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Gene Section
Review

IL17A (interleukin 17A)

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Abstract

Interleukin-17A (IL17A), a characteristic cytokine produced by the T helper 17 cells (Th17 cells), can form either a homodimer or a heterodimer with IL17F.

It is produced not only by Th17 cells, but also by cytotoxic $CD8^+$ T cells (Tc17 cells), γδ T cells, invariant natural killer T cells (iNKT cells), lymphoid tissue inducer cells (LTi cells), and other hematopoietic and non-hematopoietic cells. During development, these cells exhibit flexible or plastic features distinct from those of Th1 and Th2 cells. IL17A plays important roles in the pathogenesis of autoimmune diseases and in the host defenses against bacterial and fungal infections.

Expression of IL17A and its related factors, as well as the infiltration of IL17A-producing cells into the tumor microenvironment, has been implicated in anti-tumor or pro-tumor effects in various cancers.

Keywords: Th17 cells, RORγt, STAT3, IL23, TGFβ, inflammation

Identity

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

HGNC (Hugo): IL17A

Location: 6p12.2

Local order: pter - 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) - centromere.

DNA/RNA

Note

IL17A was initially identified in a subtractive hybridization screen of a rodent T cell library as mouse cytotoxic T lymphocyte-associated antigen 8 (mCTLA8) (Rouvier et al., 1993), but is now recognized as a characteristic cytokine of the Th17 cell subset, which has effector functions distinct from those of Th1 and Th2 cells (Korn et al., 2009; Kurebayashi et al., 2013).

Description

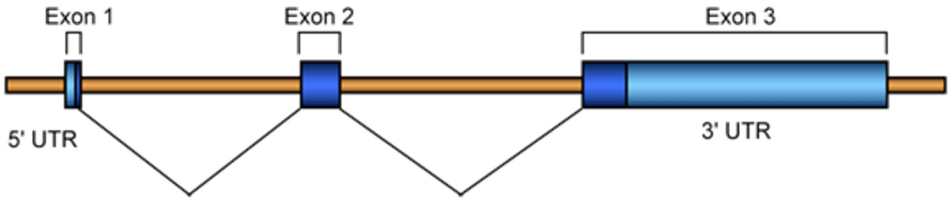
The IL17A gene spans a region of 4252 bp, consisting of three exons.

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 pseudogenes homologous to this gene exist elsewhere in the genome.

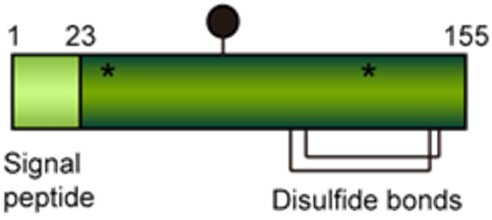


IL17A gene. The IL17A gene spans a region of 4252 bp, consisting of three exons (untranslated region (UTR), light blue; coding region, blue) and two introns (brown). Exons 1, 2, and 3 are 72 bp (45 bp 5' UTR plus 27 bp coding region), 203 bp (all coding regions), and 1584 bp (238 bp coding region plus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

Protein

Note

The IL17A protein is a glycoprotein that can form either a disulfide-linked homodimer or a heterodimer with the IL17F protein. Members of the IL17 protein family (IL17A-F) contain four highly conserved cysteine residues on each monomer (Kolls and Lindén, 2004; Iwakura et al., 2011). Structural analysis of the IL17F protein has revealed that these four cysteines participate in the characteristic cystine-knot formation observed in other growth factors such as nerve growth factor (NGF), transforming growth factor β2 (TGFβ2) and platelet-derived growth factor (PDGF)-BB (McDonald and Hendrickson, 1993), although one of the canonical disulfides of the cystine-knot is absent from the IL17 protein family (Hymowitz et al., 2001). Two additional cysteine residues participate in homodimer formation via inter-chain disulfide bonds. Crystal structures are now available for IL17A in complex with an antibody (Gerhardt et al., 2009), an IL17F/IL17 receptor A complex (Ely et al., 2009) and an IL17A/IL17 receptor A complex (Liu et al., 2013).



IL17A protein. The IL17A protein (155 amino acids) consists of a signal peptide (light green, 23 amino acids) and a mature peptide (green, 132 amino acids). 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

The IL17A monomer is a peptide consisting of 155 amino acids. The IL17A peptide comprises a 23 amino acid signal peptide and a 132 amino acid mature peptide. The IL17A homodimer has a molecular weight of 35 kD (Kolls and Lindén, 2004).

