IL-22 and IL-17: An Overview

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Abstract Many studies from recent years have shown that cytokines like IL-22, IL-17A, and IL-17F play a major role in both the defense against certain microbes and the development and maintenance of chronic inflammatory diseases. These mediators are often secreted by subpopulations of T-helper cells called Th17 cells and Th22 cells, respectively. This chapter provides an overview about the common and differing properties of IL-22, IL-17A, and IL-17F with respect to their genes, protein structure, cellular sources, receptors, target cells, and biological effects. Surprisingly, with the exception of a few similarities, most basic aspects of IL-22 and IL-17A/IL-17F are different.

1 Introduction

Cytokines are proteins secreted by numerous cells that play an important role in intercellular communication. Not only do they serve in the reaction of the immune system to pathogens, but they also regulate hematopoiesis, wound healing, angiogenesis, and physiological and pathological tissue reorganization. Cytokines elicit biological effects by binding to the extracellular moiety of specific transmembrane receptor proteins in the outer membrane of cells. Mediated by the intracellular moiety of such receptors, this binding induces a coordinated series of intracellular events leading to functional changes in these cells. Due to their similarities in regard to genome location, gene structure, secreted protein structure, and receptors used, various cytokines were grouped

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into families. It is important to note that members of the same family do not necessarily exhibit similar biological effects.

The application and repression of the cytokine action set the most successful strategy for therapy of infections and autoimmune diseases, respectively. Many studies from recent years have shown that mediators like IL-17A and IL-22 play important roles in chronic immune-mediated diseases. While IL-17A belongs to the IL-17 cytokine family, IL-22 is a member of the IL-10 cytokine family.

The IL-10 family comprises IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B, and IL-29 [1]. IL-28A, IL-28B, and IL-29 (also designated as interferon-λ s) are the "youngest" members of IL-10 family and form a theoretical bridge to the type I interferon cytokine family. Interestingly, the members of the IL-10 family are encoded by genes that have similar exon–intron structures [1]. These genes are located in the human genome in three clusters: the first comprising the genes for IL-10, IL-19, IL-20, and IL-24 on chromosome 1q; the second comprising the IL-26- and IL-22-encoding genes located on chromosome 12q; and the third comprising the genes for IL-28A, IL-28B, and IL-29 on chromosome 19q [1–3]. Apart from the high amino acid (aa) identity within the interferon-λ subgroup, the aa identity between the members of the IL-10 family is approximately 13–25 %. However, characteristic aa positions are conserved. Despite the relatively low sequence identity, all family members show a strikingly similar secondary structure; these α-helical proteins are built up of six to seven helices in an antiparallel conformation [4]. All IL-10 family members exert their biological effects via heterodimeric receptor complexes composed of an R1 subunit and an R2 subunit [1]. The subunits belong to the cytokine receptor family class 2 (CRF2), which additionally comprises the receptors of the type I and type II interferons and tissue factor, a receptor for the coagulant component VIIa [1, 2]. They are related by their extracellular moieties, which include the ligand-binding residues. These 200 aa extracellular domains are composed of two tandem fibronectin type III (FNIII) domains. Each of these domains has a structural framework of seven β-strands connected by loops. Additionally, the position of several conserved cysteines and a completely conserved tryptophan characterize the CRF2. In almost any case, the R1 subunit has the longer intracellular moiety able to bind signal transducers and activators of transcription (STAT) molecules. For IL-10 and IL-22, it is believed that ligand binding initially occurs to the R1 subunit (IL-10R1 and IL-22R1, respectively). This induces a conformational change in the respective cytokine that enables it to bind secondarily to the R2 subunit (IL-10R2 in both cases), leading to an aggregation of the two receptor subunits and initiation of signal transduction. Interestingly, in the case of IL-19, IL-20, and IL-24, the initial binding occurs to the R2 subunit. Importantly, the IL-10 family members share receptor subunits (the IL-10 family comprises nine cytokines; there are only four R1 subunits and two R2 subunits for these cytokines; Table 1). For instance, the IL-10R2 subunit is also part of the receptor complexes for IL-10, IL-22, IL-26, IL-28α, IL-28β, and IL-29. Moreover, not only single receptor subunits are shared among

Table 1 Combination of receptor subunits in receptor complexes enabling the effects of the IL-10 family members

	IL-10R1	IL-20R1	IL-22R1	IL-28R1
IL-10R2	IL-10	IL-26	IL-22	IL-28 IL-29
IL-20R2	?	IL-19 IL-20 IL-24	IL-20 IL-24	?

different IL-10 family members but even whole receptor complexes (Table 1). For instance, the complex composed of IL-20R1 and IL-20R2 is used by IL-19, IL-20, and IL-24. Despite the structural relation and the use of similar or partly identical receptors, there are great differences with respect to the biologic function between several of the IL-10 family members [3, 5–9].

The IL-17 family consists of six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F [10, 11]. The genes encoding these mediators have an only moderately similar structure, which is completely different from that of the IL-10 family genes. The genes for IL-17A and IL-17F are located on chromosome 6q; the IL-17B-encoding gene is located on chromosome 5q; that of IL-17C is on chromosome 16q, the IL-17D-encoding gene lies on chromosome 13q, and the gene for IL-17E was mapped to chromosome 14q. The IL-17 family members are also structurally related. The characteristic motif is the C-terminal, so-called cysteine-knot. The highest sequence similarity exists between IL-17A and IL-17F (47.8 % identity between the mature proteins). The similarity between other members is about 20 % only. The IL-17 family members also act via receptor complexes that are composed of two type I transmembrane proteins. The receptor subunits differently assemble into receptor complexes for IL-17A and IL-17F (IL-17RA/IL-17RC), IL-17B and IL-17E (IL-17RA/IL-17RB), and IL-17C (IL-17RA/IL-17RE), while the functional receptor complex for IL-17D is not known so far [10]. Interestingly, IL-17A and IL-17F mediate in part similar biological effects [10, 12].

2 The IL-22- and IL-17-Encoding Genes

The IL-22- and IL-17A/IL-17F-encoding genes are located on different chromosomes and have different structures (Fig. 1).

