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REVIEW

IL-22: A critical mediator in mucosal host defense

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Abstract IL-22 is an IL-10 family cytokine member that was recently discovered to be produced by Th17 cells. Current studies have revealed that IL-22 targets cells of the digestive, skin, and respiratory organ systems and plays an important role in mucosal immunity. The IL-22 receptor (IL-22R) is expressed exclusively in these tissues, thereby allowing the cytokine to mediate epithelial innate immunity in response to a variety of pathogens. Although recent studies have shown the importance of IL-22 in host defense against Gram-negative bacterial organisms (in gut and lung), there is evidence that IL-22 also plays a role in autoimmune disease, such as psoriasis. IL-22 therefore, not unlike other cytokines, has complex pro-inflammatory, anti-inflammatory, and autoimmune effects which continue to be under further investigation. This review will focus on what is known about IL-22 and its function in mucosal host defense.

Keywords IL-22 · Innate immunity · Autoimmunity

Introduction: IL-22 and IL-22R

IL-22 was initially known as IL-10-related T-cell-derived inducible factor (IL-TIF) when it was first characterized by Dumoutier et al. It was induced in mouse T lymphoma cells by IL-9 and had 22% amino acid identity with IL-10 [1]. IL-TIF did not appear to have effect on proliferation of T cells or mast cells; however, it did activate STAT3 in kidney mesangial cells [1]. IL-TIF was renamed IL-22 after the human protein was discovered, and other structurally related cytokines (IL-19, IL-20, IL-24, IL-26, IL-28αβ, and IL-29) joined IL-22 to become part of the IL-10 cytokine family [2]. Secreted human IL-22 protein is 146 amino acids in length and has 80.8% identity to murine IL-22. It has an α-helical secondary structure as do the other IL-10 family members [2]. The IL-22 receptor is part of the cytokine receptor family class 2 and consists of two subunits, IL-22R1 and IL-10R2 [2, 3]. IL-10R2 is widely expressed on immune cells (T, B, and NK cells), unlike IL-22R1 [3]. Wolk et al. had demonstrated that IL-22R1 expression is present in a variety of nonimmune tissues: skin, lung, small intestine, liver, colon, kidney, and pancreas [3]. They also showed activation of STAT3 in human keratinocytes by IL-22 [3]. IL-22R1 expression is upregulated with stimulation by the proinflammatory mediators LPS, IL-1β, and TNF-α in intestinal epithelial cells [12]. In keratinocytes, IFN-γ induced an increase in expression of both IL-22R1 and IL-10R2 [3].

There is also a soluble, secreted IL-22 receptor called IL-22-binding protein (IL-22BP), which is encoded by a different gene, and this protein has been shown to counteract IL-22 binding in vitro [2, 3]. The affinity of IL-22 to IL-22BP appears to be at least four times higher than that of IL-22 to IL-22R1 [19]. IL-22BP expression in colon was decreased in a mouse model of colitis compared to control mice, supporting the inhibitory role of IL-22BP on IL-22 function [19]. Thus, these emerging data showed that IL-22 was produced by immune cells, specifically T and NK cells, and that its biological effect appeared to be targeted on epithelial or parenchymal cells of the gut, lungs, skin, and kidney [2].

IL-22 was also known to upregulate expression of acute phase proteins, including serum amyloid A (SAA) and pancreatitis-associated protein 1 (PAP1) in liver and pancreas, respectively [2]. Wolk et al. had also shown that IL-22 increased the expression of the antimicrobial peptides

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human β-defensin (hBD) 2 and 3 in human keratinocytes. Interestingly, these antimicrobial peptides as well as IL-22 itself were detected in higher levels in skin from psoriasis sufferers, compared to healthy skin [3]. Other studies also revealed the upregulation of specific matrix metalloproteinases (MMPs) by IL-22 in the skin and digestive tract [2]. Specifically, IL-22 was found to enhance the gene expression of MMP1 and MMP3, which are cell migration and mobility-regulating proteins, in keratinocytes [8]. Andoh et al. showed that IL-22 induced MMP1, MMP3, and MMP10 in human colonic subepithelial myofibroblasts using cDNA microarrays [17].

These studies suggested that IL-22 is an important immune mediator produced by T cells and acting on mucosal tissues to regulate host defense responses. Subsequently, it was discovered that IL-22 is, in fact, a product of a subgroup of CD4+ T-cells characterized by IL-17 production (Th17 cells). A recent publication by Cella et al. has shown that IL-22 is also produced by human and mouse mucosal natural killer (NK-22) cells [18]. This subset of NK cells is present in the mucosa-associated lymphoid tissue and produce IL-22 in response to IL-23. The authors postulated that NK-22 cells may dampen inflammation (through IL-10 production) and provide mucosal protection (via epithelial cell proliferation).

