAT3 (Zeng, 2007; de Totero, 2008). Differently from IL2 and IL15, which also use the common gamma chain and JAK3 for signaling and are strong inducers of STAT5 activation, IL21 is a weak inducer of STAT5 activation.

IL21R signaling also leads to weak activation of both the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase pathways (PI3K) (Zeng, 2007).

**Homology**

IL21R displays structural homologies with other members of the type I cytokine receptor family, such as the IL2Rbeta chain (29% identity, 46% similarity), IL9R, IL4R and IL7R. It has been initially described as an orphan cytokine receptor, structurally related to the IL2Rbeta (Parrish-Novak, 2000; Ozaki, 2000).

**Mutations**

**Note**

Not yet described.

Genetic polymorphisms of IL21R have been described (Heckert, 2003). The IL21 variant bearing the (T-83C) genetic polymorphism has been associated with
Increased IgE levels in females, suggesting a possible role of this IL21R polymorphism in allergy.

**Implicated in**

**Multiple myeloma (MM)**

**Disease**

IL21R is expressed on MM cell lines and primary cells. IL21 induced proliferation and inhibited apoptosis of IL6-dependent human myeloma cell lines. Tumor necrosis factor (TNF) up-regulated the expression of IL21R and combinations of TNF and IL21 synergistically mediated myeloma cell proliferation. Four out of 9 purified primary myeloma cells showed increased DNA synthesis in response to IL21 (Brenne, 2002).

**HTLV-I-infected cell lines and Acute T cell leukemia (ATL)**

**Disease**

HTLV-I-infected and primary ATL cells expressed IL21R mRNA and surface protein. IL21 induced the proliferation of ATL cell lines and activated the phosphorylation of STAT3 and STAT5. These findings suggest that the IL21R system may represent a target for the treatment of ATL (Ueda, 2005).

**Hodgkin lymphoma (HL)**

**Disease**

IL21R as well as IL21 are expressed by HL cells. IL21 activates STAT3 and STAT5 in HL cell lines. Expression of a constitutively active STAT5 molecule in normal human B cells immortalized them. These data suggest that the IL21R system may activate auto/para-crine loops involved in HL genesis via STAT5 activation (Sheeren, 2008). IL21 also protected HRS cells from CD95 death receptor-induced apoptosis and up-regulates the CC chemokine macrophage-inflammatory protein-3alpha (MIP-3alpha), which attracts regulatory T cells towards HL cells (Lamprecht, 2008).

**B-Chronic Lymphocytic Leukemia (B-CLL)**

**Disease**

B-CLL cells express IL21R at variable levels and stimuli such as CpG-ODN (Jahrsdorfer, 2006) or CD40L (de Totero, 2006) induce up-regulation of IL21R expression. IL21 mediates apoptosis in B-CLL acting in synergy with these stimuli and may also cooperate with chemotherapy (fludarabine) or anti-CD20 therapeutic antibodies (Gowda, 2008). IL21 may limit the expansion of the CLL clone by inducing apoptosis and counteracting the mitogenic growth factors, such as IL15 (de Totero, 2008) and is being considered as a possible therapeutic agent in CLL (Gowda, 2008).

**Follicular lymphoma (FL)**

**Disease**

IL21R is expressed on FL cell lines and primary cells. In some FL cell lines IL21 induces apoptosis (Akamatsu, 2007).

**Diffuse large B-cell lymphoma (DLBCL)**

**Disease**

DLBCL is associated in about 28.6-35.5% with BCL6 translocation, which can involve either one of the immunoglobulin genes (IGs) but also other non-IG partners. IL21R gene represents one of such non-Ig fusion partners of BCL6 in the t(3;16) translocation (Ueda, 2002).

**Cytogenetics**

FISH of lymphoma metaphase cells revealed fusion signals that contained both the BCL6 and IL21R sequences on the der(3)t(3;16) chromosome.

**Hybrid/Mutated gene**

As a result of the t(3;16) translocation, the promoter region of IL21R was substituted for the regulatory sequences of BCL6. RT-PCR analyses revealed the presence of a chimeric mRNA consisting of two non-coding exons 1a/1b of IL21R and coding exons of BCL6 in the two lymphoma cells. BCL6 was moderately expressed at the mRNA and protein level under the control of IL21R promoter (Ueda, 2002).

**Abnormal protein**

None.

**Oncogenesis**

Unknown role.

**Autoimmune diseases, allergy and neoplasia**

**Note**

Several evidences in experimental murine models indicate that the IL21R system may be involved in immune-mediated disorders, such as autoimmune diabetes (Spolski, 2008b), arthritis (Jungel, 2004) and lupus (Herber, 2007). In view of its immune-enhancing activities IL21 has been regarded as a suitable molecule for cancer immunotherapy (reviewed in Di Carlo, 2007; Sploski, 2008a; Skak, 2008) and clinical phase I clinical trials in melanoma and renal carcinoma have shown acceptable toxicities and clinical activity (Thompson, 2008).

In addition, the IL21R system may play a role in several hematological neoplasias that express the IL21R. The effects of IL21R signaling may however be strikingly different in different neoplastic conditions, as it may transduce mitogenic or survival signals or on the opposite trigger apoptotic cell death. Thus the IL21R system may represent a therapeutic target for inhibitory molecules in certain hematologic neoplasias, whereas in others IL21 may represent a possible therapeutic agent.
**Rheumatoid Arthritis (RA)**

**Disease**
Both synovial macrophages and synovial fibroblasts expressed IL21R in synovial biopsy samples from RA patients. IL21R is associated with the activated phenotype of fibroblasts (Jungel, 2004).

**Helicobacter pylori (HP) gastritis**

**Disease**
Hp infection is associated with gastric inflammation. IL21R is expressed by primary gastric epithelial cells and cell lines, which respond to IL21 by increasing production of MMP-2 and MMP-9. Since IL21 is overexpressed in Hp-infected gastric mucosa it could contribute to increased epithelial gelatinase production (Caruso, 2007b).

### Breakpoints

**Note**
Two t(3;16)(q27;p11) breakpoints on 16p11 are both localized within the intron 1 of IL-21R gene in two different DLBCL (Ueda, 2002).

### References


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