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Interleukin-22: immunobiology and pathology

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Abstract

Interleukin-22 (IL-22) is a recently described IL-10 family cytokine that is produced by T-helper (Th)-17 cells, $\gamma\delta$ T cells, NKT cells and newly described innate lymphoid cells (ILCs). Knowledge of IL-22 biology has rapidly evolved since its discovery in 2000, and a role for IL-22 has been identified in numerous tissues including the intestines, lung, liver, kidney, thymus, pancreas and skin. IL-22 primarily targets non-hematopoietic epithelial and stromal cells where it can promote proliferation and play a role in tissue regeneration. In addition, IL-22 regulates host defense at barrier surfaces. However, IL-22 has also been linked to several conditions involving inflammatory tissue pathology. In this review, we will assess the current understanding of this cytokine, including its physiologic and pathologic effects on epithelial cell function.

Keywords

Interleukin-22; epithelial cells; tissue regeneration

INTRODUCTION

Interleukin-22 (IL-22), which was originally named IL-10-related T cell-derived inducible factor (IL-TIF), has generated considerable interest in recent years making it one of the best-studied members of the IL-10 family of cytokines, which also includes IL-10, IL-19, IL-20, IL-24 and IL-26, as well as the lambda-interferons IL-28A, IL-28B and IL-29. Initially described as a TH17 cytokine, as its production has been observed within the same cells that produce IL-17, subsequent evidence has indicated it can be generated independently of IL-17. Unlike most cytokines, which target hematopoietic cells, the main impact of IL-22 is on non-hematopoietic epithelial cells and fibroblasts in tissues as diverse as lung, liver, kidney, thymus, pancreas, breast, gut, skin and the synovium. Although it can have a profound effect on the regeneration of epithelial tissues following injury, largely by promoting survival by inducing proliferation and inhibiting apoptosis of epithelial cells, this same function has also been implicated in pathological states such as malignancy and

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psoriasis. In addition, a role for IL-22 has also been described in host defense within barrier tissues such as the intestine, oral mucosa, skin and lung. Given this widespread action in regeneration, host defense and pathology, IL-22 is an attractive target for clinical development. In this review, we detail the current state of knowledge about the biology of IL-22 in animals and humans, its sources and targets, and its role in tissue pathology and regeneration.

2). STRUCTURE, GENE AND SIGNALING

Gene

The human *IL22* gene is located at chromosome 12q15 in the vicinity of the genes encoding IFN- γ and IL-26 (1). The 537bp open reading frame of the *IL22* gene encodes a 179 amino acid protein that shares 79% homology between mouse and human (2). The active, secreted form of the cytokine is a 146 amino acid protein (3, 4). Although IL-22 is active as a monomer, and crystal structures have been solved for this form, dimers as well as tetramers of IL-22 have been observed in high concentrations in solution (4, 5). Although early studies found constitutive expression of IL-22 only in the thymus and brain (6), subsequent studies have found induced expression in other tissues including the gut, liver, lung, skin, pancreas and spleen (7).

Structure

The 3D crystal structure of human IL-22 has been solved in both *E. coli* and *D. melanogaster*, which revealed virtually identical structures. The IL-22 monomer is composed of six α -helices (labeled A–F) and a small N-terminal helix, forming a compact six-helix bundle cytokine (4, 8). Structural analysis has revealed three potential glycosylation sites located in helices A and C as well as in the AB loop (4), and mass spectroscopy indicated that hexasaccharides (two *N*-acetyl glucosamines, three mannoses and one fucose) are attached to the IL-22 protein expressed in *D. melanogaster* (9). Comparison with IL-10 (for which it shares 22% homology in mouse and 25% in human) indicated a putative binding site comprised of helix A, loop AB and helix F (10).

IL-22 receptor

The IL-22 receptor (IL-22R) is a Type 2 cytokine receptor and member of the IL-10 family of receptors along with the receptors for IL-10, IL-19, IL-20, IL-24, IL-26, IL-28 and IL-29 (Figure 1). It is composed of two heterodimeric subunits, IL-22R1 and IL-10R2 (2, 3, 11–13). The human gene encoding IL-22R1 is located at chromosome 1p36.11, whereas the gene encoding IL-10R2 is located on chromosome 21q22.11 (3). Binding studies have revealed that IL-22 has a high affinity for IL-22R1 ($K_D=20\text{nM}$), but no affinity for IL-10R2, however, there is a strong binding affinity of the IL-10R2 subunit for the IL-22-IL-22R1 complex ($K_D=7\text{--}45\mu\text{M}$) (11, 14–18). These data suggest that initial binding of IL-22 to the IL-22R1 subunit enables secondary binding of the IL-10R2 subunit, thereby enabling downstream signaling (19). This two-stage cytokine receptor binding and signaling has also been reported for the IL-10 system (20). Binding of IL-22 to IL-22R occurs in a 1:1 complex (14, 17) and recent work has shown that phosphorylation by GSK3 β of IL-22R1 at the serine

residue at positions 410 and 414 stabilizes IL-22R and prevents its degradation by the ubiquitin proteasome (21).

Signaling

Although STAT-3 phosphorylation appears to be the primary mediator of IL-22 signaling, phosphorylation of STAT-1 and STAT-5 has also been observed (22, 23). Phosphorylation of STAT-3 upon ligation of the IL-22-IL-22R1-IL-10R2 complex occurs at the tyrosine residue at position 705, however, it has also been found to phosphorylate a serine residue at position 727, potentially enhancing transactivation (22). This enables recruitment of the Jak signaling molecules Jak1 and Tyk2 to the receptor complex (12, 24). In addition to STAT signaling, IL-22 binding has also been found to activate the MAPK and p38 pathways (25–28).

3). CELLULAR SOURCES OF IL-22

Primarily cells of the lymphoid lineage produce IL-22; encompassing cells of both the innate and adaptive immune systems, including $\alpha\beta$ T cells, $\gamma\delta$ T cells, NKT cells and innate lymphoid cells (ILCs) (Figure 2). However, some studies have also described some myeloid and non-hematopoietic cells as capable of producing IL-22 in various tissues and states, including macrophages, neutrophils and fibroblasts.

$\alpha\beta$ T cells

IL-22 was first cloned in conventional T cells activated with IL-9 (6, 29). Human production of IL-22 by T cells has been identified in TH1, TH17 and TH22 cells; where it is estimated that approximately 33% of IL-22-producing CD4+ T cells in peripheral blood are TH1 cells (co-expressing IFN γ), 50% produce IL-22 alone (TH22), and 15% are TH17 cells also producing IL-17 (30). In mouse T cells, production of IL-22 has been largely attributed to TH17 cells (31–34). Despite their divergent functions, both TH17 cells and Tregs require TGF β for their formation (35). Additional signals from IL-6 drive T cell polarization towards the TH17 lineage (36, 37), promoting expression of ROR γ t and IL-23R (35, 38, 39); although the latter could be indirectly induced by ROR γ t (40). ROR γ t is crucial for the formation of TH17 cells (41) and IL-23 signaling is critical for the production of IL-22 by TH17 cells (34, 42–45). TGF β concentration regulates the balance between Treg and TH17 cells; at low concentrations induction of TH17 cells occurs via upregulation of ROR γ t and IL-23R, while at higher concentrations, TGF β represses IL-23R and induces FoxP3 (46). Similarly, high concentration of TGF β can inhibit the production of IL-22 (47, 48), although this can be overcome by IL-23 (46). In addition to CD4+ T cells, a subset of human CD8+ $\alpha\beta$ T cells has also been identified that expresses both IL-22 and IL-17 (49–51), as well as a subset that solely expresses IL-22, partly under the control of IL-21 (52) and particularly in the setting of inflammation (53).

$\gamma\delta$ T cells

In addition to conventional $\alpha\beta$ T cells, significant IL-22 production has been described in $\gamma\delta$ T cells; which like other IL-22 producing cells, express ROR γ t and are stimulated to produce IL-22 in response to IL-23 (54–57). However, although IL-23 signaling appears to

be important for their IL-22 production, $\gamma\delta$ T cells can also respond to innate ligands through Toll-like receptors (TLRs) (54, 58). $\gamma\delta$ T cells diverge at the DN3 (CD25+CD44-) stage of thymocyte development (59), however, unlike $\alpha\beta$ T cells antigen recognition in the thymus is not required for their development. Differential antigen recognition in the thymus during development determines the subset fate of $\gamma\delta$ T cell: IFN γ -producing or IL-22 and IL-17-producing (60). These subsets of $\gamma\delta$ T cells can be differentiated by their expression of CD25, CD27 and CCR6 (61–63)

Innate lymphoid cells (ILCs)

ILCs are a newly described heterogeneous population of immune cells possessing lymphoid ontogeny, but lacking the rearranged T cell and B cell receptors of lymphoid cells belonging to the adaptive immune system. They have no demonstrated cytotoxic capacity, and they appear to function primarily by producing cytokines. ILCs can be defined by their differential expression of transcription factors (including Tbet, GATA3 or ROR γ t) and cytokines (such as IFN γ , IL-13, or IL-22) (64), largely mirroring CD4 helper T cell subsets. A working group has recently created a nomenclature guideline to define ILC subsets (65). Group 3 ILCs (ILC3), which express ROR γ t and are potent producers of IL-22 (65), are themselves a heterogeneous population that can be broadly stratified based on their expression of Natural Killer cell cytotoxicity receptors (NCR) such as Nkp44 in humans (66) and Nkp46 in mice (67–69). IL-23 is the most potent inducer of IL-22 production by both NCR+ and NCR- ILC3 cells (66, 68).

