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The Role of Interleukin (IL-22) in immune response to human diseases

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ABSTRACT

Background and aims: IL-22 is an alpha- helical cytokine. IL-22 binds to a heterodimeric cell surface receptor composed of IL-10R2 and IL-22R1subunits. IL-22R is expressed on tissue cells, and it is absent on immune cells. L-22 and IL-10 receptor chains play a role in cellular targeting and signal transduction to selectively initiate and regulate immune responses. The aim of this study was to investigate the Role of Interleukin (IL-22) in Immune Response in human diseases.

Methods: This study was a mini-review research to investigate the role of T helper 22 (Th22) in immune response.

Results: IL-22 contributes to immune disease through the stimulation of inflammatory responses, S100s and defensins. IL-22 also promotes hepatocyte survival in the liver and epithelial cells in the lung and gut similar to IL-10. In some contexts, the pro-inflammatory versus tissue-protective functions of IL-22 are regulated by the often co-expressed cytokine IL-17A. IL-22 confirms regulation of antimicrobial proteins. Targeting the IL-22–IL-22R pathway may yield new therapeutic potential for the treatment of certain human diseases.

Conclusion: IL-22 is expressed constitutively by LTi-like cells within the small intestine, a tissue that is under the careful immune balance between inflammation and tolerance. Gaining a better understanding of the expression and role of IL-22 in health and disease is important for development of IL-22 as a potential drug target IL-22 is expressed constitutively by LTi-like cells within the small intestine, a tissue that is under the careful immune balance between inflammation and tolerance. Obtaining a better understanding of the expression and role of IL-22 in health and disease is important for development of IL-22 as a potential drug target.

Keywords: T Helper22, Immune Response, Interleukin 22.

Mini-Review article

INTRODUCTION

Interleukin 22 was first characterized in 2000 in a screen to identify previously unknown cytokine transcripts induced in an IL-9-stimulated mouse thymic T cell. Mouse IL-22 shares structural similarities and 22% sequence homology with mouse IL-10 and was originally called 'IL-10-related T cell inducible factor'1.[1,2] .IL-22 was further classified as a class 2 α-helical cytokine of the IL-10 family of cytokines, which consists of IL-10, IL-19, IL-20, IL-22, IL-24 and IL-26. IL-22 signals through a distinct

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class-2 receptor (IL-22R) composed of the subunits IL-22R1 (IL-22RA1) and IL-10R2 (IL-10RB2), which are independently shared with IL-20 and IL-24 and with IL-10 and IL-26, respectively. IL-22 at first binds to IL-22R1, and then the IL-22–IL-22R1complex binds IL-10R2 to propagate downstream signals.[1] In recent years in many studies show that cytokines like IL-22, IL-17A, and IL-17F play a major role in both the defence against certain microbes and the development and maintenance of chronic inflammatory diseases. These mediators are often secreted by subpopulations of T-helper cells called Th17 cells and Th22 cells, respectively.[1,2] Similar to other members of the IL-10 family, IL-22 uses the Jak-STAT signal transduction pathway, inducing phosphorylation of the kinases Jak1 and Tyk2 and the STAT1, STAT3 and STAT5 transcription factors.[2] IL-22 is known to be expressed in many chronic inflammatory conditions, including psoriasis and rheumatoid arthritis, and it's up-regulation often correlates with disease activity. IL-22 is known to be protective in the gastrointestinal tract in inflammatory bowel disease but may mediate either harmful or helpful inflammatory responses in different models of intestinal infection.[3] IL-22 is central to host protection against bacterial infections at barrier sites. Both innate lymphoid cells (ILCs) and T cells produce IL-22. However, the specific contributions of CD4+ T cells and their developmental origins are unclear. The enteric pathogen *Citrobacter rodentium* induced sequential waves of IL-22-producing ILCs and CD4+ T cells that were each critical to Host Defense during a primary infection.[4] Termed 'Th22' cells, these cells express the chemokine receptor CCR6, and the skin-homing receptors CCR4 and CCR10, allowing for localization to the skin. The Th22 clones continue to express IL-22 and not the other cytokines associated with these Th subsets. Th22 cells appear to be important for skin homeostasis and in inflammation as the Th22 cell population is increased in psoriasis patients.[5] These findings establish Th22 cells as an important component of mucosal antimicrobial Host Defense. In particular, the effectors cytokines IL-17 and IL-22, which are produced by the T-helper-17-cell subset, are emerging as crucial regulators of antimicrobial-peptide production in the gut and the lungs. This suggests that Th22 lineage and its cytokines have important roles in skin and mucosal immunity.

