IL-22 *vs*. IL-22: The Tissue Matters

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Abstract: IL-22 is a cytokine recently discovered to be produced by T_H17 cells. Its receptor is expressed in the skin, liver, the digestive and the respiratory tract where IL-22 conveys signals of the immune system directly to the tissue. IL-22 is involved in the host defense against extracellular pathogens as well as in autoimmune inflammatory diseases and exerts, depending on the tissue and inflammatory context, proinflammatory, protective or no evident function. Focusing on immune-mediated pathology, here we will discuss the role of IL-22 in the context of tissue inflammation to provide an overview of the complex properties of this bi-functional cytokine and to disentangle some of its apparently aberrant actions.

Keywords: IL-22, inflammation, autoimmunity, cytokines, TH17 cells.

INTRODUCTION

IL-22

The homodimeric cytokine IL-22 was first described in 2000 as an IL-9-induced gene and termed "IL-10 related T cell-derived inducible factor" (IL-TIF) and belongs, together with IL-19, IL-20, IL-24 and IL-26, to a family of cytokines structurally related to IL-10 [1]. The IL-22 gene was mapped near the IFN-γ gene on chromosome 10 in mice and on chromosome 12 in humans. Unlike in humans or the genomes of BALB/c and DBA/2 mice, genomes of other mouse strains such as C57Bl/6, FVB, and 129 possess two IL-22 genes, designated IL-22 α and β, the latter containing several single nucleotide changes and a 658 nucleotide deletion covering the first noncoding exon and a segment of a putative promoter, suggesting that the IL-22 β gene may not be expressed [2].

Wolk *et al*. have shown that in peripheral blood mononuclear cells (PBMCs), the major source of IL-22 are activated (memory) T cells, especially upon T_H1 polarization, and NK cells [3, 4]. However, soon after the characterization of T_H17 cells it became clear, that this T cell subtype is the dominant IL-22 producer, as demonstrated at both the mRNA and protein levels and now it is clearly established that IL-22 is another effector cytokine produced by T_H17 cells [5, 6]. IL-22 expression by T_H17 cells is differentially regulated from other cytokines expressed by this T_H cell subset as TGF-β and IL-6 are both required for IL-17 induction whereas IL-22 can be induced by IL-6 alone, high concentrations of TGF-β are even inhibitory to its expression and IL-23 is most important for IL-22 production and essential for its sustained expression [5, 7]. Furthermore, the transcription factor aryl hydrocarbon receptor (AHR), which has recently been reported to be important in T_H17 differentiation *in vitro* [8], had a much more pronounced effect on IL-22 expression as compared to that of other T_H17 cytokines and an "IL-22-only" subset of $CD4^+$ effector T cells lacking IL-17 expression has been delineated [9, 10].

Besides this by now very well documented cell source of IL-22, secretion in monocytes and $CD11c^+$ DCs, as well as $CD8^+$ T cells and γ/δ T cells after IL-23- and in NKT cells after αCD3/αCD28 stimulation has been reported [7, 11, 12]. Recently, several articles were published further characterizing IL-22 cell sources, in particular discrete IL-22 producing NK cell populations. Thus, murine intestinal $NKp46^+$ cells expressing the retinoic acid receptor-related orphan receptor t (RORγt) have been shown to constitute an innate source of IL-22. Their differentiation into IL-22 producing cells is "instructed" by signals from the commensal microflora in response to local microenvironmental signals and they have been shown to be involved in the immune defense against the pathogen *citrobacter rodentium* [13-15]. Furthermore, human $ROR\gamma t^+NKp46^+$ cells derived from fetal tissues also have been reported to produce small, while those derived from postnatal tonsils large amounts of IL-22 [16]. Cella *et al*. have recently introduced the term "NK-22 cells" to describe a certain $NKp44^+CCR6^+$ human NK cell subset situated in mucosa-associated lymphoid tissue (MALT) which specifically produces IL-22 and selectively responds to IL-23 [17]. However, in contrast to these NK-22 cells, which express little or no IL-22 mRNA while resting, a certain developmental stage of human NK cells, the so called stage three immature (i)NK cells, has been demonstrated to constitutively produce IL-22 in secondary lymphoid tissue without prior stimulation [18]. Moreover, splenic lymphoid tissue inducer-like cells (LTi-like cells) expressing RORγt, IL-23R, CCR6 and AHR made IL-22 upon stimulation with the yeast cell wall product zymosan [19] and a IL-17-secreting $CD8^+(T_C)$ effector population derived from memory T_C cells has been shown to also produce IL-22 [20].

