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Lauren A. Zenewicz

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IL-22: There Is a Gap in Our Knowledge

Lauren A. Zenewicz
Department of Microbiology and Immunology, College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104

ABSTRACT
IL-22 is a critical cytokine in modulating tissue responses during inflammation. IL-22 is upregulated in many chronic inflammatory diseases, making IL-22 biology a potentially rewarding therapeutic target. However, this is complicated by the dual-natured role of IL-22 in inflammation, as the cytokine can be protective or inflammatory depending on the disease model. Although scientific interest in IL-22 has increased considerably in the past 10 y, there is still much we do not know about the environmental, cellular, and molecular factors that regulate the production and function of this cytokine. A better understanding of IL-22 biology will allow us to develop new or improved therapeutics for treating chronic inflammatory diseases. In this article, I will highlight some of the outstanding questions in IL-22 biology. ImmunoHorizons, 2018, 2: 198–207.

INTRODUCTION
The cytokine IL-22 was discovered almost 20 years ago through genome analysis and identified because of its predicted structural homology to IL-10 (1, 2). It is one member of a family of cytokines termed IL-10–related cytokines that also includes IL-19, IL-20, IL-24, and IL-26 and was originally called IL-TIF, for IL-10–related T cell–derived inducible factor (3). In addition to different T cell subsets, IL-22 is also produced by group 3 innate lymphocytes (ILC3s). Of the IL-10–related cytokines, IL-22 is the best studied and was first closely examined in the context of skin inflammation, including psoriasis (4). IL-22 was promptly recognized to be upregulated in many chronic inflammatory diseases, including rheumatoid arthritis and inflammatory bowel disease (IBD) (5, 6). These correlative studies associating high cytokine levels in patient cohorts compared with healthy controls suggested that IL-22 is important in many diseases but did not reveal if IL-22 is the cause and/or result of inflammation. Experimental animal models, primarily those involving IL-22– and IL-22R–deficient mice, have elucidated the dual-natured role of IL-22 in inflammation. In some disease models, IL-22 is protective, and in others it contributes to the inflammation (7). Clearly, a better understanding of the function of IL-22, as well as its regulation, is needed for future development of therapeutics that either stimulate or neutralize IL-22 activity with the hopes of modulating the dysregulated immune system to the benefit of the patient.

In addition to patients with psoriasis, IBD, and rheumatoid arthritis, which share cause with the cytokines involved in their pathogenesis (IL-1β, IL-23, and IL-6), IL-22 is upregulated in many other diseases. Patients with systemic lupus erythematosus, multiple sclerosis, myocarditis, atopic dermatitis, asthma, uveitis, and vitiligo have elevated levels of IL-22 in their sera and/or target tissues compared with healthy controls (8, 9). IL-22 also contributes to wound healing in the skin and gastrointestinal (GI) tract (10, 11). In addition to sterile inflammatory diseases, IL-22 is also critical in combatting many infectious diseases. IL-22 has been well studied in bacterial infections, especially those of the GI tract or lungs (12). IL-22...
also has important roles in several viral, fungal, and parasitic infections (13, 14).

IL-22 signals through a heterodimeric receptor consisting of IL-22R and IL-10Rβ (1). IL-22R is not usually expressed by immune cells but is instead constitutively expressed by epithelial cells and can be further upregulated during inflammation (4). Recognition of the cytokine by responsive cells leads to induction of proliferative and antiapoptotic pathways as well as induction of tissue-specific genes. IL-22 is a potent inducer of antimicrobial peptides, including β-defensin, lipocalin-2, RegIIIγ (4, 15, 16), and mucins (17). Through induction of the Bcl family members, IL-22 is thought to protect cells from apoptosis (18). IL-22 has both conserved and unique effects on different cell types in different tissues.