IL-22 affects an acute phase response, implicating a role for IL-22 in mechanisms of inflammation. IL-22 requires the presence of the IL-22 receptor (IL-22R) and IL-10 receptor 2 (IL-10R2) chains, two members of the class II cytokine receptor family (CRF2), to affect the signal transduction within a cell. Through activation of Stat3-signaling cascades, the cytokine induces proliferative and anti-apoptotic pathways, as well as anti-microbial molecules, that help to prevent the tissue damaging and aid in its repairing.[5] IL-22 is expressed by both the adaptive arm of the immune system, such as CD4 T-cell subsets, as well as by innate lymphocytes, including NK cells and lymphoid tissue inducer (LTi) cells.[6] IL-22 plays an important role in inflammation, including chronic inflammatory diseases and infectious diseases.[7] The maintenance of barrier function at exposed surfaces of the mammalian body is essential for limiting exposure to environmental stimuli, preventing systemic dissemination of commensal and pathogenic microbes and retaining normal homeostasis of the entire body. Indeed, dysregulated barrier function is associated with many infectious and inflammatory diseases, including psoriasis, influenza, inflammatory bowel disease and human immunodeficiency virus, which

collectively afflict millions of people worldwide.[8] Effective host protection is characterized by integrated responses of innate and adaptive arms of immunity. At barrier sites (e.g., skin, respiratory, and intestinal tracts), production of IL-22 by both innate and adaptive lymphoid cells is important in Host Defense through its actions on epithelial cells.[9]

IL-22 is expressed by cells of the innate and adaptive immune responses in many mouse disease models. IL-22 seems to act exclusively on non-hematopoietic cells, with basal IL-22R expression in the skin, pancreas, intestine, liver, lung and kidney.[9-10] Ligation of IL-22R modulates the expression of many genes, including those encoding molecules involved in chemotaxis, proliferation, an acute-phase response, innate immunity and inflammation. Therefore, it is perhaps not surprising that with the development of reagents to ablate the IL-22–IL-22R pathway, IL-22 was found to have critical roles in regulating host defence, tissue homeostasis and inflammation, in particular at barrier surfaces.[11] Initial studies characterizing the functions of IL-22 showed that stimulation of keratinocytes with IL-22 resulted in marked induction of genes encoding proteins involved in antimicrobial host defence, including S100A7, S100A8, S100A9, β-defensin-2 and β-defensin-3 (Figure 1). Although ILCs are a critical source of IL-22 during mucosal infection, less is known regarding specific contributions of IL-22 produced by CD4+ T cells. The relative contribution of ILCs and CD4+ T cells in host protection against the enteric bacterial pathogen Citrobacter rodentium has been examined. ILC-derived IL-22 induced by IL-23 is critical to curb bacterial loads pending development of pathogen-induced CD4+ T cells, but not strictly dependent on IL-23.[12] The transcriptome of Th22 cells differed significantly from Th17 cells and both AhR and T-bet were required for optimal IL-22 production by Th22 cells and their host-protective function.[13] These findings identify Th22 cells as important contributors to mucosal host defence and suggest overlap between the functional programming of these cells with that of the recently described subset of Th17 cells proposed to be key contributors to autoimmune disease.[14]

