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Distinct roles of IL-22 in human psoriasis and inflammatory bowel disease

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ABSTRACT

IL-22, an IL-10 family cytokine, is produced by different leukocyte subsets, including T cells, NK cells and lymphoid tissue inducer (LTi) cells. IL-22 mediates the crosstalk between leukocytes and tissue epithelia because its receptor is preferentially expressed on various tissue epithelial cells. IL-22 is essential for host defense against infections of extracellular pathogens, such as bacteria and yeasts, by eliciting various innate defensive mechanisms from tissue epithelial cells and promoting wound-healing responses. In autoimmune diseases, however, diverse tissue microenvironments and underlying pathogenic mechanisms may result in opposing contributions of IL-22 in disease progression. For example, in psoriasis, IL-22 can synergize with other proinflammatory cytokines to induce many of the pathogenic phenotypes from keratinocytes and exacerbate disease progression. In contrast, IL-22 plays a beneficial role in IBD by enhancing barrier integrity and epithelial innate immunity of intestinal tract.
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1. Introduction

1.1. IL-22 and IL-22 receptor

IL-22 was originally cloned by Renauld and colleagues from murine lymphoma cell line treated with IL-9 [1]. Because it shares sequence homology with IL-10, they named this cytokine as IL-10 related T cell-derived inducible factor (IL-TIF) [1], which was subsequently renamed as IL-22 [2]. Human IL-22 cDNA encodes a protein with 179 amino acids and share 23% sequence homology with human IL-10 gene [2]. Interestingly, structure analyses indicate that IL-22 does not form domain swapped dimer as that of IL-10 [3]. But its structure displays the characteristic α-helical fold consisting of six helices labeled A to F and connecting loops, which is shared by all Class II cytokines [4,5]. Despite the structural differences between IL-22 and IL-10, these two cytokines share a common receptor subunit, IL-10R2 chain [2]. In addition, IL-22 and IL-10 require their own unique receptors, IL-22R1 and IL10R1, respectively, together with IL-10R2, to deliver the downstream signaling. IL-22R1, like IL-10R1 and IL-10R2, belongs to Class II cytokine receptor family [6,7].

Upon binding to the heterodimeric receptor complex, IL-22R1 and IL-10R2, IL-22 activates the Jak1 and Tyk2 [8], which further phosphorylate downstream Stat molecules, Stat1, Stat3, and Stat5 [2,8]. Similar to other IL-10 family cytokines, IL-22 predominately utilizes Stat3 to mediate its functions. Interestingly, there is a unique domain located at the c-terminal of IL-22R1 intracellular tail, which can recruit Stat3, through the interaction of the coiled-coil domain of Stat3, to the receptor independent of 8 tyrosine residues in the receptor [9]. The biological importance of this novel mechanism of Stat3 recruitment is still unclear. In addition to IL-22R1, there is also a decoy receptor, referred as IL-22BP or IL-22R2, which is structurally homologous to the extracellular domain of IL-22R1 but without the transmembrane and intracellular domains. IL-22BP binds IL-22 with high affinity and can block the binding of IL-22 to IL-22R1 [10–12].

1.2. Cellular sources and targets of IL-22

The early work by Renauld and colleagues has suggested that IL-22 is a cytokine produced by T cells [1]. They showed that IL-22 is detected from IL-9 treated T helper cell line, TS2, and from concanavalin A (ConA) stimulated mouse splenocytes, presumably mainly consisting of activated T cells. These results further confirmed by Wolk and colleagues by demonstrating that activated mouse T cells, especially Th1 cells, preferentially express IL-22 [13]. In 2005, a novel T helper subset, Th17, was identified [14,15]. These cells preferentially express IL-17 (or IL-17A), a signature cytokine distinguishing these cells from other T helper subsets, including Th1, Th2 and Treg cells. Th17 cells play essential roles in host defense against infections by various pathogens, especially extracellular bacteria, and participate in the pathogenesis of many autoimmune diseases [16]. It was soon discovered that IL-22 is another cytokine preferentially expressed by Th17 cells [17–19]. The level of IL-22 produced by Th17 cells is much higher than that produced by Th1 cells or undifferentiated Th0 cells. But the regulation of IL-22 and IL-17 produced in T cells is not parallel. IL-6 and TGF-β are both required for IL-17 induction from naïve T cells, whereas IL-6 alone is sufficient to promote the expression of IL-22