Expression

IL17A is secreted not only by $CD4^+$ T cells (Th17 cells), which also produce IL17F, IL21, and IL22 (Korn et al., 2009; Kurebayashi et al., 2013), but also by $CD8^+$T cells (Tc17 cells), γδ T cells, invariant natural killer T cells (iNKT cells), innate lymphoid cells (ILCs) including lymphoid tissue inducer cells (LTi cells), B cells, neutrophils, and other non-hematopoietic cells (Cua and Tato, 2010). These lymphocytes all express the retinoic acid receptor-related orphan nuclear receptor C (RORC, the human analogue of mouse RORγt, a splice variant of the Rorc gene). RORγt is essential for IL17A production and the development of IL17A-producing cells, at least in lymphocytes, and is thus considered a master regulator of IL17A-producing cells.

Th17 cells

Th17 cells are a subset of helper T cells that have effector functions distinct from those of Th1 and Th2 cells. Early reports showed that stimulation with transforming growth factor β1 (TGFβ1) and IL6 is required to induce differentiation of IL17-producing $CD4^+$ T cells (Th17 cells) from naïve $CD4^+$ T cells (Korn et al., 2009). More recent reports have shown that Th17 cells can be categorized into two distinct subsets: conventional Th17 cells (Th17(β) cells, also called non-pathogenic Th17 cells), which differentiate in the presence of IL6 and TGFβ1, and Th17(23) cells (also called pathogenic Th17 cells), which differentiate in the presence of IL6, IL23 and IL1β without exogenous TGFβ1 (Ghoreschi et al., 2010; Basu et al., 2013; Kurebayashi et al., 2013). IL6 and IL1β can induce the expression of IL23 receptor in naïve $CD4^+$ T cells in the absence of TGFβ1. Th17(β) cells express IL9, IL10, CCL20, and CXCR6 as well as IL17A and IL17F, whereas Th17(23) cells express IL22, CCL9 and CXCR3; relative to Th17(β) cells, Th17(23) cells make a greater contribution to pathogenesis in autoimmune diseases (Ghoreschi et al., 2010). Th17 cells stimulated with IL23, which is secreted by dendritic

cells and macrophages following stimulation with Toll-like receptor (TLR) ligands, induce expression of TGFβ3, leading to the induction of pathogenic Th17(23) cells (Lee et al., 2012). These pathogenic Th17 cells are characterized by the expression of T-bet (TBX21, T-box protein 21), a master regulator of Th1-cell development, as well as RORγt. Compared with Th1 and Th2 differentiation, Th17-cell differentiation exhibits plastic or flexible features (Oestreich and Weinmann, 2012; Basu et al., 2013). TGFβ1 signaling induces the expression of both Foxp3 and RORγt in antigen-activated naïve $CD4^+$ T cells and is involved in the differentiation of both iTreg and Th17 cells. Therefore, additional factors determine iTreg and Th17 polarization. Furthermore, iTreg and Th17 cells can transdifferentiate under specific conditions (Hoechst et al., 2011). The transition from Th17 cells to Th1 cells is also induced by IL23 and IL12 in a STAT4- and T-bet-dependent manner (Lee et al., 2009; Mukasa et al., 2010).

In addition to RORγt and the aforementioned cytokines, several transcriptional regulators positively regulate Th17 cell differentiation: signal transducer and activator of transcription 3 (STAT3), BATF (basic leucine zipper transcriptional factor, ATF-like), interferon regulatory factor 4 (IRF4), Runt-related transcriptional factor 1 (RUNX1), RORα 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)) (Hirahara et al., 2010; Kurebayashi et al., 2013). Moreover, prostaglandin E2, ATP, and C-type lectin ligands act on antigen-presenting cells to facilitate Th17-cell differentiation. By contrast, IL4, interferon-γ (IFNγ), IL27, suppressor of cytokine signaling 3 (SOCS3), and STAT5 all suppress Th17-cell differentiation.

Tc17 cells

$CD8^+$ T cells develop into Tc17 cells in the presence of TGFβ1 and either IL6 or IL21, similar to the requirements for Th17-cell development (Intlekofer et al., 2008). Tc17 cells are also characterized by the expression of RORγt, STAT3, RORα and IL23R. However, Tc17 cells do not express Granzyme B, and they exhibit impaired cytotoxic activity relative to conventional cytotoxic $CD8^+$T cells (Huber et al., 2009). A recent report suggested that TGFβ signaling is not required for in vivo differentiation of Tc17 cells (Dwivedi et al., 2012).

