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Biological and Pathological Activities of Interleukin-22

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Abstract

Interleukin (IL)-22, a member of the IL-10 family, is a cytokine secreted by several types of immune cells including IL-22⁺CD4⁺ T cells (Th22) and IL-22 expressing innate leukocytes (ILC22). Recent studies have demonstrated that IL-22 is a key component in mucosal barrier defense, tissue repair, epithelial cell survival and proliferation. Furthermore, accumulating evidence has defined both protective and pathogenic properties of IL-22 in a number of conditions including autoimmune disease, infection and malignancy. In this Review we summarize the expression and signaling pathway and functional characteristics of the IL-22 and IL-22 receptor axis in physiological and pathological scenarios, and discuss the potential to target IL-22 signaling to treat human diseases.

Keywords

IL-22; Th22; ILC22; cancer; T cell; cancer; autoimmune and infection

INTRODUCTION

A distinct feature of IL-22 is the effector route as it is the only known cytokine secreted by immune cells that acts primarily on non-immune epithelial cells bearing its cognate receptor (IL-22-R). Its receptor is a heterodimer composed of IL-10R2 and IL-22R1 subunits which are present on the membrane of several epithelial and stromal cells in various tissues[1].

IL-22 is distinct from other cytokines because of its unidirectional signaling flow: immune cells are the source of the cytokine but its targets are non-hematopoietic cells, positioning IL-22 as a key component of immune-epithelial cell cross talk.

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The function of IL-22 is variable and depends on the specific context, including location, presence and relative amounts of other cytokines, concentration, and presence of sequestering factors.

In this review we summarize the cellular sources and targets of IL-22, potential triggers of its release and regulators of its expression. We focus on its effects on different tissue environments in both physiologic and pathologic conditions, particularly in the context of cancer.

Identification of IL-22

IL-22 was first identified 15 years ago by Dumoutier et al. in IL-9-treated mouse lymphoma cells. It was thought to be a T cell inducible factor related to the IL-10 cytokine family [2]. Originally named IL-TIF (IL-10-related T cell-derived inducible factor), it is a protein composed of 179 amino acids and shares more than 20% homology with both murine and human IL-10 cytokines [3]. There is a 79% homology between the human and mouse proteins [4] and their respective genes are located on the same chromosome as Interferon γ (IFN- γ) [3]. The secreted form of human IL-22 is 146 amino acids in length [5, 6] and activates its cognate receptor by binding it as a monomer, a characteristic that is unusual for IL-10 family members, which [7] are typically only active as dimers. While IL-22 is capable of forming self-complexes of higher order, such as dimers and tetramers [6, 8, 9], these are not functional and are thought to represent non-active storage forms. Despite sharing a receptor subunit and signaling cascades with the other IL-10 family cytokines, IL-22 has vastly different and pleiotropic downstream effects.

IL-22 receptor

IL-22 membrane bound receptor and signaling (Fig. 1)—The IL-22-R is a heterodimer complex of IL-22R1 and IL-10R2. It contains three main domains: extracellular, transmembrane and an intracellular signaling region [5, 9]. IL-22R1 is almost exclusively expressed on cells of non-hematopoietic origin such as epithelial, renal tubular and pancreatic ductal cells [5, 10, 11]. While IL-22R1 expression has been reported in hematopoietic cells, specifically in circulating myeloid cells from primary Sjögren's syndrome patients (pSS), it is not thought to play a significant role in immune-immune cell communication [12]. IL-22 initially binds to the IL-22R1 subunit which undergoes a conformational change that allows binding of IL-10R2, initiating the downstream signaling cascade [13]. Upon complex formation with IL-10R2, Signal Transducer and Activator of Transcription 3 (STAT3) phosphorylation is triggered through activated Janus kinase (JAK) and tyrosine kinase 2 (Tyk2). While this is common to most IL-10 family member receptors, IL-22 also activates kinases p38, MEK/ERK (extracellular signal-regulated kinase) and JNK (Jun amino-terminal kinases) [14, 15] which sets it apart from other IL-10 related cytokines. Additionally, IL-22 can promote both STAT1 and STAT5 phosphorylation [14, 16]. Unique to IL-22 is the STAT3 phosphorylation on serine residue 727,[14, 17] which does not happen upon IL-10 activation, and was required in an *in-vitro* reporter assay for maximal transactivation of the STAT3 responsive promoter [14].

