Chapter 4
Interleukin-10 Family Cytokines Immunobiology and Structure

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Abstract The Interleukin (IL)-10 cytokine family includes IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26, which are considered as Class 2α-helical cytokines. IL-10 is the most important cytokine in suppressing pro-inflammatory responses in all kinds of autoimmune diseases and limiting excessive immune responses. Due to protein structure homology and shared usage of receptor complexes as well as downstream signaling pathway, other IL-10 family cytokines also show indispensable functions in immune regulation, tissue homeostasis, and host defense. In this review, we focus on immune functions and structures of different cytokines in this family and try to better understand how their molecular mechanisms connect to their biological functions. The molecular details regarding their actions also provide useful information in developing candidate immune therapy reagents for a variety of diseases.

Keywords Interleukine-10 · Class 2α-helical cytokines · IL-19 · IL-20 · IL-22 · IL-24 · IL-26 · IFN-λ

4.1 Introduction

The IL-10-related cytokine family includes several members. IL-10 is considered as one of the most important cytokines for suppressing unnecessary immune responses. IL-19, IL-20, IL-22, IL-24, and IL-26 are members of the IL-20 subfamily, which is part of the IL-10 family. IL-28A/B and IL-29 are also known as interferon IFN-λs. IL-10 family cytokines signal through heterodimeric receptors comprising various combinations of several shared receptor subunits: IL-20Rα (shared by IL-19, IL-20, IL-24, and IL-26), IL-20Rβ (shared by IL-20 and IL-24), IL-10Rβ (shared by IL-10, IL-22, IL-26, IL-28, and IL-29), and IL-22Rα (shared by IL-20 and IL-24) as well as IL-10Rα (specific for IL-10) (Fig. 4.1). Interestingly, IL-20 and IL-24 could bind to either IL-20Rβ/IL-20Rα or IL-20Rβ/IL-22Rα heterodimeric receptors. Whether these two signaling pathways regulate different downstream signal pathways remains

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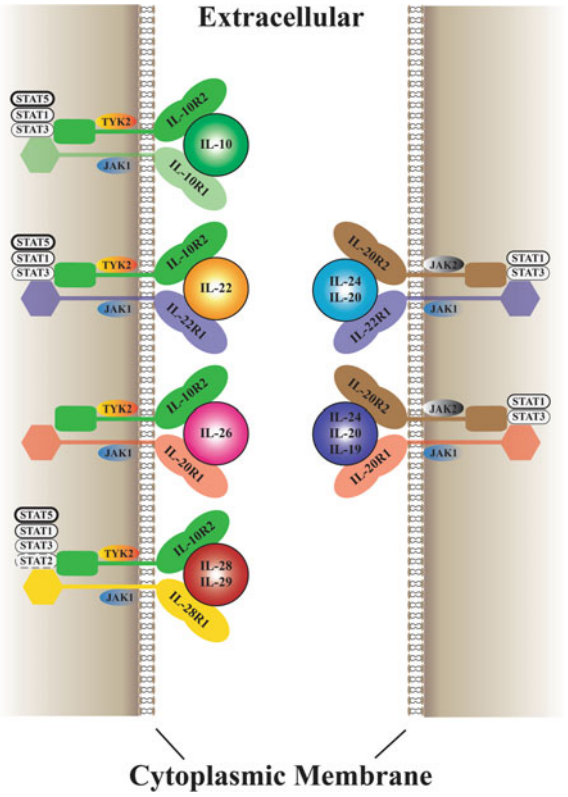

Fig. 4.1 Summary of IL-10 family cytokines and their receptors in JAK–STAT pathway. These cytokines share common features in their receptors. The IL-10R2 subunit (Green, left) is shared by IL-10, IL-22, IL-26, and IL-28/29; IL-20R2 (Brown, right) subunit is shared by IL-19, IL-20, and IL-24. Similarly, the IL-22R1 subunit (Purple) can be recognized by IL-22, IL-20, and IL-24. The IL-20R1 (Salmon) is shared by IL-26 and IL-19/IL-20/IL-24 complexes with their own receptors. These receptors signal through cytoplasmic membrane to the downstream JAK–STAT pathway

unknown. Due to the cross-usage of cytokine receptors, data collected from receptor knockout mice could not show the true functions of these receptors. For examples, IL-22 binds to IL-10Rβ and IL-20Rα, which is also shared by IL-10/IL-22 and IL-20/IL-24/IL-22, respectively.