γδ T cells

Two distinct subsets of $CD27^+$ or $CD27^-$ γδ T cells develop in the mouse fetal thymus: co-stimulation of TCR and CD27 induces $CD27^+$ γδ T cells to express T-bet and produce IFNγ whereas the absence of TCR signaling (or weak signaling) promotes the development of IL17A-producing $CD27^-$ γδ T cells, a process controlled by RORγt and RUNX1 (Cua and Tato, 2010; Prinz et al., 2013). Because peripheral $CD27^-$γδ T cells have permissive histone modification at loci involved in expression of not only Il17a but also Ifng, they can produce both IL17A and IFNγ upon stimulation with IL1β and IL23 (Schmolka et al., 2013). All innate IL17-producing lymphocytes, including γδ T cells, iNKT cells and LTi cells, express RORγt and develop in an IL6-independent manner (Cua and Tato, 2010).

iNKT cells

iNKT cells are activated in response to glycolipid antigens presented by CD1d (Cua and Tato, 2010; Guo et al., 2012). IL17A-producing iNKT cells develop in the thymus, and express RORγt and IL23R. A recent report suggested that iNKT cells can be induced to produce IL17A in the presence of TGFβ1 and IL1β (Monteiro et al., 2013).

LTi cells

Innate lymphoid cells (ILCs), a family of RAG1/2-negative lymphoid cells, require the common cytokine receptor γ-chain (also known as IL2RG) and inhibitor of DNA binding 2 (ID2), a transcriptional repressor (Guo et al., 2012; Fuchs and Colonna, 2013; Spits et al., 2013). LTi cells, which like NK cells are prototypical ILCs, belong to the Group 3 ILCs (ILC3s), defined by the production of IL17A and/or IL22 (Spits et al., 2013). ILC3s require the expression of RORγt for their development, express IL23R and IL1R, and produce IL17A and/or IL22 upon stimulation with IL23 or IL1β.

B cells

A recent report shows that Trypanosoma crusi promotes IL17A production by B cells in human and mouse (Bermejo et al., 2013). T. crusi trans-sialidase mediates addition of sialyl residues onto CD45 expressed on B cells, resulting in induction of IL17A and F via BTK activation without the involvement of the transcriptional factors RORγt and AHR.

Other cells

Although the details of the underlying signaling pathways and transcriptional factors are not known, cells other than lymphocytes, such as Paneth cells in the gut and $CD11b^+Gr1^+$ cells in the injured kidney also produce IL17A (Cua and Tato, 2010).

Localisation

IL17A is a secreted protein.

Function

IL17A is a pro-inflammatory cytokine that acts on a variety of cells (e.g., fibroblasts, epithelial cells, endothelial cells, and monocytes) to induce the production of other cytokines, including IL6, tumor necrosis factor-α (TNFα), granulocyte-macrophage colony-stimulating-factor (GMCSF), granulocyte

colony-stimulating-factor (GCSF), chemokines (chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL2, CXCL5, and CXCL8), antimicrobial peptides (defensins) and matrix metalloproteinases (MMP1, MMP3, and MMP13) (Eyerich et al., 2010; Iwakura et al., 2011). These factors mediate the recruitment, activation and migration of neutrophils and myeloid cells, and also induce angiogenesis and tissue destruction.

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; Iwakura et al., 2011). 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. IL17RA has higher affinity for IL17A than IL17F, whereas IL17RC has higher affinity for IL17F than IL17A. Although cytokines secreted by most activated helper T cells generally stimulate the Janus kinase (JAK)/STAT pathway, the IL17-family cytokines stimulate signaling pathways involved in the innate immune system, such as the TLR signaling pathway (Gaffen, 2009; Iwakura et al., 2011).

IL17 receptors contain a conserved domain, 'similar expression to fibroblast growth factor/IL17R' (SEFIR), in the cytoplasmic region. This domain is similar to the Toll-/IL1R (TIR) domain (Gaffen, 2009; Iwakura et al., 2011). 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 lysine 63-linked ubiquitination of tumor necrosis factor receptor-associated factor 6 (TRAF6) (Gaffen, 2009; Iwakura et al., 2011). Ubiquitinated TRAF6 then activates the transcriptional factor nuclear factor κB (NFκB), various mitogen-activated protein (MAP) kinases including ERKs and p38, and CCAAT/enhancer-binding proteins (C/EBPβ and C/EBPδ).