Cytokine-targeted therapies have recently become an integral part of treatment of many chronic inflammatory diseases and for some patients have replaced steroid and other broad immunosuppressive treatments. Biologics and small molecules that target cytokines, such as IL-23, IL-6, and TNF-α, or JAK and STAT inhibitors that can target multiple cytokines have transformed patient care (19). Understanding cytokine biology, including their inhibitors that can target multiple cytokines have transformed patient care (19). Understanding cytokine biology, including their regulation, has been critical for targeting these effector molecules. There is currently no Food and Drug Administration (FDA)–approved drug that directly targets IL-22; however, drugs at different stages in the pipeline (20), and many approved drugs may indirectly modulate IL-22, such as those that target IL-23, IL-1β, and IL-6.

THE GAPS IN OUR KNOWLEDGE

Many research groups have made important contributions to our understanding of IL-22 in health and disease. As this On the Horizon piece is not intended to be a comprehensive examination of the literature, I direct readers to several outstanding reviews on IL-22 (4, 14, 20, 21). In this article, I will discuss particular gaps in our knowledge that are especially important for increasing our understanding of IL-22 biology. These questions and their future answers will allow us to translate IL-22 biology into new or improved therapeutics for chronic inflammatory diseases.

WHAT ARE ALL OF THE CELLULAR SOURCES OF IL-22?

IL-22 was initially found to be produced by CD4 T cells and was considered to be a Th1-associated cytokine (22). With the advent of the identification of Th17 cells, IL-22 was quickly associated with these cells (23). However, IL-22 is regulated differently than other Th17-associated cytokines. Its expression is less dependent on the transcription factor RORγt and more dependent on aryl hydrocarbon receptor (AHR) (24, 25). In addition to AHR as a master regulator for Th22 differentiation, STAT3 is another essential transcription factor for Th22 cells (26). “Th22” is often used as nomenclature for CD4 helper T cells that produce IL-22, and these cells often also produce IL-17 and/or IFN-γ.

The other major cellular source of IL-22 is ILC3s. These rare cells were discovered in part because of their very high production of IL-22 (27). IL-23 and IL-1β are the best-known stimuli that lead to the activation and production of IL-22 as well as other cytokines, such as GM-CSF and IL-17. Identifying other factors that activate ILC3s and the signaling pathways that lead to IL-22 production is an important active area of research. Like CD4 T cells, AHR and STAT3 are essential for IL-22 production in ILC3s (28, 29). Other signaling pathways such as MAPK and Notch also contribute to IL-22 production (30, 31). Studying these other pathways that regulate IL-22 production in these cells should be a priority, as these pathways may be able to be targeted by available therapeutics co-opted from other fields, such as oncology. Ultimately, ancillary regulatory pathways may be more important than those of master regulator transcription factors to moderately modulate IL-22 production and not completely ablate the dual-natured cytokine.

Other cellular sources of IL-22 include most lymphocytes, with the exception of B cells. γδ T cells can be substantial sources of IL-22, especially in the lungs or skin (32). Activated NK cells can produce low levels of IL-22 (33). Lymphoid tissue inducer cells secrete IL-22 (34, 35), and this may have a role in lymphoid tissue formation, although IL-22 is not required for lymph node formation (33, 36, 37). A fate reporter mouse strain has allowed for screening of IL-22 production in immune cells from tissues amenable to dissociation and analysis by FACS (38). These data show, depending on the tissue, that the majority of cells that at one time produced IL-22 are innate lymphocytes, CD4 T cells, or γδ T cells, with IL-22 in the GI tract lamina propria as the site of innate lymphocyte production, the mesenteric lymph nodes as the sites of CD4 T cell production, and the lung and skin as the sites of γδ T cell production. Identification of immune cells other than lymphocytes that produce IL-22 has been complicated. An early study suggested that dendritic cells (DCs) were a source of IL-22 (15); however, more refined analysis, generation of and studies in IL-22 reporter mice, and the discovery of ILC3s have precluded this hypothesis. Neutrophils may produce IL-22 that is protective in the inflamed colon, which is contrary to the usual destructive modus operandi of neutrophil involvement in colitis (39). Future work may identify other cellular sources in very specific cell populations and/or under unique inflammatory conditions.