IL-10 and IL-22 are produced mainly by immune cells, including T cells, B cells, nature killer (NK) cells, monocytes, macrophages, and dendritic cells (DCs). Lymphoid tissue inducer (LTi)-like subsets and innate lymphoid cells (ILC) also secreted IL-22 [1]. IL-19, IL-20, and IL-24 are expressed by various immune cells, particularly T helper (Th)2 cells and tissue cells including keratinocytes, epithelial cells, and endothelial cells [2]. The IL-20 subfamily plays a critical role in host defense, tissue protection, and regulation of autoimmune responses. IL-28A/B and IL-29 are not discussed in this chapter.

Tissue distribution of the IL-10 family ligands and receptors are also different. Unlike IL-10Rα, which is mainly expressed on immune cells, IL-20Rα and IL-22Rα are highly expressed on epithelial cells, indicating important roles of the IL-20 subfamily cytokines in regulating tissue inflammation, regeneration, and protection. In autoimmune diseases, the IL-20 subfamily cytokines are involved in pathogenesis

development, such as inflammatory bowel disease (IBD), rheumatoid arthritis (RA), and psoriasis [2, 3].

In this review, we will emphasize the immune functions of the IL-10 family cytokines together with their receptor complex structure, trying to bridge these two parts for a better understanding, from the dimension of protein structure to immune system function.

4.2 Interleukin-10

IL-10 starts a wide variety of immune inhibiting functions when it binds to its cellular receptor complex IL-10Rα/IL-10Rβ. IL-10 was first discovered as a cytokine synthesis inhibitory factor by preventing cytokines production of Th1 cells [4]. Further studies showed that IL-10 could also inhibit cytokines production ability of antigen-presenting cells (Macrophages and DCs) [5, 6] as well as co-stimulation of molecular expression (CD80, CD86) [7]. Today, IL-10 is considered as a key anti-inflammatory cytokine produced by many different kinds of immune cells and tissue epithelial cells. IL-10 receptor expression is found mainly on immune cells, including $CD4^+$ T, $CD8^+$ T cells, B cells, DCs, macrophages, NK cells, mast cells, eosinophils, and neutrophils, while its expression on the newly characterized ILC1, ILC2, and ILC3 cells are not well studied.

The important function of IL-10 was established in early genetic studies. Mice deficient in IL-10 or IL-10Rβ develop spontaneous enterocolitis [8, 9]. Biallelic mutations in IL-10 lead to infantile enterocolitis. Polymorphisms in IL-10 are associated with ulcerative colitis (UC) and Crohn's disease (CD), and human IL-10Rα SNPs are related to early-onset UC [10–12], indicating that the IL-10/IL-10R signaling pathway plays an important role in the regulation of intestinal tissue homeostasis and prevention of IBD. However, which IL-10-responding immune cells play the most essential role in gut homeostasis has not been fully identified. Recently, Jung S group showed that mice with $CX3CR1^+$ macrophages, which does not express IL-10Rα, developed severe spontaneous colitis [13]. Similarly, Scott B. Snapper group proved that macrophages-derived IL-10 is dispensable for preventing gut inflammation in $Rag2^{-/-}$IL-10R$\beta^{-/-}$ mice [14]. Moreover, Geiger TL group, by using conditional knockout (KO) mice in which macrophages specifically lacking IL-10Rα, proposed a further mechanism of colitis in which IL-10 suppresses caspase-1 activation and caspase-1-dependent maturation from pro-IL-1β to IL-1β. This IL-1β is essential for the development of Th17 cells compared to the IL-6 in colon. Therefore, macrophages lacking IL-10 signaling skew the cytokine dependency of Th17 cell development required for colitis pathogenesis [15]. Together, these three studies established IL-10R signaling in intestinal macrophages as the critical factor in controlling intestinal inflammation. IL-10 was recently reported to be involved in the mTOR signaling pathway by Ruslan Medzhitov. Their study demonstrated that the expression of DDIT4 is strongly upregulated by IL-10 during macrophages activation via IL-10–STAT3–DDIT4 axis. This pathway is important for the inhibition of

mTORC1 when macrophage was fully activated [16]. Thus, it reveals a key role of IL-10 in controlling the cellular metabolism via inhibiting mTORC1, indicating that IL-10 regulates the metabolic processes might be important for controlling inflammatory responses under inflammation condition. IL-10 not only directly inhibits pro-inflammatory TH17 cells [17], but also has a direct effect on $CD4^+Foxp3^+$ regulatory T cells (Tregs) and promotes their suppression function [18].

Human IL-10 gene is 2 kb long in chromosome 1q32 and includes five exons. Each exon encodes different structure parts of IL-10: exon 1 (signal peptide and the A helix); exon 2 (AB loop and Helix B); exon 3 (C and D helices); exon 4 (DE loop and the E helix); and exon 5 (F helix) [19].

