

Gene Section

Review

IL17A (interleukin 17A)

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Identity

Other names: CTLA8; IL-17; IL-17A; IL17

HGNC (Hugo): IL17A

Location: 6p12.2

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

DNA/RNA

Description

3 exons.

Transcription

The transcript is 1859 bp and has a 45 bp 5' UTR, a 468 bp coding sequence, and a 1346 bp 3' UTR.

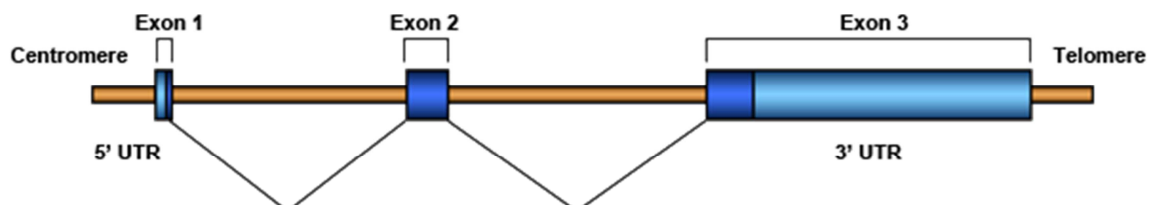
Pseudogene

No pseudogene.

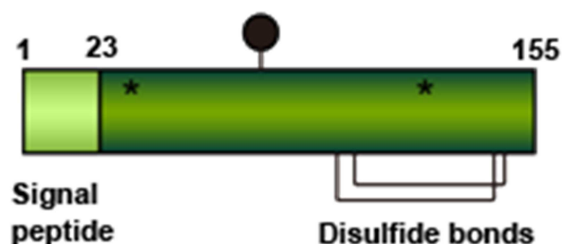
Protein

Note

The IL17A protein is a disulfide-linked homodimeric glycoprotein. Members of the IL17 protein family (IL17A to F) have four highly conserved cysteine residues on each of the monomeric peptides (Moseley et al., 2003; Kolls et al., 2004; Korn et al., 2009). Structural analysis of the IL17F protein indicates that these four cysteines participate in the characteristic cysteine-knot formation found in certain other growth factors such as nerve growth factor (NGF), bone morphogenetic proteins (BMPs), and transforming growth factor-beta1 (TGFbeta1) (Hymowitz et al., 2001). Two additional cysteine residues participate in homodimer formation via inter-chain disulfide-bonds. The IL17F peptide can also form a functional heterodimer with IL17A.



IL17A gene. The IL17A gene spans a region of 4252 bp composed of three exons (untranslated region (UTR), light blue; coding region, blue) and two introns (brown). Exons 1, 2, and 3 are 72 bp (45 bp 5' UTR plus 27 bp coding region), 203 bp (all coding region), and 1584 bp (238 bp coding region plus 1346 bp 3' UTR) in length, respectively. The two introns are 1144 bp and 1249 bp in length, respectively.



IL-17A protein. IL17A protein (155 amino acids) is composed of a signal peptide (light green, 23 amino acids) and a mature peptide (green, 132 amino acids). The four conserved cysteines (Cys) form the intra-chain disulfide bonds indicated by black lines (Cys94/Cys144 and Cys99/Cys146) (Hymowitz et al., 2001). The two cysteines indicated by asterisks (Cys33 and Cys129) participate in homodimer formation via inter-chain disulfide bonds. Asparagine 68 (Asn68, black circle) is predicted to be glycosylated.

Description

Each IL17A monomer is a 19.9-kD peptide that consists of 155 amino acids. The IL17A peptide comprises a 23-amino acid signal peptide and a 132-amino acid mature peptide (IL17A homodimer, 35 kD).

Expression

IL17A is secreted by CD4-positive T cells (Th17 cells), which also produce IL17F, IL21, and IL22 (Korn et al., 2009; Eyerich et al., 2010). CD8-positive T cells, gamma delta T cells, natural killer (NK) cells, NKT cells, and lymphoid tissue inducer (LTi) cells also secrete IL17A. These leukocytes all express the retinoic acid receptor-related orphan nuclear receptor C (RORC, the human analogue of mouse RORgammat that is a splice variant of the Rorc gene). RORC is essential for IL17A production.