WHICH SOURCES OF IL-22 ARE FUNCTIONALLY MOST IMPORTANT?

IL-22, as described above, is produced by cells of both the innate and adaptive immune systems. Functionally, both sources have been shown to be important in different inflammatory models. For example, experiments comparing dextran sulfate sodium–mediated colitic injury in Rag1–/– and Il22–/– Rag1–/– mice show that innate IL-22 can provide protection during inflammation (33). Another colonic inflammation model, CD45R+B220high CD4 T cell–mediated colitis, found that adaptive IL-22 was capable of providing protection in the absence of innate IL-22 (33).
Experimental elimination of one cell subset that produces a cytokine often has a more subtle phenotype compared with a cytokine-deficient mouse. This strongly suggests there is redundancy in cytokine source. In general, mice with a complete genetic deletion in IL-22 have greater phenotypes than mice lacking specific subsets of IL-22–expressing cells. For example, the Gram-negative pathogen *Citrobacter rodentium*, which causes an enteropathogenic *Escherichia coli*–like colitis in mice, has served as a useful model for studying IL-22 biology. IL-22–deficient mice are greatly more susceptible to infection compared with control mice (15). Elimination of ILC3s or Th22 cells in this model also results in reduced protection but to a lesser extent (40, 41).

Different cellular sources of cytokines allow for variation in activation of the cells (innate cytokines versus TCR stimulation), the involved tissue, timing (immediate versus delayed), the ability of the cell to traffic (resident versus circulatory), and the amount of the cytokine produced (low versus high levels). This results in resilience to the host when infected, allowing, one hopes, for the best possible outcome. In many different inflammatory and infection models, we still need to identify the critical and/or redundant sources of IL-22.

### HOW IS IL-22 TRANSCRIPTIONALLY REGULATED BEYOND TRANSCRIPTION FACTORS?

In both mice and humans, the gene encoding IL-22 flanks the gene encoding IFN-γ. Although *Ifng* and its regulatory features and promoters have been extensively studied (42, 43), much less is known regarding *Il22* regulation. In CD4 T cells, the *Il22* promoter contains defined STAT3 and AHR binding sites, and these two transcription factors promote *Il22* transcription (26). Furthermore, the transcriptional repressor c-Maf binds to the *Il22* promoter, preventing *Il22* transcription, especially in the presence of TGF-β (44). However, little else is known regarding transcriptional activators or repressors that bind the *Il22* promoter. Promoter analysis has revealed putative binding sites for other transcription factors, such as hypoxia-inducible factor (HIF) 1α (45), and many other factors likely regulate *Il22*. Beyond transcription factors, long noncoding RNAs that regulate IL-22 have yet to be described. A careful and thorough analysis of this region of the chromosome could reveal new signaling pathways, transcription factors, and/or long noncoding RNAs involved in regulation of IL-22. Certainly, differences in regulatory factors may exist between cell subsets, and comparisons should be drawn between different IL-22–expressing cells.

Little is known regarding the potential epigenetic modifications of the *Il22* gene upon activation of CD4 T cells. Other related cytokine genes, such as *Ifng* and *Il17a*, have been shown to undergo methylation and histone modification in activated T cells (46). Regulation in ILC3s may be different from T cells, as they are innate immune cells and rapidly produce cytokines upon activation.

Many gaps exist in our knowledge of potential intrachromosomal and interchromosomal interactions between *Il22* and other genes. The most likely candidates would be other cytokine genes. Potential interactions with *Ifng* may reveal unknown regulatory networks. Interchromosomal interactions may exist with *Il17a*, as it is often coexpressed with *Il22*. Hi-C analysis of Th22 cells or ILC3s may identify interactions between the *Il22* locus and reveal novel genes associated with cellular function. Additionally, in humans, the gene encoding the related IL-10 cytokine family member IL-26 flanks *Il22* and may share regulatory features with IL-22.

