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REVIEW

Structure and function of interleukin-17 family cytokines

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ABSTRACT

The recently identified interleukin-17 (IL-17) cytokines family, which comprises six members in mammals (IL-17A–F), plays essential roles in the host immunity against infectious diseases and chronic inflammatory diseases. The three-dimensional structures containing IL-17A or IL-17F have become available and revealed the unique structural features of IL-17s as well as their receptors. Molecular modeling in this review shows that IL-17s may adopt a "cysteine knot" fold commonly seen in nerve growth factor (NGF) and other neurotrophins. Further modeling analysis unmasks a signature interaction feature of the IL-17F/IL-17RA complex, where a small loop of IL-17RA slots into the deep groove of the interface of IL-17F homodimer. This is quite different from the interaction between the best known four-helix cytokines and their cognate receptors. On the other hand, structure of IL-17A and its monoclonal antibody (CAT-2200) shows that, albeit that the antigenic epitope of IL-17A resides outside of the IL-17A homodimer interface, its physical proximity to the receptor binding groove may explain that antibody blockage would be achieved by interfering with the ligand-receptor interaction. This review is to summarize the advance in understanding the structure and function of IL-17 family cytokines, focusing mainly on IL-17A, IL-17F and IL-17E, in the hope of gaining better knowledge of immunotherapeutic strategies against various inflammatory diseases.

KEYWORDS interleukin-17, cytokines, crystal structure, immunology

INTRODUCTION

In 1995, Yao and colleagues found a new cytokine, IL-17 (also known as IL-17A), can be produced by a novel subset of $CD4^+$ helper T cells, now known as Th17 cells (Yao et al., 1995a; Yao et al., 1995b). Further studies revealed that IL-23 stimulates Th17 to produce IL-17A (Aggarwal et al., 2003) in a RORγt dependent manner (Ivanov et al., 2006). IL-17 family (henceforth referred to as IL-17s) consists of six members in mammals, i.e., IL-17A–F. Both IL-17A and IL-17F can stimulate the production of IL-6, IL-8, and granulocyte colony-stimulating factor (G-CSF), making IL-17s *bona fide* pro-inflammatory cytokines (Yao et al., 1995a; Fossiez et al., 1996; Hymowitz et al., 2001). The IL-17 receptor family consists of 5 members, IL-17 receptor A (IL-17RA or IL-17R), IL-17 receptor B (IL-17RB or IL-17BR), IL-17 receptor C (IL-17RC), IL-17 receptor D (IL-17RD), and IL-17 receptor E (IL-17RE) (Yao et al., 1995a; Yao et al., 1997; Shi et al., 2000; Tian et al., 2000; Haudenschild et al., 2002; Moseley et al., 2003). IL-17s mainly activate nuclear factor-kappaB (NF-κB) pathway (Chang et al., 2006; Lindén, 2007) through NF-κB activator 1 (Act1) and TNF (tumor necrosis factor) receptor-associated factor 6 (TRAF6), and play important roles in promoting autoimmune diseases including rheumatoid arthritis, psoriasis and multiple sclerosis (Teunissen et al., 1998; Chabaud et al., 1999; Kurasawa et al., 2000), and in controlling certain bacterial and fungal infections (Curtis and Way, 2009). Three structures of this family have been determined, including IL-17F (Hymowitz et al., 2001), IL-17A complex with its neutralizing antibody (Gerhardt et al., 2009) and IL-17F bound to IL-17 receptor A (Ely et al., 2009). By a thorough analysis of the available structures, this review

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attempts to deduce some general correlation between the structure and function of this cytokine family.

THE PRIMARY AND SECONDARY STRUCTURES: CONSERVED CYSTEINES INVOLVE IN FORMATION OF INTERMOLECULAR DISULFIDE BONDS

By sequence homology search of IL-17A, five additional members, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F have been identified (Li et al., 2000a; Shi et al., 2000; Fort et al., 2001; Hymowitz et al., 2001; Lee et al., 2001; Starnes et al., 2001; Starnes et al., 2002). Human IL-17F gene is located adjacent to IL-17A, transcribed in a direction opposite to the IL-17A transcript, suggesting both cytokines may have evolved from gene duplication and shared the same regulatory elements. More strikingly, multiple non-coding sequences within the IL-17A and IL-17F loci are conserved across species, whose acetylation patterns of histone 3 show a lineage-specific manner (Akimzhanov et al., 2007).

IL-17A is composed of 177 amino acids, containing the N-terminal signal peptide, the N-linked glycosylation site and cysteine residues conserved among the IL-17 family (Lee et al., 2001). Sequence alignment of human IL-17s (Fig. 1) shows that IL-17A and IL-17F are closely related, with an approximately 50% sequence identity (Hymowitz et al., 2001; Starnes et al., 2001). IL-17B and IL-17D are less homologous (~40% sequence identity), and with others share a merely 20%–30% identity. IL-17E shares less than 17% homology with IL-17A (Lee et al., 2001), which may explain their differential roles in type 2 immune response and allergy (Pan et al., 2001; Angkasekwinai et al., 2007). In spite of the limited homology in primary sequence, the secondary structure elements of each member are quite conserved, especially for the four β-strands in C-terminal region. More pronouncedly, there are 4 cysteine and 2 serine residues highly conserved among IL-17s (Fig. 1), which are critical to form a cysteine knot fold (Fig. 2) of IL-17A and IL-17F (Hymowitz et al., 2001; Gerhardt et al., 2009).

THE TERTIARY STRUCTURE OF IL-17s

IL-17s adopt a cysteine knot fold

Only 3 crystal structures have been resolved in the past decade, namely, IL-17A with its neutralizing antibody, IL-17F, and IL-17F with its receptor IL-17RA (Hymowitz et al., 2001; Ely et al., 2009; Gerhardt et al., 2009). We have managed to deduce the overall topology of IL-17s by superimposing the backbone C_α atoms of IL-17A to those of IL-17F. This yields a very similar conformational arrangement with a root mean square deviation (r.m.s.d.) value of 1.232 Å (Fig. 2A). It also reveals unexpectedly that IL-17s may adopt the "cysteine knot" fold (Fig. 2B), a conformation commonly seen in nerve growth factor (NGF) and other neurotrophin proteins (Hymowitz et al., 2001; Gerhardt et al., 2009). The cysteine knot fold superfamily has the registered feature of two pairs of anti-parallel β-strands (labeled β1–β4) bundled through three disulfide bridges (McDonald and Hendrickson, 1993). IL-17A may possess the conserved two disulfide bridges (Cys^{94}-Cys^{144} and Cys^{99}-Cys^{146} for IL-17A and Cys^{102}-Cys^{152} and Cys^{107}-Cys^{154} for IL-17F) to form a 9-amino acid ring. However, the third disulfide bridge, supposedly going through the ring to form a "knot," disappears in IL-17A and IL-17F. Closer inspection (Fig. 2B) reveals that the two cysteine residues for the third disulfide bridge have been replaced by two serine residues (Ser^{72} and Ser^{112} in IL-17A and Ser^{80} and Ser^{120} in IL-17F). These two serines are conserved in all the six members of the IL-17 family (Fig. 1), suggesting an identical "cysteine knot" would exist in the IL-17 family. Indeed, the ribbon representation of the structures of IL-17F, NGF and neurotrophin-3 (Fig. 3) show that three proteins are dimerized in the overall backbone structure mimicking a garment with a skirt at the bottom, and the body composed of eight β-strands. Although speculated as a homodimer earlier (Fossiez et al., 1996), we and others have demonstrated that IL-17A and IL-17F can secrete as both homodimeric and heterodimeric proteins in humans and mice (Chang and Dong, 2007; Liang et al., 2007; Wright et al., 2007), with IL-17A/F heterodimer being less active than IL-17A or IL-17F homodimer (Chang and Dong, 2007; Liang et al., 2007; Wright et al., 2007).