One of the first cellular sources of IL-22 to be characterized were a subset of NK cells (29) that were designated NK22 cells (70, 71). Further analysis revealed that these cells were distinct from the NK cell lineage (72, 73) and, due to their expression of ROR γ t and IL-22, were designated as a subset of ILC3 in human and mouse tissues (65). NCR+ ILC3, as they are now referred, express typical NK cell markers such as CD56 (in human) and NKG2D (in mouse), but also express Nkp44 in human and Nkp46 in mice and do not express cytokines typical of NK cell function such as IFN γ (66–69, 71, 74). NCR+ ILC3 are dependent on IL-15 (like conventional NK cells) and ROR γ t for their development (66–69).

Comprising approximately 15–20% of the ILC3 population after birth (75, 76), lymphoid tissue-inducer (LTi) cells were the first of the ILC family to be described. Identified in fetal development due to their unusual CD3-CD4+ phenotype and ability to colonize lymphoid tissue anlagen (77), LTi cells were studied extensively for their important role in the formation of secondary lymphoid tissues such as lymph nodes and Peyer's patches (78–81), the generation of tertiary lymphoid structures (82–86), as well as the maturation of thymic epithelial cells (87); although these functions are largely attributed to their production of lymphotoxin (LT) α 1 β 2 (83). LTi cells can be phenotypically defined by expression of IL-7R α and ROR γ t, lack of expression of CD3 and Nkp46 (76), and variable expression of CD4 (approximately half of LTi cells) (88, 89). More recently LTi-like cells were described in the adult mouse and human as potent producers of IL-22 (76, 90) and IL-17 (91). There remains considerable uncertainty in the distinction between LTi cells and other group 3 ILC that do not express NCR, with limited understanding of the identity and function of non-LTi NCR- ILC3 cells (65, 92). The most prominent description of which was reported by the

Powrie group, who identified a subpopulation of Sca1+ROR γ t+IL-23R+IL-7R α -CD4-ckit-NCR- ILC3 that co-expressed IL-17, IL-22 and, surprisingly, IFN γ ; causing considerable pathology in experimental models of colitis (93). For the purposes of this review, unless specifically describing the functional capacity of lymphoid tissue induction, we will refer to all NCR- group 3 ILC, including LTi and LTi-like cells, as NCR- ILC3.

Although in one study no lineage relationship between NCR- and NCR+ ROR γ t+ ILC3 was found (76), there is increasing evidence that LTi-like NCR- ILC3 cells may give rise to NCR+ ILC3 (74, 91). This was confirmed by fate-mapping studies performed by Diefenbach and colleagues, providing evidence to suggest NCR- ILC3 stably upregulate their expression of NKp46 (72). Interestingly, the Diefenbach study went on to show that these newly converted NCR+ ILC3 subsequently downregulate expression of ROR γ t, which is associated with a shift in cytokine production towards IFN γ (72). This was consistent with the findings from the Colonna group identifying an NCR+ ILC3 that downregulates expression of IL-22 in favor of upregulation of IFN γ , under the control of IL-2 (70). This latter differentiation step appears to be under the control of the transcription factor T-bet (94, 95), which induces NKp46 expression and IFN γ production by ILCs (96); and is prevented by stimulation of AhR (97).

All ILC, including NCR+ and NCR- ILC3 are thought to derive from common lymphoid progenitors (CLP) (98, 99). Group 1, 2 and 3 ILCs appear to arise downstream of an Id2+ precursor (100, 101), although this precursor does not appear to give rise to NK cells (102). B cell development appears to be the default pathway for CLPs (103) and EBF, a transcription factor critical for B cell development (104), binds and represses Id2 expression, thereby inducing B-lineage over an ILC-lineage fate on CLPs (105). However, in contrast, Id2 suppresses the effects of E proteins such as E2A (106), another factor critical for B cell development (107). It is unclear what diverts CLPs from their B-lineage bias, however Notch signals may play an important role at this early stage of programming, but then needs to be shut off for efficient ROR γ t+ ILC3 generation (98, 108). Recent work has revealed additional insight into the ILC developmental hierarchy, with identification of an Id2+ α 4 β 7+ precursor of all ILC (but not conventional NK cell) (102); and a PLZF-expressing precursor capable of generating ILC1 and ILC2, and NCR+ but not NCR- ILC3 (109). Furthermore, two studies have now established Nfil3 as a crucial transcription factor regulating development of all ILC subsets including conventional NK cells (110, 111) (Figure 2). This could be due to the ability of Nfil3 to bind to the regulatory region of *Id2* and promote its transcription (112). In addition, GATA3 which is another factor involved at multiple stages of T cell development (113) and was originally thought to be only involved with ILC2 lineage development (101, 114, 115), also seems to play a crucial role in ILC3 differentiation (116).

NKT cells

A subset of NKT cells has also been described as being capable of producing IL-22 (117–120). Much like $\gamma\delta$ T cells, TH17 cells and ILC3, IL-22 producing NKT cells express CCR6, IL-23R and ROR γ t (121–124), and IL-23 stimulates their production of IL-22 (119, 120, 125, 126). Unlike $\alpha\beta$ TCR IL-22 producing cells, but similar to ILCs and $\gamma\delta$ T cells,

NKT do not require IRF4 signaling for IL-22 production (127). In contrast to other IL-22 producing cells, but consistent with NKT populations as a whole, IL-22-producing NKT cells required TCR-CD1d interaction to stimulate IL-22 production (125).

NKT cell development occurs in the thymus, where at the CD4⁺CD8⁺ double positive thymocyte stage, cells that have recombined their $\alpha\beta$ TCR to enable binding of the CD1d molecule (expressed by other DP cells) are driven towards the NKT cell lineage (128). At least 4 distinct NKT cell developmental stages have been identified that can be defined by their differential expression of CD24, CD44 and NK1.1 and under the control of transcription factors such as PLZF, c-Myc, Egr2, RelA and T-bet (121, 128). Although the development of IL-22 producing NKT cells is still poorly understood, they seem to branch off early in NKT cell development at what is known as “stage 0” (CD24⁺CD44^{lo}NK1.1⁻), potentially under the control of ROR γ t (129). Like ILCs, recent reports suggest that these NKT cells require IL-7 for their maintenance and survival (130).

Non-lymphoid production of IL-22

Although primarily cells of the lymphoid lineage have been described as producers of IL-22, some reports have revealed non-lymphoid sources of IL-22. These include macrophages in the lung of human and mouse, which produce IL-22 in response to lung injury (131); neutrophils, which are induced to express IL-22 in the gastrointestinal tract during experimental models of colitis (132); and even one report that describes fibroblast expression of IL-22 in patients with rheumatoid arthritis (RA) (26).

4). REGULATION OF IL-22 PRODUCTION

IL-23

IL-23, which like IL-22 signals through STAT3 (133), is one of the primary inducers of IL-22 production (34, 42–45), and the phenotype of *Il23a*^{-/-} mice mirrors that of *Il22*^{-/-} (35, 44, 93). IL-23 is a heterodimer of a specific p19 subunit and a shared p40 subunit, which can also combine with the specific p35 subunit to form IL-12 (134). TH17 cells, ILC3, $\gamma\delta$ T cells and NKT cells all express the IL-23R, and *in vitro* stimulation with IL-23 induces production of IL-22 (44, 54–57, 93, 119, 120, 125, 135–138). Dendritic cells (DCs) are potent source of IL-23, particularly the CD103⁺ subset (138–141), however, there is also evidence that CX3CR1⁺ cells may be important producers of IL-23 as well (142–144). Several distinct cytokines and pathways have been described as regulating IL-23 production, including TNF α , IFN α/β , IFN γ , CD40L, CCR4, PGE2, lymphotoxin, microRNAs, toll-like receptor (TLR) signaling, and sensory neurons.

Stimulation of multiple TLR pathways, including TLR-2, -4, -5, and -7/8, induces production of IL-23 production by DCs (135, 139, 145–149). Although ligation of TLRs alone is sufficient to drive IL-23 production, additional signals through nucleotide oligomerization domain-containing protein 2 (NOD2), Dectin-1 receptor, and IL-23 itself have been shown to induce maximal induction (135, 145, 146, 150). NOD2 appears to be a key regulator of IL-23 production, as it is also able to inhibit its production (151), although potentially only when NOD2 is stimulated alone with no concomitant stimulation of TLR or Dectin-1 (150). One mechanism by which TLR signaling induces IL-23 production is

through directly regulating miR-10a, which inhibits expression of the p40 common subunit (152). CD40L, which is capable of directly inducing IL-23, can also enhance production stimulated by TLR ligation (153, 154). Given that TLR stimulation can trigger both IL-12 and IL-23 production, the crosstalk between IFN γ and TLR pathways appears to be important for influencing differential regulation of the p35 and p19 subunits; inducing p35 and thus IL-12 at the expense of p19 and IL-23 (135, 155, 156). In contrast, there is evidence to suggest that TNF α is global regulator of both IL-12 and IL-23 by directly reducing expression of the common p40 subunit (157). Of note, TLR2 stimulation has been shown to also directly induce IL-22 production by ILC3 in human tonsil (58); and $\gamma\delta$ T cells express TLR1 and TLR2 as well as Dectin-1, ligation of which could enhance production of IL-22 (54). However it is unclear how widespread this mechanism of IL-22 induction is.

Dendritic cell localization also seems to be important for regulating IL-23 production. A recent elegant study provided the first evidence to suggest that the peripheral nervous system could control IL-23 production in the skin; with IL-23 producing dermal DCs located in close proximity to sensory neurons (158). In addition, Prostaglandin E2 (PGE2), which is derived from mesenchymal cells and has previously been shown to promote the survival of DCs (159), induces the production of IL-23 by DCs (160–162).