IL-22 soluble receptor—IL-22 binding protein (IL-22BP) is a soluble receptor, 231 amino acids in length, with very high affinity for IL-22 [18]. IL-22BP has 34% sequence homology to IL-22R1 [11, 19, 20] and interacts with IL-22 at overlapping binding sites with IL-22R1 thereby blocking receptor activation [21]. Because of the highly stable IL-22BP-IL-22 interaction, its overall effect is to sequester IL-22 from the local environment, away from the membrane bound receptor preventing its downstream biological activation [22]. IL-22BP is expressed in several tissues including placenta, breast, the gastrointestinal tract, lymphatic tissue, lung and skin and is constitutively produced by dendritic cells (DC) [23]. Retinoic acid is a strong inducer of IL-22BP production, and expression levels are inversely proportional to the degree of maturation with immature DCs producing the highest quantity of IL-22BP [23]. An exception to this is colonic DCs which produce high levels regardless of their maturation state [24]. Reports of other sources of IL-22BP include macrophages, epithelial cells and more recently, eosinophils [11, 19, 25–27].

Recent studies have identified IL-22BP as an important component in autoimmune diseases [28, 29]. In mouse models of colitis, levels of IL-22BP decrease [26, 30] resulting in a subsequent increase in available IL-22, promoting epithelial regeneration. In contrast, recent studies suggest IL-22BP is upregulated in certain inflammatory bowel diseases and may be directly linked to pathologic changes in the colonic epithelium [27]. Because changes in IL-22BP level could be a cause or consequence of colonic inflammation, more data is needed to provide a definitive link to the pathogenesis of colitis.

IL-22BP is released in response to tissue injury and bacterial infection, likely as a mechanism to quell IL-22 mediated pro-inflammation and can be regulated by the inflammasome system upon sensing of tissue damage [24]. IL-22BP functions seem to add complexity to the IL-22 signaling axis and may serve as an additional therapeutic target.

Sources of IL-22

Lymphoid sources—Primarily produced by cells of immune origin (Figure 2), IL-22 was initially identified in IL-9 activated T cells [2]. The principle IL-22 producing cells include: CD4⁺ lymphocytes, natural killer T cells (NKT) innate lymphoid cells (ILC) and less commonly, CD8⁺ lymphocytes [31]. Within the T cell subset there are three types of CD4⁺ cells capable of synthesizing IL-22; Th1, Th17 and Th22 [32–37]. Common features of these cells are their reliance on ROR γ t expression, presence of aryl hydrocarbon receptor (AhR) and need for IL-23 stimulation [38, 39]. Th17 polarization can be promoted by TGF- β among other factors [40], including IL-1 β and IL-23 [41]. The roles of Th17 and Th22 have been mainly associated with defense from infectious agents at mucosal barriers. Th17 cells express CC-chemokine receptor 6 (CCR6) and the skin homing CCR4, and they are found in lungs, intestine and skin [42, 43]. Th22 express CCR10 in addition to CCR4 directing them to the skin [37, 44–47]. In mice, Th17 cells represent the major source of IL-22 among T helper subsets and also rely on TGF- β for their differentiation [48].

In addition to CD4⁺ T cells non-traditional lymphocytes, such as $\gamma\delta$ T cells, are capable of producing IL-22 upon IL-23 or retinoic acid stimulation [47, 49, 50]. These cells can also produce IL-22 through activation of innate Toll-like receptors (TLRs) [51–53].

Innate lymphoid cells (ILCs) are a recently identified unique heterogeneous class of immune cells that possess many characteristics of lymphocytes but lack antigen specific receptors [54, 55]. Recent studies of the colonic and cutaneous immune microenvironments have identified ILCs as an important early source of cytokines, including IL-22 [56–60]. ILCs are derived from common lymphoid progenitors and are classified into three functional groups by their signature cytokine production and the transcription factors driving their differentiation. ILC1 produce interferon gamma and are driven by the lymphocyte transcription factor, t-bet, mainly involved in intracellular parasitic defenses [61]. ILC2 express the CD4⁺ transcription factor GATA-3 and secrete interleukins 5 and 13 [55]. The innate lymphoid IL-22-producing cells (ILC22) are found among the third group, which includes 2 subsets that are almost indistinguishable in features; ILC3 and lymphoid tissue inducer (LTi) [62]. It is unclear if these truly represent distinct subsets, or if LTi are simply functional precursors of ILC3 development [63]. While both are driven by expression of the transcription factor ROR γ t, ILC3 can often be distinguished by expression of NK cell surface marker NKp46 in mice and NKp44 in humans [64–66].