IL-22 Receptor and Signaling

IL-22 signals through a class II cytokine receptor complex composed of two chains - IL-22R1 and IL-10R2. IL-22R1 is also utilized by IL-20 and IL-24 and IL-10R2 is shared with IL-10, IL-28 and IL-29. The expression of IL-22R1 could only be detected in a limited number of tissues

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such as skin, liver, lung, kidney and pancreas, whereas cells of the immune system do not express IL-22R1 even under stimulated conditions [21]. Concordantly, IL-22 failed to stimulate immune cell functions such as cytokine secretion and surface marker expression but elicited very strong responses from many epithelial cells or cell lines, including acinar cells, hepatocytes, keratinocytes, and colon epithelial cells [1, 22, 23]. In addition to the cell surface IL-22 receptor complex, a soluble single chain IL-22 receptor exists, termed IL-22 binding protein (IL-22BP), which antagonizes IL-22 cellular binding and signaling *in vitro* [24].

The signaling of IL-22 following binding to its receptor includes activation of JAK1 and Tyk2 tyrosine kinases, primarily leading to STAT3- and, to a lesser extent, to STAT1- and STAT5-phosphorylation. STAT3 has recently been shown to be constitutively linked to the C-terminus of the IL-22R [25]. It mediates the expression of a variety of genes involved in cellular processes such as cell growth and apoptosis. IL-22 was also found to activate the ERK, JNK, and p38 MAPK in the rat hepatoma cell line H4IIE [26].

IL-22 Function

The first data on IL-22 function stem from experiments in a human hepatocyte cell line and revealed IL-22 to induce expression of acute phase reactant (APR) genes [27]. Furthermore, it has been shown to drive the production of many antimicrobial peptides, including β-defensins, S100-family proteins, and regenerating-gene (Reg)-family proteins [1] and by now a variety of IL-22 mediated functions has been reported in different settings such as cancer, infectious and inflammatory diseases.

IL-22 has been implicated in the control of tumor growth and progression as it could on the one hand reduce growth of IL-22R expressing EMT6 tumor cells [28] and on the other promote, in an autocrine manner, tumorigenicity of of ALK^+ anaplastic large cell lymphoma cells [29].

Regarding its role in host responses to infectious diseases, it could be shown that blocking of IL-22, genetically or with antibodies, resulted in increased susceptibility to the Gram-negative enteric bacterium *C. rodentium* infection and neutralization of IL-22 during *K. pneumonia* infection lead to greater bacterial loads in the lung and spleen of mice [11, 30]. Also, IL-22 has been suggested to play a role in the defense against fungal infections, such as *C. albicans*, as well as against infections with the protozoan parasite *L. donovani* in humans [31, 32]. On the other hand, $IL\text{-}22^{-/-}$ mice did not show a defect in their capacity to control the facultative intracellular bacterial pathogen *Listeria monocytogenes* [33].

Just as two sided – or even more so – as these effects of IL-22 are, is its function in inflammatory diseases (Fig. **1**) which will be described in more detail in the following.

IL-22 in Psoriasis

Psoriasis is a common, chronic autoimmune disease of the skin characterized by a thickened epidermis, hyperproliferation and abnormal differentiation of keratinocytes accompanied by infiltration of inflammatory immune cells and vascular hyperplasia. So far, all data obtained concerning the role of IL-22 in this disease point towards a proinflammatory function.