The structures of the genes encoding IL-10Rα and IL-10Rβ are very similar to each other and are also similar to other members of the Class 2 cytokine receptor family. They both contain 7 exons: exon 1 encodes the signal peptide; exon 2 to exon 5 encode two SD100 domains; exon 6 and exon 7 encode the JAK and STAT binding site [20]. When IL-10 binds to its receptor complex, JAK1 (on IL-10Rα chain) and Tyk2 (on IL-10Rβ chain) are activated [21]. This further leads to the STAT3 phosphorylation and downstream genes expression, such as SOCS-1 and SOCS-3 [22]. Mechanistically, Tschopp J group found that type I IFN could induce IL-10 in a STAT1-dependent manner, and this autocrine IL-10 diminishes IL-1β and IL-1α precursor amounts via STAT3 pathway in the earlier stage (4 h) [23]. Moreover, long-term (24 h) lipopolysaccharide (LPS) exposure could help IL-10 dampen NLRP3 expression to control inflammasome activation and subsequent caspase-8 activation, which inhibits the process of cleavage of pro-IL-1β to activate IL-1β [24]. IL-10 is a regulatory cytokine that is known for its negative role in inflammation. This might explain why *IL-10*$^{-/-}$ mice exhibit hyper-inflammation and are susceptible to IBD [8, 15].

IL-10 is considered as an immunoregulatory cytokine for a long time, although how IL-10 exerts the inhibitory function is not fully understood. A recent study found the detail about how IL-10 controlled $CD8^+$ T cells during chronic viral infections. Smith et al. observed that IL-10 could induce Mgat5, a glycosyltransferase which further helps N-glycan to branch on surface glycoproteins. N-glycan finally increases the antigenic threshold required for T cell activation [25]. This new IL-10–Mgat5–N-glycan axis may inhibit not only the function of $CD8^+$ T cells but also the function of $CD4^+$ TH17 and TH1 cells.

IL-10 expression was only partially restored by inducing ERK activation in BMDMs (Bone marrow-derived macrophage) [26], indicating that NF-κB-mediated regulation of IL-10 production involves in both ERK-dependent and ERK-independent mechanisms [27]. Moreover, NF-κB p65-activated human DCs prolonged and increased transcription level of IL-10, confirming that TLR-induced NF-κB activation is essential for IL-10 production [28]. IL-10 can also be produced by TH1, TH2, and TH17 cells, all of which require ERK activation [29], indicating that a basic molecular mechanism exists for IL-10 production by immune cells. Furthermore, LPS- or CpG-activated macrophages [30], DCs [31], and blood monocytes [32]-produced IL-10 could be greatly reduced by inhibition of p38 signaling. Chemical inhibition of the p38 did not compromise the production of IL-10 by TH1, TH2,

or TH17 cells [29, 33], suggesting that the role of ERK is dominant over that of p38 in these cells, although it remains unclear in other TH cells (TH9, TH22, and TFH cells).

The IL-10 family cytokines and their closely related interferon (IFN) family cytokines belong to a larger Class II cytokine family. The Class II family cytokines were originally defined by virtue of their interactions with Class II cytokine receptors. Overall, the Class I and Class II cytokine receptors share a similar extracellular architecture consisting of tandem repeats of Ig-like domains. The Class II receptors differ from Class I receptors on the basis of sequence analysis [19]. For instance, the Class II cytokine receptors lack the canonical Trp-Ser-X-Trp-Ser motif, which is found in the extracellular domain of the Class I receptors, and differ in the number and spacing of their cysteine residues.

Receptor-bound IL-10 contains two domains, which are almost the same as unbound IL-10. Each domain consists of six α-helices: helices A, B, C, and D are donated from one chain and helices E and F are from the other chain (Fig. 4.2a). Interestingly, soluble (s) IL-10R1 also folds into two domains and forms an L-shaped structure (Fig. 4.2b). The topology of each domain is closely related to fibronectin type III (FBN-III) modules. B strands A, B, E and G, F, C, C′ form two antiparallel β-sheets (Fig. 4.2b). sIL-10R1 D1 structure is similar to D1 of IFN-γR1, including the most notable "WSXWS-like" motif. This motif consists of residues His^{87}, Ser^{88}, Asn^{89}, Trp^{90}, and Thr^{91}.

The site I interface is characterized by extensive interactions between IL-10 and sIL-10Rα loops located at the D1/D2 interface (Fig. 4.2a, b). A total of 27 residues from IL-10 directly contact with sIL-10R1.