There is increasing evidence to suggest that signaling through LT pathway also has a key role in regulating the production of IL-22. Although LT signaling appears to be dispensable for normal development of ILCs and other producers of IL-22 (163), mice deficient for the LT β receptor (LT β R) fail to produce IL-22 in response to *C. rodentium* or those fed a high fat diet; and treatment with an LT β R agonist rescues this defective IL-22 production (164–166). Expression of LT β R has been largely attributed to epithelial cells and stromal cells (167); however, mice with LT β R deleted only in CD11c+ dendritic cells could recapitulate this phenotype (165); and exogenous administration of IL-23 could rescue the phenotype in these mice (164). Together, this strongly suggests that LT signaling is a key regulator of IL-23 expression by DCs. Although the mechanisms by which this occurs is still unclear, intriguingly, LT α 1 β 2 is expressed by many of the same cells that produce IL-22, such as ILC3 (78, 81, 168), thus creating a feedback loop where ILC3 can induce more production of IL-23 by DCs (165).

Interleukin-1 β

NKT, ILC3 and TH17 cells can all be induced to produce IL-22 under the control of IL-1 β (55, 120, 125, 169–171). IL-1 β is produced by multiple cell types, including macrophages, DCs, neutrophils, B and T cells, endothelial cells and epithelial cells (172), and in the gut appears to be dependent on stimulation by the microbiota (173). Interestingly, IL-22 production can be induced by IL-1 β , independently of IL-23, although combined they act synergistically (55). However, unlike IL-23, constant IL-1 β signaling was required for sustained IL-22 production (174). Moreover, in addition to its role in promoting IL-22 expression, IL-1 β also has the capacity to stimulate proliferation and expansion of ILCs and was sufficient to inhibit progression towards IFN γ -producing ILC differentiation (174).

Interleukin-7

Common amongst most lymphoid cells, including those that exhibit the capacity to produce IL-22, is their regulation by IL-7 (175). IL-7 is absolutely critical for the generation and development of all lymphoid IL-22 producing cells such as conventional $\alpha\beta$ T cells and $\gamma\delta$ T cells (176, 177), however its role in the formation of IL-22-producing NKT cells and ILCs is less clear (175). Although numbers of NKT and ILC3 are reduced in IL-7 or IL-7R α deficient animals, they are not completely absent suggesting that IL-7 is important for their expansion but not their development (70, 72, 73, 130, 178, 179). IL-7 signaling appears to be semi-redundant with TSLP, which also signals through IL-7R α and can rescue ILC numbers in *Il7*^{-/-} mice (180). The importance of IL-7R α signaling for LT α i expansion is highlighted by the fact that secondary lymphoid organogenesis is abnormal in mice lacking components of the IL-7 pathway (such as *Il7*^{-/-}, *Il7ra*^{-/-}, *γc*^{-/-} or *Jak3*^{-/-}) (178, 179, 181–183), although the effects of IL-7 deficiency are primarily observed in Peyer's patches. Little decrease in ILCs was observed in the LN of *Il7ra*^{-/-} mice (81, 178, 179). Reduction in ILC number likely plays an important role in the abnormal lymphoid organogenesis noted above. However, the effect of IL-7 deficiency can also be explained by its regulation of LT signaling, which is crucial for secondary lymphoid organ formation (184). Blockade of IL-7 signaling or IL-7R α deficiency led to reduction in the expression of LT α 1 β 2 by LT α i; and incubation with IL-7 led to upregulation of LT α 1 β 2 (88, 179, 185, 186). Although IL-7 has not been shown to directly regulate IL-22 production, it does appear to stabilize ROR γ t expression (72), itself critical for the differentiation of all IL-22-producing subsets and for optimal IL-22 gene expression (40, 187). Interestingly, much like other lymphopenic mice such as *Rag*^{-/-} (138, 188, 189), production of IL-22 by ILC3 is actually increased on a per cell basis in *Il7*^{-/-} and *Il7ra*^{-/-} mice (138). Thus, it seems that IL-7 is important for the expansion of IL-22 producing cells (in particular NCR+ ILC3), but may not be required for their functional production of IL-22.

Aryl Hydrocarbon Receptor (AhR)

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 (187, 190, 191). AhR is located in the cytoplasm in a complex with Hsp90 until ligand binding induces a conformational change that leads to the exchange of Hsp90 with the nuclear translocation component ARNT (192). Potential AhR ligands could be derived endogenously, from the diet, or from the gut microbiota (190), including indol-3-carbinol, 6-formylindolo[3,2-b]carbazole (FICZ) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (193, 194). In addition to these ligands, physical shear stress, cyclic AMP and Ca²⁺ as well as serum components can activate AhR (195–197). It has been reported that microbial-derived AhR ligands may not be required for ILC development, although these ligands might be important for IL-22 transcription (187, 190, 191, 198–200).

Notch

Notch signaling, which is required for normal lymphopoiesis (201), is also required for the specific development and differentiation of IL-22 producing subsets such as NCR+ and NCR- ILC3 (95, 98, 202). However, in addition to this role in cellular development, Notch

signaling also seems to provide an important signal in regulating IL-22 production (203). RBP-J κ mice, which are deficient for Notch signals, are extremely susceptible to Con-A mediated hepatitis and experimental autoimmune uveoretinitis, phenotypes that are reversed with the administration of IL-22 (203–205). Mechanisms underlying this regulation of IL-22 include the capacity of Notch signaling to directly regulate ROR γ t expression as well as other IL-22 regulatory elements such as AhR and Stat3 (203, 206, 207). In fact, Notch signaling, through its target Hes1, is able to extend the phosphorylation of STAT-3 (208), potentially affecting IL-22 targets as well as IL-22 induction.

IL-22 Binding Protein (IL-22BP)

One of the key regulators of IL-22 signaling is a soluble form of the IL-22R1 subunit, known as IL-22 binding protein (IL-22BP). The gene encoding human IL-22BP is located at chromosome 6q23.3 and is closely situated between genes encoding other Type 2 cytokine receptors; 13kb away from the gene encoding IFN γ R (*Ifngr*) and 78kb from the gene encoding for IL20R (*Il20r1*) (209–211). The overall structure of the mouse gene was found to be very similar to the human gene and encodes an open reading frame of 693 base pairs on chromosome 10. The gene encodes a 210 amino acid protein that shares 34% sequence homology to the extracellular domain of the IL-22R1 subunit (210–214). IL-22BP binds to IL-22 at an overlapping site to IL-22R1, thereby directly interfering with binding to the membrane-bound receptor (215, 216). Moreover, affinity of IL-22 to IL-22BP is up to 1000 fold higher than the membrane bound IL-22R1 form ($K_D=1\text{pM}$), primarily as the K_{off} rate for IL-22BP is up to 4.7 days compared to 7 minutes for IL-22 in complex with IL-22R1, further adding to the inhibitory effect of IL-22BP (14, 217).

IL-22BP has been identified in tissues as diverse as placenta, skin, lung, pancreas, appendix, lung, gastrointestinal tract, breast, lymph nodes, bladder, kidney and thymus (209, 210, 212, 214). Although expression has been primarily identified in dendritic cells (including CD103+ DCs that are also producers of IL-23 (218), IL-22BP has also been found in epithelial cells as well as macrophages (211–214), and there has been one report of IL-22BP expression by B cells (219). Interestingly given its ability to directly inhibit the effects of IL-22, expression of IL-22BP does not increase as levels of IL-22 increase. In models of mouse colitis or LPS administration, when IL-22 levels are significantly increased, amounts of IL-22BP actually decrease (209, 217). However, in later periods after IL-22 has been induced, levels of IL-22BP can increase indicating a regulatory role after the initial early effects of IL-22 (217, 220, 221).

Negative Regulators of IL-22 Production

Although TGF β is required for TH17 differentiation (37), and can regulate the expression of both ROR γ t and IL-23R (35, 38, 39), it can also act as an inhibitor of IL-22 production in a dose-dependent fashion (44, 47, 48, 222). IRF4, which is a downstream target of TGF β , and much like TGF β is required for TH17 differentiation (223), also inhibits the production of IL-22 possibly through direct binding of the IL-22 promoter (224). However, IL-23 is able to overcome the inhibitory effect of TGF β and induce the production of IL-22 (46). In addition to TGF β , IL-27 and ICOS have both also been identified as inhibitors of IL-22 production (225–227). Interestingly, common to the TGF β , IL-27 and ICOS pathways is the

transcription factor c-Maf, which appears to be critical for the inhibition of IL-22 production (48, 227, 228). Furthermore, IL-38, which signals through IL-36Ra, has recently been found to be a regulator of IL-22 production in a dose-dependent fashion; low concentrations of IL-38 inhibit IL-22, while high concentrations modestly induce its production (229, 230).

5). TARGET TISSUES: PATHOPHYSIOLOGY AND REGENERATIVE BIOLOGY

IL-22 is expressed in a broad array of tissues (Figure 3), including liver, lung, skin, thymus, pancreas, kidney, gastrointestinal tract, synovial tissues, heart, adipose tissue, breast and eye (7, 231–240); and its receptor is expressed on the stromal and epithelial cells of those tissues. As IL-22 is produced at sites of inflammation, it may be mediating a physiologic response to repair local tissue damage, or it may be contributing to pathophysiologic inflammation. There is extensive evidence that IL-22 mediates protection and regeneration of epithelial tissues in experimental models, including hepatitis, pancreatitis, colitis, and thymic injury (7, 138, 231, 232). However, this is not true in all models, and IL-22 can induce expression of pro-inflammatory molecules, including IL-1, IL-6, IL-8, IL-11, GCSF, GM-CSF, and LPS binding protein (25, 232, 241). This has led to conflicting conclusions as to whether IL-22 is tissue-protective or pro-inflammatory, although these two options are not mutually exclusive. Stimulating epithelial cell survival, proliferation, and production of innate antimicrobials during acute tissue damage can be protective, while chronic overexpression of IL-22 in an otherwise healthy tissue could lead to hyperproliferation, production of chemokines and other inflammatory signals, and subsequent recruitment of pathologic effector cells to the inflamed tissues. The molecular processes are the same, but the context determines protection vs. pathology.