Th17 cells are the third subset of helper T cells, with effector functions distinct from Th1 and Th2 cells. Th17 cells are differentiated from naïve T cells in the presence of IL6 plus TGFbeta1 (Bettelli et al., 2007; McGeachy et al., 2008; Awasthi et al., 2009). In the presence of TGFbeta1 alone, naïve T cells express the transcriptional factor forkhead box P3 (FOXP3) and differentiate into induced regulatory T cells (iTreg cells). In the presence of IL6 alone, the cells express the transcriptional factor BCL6 and differentiate into T follicular helper cells (Tfh cells) (Nurieva et al., 2009). Interleukin 21 is secreted from Th17 cells and amplifies Th17 cell generation by an autocrine mechanism. Interleukin 21 also induces the expression of the IL23 receptor in the Th17 cells (Bettelli et al., 2007; McGeachy and Cua, 2008; Awasthi and Kuchroo, 2009). Interleukin 23 is secreted from dendritic cells and macrophages following stimulation by Toll-like receptor ligands. IL23 in turn mediates the stabilization and maintenance of the Th17 cell phenotype, inducing IL17A production by Th17 cells (Stritesky et al., 2008; McGeachy et al., 2009). Interleukin 1beta is also involved in the induction of IL17A secretion and the promotion of Th17 differentiation (Chung et al., 2009). In addition to RORC and the aforementioned cytokines, signal transducer and activator of transcription 3 (STAT3), interferon regulatory factor 4 (IRF4), runt-related transcriptional factor 1 (RUNX1), and aryl

hydrocarbon receptor (AHR, a nuclear receptor for a number of low-molecular weight chemicals such as the tryptophan photoproduct 6-formylindolo[3,2-b]carbazole (FICZ)) all positively regulate Th17 cell differentiation (Korn et al., 2009; Hirahara et al., 2010). Moreover, prostaglandin E2, ATP, and C-type lectin ligands act on antigen-presenting cells to facilitate Th17 cell differentiation. In contrast, IL4, Interferon-gamma (IFNgamma), IL27, suppressor of cytokine signaling 3 (SOCS3), and STAT5 suppress Th17 cell differentiation. Finally, high levels of lactic acid secreted from tumors via the Warburg effect act on macrophages to mediate increased IL17A production but not Th17 cell differentiation (Shime et al., 2008; Yabu et al., 2011).

Th17 cells in both the mouse and the human have recently been shown to differentiate from naïve CD4 T cells independently of TGFbeta1 signaling. These TGFbeta1-independent Th17 cells instead differentiate in the presence of IL6, IL23 and IL1beta (Hirahara et al., 2010; Ghoreschi et al., 2010). TGFbeta1-independent Th17 cells co-express RORgammat and Tbet (TBX21, T-box protein 21) and exhibit more pathogenic potential than TGFbeta1-dependent Th17 cells in the development of experimental allergic encephalomyelitis (EAE).

Function

Interleukin 17A is a pro-inflammatory cytokine and act on a variety of cells (e.g., fibroblasts, epithelial cells, and monocytes) to induce the production of cytokines (IL6, tumor necrosis factor-alpha TNFalpha, granulocyte-macrophage colony-stimulating-factor (GM-CSF), granulocyte colony-stimulating-factor (G-CSF)), chemokines (chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, CXCL5, CXCL8) and matrix metalloproteinases (MMP2, MMP13) to mediate the recruitment, activation and migration of neutrophils and myeloid cells (Kolls and Linden, 2004; Eyerich et al., 2010).

IL17A, IL17F, and the IL17A-IL17F heterodimer bind to a heteromeric receptor complex composed of IL17 receptor A (IL17RA) and IL17 receptor C (IL17RC). IL17RA is expressed at high levels in hematopoietic cells and at low levels in epithelial cells, fibroblasts and

endothelial cells (Gaffen, 2009). On the other hand, IL17RC is expressed at low levels in hematopoietic cells and at high levels in the adrenal gland, prostate, liver, and thyroid. Although cytokines secreted by most activated helper T cells generally stimulate the Janus kinase (JAK)/STAT pathway, the IL17 family cytokines stimulate signal pathways that are common in the innate immune system, such as the Toll-like receptor signaling pathway.

IL17 receptors have a conserved domain termed the "similar expression to fibroblast growth factor/IL-17R (SEFIR)" domain in the cytoplasmic region. This domain is similar to the Toll/IL-1R (TIR) domain (Gaffen, 2009). When the IL17 receptor is activated, the adaptor molecule actin related gene 1 (Act1, a U-box E3 ubiquitin ligase) is recruited to the SEFIR domain and mediates the lysine63-linked ubiquitination of tumor necrosis factor receptor-associated factor 6 (TRAF6). Ubiquitinated TRAF6 then activates the transcriptional factor nuclear factor-kappaB (NFkappaB), various mitogen-activated protein (MAP) kinases including Erk and p38, and CCAAT/enhancer-binding proteins (C/EBP beta and C/EBP gamma).