The human *IL22* gene is located on the longer arm of chromosome 12, on 12q15, approximately 52 kbp and 99 kbp upstream from the *IL26* and *IFNG* locus, respectively, and has the same transcriptional orientation as these two adjoining genes (reverse strand) [13]. The *IL22* gene is 5,257 bp long and is comprised of five exons with the following lengths: exon 1, 239 bp; exon 2, 66 bp; exon 3, 144 bp; exon 4, 66 bp; and exon 5, 632 bp. The IL-22 mRNA straddles 1.147 bp (NM_020525, National Center of Biotechnology Information (NCBI), February 2012). The first 53 bp of exon 1 encode the 5′-untranslated region. The other portion of exon 1 (186 bp), the exons 2–4, and the first portion (75 bp) of exon 5 contain the

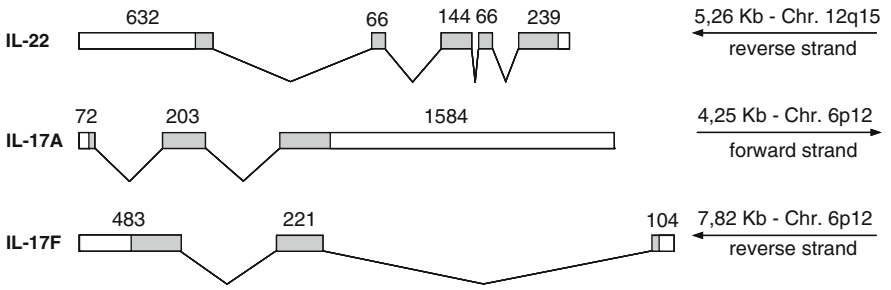

Fig. 1 *The IL-22 and IL-17A/IL-17F coding genes have different structures*. Shown are the exon–intron structures of the genes. Exons (1 cm corresponds to 250 bp) are presented as *boxes* comprising noncoding regions (in *white*) and coding regions (in *gray*). Introns (1 cm corresponds to 875 bp) are presented as *lines*. Genomic localization is also indicated

protein-coding part. The rest of exon 5 (554 bp) encodes the 3′-untranslated region, which includes six single and two overlapping copies of the ATTTA motif known to be involved in the regulation of mRNA degradation. Altogether, the open reading frame is comprised of 537 bp (without the stop codon), predicting a length of 179 aa for the encoded protein.

The human IL-17A- and IL-17F-encoding genes are located on the longer arm of chromosome 6, on 6q12, and have similar structures [11, 14]. The distance between these genes is 46 kbp. *IL17A* is located on the forward strand and has a length of 4,252 bp, and *IL17F* is located on the reverse strand and has a length of 7,815 bp. Both genes are comprised of three exons with the following lengths: exon 1, 72 (*IL17A*)/104 (*IL17F*) bp; exon 2, 203 (*IL17A*)/221 (*IL17F*) bp; and exon 3, 1,584 (*IL17A*)/483 (*IL17F*) bp. The IL-17A mRNA straddles 1,859 bp (NM_002190, NCBI, February 2012) and IL-17F mRNA 808 bp (NM_052872, NCBI, December 2011). The first 45 bp and 71 bp of *IL17A* and of *IL17F* exon 1, respectively, encode the 5′-untranslated region. The other portion of exon 1 and exon 2 and the first portion of exon 3 contain the protein-coding part. The rest of exon 3 encodes the 3′-untranslated region. Consequently, the open reading frame is comprised of 565 bp (*IL17A*) and 489 bp (*IL17F*) (without the stop codon), predicting a length of 155 aa (IL-17A) and 163 aa (IL-17F) for the encoded proteins.

3 The Structures of Secreted IL-22, IL-17A, and IL-17F

The secondary structures of IL-22 and IL-17A/IL-17F are very different.

As described above, the human *IL22* gene encodes a protein of 179 aa in length, which, after splitting off the signal peptide (33 aa), is secreted as a polypeptide of 146 aa [15]. Amino acid sequence alignment (mature proteins) revealed that human IL-22 has an 80.8 % identity to murine IL-22 [13]. Like all other IL-10 family members, IL-22 has an α-helical structure. The six helices (referred to as helices

A to F) are arranged in an antiparallel conformation resulting in a monomeric, bundle-like protein. This structure was proved upon its resolution by X-ray diffraction [16, 17]. Monomeric conformation of IL-22, at least at physiologically relevant concentrations, was also confirmed by gel filtration chromatography and dynamic light-scattering studies [16, 18]. It should be noted that in the IL-10 structure, there is a 90° angle between the first four helices and the helices E and F that leads to an entwining of two monomers forming a V-shaped dimer in which each domain of the V-shape is formed by helices A to D from one partner and helices E and F from the other partner [19, 20]. The IL-22 primary structure contains four Cys, which form two intramolecular disulfide bridge bonds (Cys40-Cys132 linking the N-terminus to the DE loop and Cys89-Cys178 linking helix C to helix F) as deduced from the X-ray structure analysis of IL-22 [16].

The theoretical molecular weight of human IL-22 is 16.7 kDa. However, the recombinant protein expressed in eukaryotic cells migrated as several bands of more than 17 kDa [21, 22]. In fact, glycosylation was found on all three potential N-linked glycosylation sites in the IL-22 sequence: one located in helix A (Asn54-Arg55-Thr56), one in the AB loop (Asn68-Asn69-Thr70), and one in helix C (Asn97-Phe98-Thr99) [22]. Interestingly, the glycosylation is not associated with a noteworthy change of the tertiary structure of IL-22 [16, 17]. However, the glycosylation on Asn54 has been found to be important for IL-22's interaction with IL-10R2, whereas no influence of any glycosylation was observed for IL-22R1 binding [22].

IL17A and *IL17F* encode proteins of 155 aa and 163 aa, respectively, in length. After splitting off the signal peptides (23 aa for IL-17A and 30 aa for IL-17), the secreted polypeptides are 132 aa (IL-17A) and 133 aa (IL-17F) long. The crystal structure of IL-17A and IL-17F was resolved and shows that the proteins form similar disulfide-linked homodimers [23, 24]. The core of the IL-17F monomer is composed of two pairs of antiparallel strands; one pair includes strands 1 and 2, while the other includes strands 3 and 4. Two disulfide bridges (Cys72-Cys122 and Cys77-Cys124) connect strands 2 and 4. A third disulfide bridge (Cys17-Cys107) connects the loop between strands 3 and 4 of one monomer to the N-terminus of the other monomer [23]. The structure of the IL-17F homodimer includes a classical Cys-knot motif, which is also found in the transforming growth factor (TGF)-β and nerve growth factor superfamilies [25]. One difference in the cysteine-knot motif of IL-17F compared with the other known Cys-knot protein families is that it only utilizes four Cys instead of the classical six Cys to form the knot. In addition to IL-17A and IL-17F homodimers, an IL-17A–IL-17F heterodimer also exists. The theoretical molecular weight of secreted human IL-17A and IL-17F is 15.1 and 14.9 kDa, respectively.