IL-17A expression and Th17 cell development are remarkably affected not only by microorganisms and tumors, but also by several environmental factors such as nutrients, metabolites, hypoxia, toxins, NaCl concentrations, and circadian rhythm.

The tryptophan photoproduct FICZ positively regulates Th17-cell differentiation through AHR, whereas 2,3,7,8-tetrachlorodibezo-p-dioxin (TCDD) negatively regulates differentiation through that receptor (Quintana et al., 2008; Veldhoen et al., 2008). Activation of mTORC1 (mTOR complex containing mLST8 and Raptor) promotes Th17-cell differentiation via positive regulation of hypoxia-inducible factor 1α (HIF1α expression and the activation of S6 kinase (Barbi et al., 2013; Kurebayashi et al., 2013). HIF1α directly upregulates expression of RORγt and IL17A. Therefore, amino acid deprivation selectively blocks Th17-cell development through inhibition of mTORC1, whereas hypoxia promotes Th17 development through the activation of HIF1α. High levels of lactic acid, secreted from tumors due to the Warburg effect, induce macrophages or monocytes to mediate increased IL17A production by Th17 cells in an antigen-dependent manner, but do not Th17-cell differentiation or proliferation (Shime et al., 2008; Yabu et al., 2011).

The circadian rhythm is controlled by a series of feedback loops between the transcriptional factors, a CLOCK-BMAL1 complex and REV-ERBα (Arjona et al., 2012). The expression of RORγt is suppressed by the leucine zipper transcriptional factor NFIL3, which is negatively regulated by REV-ERBα (Yu et al., 2013). Accordingly, $CD4^+$ T cells purified during the day express RORγt at higher levels than those purified at night, and tend to differentiate into Th17 cells.

High salt concentration (e.g., 40 mM NaCl) induces phosphorylation of p38 and the expression of serum glucocorticoid kinase 1 (SGK1) and nuclear factor of activated T-cells 5 (NFAT5) to promote the IL23-dependent differentiation of pathogenic Th17 cells (Kleinewietfeld et al., 2013; Wu et al., 2013a). In vivo, a high salt diet promotes Th17-cell differentiation and exacerbates neuropathy in mice with experimental autoimmune encephalomyelitis.

Homology

IL17A is a prototypical member of the IL17 family. This family includes six proteins: IL17A, IL17B, IL17C, IL17D, IL17E (also called IL25), and IL17F. Interleukins 17A-F are not homologous to any other known proteins. IL17A has the highest sequence identity with IL17F (46.5 %). It is less similar to the other IL17 family members: IL17B, 26.4 %; IL17C, 28.9 %; IL17D, 21.8 %; and IL17E, 17.7 %.

Implicated in

Ovarian cancer

Note

Tumor infiltration by Th17 cells is positively correlated with infiltration by Th1 cells, IFNγ-producing $CD8^+$ cells (Tc1 cells), IL17A- and IFNγ-double-positive T cells, and NK cells, but negatively correlated with the presence of Treg cells (Kryczek et al., 2009a). Increased IL17A levels in ascites are well correlated with better patient survival and lower grades of ovarian cancer.

Esophageal cancer

Note

Elevated levels of IL17A-producing cells, including Th17 cells, in esophageal cancer tissues are

associated with the intratumoral accumulation of $CD8^+$ T and NK cells, as well as with better prognosis (Lv et al., 2011).

Prostate cancer

Note

In prostate tumors, elevated levels of Th17 cells are associated with a lower pathologic Gleason scores (Sfanos et al., 2008). However, in prostate cancer patients, a higher frequency of $CCR4^-$ Th17 cells in peripheral blood is correlated with shorter time to metastatic progression after immunotherapy with an allogeneic whole-cell vaccine (Derhovanessian et al., 2009).

