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Gene Section
Review

IL7R (interleukin 7 receptor)

Daniel Ribeiro, João T Barata

Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal (DR, JTB)

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Abstract

Review on IL7R, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CD127, CDW127, IL-7R-alpha, IL7RA, ILRA

HGNC (Hugo): IL7R

Location: 5p13.2

DNA/RNA

Transcription

The gene is composed of 8 exons. The canonical transcript is 4619 bp long.
Alternative splicing generates a soluble isoform lacking exon 6 and introducing a premature stop codon (Goodwin et al., 1990; Rose et al., 2009).

Pseudogene

No pseudogene.

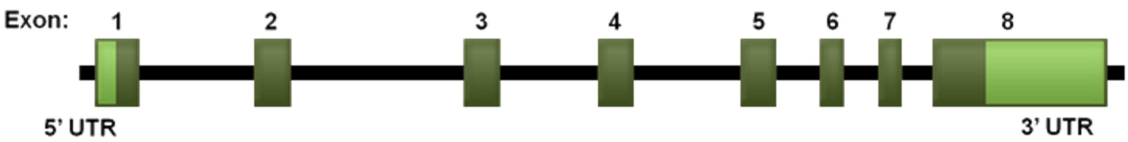
Protein

Description

The precursor IL-7Rα protein includes a signal peptide (20 aminoacids) and has 459 aminoacids in total. The mature protein undergoes several post-translational modifications including glycosylation (6 potential N-glycosylation sites in the extracellular domain) and dissulfide bond formation.
The extracellular domain has 219 aminoacids (spanning from aminoacids 21 to 239), the transmembrane domain has 25 aminoacids (spanning from aminoacids 240 to 264), and the cytoplasmic tail spans from aminoacids 265 - 459 (195 aminoacids).
The soluble isoform of the receptor lacks the transmembrane domain (exon 6) and, due to an altered translation reading frame, it thereafter contains 27 unique aminoacids in the C-terminus (Goodwin et al., 1990; Rose et al., 2009).

Expression

IL-7Rα expression and signaling is required for normal T-cell development and homeostasis (Puel et al., 1998; Ribeiro et al., 2013).
Although IL-7 signaling is not required for normal human B-cell development (in contrast to the mouse, where it is fundamental) IL-7Rα is also expressed in B-cell precursors (Mazzucchelli and Durum, 2007).



IL7R gene. The gene is composed of 8 exons highlighted in dark green. The 5' and 3' untranslated regions (UTR) are highlighted in light green.

IL-7Rα protein. This receptor belongs to the type-I cytokine receptor family. In the extracellular domain, it displays 4 paired cysteines (represented in yellow) in 2 fibronectin type III-like domains and, closer to the transmembrane domain, a WSxWS motif. The intracellular domain has a Box 1 motif and at least 2 tyrosines (Y401, Y449) involved in signal transduction (Lin et al., 1995; Venkitaraman and Cowling, 1994).

Localisation

The functional protein is localized at the plasma membrane where it forms an heterodimeric complex with the common gamma chain (IL-2Rγ, CD132) to transduce IL-7 signaling or the cytokine receptor-like factor 2/ thymic stromal lymphopoietin receptor (CRLF2/TSLPR) to transduce TSLP signaling. IL-7Rα endocytosis via clathrin-coated pits appears to be required for maximal IL-7-mediated signaling (Henriques et al., 2010).

Function

IL-7Rα mediates the signaling of IL-7 and TSLP cytokines. The cytoplasmic tail of IL-7R associates directly with JAK1 to transduce intracellular signaling together with JAK3 or JAK2 that are associated with the IL-2Rγ or TSLPR, respectively. The intracellular signaling pathways activated upon IL-7/IL-7R engagement in T-cells are the JAK/STAT (Lin et al., 1995; Rosenthal et al., 1997), PI3K/Akt/mTOR (Dadi and Roifman, 1993; Venkitaraman and Cowling, 1994; Rathmell et al., 2001) and, in some instances, MEK/Erk (Fleming and Paige, 2001; Maki and Ikuta, 2008; Patel and Chang, 2012).

IL-7/IL-7R signaling is required for T-cell development at different stages. At the double-negative stage (DN; CD4- CD8-), it is required for survival and proliferation of T-cells. It is also required to initiate the recombination of the TCRγ locus (Ye et al., 2001), the reason why it is absolutely required for γδ T-cell development. The receptor is down-regulated at the double-positive stage (DP; CD4+ CD8+) and up-regulated again at the single-positive stage (SP; CD4+ or CD8+). At this stage, IL-7R appears to be involved in CD4 versus CD8 lineage specification (at least in the mouse, possibly in humans) and overall cell survival (Park et al., 2010; Sinclair et al., 2011). Mature T-cells also benefit from IL-7R signaling for homeostatic maintenance and function (Soares et al., 1998).

The function of the TSLP/IL-7R signaling is much less known. Most studies, suggest an important role in the normal function of dendritic cells, immune tolerance and allergy (Watanabe et al., 2005; Lee et al., 2008; reviewed in Ziegler, 2012 and Hanabuchi et al., 2012).