Around two-third residues in the interface are polar residues and are clustered into two interaction surfaces, Ia and Ib. Site Ia having the AB loop is located in the center of the bend in helix F. Site Ib is near the N-terminus of helix A and the C-terminus of helix F. Site Ia accounts for approximately 67% of the total buried surface area in the site I interface and receptor-binding loops L2–L4 interact exclusively with site Ia; site Ib is centered on the ion pair between IL-10 residues Arg^{27} and Glu^{151} with loops L5 and L6 in D2 interacting with site Ib (Fig. 4.2c, d) [34].

4.3 Interleukin-22

The major function of IL-22 is to provide a protective inflammatory response toward pathogens at boundary tissues, such as skin, lung, and gut. IL-22 receptor is mainly expressed on epithelial cells located in skin, pancreas, intestine, liver, and lung. The IL-22–IL-22R pathway has been shown to modulate the expression of many genes involved in tissue protection, survival, differentiation, and remodeling [35–37].

IL-22 was first cloned in IL-9-activated conventional T cells [38]. Human *IL-22* gene is located at chromosome 12q15, near the genes encoding IFN-γ and IL-26, which also belongs to the IL-10 family [39]. IL-22 gene includes five exons, the

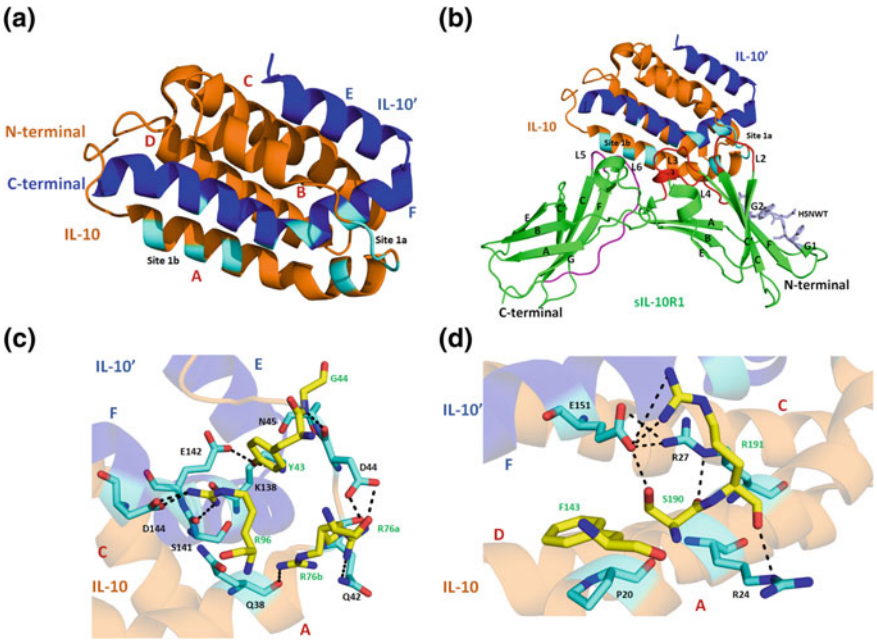

Fig. 4.2 Structure of IL-10 (PDB ID: 1J7 V). **a** Helices A, B, C, and D are donated from one copy (IL-10, orange) and helices E and F from the asymmetric copy (IL-10′, blue). Residues on site 1a and 1b are colored in cyan. **b** Structure of IL-10/sIL-10R1 complex. IL-10 is from one copy (orange), and IL-10′ is from the asymmetric copy (blue). Residues on site 1a and 1b are colored in cyan. sIL-10R1 is colored in green. L2, L3, and L4 are colored in red. L5 and L6 are colored in magenta. HSNWT region is colored in light blue. **c** Stick diagram of IL-10/sIL-10R1 interface. Site 1a of IL-10 residues are colored in cyan and sIL-10R1 residues are colored in yellow. Oxygen atoms are red and nitrogen atoms are blue. Helices A and C are donated from one copy (IL-10, orange) and helices E and F from the asymmetric copy (IL-10′, blue). **d** Key residues of IL-10/sIL-10R1 interface at site 1b

537 bp open reading frame (ORF) of *IL-22* gene encodes a 179 amino acid protein; mouse and human IL-22 share 79% homology [40].

Primarily, lymphoid lineage cells produce IL-22, encompassing cells of adaptive immune systems, including αβ T cells and γδ T cells, as well as innate immune cells. A subset of NKT cells has also been described as being capable of producing IL-22 [41]. Much like γδ T cells, TH17 cells, ILC3-, and IL-22-producing NKT cells express CCR6, IL-23R, and RORγt [42, 43]. IL-22-producing NKT cells required TCR-CD1d interaction to stimulate IL-22 production; neutrophils also produce IL-22 in gastrointestinal tract in experimental models of colitis [36, 44].