All ILC subsets require the presence of inhibitor of DNA binding2 (Id2) and the common γ -chain (γ_c) of the IL-2 receptor to develop, and lack recombined antigen receptors on their surface [66]. The transcription factor Nfil3 (Nuclear factor interleukin-3-regulated protein) is crucial in the development of all ILCs and NK cells [67–70]. PLZF (promyelocytic leukaemia zinc finger), however, is found only in progenitors of ILC1, ILC2 and ILC3, and not LTi and NK cells [71]. ILC3s are innate effectors involved in epithelial barrier homeostasis and protection against extracellular pathogens [72]. They are capable of producing IL-22 and 17 and express ROR γ t and IL-7 receptor- α (IL-7R α) in both mice and humans [73–75]. They are mainly located in the intestinal epithelium, tonsil and spleen [76–78].

IL-23 is an important promoter of IL-22 secretion not only from ILC3, but also Th17 and NKT cells. IL-1 β can synergize with IL-23 to act as a potent inducer of IL-22 production from those cells [49].

Non-lymphoid sources—Non-lymphoid cells including fibroblasts, mast cells, macrophages and neutrophils may produce IL-22 in different diseases [79–82]. In rheumatoid arthritis, synovial fibroblasts and macrophages display IL-22 staining within synovial tissue samples, suggesting possible promotion of inflammation through fibroblast activation [79]. Mast cells were reported to be the major producers of IL-22 in the skin of patients with dermatitis and psoriasis [80]. In the lungs, activated murine alveolar macrophages are capable of secreting IL-22 cytokine although its function is not entirely clear [81]. Lastly in colitis, IL-22 producing neutrophils contributed to the resolution of inflammation, promoting antimicrobial peptide secretion and mucosal integrity within intestinal tissue [82]. While the expression of IL-22 in non-immune cells has been reported, further genetic and functional data are needed before its relevance can be validated.

IL-22 Function

Biologic effects of IL-22—The key physiologic functions of IL-22 are summarized (Table 1, Figure 2). While its effects vary by tissue, IL-22 is primarily involved in preservation of mucosal barriers and protection of the host from microbial parasites in the skin, lung and intestine [83–87]. Its role in solid organs such as the liver and pancreas appear to be prevention of cellular apoptosis and promotion of cell survival and proliferation. For example, studies in pancreatitis have demonstrated IL-22's ability to up-regulate survival genes such as Reg III, protecting cells from apoptosis and promoting tissue repair. IL-22-deficient mice have a dramatic increase in tissue damage following induction of pancreatitis and fail to repair the gland leading to increased fibrosis [88]. In the liver, IL-22 induces regeneration during inflammation as in the case of hepatitis infection, as well as after partial resection of the organ [89–92].

The anti-apoptotic effects of IL-22 together with the capability to promote regeneration and proliferation are key features in IL-22's ability to aid in wound healing and tissue repair. These functions together with the induction of acute phase response proteins in the colon and skin preserve the integrity of barriers after injury or infection. Additionally, IL-22 can prevent intestinal and lung bacterial invasion by promoting expression of several antimicrobial peptides. A study of lung infection with *K. pneumoniae* demonstrated a severe increase in mortality in IL-22^{-/-} mice due to increased bacterial adhesion and invasion[93]. In studies performed with *C. rodentium* infection of IL-22 knockout mice, there was significant damage to mouse colonic epithelial cells and high mortality which was partially reversed by exogenous addition of Reg antimicrobial peptides [94].

Role of IL-22 in pathologic conditions—The biological effects of IL-22 expression are tightly related to associated cytokines and the surrounding physiologic context. As previously mentioned, IL-22 can be protective for several tissues, but in some cases its uncontrolled expression can cause tissue damage and chronic inflammation. The first and most studied condition in which dysregulation of IL-22 leads to pathologic inflammation is psoriasis. In other conditions such as inflammatory bowel disease, pancreatitis and hepatitis [95, 96], IL-22 serves a protective role by reducing inflammation and promoting tissue regeneration. Along with chronic inflammation, persistently elevated levels of IL-22 are associated with development of several types of cancer [97–103].