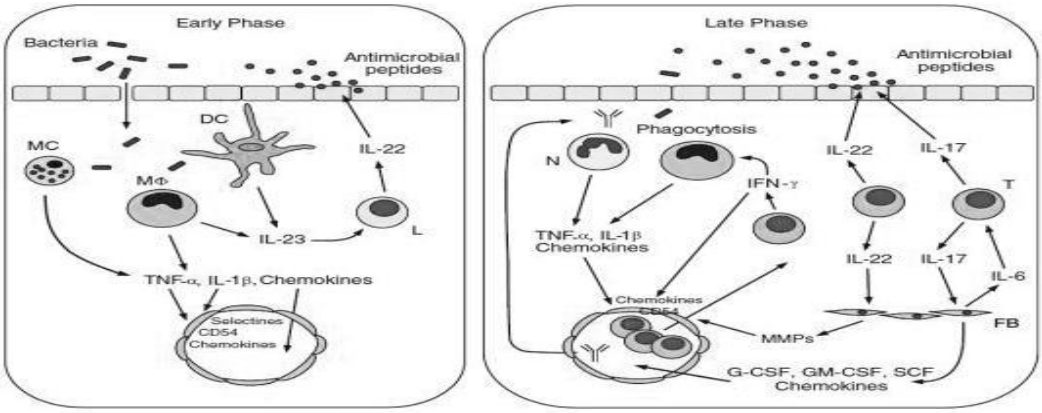

Figure 1: The role of IL-22 and IL-17A/IL-17F during mucosal infections. MC mast cell, macrophage (Mϕ). DC dendritic cell. L lymphocyte
N: neutrophile, T: Tcell, FB: fibroblast.

Subsequent studies have also shown that the induction of two intestinal antimicrobial peptides, RegIIIβ and RegIIIγ, is also dependent on IL-22 production, and stimulation of airway epithelial cells with IL-22 results in the upregulation of many

genes encoding molecules involved in mammalian Host Defense against bacterial infection, including the chemokines CXCL1, CXCL5 and CXCL9 and the cytokines IL-6 and G-CSF.[15] IL-22 act synergistically or additively with IL-17A, IL-17F or tumour necrosis factor (TNF) to promote the expression of many of the genes that encode molecules involved in host defence in the skin airway or intestine.[16] Demonstrating the functional importance of IL-22 in promoting barrier immunity, IL-22 is essential for host protective immunity to the extracellular Gram-negative pathogens of *Klebsiellap neumoniae* in the lung and *Citrobacter rodentium* in the intestine .[14,16] IL-22 is critical for limiting bacterial replication and dissemination, probably in part by inducing the expression of antimicrobial peptides from epithelial cells at these barrier surfaces. The influence of IL-22 on the elicitation of host protective immunity is dependent on the pathogen, as IL-22 seems to have no substantial role in host defence after infection with *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Listeria monocytogenes* or *Schistosoma mansoni*.[16,17] IL-22 may not be required for immunity to these specific infectious agents because, unlike *C. rodentium* or *K. pneuomiae*, these pathogens do not intimately associated with the barrier surface or selectively induction of functional or pathological changes in epithelial cells.[18] Furthermore, although it does not have a direct role in immunity, IL-22 seems to promote intestinal inflammation after oral infection with *Toxoplama gondii* which demonstrates that some infectious agents elicit a non-beneficial pro-inflammatory IL-22-dependent response.[19] Although this is still in the early stages of investigation, IL-22 does not seem to have a substantial direct role in immunity to viral pathogens. For example, IL-22 deficiency does not influence the outcome of influenza infection.[20] However, IL-22 may have an important role in providing protective innate immunity when the adaptive immune system is impaired, such as after infection with human immunodeficiency virus. This is evident in immunity to gastric *Candida albicans*, in which IL-22 promotes protective immunity to infection when immunity dependent on T helper type 1 (TH1) cells is impaired. In animal models of candidiasis, there are conflicting reports as to the importance of IL-22 to pathogenesis.[21] In contrast, oral inoculation of the parasite into IL-22-deficient mice results in less disease pathology in the small intestine compared with wild-type controls. Thus, IL-22 is pathogenic in the course of *T. gondii* infection in the GI tract, but not other tissues.[21] When infection by the parasite *Toxoplasma gondii* is introduced via the peritoneal cavity or the bloodstream, IL-22 does not play a detectable role in its pathogenesis, including parasite loads in the brain and liver lesions.[21] IL-22 can be an inflammatory factor and mediate disease in the GI tract.[22] IL-22 helps to prevent dissemination of pathogenic bacteria, such as *Klebsiella pneuomniae* in the lung, or enteropathogens, including *Citrobacter rodentium* and *Salmonella* enterica serotype *Typhimurium*, in the GI tract; thereby it limits bacterial growth.[23] Additionally, IL-22 aids in the elimination of pathogens by inducing different anti-microbial proteins (RegIIIβ and RegIIIγ). Although human data indicating a role for IL-22 in infection are sparse, Patients with autoimmune polyendocrine syndrome type I have a high rate of chronic mucocutaneous candidiasis.[23] In the study of Puel et al. It has been showed that these patients have high levels of auto-antibodies to IL-17A and IL-22, in effect leading to cytokine neutralization and suggesting that these cytokines are important for controlling yeast infections.[24]