In addition to the context of IL-22 production, potential pathologic effects of IL-22 could be related to other cytokines expressed with IL-22. It has been proposed that IL-22-related pathology may be due to tissue “priming” by type I interferons that shift IL-22 signaling away from STAT-3 toward a STAT-1 response (242). Furthermore, IL-17 and IL-19 have additive effects with IL-22 in inducing production of other inflammatory molecules (243). Prominent examples of such interplay in inflammation are: in oral mucosa, where IL-1 β and IL-22 cooperate in inducing CCL20 expression by human gingival fibroblasts, leading to recruitment of Th17 cells and periodontal disease (244); in a model of psoriasis, where a combination of IL-22, IL-17A, IL-1 α , OSM and TNF α synergistically increased chemokine and antimicrobial-peptide expression (245); in the lungs, IL-22 reduced bleomycin-related lung toxicity in IL-17 deficient mice, but promoted airway inflammation if IL-17 was present (246); in chronic hepatitis, where IL-22-related pathology was dependent on the recruitment of Th17 cells (247); and in an anti-CD40 administration model colitis, where IL-22 was reported to exacerbate colon inflammation that was dependent on IL-23 and IFN γ for intestinal pathology (72, 248, 249). Moreover, IL-22 had no effect on anti-CD40-induced colitis in mice lacking ILCs (93, 248), further suggesting that pathologic effects of IL-22 may be dependent on co-expression with other inflammatory cytokines.

Systemic expression in peripheral blood

IL-22 expression has been reported in murine and human peripheral blood under stress conditions, however the baseline serum expression is extremely low (137, 217). Mirroring findings in mice, where TBI conditioning and T cell-depleted bone marrow transplantation (BMT) led to increased serum IL-22 protein in two different murine strains (137), elevated expression of IL-22 has also been reported clinically in patients with inflammatory conditions, including IBD, RA and malignancy (217, 250). Serum IL-22 is also elevated in patients with IL-23 receptor polymorphisms associated with Crohn's disease, which could indicate a pathologic role for IL-22 in IBD, a compensatory IL-22 response in IBD patients, or a coincidental finding, as Crohn's disease may actually be dependent on other pathways that are also activated by IL-23 receptor signaling (251). Furthermore, the overall relevance of serum IL-22 expression to disease states is unclear, as this could represent systemic dissemination of an immune response, or leakage into the vascular compartment from a compromised tissue site where IL-22 may be intended to mediate tissue repair. Interestingly, IL-22 can induce production of coagulation factors including fibrinogen (252). While this may simply be indicative of IL-22 function in target tissues such as the liver, regulation of systemically disseminated molecules suggests that serum IL-22 may indeed function in coordination of a general inflammatory response.

Gastrointestinal Tract

IL-22 and its receptor have been described in the human upper GI tract, including the oral cavity, salivary glands, tonsils, stomach, and esophagus, where IL-22 expression has been associated with inflammation and antimicrobial immunity as well as malignancy (66, 91, 253–258). IL-22 levels are increased in colonic tissue from patients with Crohn's disease and ulcerative colitis (25), and in murine colon during DSS-induced and T cell transfer-mediated colitis (259). Colon IL-22 expression is also increased in experimental colitis due to infection with *Clostridium difficile* and *C. rodentium* (45, 260). Intestinal IL-22 is critical for orchestrating antibacterial immunity against *C. rodentium*, which is used in experimental murine modeling of enterohemorrhagic and enteropathogenic *E. coli* colitis (45, 187). Although the adaptive immune response does contribute to immunity against *C. rodentium*, ILCs are the dominant source of IL-22 critical for initial resistance against the infection (45, 69, 136). Moreover, ILCs appear to be the essential source of IL-22 for protection against DSS-induced colitis and protection against GI graft versus host disease (GVHD) (137, 261), although other innate sources of IL-22 such as neutrophils may contribute as well (132).

The single common function of IL-22 in the GI tract relates to maintenance of the epithelial barrier. Sonnenberg and colleagues demonstrated that ILC-derived IL-22 was important for routine containment of *Alcaligenes* species and preventing subsequent systemic inflammation (262). However, the phenotype of IL-22 deficiency in the gut is much more pronounced after challenge with pathologic inflammatory injury, whether infectious, chemical, or alloreactive (7, 231, 232). IL-22-deficient mice exhibit only minimal epithelial perturbations at baseline. However they demonstrate severely exacerbated colitis in response to *C. rodentium* infection, which can be reversed by exogenous administration of IL-22 (45, 136). Similarly, mice lacking ILC3 are highly susceptible to DSS-induced colitis (263).

IL-22-mediated barrier maintenance involves support of the epithelial lining's structural integrity as well as its functional activation. IL-22 provides direct support to intestinal epithelial cells by inducing expression of genes regulating proliferation, wound healing, and apoptosis (243, 264). It has also been suggested that IL-22 may regulate tight junctions between intestinal epithelial cells (265). This is consistent with a recent report describing upregulation of mRNA expression for the tight junction protein claudin-1 in human intestinal epithelium after culture with IL-22 *in vitro* (266). In addition to these examples of IL-22-mediated regulation of the physical barrier, IL-22 provides functional barrier support by inducing the production of innate antimicrobials, including defensins, Reg family molecules, and S100 proteins (23, 28, 34, 45, 262, 264, 267). Bridging the structural and functional barrier, IL-22 also protects goblet cells during colitis and induces production of mucins (Muc1, 3, 10, and 13), which are necessary to create a protective layer between the epithelium and enteric contents (221).

The intestinal barrier regulated by IL-22 is dynamic, involving cross-talk between ILC3 and the intestinal microbiota (69). IL-22 is critical for bacterial containment (262), and AhR stimulation by microbiota-derived ligands may be important for suppression of colitis by mediating bacterial containment and prevention of inflammation induced by gut microbes (199). In addition, the gut microbiota can contribute to retinoic acid production by DCs (268). Retinoic acid has been shown to attenuate colitis due to DSS administration and *C. rodentium* infection by promoting binding of the retinoic acid receptor to the IL-22 promoter, thereby enhancing IL-22 production by ILCs and $\gamma\delta$ T cells (57). Conversely, retinoic acid can also enhance DC production of the negative regulator IL-22BP (218), and gut flora can inhibit IL-22 expression via induction of enterocyte IL-25 production (263). Therefore, there is a fine balance in the GI tract between the microbiota, the immune system, and the epithelial barrier, where flora can induce the IL-22 production that is necessary for its containment. Dysregulation of this system can result in inflammatory epithelial pathology.

The intestinal epithelium contains diverse subsets of functionally distinct cell types (269), and the specific cellular targets of IL-22 remain to be fully elucidated. While it is known that goblet cells produce mucins in the intestines, there is little direct evidence indicating that intestinal mucin production downstream of IL-22 is due to a direct effect of IL-22 on goblet cells. Similarly, although IL-22 is thought to regulate Paneth cell production of Reg3 molecules and defensins, and while Paneth cells are reported to produce these molecules (270, 271), there is little direct evidence indicating that IL-22 is instructing this function. Reg3 β and Reg3 γ can be produced by crypt epithelium and mature enterocytes (272). Furthermore, mice with Paneth cell deficiency due to GVHD demonstrate increased expression of Reg3 γ , indicating that enterocytes are potent sources of intestinal antimicrobials (273). Additionally, we have found that IL-22R is expressed on Lgr5⁺ intestinal stem cells (137), although the functional significance of this is unknown.

Secondary lymphoid tissue

Intestinal IL-22⁺ ILCs are present in cryptopatches within the lamina propria, and they contribute to the development of secondary lymphoid tissues and mucosa associated

lymphoid tissues (MALT), including lymph nodes, cryptopatches, isolated lymphoid follicles (ILFs), and Peyer's patches (79, 80, 82, 83, 86, 88). It is thought that cryptopatch development is dependent on activation of stromal cells by LT from ILCs and recruitment of DCs and other hematopoietic cells (184, 274–276). Initial cryptopatch development seems intrinsically regulated, but subsequent post-natal recruitment of B cells may induce formation of ILFs in a microbiota-dependent fashion, as ILFs are absent in mice treated with broad antibiotics to clear the microbial flora (86, 277, 278). While the ROR γ ⁺ LT_i cells critical for lymph node development are robust producers of IL-22, and mice deficient in IL-22⁺ ILCs due to loss of either ROR γ ^t or AhR are lacking both cryptopatches and ILFs, it does not appear that IL-22 itself is critical for the formation of either of these structures (45). Cryptopatches in the small intestine, their large intestine counterpart colonopatches, and ILFs throughout the GI tract were reported by Zheng and colleagues to be present in IL-22-deficient mice. Interestingly though, after *C. rodentium* infection they found that treatment with an anti-IL-22 neutralizing antibody led to the loss of both colonopatches and ILFs, suggesting that while IL-22 is dispensable for normal development and maintenance of MALT, it may have an important role in maintenance of intestinal lymphoid structures in the setting of inflammatory pathology. It is unknown however if this role of IL-22 is due to direct maintenance of the structures or indirect support of the structures by maintaining the epithelium and/or controlling the infection.

