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Gene Section
Review

IL17F (interleukin 17F)

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Abstract

Review on IL17F, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: CANDF6, IL-17F, ML-1, ML1

HGNC (Hugo): IL17F

Location: 6p12.2

Local order: Centromere - PKHD1 (polycystic kidney and hepatic diseases 1) - MIR206 (microRNA 206) - MIR133B (microRNA 133b) - IL17A (interleukin 17) - **IL17F** - SLC25A20P1 (solute carrier family 25, member 20 pseudogene 1) - MCM3 (minichromosome maintenance complex component 3) - Telomere.

DNA/RNA

Description

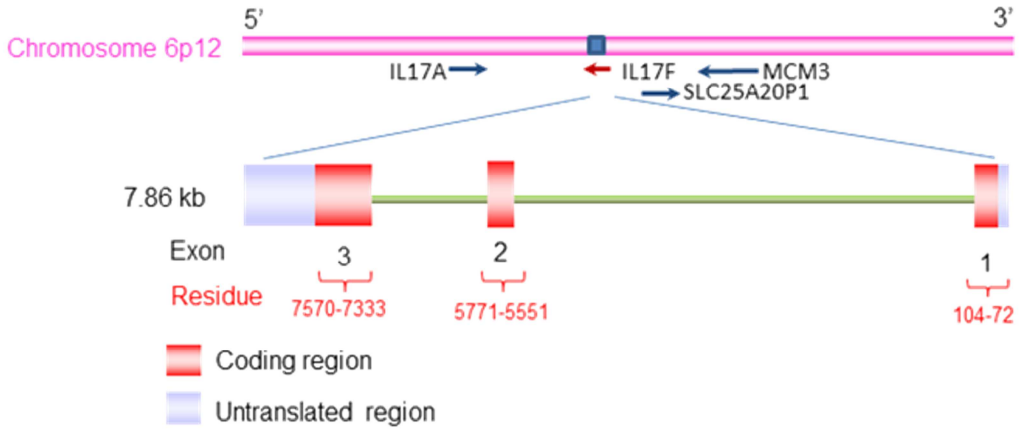
The gene spans a region of 7857 bases and the coding part is divided into three exons.

Transcription

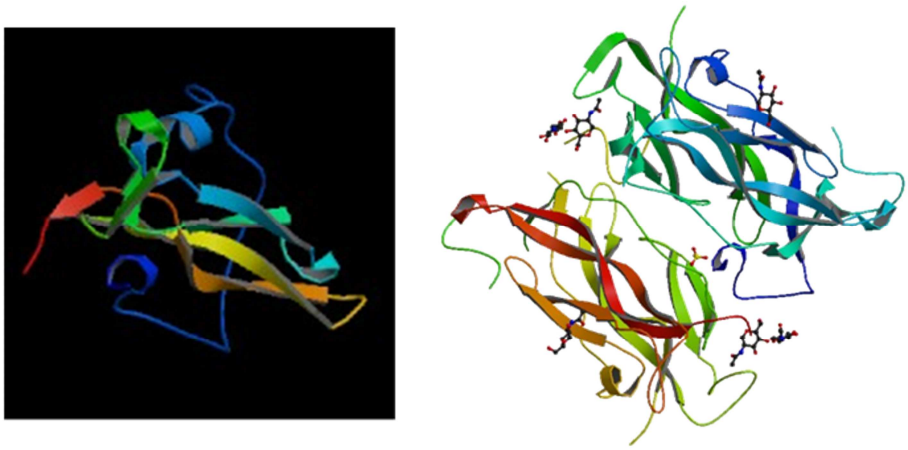
The 492-nucleotide transcript encodes a protein of 163 amino acid residues. The first and last exons are partially untranslated.

Pseudogene

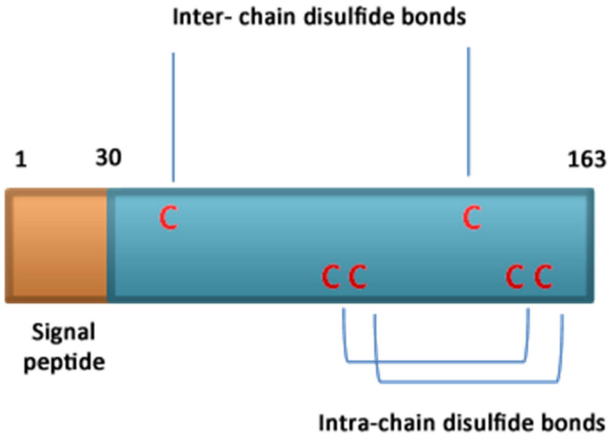
None described so far.