IL-22 mediates keratinocyte activation *via* phosphorylation of the STAT3 transcription factor associated with keratinocyte hyperproliferation, and constitutive expression of active STAT3 in kerationocytes lead to spontaneous psoriaform lesions in a STAT3 transgenic model [34]. Furthermore, IL-22 induced STAT3 activation in keratinocytes upregulated the expression of a group of proinflammatory molecules such as S100A7, S100A8 and S100A9, MMP3, platelet-derived growth factor A and CXCL5, downregulated the expression of genes associated with keratinocyte differentiation and induced keratinocyte migration as well as hyperplasia of reconstituted human epidermis. These observations, already implicating a proinflammatory role of IL-22 in psoriasis, could be confirmed by clinical data showing IL-22 levels being strongly elevated in psoriatic skin lesions as well as in the plasma of psoriatic patients, where cytokine levels correlated with disease severity [35-37]. Further complementing these data, another report [38] described genes involved in keratinocyte mobility and terminal differentiation like Keratin 1, Filaggrin and CALML5 that were downmodulated by IL-22. Zheng *et al*. injected IL-23 into the mouse ear thereby inducing acanthosis with increased numbers of neutrophils and eosinophils and increaded STAT3 activation in epidermal keratinocytes. This effect was reduced in $IL\text{-}22^{-/-}$ mice or wt mice treated with IL-22 neutralizing antibody whereby mainly neutrophils and not T cells accounted for the decrease in inflammatory cellular infiltration. However, IL-22 blockade or deficiency had no effect at all on epidermal acanthosis or dermal inflammation when induced by IL-12 [7]. Strong evidence for a disease promoting role of IL-22 in psoriasis stems from a recent report, in which a psoriasis-like disease was induced in a mouse model through adoptively transferring $CD4^+CD45RB^{hi}$ T cells depleted of $CD25^+$ T_{regs} into *scid*/*scid* mice [39]. In this study, mice treated with an IL-22 neutralizing antibody for the first time immediately before adoptive transfer, showed drastically decreased skin pathology with reduced acanthosis, a decreased infiltration of inflammatory cells into the skin and expression of T_H17 cytokines. Even in a more therapeutic setting, that is with antibody treatment starting after the emergence of the first symptoms, IL-22 neutralization was efficacious which suggests IL-22 antagonism as a potential therapeutic approach in psoriasis.

To further elucidate the role of IL-22 in psoriasis, Wolk *et al.* generated transgenic mice overexpressing IL-22 either in cells of the lymphoid lineage or in pancreatic islet cells [40]. In both cases, IL-22 overexpression led to neonatal death of most pubs and to a reduction in body size and weight. Most importantly, it let to psoriasis-like skin alterations including acanthosis and hypogranularity and a shiny and stiff skin – however, without prominent cutaneous T cell infiltration. Normally, psoriatic skin is infiltrated by T cells of the T_H1 and T_H17 phenotype but little is known about how these cells migrate into the inflamed tissue. Recent data on this subject suggested a possible role for IL-22, next to the other T_H17 cytokines IL-17A and TNF-α, in this process. Harper *et al.* found that these cytokines stimulated the expression of the CCR6 ligand CCL20 by keratinocytes, thereby providing a possible mechanism of how $CCR6^+$ T_H17 cells continue being present in inflamed skin through a positive chemotactic feedback loop [41]. Interestingly,