Augmented expression of IL-22 has been documented in several disease states and, furthermore, spontaneous mutations arising in the human population that affect the IL-22–IL-22R pathway correlate with defects in

barrier immunity. These data suggest that targeting the IL-22–IL-22R pathway may yield new therapeutic potential for treatment of certain human diseases.[25] IL-22 expression is detected in many inflammatory and infectious human diseases. For example, higher concentrations of IL-22 derived from Th17 cells are observed in the peripheral blood and tissues of patients with psoriasis or arthritis, and on the basis of preclinical model studies, it is predicted that IL-22 promotes pathological inflammation in these disease settings.[18,25] In contrast to its concentration in psoriasis, higher concentrations of IL-22 from Th22 and TC22 cells are observed in the inflamed skin of patients with atopic dermatitis.[26] IL-22 concentrations are also higher in the peripheral blood and intestine of patients with inflammatory bowel disease. Although IL-22 is tissue protective in mouse models its role in human intestinal inflammation, as IL-22 expression correlates with
pro-inflammatory gene expression.[27] Infection with Leishmania donovani, which causes a lethal visceral disease, is associated with Th17 cell expression of IL-22 and is also positively correlated with disease protection. Further, patients with cystic fibrosis who have exacerbated infection with Pseudomonas aeruginosa have more T cell secretion of IL-22 in lung-draining lymph nodes.[28] This induction of IL-22 expression in infectious settings is consistent with its identified role in mouse models for the promotion of immunity at barrier surfaces. Thus, most reports have examined T cell expression of IL-22 in human disease; however, given the characterization and critical importance of IL-22 expression by innate cells, it will also be important to examine innate sources of IL-22, such as ILCs, in future studies.[27-28]