(I) Autoimmune and inflammatory diseases—Psoriasis is a skin condition characterized by abnormal and rapid growth of keratinocytes leading to formation of plaque like skin lesions. The pathogenesis of psoriasis is complex and involves an intricate interplay between IL-23, IL-22, Th17 cells and neutrophils. While the exact immunologic mechanisms underlying psoriasis are not fully understood, it has been shown that CD4⁺ T cells (Th17) migrate from the dermis to the epidermis where, after stimulation with IL-23, they release IL-22. Consequently, IL-22 promotes keratinocyte proliferation and inhibits their differentiation [104, 105]. IL-22 exposure also results in release of neutrophilic chemoattractants from keratinocytes, promoting inflammation and granulocytic skin infiltration[104, 106, 107]. While lymphocytes are the primary source of IL-22 in the skin,

studies have also identified mast cells as potential reservoir for IL-22 within psoriatic skin lesions [80].

IL-22 is thought to play an important role in chronic inflammation of the colon, seen in IBD including both ulcerative colitis (UC) and Crohn's disease (CD) [108, 109]. In both conditions, there is an elevated number of IL-22 expressing CD4⁺ T cells located throughout the colon wall in CD or in the lamina propria in UC. In murine models of colitis, IL-22 serves a protective role and its inhibition is associated with worsening of inflammation. The local protective effect of IL-22 is believed to be through induction of intestinal mucus production and restoration of goblet cells [110]. Elevated systemic IL-22 induces hepatic production of the lipopolysaccharides (LPS) binding protein which abrogates its systemic and local inflammatory effects [30, 108, 111–114]. A similar role is seen in graft versus host disease (GVHD) where IL-22 protects intestinal stem cells from immune mediated damage [115].

Pancreatic acinar cells express the highest amount of IL-22R in the body although the role of IL-22 is not fully understood [10]. In murine models of pancreatitis induced by cerulean or duct ligation, IL-22 has a protective role by decreasing inflammation and promoting reconstitution of acinar cells [88, 116]. Supporting this evidence is the finding that administration of an exogenous AhR agonist reduces the necrosis of pancreatic cells in pancreatitis. The mechanism of this protection appears to be increased expression of RegIII and inhibition of autophagosome formation [88]. A similar phenomenon is seen in murine models of liver injury where inflammation induced by Concanavalin A [89, 90, 117] is abrogated by exogenous delivery of IL-22.

(II) Infectious diseases—The most widely studied function of IL-22 is in protection against bacterial and parasitic infections in the lungs and gastrointestinal tracts [93, 118, 119]. It also plays an important role in various viral infections by lessening the sequelae of infection and aiding in tissue recovery.

IL-22 is critical in protecting the gastrointestinal tract from infection by both pathogenic and commensal bacteria. IL-22 plays an important role in regulating the gut microbiota. In murine models of enteric infection with the Gram-negative bacterium *Citrobacter rodentium*, mice deficient in IL-22 die from infection within 2–3 weeks [93]. IL-22 also plays an important role in protection against another Gram negative *Klebsiella pneumoniae* in the lungs [94]. Additionally ILC-derived IL-22 is shown to be protective against both *S. pneumoniae* and *P. aeruginosa* [120, 121]. High levels of IL-22 have been reported in the pleura of patients with Tuberculosis [94, 122]. Although its role in combating this infection is not fully understood, IL-22 improves Calgranulin production and promotes lysosomal fusion inhibiting intracellular growth of the *M. tuberculosis* parasite [123, 124].

IL-22 has been shown to play both protective and pathologic roles in different viral infections [16, 125–131]. During intestinal rotavirus (RV) infection, IL-22 acts synergistically with interferon-lambda to control the infection [16, 125]. IL-22 was also reported as protective during Influenza A infection [128, 132, 133] by protecting lung epithelial cells and promoting tissue regeneration. Similarly, in Hepatitis B and C infections,

IL-22 does not appear to play a direct role in controlling the viral infection or replication, but instead supports the anti-apoptotic and regenerative capability of hepatocyte progenitor cells, lessening the consequence of infection [134, 135]. While IL-22 is most often a protective cytokine in viral infections, persistently elevated levels can be damaging. In murine West Nile virus (WNV) encephalitis, IL-22 plays a role promoting harmful inflammation and neuro-invasion. In this murine model, IL-22 deficient mice were resistant to lethal encephalitis despite bearing comparable circulating levels of the virus as their IL-22 wild type counterparts [131].