### WHAT ARE THE ENVIRONMENTAL FACTORS THAT REGULATE IL-22?

As IL-22 can be protective or inflammatory during inflammation, it is important to understand where and when the cytokine is produced. Environmental signals are key for transmitting information to cells in order for them to respond to their surroundings. This allows immune cells to upregulate or downregulate cytokines and other effector molecules so that they are produced only where and when they are needed. This is essential for the host’s wellbeing, as these factors are potent and can be tissue damaging and detrimental if not properly regulated. Environmental signals include other cytokines, metabolites, and oxygen.

As adaptive immune cells, Th22 cells receive signaling from the TCR complex. However, environmental signals are also key to their differentiation and production of IL-22. Differentiation of Th22 cells is controlled by cytokines, such as IL-1β, IL-6, and IL-23. AHR ligands, which activate the transcription factor AHR, are also key. These AHR ligands include environmental toxins such as dioxin, amino acid derivatives of aromatic amino acids such as tryptophan, and the breakdown products of cruciferous vegetables (25, 47). Hypoxia, or low oxygen, is important for regulating differentiation of T cells and has effects on Th17 cell differentiation (48). My laboratory has further shown that hypoxia is a signal for increased IL-22 production in Th22 cells, and this occurs in part through the transcription factor HIF-1α (45). We have proposed that hypoxia is an exceptional signal to T cells to sense that they are in an inflammatory environment and should produce IL-22.

In ILC3s, the most potent environmental signals to induce IL-22 production are cytokines, mainly IL-23 or IL-1β. TLR2 agonists have been proposed to activate human, but not mouse, ILC3s but only in the presence of certain cytokines (49). AHR ligands also modulate ILC3 development and function, including IL-22 production (28). NK cell–activating receptors, such as NKP44, through recognition of their cognate ligand may activate ILC3s to produce IL-22 (50). There are likely other sensors that are involved in ILC3 activation and IL-22 upregulation that still need to be identified, such as those that potentially regulate cellular stress responses.

Environmental factors are important for regulation of IL-22 in both innate and adaptive immune cells. These external cues allow the cell to produce IL-22 when and where it is needed during inflammation. Failure to properly interpret these signals by the cells, or overabundance of these signals, may lead to the dysregulation of Th22 cells or ILC3s that accompanies chronic...
inflammatory diseases. This is especially important because IL-22 is a dual-natured cytokine, which will be discussed further in this opinion.

HOW IS IL-22 DOWNREGULATED, ESPECIALLY IN ILC3s?

Resolution of inflammation is critical to avoid the development of chronic inflammatory diseases. We know that IL-23 or IL-1β are the most potent activators of ILC3 activation, but less is known on what downregulates cytokine production from activated ILC3s. Recently, the β2-adrenergic receptor (β2AR) was shown to downregulate activation of related ILC2s (51). There may be environmental factors that regulate specific signaling pathways that result in reduced If22 expression. One potential negative regulator is c-Maf, which downregulates If22 expression in T cells (44). Another candidate is SOCS3, which is a potent downregulator of STAT3 activation. A second and not mutually exclusive hypothesis is that IL-22 production is downregulated not by the cell but by elimination of the IL-22-producing cell by undergoing cell death. Understanding how ILC3s cease the elevated IL-22 production that accompanies activation is important for better understanding the resolution of inflammation.

HOW DO TARGET CELLS RESPOND TO IL-22?