4 The Cellular Sources of IL-22 and IL-17

During immune responses, IL-22 and IL-17A/F are often simultaneously present at high levels in inflamed tissues. Compatibly, these mediators can be secreted by numerous identical types of cells from the lymphoid lineage. In humans, these cell

types include activated $CD4^+$ T cells [26–28], $CD8^+$ T cells [26, 29, 30], and γδ T cells [31] as well as various innate lymphoid cells such as NK cells [26, 32–34], NKT cells [35, 36], lymphoid tissue inducer (LTi) [37, 38], and LTi-like cells [39, 40]. However, in humans IL-22 and IL-17A/F are rarely secreted by exactly the same cell population. For example, regarding the $CD4^+$ T cells, IL-22 is produced by the Th22 [41, 42] and the Th1 subpopulation [26, 43]. In contrast, IL-17A/F are secreted by the Th17 subpopulation [27, 28], which does not produce IL-22 [43–45]. Likewise, the simultaneous expression of IL-22 and IL-17A/F by the same γδ T cell [31] or NKT cell [35] is rather an exception. Interestingly, in humans the IL-17 production by $CD8^+$ and γδ T cells is often accompanied by IFN-γ secretion [29, 31].

It is important to note that no expression of IL-22 was found in monocytes, macrophages, immature or mature DCs that were generated in vitro from human blood monocytes, or mast cells that were isolated from the skin of healthy donors [26, 46]. Furthermore, non-hematopoietic tissue cells do not produce IL-22 either [46–49]. In contrast to IL-22, the cellular sources of IL-17A/F do not seem to be restricted to hematopoietic cells. In fact, IL-17A production has been described by Paneth cells, highly specialized epithelial cells of the small intestine [50].

The above-mentioned Th1 cells develop in the presence of IL-12 as IFN-γ-producing, IL-12Rβ2 and CXCR3, and mostly CCR6 chemokine receptor-expressing cells. They are programmed by the transcription factors T-bet and STAT4 [51].

Th22 cells particularly develop from naive $CD4^+$ T cells via interaction with pDCs in dependency of TNF-α and IL-6 [41]. Apart from IL-22, these cells do not produce any other known Th prototypical mediator such as IFN-γ, IL-4, or IL-17. Th22 cells carry a unique cell surface set of chemokine receptors (CCR6/CCR4/CCR10) and strongly express the aryl hydrocarbon receptor (AHR) as transcription factor [41, 42]. Via induction of endogenous AHR stimulators, Notch signaling then drives the production of IL-22 by these cells [52]. Interestingly, AHR ligation inhibits the production of IL-17 by human $CD4^+$ cells [42, 53].

Like Th1 and Th22 cells, Th17 cells are characterized by their cytokine production: IL-17A, IL-17F, and IL-26. Furthermore, they specifically express transcription factors such as RORγt and a cytokine/chemokine receptor pattern including IL-23R, CCR6, and CCR4, while lacking the expression of IL-12Rβ2, CXCR3, and CCR10. It was first in 2005 that two independent groups demonstrated that the activation of murine naïve T cells with mature dendritic cells (DCs) in the presence of IL-6 and TGF-β upregulated the receptor for IL-23 (p19/p40) on the T cells and, together with IL-23, induced their development into Th17 cells [27, 28]. In the human system, the combination of IL-23, TGF-β, IL-1β, and IL-6 appears to be necessary for development of Th17 cells. Many years later, Th17 differentiation-promoting activities were also assigned to PGE_2 and TLR2 stimulation [54–56]. The Th1 cell cytokines IL-12 and IFN-γ as well as the Th2 cell cytokine IL-4 actively suppress the development of Th17 cells [27, 28]. Interestingly, whereas in the human system Th22 and Th1 cells seem to be most important Th cell sources of IL-22 (as mentioned above), in the murine system Th17 cells were suggested to be the major IL-22 producers [43–45].

These observations suggest a profound species difference and imply caution in extrapolating mouse data onto humans.

Which type of cells actually contributes to IL-22 or IL-17A/IL-17F production in vivo depends on the kind (acute or chronic) and extent (local or systemic) of inflammation, the type of pathogen, and the site of pathogen entry. Corresponding to the preferential production of IL-22 and Th17A/F by Th1/Th22 and Th17 cells, respectively, elevated levels of these cytokines exist in chronic diseases, which are mediated by these T cells. Indeed, high IL-22 and IL-17A mRNA levels can be found in lesional skin from psoriasis patients, whereas IL-22 and IL-17A were completely absent in healthy skin of control donors [43, 47, 48, 57]. Importantly, besides its high cutaneous expression, IL-22 is also systemically present in these patients, and circulating IL-22 levels strongly correlate with the disease severity [48]. This is in contrast to other Th cell cytokines overexpressed in lesional psoriatic skin, making IL-22 a unique mediator. In addition to psoriasis, high cutaneous levels of IL-22 are present in the chronic T cell-mediated skin disease atopic dermatitis [47], whereas both IFN-γ and IL-17A are not or at low level present in lesions of these patients [43, 47, 58]. Interestingly, in another chronic skin disorder, acne inversa, the contrary situation exists: Cutaneous IFN-γ and IL-17A are strongly elevated, whereas IL-22 expression is only minimally upregulated [43]. Abundant presence of IL-22 and IL-17 has been demonstrated in active Crohn's disease and ulcerative colitis lesions [59, 60]. As in psoriasis, systemic IL-22 levels in Crohn's disease patients correlate with disease activity, although other disease-associated Th cell cytokines are scarcely detectable [60, 61]. A massive IL-22 and IL-17 presence was also found in inflamed tissues of patients suffering from rheumatoid arthritis [62–64]. However, in contrast to IL-22, IL-17 does not appear to be present in the blood of rheumatoid arthritis patients [65, 66]. Finally, IL-22 expression was found during various infectious diseases (e.g. *Mycobacterium tuberculosis* infection, *Campylobacter jejuni* infection, abdominal sepsis, and HIV infection) [67–69].