Thus, IL-22 can generally promote mucosal barrier integrity and inhibit the growth of the majority of pathogens via inducing anti-microbial peptide production and aiding in cell survival and regeneration. An exception to this is that persistent exposure of IL-22 may be harmful particularly for immune privileged organs.

(III) Cancer—IL-22 plays an important role in the initiation and progression of cancers. Cancer (stem) cells can survive and proliferate by exploiting the IL-22/IL22R signaling cascade [103, 136]. Elevated IL-22 levels are detrimental in a number of malignancies including lung, liver, gastric, colon and pancreatic cancers [101, 137–142] (Figure 3). IL-22-mediated STAT3 activation may promote pro-survival and anti-apoptotic genes and enhance carcinogenesis.

The link between IL-22 and cancer has been well studied in colon cancer [103, 143, 144]. In both carcinogen and genetically induced models of murine colon cancer, increased IL-22 activity results in a greater tumor burden and worsened survival [58]. Conversely, IL-22BP is protective in colitis associated colon cancer by sequestering IL-22 in an IL-18-dependent mechanism[24]. IL-22 is capable of inducing colon cancer stemness through STAT3 mediated increased expression of the histone 3 lysine 79 (H3K79) methyltransferase DOT1L (disruptor of telomeric silencing 1- like) [103]. Additionally, IL-22 enhances tumor cell proliferation by promoting the PRC2 complex-mediated removal of H3K27me3 modification from the promoters of cell cycle check-point genes p16 and p21. This results in increased expression of the stem cell genes NANOG, SOX2 (SRY (sex determining region Y)-box 2), and Pou5F1 and subsequently enhanced tumorigenicity [136] (Figure 3).

The primary source of IL-22 in colon cancer includes both Th22 cells and ILC3. There are heightened numbers in both, cancers and dysplastic lesions suggesting their importance in both development of pre-neoplastic and maintenance of established tumors [58]. Consistent with these observations, ablation of ILCs in a murine model of inflammation mediated colon cancer results in abrogation of formation of tumors and adenomas. Treatment with anti-IL-22 antibody ameliorated colitis symptoms and reduced tumor burden as well [58].

IL-22 has been associated with malignancy elsewhere in the gastrointestinal tract. In gastric cancer, elevated levels of circulating IL-22 correlates with disease progression and is a predictor of poor patient survival [145, 146]. In a genome wide analysis of an East Asian population, polymorphisms in the IL-22 gene were associated with an increased lifetime risk of gastric cancer [101]. In-vitro studies have shown that IL-22 is capable of promoting invasion and migration through activation of AKT and expression of MMP9 [147].

In liver cancer, IL-22 is also associated with disease progression and poor prognosis [141–143]. This is somewhat paradoxical as IL-22 protects against hepatic inflammation and Hepatitis B and C infections which are major risk factors for development of hepatocellular carcinoma (HCC). High numbers of Th22 cells have been identified in HCCs suggesting they may be involved in the pathogenesis of this malignancy. Furthermore, higher levels of circulating IL-22 is seen in later stage disease [148]. In mouse models of HCC, IL-22 promoted metastasis and tumor growth, and resulted in up-regulation of anti-apoptotic genes [142, 143]. IL-23 and IL-22RA1 are increased in HCC compared to normal surrounding tissue and tumor formation is reduced when IL-22 is genetically deleted [143]. In a transgenic mouse model of liver specific IL-22 overexpression, researchers showed that although IL-22 could be hepato-protective and does not promote spontaneous tumor development, it still makes the liver more prone to drug induced tumor development [149]. The anti-diabetic drug metformin dramatically reduces HCC growth in an orthotopic mouse model, which may be the result of inhibition of IL-22 production [150] (Figure 3).

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor, usually diagnosed at advanced stages and with a remarkably low 5-year survival of less than 5% [151]. Despite its protective role in pancreatitis, elevated levels of systemic IL-22 and tissue IL-22RA1 expression are associated with poor overall survival in patients undergoing resection for PDAC. In support of this, the levels of intratumoral IL-22 as well as Th22 tumor infiltrating lymphocytes are associated with a poor overall pancreatic cancer outcome [152]. In-vitro, IL-22 promotes invasion of pancreatic cancer cell lines by STAT3 mediated up-regulation of MMP9 expression [140]. It leads to expression of immunosuppressive cytokines, the anti-apoptotic factor Bcl-X(L) and vascular endothelial growth factor (VEGF) [153] (Figure 3).