Structure of IL-17F and IL-17RA: a novel cytokine receptor family?

A complex structure of IL-17RA bound to IL-17F at a resolution of 3.3 Å (Fig. 4B) has been reported (Ely et al., 2009). The extracellular domain of IL-17RA is composed of two fibronectin III-like domains (D1 and D2). The additional 40 residues in the N-terminal region (strand A') form a unique fold, which is different from the canonical fibronectin III (Fig. 4A). D1 and D2 domains of IL-17RA are composed of a series of anti-parallel β-sheets (strand A–G, A', and C') and use a small loop of edge strands (C and C') to insert into the groove on the dimeric interface of IL-17F. Such interaction thereby occupies a buried surface area (about 2200 $Å^2$) much larger than that of other cytokine and receptor complexes (Fig. 4C), and is dominated by salt bridges and hydrogen bonds with superior charge complementarity (further discussed below).

Comparison with other interleukins and their receptors

The cytokine receptors can be classified into six major families: IL-1 receptors, class I cytokine receptors, class II cytokine receptors, TNF receptors, tyrosine kinase receptors and chemokine receptors (Wang et al., 2009). IL-17 receptors, however, do not belong to any of these six families,

Figure 1. Sequence alignment of IL-17 family members. ClustalX was used to align the sequence. Identical and conserved residues among the family members are highlighted with cyan and magenta background, respectively. When the other members of the family have an identical residue at the same position, they are indicated with the same color. The signal sequence of each family member is predicted by SignalP 3.0 (Bendtsen et al., 2004) and indicated by black boxes. The secondary structure elements of each member are shown below the alignment as purple boxes (α-helix), blue boxes (β-strands) and orange lines (the rest). The secondary structures of IL-17A and IL-17F were performed according to the three-dimensional structures of the two proteins and others were performed using PORTER (Pollastri and McLysaght, 2005). Disulfide bonds which are expected to be conserved among the IL-17 family members are indicated by red dashed lines connecting the two cysteines. The conserved serines which replace the cysteines in the position of the third disulfide in cysteine knot fold are marked with asterisks. The positively charged arginines which are involved in the interaction with receptor IL-17RA are marked with filled triangles.

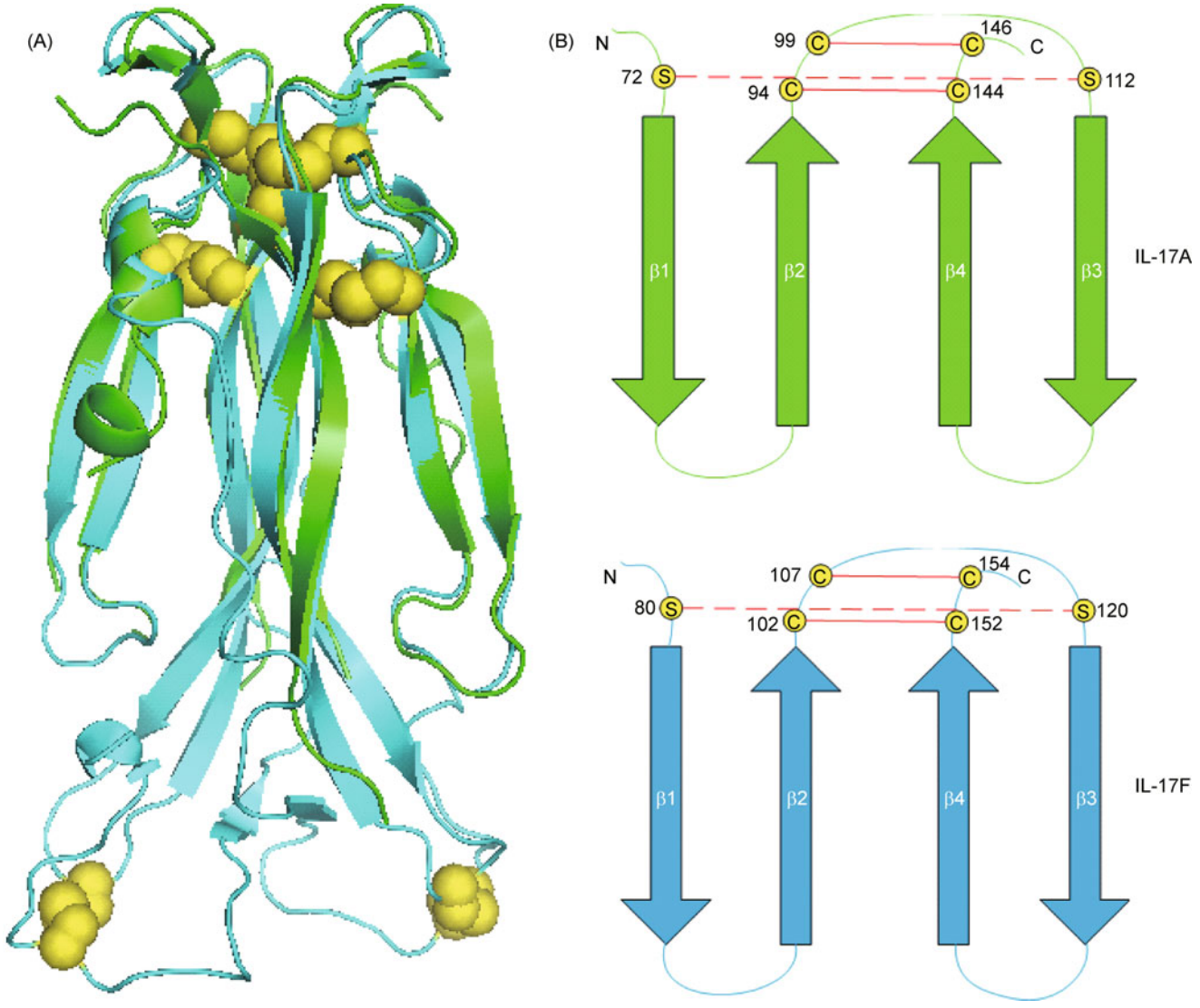

Figure 2. Structures of IL-17A and IL-17F. (A) Superimposition of the IL-17A structures (green) onto the IL-17F structure (cyan) r.m.s.d. = 1.232 Å. 145 C_α atoms were involved in the superimposition. Disulfide bonds in IL-17F are rendered as spheres and colored yellow. All figures were generated using the program PyMOL unless noted otherwise. (B) Topological diagram of the cysteine knot fold in IL-17A and IL-17F structure. The N and C termini of the fold are labeled. Conserved cysteines and serines are rendered by circles filled with yellow. The two disulfide bonds presented in the protein are indicated by red lines while the third missing one is indicated by a red dashed line. The secondary structural elements are not to scale and colored the same as A.

based upon knowledge of the available complex structure of IL-17F/IL-17RA.