Gastric cancer

Note

The relationship between IL17A and gastric cancer is controversial. Expression of IL17A in peripheral blood mononuclear cells (PBMC) and gastric cancer tissue is elevated, especially in patients with advanced-stage gastric cancer (Zhang et al., 2008; Zhuang et al., 2012; Su et al., 2014). One group suggested that increased infiltration of Tc17 cells in tissues is associated with higher stages and lower overall survival rates (Zhuang et al., 2012). Th17 cells also infiltrate tumors, but the percentage of Th17 cells is lower than that of Tc17 cells. CXCL12, which is produced by tumors stimulated with IL17A, promotes the recruitment of CXCR4-dependent MDSCs and suppresses the function of the cytotoxic $CD8^+$ T cells (Zhuang et al., 2012). However, another group's report showed that intratumoral expression of IL17A is associated with good prognosis (Chen et al., 2011). Several studies have examined the relationship between gastric cancer risk and a single nucleotide polymorphism (SNP) in the IL17A gene promoter region. This SNP (rs2275913, G/A SNP, 52051033 bp from pter) is located at position -197 relative to the start codon within the NFAT-binding motif. The A-allele is associated with higher IL17A promoter activity and higher affinity for NFAT, which plays critical roles in the IL17A production, than the G-allele (Espinoza et al., 2011). Studies of the association between rs2275913 and gastric cancer have yielded different results in different populations. Four groups reported that the AA-genotype and A-allele of SNP rs2275913 are significantly associated with gastric cancer risk in Japanese (Shibata et al., 2009), Iranian (Rafiei et al., 2013), and Chinese populations (Qinghai et al., 2014; Zhang et al., 2014a), whereas one Chinese group reported that this SNP is not associated with total cancer risk or survival in gastric cancer patients (Wu et al., 2010). Two studies suggested that this SNP is significantly associated with gastric cancer risk in Helicobacter pylori-infected patients, smokers, or non-cardia gastric cancer patients (Qinghai et al., 2014; Zhang et al., 2014a). The TT-genotype of the SNP rs3748067, which is localized in 3' UTR of the IL17A gene (C/T SNP, a position at 52055339 bp from pter), was associated with increased risk of gastric cancer in two studies (Qinghai et al., 2014; Zhang et al., 2014a).

Colorectal cancer

Note

Elevated levels of IL17A-producing cells are associated with poor prognosis as a result of increased VEGFA expression in colorectal cancer patients (Liu et al., 2011; Tosolini et al., 2011; Wu et al., 2013b). Furthermore, the A-allele of SNP rs2275913 is positively associated with susceptibility to colorectal cancer, as well as with clinical features as tumor location, tumor differentiation, and TNM stage (Omrane et al., 2014). In a mouse model of colorectal cancer, loss of effective barrier function in the transformed epithelial cells of colonic adenoma results in the infiltration of non-pathogenic bacteria and their products, leading to the production of inflammatory cytokines (including IL23 and IL17A) and the induction of tumor-elicited inflammation, which promotes tumor development (Grivennikov et al., 2012).

Hepatocellular cancer

Note

In patients with hepatocellular carcinoma, increased intratumoral accumulation of IL17A-producing cells is significantly associated with poor prognosis and increased tumor vasculogenesis (Zhang et al., 2009).

Uterine cervical cancer

Note

Levels of Tc17 cells are higher in PBMCs and tumors of uterine cervical cancer patients with lymph-node metastasis than in patients without metastasis (Zhang et al., 2014b). Higher accumulation of Tc17 cells in tumors is associated with a greater degree of tumor vasculogenesis and increased infiltration by Th17 cells and Treg cells. In Chinese women, the AA-genotype and A-allele of IL17A polymorphism rs2275913 are positively associated with susceptibility, peritumoral intravascular cancer emboli, and high clinical stage (Quan et al., 2012).

Breast cancer

Note

Increased infiltration of IL17A-producing cells in tissues is associated with shorter disease-free survival in breast cancer patients and higher histopathological grades (Chen et al., 2013). Among Han Chinese women, the frequency of the AA-genotype of the IL17A SNP rs2275913 is also

higher in patients than controls (Wang et al., 2012). IL17A-producing T cells and Treg cells are synchronically increased in peripheral blood and tumor tissues of breast cancer patients relative to those of healthy individuals (Benevides et al., 2013). Levels of the angiogenic factors CXCL8, MMP-2, MMP-9, and VEGFA, which are induced by IL17A, are also elevated in breast cancer tissue. Thus, IL17A is an important prognostic factor in breast cancer.

