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Healing of intestinal inflammation by IL-22

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Abstract

An IL-10 family cytokine IL-22 is characterized by several unique biological properties, including 1) the target restricted to innate cells, 2) the distinct expression pattern between large and small intestines, 3) alteration of the cellular source depending on several factors, 4) the dual abilities to serve as protective versus proinflammatory mediators in inflammatory responses, and 5) the close association with some major IBD susceptibility genes. The major functions of IL-22 in the intestine are the stimulation of epithelial cells to produce a wide variety of antibacterial proteins, the reinforcement of mucus barrier through stimulation of mucin 1 production under intestinal inflammatory conditions, and the enhancement of epithelial regeneration with goblet cell restitution. Through these beneficial functions, IL-22 contributes to the improvement of some types of experimental chronic colitis, which are mediated by Th1 or Th2 responses. Most importantly, studies using both loss-of-function and gain-of-function approaches have clearly demonstrated the ability of IL-22 to promote intestinal wound healing from acute intestinal injury. These findings highlight IL-22 as an attractive and promising target for future IBD therapy. Alternatively, the enormous progress in the field of IL-22 biology has also suggested more complicated mechanism with IL-22 pathway than previously predicted. This review article briefly summarizes previous and current knowledge on IL-22 particularly associated with intestinal inflammation.

Keywords

epithelial defense; mucin 1; antibacterial proteins; epithelial regeneration; susceptibility genes; inflammatory bowel disease

Introduction

Interleukin (IL)-22 is an IL-10 cytokine family member that was originally discovered in 2000 from a mouse T cell line stimulated with IL-9 (1). Enormous progress in this area has since been seen particularly during last five years (2–6). The growing body of evidence highlights several characteristic properties with IL-22. First characteristic is the cellular targets. IL-22 can specifically target innate cells such as intestinal and respiratory epithelial cells, keratinocytes, and hepatocytes – this is due to the restricted expression of IL-22 receptor (IL-22R) on these innate, but not adaptive immune, cells (7). Second characteristic is the unique expression pattern in the intestine. IL-22 expression in the large intestine of mice and humans is elicited under inflammatory conditions (8–10), whereas IL-22 is constitutively expressed in the normal small intestine (11,12). Third characteristic is the dual abilities to serve as protective versus proinflammatory factors -presumably depending upon the tissue targeted, the disease mechanism involved, or the local cytokine environment

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exposed. For example, IL-22 contributes to the improvement of experiment colitis and hepatitis (9,10,13), but it also causes psoriasis (14,15). Therefore, IL-22 has been metaphorically called as “a sheep in wolf's clothing” (16) or “a two-headed cytokine” (2). Fourth characteristic is the close association of IL-22 with IBD susceptibility genes. Several IBD susceptibility genes such as IL-23R, IL-10R2, and STAT3 are functionally associated with IL-22 directly or indirectly (17). Therefore, these findings suggest that further works on IL-22 would have the potential to not only dissect the fundamental mechanism of IBD but also provide important rationale to develop novel therapeutic measures for this disorder.

Distinct expression pattern of IL-22 in large versus small intestines

IL-22 is constitutively expressed in the small intestine of humans and mice to preserve the intestinal homeostasis against enteric microorganisms (11,12,18). In contrast, IL-22 expression is hardly detectable in the normal colon of humans (8,9,19,20) and mice (9,10,21). Diverse intestinal inflammatory conditions, which range from IBD to infectious colitis, elicit the expression of IL-22 in the colon (8–10,19–21). Interestingly, the expression level of IL-22 in the inflamed colon tends to be higher in CD patients as compared to UC patients (8,9,19). In CD, serum IL-22 levels are significantly higher in patients with risk-increasing *il23r* variants than in those with risk-decreasing *il23r* variants (22).

In mice, IL-22 is highly expressed in the inflamed colon of Th1-mediated colitis model (CD45RB model) as compared to Th2-mediated colitis model (TCRα KO mice) (9). CD45RB model has widely been used for the study of human CD (23), and TCRα KO model shares some characteristic features with human UC (24). These findings suggest that colonic IL-22 expression, which can be elicited by inflammatory insults, is further conditioned by the local cytokine environments in the inflamed colon (e.g. Th1 versus Th2). Indeed, in skin, atopic dermatitis with significant contribution from Th2 responses exhibits lower levels of IL-22 expressions as compared to psoriasis characterized by enhanced Th1/Th17 responses (25).