First, IL-1 family proteins include IL-1α, IL-1β, IL-18, and IL-33 (Barksby et al., 2007; Arend et al., 2008; Dinarello, 2009), and IL-1 receptor family typically comprises three extracellular immunoglobulin (Ig)-like domains (Dinarello, 2009). IL-1 family members adopt a β-trefoil fold and have two separate binding sites for IL-1 receptors (Fig. 5A): site A nestles against the D1-D2 Ig repeat segment and site B contacts with D3 domain (Vigers et al., 1997; Lingel et al., 2009). Secondly, about 20 different interleukins (Nicola and Hilton, 1998) belong to the four-α-helix bundle superfamily (e.g., IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-10, IL-11, IL-12, IL-13, IL-15, IL-21, and IL-23). These helical cytokines usually adopt an up-up-down-down four-helix bundle topology with two crossover loops (Fig. S1). Some can bind to the class I cytokine receptor, including three shared receptors: gp130, γ_c and β_c. The extracellular segments of the class I cytokine receptors consist of two fibronectin type III domains connected by a helical linker, forming an L-shaped architecture. The helical cytokines contact with their receptors at the apex of the elbow region (Boulanger et al., 2003; de Moura et al., 2009; McElroy et al., 2009), as represented by the interaction of IL-7 with IL-7Rα (Fig. 5B). The average buried surface area of the

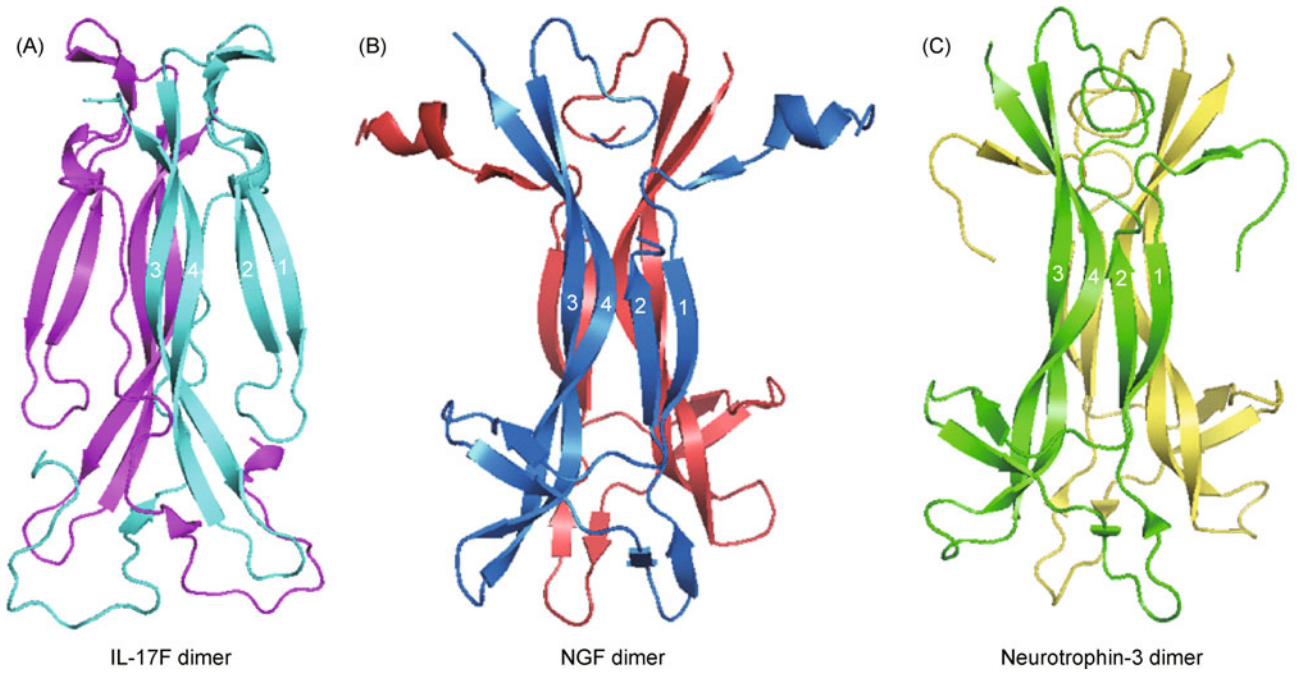

Figure 3. IL-17F structure comparison among the known structures of the cysteine knot fold family. (A) Ribbon representation of the IL-17F dimer (PDB ID code 1JPY). The individual monomers are colored magenta and cyan. (B) Ribbon representation of the NGF dimer (PDB ID code 2IFG). The individual monomers are colored red and blue. (C) Ribbon representation of the neurotrophin-3 dimer (PDB ID code 3BUK). The individual monomers are colored yellow and green.

IL-7/IL-7Rα interface is reportedly as 720 Å^2 (McElroy et al., 2009). Lastly, interaction between neurotrophins (NTs) and their common receptor, p75 neurotrophin receptor (p75^{NTR}), also possesses unique features. The p75^{NTR} belongs to tumor necrosis factor receptor (TNFR) superfamily, containing an intracellular death domain (DD) and four extracellular tandem cysteine-rich domains (CRDs). In the structure of p75^{NTR} and NT-3 complex, p75^{NTR} binds NT-3 in a 2:2 stoichiometry. CRD1 is located distal to the cell membrane. CRD2, CRD3 and CRD4 interact the most with NT-3 (Fig. 5C). The interaction buried surface area between NT-3 dimer and p75^{NTR} is also large in this manner (2314 Å^2), dominated by hydrophobic interactions, salt bridges and hydrogen bonds (Gong et al., 2008).

Structures of IL-17A/antibody and IL-17F/IL-17RA complexes

The crystal structure (Gerhardt et al., 2009) of IL-17A in complex with its neutralizing antibody (CAT-2200) shows that each IL-17A dimer is sandwiched by two Fab' fragments and the buried surface area per interface is around 760 Å^2 (Fig. 6A). A closer inspection reveals that the intermolecular interaction areas are mainly localized in the upper half of IL-17A (Fig. 7A), the front facet of the "garment," leaving the groove essential for contacting the receptor (as seen with IL-17F/IL-17RA complex, Fig. 4B and 5D) drifted 30° away from the front (Fig. S2). Therefore, IL-17 may use two different areas to contact either antibody or its cognate receptors. Indeed, when we superimpose IL-17A in the IL-17A/Fab complex onto IL-17F in the IL-17F/IL-17RA structure, due to the physical proximity of the two binding epitopes, the neutralizing antibody would apparently interfere with IL-17RA stereotically (Fig. 6B). It therefore provides structural explanation for the neutralizing effect of CAT-2200 (Gerhardt et al., 2009) by competing with IL-17RA for IL-17A binding.

The interface of the IL-17F and IL-17RA complex is of excellent charge complementarity (Fig. 7B). IL-17F mainly uses positive charged side chains, especially the two arginines (R77 and R132) to interact with negatively charged side chains (D262 and D29) in IL-17RA (Fig. 1). We suggest that the complementary surface charge is likely the driving force of the interaction between IL-17F and IL-17RA.

In the two complex structures of IL-17A/CAT2200 and IL-17F/IL-17RA, the "skirt" portion of both IL-17A and IL-17F dimers are disordered and invisible in electron density map, indicating that this area of IL-17s is highly flexible and may be essential for its regulatory function when complexed with other proteins. Such flexibility can also explain the daunting difficulty in crystallization of IL-17s protein family.