IL17F gene. The IL17F gene spans a region of 7.86 kb composed of the three exons (untranslated region (UTR), light blue; coding region, red) and two introns (green). Exons 1, 2, and 3 are 141 bp (108 bp 5' UTR plus 33 bp coding region), 221 bp (all coding region), and 488 bp (238 bp coding region plus 250 bp 3' UTR) in length, respectively. The two introns are 5446 bp and 1561 bp in length, respectively.



Crystal structure of IL-17F at 2.85 A resomution. Adapted from PDB (access number: 1JPY).



IL-17F protein. IL-17F protein (163 amino acids) is composed of a signal peptide (orange, 30 amino acids) and a mature peptide (blue, 133 amino acids). Four conserved cysteine residues form intra-chain disulfide bonds (Cys102/Cys152 and Cys107/Cys154). Other two cysteines (Cys47 and Cys137) participate in homodimer formation via inter-chain disulfide bonds (Hymowitz et al., 2001). There is an intersubunit disulfide linkage between Cys47 from IL-17F and Cys129 from IL-17A. The presence of another intersubunit disulfide bond between Cys137 (IL-17F) and Cys33 (IL-17A) was also reported (Wright et al., 2007).

Protein

Description

Each IL-17F monomer forms homodimer with another IL-17F or heteromer with IL-17A (Chang and Dong, 2007; Wright et al., 2007).

Calculated molecular weight of IL-17F monomer is a 15-kD. In non-reducing SDS-PAGE gel, IL-17F homodimer runs between 35 to 50kD depending on the level of glycosylation (Wright et al., 2007).

Expression

Compared to IL-17 expression, IL-17F was detected more broadly in different tissues (Kawaguchi et al., 2001). In lymphoid lineages, IL-17F expression is tightly regulated. Results from IL-17F^{RFP} reporter mouse or intracellular cytokine staining of IL-17F indicate that differentiated CD4 helper T cell Th17 cells, lamina propria CD4 T cells, memory CD4 T cells, γδ T cells, iNKT cells, and innate lymphoid cells (ILC3) produce IL-17F (Cua and Tato, 2010; Pantelyushin et al., 2012; Yang et al., 2008b). Regulation of IL-17F closely resembles its homologous protein IL-17A. In addition to TCR stimulation, TGFβ, IL-6, IL-23 and IL-1β are necessary to shape naïve CD4 T cells to Th17 cells. Transcription factors STAT3 and RORγτ are essential for production of IL-17F as well as IL-17 (Martinez et al., 2008; Peters et al., 2011; Zhou and Littman, 2009). IL-17F expression by either ILC3 or γδ T is induced by IL-1β or IL-23 (Geremia et al., 2011; Sutton et al., 2009). While IL-17A production from iNKT cells is independent from IL-6 (Doisne et al., 2009) and required TGFβ and IL-1β (Monteiro et al., 2013), it is not clear whether IL-17F expression is regulated by the same cytokines in iNKT cells.

Distinctive regulatory pathways of IL-17F have been reported. Itk-mediated activation of NFATc1

upon TCR stimulation induces IL-17A but not IL-17F (Gomez-Rodriguez et al., 2009).
Conserved noncoding sites (CNS)2 in the Il17-Il17f locus is required for IL-17A expression but partially required for IL-17F expression, indicating other regulatory elements are involved in the regulation of IL-17F expression (Wang et al., 2012).
While signaling pathways or transcription factors governing γδ T cells (Korn and Petermann, 2012) or iNKT cells producing IL-17A (Engel et al., 2012; Watarai et al., 2012) were reported before, the specific regulatory pathways of IL-17F in these innate cells remain elusive.
IL-17A production is restricted to lymphoid lineages but IL-17F was reported to be expressed by non-lymphoid cells that do not express IL-17A, such as human colonic epithelial cells (Tong et al., 2012).
IL-17F is produced by non-T, non-B innate immune cells and mouse colonic epithelial cells in response to infection with C. rodentium (Ishigame et al., 2009).
IL-17F is predominantly expressed in bronchial epithelial cells in addition to the infiltrating inflammatory cells upon asthma induction (Suzuki et al., 2007).