IL-22 and the T_H17 cell lineage

Th17 cells are a separate lineage of $CD4^+$ effector T cells distinct from Th1 and Th2 cells [4]. They produce IL-17A, IL-17F, and IL-22 [5, 6]. IL-17 is a proinflammatory cytokine important in granulopoiesis and neutrophil chemotaxis. Th17 cells are known to contribute to autoimmune disease in certain organs [5]. Liang et al. showed that IL-22 is expressed by murine Th17 cells, in addition to IL-17A and IL-17F. Some IL-22 was produced by Th1 cells and even Th2 cells, but Th17 cells were the predominant source of the cytokine [6]. Furthermore, although TGF-β and IL-6 are sufficient to differentiate naive T-cells into IL-17-producing T cells, IL-23 increases the production of IL-22-positive cells in the presence of TGF-β and IL-6 [6].

IL-22 in the regulation of keratinocyte gene products and in pathogenesis of psoriasis

Liang et al. furthermore showed that IL-22 (200 ng/ml) and IL-17A (20 ng/ml) synergistically upregulated hBD-2, S100A7 (psoriasin), S100A8, and S100A9 transcripts in primary keratinocytes. A similar effect was seen with IL-22 and IL-17F [6]. The group postulated that both IL-17 and IL-22 may act cooperatively in mediating tissue inflammation. Previous to this study, Boniface et al. showed induction of S100A7, S100A8, S100A9, and MMP-3 in normal human epidermal keratinocytes stimulated with IL-22 (20 ng/ml) [7]. IL-22 also upregulated CXCL5, keratin 6 and platelet-derived growth factor (PDGF-A) in reconstituted human epidermis. IL-22 downregulated a variety of genes associated with keratinocyte differentiation, including filaggrin and involucrin [7].

In their mouse model of inflammatory skin disease, Zheng et al. showed that the IL-23 driven dermal inflammation was mediated by IL-22 [20]. IL-22 knockout mice had significantly decreased inflammation and epidermal hyperplasia compared to wild-type controls [20].

Wolk et al. noted in their study that IL-22 appears to be regulating three distinct gene groups in keratinocytes: antimicrobial proteins, differentiation-associated proteins, and mobility-/migration-associated proteins [8]. They also show increased IL-22 expression in skin biopsies from subjects with plaque psoriasis compared to healthy controls. These subjects also had largely elevated IL-22 protein in the blood compared to healthy controls, which decreased after anti-psoriatic therapy [8]. A mouse model of psoriasis-like skin disease was then studied in the context of Th17 cells and IL-22 [9]. When these mice were treated with IL-22 neutralizing antibody, there was either no development or extremely mild development of the disease. There was also significant reduction of antimicrobial peptides in the IL-22 neutralized group. The authors note that IL-22 antagonism may lead to a therapeutic approach for Th17-mediated skin disease [9].

A recent study indirectly addressed IL-22 in psoriasis in the context of anti-psoriasis therapy. This randomized controlled trial investigated serum levels of IL-17 and IL-22 in human subjects with moderate to severe plaque-type psoriasis pre- and posttreatment with two different agents [10]. Subjects received either etanercept (TNF inhibitor) or acitretin (systemic retinoid). There were higher levels of IL-17 and IL-22 in subjects with psoriasis compared with controls, and only after etanercept treatment was there reduction of serum IL-17 and IL-22 levels [10]. Interestingly, although both treatments led to improvement of clinical disease, etanercept was more effective and had a lower psoriasis area and severity index compared with acitretin. The authors suggest that this may be related to the reduction of IL-17 and IL-22 by the TNF inhibitor.

IL-22 in the regulation of intestinal epithelium gene products and in pathogenesis of inflammatory bowel disease

Similar to its effect on keratinocytes, IL-22 also targets colon epithelial cells via activation of STAT3. The acute

phase proteins α antichymotrypsin B and serum amyloid A (SAA) were upregulated in these cells [11]. Intestinal epithelial cells express IL-22R, and both proinflammatory cytokines TNFα and IL-8 transcripts were upregulated by IL-22 [12].

IL-22 transcripts are elevated in biopsies of subjects with Crohn's disease compared to those with ulcerative colitis. IL-22 also promoted wound healing by increased cell migration in intestinal epithelial cells in a wound assay [12]. IL-22 had a similar effect in a keratinocyte in vitro injury model [7]. Although IL-22 obviously contributes to a pro-inflammatory environment in some circumstances, it was found to improve disease in a mouse model of ulcerative colitis via an IL-22 gene delivery method [13]. This improvement was thought to be secondary to IL-22-enhanced mucus production and goblet cell replacement, leading to the formation of this external barrier at the epithelial surface [13]. This role of epithelial barrier protection by IL-22 was further investigated in a mouse model of intestinal bacterial infection, *Citrobacter rodentium*, which is a mouse attaching and effacing (A/E) pathogen [14]. IL-22 is critical for host defense against this pathogen, as IL-22 knockout mice had significantly increased mortality compared to wild-type control mice, in part secondary to disrupted epithelial barrier integrity. The downstream mediators of IL-22 were the antimicrobial proteins RegIIIβ and RegIIIχ. There was also increased expression of the RegIIIβ and RegIIIχ transcripts in IL-22-stimulated human colonic epithelial cell lines [14]. IL-22 is again shown to be important in both innate and adaptive immunity in this role promoting early host defense against A/E bacterial infection. Interestingly, a recent paper by Sanos et al. revealed the source of IL-22 in the intestine being a subset of natural killer (NK) cells, that is, mucosal NKp46^{+} cells [22]. These NK cells localized in cryptopatches in intestinal mucosa and were dependent on transcription factor RORγt as well as commensal gut microflora for differentiation and IL-22 production [22]. It is proposed that these IL-22-producing NK cells in the gut function in epithelial innate immunity through tissue repair and involvement in epithelial homeostasis [21].