It is important to note that in experimental mice models, innate lymphoid cells are often the source of IL-22. For example, the high IL-22 levels in mice, found in certain organs during acute systemic inflammation after LPS application or during intestinal infection with *Citrobacter rodentium*, seem to derive from IL-23- and RORγt-dependent LTi(-like) cells as demonstrated by the use of T cell-deficient (Rag2-/-), p19-/-, or RORγt-/- mice (Sabat and Wolk, unpublished data, [70, 71]). In contrast, NKT cells have been demonstrated as being principal IL-22 sources in experimental *influenza A* virus lung infection [72].

5 Receptors

Both IL-22 and IL-17A/IL-17F conduct their biological effects via receptor complexes that are each composed of two different transmembrane proteins. However, the subunits of the IL-22 receptor complex are completely different from those of the IL-17 receptor complex.

The IL-22 receptor complex is composed of IL-22R1 and IL-10R2 (Table 1 and [15, 21, 73]). In accordance with the CRF2 characteristics, both transmembrane subunits have an extracellular moiety containing two tandem FNIII domains with several aa positions conserved within this receptor family [2]. The human IL-22R1-encoding gene (*IL22RA1*) is located on chromosome 1p36.11 (reversed strand), near the *IL28RA* locus, whereas the IL-10R2-encoding gene (*IL10RB*) is located on 21q22.11 (forward strand), near the *IFNAR1*, *IFNAR2*, and *IFNGR2* loci. *IL22RA1* and *IL10RB* have similar structures being comprised of seven exons with exons 2–7 containing the sequences for the 574 (sequence under NP_067081) and 325 (sequence under NP_000619) aa mature proteins, respectively. The transmembrane moieties are predicted to be encoded by sequences derived from exon 6 of the corresponding genes. The longer intracellular moiety of IL-22R1 (predicted 325 aa versus 79 aa in the IL-10R2) contains four Tyr-X-X-Gln motifs indicating putative STAT recruitment sites [74]. The extracellular domains of IL-22R1 and IL-10R2 contain three and four putative N-linked glycosylation sites (Asn-X-Thr/Ser), respectively.

With the identification of the components of IL-22 receptor complex, the question arose as which receptor subunit is the primary IL-22-binding subunit. The initial studies published by Xie et al. and Kotenko et al. described direct IL-22 binding to IL-10R2 [15] and to both IL-22R1 and IL-10R2 [74], respectively. In contrast, Logsdon et al. determined the kinetic binding data by surface plasmon resonance techniques showing that IL-22 has a high affinity toward IL-22R1 ($K_D <$ 20 nM) but no actual affinity for IL-10R2 [18, 22]. However, IL-10R2 showed a measurable affinity for the IL-22/IL-22R1 complex. Moreover, Fouser's group described that biotinylated IL-22 binds soluble IL-22R1-Fc but not IL-10R2-Fc in an ELISA-based format, although IL-10R2-Fc stabilized an established association of IL-22 with IL-22R1-Fc [75]. This work additionally provided the initial evidence for a conformational change of the IL-22 molecule during the interaction with its receptor subunits. Our own experiments aimed to identify the possible binding sites for the interaction between IL-22 and IL-10R2 using scans of overlapping peptides derived from the protein aa sequence. By this approach we showed missing interaction between native IL-22 and the peptide scan derived from the IL-10R2 aa sequence, although native IL-10R2 was able to bind defined peptides of the peptide scan derived from the IL-22 aa sequence (see below) [76]. This underpins the notion that the IL-22 binding site for IL-10R2 may include sequence residues of this cytokine that are normally not accessible on the surface, but become accessible after a conformational change induced by initial interaction with IL-22R1 (Fig. 2).

The crystal structure analysis of the IL-22/IL-22R1 complex revealed key residues for interaction at the IL-22/IL-22R1 interface [77]. The identified residues of the IL-22 molecule contacting IL-22R1 include Phe47, Gln49 (pre-helix A), Thr53, Ser64 (helix A), Asp67, Thr70, Asp71, Arg73 (the AB loop) and Lys162, Gly165, Glu166, Asp168, and Arg175 (helix F). On the IL-22R1 side, the binding interface comprises residues of the L2–L6 loops (Lys58, Tyr60, Gly61, Glu62, Leu88, Thr89, Glu90, Tyr93, Arg112, Ser114, Pro206, Thr207), whereby IL-22 AB

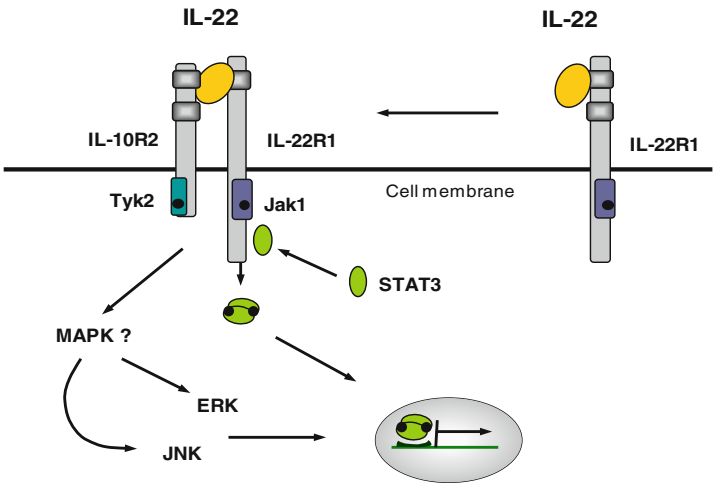

Fig. 2 *The interaction between IL-22 and the IL-22 receptor complex*. IL-22 affects their target cells via the IL-22 receptor complex consisting of IL-22R1 and IL-10R2. There is evidence that IL-22 binds first to the high-affinity chain IL-22R1. This induces a conformational change in the cytokine allowing its interaction with IL-10R2. These interactions lead to signal transduction via JAK/STAT pathways. In some cell types, activation of MAP kinase pathways was described as well

loop and helix F contact IL-22R1 loops L2–L4 (D1 domain) and the IL-22N-terminal helix A interacts with IL-22R1 loops L5–L6 (D2 domain). Essentially, site-directed mutagenesis confirmed the IL-22R1 residues Tyr60 and Lys58 as functionally critical and important aa for IL-22 binding, respectively [77].