Skin

IL-22 has multiple effects on keratinocytes, such as induction of proliferation, migration, tissue remodeling and secretion of anti-microbial peptides and chemokines, as well as delayed differentiation (reviewed in (7)). IL-22 induces keratinocytes to produce anti-microbial proteins, including β -defensin 2, β -defensin 3, S100A7, S100A8, S100A9 and lipocalin 2 (279–281). IL-22 also promotes the production of neutrophil-attracting chemokines, such as CXC-chemokine ligand 1 (CXCL1), CXCL2, CXCL5 and CXCL8, and inhibits the expression of CCL22, which attracts Th17 and Th2 (282). IL-22 can also induce the expression of extracellular matrix (ECM)-degrading enzymes matrix metalloproteinases (MMP)-1 and -3, which are required for epithelial migratory capacity during epithelial repair (280). In addition to its role in innate immunity by promoting anti-microbial molecules or attracting neutrophils, IL-22 also inhibits differentiation and maturation of keratinocytes through downregulation of molecules such as keratin 1 (KRT1), KRT10, profilaggrin, involucrin, loricin, kallikrein 7, desmocollin 1 and the late cornified envelope protein 1B (280, 282).

IL-22 also increases the expression of IL-20, which shares the IL-22R1 chain in its receptor complex (IL-22R1/IL-20R2) and has similar effects as IL-22 on keratinocytes, resulting in a positive feedback loop to amplify the effects of IL-22 (282). IL-22 has major effects on epidermal architecture, resulting in acanthosis (thickening of stratum spinosum in epidermis), parakeratosis (nuclear remnants in stratum corneum due to dysfunctional keratinocyte cornification) and hypogranularity in both 3-D tissue models, as well as IL-22 overexpressing transgenic mice (282, 283). These architectural changes of the epidermis are similar to those seen in psoriatic plaques. In addition, psoriatic plaques contain neutrophils

and increased expression of IL-20 and STAT-3, which could be related to the increased IL-22 levels in the plaques (282, 284–286).

There has been considerable pathology related to IL-22 documented in the skin, where IL-22 is thought to contribute to psoriasis (7, 44). Psoriasis is common chronic skin disease, which affects approximately 2% of the population (287), and shares features with other chronic inflammatory diseases, such as IBD, diabetes mellitus, as well as an associated arthropathy: psoriatic arthritis. The characteristic skin lesions are raised, well-demarcated scaly plaques due to hyperproliferation of the epidermis with premature maturation of keratinocytes and incomplete cornification and retention of nuclei in the stratum corneum (287). The skin lesions contain an inflammatory infiltrate, which consists of dendritic cells, macrophages and T cells in the dermis, as well as neutrophils and T cells in the epidermis. The pathophysiology of psoriasis is multi-factorial with roles for autoimmunity, dysregulation of the innate immune system, proinflammatory cytokines, as well as imbalance of epithelial homeostasis, angiogenesis and genetic and environmental risk factors. However, dendritic and T cells seem to play a predominant role and the primary axis seems to be the production of IL-23 and IL-12 by dermal myeloid dendritic cells, which subsequently activates Th1, Th17 and Th22 cells to secrete IL-17, IFN- γ , TNF and IL-22 (288).

Polymorphisms in the IL-22 gene have been associated with psoriasis in a Japanese population (289) and a polymorphism in the promoter region of IL-22 is associated with increased production of IL-22 and increased risk of psoriasis onset in childhood (290). In addition, copy number variation of IL-22 gene exon1 was significantly associated with psoriasis severity (291). Finally, polymorphisms in both IL-23R and IL-12B (coding for common p40 chain) are associated with psoriasis (292).

Initial studies regarding the effects of IL-22 in pathologies of the skin demonstrated that IL-22 levels were increased in T cell dermatoses, such as psoriasis and atopic dermatitis (23, 53). Consistent with a role in its pathophysiology, psoriasis patients have increased levels of IL-22 in their blood and serum, which has been associated with disease severity (293–295). Interestingly, psoriatic plaques also have increased expression of IL-20 and IL-24 (285, 286), which both bind to IL-22R1 and seem to have similar effects as IL-22 on keratinocytes *in vitro* and in transgenic mice (282, 283, 296, 297).

Notably, effective therapy for psoriasis results in a decrease in IL-22 levels both in the serum and the psoriatic skin lesions (28). A series of recent studies have demonstrated increased numbers of NCR+ ILC3 in the peripheral blood and lesions of psoriasis patients and therapeutic response to anti-TNF resulted in a decrease in the numbers of circulating NCR+ ILC3 (298–300). Interestingly, NCR– ILC3 could be shown to be converted to NCR+ ILC3 upon culture with IL-1 β and IL-23, which are both involved in psoriasis (299). Studies with IL-23 administration in IL-22-deficient mice demonstrated that IL-22 is required for both acanthosis and neutrophil infiltration (44) and injection of IL-22 into human normal skin xenografts in immunodeficient AGR129 mice resulted in changes similar to psoriasis, including epidermal thickening, expression of the psoriasis-associated marker K16 and increased vascularization (301). In addition, administration of neutralizing antibodies to IL-22 prevented the development of disease, acanthosis, inflammatory

infiltrates, and expression of Th17 cytokines in experimental models as well as in human xenografts (301, 302).

IL-22 neutralization has been tested in a phase 1 study evaluating a single subcutaneous dose of anti-IL-22 antibody (ILV-094) in individuals with moderate-to-severe chronic plaque psoriasis ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01010542) NCT01010542) as well as in a phase 2 randomized double-blind placebo-controlled study of six infusions of ILV-094 in subjects with atopic dermatitis ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01941537) NCT01941537). However, given that the other IL-22R1 ligands, IL-20 and IL-24, also have a primary role in the pathology of psoriasis (283), inhibition of IL-22R1 could be a more effective clinical approach than neutralization of IL-22.

Lung

Consistent with other tissues, IL-22 production in the lung is primarily regulated by alveolar macrophages and dendritic cells (reviewed in (303)). Alveolar macrophages and CD11b+ DCs can be stimulated through their innate pattern recognition receptors (PRRs), such as TLRs, NODs and Dectin, resulting in the secretion of IL-1 β , IL-23 and other pro-inflammatory cytokines (such as IL-18 and IL-6), which can stimulate NF- κ B and STAT3 in lymphocytes (both CD4+ and ILCs) resulting in the expression of ROR γ t, Th17 differentiation and the production of IL-17 and IL-22. Conversely, stimulation of plasmacytoid and CD103+ DCs by viral antigens results in the secretion of type I IFNs, which counteract Th17-polarizing cytokines, as well as IFN- γ and IL-27, which activates STAT1 and suppresses IL-17/22 production in lymphocytes.

The epithelium in the lung has two important functions: barrier to pathogens and facilitation of gas exchange. IL-22 has several effects on the lung epithelium: (a) production of antibacterial proteins, including (in combination with IL-17) lipocalin-2 and β -defensin 2 (42), and chemokines, (b) proliferation and (c) repair after injury. IL-22 can synergize with IL-17 to induce production of G-CSF and IL-6 (42). The combination of IL-17 and IL-22 can induce MMPs, which play a role in the pathophysiology of emphysema (304). However, IL-22 can have multiple and even opposite effects in the lung depending on the stressor, kinetics and environment.

IL-22 levels in the serum are increased in the peripheral blood of patients with asthma and in the lungs of mice in preclinical asthma models (305, 306). IL-22 has a dual role in asthma: it can promote the initiation of asthma in a preclinical model, but ameliorates inflammation during antigen challenges and exacerbation (305). During allergic airway inflammation IL-22 neutralization with an antibody had dual effects: neutralization during allergen sensitization resulted in less lung pathology and lower levels of IL-5 and eosinophils, whereas IL-22 neutralization during antigen challenge increased lung inflammation and pathology (such as goblet cell hyperplasia) (305, 307). Conversely, subcutaneous (but not intraperitoneal) IL-22 administration during sensitization resulted in worse inflammation (305, 307–309), whereas IL-22 administration during antigen challenge could reduce eosinophil infiltration, chemokine expression, production of Th2 cytokines (such as IL-13 and IL-25), goblet cell hyperplasia and airway constriction (305, 307, 309). In this same model IL-17 had pro-inflammatory effects in wild type mice, but was anti-inflammatory in

IL-22^{-/-} mice. The mechanisms behind this dual role during allergic airway inflammation are not clear, but could involve inhibition of CCL17 and IL-25 production by airway epithelium (307, 309), epithelial repair (120), and possibly involve IL-10 (308).

IL-22 also plays an important role in host defense against several pulmonary pathogens. During *Streptococcus pneumoniae* infection, DC activation involving MyD88 results in rapid accumulation of ILC3 in the lung tissue to produce IL-22 (310). Administration of the TLR5 agonist flagellin increases IL-22 production by ILC3 resulting in protection against *S. pneumoniae* infection. During infection with *Klebsiella pneumoniae* IL-22, produced primarily by NK cells (311), has a protective effect (42) and during infection with the intracellular bacterium *Chlamydia muridarum* IL-22 levels in the lung rapidly increase (312). IL-22 inhibition with neutralizing anti-IL-22 monoclonal antibodies resulted in impaired Th1 and Th17 responses and exacerbation of disease. Intranasal administration of IL-22 significantly enhanced the Th17 response and resulted in protection following chlamydial lung infection.

IL22^{-/-} mice have an increased fungal burden after infection with *Aspergillus fumigatus* demonstrating a role in the clearance of this pathogen; through activation of Dectin-1 which results in IL-23 production (313). Studies with human PBMCs pointed at CD4⁺ T cells as the major IL-22 producers after exposure to *A. fumigatus* involving IL-1 signaling (314). In contrast, studies also suggest IL-22 may contribute to lung pathology during chronic exposure to *A. fumigatus* (315). Interestingly, during *Candida albicans* infection IL-22 produced by ILCs reduces the fungal burden and provides cross-protection against *Pseudomonas aeruginosa* possibly through stimulation of epithelial repair (316).