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[18,20,21]. In fact, TGF-β inhibits IL-22 production in a dose dependent manner [18]. In addition to CD4 T cells, CD8 T cells, γδ T cells, and NKT cells also express high level of IL-22 upon activation, especially in conjunction with IL-23 treatment [18,22]. NK cells treated with IL-2 and IL-12 also express IL-22 [13]. Recently, lymphoid tissue induce (LTi) cells and developmental related NK like cells (NK22), which express NK marker NKp46, were demonstrated to be the major innate sources of IL-22, especially in the intestine [23–27]. Finally, subsets of myeloid cells express IL-23R and response to IL-23 treatment to produce lower level of IL-22 [18,28–30].

The IL-22 expressing human leukocytes are similar to those in mouse. Human T cells activated by anti-CD3 or ConA produce IL-22 [2]. Human Th17 cells generated in vitro or purified ex vivo from blood, based on lineage marker CCR6 and CCR4, preferentially express IL-22 [31,32]. CD161 is another surface marker that defines IL-17 and IL-22 expressing cells in human PBMC [33]. In addition to Th17 cells, CD161+ human CD8+ cells can also produce IL-22 as well as IL-17 [34]. Recently, a unique IL-22 producing CD4+ T helper subset, which express neither IL-17 nor IFN-γ, has been identified in human blood [35–37]. These cells express CCR10 and preferentially home to skin. Similar to what has been reported in the mouse system, these IL-22 producing human T cells can be generated from naïve CD4+ T cells in the presence of IL-6, but not TGF-β [18,35]. Interestingly, human Langerhans cells are able to differentiate T cells into the IL-22 only producing T helper phenotype in vitro [38]. Finally, innate human immune cell types such as NK cells and LTi cells are also produce IL-22 [39,40]. Human immature NK cells defined as CD161+CD117+CD34−CD94− express aryl hydrocarbon receptor (AHR) and IL-22 [41]. The murine equivalent NKp46+ NK like cells are developmentally linked to lymphoid tissue inducer cells [23,42,43]. These cells produce high level of IL-22 and may be the main sources of IL-22 in mucosal immunity.

Contrary to its production from leukocytes, IL-22 targets mainly tissue epithelial cells but not immune cells [44]. While IL-10R2 is ubiquitously expressed, IL-22R1 is restrictedly detected on cells with epithelial origins. Upon binding to its receptors on epithelial cells, IL-22 promotes cell proliferation and differentiation, and induces genes involved in host defense and wound-healing responses [16,45]. These cellular functions of IL-22 endow its essential role in epithelial defense mechanisms, especially against extracellular bacteria. Indeed, studies in preclinical models have demonstrated indispensible functions of IL-22 in mucosal immune responses to Gram-bacteria such as *Klebsiena pneumonia* and *Citrobacter rodentium* [28,46]. In addition, IL-22 is involved in the development of many human autoimmune diseases [16]. IL-22 expression is upregulated in autoimmune diseases, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis. However, in autoimmune diseases, IL-22 can exert both protective and pathogenic functions. This review discusses the potential mechanisms underlying the distinct functions of IL-22 in psoriasis and IBD.

2. Pathogenic functions of IL-22 in psoriasis

Psoriasis is a common chronic inflammatory skin disease [47,48]. Psoriasis vulgaris is the predominant form of psoriasis, featured as erythematous and raised plaque scattered with silvery scales. Histologically, psoriatic skin is manifested as thickening of epidermis (acanthosis) with elongation of rete ridges. Keratinocytes in epidermis are hyperproliferative and associated with prematuration and incomplete cornification in the stratum corneum (parakeratosis). In addition, there is vascular elongation and dilation as well as significant leukocytes infiltration in both the dermis and epidermis of the skin lesions. Although, historically psoriasis has been primarily considered as keratinocytes disorder, evidence from clinic, human genetics, and preclinical models has strongly supported a central role of the immune system in the pathogenesis of psoriasis [48,49]. It has been proposed that various cytokines from infiltrating leukocytes orchestrate the development of psoriasis.