Aryl hydrocarbon receptor (AhR), notch signaling, IL-23, IL-1β, and IL-7 can control IL-22 production [36, 45]. AhR is critical for ILC3-derived IL-22 production, either as a direct regulator of IL-22 gene expression or as a regulator of ILC3 and TH17 development [46, 47]. T-bet is also required for the specific development and differentiation of IL-22-producing subsets, such as NCR^+ and NCR^- ILC3 [48].

Notch signaling also provides an important signal in regulating IL-22 production [49]. IL-23 and IL-1β signaling is essential for the production of IL-22 by TH17 and ILC3 cells [35, 50, 51]. ILCs are a newly described heterogeneous population of immune cells possessing lymphoid ontogeny. ILC3 cells expressing RORγt are potent producers of IL-22 [52]. More recently, LTi-like cells were described as potent producers of IL-22 in adult mouse and human [53, 54]. On the other hand, TGF-β can prevent IL-22 production [55]; IL-27 and ICOS have also been shown to have the inhibition ability of IL-22 production [56, 57].

IL-22 is expressed in a broad array of tissues, including liver, lung, skin, thymus, pancreas, kidney, gastrointestinal tract, synovial tissues, heart, adipose tissue, breast, and eye [58, 59]; and its receptor is expressed on stromal and epithelial cells of those tissues.

IL-22 shows a double-edged sword function in autoimmunity, displaying both pro-inflammatory and anti-inflammatory properties in different animal models. For example, the role of IL-22 in asthma and allergic rhinitis is controversial: some authors suggest that IL-22 has a pro-inflammatory effect, while others state that it has anti-inflammatory properties.

On the other hand, there is extensive evidence that IL-22 mediates protection and regeneration of epithelial tissues in experimental models, including hepatitis, pancreatitis, and colitis [60]. IL-22 can also greatly induce expression of pro-inflammatory molecules, including IL-1-, IL-6-, IL-8-, IL-11-, GM-CSF-, and LPS-binding protein in other models [61, 36]. These have led to debate about whether IL-22 is tissue protective or proinflammatory. Further studies are needed to explore the detailed mechanisms.

The IL-22/sIL-22R1 crystal structure was solved by SAD phasing and refined at 2.5 Å resolution [62]. IL-22 and sIL-22R1 form a 1:1 complex in the crystal (Fig. 4.3a). sIL-22R1 has two FBN-III domains (D1 and D2) and shapes an "L" structure. The IL-22/sIL-22R1 complex is very similar to the dimeric IL-10/sIL-10R1 complex.

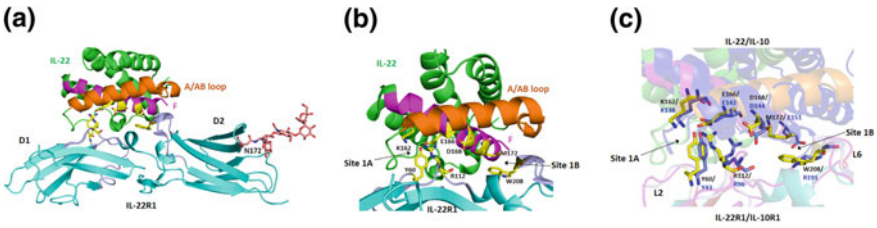

Fig. 4.3 Structure of IL-22 (PDB:3DGC). **a** IL-22 and IL-22R1 are shown as ribbon and colored in green and cyan, respectively. Helix A/AB loop and helix F that form the sIL-22R1 binding site are colored orange and magenta, respectively. Glycosylation of N172 at IL-22R1 is shown as stick. **b** IL-22/sIL-22R1 site 1 interface. Residues involved in site 1 interface are shown as yellow sticks. **c** Key residues of IL-22 and IL-10 site 1 interfaces. Residues from IL-22/IL-22R1 are colored in yellow, and residues from IL-10 and IL-10R1 are shown in blue color

The IL-22/sIL-22R1 interface consists of five sIL-22R1 loops (L2–L6) of D1 and D2 domains, together with IL-22 residues presented on helix A, helix F, and AB loop (Fig. 4.3b). This interface may also be separated into two major contact surfaces, site Ia and site Ib, which are also shown in IL-10/IL-10R complex [34]. L2–L4 loops of the D1 domain form contacts in site Ia, while loops L5 and L6 from D2, contact site Ib (Fig. 4.3b). The important feature of site Ia Tyr^{60} and Gly^{61} on IL-22R1 are inserted into a small cavity, helix F, and the AB loop on IL-22 (Fig. 4.3c) [62]. In contrast to the extensive site Ia interface, IL-22/sIL-22R1 site Ib is made up almost entirely of Van der Waals interactions between IL-22 helix F residues Met^{172} and Arg^{175}, paired with Thr^{207} and Trp^{208} of IL-22R1. In IL-22/sIL-22R1, it contains 1,141 $Å^2$ of buried surface area and 11 of 12 hydrogen bonds identified in the complex [62].