Cellular sources of IL-22 in the small intestine

IL-22 can be produced by a wide variety of innate and adaptive immune cells, including Th17 $CD4^+$ T cells, Th22 $CD4^+$ T cells, $CD8^+$ T cells, TCRγδ T cells, dendritic cells (DCs), NK cells, lymphoid tissue inducer (LTi) cells, and innate lymphoid cells (ILCs) (2–6). Interestingly, the major cellular source of IL-22 seems to differ depending upon the tissue involved (4) (Fig. 1). For example, Th22 cells, which express skin homing receptors (CCR4 and CCR10) and produce IL-22 but not IL-17, represent the major source of IL-22 in the skin (26,27). In pulmonary immune response, TCRγδ T cells and Th17 cells primarily contribute to the production of IL-22 (28,29). In human tonsile, stage-3 immature conventional NK cells serve as the source of IL-22 (30). IL-1β is required to retain the expression of aryl hydrocarbon receptor (AHR) and thus IL-22 in the immature NK cells (30). Similarly, such immature NK cells are also the source of IL-22 in human uterine mucosa (31).

In the small intestine under healthy steady state and also under an inflammatory condition caused by *Citrobacter rodentium* infection, RAR-related orphan receptor (ROR)γt-dependent innate lymphoid cells (ILCs), which share some characteristics with NK cells and lymphoid tissue inducer (LTi) cells (Lin^- $Thy1^+$ $cKit^+$ $CD4^+$ $CD3^-$), are primarily responsible for the production of IL-22 (11,12,18,32,33). These IL-22-producing ILCs are referred as “ILC22 cells” (32). The ILC22 cells include NK receptor-expressing LTi cells, ILCs ($Lin^-Thy1^+CD127^+cKit^+CD3^-$) expressing a natural cytotoxicity receptor NKp46 with low to no NK1.1 expression, and human NK22 cells expressing NKp44, CD56 and CCR6 with low expression of NKp46 (32). Recent studies suggest that $NKp46^+$ ILCs are progeny

of LTi cells (33). Gut commensals promote the activation of RORγt in ILC22 cells to enhance their development (11), but microbiota are not strictly required for the development of ILC22 cells as indicated by the presence of these cells in germ-free mice (18,34). In response to *Toxoplasma gondii*-infection, major source of IL-22 in the small intestine may shift from ILC22 cells to $CD4^+$ T cells (35). Commensals may be required for the shift, as IL-22 becomes undetectable in the small intestine of germ-free mice after a mono-associated infection with *T. gondii* (35).

Cellular sources of IL-22 in the large intestine

As compared to other tissues mentioned above, cellular sources of IL-22 in the inflamed colon seem to differ depending upon the type of inflammation. NK cells and Th17 $CD4^+$ T cells have been reported to produce IL-22 in the inflamed colon of UC patients (20). In contrast, $CD4^+$ T cells expressing natural killer group 2 member D (NKG2D) have been proposed to produce IL-22 in the inflamed intestine of CD patients (36). In addition, intestinal $NKp46^+$ $NKp44^-$, but not $NKp46^-$ $NKp44^+$, NK cells have also been demonstrated to produce IL-22 (37). Interestingly, IL-22-producing $NKp46^+$ $NKp44^-$ NK cells are more increased in the inflamed colon of CD patients as compared to that of UC patients (37). In addition to such NK cells, ILCs, which are characterized by linage marker (Lin) $^-CD45^+$, $CD3^-$, IL-$7R\alpha^+$ phenotype, have recently been identified to exist in human colon (38). These ILCs are further classified into two subsets depending on the expression pattern of neural cell adhesion molecule (NCAM, CD56). $CD56^+$ ILCs produce IL-22 and IL-26 in response to IL-23, while $CD56^-$ ILCs produce IL-17A and IL-17F. Interestingly, increased number of both IL-22-producing $CD56^+$ ILCs and IL-17-producing $CD56^-$ ILCs are observed in the inflamed colon of CD patients as compared to UC patients (38). These findings indicate that innate cell populations (NK cells and $CD56^+$ ILCs) producing IL-22 more expand in CD as compared to UC. The enhanced expansion of these NK cells and ILCs may contribute for maintaining higher levels of IL-22 expressions in CD mucosa as compared to UC mucosa.