What molecular links mediate the crosstalks between the infiltration of leukocytes and the abnormities of keratinocytes in psoriatic skin is one of the important questions underlying the pathogenesis of psoriasis. Progress in the past several years has identified IL-22 as one of the key mediators that regulates many of the important pathogenic features of epidermis in psoriatic skin [50]. As discussed in detail later, IL-22 is augmented in psoriatic skin and targets epidermal keratinocytes that express IL-22 receptor complex. The expression of IL-22 from leukocytes in psoriatic skin is directly regulated by IL-23, whose indispensible role in psoriasis has been proven by clinic data with therapeutics blocking IL-23 pathway and by genome-wide genetic association data [51,52]. Finally, IL-22 induces hyperplasia, abnormal differentiation, and the expression of many psoriatic marker genes such as psoriasin (S100A7) from keratinocytes [53,54].

Elevated expression of IL-22 mRNA has been found in lesional skin [44]. Consistently, there is also increased IL-22 protein detected in the serum samples from psoriasis patients [55]. Recently, studies have indicated that T cells might be the major sources of IL-22 in psoriasis [56,57]. Leukocytes infiltrating the psoriatic skin consist of T cells, dendritic cells (DCs), and macrophages in the dermis as well as neutrophils and some T cells, mainly CD8+ T cells, in the epidermis [47,48]. Although myeloid cells and neutrophils play essential roles in the pathophysiology in psoriasis, several lines of evidence support T cells as central players during the progression of the diseases [49]. First, the only consistently identified genetic locus, PSORS1, is the MHC locus residing on chromosome 6p21, although the potential antigens in psoriasis triggering T cells activation in skin lesions are still unclear [47]. Activated $CD4^+$ and $CD8^+$ T cells have been identified in psoriatic plaques and blood of psoriatic patients [58]. Second, in models using xenograft transplantation where uninvolved skin from psoriatic patients are grafted to severe combined immunodeficient (SCID) mice, injection of T cells from the donors into these mice is required for the development of psoriatic lesions. More specially, $CD4^+$ T cell, but not $CD8^+$ T cells are necessary and sufficient to induce the psoriatic phenotypes of the skin grafts. Finally, therapeutics that specifically target T cells, such as cyclosporine, tacrolimus, or antibodies targeting CD3 or CD4, resulted in clinical improvement of psoriasis, at least in some patients [59].

It has been proposed that psoriasis is a 'type 1' disease since both $CD4^+$ and $CD8^+$ T cells in psoriatic skin demonstrated IFN-γ expressing Th1 and Tc1 phenotypes, respectively [58]. The discovery of the IL-17 producing Th17 subset prompted people to investigate the association of Th17 cells with psoriasis [60]. Indeed, Th17 cells and downstream cytokine, IL-17, are also elevated in the lesional psoriatic skin [57,61]. As we discussed above, both Th1 and Th17 cells are potential sources of IL-22. CD8 cells from inflamed psoriatic skin also produce IL-22, in addition to other Th1/Th17 cytokines such as IFN-γ, TNF-α, IL-17, and IL-21 [62]. Recently, IL-22 but not IL-17 producing T helper cells have also been identified in psoriatic skin samples. These IL-22 producing cells express skin homing chemokines receptor CCR10 [35,36]. Finally, it is currently unclear whether innate immune cells such as NK cells contribute to IL-22 expression in psoriatic skin, although these cells are known sources of IL-22.