STRUCTURAL INSIGHT INTO THE BIOLOGIC FUNCTIONS OF IL-17s

IL-17A and IL-17F

IL-17 and IL-17F are associated with several immune regulatory functions. Most notably, they are involved in the

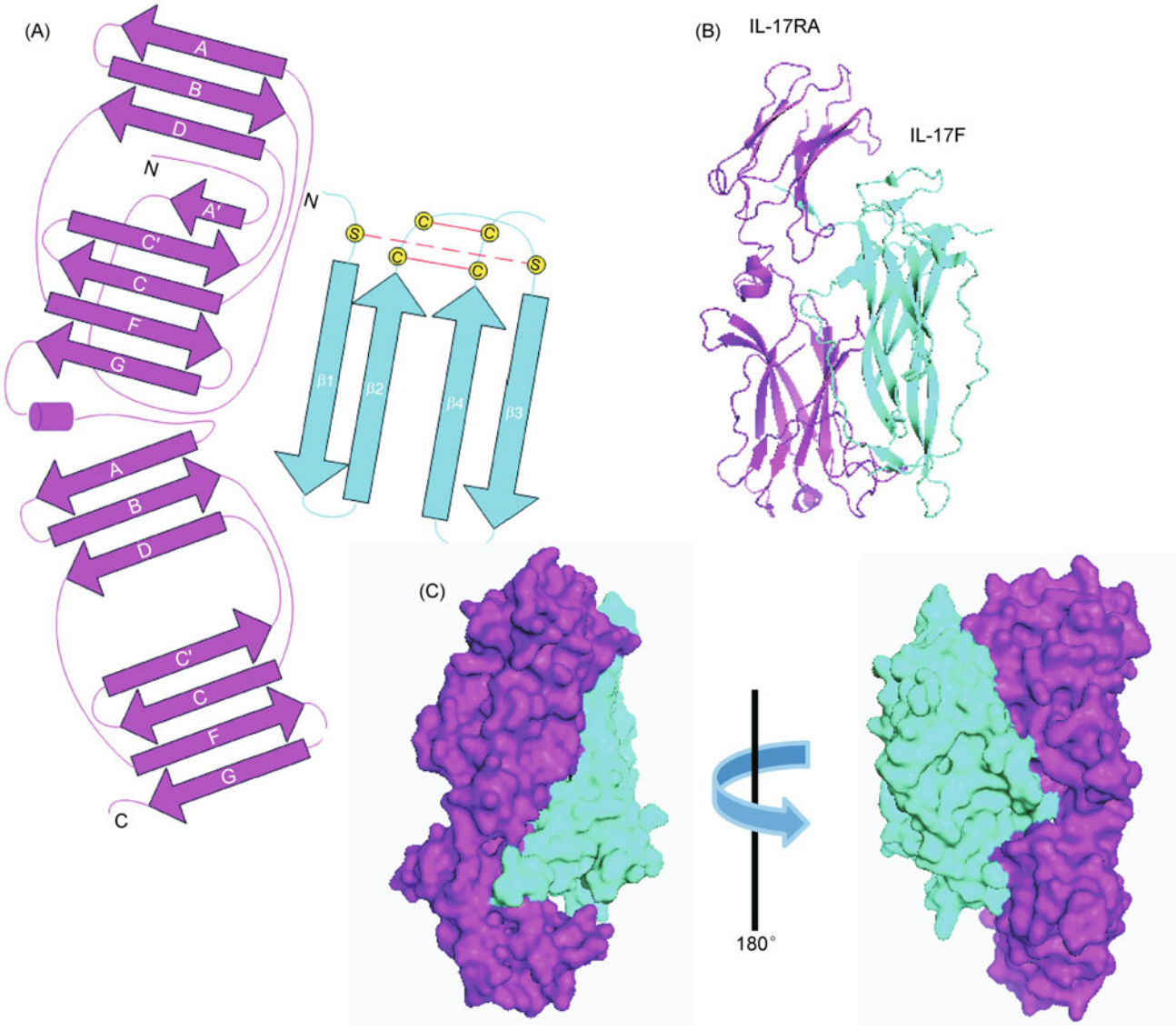

Figure 4. Structure of IL-17F/IL-17RA complex. (A) Topological diagram of the domains of IL-17F/IL-17RA complex. IL-17F and IL-17RA are colored cyan and magenta, respectively. (B) A stereoribbon view of the complex. Color scheme is as in A. (C) Molecular surface representation of the complex structure shown in two views related by a 180° rotation about the vertical axis and colored the same as A and B. The buried surface area is much larger than that of other cytokine and receptor complexes.

inflammatory process during infection and in the pathogenesis of chronic inflammation in autoimmune diseases. Fibroblasts, epithelial cells and macrophages are known targets for IL-17A in inducing the expression of many proinflammatory cytokines and chemokines, including CXCL1 (Gro1), CCL2, CCL7, CCL20, and matrix metalloproteinase (MMP) 3 and 13 (Park et al., 2005). As a result, IL-17A mediates the recruitment of neutrophils and macrophages during inflammation. IL-17A blockade led to reduced severity of experimental autoimmune encephalomyelitis (EAE), while overexpression of IL-17A in lung epithelial cells caused airway inflammation (Park et al., 2005). Because IL-17A and IL-17F share the highest homology, there is a considerable overlap in their biologic functions. Although less active than IL-17A, IL-17F also has an ability to induce the production of antimicrobial peptides (defensins), cytokines (IL-6, G-CSF, and GM-CSF), chemokines (CXCL1, CXCL2, and CXCL5), as well as enhance granulopoiesis and neutrophil recruitment (Kawaguchi et al., 2004; Kolls and Lindén, 2004). Overexpression of IL-17F in the lungs resulted in increased proinflammatory cytokine and chemokine expression, airway inflammation predominantly infiltrated with neutrophils and macrophages (Oda et al., 2005; Yang et al., 2008).

On the other hand, several reports also suggest their

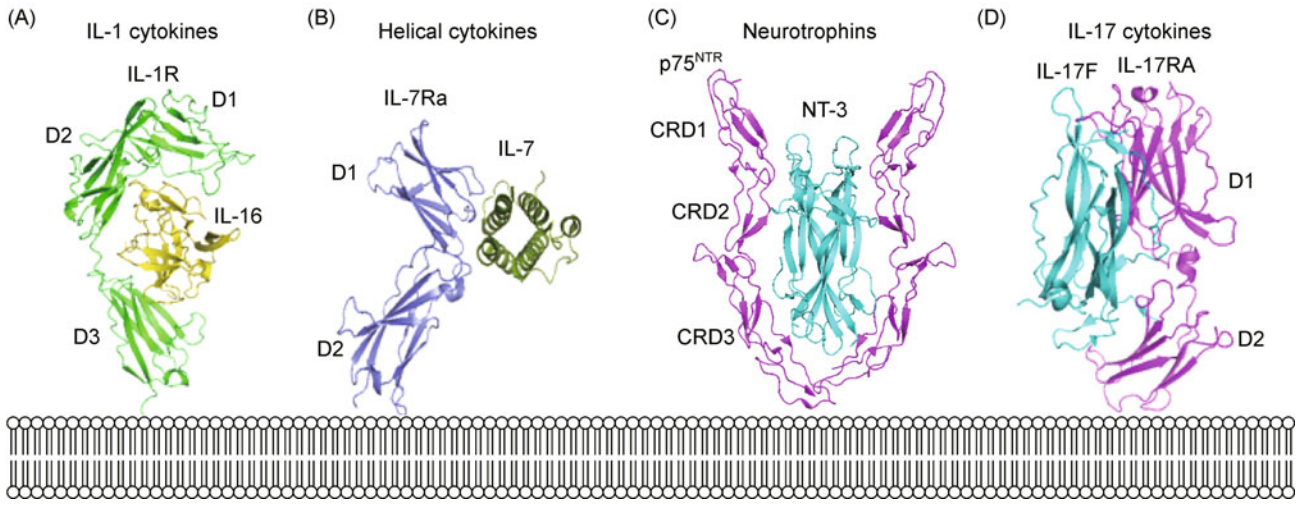

Figure 5. Diversity of cytokine-receptor interactions. The structures of cytokine-receptor extracellular complexes are represented from the side with a cartoon of a membrane underneath. (A) Ribbon diagram of the IL-1β (green)/IL-1R (yellow) complex from PDB ID code 1ITB. (B) Ribbon diagram of the IL-7(dark green)/IL-7Rα (slate) complex from PDB ID code 3DI2. (C) Ribbon diagram of the NT-3 (cyan)/$p75^{NTR}$ (magenta) complex from PDB ID code 3BUK. (D) Ribbon diagram of the IL-17F (cyan)/IL-17RA (magenta) complex from PDB ID code 3JVF.