The current knowledge regarding the IL-22 residues interacting with IL-10R2 binding is based on homology models and on experimental data. To map the IL-10R2 binding site of human IL-22, we recently analyzed the binding of soluble IL-10R2 to a scan of immobilized overlapping peptides derived from IL-22's aa sequence [76]. Our data revealed distinct binding of IL-10R2 to the N-terminal end of helix A and a region comprising the helix D and the DE loop of IL-22. As deduced from the IL-22 X-ray structural data [16], these two separate segments in the primary sequence form a discontinuous epitope in the IL-22 molecule, which is located next to a region which has been proposed as a binding site for IL-22R1. Our data basically are in good accordance with the data from Walter's group that showed that IL-22 mutations at Tyr51, Asn54, or Arg55 (N-terminal end of helix A), to a greater extent, and at Tyr114 and Glu117 (helix D), to a lesser extent, impaired its affinity of IL-22 to soluble IL-10R2 in the presence of soluble IL-22R1 [22]. As noted above, Asn54 represents the residue whose glycosylation is important for the interaction between IL-22 and IL-10R2 [22]. It is currently not clear whether this carbohydrate interacts with IL-10R2 or whether it functions as a lever with which IL-22R1 creates the binding site for IL-10R2 in IL-22. However, there are no published data clarifying whether there is any interaction between both receptor subunits within the ternary IL-22/IL-22R1/IL-10R2 complex.

The receptor complex for IL-17A and IL-17F is composed of IL-17RA and IL-17RC [78–80]. IL-17RA and IL-17RC together with IL-17RB, IL-17RD, and IL-17RE are transmembrane proteins that constitute a receptor family. Together with TLR and IL-1 receptors, they are assigned to the so-called SEFIR (similar expression to fibroblast growth factor genes, IL-17 receptors, and Toll–IL-1R) protein family, which is defined by a conserved cytoplasmic SEFIR domain. The human IL-17RA-encoding gene (*IL17RA*) is located on chromosome 22q11.1 (forward strand), whereas the IL-17RC-encoding gene (*IL17RC*) is located on 3p25.3-p24.1 (forward strand), near the *IL17RE* locus. Multiple, alternatively spliced transcript variants of *IL17RC*-encoding isoforms have been detected [81]. *IL17RA* and *IL17RC* have limited similarity and contain the sequences for the 866 (sequence under NP_055154) and 791 (sequence under NP_703191) aa mature proteins, respectively. IL-17RA is composed of a 293 aa-long extracellular domain, 21 aa-long transmembrane domain, and 525 aa-long intracellular moiety. IL-17RC shares 23 % aa identity with IL-17A. IL-17RC is the binding subunit in the IL-17 receptor complex. In fact, both IL-17A and IL-17F interacted with IL-17RC with comparable high affinity (K_D ca. 0.5 nM). In contrast, IL-17RA binds IL-17A effectively (K_D ca. 2 nM), but binds IL-17F with ca. a 1,000-fold lower affinity [78]. By means of computational modeling, Kramer et al. identified two FNIII domains in the extracellular part of IL-17RA connected by a nonstructured linker [82]. The resolution of the crystal structure of IL-17F bound to IL-17RA revealed a unique mechanism of complex formation. In this complex, the two fibronectintype domains of IL-17RA engage the cytokine in the groove of the homodimer [83].

6 Target Cells

The targets cells of IL-22 and IL-17A/IL-17F are only partially identical. The big difference is that immune cells do not bear the IL-22 receptor complex but are sensitive toward IL-17A/IL-17F. In addition, the number of different tissue cells that IL-22 acts on is smaller than the number of tissue cells whose function is regulated by IL-17A/IL-17F.

Several research groups including our own have extensively studied the expression of the IL-22 receptor complex components. IL-10R2 is ubiquitously expressed [47], which can be explained by its function as part of several cytokine receptors [1]. Therefore, the expression of the IL-22R1 subunit determines whether a cell is an IL-22 target or not. Our numerous studies demonstrated lacking IL-22R1 expression in bone marrow, blood mononuclear cells, thymus, and spleen, as well as in resting and activated primary immune cells including monocytes, B cells, T cells, NK cells, macrophages, and DC populations [46, 47, 49, 76]. In accordance with these results, no signal transduction was induced by IL-22 in any of these cells [47]. Finally, no influence of IL-22 was found in vitro or in vivo upon the screening of a large range of immunological parameters in the presence or absence of cell-specific stimuli [47, 76].

In contrast to immune cells, our data showed that a few organs expressed IL-22R1 and therefore contain putative target cells of IL-22 [47]. These organs include the skin and kidney and those from the digestive (pancreas, small intestine, liver, colon) and the respiratory (lung, trachea) systems with the highest expression found in the skin and pancreas [47]. These quantitative results are in line with the semiquantitative data published earlier by Aggarwal et al. [84] and Parrish-Novak et al. [85]. Interestingly, most IL-22R1-expressing tissues form outer body barriers and contain epithelial cells. Regarding isolated cell populations, IL-22R1 is expressed on keratinocytes, bronchial and intestinal epithelial cells, intestinal subepithelial myofibroblasts, hepatocytes, pancreas acinar cells, and a range of respective tissue cell-derived cell lines [13, 86]. Interestingly, the expression of IL-22R1 and IL-10R2 in keratinocytes and fibroblasts can be further upregulated by IFN-γ and TNF-α suggesting an amplification of IL-22 effects in the presence of these cytokines upon inflammation [47, 87].

As mentioned above, IL-17A/F signals through the IL-17RA/IL-17RC receptor complex [10]. Whereas IL-17RA is broadly expressed in hematopoietic and non-hematopoietic cells [80], IL-17RC is thought to be mainly expressed by non-hematopoietic cells [81]. There seems to be one exception, namely, for macrophages, expressing both IL-17RA and IL-17RC [88]. Therefore, it appears that numerous cell types are sensitive toward IL-17 action.

7 Signal Transduction

IL-22 and IL-17A/IL-17F use different signal transduction pathways to activate target cells.