Homology

IL17A is a prototypical member of the IL17 family. This family includes six proteins, termed IL17A, IL17B, IL17C, IL17D, IL17E (also called IL25), and IL17F. Interleukin 17A to F are not homologous to any other known proteins. IL17A shows the highest homology with IL17F (55%). It is less similar to the other IL17 family members (IL17B, 29%; IL17C, 23%; IL17D, 25%; and IL17E, 17%) (Kolls and Linden, 2004).

Implicated in

Various cancers

Note

Infiltration of IL17A-producing T cells in tumors. IL17A-producing T cells and/or IL17A expression are detected in many human tumor tissues, including ovarian, pancreatic, renal cell, prostate, gastric, and hepatocellular cancers (Zou et al., 2010; Maniati et al., 2010). Although IL17A-producing cells are not the dominant T cell subset in the tumor microenvironment, they are increased to greater extent in the tumor site than in the peripheral blood of the patients (Kryczek et al., 2009a).

Anti-tumor effects.

In some human tumors, such as ovarian and prostate cancer, IL17A and IL17A-producing cells are associated with antitumorogenic actions. Increased IL17A levels in ascites are well-correlated with better patient survival and lower grading stages of ovarian cancer (Kryczek et al., 2009a). An increased population of Th17 cells is also associated with lower grading stages of prostate cancer (Sfanos et al., 2008). In

addition, Immunotherapy is more effective in patients with prostate cancer that have a higher number of Th17 cells.

In the mouse system, the overexpression of IL17A in tumor cells suppresses tumor growth in a cytotoxic T lymphocyte-dependent manner (Benchetrit et al., 2002). The transfer of tumor antigen-specific T cells polarized to the IL17-producing phenotype also induces the eradication of tumor cells by inducing strong CD8-positive T cell activation (Martin-Orozco et al., 2009). Furthermore, the deficiency of IL17A in mice promotes the growth and metastasis of tumors (Martin-Orozco et al., 2009; Kryczek et al., 2009b). Interleukin 17A-producing T cells are predicted to induce the recruitment of other effector cells (e.g., cytotoxic CD8-positive T cells and NK cells) to the tumors by inducing the expression of CXCL9 and CXCL10 by tumors (Kryczek et al., 2009a). Moreover, Th17 cells induce the expression of chemokine (C-C motif) ligand 20 (CCL20, a ligand for chemokine (C-C motif) receptor 6 (CCR6)) in tumor tissues. Chemokine (C-C motif) ligand 20 recruits dendritic cells to mediate anti-tumor effects in a CCL20/CCR6-dependent manner (Martin-Orozco et al., 2009).

Pro-tumor effects.

The proportion of Th17 cells in the peripheral blood is increased in patients with advanced stage gastric cancer compared with patients with early stage diseases (Zhang et al., 2008). In patients with hepatocellular carcinoma, increased intratumoral accumulation of IL17A-producing cells is significantly associated with a poor prognosis (Zhang et al., 2009).

In the mouse system, the overexpression of IL17A in tumors facilitates tumor growth via the induction of angiogenesis in the tumor microenvironment (Numasaki et al., 2003; Numasaki et al., 2005). Furthermore, IL17A-deficient or IL17RA-deficient mouse models were used to show that IL17A was involved in the promotion of tumor growth via induction of myeloid derived suppressor cells (MDSC) (He et al., 2010), activation of IL6-STAT3 pathway (Wang et al., 2009), and production of IL17A by tumor-infiltrating gamma delta T cells (Wakita et al., 2010).

The discrepancies between anti-tumor and pro-tumor effects may be due to distinct roles of IL17A and IL17A-producing cells in different tumors.

Gastric cancer

Note

The single nucleotide polymorphism (SNP) in the IL17A gene promoter region, which is located at a position -197 from the start codon (rs2275913, G/A SNPs, a position at 52051033 bp from pter), has been examined in Japanese gastric cancer patients (Shibata et al., 2009). The frequency of the A-allele (odds ratio, 1.42) and the A/A homozygote (odds ratio, 3.02) is significantly increased in gastric cancer patients compared with healthy controls.