distinctive function (Yang et al., 2008; Ishigame et al., 2009). Using IL-17A and IL-17F-deficient mice, we were able to find that IL-17F and IL-17A play important but perhaps differential roles in humoral immunity, inflammatory responses in EAE, asthma and dextran sulfate sodium (DSS)-induced colitis (Yang et al., 2008). A similar approach by others suggests that both cytokines exert distinct functions in immune responses against bacterial infection (Ishigame et al., 2009), with IL-17A playing a major role in T cell-dependent autoimmunity, but IL-17F contributing marginally. However, both IL-17A and IL-17F are critically important to protect the mice against mucocutaneous *S. aureus* infections, even though the cellular source of both cytokines seems to be different: IL-17A is produced mainly in T cells, whereas IL-17F is produced in T cells, innate immune cells, and epithelial cells (Ishigame et al., 2009). The reason why IL-17A and IL-17F possess different functions may be explained by their receptors. Homodimers of IL-17A, IL-17F and IL-17A/F heterodimer signal through a heterodimeric complex of IL-17RA and IL-17RC (Toy et al., 2006; Kuestner et al., 2007; Wright et al., 2008). Lack of either IL-17RA or IL-17RC completely abrogates the inflammatory function of IL-17A and IL-17F. However IL-17A and IL-17F have a biased binding affinity for the hetero-receptor (Toy et al., 2006; Kuestner et al., 2007; Wright et al., 2008). IL-17A binds better to IL-17RA than IL-17RC and IL-17F binds to IL-17RC with an ~10-fold higher affinity than to IL-17RA, while IL-17F/IL-17A heterodimer binds with a similar affinity to both receptors. In addition, IL-17RA binds to IL-17A with an affinity about 100-fold higher than its affinity for IL-17F (Wright et al., 2008; Ely et al., 2009). To provide structural insight into the different binding affinities, we are able to model a putative complex of IL-17A/IL-17RA, based on the structures of IL-17A associating with CAT-2200 Fab' and IL-17RA in association with IL-17F, on the assumption that the interactions of IL-17RA are in general the same with either IL-17A or IL-17F (Fig. 8). With this information in hand, we compared the structures of IL-17F before and after binding its receptor by superimposing unbound IL-17F dimer onto IL-17F in the IL-17F/IL-17RA structure. Although the main backbone structures of IL-17F before and after IL-17RA binding are basically the same, the N-terminal loops of IL-17F shift appreciably to avoid clashing with the receptor for appropriate binding (Fig. 8A). The same N-terminal region in IL-17A, however, is substituted with a small α-helix including 4 amino acids of IL-17A chain B (Pro60, Lys61, Arg62, and Ser63) which would potentially clash with the C-C' loop of IL-17RA. The surface representations of the "knob-in-hole" binding pocket of bound IL-17F, unbound IL-17F and IL-17A have been demonstrated in Figs. 8C–E. Looking from the other side of the C-C' loop of IL-17RA, interaction of IL-17RA and IL-17A is different from that of IL-17RA and IL-17F (Fig. 8B). A potential salt bridge forms between Glu127 of IL-17RA and Arg78 of IL-17A chain B, while the counterpart amino acid in IL-17F is a Val. In addition, the side chain of Trp90 in IL-17A chain B fits perfectly in a hydrophobic pocket formed by Leu86 and Leu88 of IL-17RA and Leu76 of IL-17A, while the same position is replaced by Val98 in IL-17F. These differences in side-chain interactions by IL-17A and IL-17F may contribute to the higher affinity of IL-17RA to IL-17A than to IL-17F. However, limited information prohibits us from explaining the 100-fold difference in affinity between IL-17RA and its shared ligand, IL-17A and IL-17F before the structures of IL-17A and its complex with the receptor are solved.