Keratinocytes are the major downstream targets of IL-22 in the skin [53,54,63]. Many of the downstream phenotypes induced by IL-22 from keratinocytes are also observed in epidermal

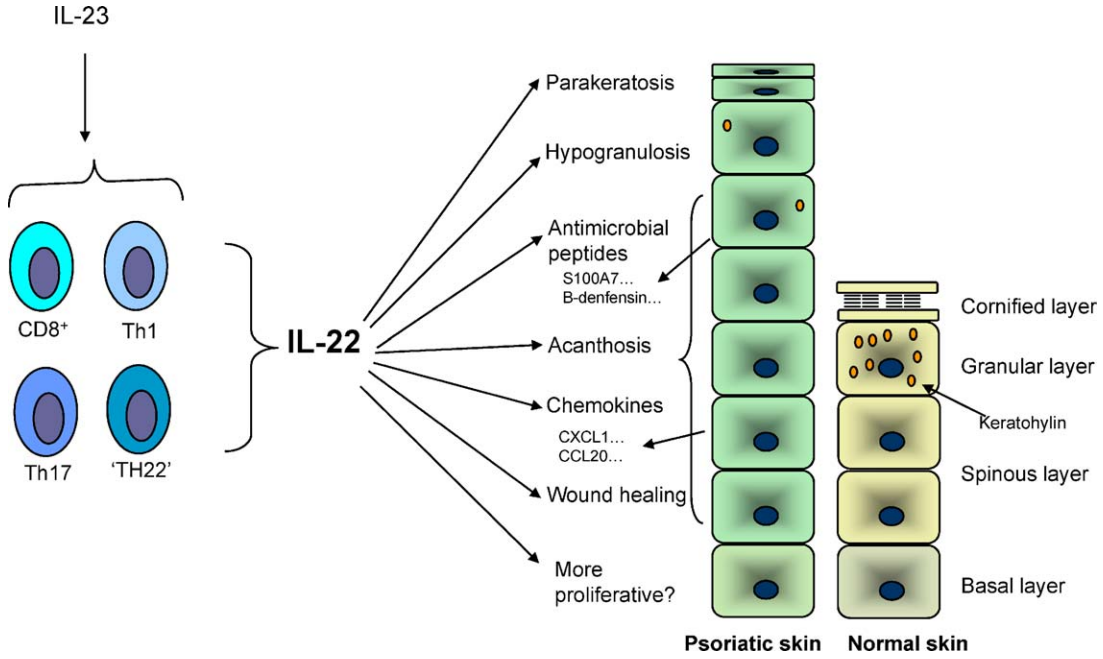

Fig. 1. Pathogenic role of IL-22 in psoriasis. In psoriasis, IL-23 promotes the production of IL-22 from various T cell subsets, including Th1, Th17, Th22, as well as CD8 T cells. IL-22 induces many histological features of psoriasis in the epidermis, such as acanthosis, hypogranulosis, and parakeratosis. In addition, IL-22 also stimulates the expression of antimicrobial peptides, chemokines, and proteins involved in wound healing.

keratinocytes from lesional psoriatic skin. For example, in cultured reconstituted human epidermis (RHE), IL-22 induces prolonged Stat3 activation, which is readily detectable in involved psoriatic epidermis [53,64]. In vitro, IL-22 treatment results in pronounced proliferation and altered differentiation process of the cultured epidermal keratinocytes, resembling acanthosis of psoriatic skin [53,54]. Normal epidermis contains four major keratinocyte layers, basal layer, spinous layer, granular layer, and cornified layer (Fig. 1) [47]. In cultured epidermis, IL-22 enhances the proliferative capacity of epidermal keratinocytes, leading to increase overall thickness of the RHE [53,54]. Similar to what observed in psoriatic epidermis, there is an increase of total spinous layers when RHE is treated with IL-22. Interestingly, IL-22 treatment also resulted in the loss of granular layer (hypogranulosis), which is characterized with cytoplasmic keratohyalin granules, in the RHE. Hypogranulosis is a key histological feature of psoriatic skin. Finally, IL-22 endows the development of parakeratosis, another histological feature of psoriatic skin, in the cornified layer in culture [65].