Like other IL-10 family members, IL-22 activates in its target cells a signaling cascade via the JAK/STAT pathway resulting in tyrosine phosphorylation of STAT3. Upon detailed studies using primary human cells, this was first demonstrated by our own research groups for keratinocytes and subsequently by the Fujiyama, Kolls, and Mizoguchi research groups for intestinal subepithelial myofibroblasts as well as bronchial and intestinal epithelial cells [47, 48, 59, 89, 90]. However, most studies investigating IL-22-induced signal transduction in cells with endogenous receptor expression refer to tumor cell lines. In the cell lines, activation of STAT1 and/or STAT5 additionally to STAT3 tyrosine phosphorylation was often observed [9, 47]. Using the H4IIE rat hepatoma cell line, Lejeune et al. clearly demonstrated that intracellular events involve tyrosine phosphorylation of Jak1 and Tyk2, but not Jak2 [91]. Since Tyk2 has been known to be associated with IL-10R2, these studies suggest Jak1 as the kinase associated with the IL-22R1. Despite four potential STAT binding sites on the IL-22R1, this receptor was recently shown to be pre-associated with STAT3 independently of these sites and to forward the IL-22 binding signal by this alternative mechanism [92]. In addition to tyrosine phosphorylation of STAT molecules, serine phosphorylation of STAT3 and an activation of the three major MAP kinase pathways (p38 kinase, JNK, and ERK1/2)

by IL-22 was reported [91]. An activation of MAP kinase pathways by IL-22 was also shown for primary human keratinocytes (ERK1/2 and JNK), intestinal subepithelial myofibroblasts (ERK1/2, JNK, p38 kinase), and synovial fibroblasts from rheumatoid arthritis patients (ERK1/2, p38) [48, 59, 62].

Following interaction with its receptor complex, IL-17A/F preferentially activate the NFκB and MAP kinase (p38 kinase, JNK, and ERK1/2) pathways [93, 94]. The binding of IL-17 to its receptor complex leads to recruitment of the adaptor protein Act1 to IL-17RA. For this recruitment, the conserved cytoplasmic "SEFIR" domain of IL-17RA is required. Unlike IL-1R signaling, the SEFIR domain of the IL-17 receptor mediates signal transduction independently of classical TIR adaptors like MyD88 or TRIF [94]. In its coiled-coil region at the C-terminus, Act1 also contains a SEFIR domain. Afterward, TAK1 kinase (TGF-β-activated kinase 1) and the E3 ubiquitin ligase TRAF6 (TNFR-associated factor 6) are recruited to the IL-17 receptor complex followed by NFκB and C/EBPβ/δ activation [95–97]. Already in 2002, it was demonstrated that TRAF6 is necessary for IL-17 activation of NFκB and JNK [98]. Additionally, Act1 may directly lead to p38 activation. The phosphorylation of C/EBPβ inhibited proinflammatory gene expression induced by IL-17 [96]. Moreover, IL-17 treatment of target cells increased the Act1-independent phosphorylation of JAK1/2-activated PI3K signaling [99].

8 Biological Effects of IL-22 and IL-17A/IL-17F

The biological effects of IL-22 and IL-17A/IL-17F differ in many aspects. IL-22 seems to be a novel type of immune mediator that increases the innate immunity of tissue cells, protects tissues from damage, and enhances their regeneration. IL-17A and IL-17F are typical proinflammatory mediators (Fig. 3).

As described above, cells of the digestive tract, skin, lung, and kidney appear to be the most important target cells of IL-22, whereas immune cells are not responsive to this cytokine [47].

The effects of IL-22 that are most precisely characterized to date concern those on the biology of epithelial cells, in particular of keratinocytes. Following our initial study that worked out human keratinocytes as important target cells and demonstrated the first effects of IL-22 on these cells, the induction of antimicrobial molecules [47], few independent studies were conducted that identified a broad range of IL-22 effects on these cells [48, 87, 100–102]. These studies demonstrated that IL-22 basically influences five different keratinocyte functions. It enhances the innate immunity of these cells, inhibits their terminal differentiation (indicative of a regenerative state induction), increases their cellular mobility, induces the production of a few chemokines, and shows mechanisms that prolongs its own effects. These effects are described now in more detail:

IL-22 enhances the innate immunity of keratinocytes by strong upregulation of the expression of numerous antimicrobial molecules like the β-defensin (BD) 2 and

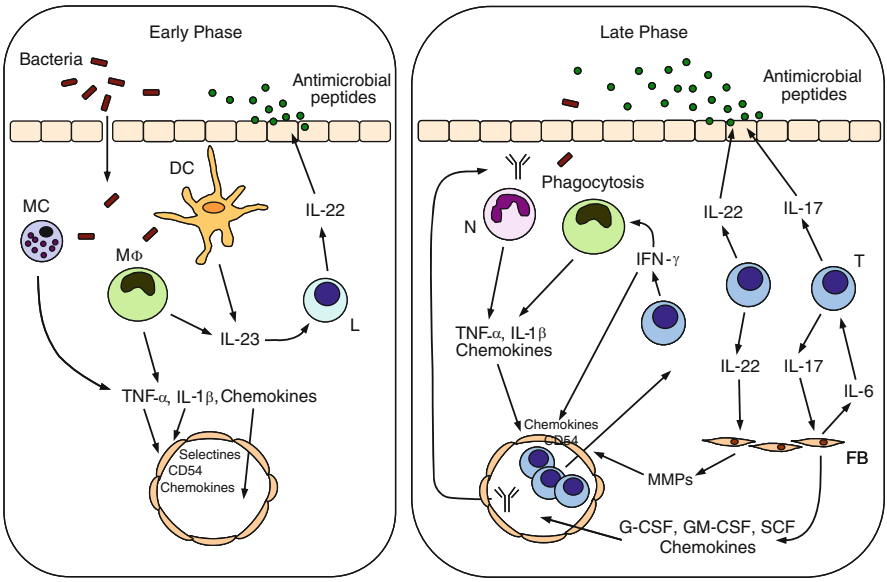

Fig. 3 *The role of IL-22 and IL-17A/IL-17F during mucosal infections (see text). MC* mast cell, *MΦ* macrophage, *DC* dendritic cell, *L* Lymphocyte, *N* neutrophile granulocyte, *T* T cell, *FB* fibroblast