In recent studies, high levels of IL-22 and Th22 were found in the primary lung tumor as well as in the malignant pleural effusions [139, 154, 155]. IL-22 exhibited anti-apoptotic effects in lung cancer xenografts [156] and induced growth of chemoresistant cancer cells [138]. Similar to gastric cancer, a correlation between genetic polymorphisms and IL-22 blood levels suggests that IL-22 may promote non-small cell lung cancer formation [137].

Both pro and anti-tumor roles for IL-22 are reported in breast cancer. IL-22 promoted breast tumor formation through MAP3K8-mediated epithelial cell transformation[157]. Contrary to this, IL-22 inhibited tumor growth and proliferation by interrupting ERK1/2 and AKT signaling in a murine breast cancer cell line [158] and by STAT1 activation in a renal cell carcinoma (RCC) line [159, 160].

The role of IL-22 in cutaneous malignancies has been poorly studied. Th22 cells infiltrate cutaneous squamous cell carcinomas (SCC) and increased expression of IL-22 and its receptor are found in the tumor microenvironment of post-transplant associated SCC (TSCC) [161]. In cutaneous T-cell lymphoma (CTCL) IL-22 is present at high levels in skin lesions and circulating blood and in conjunction with elevated IL-10 and CCL20, is a marker of disease progression[162].

It is important to note that although IL-22 is elevated in many cancers both systemically and in the local tumor microenvironment, a direct link between IL-22 and tumorigenesis, in-

vivo, is lacking. Its elevation in human blood samples, such as in pancreas cancer, may simply be a function of heightened state of inflammation as other cytokines such as IL-6 are also elevated. A vast majority of murine models linking IL-22 to cancer formation rely on inflammation induced tumorigenesis which complicates the overall picture. More convincing data definitively linking IL-22 to initiation or progression of malignancy is needed.

In summary, IL-22 released from Th22 and ILC3s enhances tumorigenesis in multiple tissue types by increasing cellular proliferation and invasion and promoting cancer stem cells. It is possible that the same survival and regenerative properties that make IL-22 important in protection from damage and infection may promote malignant transformation.

Clinical implications

As has been demonstrated, the IL-22/IL-22R axis plays an important role in both physiologic and pathologic conditions and therefore represents an attractive therapeutic target both as an agonist and antagonist. It is thought that blockade of IL-22 may offer clinical benefit to the patients with cancer or autoimmunity. An IL-22 neutralizing antibody ILV-094 is currently undergoing Phase I and II study to determine its efficacy in the treatment of psoriasis (NCT01010542).

Because IL-22 has anti-pathogenic and regenerative effects in the gastrointestinal tract, recombinant IL-22 (rIL-22) may be an attractive modality for treatment of colitis and infection. A phase II study is underway investigating the benefit of rIL-22 administration in patients with GVHD after bone marrow transplant (NCT02406651). Other potential strategies moving forward include administration of AhR agonists to enhance IL-22 release, or cytokine sequestration through use of IL-22BP.

Concluding remarks

Since its discovery 15 years ago, IL-22 has gained notoriety because of its pleotropic effects and its unique role in immune-epithelial cell cross talk. As with other cytokines its effects are influenced by the environment and cytokine milieu in which it is found. Current research has established its protective role in mucosal barrier integrity and tissue repair, however, its pro-survival and anti-apoptotic effects can cause detrimental outcomes. Prolonged expression has been linked to damaging chronic inflammation and carcinogenesis. Current strategies are to target the IL-22/IL-22R axis using neutralizing antibodies and recombinant cytokines are in its infancy with further research needed. The ultimate goal is to exploit the pathway to reduce inflammation and enhance mucosal regeneration in autoimmune diseases and prevent cell proliferation and invasion in malignancy.

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Figure 1.

IL-22 signaling pathway. IL-22 binds to a heterodimer receptor complex of IL-22R1 and IL-10R2, present in the surface of several non-hematopoietic cells [5, 9–11]. A monomer of IL-22 activates its receptor [6, 18] by sequentially binding with IL-22R1, and as a complex undergoes a conformational change that allows the complex association to IL-10R2 which initiates the downstream signaling cascade [13]. Upon complex formation with IL-10R2 tyrosine and serine STAT3 phosphorylation is triggered through activated Jak1 and Tyk2; IL-22 can additionally activate kinases p38, MEK/ERK JNK and **STAT1 and STAT5** [14, 163]. Alternatively, IL-22 function can be negatively regulated by the soluble high affinity receptor IL-22BP [11]. Upon activation of these signaling pathways, IL-22 enhances epithelial cell survival and regeneration and protects barrier integrity and microbial protection.