In addition to these cellular changes, IL-22 induces the expression of many genes that involved in innate host defense, inflammatory response, wound healing, re-epithelialization and differentiation from RHE [53,54,63]. For examples, IL-22 regulates the expression of many antimicrobial peptides such as S100 family proteins (e.g., S100A7, S100A8) and β-defensin family proteins. In addition, it induces chemokines including IL-8, CXCL1, CXCL7 and CCL20 from keratinocytes. IL-22 also promotes the expression of autocrine growth factors, such as IL-20 and HB-EGF, from these cells [53,66]. Finally, many genes, including kallikrein subgroup of serine proteases and serpin family of protease inhibitors, induced by IL-22, may participate in wound healing and tissue repairing.

In the pathogenesis of psoriasis, many other cytokines are also upregulated [48,49]. Many downstream effects and genes induced by IL-22 from keratinocytes can be regulated by other cytokines [53]. It is relatively easy to differentiate the functions of IL-22 from those factors that regulate only inflammation or epithelial homeostasis. For instance, IL-1β and TNF-α can induce the expression of many of the same antimicrobial peptides and chemokines. But these two cytokines do not promote kerotinocyte hyperplasia and differentiation. On the other hand, EGF and TGF-α are strong stimuli for the proliferation of keratinocytes, whereas both of them do not induce hypogranulosis, persistent Stat3 activation, and the expression of many antimicrobial peptides, such as S100A7 [53]. In fact, the overall gene signatures regulated by EGF and TGF-α are negatively correlated with genes altered in psoriatic skin, while genes regulated by IL-22 are strongly correlative [53].

Nevertheless, the overall functions of IL-22 on keratinocytes are shared by other Stat3-activating cytokines, including proteins in its own family, IL-19, IL-20 and IL-24, as well as Oncostatin M (OSM) and IL-6 [53,67]. All these cytokines are upregulated in psoriatic skin. One feature makes IL-22 unique among these cytokines is its tight association with IL-23 pathway. IL-23 is a heterodimeric cytokine composed of its unique p19 subunit and the p40 subunit, which is shared with IL-12 [68]. IL-23 signals through IL-23R chain and IL-12Rβ1 chain that are expressed primarily on various leukocyte subsets. IL-23 is upregulated in psoriatic skin and plays an indispensible pathogenic role in the development of psoriasis [69,70]. Genome-wide association studies have linked both *Il23R* and *Il12B* (encoded p40) genes to psoriasis [51]. In preclinical mouse models, overexpression of IL-23 or injection of IL-23 into the skin leads to the development of inflammatory skin phenotypes bearing some features of human psoriatic skin [18,71,72]. Most importantly, anti-p40 antibodies, which neutralizes both IL-12 and IL-23, in clinic have generated great efficacy in the treatment of psoriasis [52]. We have shown that IL-23 treatment in vitro can induce IL-22 production from many different leukocytes [18]. Furthermore, in multiple in vivo models, the induction of IL-22 is compromised in mice deficient of IL-23, suggesting that IL-22 is one of the direct downstream effector cytokines of IL-23 [28,46,73]. In preclinical psoriatic models such as the $CD45Rb^{hi}$ T cell transfer model of psoriasis, blocking IL-22 or IL-23 results in similar efficacy in ameliorating the skin symptoms [74]. IL-23 triggered skin inflammation and keratinocytes hyperplasia is reduced in IL-22 deficient mice or in WT mice treated with anti-IL-22 antibody, again supporting IL-22 as a direct downstream mediator of IL-23 pathway