BD3, as well as S100A7, S100A8, and S100A9 [43, 47, 48, 100]. Next, IL-22 inhibits the expression of profilaggrin, keratin (K) 1 and K10, calmodulin-like 5, keratinocyte differentiation-associated protein, kallikrein 7, desmocollin-1, and late cornified envelope protein 1B [48, 87]. These proteins are involved in the terminal differentiation of keratinocytes, which is a particular apoptotic process that results in the formation of the *stratum corneum*. The impressive consequences of this IL-22 influence were demonstrated using a three-dimensional epidermis model: acanthosis (thickening of the epidermis), parakeratosis (retention of nuclei in the stratum corneum), and hypogranularity (loss of keratohyalin granules) [87, 102]. Interestingly, the influence of IL-22 on the keratinocyte differentiation is not shared by the Th1 and Th17 cell lead cytokines, whereas the latter also have a clear impact on antimicrobial protein (IFN-γ, IL-17; see below) and MMP (IFN-γ) expression [87]. The third group of IL-22-sensitive genes encode the matrix metalloproteinases (MMPs) 1 and 3, which are increased by IL-22, and annexin A9, which is decreased by IL-22 [48, 100]. Their regulation might be responsible for the IL-22-induced increase of the keratinocyte cellular mobility. Furthermore, IL-22 slightly enhances the expression of neutrophilic granulocyte-attracting chemokines: CXCL1, CXCL2, CXCL5, and CXCL8 [87, 100]. Finally, once exerting its effects on keratinocytes, IL-22 promotes an amplification circle by driving positive feedback regulation mechanisms [87, 101]. In fact, IL-22 induces the mRNA and protein expression of STAT3, the major and essential IL-22-signaling element [87]. Moreover, IL-22 induces the production of another member of the IL-10-family with

similar effects as its own and the capacity to strengthen and prolong the IL-22 effects: IL-20 [101]. Interestingly, inflammatory mediators like TNF-α, IL-1β, and IL-17 enhance some IL-22 effects [43, 48, 87, 101].

In other epithelial cells, IL-22 induces effects similar to those in keratinocytes. In fact, the Kolls group found that human bronchial epithelial cells respond to IL-22 stimulation by upregulation of BD2, S100A7, and S100A12; the neutrophilic granulocyte-attracting chemokines CXCL1 and CXCL5; thyroid oxidase 2; and G-CSF [89]. Likewise, in mouse tracheal epithelial cells, IL-22 enhanced the expression of the antimicrobial protein lipocalin (LCN)-2, of CXCL5, polymeric immunoglobulin receptor, and the mucus-associated protein MUC1 [89]. In colonic epithelial cells isolated from mice, locally overexpressed IL-22 enhanced the expression of MUC1, MUC3, MUC10, and MUC13, which are important for mucus layer formation and mucosal damage protection, as found by the Mizoguchi group [90]. Furthermore, IL-22 upregulates the expression of Reg family members (RegIIIβ, RegIIIγ, Reg1α) in these cells [103].

The few non-epithelial tissue cells the IL-22′ influence on was reported involve hepatocytes and pancreas acinar cells. In hepatocytes IL-22 strengthens the production of acute-phase proteins such as serum amyloid A (SAA), α1-antichymotrypsin, haptoglobin, and LPS-binding protein (LBP) [61, 73, 76]. These hepatic proteins display systemic inflammation-limiting and protective roles. In fact, α1-antichymotrypsin favors the degradation of proteases known to be produced in large amounts during inflammation, SAA enhances the opsonization and phagocytosis of gram-negative bacteria, haptoglobin protects against hemoglobin-induced oxidative tissue damage, and high LBP levels neutralize bacterial components and therefore limit their immunostimulatory capacity. Regarding the exocrine pancreas, Gurney's group showed that IL-22 induced the upregulation of mRNA expression of two tissue-protective proteins, pancreatitis-associated protein 1 (PAP1/RegIIIα), and osteopontin [84]. Only the last years provided more and more evidence that PAP1 plays an important role in the protection against tissue injury. Besides its anti-apoptotic effects and the promotion of cellular immune responses by influencing Th1 cell development, osteopontin plays an important role in mucosal tissue protection and wound healing.

The above-described IL-22 effects suggest that this mediator might have an important role for the avoidance/clearance of epithelial and mucoepithelial infections and the regeneration and protection against damage in some chronic inflammatory cutaneous, pulmonary, and intestinal diseases. The effect of IL-22 on keratinocyte functions is indeed mirrored by the keratinocytes from psoriasis patients [47, 48, 87, 101]. These data, together with the high IL-22 expression levels in the plaques and the blood of psoriasis patients, led us to consider IL-22 as a key mediator in the dramatic keratinocyte functional alterations in psoriasis [104, 105]. A role of IL-22 was also demonstrated in psoriasis-like skin alterations in mice, which were induced either by the transfer of T cells to pathogen-free scid/scid mice [106] or by overexpression of IL-22 [87]. Regarding chronic inflammatory pulmonary diseases, it seems that IL-22 is required for the onset of allergic asthma, while functioning as a negative regulator in established allergic inflammation [107].

Few studies suggest a protective role of IL-22 in inflammatory bowel disease. Using a mouse model for ulcerative colitis (TCRαKO mice), Mizoguchi's group demonstrated that mice locally supplemented with IL-22 showed attenuated severity of colitis. This attenuation was attributed to the IL-22-induced STAT3-dependent expression of mucus-associated molecules and restitution of mucus-producing goblet cells [90]. Additionally, a protective role for IL-22 was demonstrated in two further murine colitis models. In fact, a more severe phenotype and higher mortality was associated with IL-22 deficiency in DSS-induced, innate immunity-mediated colitis and in Th1-mediated colitis induced by the adoptive transfer of IL-22-deficient compared to wild-type $CD4^{+}CD45RB^{++}CD25^{-}$ T cells into $Rag1^{-/-}$/$IL\text{-}22^{-/-}$ mice [108].

Furthermore, there might be some protective action of systemic IL-22, whose levels are elevated in CD compared to healthy individuals and correlate with the disease activity [61]. These levels might contribute to the prevention of systemic inflammation provoked by LPS present in the blood of CD patients through its induction of hepatic LBP. The role of IL-22 in chronic inflammatory diseases that do not primarily involve epithelial tissues is less characterized. In rheumatoid arthritis IL-22 is assumed to play a pathogenetic role. This assumption was mainly based on the observed minimally reduced susceptibility of $IL\text{-}22^{-/-}$ mice to collagen-induced arthritis [109]. Furthermore, IL-22 does not seem to play a major role in the murine model of multiple sclerosis [110].