4.4 Interleukin-19

IL-19, IL-20, and IL-24 are the IL-20 subfamily members within the IL-10 family, all of which can bind to IL-20Rs, and lead to activation of the STAT3 signaling pathway. IL-20Rβ can pair with either IL-20Rα or IL-22Rα, forming type I IL-20R complex or type II IL-20R complex. IL-20 and IL-24 have both signaling ways while IL-19 can only signal through the IL-20Rα/IL-20Rβ receptor complex [63, 64].

IL-19 can regulate different immune cell populations, including T cells and monocytes. IL-19 is considered to be a Th2 cytokine. It is not only produced by Th2 cells, but also exerts positive feedback on Th2 cells for further Th2 cell differentiation and cytokine production such as IL-4, IL-5, IL-10, and IL-13. IL-19 can suppress *S. aureus*-induced IL-17A production from human PBMC26 [65]; along with this finding, blockade of IL-19 increases the production of IFN-γ [66]. In contrast, the study showed that *S.aureus* infection could trigger IL-19 production of keratinocytes, which significantly suppresses the production of IL-17A from γδT cells [67]. These reports indicate that IL-19 may affect the functions of adaptive and innate T cells in different manners. A similar dichotomy in response to IL-19 may also occur in non-T cells. IL-19 induced IL-10 production in human monocytes with M2 phenotype, whereas it induced IL-6 and TNF-α expression in mouse M1 monocytes [68, 69]. Similarly, IL-19-treated monocytes [70] and synovial fibroblasts [71] induce large amount of IL-6, TNF-α, and ROS. IL-19 stimulation also leads to lung epithelial cytokines (IL-1β, IL-6, and IL-8) production and chemokines (CCL5 and CXCL9) expression [72, 73].

IL-19 is also involved in the development of autoimmune diseases, such as psoriasis [74, 60], and IBD [75–77]. In dextran sodium sulfate (DSS) induced colitis model, the disruption of the epithelial barrier with DSS leads to increased IL-19 expression together with activated macrophages in the inflamed colonic lamina propria [78].

The crystal structure of IL-19 was solved at the resolution 3.5 Å and was later refined with the resolution of the 1.95 Å [79]. The structure of IL-19 includes residues 4–104, residues 108–159, and 164 water molecules. All residues have conformations corresponding to either most favorable (93%) or allowed (7%) regions on the

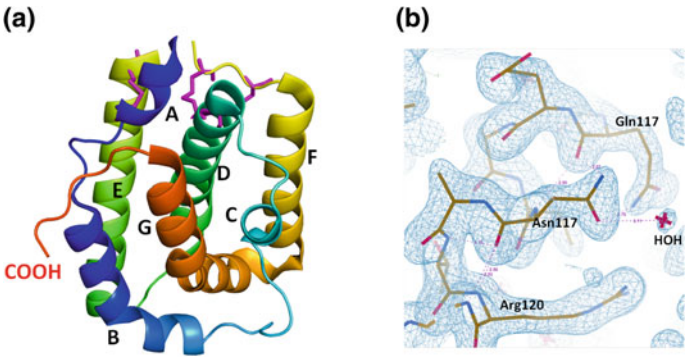

Fig. 4.4 Stereo view of IL-19 Crystal structure (PDB:1N1F). **a** Cartoon diagram of helices A–G, rainbow-colored with blue at N-terminal, and red at C-terminal. S–S bond formed by Cys^{10}–Cys^{103}, Cys^{57}–Cys^{109}, and Cys^{58}–Cys^{111} are colored in magenta. **b** Electron density map near the second putative glycosylation site, Asn^{117}. Atoms are colored as follows: carbon atoms are *brown*, nitrogen atoms are *blue*, and oxygen atoms are *red*. Possible interactions of the side chain atoms of Asn^{117} (distances less than 3.2 Å) are shown as *dashed lines*

Ramachandran plot (Fig. 4.4a). The glycosylation sites Asn^{38} was found to be bound with oligosaccharide while Asn^{117} was not. IL-19 contains seven amphipathic helices (A–G) of different lengths [79], forming a unique seven-helix bundle with an extensive internal hydrophobic core and three disulfide bridges located on the top of the bundle. The position of helix A is linked with C-terminus of helix E by the disulfide bridge Cys^{10}–Cys^{103}. The second and third disulfide bridges, Cys^{57}–Cys^{109} and Cys^{58}–Cys^{111}, hold together the N-terminus of helix D, the interhelical loop EF, and the N-terminus of helix F (Fig. 4.4b) [79].