In target cells, such as epithelial cells, recognition of IL-22 by the IL-22 receptor complex (IL-22R and IL-10Rβ) leads to activation of the transcription factor STAT3, which translocates to the nucleus and binds and promotes the transcription of selective genes. Other signaling pathways also become activated in different cell types—including STAT1, Akt, and various MAPKs (18)—and may fine tune this response, as the contribution of each of these ancillary pathways has not been fully examined. Genes upregulated by IL-22 signaling include mucins, antimicrobial peptides, antiapoptotic proteins, serum amyloid A, LPS binding protein, and fibrinogen. Much focus has been on effects of IL-22 in the GI tract, and the cytokine was recently shown to modulate fucosylation and tight junctions (52, 53).

Some IL-22 target genes have been identified by speculation and others through unbiased approaches such as microarrays and RNA sequencing. For example, lipocalin-2 was identified by complementary gene expression profiling using an in vitro cell line and an in vivo rhesus macaque infection model (16). The IL-22–regulated genes that have been identified through these means tend to be highly regulated by IL-22 and increase upwards of 10- to 100-fold after IL-22 stimulation. Many interesting and/or important genes may be regulated by IL-22 but have been unnoticed, as they are not highly upregulated. In contrast, genes that are potentially downregulated by IL-22 have garnered little attention. There may be interesting target genes that are suppressed by IL-22 during inflammation that would be important in the design of therapeutics.

A few studies have examined how environmental factors influence cellular responses to IL-22. IL-22R expression is upregulated by IFN-γ (4), which may enhance responses to IL-22 during inflammation. In other circumstances, cells may downmodulate their response to IL-22. My laboratory has shown that under hypoxic conditions, hepatocytes do not respond to IL-22 as well as under normal oxygen levels (54). STAT3 phosphorylation is reduced, and this leads to reduced expression of target genes, which may allow hypoxic, chronically inflamed tissues to downregulate their response to IL-22, as chronic IL-22 signaling may be detrimental to the host. Studies have also examined how IL-22 may synergize with other cytokines, especially IL-17 and/or IFN-γ, to modulate target cell function (55, 56). Other data show that same cytokine, IL-17, can antagonize IL-22 function (57). This suggests that IL-22 function may be unique in each inflammatory milieu. Further investigation is needed, as IL-22 may synergize and coordinate expression with many other cytokines and inflammatory mediators, such as PGs or resolvins.

HOW IS IL-22R EXPRESSION REGULATED?

In addition to studying IL-22 downstream signaling in different target cells, IL-22R expression itself is poorly understood. IL-22R is mainly limited to nonhematopoietic cells, allowing for directional signaling from immune cells to tissues. This includes cells from many types of tissues, including epithelial cells (e.g., keratinocytes, hepatocytes) as well as fibroblasts and intestinal stem cells within the GI tract (4, 10, 18).

Although in healthy humans IL-22R is limited to non-hematopoietic cells, it can become dysregulated in disease. In several instances, IL-22R has been found on the surface of immune cells. In autoimmunity, IL-22R has been found to be expressed on myeloid cells in primary Sjögren patients (58). IL-22R has also been found to be expressed on the surface of a lymphoma, and the cells showed high levels of phosphorylated STAT3 (59, 60). Forced expression of IL-22R on Jurkat cells allows the T cells to undergo more rapid proliferation and have constitutive STAT3 phosphorylation, suggesting that aberrant expression of IL-22R on T cells may be one trigger in the complicated pathways to cellular transformation. More careful examination of the factors controlling IL-22R expression and the events that lead to its aberrant expression will allow us to potentially modulate responses to IL-22.

HOW DOES IL-22 BINDING PROTEIN REGULATE IL-22 BIOLOGY?