Figure 2. Sources of IL-22

IL-22 is primarily produced by immune cells [2] including Th1, Th17 and Th22 [32–37], natural killer T cells (NKT) and innate lymphoid cells (ILCs). Non-lymphoid sources of IL-22 include fibroblasts (Fb), mast cells (Mc), macrophages (M ϕ) and neutrophils (Ne) in different diseases [79–82].

Figure 3. Roles of IL-22 in cancer

A) In mouse models of HCC, IL-22 promoted tumor growth and metastasis via upregulating anti-apoptotic genes [142, 143] and IL- 23 and IL-22RA1 expression [143]. **B)** High levels of IL-22 and Th22 were present in the primary lung tumor and in pleural effusions [163,149,164]. IL-22 exhibited anti-apoptotic effects in lung cancer xenografts [165] and induced growth of chemoresistant cancer cells [148]. **C)** In PDAC elevated levels of systemic IL-22 and tissue IL-22R are observed. In-vitro, IL-22 promotes invasion of pancreatic cancer cell lines by STAT3-mediated MMP9 expression [140], immunosuppressive cytokine expression, anti-apoptotic Bcl-XL gene and VEGF expression [153]. **D)** IL-22 induces colon cancer stemness and proliferation through STAT3 mediated DOT1L and EZH2 expression [103, 136].

Table 1

Biological target of IL-22

Tissue and organ targets	Molecular targets	Major effects	References
Liver, progenitor cells (Hepatitis B)			[154]
Pancreas, acinar & islet cells		Proliferation	[74,75]
Thymus & Lung, epithelial cells			[76]
Skin, keratinocytes & fibroblasts	Gab1, Gab2		[77,78]
Skin	Fibronectin, Collagen IαI & IIEC-STAT3		[155]
	Claudin-1	Wound healing	[156]
Intestinal mucosa	Muc1,Muc3, Muc10, Muc13		[101]
Corneal epithelial	CXCL1		[157]
Liver	cyclinB1, cyclinD1, Gas5, Gas6, Nrp1		[138,158]
Kidney		Regeneration	
Thymus			
Lung			
Pancreas	Reg3β, Reg3γ,OPN		[75,106]
Lung	IL-22-secreting γδ-T cells		[159,160]
Liver	STAT3	Fibrosis	[161,162]
Keratinocytes	MMP1,Gab1,Gab2	Cell motility	[95,78]
Pancreas	Reg3β, Reg3γ, OPN		[75,106]
Skin keratinocytes	S100A7, S100A8, S100A9,BD- 2 ,BD-3		[95]
		Anti-microbial	[28,163,164]
Intestinal epithelia	Hes-1		[165]
	Pro-IL18		[166]
Lung	CXCL1,CXCL5,CXCL9,Lcn2		[84]
Hepatic stellate cells & Keratinocytes, Colon myofibroblasts and epithelial			[167,168]
	IL-6, IL-8, TNFα,IL-1β	Pro- inflammatory	[166]
	IL-18		[169]
Liver	Fibrinogen, SAA	Acute phase response	[4,164,24,170,171]

Tissue and organ targets	Molecular targets	Major effects	References
Liver	Bcl-2, Bcl-XL, CDK4, cyclin D1, c-myc, p21		[107,81]
Pancreas	Bcl-2, Bcl-XL	Anti-apoptotic	[79,154,10,172]
Colon	IEC-STAT3		[156]
Tight junctions-Intestinal epithelia	Claudin-1		[102]
Goblets cells	Muc1,Muc3, Muc10,Muc13	Tissue integrity	[101]

* Abbreviations: Gas: growth arrest specific gene; Nrp: neuropilin; SAA: Serum Amyloid A; Bcl-2: B-cell lymphoma 2; Bcl-XL: B-cell lymphoma extra large; CDK4: cyclin D dependent kinase 4; OPN: Osteopontin; Reg3β: regenerating islet-derived 3β; Reg3γ: regenerating islet-derived 3γ; MMP1: matrix metalloproteinase 1; BD-2: β-defensin 2; BD-3: β-defensin 3; IEC: intestinal epithelial cells; Muc: mucin.