Autoimmune and inflammatory diseases

Note

Interleukin 17A and IL17-producing cells are associated with the pathogenesis of many autoimmune and inflammatory diseases such as EAE/multiple sclerosis, inflammatory skin diseases/psoriasis, inflammatory bowel diseases, and experimental arthritis/rheumatoid arthritis in humans as well as mice (Korn et al., 2009; Awasthi and Kuchroo, 2009).

Infections

Note

Both IL17A and IL17F are preferentially produced during infections with the Gram-negative bacteria *Klebsiella pneumoniae*, *Borrelia burgdorferi*, and *Salmonella enterica enteritidis*; the Gram-positive bacterium *Listeria monocytogenes*; the acid-fast bacterium *Mycobacterium tuberculosis*; and the yeast-like fungi *Pneumocystis jirovecii* and *Candida albicans* (Korn et al., 2009; O'Connor et al., 2010). In an early response to the infection, IL17A is predominantly secreted by gamma delta T cells (Roark et al., 2008; Cua et al., 2010). This results in the rapid recruitment of neutrophils to sites of infection for efficient pathogen clearance. Later, antigen-specific alphabetaTh17 cells contribute to the response.

References

Hymowitz SG, Filvaroff EH, Yin JP, Lee J, Cai L, Risser P, Maruoka M, Mao W, Foster J, Kelley RF, Pan G, Gurney AL, de Vos AM, Starovasnik MA. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. *EMBO J*. 2001 Oct 1;20(19):5332-41

Benchetrit F, Ciree A, Vives V, Warnier G, Gey A, Sautès-Fridman C, Fossiez F, Haicheur N, Fridman WH, Tartour E. Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. *Blood*. 2002 Mar 15;99(6):2114-21

Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev*. 2003 Apr;14(2):155-74

Numasaki M, Fukushi J, Ono M, Narula SK, Zavodny PJ, Kudo T, Robbins PD, Tahara H, Lotze MT. Interleukin-17 promotes angiogenesis and tumor growth. *Blood*. 2003 Apr 1;101(7):2620-7

Kolls JK, Lindén A. Interleukin-17 family members and inflammation. *Immunity*. 2004 Oct;21(4):467-76

Numasaki M, Watanabe M, Suzuki T, Takahashi H, Nakamura A, McAllister F, Hishinuma T, Goto J, Lotze MT, Kolls JK, Sasaki H. IL-17 enhances the net angiogenic activity and in vivo growth of human non-small cell lung cancer in SCID mice through promoting CXCR-2-dependent angiogenesis. *J Immunol*. 2005 Nov 1;175(9):6177-89

Bettelli E, Korn T, Kuchroo VK. Th17: the third member of the effector T cell trilogy. *Curr Opin Immunol*. 2007 Dec;19(6):652-7

McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. *Immunity*. 2008 Apr;28(4):445-53

Roark CL, Simonian PL, Fontenot AP, Born WK, O'Brien RL. gammadelta T cells: an important source of IL-17. *Curr Opin Immunol*. 2008 Jun;20(3):353-7

Sfanos KS, Bruno TC, Maris CH, Xu L, Thoburn CJ, DeMarzo AM, Meeker AK, Isaacs WB, Drake CG. Phenotypic analysis of prostate-infiltrating lymphocytes reveals TH17 and Treg skewing. *Clin Cancer Res*. 2008 Jun 1;14(11):3254-61

Shime H, Yabu M, Akazawa T, Kodama K, Matsumoto M, Seya T, Inoue N. Tumor-secreted lactic acid promotes IL-23/IL-17 proinflammatory pathway. *J Immunol*. 2008 Jun 1;180(11):7175-83

Stritesky GL, Yeh N, Kaplan MH. IL-23 promotes maintenance but not commitment to the Th17 lineage. *J Immunol*. 2008 Nov 1;181(9):5948-55

Zhang B, Rong G, Wei H, Zhang M, Bi J, Ma L, Xue X, Wei G, Liu X, Fang G. The prevalence of Th17 cells in patients with gastric cancer. *Biochem Biophys Res Commun*. 2008 Sep 26;374(3):533-7

Awasthi A, Kuchroo VK. Th17 cells: from precursors to players in inflammation and infection. *Int Immunol*. 2009 May;21(5):489-98

Chung Y, Chang SH, Martinez GJ, Yang XO, Nurieva R, Kang HS, Ma L, Watowich SS, Jetten AM, Tian Q, Dong C. Critical regulation of early Th17 cell differentiation by interleukin-1 signaling. *Immunity*. 2009 Apr 17;30(4):576-87

Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol*. 2009 Aug;9(8):556-67

Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. *Annu Rev Immunol*. 2009;27:485-517

Kryczek I, Banerjee M, Cheng P, Vatan L, Szeliga W, Wei S, Huang E, Finlayson E, Simeone D, Welling TH, Chang A, Coukos G, Liu R, Zou W. Phenotype, distribution, generation, and functional and clinical relevance of Th17 cells in the human tumor environments. *Blood*. 2009a Aug 6;114(6):1141-9

Kryczek I, Wei S, Szeliga W, Vatan L, Zou W. Endogenous IL-17 contributes to reduced tumor growth and metastasis. *Blood*. 2009b Jul 9;114(2):357-9

Martin-Orozco N, Muranski P, Chung Y, Yang XO, Yamazaki T, Lu S, Hwu P, Restifo NP, Overwijk WW, Dong C. T helper 17 cells promote cytotoxic T cell activation in tumor immunity. *Immunity*. 2009 Nov 20;31(5):787-98

McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM, McClanahan TK, O'Shea JJ, Cua DJ. The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. *Nat Immunol*. 2009 Mar;10(3):314-24

Nurieva RI, Chung Y, Martinez GJ, Yang XO, Tanaka S, Matskevitch TD, Wang YH, Dong C. Bcl6 mediates the development of T follicular helper cells. *Science*. 2009 Aug 21;325(5943):1001-5

Shibata T, Tahara T, Hirata I, Arisawa T. Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis. *Hum Immunol*. 2009 Jul;70(7):547-51

Wang L, Yi T, Kortylewski M, Pardoll DM, Zeng D, Yu H. IL-17 can promote tumor growth through an IL-6-Stat3 signaling pathway. *J Exp Med*. 2009 Jul 6;206(7):1457-64

Zhang JP, Yan J, Xu J, Pang XH, Chen MS, Li L, Wu C, Li SP, Zheng L. Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients. *J Hepatol*. 2009 May;50(5):980-9

Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol*. 2010 Jul;10(7):479-89

Eyerich S, Eyerich K, Cavani A, Schmidt-Weber C. IL-17 and IL-22: siblings, not twins. *Trends Immunol*. 2010 Sep;31(9):354-61

Ghoreschi K, Laurence A, Yang XP, Tato CM, McGeachy MJ, Konkel JE, Ramos HL, Wei L, Davidson TS, Bouladoux N, Grainger JR, Chen Q, Kanno Y, Watford WT, Sun HW, Eberl G, Shevach EM, Belkaid Y, Cua DJ, Chen W, O'Shea JJ. Generation of pathogenic T(H)17 cells in the absence of TGF- β signalling. *Nature*. 2010 Oct 21;467(7318):967-71

He D, Li H, Yusuf N, Elmets CA, Li J, Mountz JD, Xu H. IL-17 promotes tumor development through the induction of tumor promoting microenvironments at tumor sites and myeloid-derived suppressor cells. *J Immunol*. 2010 Mar 1;184(5):2281-8

Hirahara K, Ghoreschi K, Laurence A, Yang XP, Kanno Y, O'Shea JJ. Signal transduction pathways and transcriptional regulation in Th17 cell differentiation. *Cytokine Growth Factor Rev*. 2010 Dec;21(6):425-34

Maniati E, Soper R, Hagemann T. Up for Mischief? IL-17/Th17 in the tumour microenvironment. *Oncogene*. 2010 Oct 21;29(42):5653-62

O'Connor W Jr, Zenewicz LA, Flavell RA. The dual nature of T(H)17 cells: shifting the focus to function. *Nat Immunol*. 2010 Jun;11(6):471-6

Wakita D, Sumida K, Iwakura Y, Nishikawa H, Ohkuri T, Chamoto K, Kitamura H, Nishimura T. Tumor-infiltrating IL-17-producing gammadelta T cells support the progression of tumor by promoting angiogenesis. *Eur J Immunol*. 2010 Jul;40(7):1927-37

Zou W, Restifo NP. T(H)17 cells in tumour immunity and immunotherapy. *Nat Rev Immunol*. 2010 Apr;10(4):248-56

Yabu M, Shime H, Hara H, Saito T, Matsumoto M, Seya T, Akazawa T, Inoue N. IL-23-dependent and -independent enhancement pathways of IL-17A production by lactic acid. *Int Immunol*. 2011 Jan;23(1):29-41

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