Another layer of regulation of IL-22 biology is through the secreted factor IL-22 binding protein (IL-22BP). IL-22BP is an IL-22R homolog encoded by its own gene, and the secreted protein binds to IL-22 with greater affinity than the receptor (61, 62). Three isoforms generated by alternative splicing exist in humans, and they have different inhibitory activities and expression patterns, but only one isoform is known in mice (63). In mice, IL-22BP is
expressed in CD11c+ CD8– DCs in the subepithelial dome of the Peyer’s patches (64). There it blocks IL-22 signaling through the follicle-associated epithelium (FAE), allowing for reduced expression of mucin and antimicrobial peptides at a key Ag sampling locale. In DCs, IL-22BP is upregulated by retinoic acid (65) and downregulated by IL-18, inflammasome activation, or PGE₂ (66, 67). This makes IL-22BP a scientifically interesting protein, as the majority of proteins studied in DC biology are upregulated, not downregulated, upon inflammation. In addition to DCs, IL-22BP was also recently shown to be expressed by both mouse and human pathogenic T cells (68).

Functional studies using IL-22BP–deficient rodents have shown a protective role for IL-22BP in ischemia reperfusion and acetaminophen-induced liver injury (69). In rats, deficiency of IL-22BP led to exacerbated skin disease in a psoriasis model that was associated with increased IL-22 and antimicrobial peptides (70). IL-22BP has been proposed to have therapeutic potential. Administration of rIL-22BP during bacterial sepsis can provide protection (71). Potentially designing rIL-22BP with greater affinity, stability, and/or targeting to specific tissues could be used to alleviate inflammation associated with chronic inflammatory diseases in which IL-22 is known to be inflammatory. IL-22BP is a vastly understudied aspect of IL-22 biology, in part because there are few commercially available reagents, and those that do exist are difficult to authenticate. Development of better tools, including Abs to distinguish between free and complexed IL-22 and IL-22BP, will be of much use for future investigations.

WHAT RELATIONSHIPS EXIST BETWEEN IL-22 AND THE MICROBIOTA?

The microbiota strongly controls the proper development of all immune tissues but has the largest impact on the mucosal immune system (72, 73). Production of IL-22 in the GI tract is dependent on signals induced by the microbiota. Germ-free mice lack IL-22 production, and in contrast, IL-22BP production is not affected when compared with levels in control mice with microbiota (64, 74). Clostridia colonization of antibiotic-treated neonatal mice induces IL-22 and aids in regulation of food allergen access to the bloodstream, reducing the development of food allergies (75).

In addition to the effects of the microbiota on IL-22 production, IL-22 in turn influences the microbiota. The ability of IL-22 to regulate mucins, antimicrobial peptides, fucosylation, and more in the GI tract suggests that the cytokine may have indirect effects on the composition and localization of commensal bacteria. Mice genetically deficient in IL-22 have altered flora, which in part contributes to their exacerbated disease in a dextran sulfate sodium–mediated colitis model (76). This dysbiotic flora is transmissible to wild-type mice and exacerbates colitis in these hosts as well. Through 16S rRNA sequencing, many genera were found increased in the IL-22–deficient mice, and we still need to identify the species or species complex that mediates this disease. IL-22 also plays a role in preventing dissemination of Alcaligenes bacterial species from the GI tract to the liver (77). A similar phenotype is also observed during Clostridium difficile infection, in which mice deficient in IL-22 have greater amounts of pathobiont commensals translocating from the GI tract to peripheral tissues because of the intestinal damage associated with infection (78).

Many questions remain to be answered to further define the interactions between IL-22 and the microbiota. Further exploration of the GI tract interface (as well as other tissues), studies neutralizing IL-22 at specific times and locations, and human studies including patients on different cytokine-targeting therapeutics will be important in furthering our understanding of this research area.

HOW IS IL-22 BOTH PROTECTIVE AND INFLAMMATORY, DEPENDING ON THE INFLAMMATORY CONTEXT?

The dual nature of IL-22 has been well described in a plethora of experimental animal disease models. In some inflammatory settings IL-22 is pathogenic, and in others it is protective (7). Many factors may contribute to why the cytokine is dual natured. A first thought is that the target tissue dictates the function of IL-22. In skin, IL-22 was first shown to be inflammatory (79), and in tissues such as the liver and GI tract, IL-22 was found to be protective (18, 33, 80). However, several studies have shown a pathogenic role for IL-22 in the GI tract (81, 82).