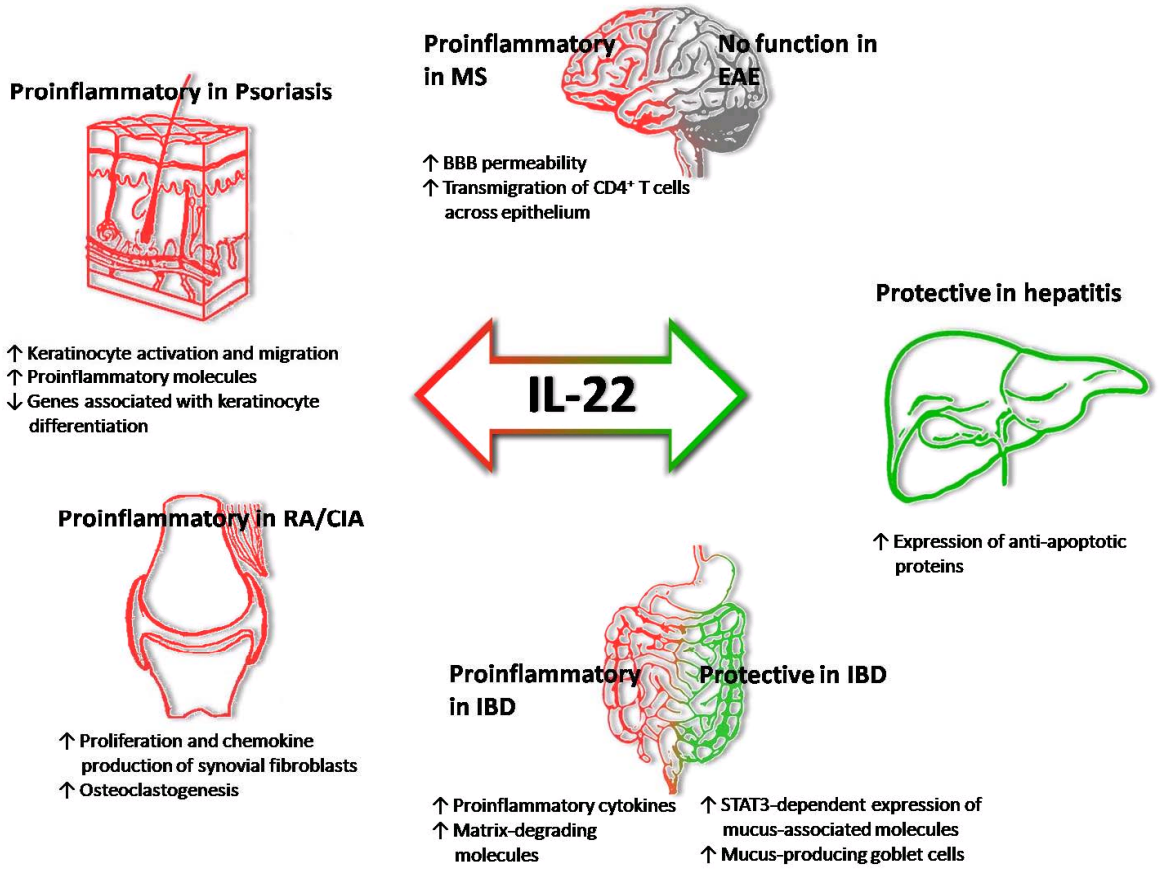

Fig. (1). Proinflammatory and protective properties of IL-22. IL-22 is a cytokine produced by T_H17 cells and its receptor is expressed in the skin, liver, the digestive and the respiratory tract where IL-22 conveys signals of the immune system directly to the tissue. IL-22 is involved in various inflammatory diseases like psoriasis, arthritis or inflammatory bowel disease. Depending on the tissue and inflammatory context, it exerts proinflammatory, protective or no evident function. Depicted are the so far described effects of IL-22 under inflammatory conditions in distinct tissues.

CCR6 not only on T cells seems to act in the context of skin inflammation. New data reveal it being required in IL-23 induced, IL-22 mediated psoriasis-like skin inflammation, also for an initially T cell independent development that includes a non T cell source of IL-22 [42].

IL-22 in Rheumatoid Arthritis and Collagen Induced Arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory disorder causing progressive joint damage and is histologically characterized by infiltration of inflammatory cells. The corresponding animal model, collagen induced arthritis (CIA), can be induced through immunization with autologous or heterologous type II collagen (CII) in adjuvant. Until now, the role of IL-22 has not extensively been documented in RA or CIA, but so far data point towards a possible proinflammatory role of this cytokine.

Ikeuchi *et al*. detected IL-22 in synovial tissues and in mononuclear cells isolated from RA synovial fluid samples and found it to promote proliferation and chemokine production of synovial fibroblasts [43]. Complementary to these results, Geboes *et al*. detected high levels of IL-22 after stimulation with αCD3 antibody in the sera of mice immunized with type II collagen, suggesting a proinflammatory function of IL-22 in CIA [44]. To verify this notion, they induced CIA in IL-$22^{-/-}$ animals and observed a decreased incidence and severity of arthritis with decreased pannus formation in these mice as compared to wt mice. This was accompanied with increased antibody production whereby the cellular immune response against CII was unaltered in IL-$22^{-/-}$ as compared to wt mice as measured in a DTH ear swelling assay. They suggested a possible mechanism through which IL-22 exerts its proinflammatory activity in CIA being a stimulatory role of this cytokine in osteoclast differentiation and activity, as the authors demonstrated IL-22 to promote osteoclastogenesis *in vitro*.