4.5 Interleukin-20

The cDNA of IL-20 is 925 bp with an ORF of 531 bp encoding a putative polypeptide of 176 amino acids. The IL-20 protein shows 40%, 33%, and 28% amino acid identity to IL-19, IL-24, and IL-10, respectively [19]. IL-20 is produced by monocytes, epithelial cells, and endothelial cells [63]. IL-20 can bind with different receptor complexes: IL-20R1/IL-20R2 or IL-22R1/IL-20R2 [64], however, the biological function is not clearly studied.

IL-20 is thought to be a cytokine involved in the pathogenesis of inflammatory diseases, such as psoriasis, rheumatoid arthritis, and atherosclerosis [80, 81]. It also plays an important role in regulating angiogenesis [82], osteoblastogenesis [83], and osteoclastogenesis [84]. Moreover, IL-20 was shown to increase cancer cell proliferation and migration [84] while the anti-IL-20 monoclonal antibody suppressed breast tumor growth in vivo. This migration and invasion rely on NF-κB-mediated MMP-9 and MMP-12 expression [85].

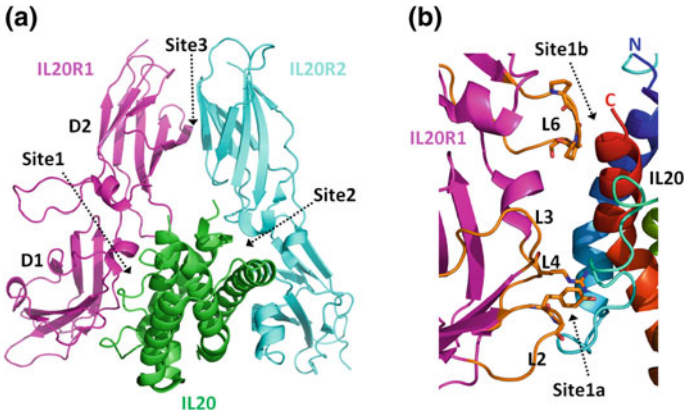

Fig. 4.5 Cartoon diagram of IL-20/IL-20R1/IL20R2 complex structure (PDB:4DOH). **a** IL-20, IL-20R1, and IL-20R2 are colored in green, magenta, and cyan, respectively. **b** Site 1a and site 1b of IL-20/IL-20R1 interface. **b** IL-20R1 is colored in magenta and IL-20 is colored in rainbow with N-terminus in blue and C-terminus in blue. L2, L3, L4, and L6 are colored in orange

The crystal structure of IL-20/IL-20R1/IL-20R2 was solved at 2.8 Å [86]. IL-20 adopts an α-helical fold and the N-terminus of IL-20 adopts a novel β-hairpin structure (Fig. 4.5a). IL-20/IL-20R1/IL-20R2 ternary complex formation is mediated by three protein interfaces, IL-20/IL-20R1 (site 1), IL-20/IL-20R2 (site 2), and IL-20R1/IL-20R2 (site 3), which bury a total of 4,236 $Å^2$ of accessible surface area (Fig. 4.5a). The IL-20/IL-20R1 site 1 interface (1,576 $Å^2$) consists of two contact surfaces, site Ia and site Ib (Fig. 4.5b). Site Ia is formed by IL-20R1 L2–L4 loops while Site 1b contacts occur between IL-20R1 L6 and the N-terminus of helix A. Site Ia contributes over 80% of the total buried surface area and most hydrogen bond interactions are identified in the IL-20/IL-20R1 interface [86]. The IL-20/IL-20R1/IL-20R2 structure clearly shows how interfaces make their distinct signaling and contribute to their specific biological properties in vivo.

4.6 Interleukin-24

IL-24 was originally identified as a tumor-suppressing protein named melanoma differentiation-associated 7 (MDA-7) [87]. IL-24 also belongs to the IL-20 subfamily, which is a part of the IL-10 family. In several autoimmune diseases, the level of IL-24 was found increased in organ-specific tissue, including inflammatory bowel disease (IBD) [88], psoriasis [89], rheumatoid arthritis (RA) [90], and keratitis [91]. Also, IL-24 was reported to play a protective role in *Mycobacterium tuberculosis*-induced infection [92]. More importantly, IL-24 has unique antitumor activity in lung, breast, and colorectal cancer model [93], while IL-20 does not. IL-24 is currently under an investigation for cancer immune therapy.