Homology

IL-7R displays aminoacid sequence identity with other human cytokine receptors, such as IL-2R (14.6%), IL-6R (13.2%) GM-CSF receptor (16.0%) GH receptor (12.9%) (Goodwin et al., 1990).

Orthologs of the human IL-7R are found in other species. The murine Il7r has 64%/67.2% DNA/protein identity (Goodwin et al., 1990) and the zebrafish il7r has 20.5% protein identity (Liongue and Ward, 2007) compared with the human receptor.

Mutations

Germinal

Hereditary recessive inactivating mutations in the IL7R gene have been found to cause severe combined immunodeficiency (SCID)(Puel et al., 1998; Roifman et al., 2000; Jo et al., 2004; Giliani et al., 2005).

The mutations occur in the extracellular domain coding region and comprise missense, nonsense mutations and splicing affecting mutations.

The IL-7R SCID is characterized as T-B+NK+. The treatment is hematopoietic stem cell transplantation.

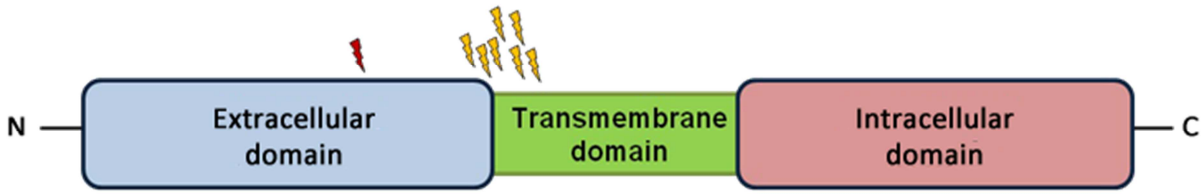
Somatic

Somatic and heterozygous IL7R gain-of-funtion gene mutations have been found in around 9-10% of childhood T-cell acute lymphoblastic leukemia (T-ALL) cases (Zenatti et al., 2011; Shochat et al., 2011; Zhang et al., 2012).

Later, mutations in the IL7R in adult T-ALL (1.7%) were also found (Kim et al., 2013). So far, all T-ALL mutations described are restricted to exon 6, affecting the extracellular juxtamembrane-transmembrane domain of the protein.

The mutations are in-frame insertions or deletions-insertions.

The majority include an unpaired cysteine addition responsible for the homodimerization of two IL7-Rα chains via disulphide bond formation.



IL-7Rα mutational hotspot for gain-of-function mutations. The figure depicts the 3 major domains of the IL-7R with the mutational hotspots present. The T-ALL mutations are restricted to exon 6 (coding for the transmembrane domain) and affect the juxtamembrane-transmembrane region (yellow lightning bolts). B-ALL mutations, although rarer, can also affect exon 5 (S185C; red lightning bolt).

The dimerization of the receptor leads to ligand-independent constitutive signaling via JAK1 (Zenatti et al., 2011), contrasting with the physiological heterodimeric IL-7-dependent activation of the receptor that additionally requires IL-2Rγ and JAK3.
IL7R somatic, heterozygous mutations have also been described in a small fraction of B-cell ALL (B-ALL) cases (less than 1%), significantly associated with aberrant TSLPR expression (Shochat et al., 2011). These included similar mutations to those found in T-ALL, as well as, in half of the cases, mutations in exon 5 leading to an S185C aminoacid substitution (Shochat et al., 2011).

Implicated in

Severe combined immunodeficiency (SCID)

Disease
IL-7R SCID of T-B+NK+ type results from loss-of-function mutations. For further details see the Mutations section.

Prognosis
IL-7R SCID is a fatal disease. The treatment is bone marrow transplantation.

T-cell acute lymphoblastic leukemia (T-ALL)

Prognosis
IL7R mutations are not associated with prognosis (Zenatti et al., 2011). Increased IL-7 responsiveness in vitro was associated with better initial response to treatment in vivo (Karawajew et al., 2000). Low expression of IL-7R was found correlated with poor prognosis (Cleaver et al., 2010).

Oncogenesis
IL-7/IL-7R signaling has a major impact in the survival and proliferation of T-ALL cells in vitro (e.g. Touw et al., 1990; Dibirdik et al., 1991; Barata et al., 2004a; Barata et al., 2004b) and leukemia expansion in vivo (Silva et al., 2011).
Oncogenic IL7R activating mutations occur in T-ALL. See the Mutations section for details.

Truncated forms of the IL-7R originated by alternative splicing were found in childhood T-ALL primary samples (Korte et al., 2000). The truncated receptors still bind IL-7 and it was postulated, but not functionally demonstrated, that they might modulate IL-7 downstream signaling.

B-cell acute lymphoblastic leukemia (B-ALL)

Oncogenesis
IL-7R mutations occur in B-ALL. See the Mutations section for details.
Expression of survival and proliferation markers is associated with CD127+ B-ALLs vs CD127- B-ALLs (Sasson et al., 2010).