IL-22, IL-17A and IL-17F have been shown to cooperate in the induction of antimicrobial-protein expression, such as HBD2, HBD3 and calgranulin, by human skin keratinocytes and bronchial epithelial cells.[25,28] (Figure 2). Furthermore, in mouse tracheal epithelial cells, IL-22 and IL-17 synergistically induce lipocalin-2 expression, and this induction is required for antimicrobial activity against the Gram-negative pathogen Klebsiella pneumonia, the mechanism of synergism between IL-17 and IL-22 is yet to be defined, but may be the result of a convergence of the STAT3 (signal transducer and activator of transcription 3) and NF-κB signalling pathways, which are induced downstream of the IL-22 and IL-17 receptors,respectively.[29] Exactly how IL-22-induced STAT3 signalling converges with the ACT1–PI3K–NF-κB pathway to cooperate with IL-17 in antimicrobial-protein induction is unclear. However, it is possible that this synergy occurs at the level of downstream kinases that have been implicated in both IL-22R and IL-17R signalling, including the mitogen-activated protein kinases and the JUN N-terminal kinases.[30] In the mouse gastrointestinal tract, IL-22 was recently shown to be required for the induction of expression of the C-type lectins regenerating protein 3β (REG3β) and REG3γ following challenge with *Citrobacter rodentium*. Consistent with this, also showed that IL-22-deficient mice are highly susceptible to infection with *C. rodentium* can be rescued from a lethal challenge through the administration of recombinant human or mouse REG3γ. REG3γ is a soluble C-type lectin that is produced by Paneth cells and has direct antimicrobial activity against Gram-positive bacteria by interacting with bacterial peptidoglycan.[31] REG3γ is not known to have direct antimicrobial activity against Gram-negative organisms, although commensal flora can induce its expression. In addition, the study by Zheng et al. suggested that REG3γ has antimicrobial activity (albeit not directly microbicidal) against certain pathogenic Gram-negative bacteria.[29] Pathogenic Gram-positive bacteria, such as Listeria

monocytogenes, can induce REG3γ production in a MyD88- dependent manner, which indicates that TLR or IL-1R signalling might be involved in REG3γ expression and regulation.[31] The effects of IL-22 in this model imply that this cytokine has a role in inflammation, although this remains a controversial issue. A role for IL-22-driven TH17-cell-mediated antimicrobial-protein expression in inflammatory disease is most apparent in the skin. Antimicrobial peptides are highly expressed in the skin of patients with psoriasis.[31] The preferred action of REG3γ against Gram-positive or commensal organisms presents an intriguing possibility: the balance of inflammation and tolerance against a constant presence of bacteria in the gut could be linked to differential cytokine-mediated regulation of antimicrobial proteins.[32] IL-22 strongly induces both the proliferation of keratinocytes and the expression of antimicrobial proteins, such as S100A7. Moreover, neutralization of IL-22 can reduce cutaneous acanthosis (thickening of the skin) in models of psoriasis.[33] A role for TH17 cells in antimicrobial responses is also supported by the finding that patients with mutations in STAT3 that cause Job's syndrome (hyper-IgE syndrome) and increased susceptibility to cutaneous infections with Staphylococcus aureus and *C. albicans* lack antigen-specific Th17 cells in the peripheral blood.[34] Curiously, these patients have an exaggerated Th2-cell-associated hyper-IgEsyndrome.[33-34] In individuals with atopic dermatitis, the Th2-type cytokines IL-4 and IL-13 are highly expressed in the skin.[35] This may explain the frequent occurrence of S. aureus infections in patients with atopic dermatitis. IL-4 and IL-13 can activate STAT6, as well as SOCS1 and SOCS3, which then inhibit both tumour necrosis factor (TNF) and interferon-γ (IFNγ) mediated induction of HBD2, and HBD3 expression by keratinocytes.[36] Further work is required to determine the role of IL-22 (or other activators of STAT3) in Job's syndrome, and whether myeloid-cell or epithelial-cell expression of STAT3 contributes to the clinical phenotype of this syndrome, including the high IgE levels and susceptibility to *S. aureus* and *C. albicans* infections.[37]