IL-22 in the regulation of respiratory epithelium gene products and host defense

In contrast to the skin and gut, there are relatively few studies regarding IL-22 and lung inflammatory disease. IL-22 does induce STAT3 phosphorylation in the alveolar type II lung epithelial cell line, A549 [15]. The IL-22R1 transcript is expressed in alveolar epithelial cells [15]. Our lab recently has shown that IL-22R is expressed in human bronchial epithelial cells and that IL-22 can augment IL-17-induced G-CSF, IL-6 and a variety of antimicrobial gene products, including hBD2 (Fig. 1). IL-22 treatment of HBE cells increased their clonogenic potential in a limiting dilution assay as well as accelerated repair in an epithelial wound model. Neutralization of IL-22 in a mouse model of *Klebsiella pneumoniae* pneumonia showed that anti-IL-22-treated mice did not survive the infection compared with wild-type controls or mice lacking IL-17a. In contrast to either control or IL-17a-deficient mice, anti-IL-22-treated mice rapidly succumbed to infection and developed rapid dissemination of bacteria from the lung to the spleen within 24 h [16]. These data are consistent with a loss of barrier function when IL-22 is neutralized. IL-22 induced the expression of another antimicrobial protein, lipocalin-2, in mouse lung epithelium [16]. Lipocalin-2 can

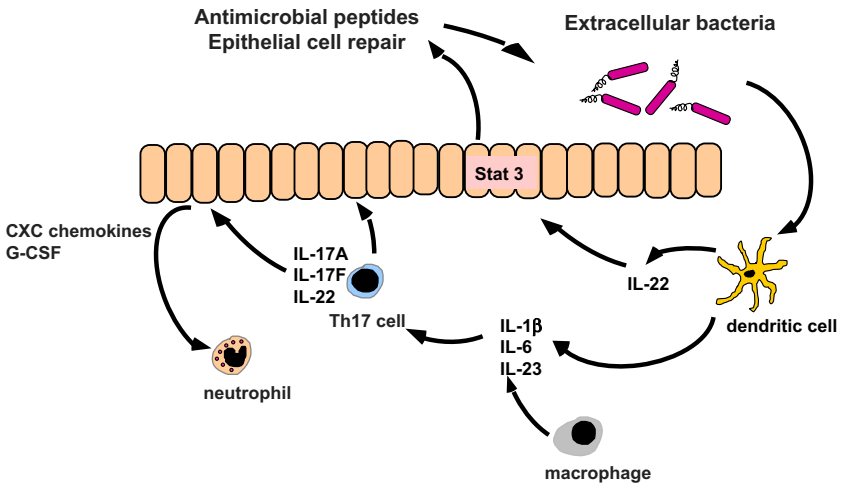

Fig. 1 IL-22 is produced by dendritic cells as well as activated Th17 cells in response to extracellular bacteria. IL-22 increases production of antimicrobial peptides and promotes wound repair via STAT3 pathways by the epithelium. In conjunction with IL-17, there is also an upregulation of proinflammatory mediators including G-CSF which in turn increases neutrophil recruitment

compete with bacterial siderophores to scavenge iron from specific strains of bacteria. Moreover, IL-22 treatment of mouse lung epithelial cells increases the antimicrobial activity of the epithelium in a lipocalin-2-dependent fashion. Thus, IL-22 appears to be a critical regulator of antimicrobial genes and various mucosal surfaces.

Conclusions

There is much excitement regarding the recent discoveries surrounding IL-22 in the organ systems described above. As the IL-22 story continues to unfold, it is clear that this cytokine has functions independent of its Th17 sister product, IL-17. We can conclude that IL-22 is indeed a mediator of mucosal host defense, it enhances wound repair, and is crucial for epithelial barrier integrity (Fig. 1). Unfortunately, like many cytokines that hold dual roles, IL-22 is the major arbitrator in the chronic autoimmune T-cell skin disease, psoriasis. Although IL-22 contributes to the pathogenesis of inflammatory bowel disease, delivering it in a mouse model of ulcerative colitis appears to have beneficial effects. Further studies aimed at elucidating these conflicting effects in various types of inflammatory bowel disease are needed.

There is current discussion regarding the use of both IL-22 and IL-22 antagonists as therapies for different disease states. Caution must be used as we do not yet know whether in certain patient subgroups using an IL-22 antagonist for psoriasis would put patients at increased risk for certain bacterial infections or if using IL-22 itself would put patients at risk for autoimmune disease or an undesirable proinflammatory state. Moreover, additional work is needed to determine the cellular sources and the regulation of this cytokine in different human disease states.

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