During influenza infection NK and NKT cells produce IL-22 in response to IL-23 and IL-1 β (secreted by DCs) resulting in epithelial regeneration of airway epithelium, as well as parenchymal epithelium, which has upregulated IL-22R expression after influenza infection (120, 317–319). IL-22^{-/-} mice infected with influenza display defective epithelial regeneration with increased collagen deposition. $\alpha\beta$ and $\gamma\delta$ T cells can also produce IL-22 during influenza infection and might be involved in survival after superinfection with *S. pneumoniae* through protective effects on lung epithelium (320). IL-22 can also protect against lung fibrosis in a model based on repeated exposure to *Bacillus subtilis*. Neutralization of IL-22 resulted in enhanced collagen deposition in the lungs, whereas IL-22 administration could decrease lung fibrosis (321). In addition, IL-22 can have a protective effect in a rat model of barotrauma resulting in decreased pulmonary disintegration and edema (322).

The role of IL-22 in *Mycobacterium tuberculosis* infection is still unclear, although it has been found that IL-22 producing $\gamma\delta$ T cells can migrate into the granulomas during *M. tuberculosis* infection (323). A recent study using primary epithelial cells demonstrated that mycobacteria might subvert the host defense and establish chronic infection, bypassing NF- κ B signaling through GSK3 inhibition and promoting the anti-inflammatory transcription factor CREB resulting in IL-10 and IL-22 production (324). However, IL-22 produced by NK cells seems to be required for effective BCG vaccination for *M. tuberculosis* and NK cell depletion during vaccination resulted in increased numbers of Tregs and bacilli (325).

IL-22 administration could overcome the effects of NK depletion and enhanced memory CD4⁺ T cell generation in the lungs.

As proposed by McAleer and Kolls (303), IL-22 in the lung has a role in non-redundant epithelial regeneration as well as host defense after pulmonary infection or trauma. Its dual pro- vs anti-inflammatory role in lung inflammation might be particularly dependent on the presence or absence of IL-17, therefore from a therapeutic standpoint, it may be better to inhibit IL-17 without affecting IL-22 levels or administer IL-22 in combination with IL-17 inhibition.

Liver

In the liver hepatocytes are the main targets of IL-22; in which IL-22 is thought to induce the production of acute-phase proteins such as Amyloid A, α 1-antichymotrypsin, haptoglobin, and LPS-binding protein (2, 23, 217, 252, 326). Consistent with other tissues, IL-22 also induces proteins involved with protection and regeneration from damage such as the anti-apoptotic proteins Bcl-2 and Bcl-X_L, cyclin-dependent kinase 4 (CDK4), cyclin D1, c-myc and p21 (327–330). In fact, IL-22 has been shown to have a considerable protective role in several different experimental models of hepatic injury, including T cell-mediated hepatitis, acute hepatitis, liver ischemia-reperfusion injury, bacterial and parasitic infection, as well as models of acute and chronic alcohol-induced liver damage (327–334). IL-22 promotes the proliferation of liver stem and progenitor cells (335), inducing their expression of cyclin D as well as the anti-apoptotic proteins Bcl-2 and Bcl-X_L in a STAT-3 dependent fashion (335). This stimulation of hepatic stem and progenitor cells is consistent with its ability to promote the regenerative response in the liver to partial hepatectomy (330, 336). Further supporting this role of IL-22 in liver regeneration, levels of IL-22 are increased in patients with hepatitis B or C viral infections (330, 337), and receptor expression is upregulated by hepatocytes in periods of injury (330, 331, 333).

Kidney

Low constitutive expression of IL-22R was identified in kidney in the earliest studies looking for its expression (13, 23, 338, 339). Subsequent analysis has revealed that tubular epithelial cells are the main cells expressing IL-22R (340). Consistent with these findings, a human kidney cell line, TK-10, has been shown to respond to IL-22, inducing STAT-3 phosphorylation (3).

Although little is known about its regulation or role in kidney function, IL-22 is induced in the kidney after LPS stimulation (2) as well as in a model of polymicrobial peritonitis (341). However, there is some discrepancy regarding the role of IL-22 in kidney regeneration. In several studies IL-22 has been shown to have a detrimental effect on kidney regeneration where blockade of IL-22 with an IL-22BP-Fc led to reduced kidney injury and enhanced bacterial clearance in polymicrobial peritonitis (341); and *in vitro* incubation with IL-22 suppresses the growth of the renal carcinoma cell line A498 (342). In contrast, and consistent with other tissues such as gut, thymus, lung and liver, Kulkarni and colleagues have recently found that IL-22 can in fact enhance kidney regeneration in a TLR4-dependent manner (340). In addition, polymorphisms in the IL-22R are associated with development of

nephropathy (343). The discrepancies in these studies will clearly need to be reconciled in order to develop IL-22 (or anti-IL-22) as a potential therapy for kidney pathology.

Pancreas

Initial studies of tissues expressing IL-22R1 revealed the pancreas as the tissue with the highest levels of expression (23, 338, 344), likely due to the high relative proportion of cells within the pancreas expressing IL-22R as both acinar cells as well as islet α and β cells express IL-22R1 (338, 345). Within acinar cells, IL-22 is thought to induce production of molecules such as Reg3 β , Reg3 γ , and osteopontin (338, 346), as well as inducing the anti-apoptotic proteins Bcl-2 and Bcl-X_L (335, 338, 345). IL-22 is also thought to induce Reg1 and Reg2 expression within islet cells (347). These findings have led to the idea that IL-22 could be used to treat pancreatitis, which has proven experimentally successful using transgenic overexpression of IL-22 as well as small molecule activators of AhR (346, 348).

Synovial tissue

Although in most tissues epithelial cells are the predominant targets of IL-22, fibroblasts have also been described as targets of IL-22 in the skin, synovial tissues, lung and colon (22, 25, 26, 282); although at least in the skin they appear to express the IL-22R at considerably lower levels than keratinocytes (282). Much like epithelial tissues, but in contrast to colonic or lung fibroblasts (25, 349), IL-22 has been shown to induce proliferation of synovial fibroblasts (26), likely contributing to the pathophysiology of RA. In fact, IL-22 is increased in the synovial tissue and in the serum, and IL-22+ CD4 T cells are increased in the peripheral blood of patients with RA (26, 350–353). In addition to promoting proliferation amongst synovial fibroblasts, IL-22 also induces the production of CCL2 (26), thereby attracting monocytes to the synovium, as well as RANKL which induces their differentiation into osteoclasts (354).

6). SYSTEMIC EFFECTS OF IL-22

Cancer

Perhaps the most dramatic example of pathologic production of IL-22 occurs in the setting of malignancy, where the tissue regenerative effect of IL-22 can be coopted to contribute to tumor growth. IL-22 has been associated with cancers in several sites, including skin, thyroid, lung, breast, stomach, pancreas, liver, cervix, and colon (355–365). Kirchberger and colleagues identified IL-22⁺ cells in human colon cancer specimens and found that a model of bacteria-induced colon cancer led to accumulation of double positive IL-17⁺IL-22⁺ ILCs (366). IL-22 in this experimental cancer model activated STAT-3 in colon epithelium and contributed to colon cancer progression. In an experimental model of colon cancer induced by DSS and azoxymethane, it was also shown that IL-22 could contribute to tumor development (220). IL-22 protected mice from the initial colitis that was induced by the chemical treatment, however excessive IL-22 expression due to elimination of IL-22BP increased tumor growth. While IL-22 was functionally linked to tumor progression in both of these model systems, IL-22 was not shown to have a causative role in tumor transformation. Rather, malignancy was induced by the experimental model and IL-22 then contributed to progression. Additionally, the IL-22/STAT-3 axis has been shown to activate

STAT-3 in human colon cancer cells, inducing Dot1L expression and promoting tumorigenic potential (356), although this still may reflect a property of transformed cells using IL-22, rather than IL-22 playing a causative role in malignant transformation. Therefore, given the connection between inflammation and colon cancer, it is possible that IL-22 could have both protective and pathologic effects in malignant transformation. IL-22 could prevent tumorigenesis by inducing tissue regeneration, promoting barrier function, and reducing chronic inflammation. However, if IL-22 is overexpressed due to chronic inflammation, then malignant cells could utilize this trophic signal to feed their progression.

Graft versus host disease (GVHD)

Contrasting effects of IL-22 have also been reported in GVHD, where recipient-derived IL-22 was shown to reduce mortality and tissue pathology in the liver and GI tract, whereas donor-derived IL-22 increased mortality and target tissue inflammation (137, 367–369). Protective recipient-derived IL-22 was produced by tissue resident ILCs (137). In contrast, donor T cells producing IL-22 led to an overall heightened inflammatory state in recipient mice, with concomitant reduction in regulatory T cells. This dichotomy in experimental GVHD models is supported by clinical investigations indicating that ILC activation and recovery from chemotherapy is associated with reduced susceptibility to mucositis and acute GVHD (370), but acute GVHD skin lesions demonstrate increased infiltration with CD4⁺ T cells (371). Therefore, the distinct effects of IL-22 in GVHD could be due to 1) the timepoint post-BMT when IL-22 is produced by distinct cellular sources, 2) distinct additional cytokines co-produced by these cellular sources or their neighbors, or 3) distinct localization and cellular targets of donor T cells and recipient ILCs within tissues. Although recipient-derived IL-22 was shown to be protective for gut tissue after allogeneic BMT, the potential benefit of IL-22 was limited during GVHD due to the elimination of recipient-derived IL-22⁺ ILCs by alloreactive donor T cells (137). This pathophysiology of IL-22 deficiency in GVHD may have a natural parallel in autoimmune polyendocrinopathy - candidiasis - ectodermal dystrophy (APECED) patients who have neutralizing antibodies to cytokines including IL-22, contributing to their susceptibility to candidal infections (372, 373). Furthermore, colon biopsy samples from patients with IBD have also demonstrated a deficiency of IL-22⁺ cells, and impaired T cell and innate cell IL-22 production has been reported in a primate model of celiac disease, indicating that intestinal pathology due to loss of IL-22-producing cells is not limited to GVHD pathogenesis and the transplant setting (374, 375).