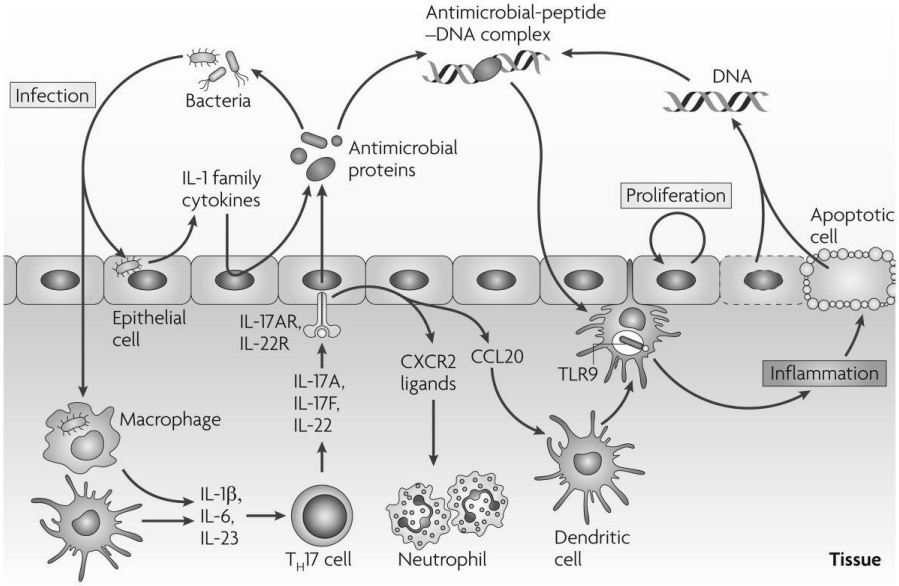

Figure 2: Cytokine networks and antimicrobial peptides at epithelial-cell surfaces

In response to bacterial infection, the interleukin-1 (IL-1) family cytokines, such as IL-1β, potently induce the expression of antimicrobial proteins by the epithelium. IL-1β, together withIL-6 and IL-23, can also induce the differentiation of T helper 17 (TH17) cells, which produceIL-17A, IL-17F and IL-22. These cytokines further induce antimicrobial-protein expression by the epithelium. IL-17A can also induce the production of CC-chemokine ligand 20 (CCL20), which has antimicrobial activity, recruits dendritic cells and increases the production of CXC chemokine receptor 2 (CXCR2) ligands that are important in neutrophil recruitment. This response is beneficial to the host during an acute infection. However, in autoimmune diseases (such as psoriasis) cationic antimicrobial peptides, which are present at high levels, can interact with negatively charged DNA that is released from dying cells (cell death occurs as a result of increased cell turnover during inflammation). Antimicrobial-peptide–DNA complexes can amplify inflammation in the skin by activating Toll-like receptor 9 (TLR9) signalling.

CONCLUTION

There exist so many outstanding questions regarding IL-22 and inflammation. Most in vivo studies have not elucidated IL-22-expressing cell subset which mediates the observed effects. For example, Th17 cells have been shown to be able to provide protection against hepatitis. Other studies have distinguished between innate and adaptive immune system-derived IL-22 by comparing models between immunocompetent mice and mice with deficient adaptive immune responses. Further examination pin-pointing the role of different IL-22-expressing subsets will allow us for better understanding this cytokine. The role of IL-22 not under the inflammatory conditions, but instead during homeostasis needs to be more closely examined. IL-22 is expressed constitutively by LTi-like cells within the small intestine, a tissue that is under the careful immune balance between inflammation and tolerance. Gaining a better understanding of the expression and role of IL-22 in health and disease is important for development of IL-22 as a potential drug target. An increasing number of reports of human- and mouse-based studies have highlighted the fact that IL-22–IL-22R interactions are an integral pathway through which cells of the innate and adaptive immune responses regulate host defence, inflammation and tissue homeostasis at barrier surfaces. Although important advances have been made in understanding the factors that influence the expression, regulation and functions of IL-22 and IL-22R, the development, plasticity and cell-lineage relationships of innate sources of IL-22 in mouse and human diseases remain unclear. In addition, future challenges include defining the context-dependent functions of IL-22 expression in tissue inflammation and repair, including the effect of microbial communities at barrier surfaces and the spatial and temporal co-expression of other pro-inflammatory or regulatory cytokines. Advancing knowledge in these areas will aid in the design of therapeutic treatments targeting the IL-22–IL-22R pathway for the treatment of persistent infections, chronic inflammation and autoimmune diseases.

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