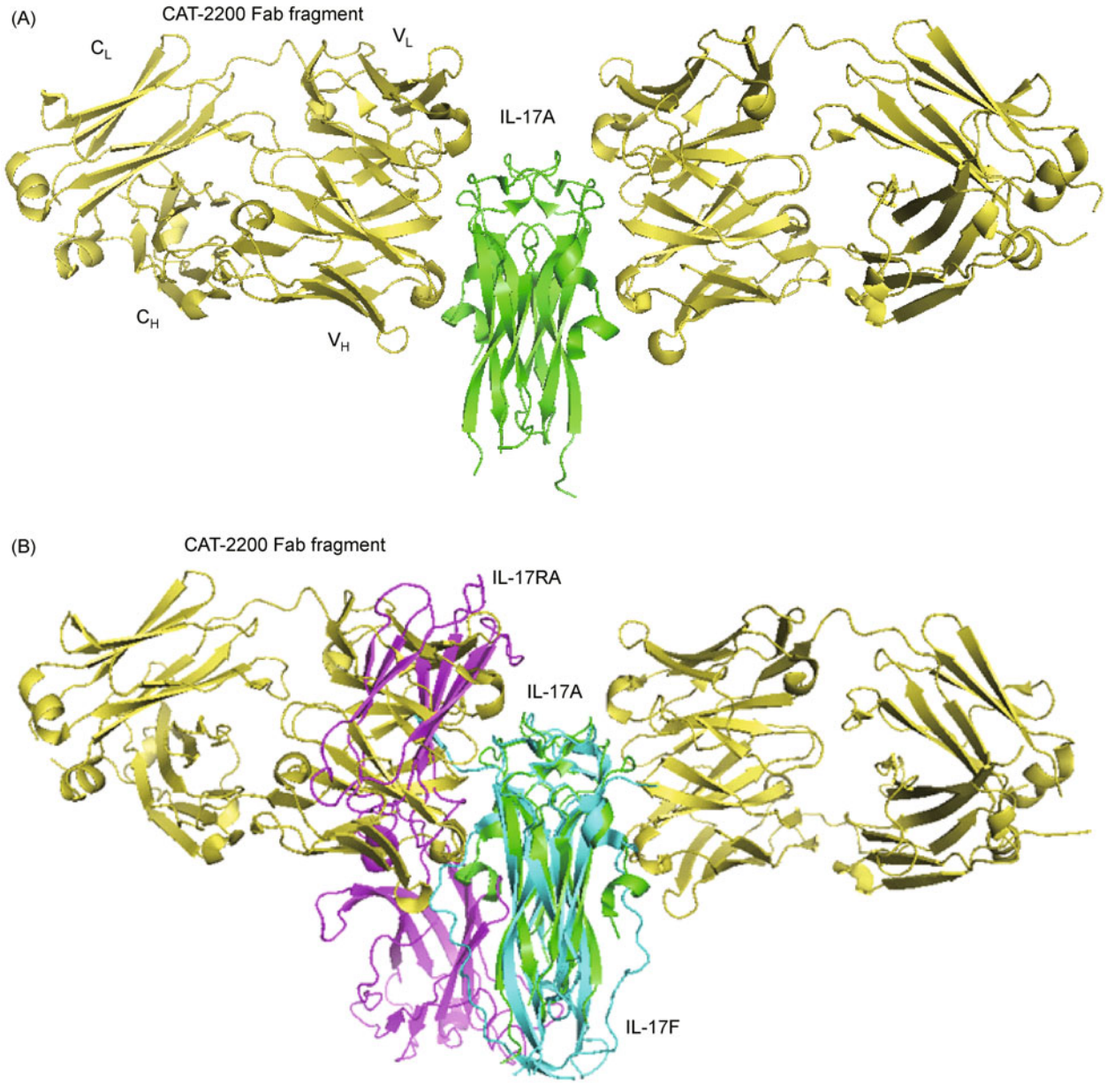

Figure 6. Comparative structural analysis of IL-17A/Fab and IL-17F/IL-17RA complexes. (A) The structure of IL-17A complexed to its neutralizing antibody (CAT2200) Fab fragments (Gerhardt et al., 2009) is rendered as ribbons. IL-17A and the antibody are colored green and yellow, respectively. (B) Superimposing the IL-17A from the IL-17A/Fab complex onto IL-17F from IL-17F/IL-17RA complex results in steric clash between the antibody and the receptor.

Nevertheless, different binding affinities of ligand to cognate receptor may explain the different cytokine effects. In humans, IL-17A activity can be inhibited by soluble IL-17RA and IL-17F inhibited by IL-17RC, respectively, whereas soluble IL-17RA/IL-17RC heterodimeric receptors are required to inhibit IL-17F/IL-17A activity (Wright et al., 2008). Furthermore, the distribution of IL-17RA and IL-17RC in tissues seems to be different. IL-17RA mRNA highly expresses in T cells and lymphoid tissues, while IL-17RC mRNA in non-hematopoietic tissues such as the colon, small intestine, and lung (Ishigame et al., 2009). In addition, the existence of several isoforms of these receptors suggests a large number of splicing variants. Thus, the differential expression and their alternative splicing forms of IL-17 receptors may contribute to different roles of IL-17A and IL-17F.

Early studies showed that IL-17A and IL-17F induced inflammatory cytokines in mouse embryonic fibroblasts

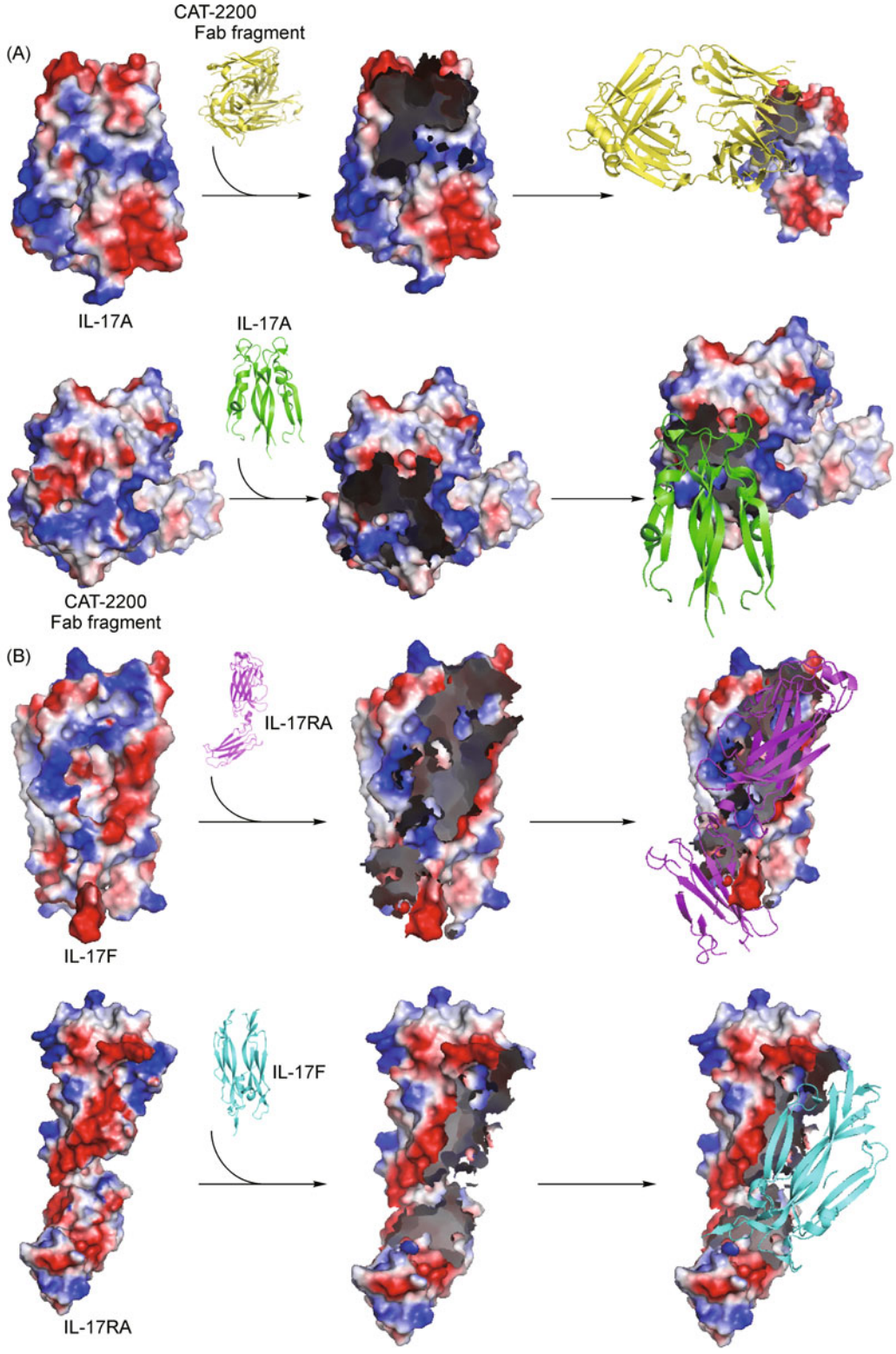

Figure 7. Electrostatics surface potentials of the complex structures before and after interactions. The buried surface areas are missing to indicate the interaction area. (A) The electrostatic potential surfaces of IL-17A and CAT-2200 Fab fragment are displayed at a level of ± 58.8 kT/eV (blue, +; red, −) before and after interaction with each other. (B) The electrostatic potential surfaces of IL-17F and IL-17RA are displayed at a level of ± 61.1 kT/eV (blue, +; red, −) before and after interaction with each other.