Regulation of adaptive immunity

Interestingly, in some of the earliest studies of IL-22, constitutive expression of both IL-22 and IL-22BP were found to be highest in the thymus (6, 209, 210, 212). In fact, the thymus was the tissue chosen to isolate IL-22 cDNA for sequencing (1). Although IL-22 does not seem to be required for normal thymus organogenesis or maintenance, as there is no gross defect in *Il22*^{-/-} mice (138), constitutive expression of high levels of IL-22 in the steady-state does seem to lead to some thymic involution (252). However, in periods of thymic injury, IL-22 is critical for the endogenous regeneration of thymic tissue and restoration of T cell development (138). Despite its importance for generating a diverse adaptive immune repertoire, the thymus is extremely sensitive to injury, which can be caused by infection,

shock, and cytoreductive chemo- or radiation therapy (376, 377). It also has a remarkable capacity for repair, although prolonged T cell deficiency is a major clinical hurdle in patients receiving common cancer cytoreductive therapies and in BMT recipients (377, 378). Post-transplant T cell deficiency is associated with an increased risk of infections, relapse of malignancy, the development of secondary malignancies, and impairment in application of immunotherapeutic strategies, such as vaccination against microbes or tumors (379–383).

Although initial studies did not identify IL-22R expression in the thymus by PCR (279, 338), subsequent analysis of protein expression revealed a population of thymic epithelial cells (138). These discrepancies can likely be explained by the rare thymic epithelial cell (TEC) population not being assayed by common dissociation protocols (384). IL-22R signaling promotes TEC proliferation and survival (138), and one recent report suggested that IL-22 might even regulate FoxN1 (385), a forkhead box transcription factor that is critical for TEC development, maintenance, and regeneration (386–390). However, while Pan and colleagues did observe increased expression of FoxN1 at the same time as there was increased expression of IL-22 (385), there is not yet direct evidence supporting the regulation of FoxN1 by IL-22. Intriguingly, in addition to the role of IL-22 in adaptive immunity by regulating thymopoiesis, ILCs themselves appear regulate CD4⁺ T cells in the gut (391). Murine intestinal ILC were found to express MHC II, but not co-stimulatory molecules, thus leading to tolerance of mucosal T cells to enteric contents.

7). CONCLUDING REMARKS

In summary, IL-22 has a variety of functions, most notably its trophic effect 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. Its involvement in a variety of diseases makes it an attractive target for clinical development. However, therapeutic strategies will have to be individualized based on organ and/or pathology; in some cases the therapeutic goal would be to decrease IL-22 levels (for example: psoriasis or malignancy), whereas in other situations, therapeutic IL-22 administration could be considered (for example: tissue damage such as that caused during GVHD). Successful implementation of either of these strategies will require further investigation into the molecular mechanisms and cellular targets of IL-22 in health and disease.

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DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. Patent applications have been filed on the therapeutic use of IL-22 (US 61/487,517; US 61/901,151) with J.A.D, A.M.H and M.R.M.vdB listed as inventors.

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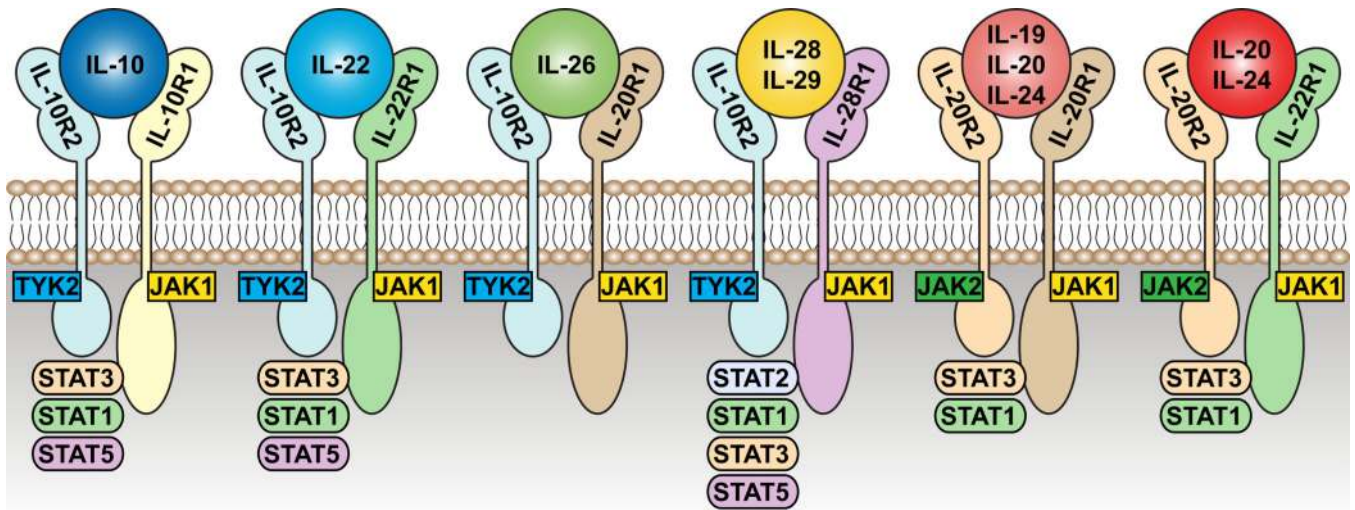


Figure 1. Receptors and JAK-STAT molecules of the IL-10 family of cytokines

IL-22 is a member of the IL-10 family of cytokines, all of which share common features in their receptors. IL-22R is composed of two subunits: the common IL10R2 subunit, which is shared with the receptors for IL10, IL-26, IL-28 and IL-29; and the IL-22R1 subunit, which itself can also pair an IL-20R2 subunit forming the receptor for IL-20 and IL-24. IL-20 and IL-24 (in addition to IL-19) can also signal through another receptor composed of IL-20R1 and IL-20R2. Each of these receptors signals through components of the JAK-STAT pathway, although there is evidence that IL-22 can also signal through p38 and MAP kinase pathways.