IL-22 in Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis

Multiple sclerosis (MS) is a complex demyelinating disease associated with inflammation in the central nervous system (CNS) and is thought to be driven by an autoimmune process. Experimental autoimmune encephalomyelitis (EAE) serves as an animal model of MS and can be induced by immunization with myelin antigens or by adoptively transferring an expanded population of myelin-reactive encephalitogenic $CD4^+$ T cells. T_H17 cells, one of whose hallmark cytokines is IL-22, could be found in MS lesions raising the question of whether IL-22 contributes to MS pathology.

IL-22R and IL-17R could be detected on the surface of a subset of human blood brain barrier (BBB) epithelial cells in primary culture and were expressed on CNS vessels within infiltrated MS lesions. Furthermore, IL-22 and IL-17 could affect BBB permeability and promote transmigration of human *ex vivo* $CD4^+$ T cells across epithelial cells in an *in vitro* model of the human BBB [45], thereby implicating a possible mechanism through which IL-22 attributes to CNS inflammation in humans. However, although we found that self-reactive T_H cells expressed IL-22 in EAE, we could clearly rule out IL-22 to be directly involved in autoimmune pathogenesis of the CNS in mice, as IL-$22^{-/-}$ animals were fully susceptible to MOG-induced EAE and showed the same disease course and degree of inflammation as wt mice [6].

IL-22 in Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a chronic inflammatory disease involving an aberrant immune response leading to the destruction of the epithelium of the gastrointestinal tract. The major types of IBD are Crohn's disease (CD) and ulcerative colitis (UC) which can be distinguished by the location and nature of the inflammatory changes. A number of studies clearly linked IL-22 to IBD, however, without allowing a final conclusion on an inflammatory or protective nature of its action.

Andoh *et al.* found an increased number of IL-22 expressing $CD4^+$ T cells in human colonic mucosa in UC and even more so in CD [23]. IL-22 derived from these activated T cells acted on colonic subepithelial myofibroblasts and elicited expression of proinflammatory cytokines and matrix-degrading molecules indicating a proinflammatory role in IBD. Consistently, IL-22 expression was upregulated in the murine dextran sodium sulphate (DSS) induced colitis model [46]. Even though IL-22R engagement in intestinal epithelial cells (IEC) resulted in increased proinflammatory gene transcription (i.e. for IL-8), IL-22 promoted the integrity of the intestinal barrier through inducing IEC migration and defensin production. Furthermore, IL-22 serum levels correlated with disease activity as well as the genotype status of IL23R [47]. IL-23R constitutes a susceptibility gene in Caucasian IBD patients; accordingly, the IL-22 levels in carriers of CD risk-increasing IL-23R variants were elevated in comparison to those of risk-decreasing variant carriers. Complementing the previous data on the presence of IL-22 in the inflamed intestine, Wolk *et al*. furthermore found elevated levels of LPS binding protein (LBP) in CD patients and the mouse colitis model. They could show that IL-22 was able to induce LBP expression in hepatocytes, thereby suggesting a potential IL-22 mediated protective mechanism how inflammation in CD is limited to the intestine without becoming systemic [48]. A clear demonstration of a protective role of IL-22 in intestinal inflammation in a T_H2 mediated mouse model of UC was published recently by Sugimoto *et al.* [49]. The group developed a microinjection-based local gene-delivery system with which they could specifically deliver the IL-22 gene to the inflamed intestine. Following IL-22 gene delivery, they observed STAT3-dependent expression of mucus-associated molecules as well as restitution of mucus-producing goblet cells which resulted in a clear amelioration of intestinal inflammation. This effect could be reversed through IL-22BP mediated inhibition of IL-22 activity. By employing both T cell driven and innate animal models in which disease is induced through either transfer of $CD45RB^{hi}$ cells or through administration of DSS, respectively, Zenewicz *et al.* could furthermore show that not only $CD4^+$ T cells provided IL-22 but that NK cells constituted another, innate source of this cytokine. IL-22 mediated protection independently of effects on T cells, but it rather directly acted on colon epithelial cells.