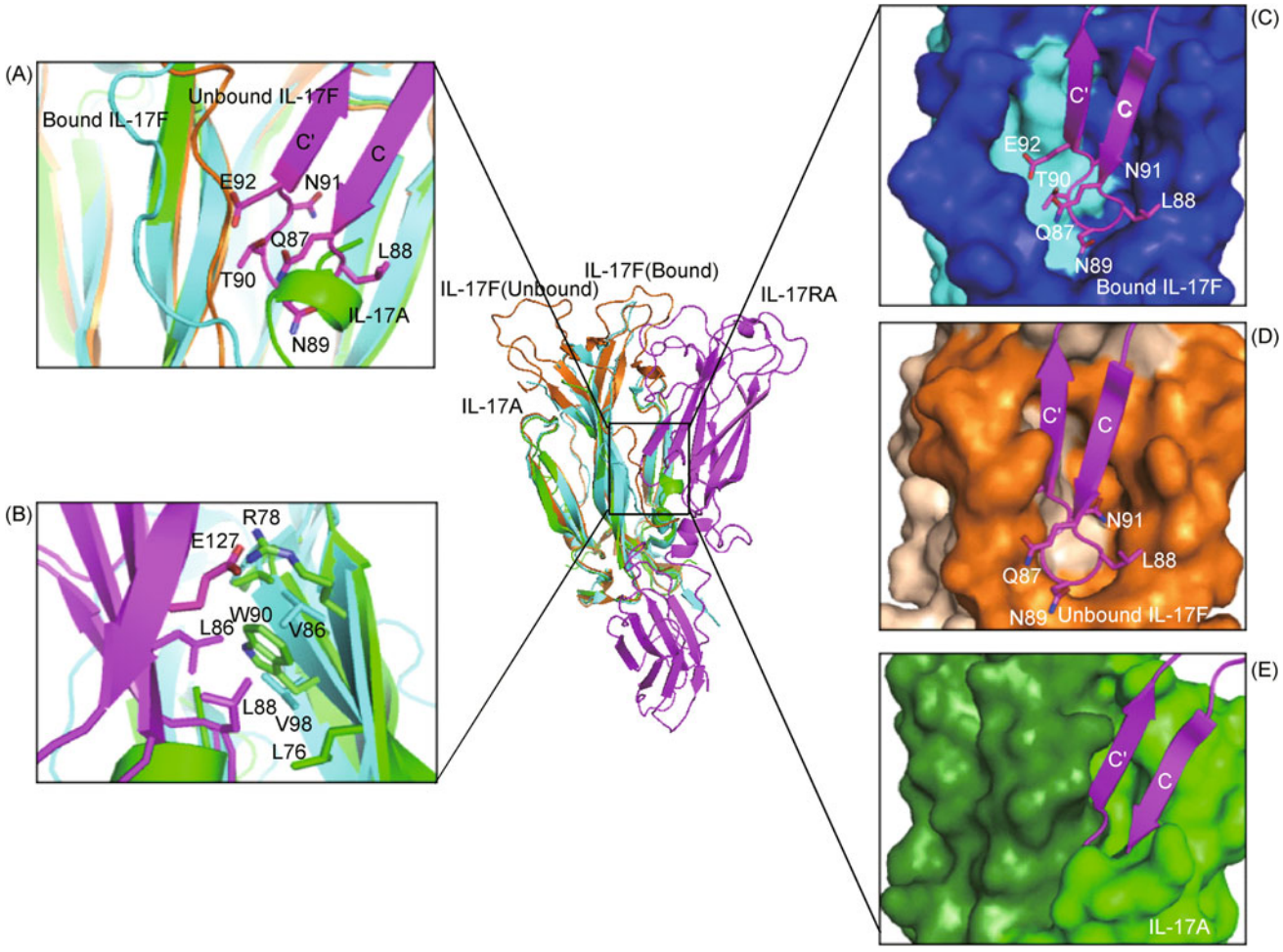

Figure 8. The interactions of IL-17RA and IL-17s are different between IL-17A and IL-17F. We superimposed IL-17A (green) from the IL-17A/Fab structure or unbound IL-17F (orange) onto bound IL-17F (cyan) from IL-17F/IL-17RA structure to model the interaction between IL-17RA (magenta) and IL-17s (in the center). The boxed regions present the regions of the interface in a greater detail. (A) The N-terminal coil region near the C-C' loop of IL-17RA undergoes a conformational change between the bound and unbound IL-17F conformations. The same region in IL-17A is substituted with a small α-helix which is potentially clashed with the C-C' loop of IL-17RA. (B) The interactions of IL-17RA and IL-17A. Contact residues are presented as "stick" models, and black dotted lines represent salt bridges. (C) Surface representation of the "knob-in-hole" IL-17F binding pocket. (D) The counterpart of the "knob-in-hole" IL-17F binding pocket in unbound IL-17F dimer modeled by superimposing on bound IL-17F. (E) The counterpart of the "knob-in-hole" IL-17F binding pocket in IL-17A modeled by superimposing on bound IL-17F.

(MEFs) through the activation of NF-κB and mitogen-activated protein (MAP) kinase pathways (Shalom-Barak et al., 1998; Awane et al., 1999). Following studies showed that tumor necrosis factor receptor-associated factor 6 (TRAF6), an E3 ubiquitin ligase, was required for this activation (Schwandner et al., 2000). The existence of other adaptor (s) is proposed because there is no TRAF6 binding site(s) in the IL-17 receptor (Novatchkova et al., 2003). All members of IL-17 receptor family contain a conserved sequence segment that shares similar residues to the conserved motifs of Toll-like receptors/IL-1R domain (TIR). This domain was named as STIR [SEFIR (similar expression to fibroblast growth factor genes and IL-17Rs) and TIR] (Novatchkova et al., 2003). The SEFIR domain is also observed in another cytoplasmic protein, Act1, also known as CIKS, a connection to IκB kinase and stress-activated kinase (Leonardi et al., 2000; Li et al., 2000b). Further characterization by our group shows that Act1 indeed physically associates with IL-17RA through the SEFIR domain (Chang et al., 2006). The deficiency of Act1 resulted in the defect of IL-17-mediated function in fibroblasts (Chang et al., 2006). IL-17 does not utilize MyD88 and IRAK4 for cytokine induction (Chang et al., 2006). Further studies indicated that Act1 is essential for IL-17-dependent signaling in autoimmune and inflammatory diseases (Qian et al., 2007). Because both IL-17RA and IL-17RC are required for IL-17A function, it remains elusive whether Act1 and TRAF6 are recruited through IL-17RA or IL-17RC or both in mediating IL-17A and IL-17F function.

IL-17E (IL-25)

IL-25 is a distinct cytokine in the IL-17 family originally identified by sequence homology search (Fort et al., 2001; Lee et al., 2001) and its expression was first characterized in highly polarized Th2 cells, implicating its role in type-2 immune responses (Fort et al., 2001). Latter studies have suggested that IL-25 also expresses in mast cells upon IgE cross-linkage (Ikeda et al., 2003), in alveolar macrophages (Kang et al., 2005), eosinophils (Wang et al., 2007; Dolgachev et al., 2009) and basophils (Wang et al., 2007). We and others also found that IL-25 mRNA expresses in lung epithelial cells treated with allergen (Angkasekwinai et al., 2007) or intestinal epithelial cells exposed to commensal bacteria (Zaph et al., 2008). Indeed, airway epithelial MMP7 can modulate IL-25 activities in the airway during allergic asthma (Goswami et al., 2009). Furthermore, IL-25 is constitutively expressed in brain microglia and brain capillary endothelial cells to control local inflammation in the brain (Kleinschek et al., 2007) and maintain blood brain barrier integrity (Sonobe et al., 2009). These data indicate that there might be several potential IL-25 producers *in vivo*. Although data so far suggest the importance of IL-25 in type-2 immunity, the downstream signaling pathway regulating IL-25 expression and function has not yet been clarified.