Since IL-22 prominently stimulates the production of antimicrobially acting proteins in various epithelia (see above), it is not surprising that IL-22 seems to play an important role in the innate immune defense, especially against extracellular bacteria. Two studies in mice confirmed the significance of this property of IL-22. Zheng et al. demonstrated that IL-22-deficient mice died as a result of intestinal infection with *Citrobacter rodentium* [103]. Furthermore, the Kolls group found that neutralization of IL-22 during pulmonal *Klebsiella pneumoniae* infection led to animal death [89]. Furthermore, we very recently found a relative IL-22-deficiency of the affected skin of patients suffering from acne inversa [43]. This may contribute to the persistence and propagation of bacteria in the lesions and consequently inflammation and superfluous exudate of purulence that heavily overloads the patients. In contrast to epithelial infections, little to no role for IL-22 is assumed for the control of facultative intracellular bacteria [89, 111–113].

In line with the above-described protective and regenerative features of IL-22, this cytokine plays a protective role in experimental (ConA, CCl_4, or FAS ligand-induced) liver injury [114, 115]. IL-22 also protected $p35^{-/-}$ mice during *Salmonella enteritidis* infection from hepatic necrosis [111]. A recent study by the Gao group nicely showed that IL-22 protected mice from cerulein-induced pancreatitis. This protection likely involved the inhibition of autophagosome formation by upregulating BcL-2 and BcL-XL protein in the acinar cells [111].

In contrast to IL-22, IL-17A and IL-17F have clear proinflammatory properties and act on a broad range of cell types.

IL-17A and IL-17F induce the production of many neutrophilic granulocyte-attracting chemokines, such as CXCL1, CXCL2, CXCL5, and CXCL8, and of T

cell- and myeloid cell-attracting chemokines CCL20, CCL2, and CCL7 in fibroblasts, epithelial cells, endothelial cells, and keratinocytes [28, 87, 116–118]. In dendritic cells IL-17A reduces the production of CCL17, a chemokine that is responsible for the recruitment of Th2 cells to the site of inflammation [119]. Furthermore, IL-17A and IL-17F enhance the expression of G-CSF, GM-CSF, and stem cell factor in tissue cells, macrophages, and T cells and thereby led to strengthened granulopoiesis [88, 120, 121]. In line with this, adenovirus-mediated gene transfer of the murine IL-17A cDNA resulted in a transiently transgenic phenotype, with dramatic effects on the in vivo granulopoiesis. There was a significant increase (tenfold) in the absolute neutrophil count in the peripheral blood that was associated with a doubling in the spleen size [122]. By means of the enhancement of chemokine production and granulopoiesis, IL-17 might lead to a significant increase in the immigration of neutrophilic granulocytes to the site of inflammation. Furthermore, the treatment of tissue cells with IL-17A and IL-17F induces the expression of IL-1β, TNF-α, IL-6, and a variety of metalloproteinases (MMP1, MMP2, MMP3, MMP9, and MMP13) [93, 116, 123–126]. IL-17A also upregulates the IL-1β and TNF-α production in human macrophages [88, 127]. Additionally, IL-17A/IL-17F increases the production of a range of antimicrobial proteins including BD2, S100A7, S100A8, S1200A9, lipocalin-2, and LL-37 in their target cells [43, 128–130]. In primary human tracheobronchial epithelia, IL-17A enhances the expression of the mucin genes MUC5B and MUC5AC [131]. Interestingly, further investigation of MUC5B expression demonstrated that the IL-17 effect is at least partly mediated through IL-6 by an autocrine/paracrine loop. Furthermore, the increase in the production of cyclooxygenase 2 (COX-2)/prostaglandin-2 (PGE_2) and inducible NO synthetase (iNOS) seems to also belong to the repertoire of IL-17 action on tissue cells [93, 116, 132]. Interestingly, IL-17 also influences CD4+ T cell and B cell interactions required for the formation of the germinal center. Indeed, mice lacking the IL-17RA have reduced B cell development and humoral responses [133].

All these observations suggest that IL-17 has an important role in the host protection against specific pathogens. Indeed, as demonstrated by means of IL-17RA-deficient animals, IL-17 was critical for the protection against *Klebsiella pneumoniae* [134], *Citrobacter rodentium* (in later stages) [88], *Toxoplasma gondii* [135], and systemic and oropharyngeal candidiasis [136, 137]. It should be noted that IL-17A/IL-17F do not play an essential role in every infection since IL-17RA-deficient mice do not show increased susceptibility to most infections with intracellular pathogens such as *Mycobacterium tuberculosis* or *Listeria monocytogenes*. The role of IL-17 in antiviral protection remains controversial so far.

IL-17A and IL-17F are also important mediators of certain autoimmune diseases. Already in 2002, Nakae et al. generated IL-17A-deficient mice and found that contact, delayed-type, and airway hypersensitivity responses as well as T cell-dependent Ab production were significantly reduced in this mutant [138]. Lubberts et al. showed that blocking of endogenous IL-17A/IL-17F by means of an IL-17RA-Fc fusion protein in the autoimmune collagen-induced arthritis model results in suppression of arthritis, whereas various studies show that overexpression

of IL-17 enhanced collagen-induced arthritis [139, 140]. This clear proinflammatory effect of IL-17 seems to be TNF-α and IL-1β independent under arthritic conditions [141]. Furthermore, the treatment of rats suffering from adjuvant-induced arthritis with IL-17RA-Fc fusion protein also led to significantly reduced paw volume and radiographic scores [142]. Regarding the role of IL-17 in EAE, the development of this murine multiple sclerosis model was significantly suppressed in IL-17A-deficient mice. These animals exhibited delayed onset, reduced maximum severity scores, ameliorated histological changes, and early recovery [88, 143]. Interestingly, IL-17A, but not IL-17F, seems to play an important role in the development of experimental contact delayed-type hypersensitivity, airway hypersensitivity, arthritis, and EAE [88, 144]. The role of IL-17 in experimental colitis in mice is less clear. It was described that IL-17F deficiency resulted in reduced DSS colitis, whereas IL-17A deficiency or neutralization caused more severe colitis [144, 145]. Furthermore, Zhang et al. found that IL-17RA-deficient mice were significantly protected against TNBS-induced weight loss and colonic inflammation [146].

Interestingly, some effects of IL-22 and IL-17 are additive. This is the case for the induction of antibacterial proteins in epithelial cells [43, 130]. However, it becomes clear from all these data that we do not have a complete understanding of the biological functions of IL-17A/IL-17F and IL-22. What we currently do know, however, is that IL-22 and IL-17A/IL-17F are different in many of their basic aspects and in their biological importance.

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