I propose that, in general, in acute settings of inflammation IL-22 is protective, and in more chronic settings IL-22 is pathogenic. Fundamentally, the same functions of IL-22 that help protect in acute events may be detrimental in chronic inflammation. In acute infection, in the short term, IL-22’s ability to drive proliferation, inhibit apoptosis, and increase mucin and antimicrobial peptide production is to the immediate benefit of the host. In chronic infection, increased proliferation and less apoptosis can lead to hyperplasia. Supporting this, transgenic mice with constitutive expression of IL-22 from an albumin promoter have increased skin thickness (83), and a mouse model of colitis that features hyperplasia is dependent on IL-22 (56). There are, of course, exceptions to this generalization, but this hypothesis is supported by many experimental disease models in which the role of IL-22 has been investigated using gene-deficient mice or Ab neutralization.

Many factors may be important for how IL-22 is protective versus inflammatory, and elucidating them should be of high priority. Differential regulation of IL-22 production by different immune cells in different inflammatory contexts may be important for modulating responses to IL-22. In addition to the levels of IL-22, IL-22BP levels also modulate responses to IL-22, and this has been best shown in vivo in the FAE, where DCs produce high quantities of IL-22BP (64). Understanding how IL-22 and IL-22BP are regulated under immune homeostasis and inflammatory environments is important for understanding IL-22 biology and how the host responds to the cytokine.

From the other side of this cytokine interaction, the responding cell also directs the response to IL-22. The levels of IL-22 in the microenvironment, other cytokines and their levels in the
inflammatory milieu, and other inflammatory mediators such as reactive oxygen species may dictate their response. Differences in the responding cells themselves may also modulate the effects of IL-22. For example, some tissues, such as that of the GI tract, have many different types of IL-22-responsive cells. In addition to epithelial cells, there are epithelial stem cells, Paneth cells, and goblet cells. FAE cells have reduced expression of IL-22R and reduced responses to IL-22, which may reduce inflammatory signals to the Peyer’s patches (64). There are many unanswered questions. Do cells respond differently to IL-22 after repeated exposure to the cytokine? Are there changes in IL-22R levels or downstream signaling pathways? This would be significant in chronic inflammatory settings in which IL-22 tends to be pathogenic.

Determining the triggers that modulate the role of IL-22 inflammation is essential. If we lack understanding of the effects of IL-22 in an inflammatory situation, we do not know if we should inhibit or enhance the cytokine. These data will also give us insight into potential undesirable effects of therapeutics targeting IL-22 biology.

**HOW MUCH IL-22 IS BIOACTIVE IN A HEALTHY INDIVIDUAL?**

As the only place IL-22 is produced in detectable quantities in healthy individuals is the GI tract (38), and because we also produce high levels of IL-22BP in our GI tract, it is likely that in healthy people most IL-22 is not biologically active, as it is bound by IL-22BP. However, “healthy people” may not be as broad a group as we first think. Low-grade inflammation, such as that which accompanies obesity, may lead to elevated levels of IL-22 (84). This may be juxtaposed by slightly reduced levels of IL-22BP, again due to low-grade inflammation, and in turn effectively raise the level of bioactive IL-22. This low level of IL-22 production may adversely affect the health of many tissues, especially those within the GI tract. Studies are needed to more accurately quantitate the levels of bioactive IL-22 within sera, lymph, and different tissues. This measure may be a more accurate reflection of the immune status of an individual than measuring levels of IL-22 in sera.