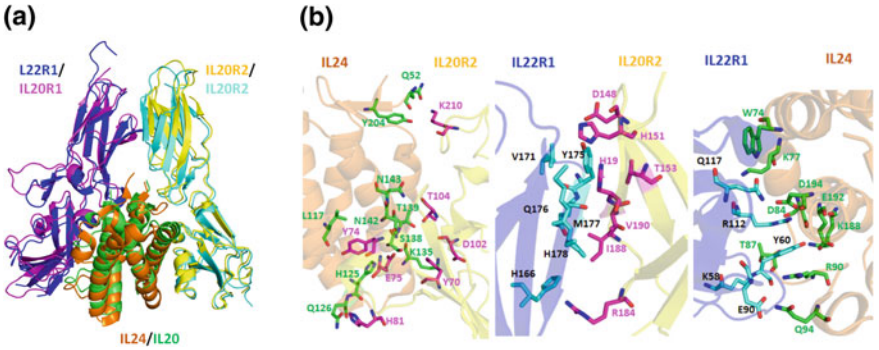

Fig. 4.6 Superposition of IL-24/IL-22R1/IL20R2 complex structure (PDB:6DF3) and IL-20/IL-20R1/IL20R2 complex (PDB:4DOH). **a** IL-24, IL-22R1, and IL-20R2 from IL-24/IL-22R1/IL-20R2 complex are colored in orange, blue, and yellow, respectively. IL-20, IL-20R1, and IL-20R2 from IL-20/IL-20R1/IL-20R2 complex are shown in green, magenta, and cyan, respectively. **b** High-affinity interface between IL-24 (orange) and IL-20R2 (golden). Residues involved in the interaction interface are shown as sticks, and colored in green and magenta for IL-24 and IL-20R2, respectively

Crystal Structure of IL-24 together with its two receptors (IL-22R1 and IL-20R2) was recently reported [94]. The extracellular fragments of IL-20R1 and IL-20R2 each consists of tandem β-sandwich domains that assemble around IL-24 to form a V-shaped complex (Fig. 4.6a) [86]. The complex structure showing the primary formation is provided by interactions between IL-24 and IL-20R2 with 13 hydrogen bonds involved. Two interactions (His^{125}–Glu^{75} and K^{135}–D^{102}) represent potential salt bridges. These salt bridges are made by Arg^{90}–Glu^{90} and Asp^{84}–Arg^{112} of IL-24 and IL-22R1, respectively. The interface between two receptor chains is tiny, with only four hydrogen bonds involved (Fig. 4.6b).

4.7 Interleukin-26

IL-26 is initially called as AK155 [95]. It also belongs to the IL-10 cytokine family. The IL-26 gene is located on chromosome 12q14, in a cluster where IFNγ and IL-22 are also positioned. Epithelial cells, macrophages, NK cells, Th1, and Th17 cells are predominant sources of IL-26 [96]. IL-26 can bind to IL-10R2/IL-20R1 and form a heterodimeric receptor complex, which is expressed exclusively by epithelial cells [97]. IL-26-mediated signaling through this receptor complex induced STAT1 and STAT3 phosphorylation.

Recently, IL-26 was found to be involved in autoimmune diseases such as rheumatoid arthritis, psoriasis, and colitis [75]. IL-26 also shows antiviral and antimicrobial effects on various immune cells. NK cells from healthy people and from HCV-infected patients are sensitive to IL-26. IL-26 could induce human $CD56^{bright}$ NK

cells upregulating TRAIL and enhancing the efficiency of killing HCV-infected hepatoma cells [98]. Moreover, TH17 cells-produced IL-26 can bind with bacterial DNA or self-DNA, indicating a specific immune function which was not observed in other cytokines. These complexes further triggered the pDC-derived IFN-α production and activation of Toll-like receptor 9, independently of the IL-26 receptor [99], indicating a unique function of IL-26 to bypass the traditional signaling pathway.

The crystal structure of the IL-26 receptor complex is not available. IL-26 could form not only dimers but also higher degree multimers. 3D homology model suggests that Cys^{11}, Cys^{100} can pair with Cys^{58}, Cys^{103} to form disulfide bonds and stabilize the helices of IL-26 [99].

4.8 Conclusions

In summary, IL-10 family cytokines have a variety of functions, IL-10 is important for immune cells while IL-22 subfamily cytokines (IL-22, IL-19, and IL-20) have effects on non-hematopoietic cells, especially epithelial cells. IL-22 is involved in epithelial regeneration and pathology in several organs depending on the context and/or cytokine milieu. All IL-10 family cytokines have similar structures and are involved in autoimmune disease. This involvement in a variety of diseases makes it an attractive target for clinical development. Exploring the crystal structure information of these cytokines and their receptor complexes is necessary to provide a more comprehensive understanding of how these molecules exert their immune function.

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