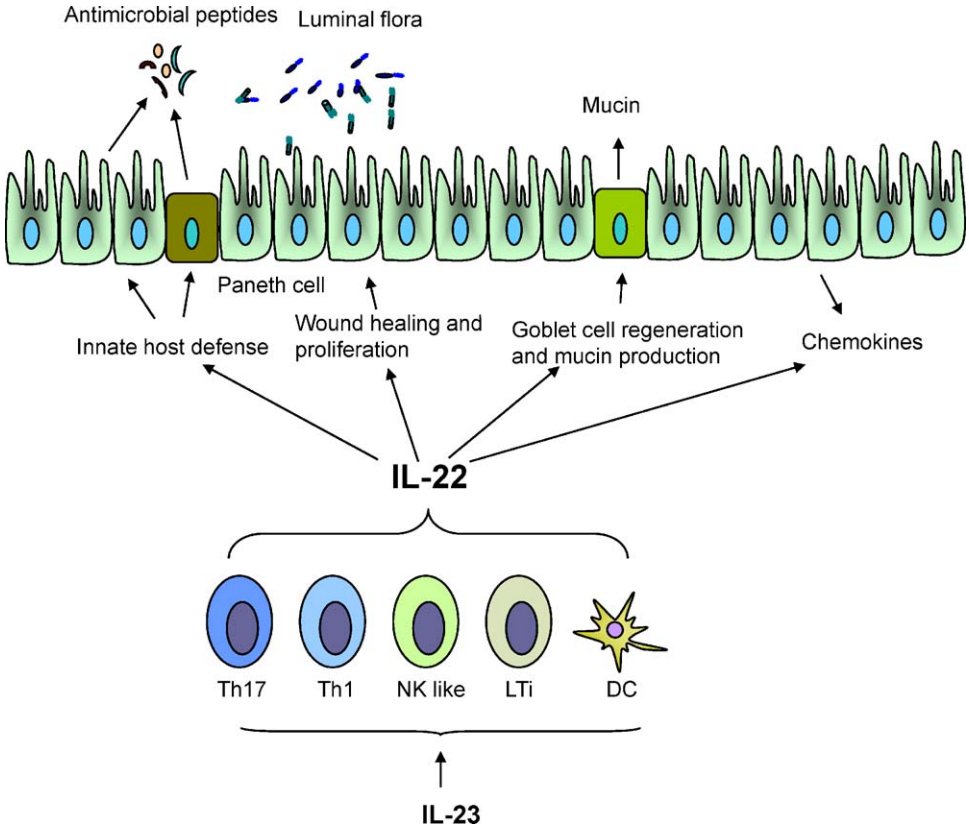

Fig. 2. Protective function of IL-22 in IBD. In the intestine, both innate and adaptive immune cells are capable in making IL-22 in responding to the stimulation of IL-23. NK like cells and LTi cells are the major innate sources of IL-22. IL-22 induces the expression of various antimicrobial peptides from intestinal epithelial cells. IL-22 also helps the regeneration of goblet cells and the production of mucin proteins. In addition, IL-22 promotes the wound healing responses and help to restore the integrity of the epithelial layer.

in psoriasis [18]. Taken together, IL-22 mediates the crosstalk between leukocytes and keratinocytes in psoriasis.

In spite of its functional importance, IL-22 is probably not sufficient in triggering psoriasis by itself. IL-22 primarily targets epithelial cells and is not able to profoundly amplify and sustain the inflammatory responses in disease [44]. The first evidence linking IL-20 subfamily cytokines including IL-22 to psoriasis came from the phenotypes observed in IL-20 transgenic mice [75]. These mice die soon after birth with skin phenotypes similar to psoriatic skin. The infiltration of leukocytes, especially T cells, however, is not prominently observed in the affected skin. Similar phenotypes have also been observed in IL-22 transgenic mice, which suggest IL-22 alone is not sufficient in initiation and amplification of inflammation [76]. In fact, in many other tissues, the role of IL-22 in tissue protection and in innate host defense helps to dampen the inflammatory responses [77–79]. By comparing the functions of IL-22 with those of IL-17, anther tissue targeting cytokine, it is clear that IL-22 induces less proinflammatory responses from keratinocytes [65]. For example, the expression of chemokines such as CXCL1 and CXCL3 induced by IL-17 is much higher than that by IL-22 from keratinocytes. In addition, IL-17 but not IL-22 induces high level of IL-6 and GCSF from primary fibroblasts. Therefore, in order to sustain the inflammatory cascades during psoriasis, IL-22 needs to synergize with other cytokines. It has been reported that IL-22 synergizes with IL-17 to enhance the induction of antimicrobial proteins from keratinocytes [17]. Furthermore, IL-22, IL-17, OSM, IL-1α and TNF-α can synergistically induce some skin features recapitulating psoriasis closely both in vitro and in vivo [80].