A study in renal carcinoma cell lines shows that IL-25 induces the expression of proinflammatory cytokine, IL-8, through NF-κB activation (Lee et al., 2001). However, studies *in vivo* indicate that the major biologic function of IL-25 is involved in type-2 immune response (Fort et al., 2001; Pan et al., 2001; Kim et al., 2002). The receptor for IL-25 appears to be the same as the receptor for IL-17B (EVI27) but with a higher binding affinity (Shi et al., 2000; Tian et al., 2000; Lee et al., 2001). Recent finding indicates that the functional IL-25 receptor indeed needs not only IL-17RB but also IL-17RA, because mice deficient of IL-17RA or IL-17RB do not respond to IL-25 (Rickel et al., 2008). Intriguingly, we analyzed the mRNA expression of IL-17RB in helper T cell subsets and found that *in vitro* generated Th2 cells but not Th1 cells expressed IL-17RB, indicating its function in the regulation of helper T cell development (Angkasekwinai et al., 2007). By using anti-IL-17RB receptor antibody (Terashima et al., 2008), we show the surface IL-17RB expression in Th2 cells (Angkasekwinai et al., 2010). These data indicate that there might be several cell types contributing to the function of IL-25 in regulating type-2 immune response. Depending on the disease models and timing of analysis, different IL-25 responding cells may appear and participate in promoting type-2 immune responses.

The downstream signal regulating IL-25-mediated type-2 immunity is largely unclear. The adaptor protein Act1 is necessary to transmit IL-17 signals. Recent data have indicated the requirement of Act1 for not only IL-17 but also IL-25 function, although these cytokines induce very distinct biologic responses (Claudio et al., 2009; Swaidani et al., 2009). Act1 is required for IL-25-mediated allergic inflammation (Claudio et al., 2009; Swaidani et al., 2009); however, how Act1 is involved in IL-25 signaling is still elusive.

Besides participation in the regulation of type-2 immunity and Th2-associated diseases, recent studies have demonstrated the role of IL-25 in inhibiting autoimmune diseases. In EAE mouse model of multiple sclerosis, IL-25-deficient mice are highly susceptible to EAE, correlating with the increased production of IL-17 (Kleinschek et al., 2007). IL-17 blockade in IL-25-deficient mice inhibited EAE, suggesting that IL-25 can inhibit pathogenic IL-17 (Kleinschek et al., 2007). In humans, IL-25 mRNA is highly expressed in autoimmune uveitis diseases (Wright et al., 2008). Furthermore, IL-25 therapy results in a T cell-mediated dominant protective effect against autoimmune diabetes in NOD mice (Emamaullee et al., 2009). Further studies on the roles of IL-25 will provide better understanding of IL-25 function in autoimmune diseases. In addition, IL-25 has recently been found to be involved in tumor immunity (Benatar et al., 2008; Benatar et al., 2009). Treatment with IL-25 in tumor-bearing mice leads to tumor growth inhibition, in association with increased eosinophils (Benatar et al., 2009). The mechanisms by which IL-25 is involved in tumor immunity require further investigation.

CONCLUSION

In summary, three structures of IL-17 family members demonstrate limited yet unique structural features of this family. IL-17s adopt a cysteine knot fold and the interaction with their receptors is quite different from other cytokine-receptor interactions. The chemical nature of the IL-17F/IL-17RA interface is highly polar, suggesting that the interactions between IL-17s and their receptors may occur via complementary electrostatic surfaces. Extensive analyses of the IL-17 cytokine family reveal crucial roles of individual IL-17 members in immune regulation of infectious and inflammatory diseases. A novel identified Th17 lineage that expresses both IL-17A and IL-17F appears as a central regulator for autoimmune diseases and bacterial and fungal infections. These two cytokines may function as homodimeric or heterodimeric secreted protein with similar activities. However, recent characterizations of mice lacking either IL-17 or IL-17F have revealed a distinction of individual cytokines, largely mediated by the receptors and their isoforms. Unlike IL-17 and IL-17F, on the other hand, IL-25 promotes type-2 immune responses but inhibits autoimmune diseases. The usage and regulation of IL-17 family receptors and the regulation and function of individual IL-17 family cytokines require further investigation. The structure and function of other IL-17 cytokines, including IL-17B, IL-17C and IL-17D, are largely unknown (Table 1). Further studies on the structure and function of this important cytokine family may

Table 1 Distribution and functions of IL-17 family and their receptors

Family member	Other names	Ligand or receptor	Distribution	Main functions	Binding biases
IL-17A	IL-17, CTLA8	IL-17RA, IL-17RC	Th17 cells, CD8+ T cells, γδ T cells, NK cells, NKT cells and LTi cells	Promote autoimmune diseases and control certain bacterial and fungal infection	Prefer IL-17RA to IL-17RC
IL-17B	CX1, IL-20	IL-17RB	Cells of the gastrointestinal tract, pancreas and neurons	Activate TNF-α and IL-1β release in THP-1 cells	High affinity to IL-17RB
IL-17C	CX2, IL-21	IL-17RE	Cells of the prostate and fetal kidney	Activate TNF-α and IL-1β release in THP-1 cells	Prefer IL-17RE
IL-17D	IL-22, IL-27	Unknown	Cells of the muscles, brain, heart, lung, pancreas and adipose tissue	Promote a pro-inflammatory gene expression profile in endothelial cells	Unknown
IL-17E	IL-25	IL-17RA, IL-17RB	Th2 cells, mast cells, alveolar macrophages, eosinophils , epithelial cells, brain capillary endothelial cells	Promote type 2 immune response and inhibit autoimmune diseases	Prefer IL-17RB to IL-17RA
IL-17F	ML-1	IL-17RA, IL-17RC	T cells, innate immune cells, and epithelial cells	Drive inflammation and autoimmunity, neutrophil recruitment	Prefer IL-17RC to IL-17RA
IL-17RA	IL-17R, CD217	IL-17A, IL-17F, IL-17E	Ubiquitously expressed, particularly high levels in haematopoietic tissues	Necessary for signal transduction mediated by IL-17A, IL-17A–IL-17F and IL-17F	Prefer IL-17A to IL-17F
IL-17RB	EVI27, IL-17RH1	IL-17B IL-17E	Expressed by various endocrine tissues as well as the kidneys, liver and Th2 cells	Pair with IL-17RA to form a functional receptor complex for IL-17E	Prefer IL-17B to IL-17E
IL-17RC	IL-17RL	IL-17A IL-17F	Nonhematopoietic tissues such as the colon, small intestine, and lung	Complex with IL-17RA to mediate IL-17 signaling	Prefer IL-17F to IL-17A
IL-17RD	SEF, IL-17RLM	IL-17A? FGF-R?	High expression kidney, heart, small intestine, colon, skeletal muscle, brain, lung and spleen	Mediate IL-17 signaling Inhibit FGF signaling and facilitate EGF signaling	Interaction with IL-17RA or IL-17RB
IL-17RE	NA	IL-17C	NA	Might promote proliferation	Prefer IL-17C

CTLA8, cytotoxic T lymphocyte antigen 8; IL-17R, interleukin-17 receptor; SEF, similar expression to FGF genes; FGF, fibroblast growth factor; EGF, epidermal growth factor; FGF-R, FGF receptor; NKT, natural killer T; LTi, lymphoid tissue inducer; NA, not applicable; TNF-α, tumor necrosis factor α; THP-1 cells, a human leukemia monocytic cell line; Th, T helper.

provide better understanding of the IL-17 family in immunopathology and development of immunotherapeutic strategies for the treatment of associated diseases.

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ABBREVIATIONS

EAE, experimental autoimmune encephalomyelitis; DSS, dextran sulfate sodium; G-CSF, granulocyte colony-stimulating factor; IL-17, interleukin-17; MAP, mitogen-activated protein; MEFs, mouse embryonic fibroblasts; MMP, matrix metalloproteinase; NGF, nerve growth factor; NF-κB, nuclear factor kappa B; NTs, neurotrophins; TNFR, tumor necrosis factor receptor; TRAF6, TNF receptor-associated factor 6

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