**IS IL-22 A VIABLE THERAPEUTIC TARGET?**

No therapeutics directly targeting IL-22 have yet received FDA approval. Potentially, Abs neutralizing IL-22 or rIL-22BP would be the most efficient treatments to develop to inhibit IL-22 activity as opposed to development of small molecule inhibitors that reduce IL-22 production. A recent clinical trial (phase 2a) showed efficacy of an IL-22–neutralizing Ab, fezakinumab (ILV-094), in patients with moderate to severe atopic dermatitis (85). The drug was
found to be well tolerated and efficacious. The only reported adverse effects were several viral upper respiratory tract infections. Patients treated with anti–IL-22 therapeutics may also have increased susceptibility to fungal infections, as suggested by autoimmune polyendocrine syndrome type I patients. These patients generate autoantibodies against IL-22, resulting in a significant decrease in IL-22 in circulation, often leading to chronic mucocutaneous Candida infections (86). Future trials will need to evaluate not only increased susceptibility to certain mucosal pathogens but also if IL-22 Ab treatment modulates commensal bacteria. Mice deficient in IL-22 have altered flora, which contributes to their exacerbated colitis and is transmissible to healthy mice (76).

Several FDA-approved drugs for chronic inflammatory diseases target cytokines that regulate IL-22 expression, including IL-1β, IL-6, IL-23, and TNF-α (19). How these small molecule inhibitors or Abs may modulate IL-22 is not well studied. For example, ustekinumab targets the p40 subunit shared by IL-12 and IL-23 and is approved for use in psoriasis and IBD patients. Limited studies have shown that it is effective in reducing IL-22 levels in psoriasis patients (87), and clearly more comprehensive studies are needed to fully evaluate the modulation of upstream signaling on IL-22 levels in patients with many different chronic inflammatory diseases. There is also the potential that perturbation of IL-22 during treatment may be an unwanted side effect, as IL-22 is proposed to be beneficial and not always inflammatory in nature.

Most IL-22–based therapeutics under development target inhibition of IL-22 production and/or activity. However, there is some research interest in enhancing IL-22 levels to combat inflammation. Recombinant IL-22 molecules with various modifications to increase in vivo stability are in the process of being developed (88, 89). Genentech has an IL-22–Fc molecule (UTRI147A) under phase 1 trials with the eventual strategy for short-term use in active IBD patients (90). Probiotic Lactobacillus-expressing IL-22 has been proposed to benefit graft-versus-host disease patients (91). These research directions are still in early stages, and much needs to be done to translate these studies from the laboratory to the clinic.

**IS IL-22 RELEVANT TO VACCINOLOGY?**

Few studies have examined the role of IL-22 in memory CD4 T cell responses. This is an area of potential discovery and innovation, as IL-22 provides protection against infection to many diverse bacterial pathogens in the lung or GI tract. Enhancing IL-22 responses may be instrumental in designing more effective mucosal vaccines. Many vaccines have the potential to induce a memory CD4 T cell response that includes the capacity to produce IL-22. However, IL-22 is not routinely included in cytokine panels that are used as correlates of protection. Inclusion of IL-22 for evaluation of mucosal vaccines may aid in their development. In contrast, neutralizing or limiting IL-22 responses at the time of mucosal vaccination may enhance the generation of T cell responses through increased barrier permeability and enhanced Ag presentation (92). Thus, the gap in knowledge regarding IL-22 biology in vaccine development is an area of potential high rewards for current and future investigations.

**CONCLUSIONS**

IL-22 is a remarkable mediator of signaling from immune cells to tissues during inflammation and infection. Contributions from many facets of immunology and microbiology have provided insight into this cytokine. We have learned much about IL-22, especially in the last 10 years, but many gaps in our knowledge remain (Fig. 1). As is often said, as we learn more, we know less. Research into the function of IL-22 biology in different contexts of inflammation or infection and investigation into the regulatory networks that control the cytokine’s expression are two major areas of importance. Further insight into IL-22 biology will unquestionably lead to a better understanding of many chronic inflammatory diseases and potential therapeutics for targeting the cytokine.

**DISCLOSURES**

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**REFERENCES**


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