Localisation

IL-17F is a secreted protein.

Function

IL-17F exerts its biological effects through the IL-17RA/RC signaling complex. While the expression of IL-17RA is universal, IL-17RC expression is largely restricted to epithelial cells, fibroblasts and other stromal cells.
IL-17RA/RC complex recruits an adaptor molecule, Act1, for signaling (Chang et al., 2006; Qian et al., 2007). Upon binding IL-17F, IL-17RA/RC can activate NF-kB and MAPK pathways. IL-17F shares the receptor complex with IL-17A homodimer and IL-17A/F heterodimer.
They do not compete for the binding to the receptor complex since these cytokines together in the culture resulted in additive effects on production of pro-inflammatory molecules.
Binding affinity of IL-17F to IL-17RA is weaker compared to IL-17F binding to IL-17RC (Kuestner et al., 2007).
A crystal structure revealed that IL-17RA bound to IL-17F in a 1:2 stoichiometry and IL-17RA - IL-17F complex prefers to form heterodimers with a second receptor, IL-17RC, possibly due to steric hindrance (Ely et al., 2009).

Homology

IL-17A is the most homologues protein.

Mutations

Note

Familial chronic mucocutaneous candidiasis-6 (CANDF6) is caused by heterozygous ser65-to-leu mutation in the IL17F gene (Puel et al., 2011).
Chronic mucocutaneous candidiasis (CMC) is characterized by infections of the skin, nails, and oral and genital mucosae with Candida albicans, which is commensal in healthy individuals. S65L IL-17F behaves dominant-negative IL17F allele, which impairs the receptor binding and bioactivity of both IL-17F homodimers and IL-17A - IL-17F heterodimers.
A coding region variant (His161Arg) of IL-17F gene, possibly encoding an antagonist for IL-17F, has been linked to asthma patients in Japanese populations (Kawaguchi et al., 2006).

Implicated in

Host defense against infections

Note

IL-17F expression has been detected in various types of infections.
So far, IL-17F has been mainly involved in mucosal host defense mechanisms.
IL-17F deficient mice are susceptible in C. rodentium infection and defective in producing β defensin during the infection (Ishigame et al., 2009).
IL-17F is also required to protect the mice against mucocutaneous S. aureus infections (Ishigame et al., 2009).

Intestinal inflammation

Note

In acute colitis model using dextran sulfate sodium, IL-17F deficiency resulted in reduced colitis symptoms (Yang et al., 2008a).
This phenotype is opposite to IL-17 deficiency, where IL-17 knockout mice developed more severe colitis.
However, in chronic colitis using CD4 transfer system, pathology was mediated by redundant effects of IL-17A and IL-17F (Leppkes et al., 2009), suggesting therapeutic blocking of both IL-17A and IL-17F is likely to be required to suppress the inflammation in colon.

Colon cancer

Note

IL-17F deficiency resulted in increased colonic tumor numbers. IL-17F is expressed in normal human colonic epithelial cells, but this expression is greatly decreased in colon cancer tissues in this study (Tong et al., 2012).

Autoimmune diseases

Note

In experimental autoimmune encephalitis, IL-17F is not required for the initiation of the disease (Yang et al., 2008a) and may play a redundant role in promoting inflammation (Haak et al., 2009). IL-17F is not required to induce inflammation either in collagen induced arthritis model, or arthritis model using IL-1rn deficient mice (Ishigame et al., 2009).

Lung inflammations

Note

IL-17F has been detected in the lungs from asthma and COPD. IL-17F was detected in BALF of allergic patients (Kawaguchi et al., 2001) or bronchial epithelial cells after asthma induction (Suzuki et al., 2007). The role of IL-17F in allergic asthma has been argued. While several studies have shown that IL-17A and IL-17F are dispensable or negative regulator in eosinophilia of allergic asthma (Schnyder-Candrian et al., 2006; Suzukawa et al., 2012), asthmatic inflammation is heterogeneous. Steroid-resistant airway inflammation, airway remodeling, or airway hyperreactivity during asthmatic inflammation were reported to be dependent on Th17 or IL-17A (Kudo et al., 2012; Lajoie et al., 2010; McKinley et al., 2008; Pichavant et al., 2008). IL-17F, on the other hand, was required for neutrophil recruitment upon acute allergen challenge (Yang et al., 2008a).

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