Chronic lymphocytic leukemia (CLL)

Oncogenesis
IL-7 mRNA was detected in a whole cohort of 20 CLL primary samples (Frishman et al., 1993).
IL-7 was found to induce proliferation of CLL primary samples (Digel et al., 1991).

Acute myeloid leukemia (AML)

Oncogenesis
IL-7 was found to induce proliferation of AML primary samples (Digel et al., 1991).
An Exon 6 mutation in the IL7R gene was found in one case of adult AML (Kim et al., 2013). The functional impact of this mutation, which does not conform to the T-ALL or B-ALL type of mutations, was not evaluated.

Hodgkin's lymphoma (HL)

Oncogenesis
Both IL-7 and IL-7R proteins were found to be expressed in HL cell lines. An IL-7 autocrine loop was present that could sustain basal proliferation of these cells and the cells could further respond to exogenous added IL-7 (Cattaruzza et al., 2009).

Cutaneous T-cell lymphoma (CTL)

Oncogenesis
Both IL-7 and IL-7R expression was found in CTL primary samples (Foss et al., 1994). All 7 samples analyzed proliferated in the presence of IL-7. There was evidence for a possible autocrine loop.

Breast cancer

Oncogenesis

Both IL-7 and IL-7R were found to be expressed in some breast cancer cases.

Patients with poorer prognosis had higher expression of both genes in the cancer tissue than those with better prognosis (Al-Rawi et al., 2004).

Colorectal cancer

Oncogenesis

IL-7 was found to be secreted in vitro by cultured colorectal cancer cell lines (2/4) and primary samples (16/18) (Maeurer et al., 1997).

Mutations in the exon 6 of the IL7R (0.5%) were found in a cohort of primary samples (Kim et al., 2013).

However, these were frameshift mutations generating an early stop codon. Their functional impact was not evaluated.

Esophageal cancer

Oncogenesis

The expression levels of a small array of 21 cytokines in 6 esophageal cancer cell lines showed that IL-7 is expressed in 5 (Oka et al., 1995). Whether the IL-7R is also expressed remains to be investigated.

Renal carcinoma

Oncogenesis

Both IL-7 mRNA and protein were found to be secreted in renal carcinoma cell lines dependent on interferon gamma (IFNg) constitutive stimulation (Trinder et al., 1999).

In another study, IL-7R mRNA was found expressed in 2/7 renal carcinoma cell lines (Cosenza et al., 2002).

Lung cancer

Prognosis

High expression of IL-7R in tumor cells isolated from patients with stage I lung adenocarcinoma was predictive of poor overall outcome and increased probability of tumor recurrence (Suzuki et al., 2013).

Oncogenesis

IL-7R mRNA and protein (3/7) were detected in lung cancer cell lines (Cosenza et al., 2002).

A missense mutation in the exon 6 of the IL7R was found in a member (0.6%) of a cohort of primary non-small cell lung cancer samples (Kim et al., 2013).

The mutation does not conform to the type of mutations found in T-ALL or B-ALL.

The functional impact of this mutation, which is unlikely to be gain-of-function, was not evaluated as yet.

Multiple sclerosis

Disease

A single nucleotide polymorphism at position 244(T/I) is associated with increased risk of mutiple sclerosis. T244 promotes increased exon 6 skipping leading to higher production of soluble IL7-Ra (Lundmark et al., 2007; Hafler et al., 2007). The role of the soluble form of the receptor in MS warrants investigation.

Rheumatoid arthritis

Disease

The 244(T/I) polymorphism was also found to be associated with rheumatoid arthritis risk (O'Doherty et al., 2009).

Omenn syndrome (OS)

Disease

A patient with OS, a SCID syndrome with graft-vesus-host disease symptoms, was found to have a mutation (C118Y) in the IL-7R (Giliani et al., 2006). This mutation was previously found correlated with SCID (Giliani et al., 2005).

Allogeneic stem cell transplantation (SCT)

Note

The single nucleotide polymorphism (SNPs) IL7Ra +1237 A/G (position) in the donors for SCT was found to correlate with survival of the recipient after SCT (Shamim et al., 2006).

HIV infection

Disease

Although the effects of IL-7/IL-7R during HIV infection on T-cells are well established, they are complex and still under heavy investigation. This entry only superficially covers some aspects of this relationship.

During HIV infection, T-cells have decreased IL-7R expression compared to healthy controls as well as decreased responsiveness to IL-7 (Carini et al., 1994; Vingerhoets et al., 1998).

The HIV Tat protein was found to be responsible for the downregulation of the receptor in CD8 T-cells (Faller et al., 2006).

The soluble IL-7R is increased in HIV+ individuals and can decrease the IL-7 activity in CD8 T-cells (Crawley et al., 2010).

Administration of IL-7 to HIV+ individuals under anti-retroviral therapy leads to an expansion of the T-cell compartment (Sereti et al., 2009; Levy et al., 2009) which may help to restore normal T-cell levels, however increased persistence of the virus in the affected individuals during therapy (Vandergeeten et al., 2013) may raise some concerns regarding the IL-7 therapy.

Comprehensive reviews on this topic include, but are not restricted to: Crawley and Angel, 2012; Sieg, 2012.

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