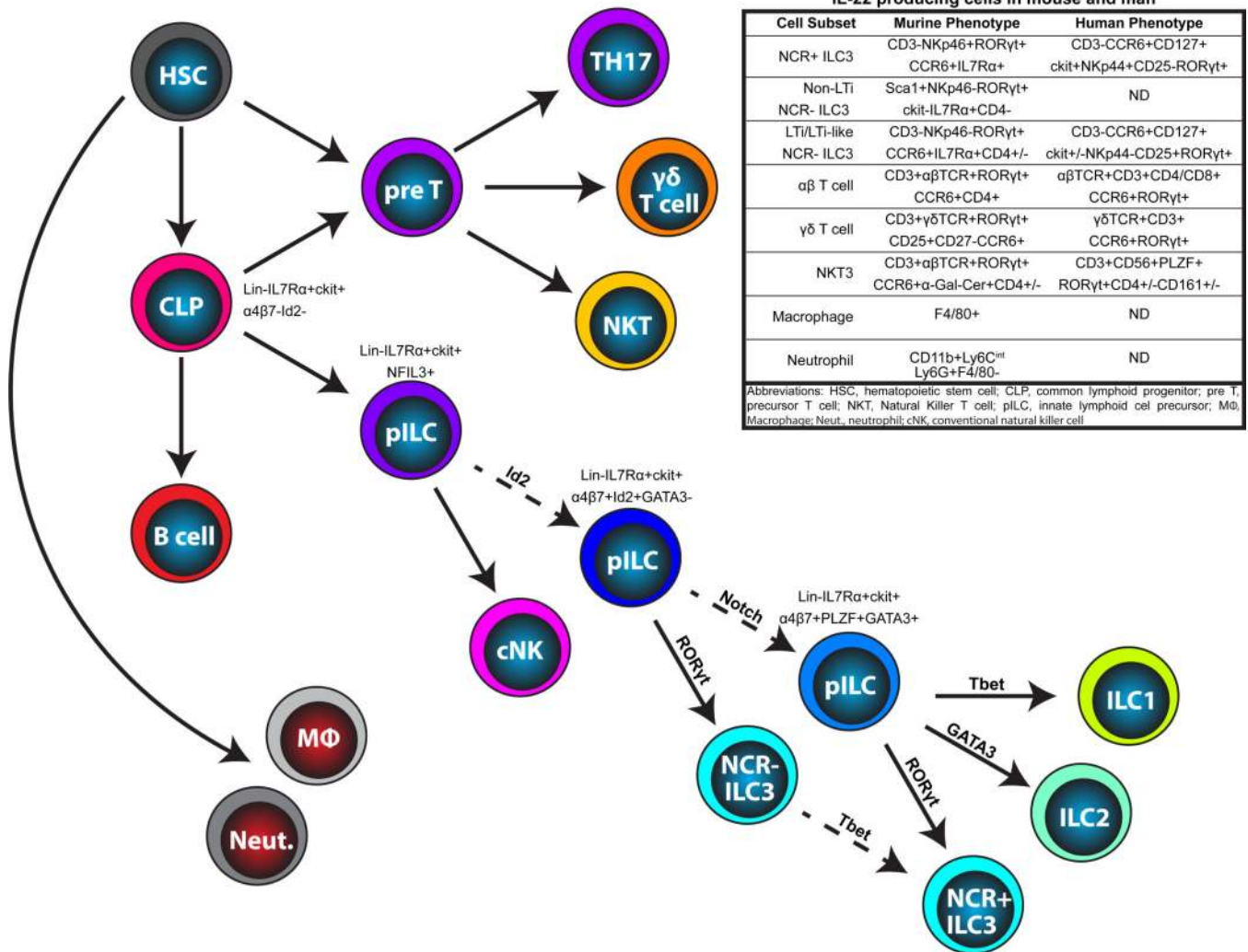


Figure 2. Cellular sources of IL-22 and their lineage relationships

All IL-22 producing cells derive from a hematopoietic stem cell located in the bone marrow (BM). TH17 cells, $\gamma\delta$ T cells and NKT cells develop in the thymus, branching off from conventional T cell development at different stages: NKT cells at the DN3 stage of thymocyte development; $\gamma\delta$ T cells upon TCR rearrangement; and TH17 cells at the naïve T cell stage outside the thymus. All ILCs derive from a common ckit+IL7R α + common lymphoid progenitor (CLP). Several recent papers have described ILC precursors (pILC) with varying capacity for differentiation. An NFIL3+ pILC has recently been described with the capacity to differentiate into all ILC subsets as well as conventional NK cells. This precursor gives rise to an Id2+ cell giving rise to all ILC populations except for NK cells. A PLZF+ pILC has also been described, differentiating into ILC1, ILC2 and NCR+ ILC3, but not into conventional NK cells or into NCR- ILC3. Evidence also suggests that NCR- group 3 ILC can differentiate into NCR+ ILC3. Solid lines represent known, and dashed lines represent putative, progenitor-progeny relationships.

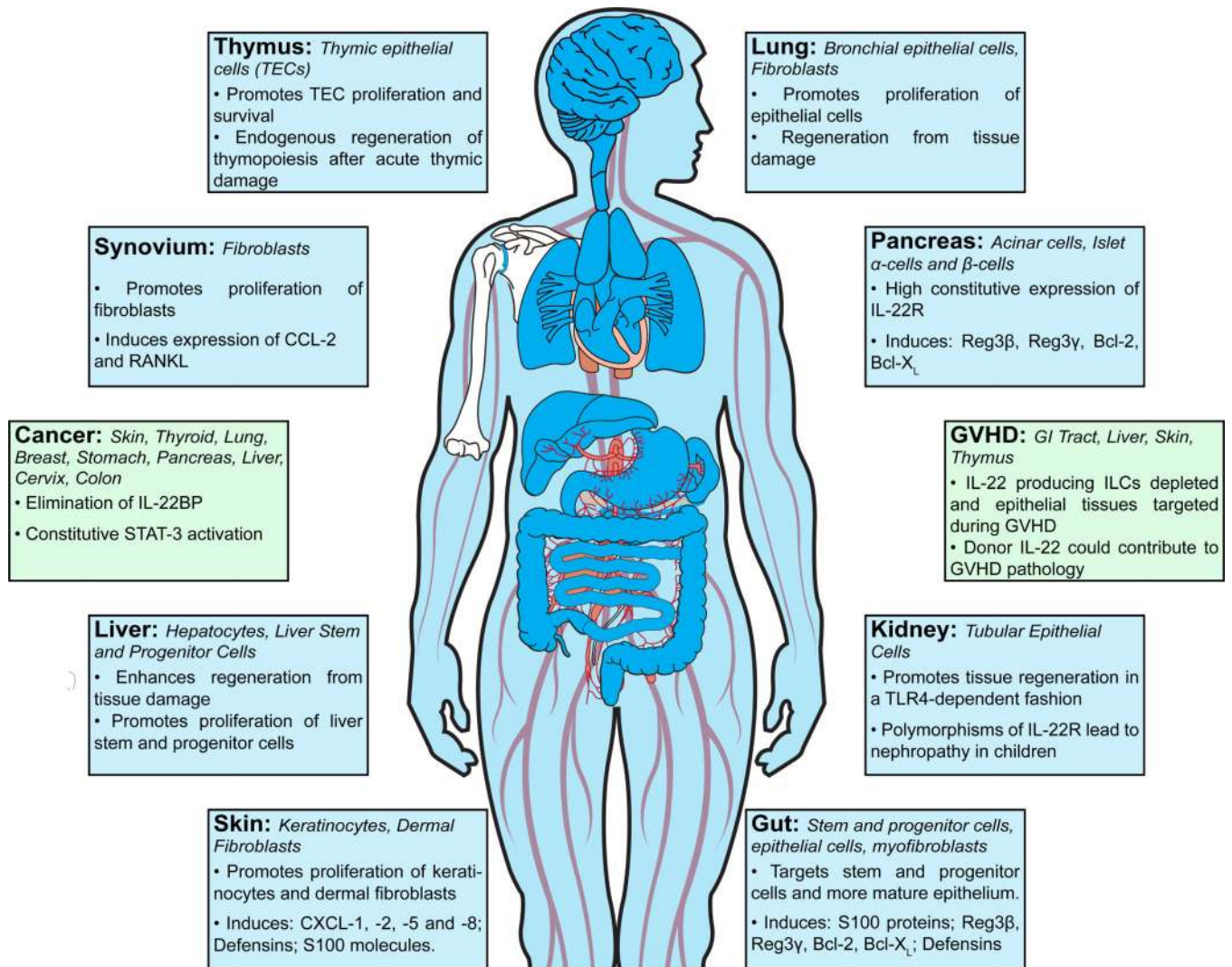


Figure 3. Target tissues and physiological effects of IL-22

A role for IL-22 has been described in numerous tissues including gut, liver, lung, skin, thymus, kidney, heart, pancreas and synovial tissue. IL-22R is expressed on epithelial cells and some fibroblasts in those tissues. IL-22 can promote their cellular proliferation, resistance to apoptosis, and wound healing. In barrier organs such as gut, lung and skin, IL-22 also promotes the production of antimicrobial molecules such as S100, Reg3 β and Reg3 γ , as well as defensins, thereby aiding in host defense and barrier function. IL-22 is important for promoting tissue regeneration after injury in several organs. However, studies have also indicated that IL-22 is associated with malignancies of the skin, thyroid, breast, stomach, pancreas, liver, cervix and colon, as well as other inflammatory pathology including psoriasis. In BMT, ILC-derived IL-22 is important for tissue regeneration after injury caused by alloreactive T cells, however, there is also some evidence that IL-22 produced by donor T cells can contribute to inflammation and GVHD pathology.

Table 1

Role of IL-22 in host defense against infection

Infection	Type	Tissue	Role	Refs
<i>Klebsiella pneumoniae</i>	Bacterial	Lung	Maintenance of barrier function; induction of defence mechanisms; mediates recruitment of leukocytes	(42)
<i>Citrobacter rodentium</i>	Bacterial	Gut	Maintenance of barrier function; induction of defence mechanisms; mediates recruitment of leukocytes	(33, 45)
<i>M avium</i>	Bacterial	Intestine	No apparent role	(392)
<i>Toxoplasma gondii</i>	Protozoa	Intestine	Neutralizing IL-22 leads to less tissue pathology despite equivalent parasite burdens	(392)
<i>Listeria monocytogenes</i>	Bacterial	Systemic	No apparent role	(392, 393)
<i>Salmonella enterica</i>	Bacterial	Intestine	No apparent role	(332)
Commensal Bacteria	Bacterial	Intestine	Regulates composition of microbiota	(262, 391, 394)
<i>Aspergillus fumigatus</i>	Yeast	Lung	Controls fungal burden	(313)
<i>Candida albicans</i>	Yeast	Mucosa, Skin	Aides in preventing dissemination; mucocutaneous defence	(395, 396)
Influenza	Viral	Lung	Limits tissue damage	(120, 317, 319, 320)
Hepatitis B	Viral	Liver	Limits tissue damage	(328, 330, 335, 397)

Table 2

Known regulators of IL-22 production

Molecule	Type of regulation	Mode of action	Refs
IL-23	Positive	Main stimulator of IL-22 production, mediated by STAT-3	(34, 42–45, 133)
IL-1 β	Positive	Directly induces IL-22 production by TH17, NKT and ILCs and inhibits progression of ILCs into IFN γ -producing subsets	(55, 120, 125, 169–171, 174)
IL-7	Positive	Differentiation and expansion of IL-22 producing cells and stabilizing ROR γ t expression	(70, 72, 175–177)
AhR	Positive	Promotes development of ILCs and TH17 cells and directly promotes IL-22 production	(187, 190, 191)
Notch	Positive	Differentiation of IL-22 producing lymphoid cells as well as promoting IL-22 production by mediating AhR signals	(95, 98, 202, 203, 205)
IL-22BP	Negative	Soluble IL-22R with 1000-fold higher affinity for IL-22 than membrane bound receptor	(14, 215–217)
TGF β	Negative	Inhibits IL-22, potentially binding to IL-22 promoter but also mediated through c-Maf	(224)
IL-27	Negative		(225, 226)
ICOS	Negative	Induction of c-Maf and reduced expression of IL-22	(227, 228)
c-Maf	Negative	Common pathway of TGF β , IL-27 and ICOS mediated negative regulation of IL-22	(48, 227, 228)
IL-25	Negative	Produced by epithelial cells, inhibits the production of IL-22 by ILCs	(263)