IL-22 in Hepatitis

Hepatitis B or C virus infections or alcohol abuse can lead to chronic inflammation of the liver associated with T cell activation and mediated through various processes including cytolytic pathways and the production of proinflammatory cytokines. In mice, T cell dependent hepatitis can be induced by intravenous injection of the T cell mitogen ConA. Until today, data published on the function of IL-22 in this disease implicate it to mediate protection of hepatocytes.

One of the first publications on IL-22 described it to protect hepatocytes *in vitro* from serum starvation-induced apoptosis [27]. In line with these *in vitro* data, Radaeva *et al*. demonstrated a protective role of IL-22 in ConA induced T cell mediated murine hepatits, in which IL-22 levels where strongly elevated [50]. Administration of recombinant IL-22 attenuated liver injury *in vivo* and promoted cell growth and survival of human hepatocellular carcinaoma HepG2 cells *in vitro*. Accordingly, IL-22 blockade through antibody mediated neutralization led to increased liver injury. In a following report they further confirmed these observations and demonstrated that overexpression of IL-22 by hydrodynamic gene delivery results in the expression of several anti-apoptotic proteins such as Bcl-xL or Bcl-2 in the liver, thereby exerting a protective effect [51]. However, no effect of recombinant IL-22 on viability and proliferation was found when primary hepatocytes and HepG2 cells were cultured under standard conditions by another group [48]. In a study in which IL-$22^{-/-}$ mice were used in a ConA mediated hepatitis model, the protective effect of this cytokine could be further confirmed, as IL-$22^{-/-}$ mice were more susceptible to liver damage as compared to wt mice. Moreover, IL-22 expressing T_H17 cells were able to protect hepatocytes from the destructive effects during hepatitis as shown by adoptive transfer of IL-22 expressing cells [33]. Regarding the role of IL-22 in hepatitis C virus infection, no significant difference between hepatic IL-22 mRNA levels in patients with viral and non-viral hepatitis could be found [52] implying that not the viral infection itself, but rather the infiltration of T cells causes increased IL-22 expression. Furthermore, IL-22 did not directly regulate antiviral protein expression and had no effect on hepatitis C virus replication. Recently, Wahl *et al*. applied the ConA induced T cell dependent hepatitis model in mice deficient in the coinhibitor Herpes Virus Entry Mediator (HVEM) [53]. In conflict to a previous report [54], these mice showed an attenuated disease course with higher serum levels of IL-22 as compared to wt mice. Furthermore, the number of disease initiating liver type I invariant NKT (iNKT) cells was reduced in $HVEM^{-/-}$ mice. Most importantly, these iNKT and not conventional liver $CD4^+$ cells or T_H17 cells displayed the main IL-22 producers. After antibody mediated neutralization of IL-22, the disease course was aggravated in $HVEM^{-/-}$ mice, albeit not to the same ex-

tend as in wt mice which suggests additional IL-22 independent mechanisms contributing to the protection from acute hepatitis in $HVEM^{-/-}$ mice.

CONCLUDING REMARKS

Lately, a considerable amount of literature has been published on cell sources, structure and functions of the previous to the discovery of T_H17 cells somewhat overlooked cytokine IL-22. Just as more and more functions, especially with respect to therapeutically interesting roles in immune disorders are revealed, more and more questions emerge due to its dual role in mediating protection or inflammation. Whether one or the other effect dominates likely depends on the tissue as well as the inflammatory milieu whose understanding would be greatly beneficial. In that its receptor is absent on cells of the immune system and exclusively expressed on tissue, using IL-22 as a therapeutic could depict a promising approach to specifically target affected sites without influencing the whole immune system. Therefore, the challenge will be to gain more insights into the complex actions of this cytokine in order to ensure that either blocking or adding IL-22 only results in the desired beneficial effect and does not, at the same time, cause damage.

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