Taken together, current data support that IL-22, although is not sole actor, plays an essential role in the pathogenesis of psoriasis. IL-22 synergizes with other leukocyte cytokines to form a cytokine network that orchestrates the progression of many different pathogenic features of psoriasis.

3. Protective role of IL-22 in IBD

IBD is chronic, relapsing inflammatory diseases of gastrointestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are two idiopathic forms of IBD, which have distinct clinical and histological features [81,82]. Inflammation in CD is usually transmural and discontinuous and involves the ileum and colon, while in UC inflammation is typically superficial and only affects colon [82]. Although the exact causes of IBD are still unclear, both environmental factors and genetic predisposition are involved in the onset and progression of the disease. Genetic evidence and data from preclinical models suggest that the inflammatory responses in IBD may result from inappropriate activation of the immune system by the normal luminal flora. Recent genome-wide association studies in IBD have identified the major genetic associations, which can be divided into genes that contribute to the epithelial integrity, innate immune response and adaptive immune response. UC and CD share some common genetic association alleles such as *IL23R* and *IL12B*, as well as alleles that are unique for each disease [83–86].

Detailed functional analysis of the SNPs associated IL-23R and data from preclinical studies support a pathogenic role of IL-23 pathway in the pathogeneses of IBD [87]. First, T cells from people bearing the protective SNP (R381Q) in IL-23R are less responsive to the stimulation by IL-23 in vitro, resulting in decreased Stat3 activation and IL-22 production, than those from control group (Pidasheva S. Manuscript submitted). Second, elevated IL-23 expression has been detected in CD and UC patients with activated

disease [88,89]. Finally, blocking IL-23 pathway lead to reduced disease severity in several preclinical IBD models [90–93]. Taken together, one would expect that blocking IL-23 might provide promising therapeutic benefits for the treatment of IBD in human as well. However, the initial data from clinic trials with anti-p40 antibody (ustekinumab) for the treatment of CD indicate only mild efficacy, less impressive than that in psoriasis [94]. Although further clinic trials are required to explore the potential therapeutic value of anti-p40 in the treatment of IBD, it is important to understand the downstream mechanisms, which may result in different clinic outcomes in psoriasis and IBD, of IL-23 pathway.

As we discussed above, IL-22 is a direct downstream effector cytokine of IL-23. Unlike its pathogenic functions in psoriasis, IL-22, supported by accumulating data, may exert a protective role in IBD. In the gastrointestinal tract, IL-23 is indispensible for IL-22 production, as in IL-23 deficient mice the induction of IL-22 triggered by various infections, for example, *C. rodentium* or *Toxoplasma gondii*, are abolished [73,95]. Although IL-22 and its receptor have not been linked with IBD genetically, expression of IL-22 is augmented in patients with IBD [96,97]. Increased IL-22, but not IL-17 and IFN-γ, has been reported in serum samples from CD patients [98]. The IL-22 levels also correlate with disease severity [99]. Interestingly, there is a correlation of IL-22 expression with IL-23R minor alleles. The proactive allele of IL-23R, which leads to hypo-responsiveness of T cells to IL-23 as discussed above, results in lower IL-22 expression in patients [99].