Lung cancer

Note

Higher levels of IL17A-producing cells are associated with poor prognosis and increased lymphangiogenesis in non-small cell lung cancer tissues (Chen et al., 2010). Although no significant relationship between SNP rs2275913 in the IL17A gene and lung cancer risk has been observed in the total Tunisian population, the A-allele is associated with increased lung cancer risk in the male and smoker subgroups (Kaabachi et al., 2014).

Bladder cancer

Note

The frequency of the AA-genotype and A-allele of SNP rs2275913 in bladder cancer patients is significantly higher than in control Han Chinese populations (Zhou et al., 2013). This SNP is also associated with increased bladder cancer risk in males and non-smokers, as well as with invasion of bladder cancer.

Autoimmune and inflammatory diseases

Note

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, ankylosing spondylitis, and experimental arthritis/rheumatoid arthritis, in both human patients and mouse models (Awasthi and Kuchroo, 2009; Korn et al., 2009). Recent reports have shown that treatment of psoriasis patients with the antibodies that neutralize IL17A and IL17A-IL17F heterodimer or block IL17RA results in reduction in the affected skin area and disease severity (Leonardi et al., 2012; Papp et al., 2012). Thus, therapies targeting the IL17A signaling pathway are predicted to be effective in psoriasis patients.

Infections

Note

Both IL17A and IL17F are preferentially produced during infections with the Gram-negative bacteria Klebsiella pneumoniae in the lungs and Citrobacter rodentium in the colon, the Gram-positive bacterium Staphylococcus aureus in the skin, and the fungus Candida albicans in the mouth; IL17A appears to protect against all of these types of infections (Korn et al., 2009; O'Connor et al., 2010; Iwakura et al., 2011). During the early response to infection, IL17A is predominantly secreted by γδ T cells and iNKT cells, and it induces the production of antimicrobial peptides such as β-defensins, regenerating (REG) proteins, and S100 proteins, as well as granulopoietic factors such as GCSF and CCL20, from epithelial cells (Cua and Tato, 2010). This results in the rapid recruitment of neutrophils to sites of infection, which in turn promotes efficient pathogen clearance. Later, antigen-specific αβ Th17 cells contribute to further responses to infection.

Cancers in mouse models

Note

Elevated expression of IL17A and increased accumulation of IL17A-producing cells in the tumor microenvironment are associated with anti-tumor or pro-tumor effects in various types of cancer in human patients and mouse models (Zou and Restifo, 2010). Although IL17A-producing cells are not the dominant T-cell subset in the tumor microenvironment, their levels are elevated to a greater extent in the tumor site than in peripheral blood of patients (Kryczek et al., 2009a). Recent reports have suggested that the increased accumulation of not only Th17 cells, but also Tc17 (Hinrichs et al., 2009; Zhuang et al., 2012), IL17-producing γδ T cells (Wakita et al., 2010; Schmolka et al., 2013), and ILC3s (Kirchberger et al., 2013), regulates tumor development.

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 eradication of tumor cells by inducing strong $CD8^+$ T-cell activation (Martin-Orozco et al., 2009). Furthermore, deficiency of IL17A in mice promotes growth and metastasis of tumors (Kryczek et al., 2009b; Martin-Orozco et al., 2009). IL17A-producing T cells are predicted to induce recruitment of other effector cells (e.g., cytotoxic $CD8^+$ T cells and NK cells) to tumors by inducing expression of CXCL9 and CXCL10 within tumor sites (Kryczek et al., 2009a). Moreover, Th17 cells induce expression of CCL20, a ligand for chemokine (C-C motif) receptor 6 (CCR6), in tumor tissues. CCL20 recruits dendritic cells, which mediate anti-tumor effects in a CCL20/CCR6-dependent manner (Martin-Orozco et al., 2009).

On the other hand, overexpression of IL17A in tumors facilitates tumor growth by inducing 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 elevated angiogenesis (Wakita et al., 2010). The discrepancies between anti-tumor and pro-tumor effects may be due to the distinct roles of IL17A-producing cells in different tumors.

A recent report showed that IL17A is involved in tumor resistance to anti-angiogenic therapy targeting vascular endothelial growth factor A (VEGFA) (Chung et al., 2013). In this case, the primary effect of IL17A is the induction of granulocyte colony-stimulating factor (GCSF) expression in tumor-associated fibroblasts, leading to recruitment of MDSC in the tumor microenvironment and induction of another angiogenic factor, prokineticin 2 (PROK2, Bv8). These results suggest that inhibition of IL17A function may improve the efficacy of anti-angiogenic therapies.

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