Despite the fact that IL-22 is correlated with disease activities in IBD patients, data from several preclinical models suggest that IL-22 exerts protective functions (Fig. 2). IL-22 deficient mice or WT mice treated with IL-22 neutralizing antibody lead to more severe weight loss, delayed recovery, and augmented epithelial damage and inflammation in the colon during dextran sodium sulfate (DSS) induced colitis [29,79,100,101]. In addition, T cells from IL-22−/− mice cause a more severe disease in the T cell transfer model of IBD [101]. On the contrary, overexpression of IL-22 in TCRα deficient mice reduces colonic thickness and disease score [79]. Finally, IL-22 plays an essential role in infection induced colitis as well. *C. rodentium* is bacterium that specifically attacks murine colon epithelial cells and causes severe colitis within two weeks following infection. But the infection and colitis can be self-resolved in WT mice upon the development of the host adaptive immune responses, especially the generation of anti- *C. rodentium* antibodies. However, in IL-22 deficient mice, all mice develop exacerbated colitis during the infection and most of the mice succumb to the infection in the second week of infection [95]. These data suggestion IL-22 endows essential defense mechanisms against invading pathogens in the intestine.

What are the mechanisms that cause the apparently different functions of IL-22 in psoriasis and IBD? The distinct pathogenic features and the different cellular sources of IL-22 in these diseases may provide possible explanation. Although the exact environmental triggers for psoriasis and IBD are still unclear, the presence of vast microbial microbes in the gut is essential for the development of IBD [81,82]. The inappropriate activation of mucosal immune system by the massive luminal microbial flora underlies the progression of IBD. On the other hand, while streptococcal infection has been linked with the onset of psoriasis, psoriatic skin is considered relatively sterile [102]. Therefore, the protective role of IL-22 in IBD is likely linked to its functions in enhancing epithelial innate defense mechanisms and barrier integrity, which sequester the direct interactions between the immune system and luminal commensal bacteria (Fig. 2). Similar protective functions of IL-22, nonetheless, are not obvious in the pathogenesis of psoriasis. In the intestinal tract, IL-22 induces the proliferation and reconstitution of mucosal epithelial cells through the activation of Stat3 [29,79,96,100]. This increased healing response prevents further penetration of microbes into the epithelial layer. Second, IL-22 helps goblet cell to regenerate and produce mucus-associated proteins, which form the essential static external barrier separating intestinal flora with intestinal epithelial cells [79]. Finally, IL-22 stimulates the production and secretion of various antimicrobial peptides, including defensins, cathelicidins and C-type lectins, from intestinal epithelial cells and Paneth cells [28,29,79,100,101]. These antimicrobial peptides further sequester and directly kill the invading pathogens through various mechanisms [103].

Another distinction of IL-22 in psoriasis and IBD is its cellular sources. In human psoriasis, various T cell subsets are the major sources of IL-22, whereas in IBD innate immune cells as well as T cells in the intestine produce IL-22 upon activation [23,42,43]. T cells, upon activation concurrently produce other proinflammatory cytokines such as IL-17, IFN-γ and TNF-α, all of which can synergize with IL-22 in promoting the psoriatic features of keratinocytes and inflammatory cascades as discussed before. In the intestine, innate immune cells, such as LTi cells, NK cell subsets, and DCs may produce IL-22 in response to IL-23 stimulation alone [23,27,42,43,95]. It is unclear whether these cells can secrete other proinflammatory cytokines under the same condition. It is possible that IL-22 is the dominant cytokine from these cells under certain conditions in disease. As a result, IL-22 itself will not amplify the inflammatory responses in the absence of concurrent expression of other cytokines. Instead, its major function in gut is protective through promoting epithelial defense and healing process.

4. Conclusion

Clearly, we are still at the early stage of understanding the functional roles of IL-22 in various human diseases. Future studies will focus on dissecting specific biology of IL-22 in a given tissue environment and disease context, since its complicated functions so far forbid us to generalize its role. The protective functions of IL-22 in IBD also suggest IL-23 may rely on other factors mediating its pathogenic functions. Identifying these factors may offer better therapeutic opportunities in IBD, in which one only needs to block these factors downstream of IL-23 pathway, but leave the protective functions of IL-22 intact.

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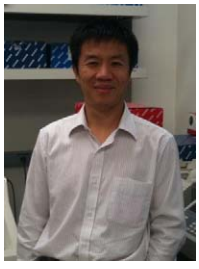

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