Like observed in IBD patients, major cellular sources of IL-22 in the inflamed colon of mouse IBD models also tend to alter depending upon the fundamental disease mechanisms. In Th1-mediated experimental colitis model (CD45RB model), both NK cells and Th17 cells are primarily responsible for the production of IL-22 in the inflamed colon (10). The NK cells are further classified into $CD27^{high}$ versus $CD27^{low}$ NK cell subsets. Interestingly, IL-23 can induce the IL-22 expression in both NK subsets, whereas IL-12 and IL-18 induce IL-22 expression only in $CD27^{high}$ NK cell subset (10). $CD11c^+$ dendritic cells (DCs) may represent a major source of IL-22 in an acute intestinal injury model induced by oral administration of dextran sulfate sodium (DSS) (21). In *C. rodentium*-induced infectious colitis model, DCs may also serve as a major source of IL-22 (39). Alternatively, a recent study demonstrates in the *C. rodentium* infectious model that RORγt$^+$ LTi cells, but not DCs, produce IL-22 in the inflamed colon, and DCs rather contribute to the activation of the naïve LTi cells through production of IL-23 (40). Similarly, IL-23-dependent $CD4^+$ LTi cells, which are characterized by the expression of NKp46 and CD90 and by the localization within the intraepithelial compartment of colon, have been proposed to represent the dominant source of colonic IL-22 in the context of *C. rodentium* infection (41).

Signaling machinery to induce IL-22 expression

IL-22 production by Th17 T cells is induced by IL-23 or IL-6 (14). Notably, TGF-β, although critical for Th17 differentiation, inhibits the IL-22 production (14). The inhibition of IL-22 production by TGF-β is mediated by a transcription factor c-Maf (42). Like observed in Th17 cells, IL-23 also acts on ILCs to induce the expression of IL-22 (43). Aryl hydrocarbon receptor (AHR), which serves as a cytosolic sensor of aromatic hydrocarbons

and plays critical roles in the metabolism of benzopyrene as well as in the acute toxicity of halogenated dioxins, is also required for the ability of Th17 T cells to produce IL-22 (44). Significantly decreased expression of AHR is observed in CD patients as compared to UC patients (45). In addition, AHR sustains the expression of NKp46 in small intestinal ILCs through activation of Notch pathway and consequently drives the development of IL-22-producing ILCs (18). AHR is also required for the development of colonic ILCs (46). In DSS-induced colonic injury model, IL-22 expression in the colon may be induced through TLR4 (LPS), TLR9 (CpG), or to a lesser extent TLR2 (lipteichoic acid) (21).

Responder cells to IL-22

IL-22 is recognized by a heterodimeric receptor consisting of IL-22R1 and IL-10Rβ (2–6). IL-10Rβ is ubiquitously expressed by majority of cell types, while the expression of IL-22R1 is restricted to innate cells such as epithelial cells, hepatocytes, and keratinocytes (2–6). Therefore, this expression pattern of IL-22R1 allows IL-22 to specifically target innate, but not adaptive immune, cell populations (7). In the intestine of mice and humans, IL-22R1 is expressed by epithelial cells and myofibroblasts (8,9,20). However, the responsiveness of myofibroblasts to IL-22 may be much weaker as compared to that of epithelial cells, as indicated by the requirement of high (200 ng/ml) versus low (5ng/ml) doses of IL-22 for the activation of myofibroblasts versus epithelial cells, respectively (8,9).

Activation of STAT3 by IL-22

IL-22 stimulation can activate STAT3, to a lesser extent STAT1, and in certain cells STAT5 (47,48). In addition, ability of IL-22 to activate Erk1/2, JNK, and p38 MAP kinase pathways has been proposed in a rat hepatoma cell line (47,48). High dose of IL-22 also induces a transient activation of Erk1/2 in colonic cancer cell line HT29 (19). However, the concept on the Erk1/2 activation by IL-22 has been challenged by some reports showing the inability of IL-22 to activate Erk/1/2 in a HepG2 cell line (49) and in primary epithelial cells from human and mouse colons (9). In contrast, the strong activity of IL-22 to stimulate STAT3 has been well confirmed using human colonic biopsies, human colonic cancer cell lines, and primary mouse colonic epithelial cells (9,10,20,21). Most importantly, epithelial STAT3 activation under DSS-induced colitis has been demonstrated to depend more on IL-22 rather than IL-6, a well known STAT3 activator (21). This observation may be unexpected but consistent with a recent discovery that IL-22R1 uses a novel mechanism to “constitutively” activate STAT3 through constitutive interaction of its C-terminal tail with the coiled-coil domain of STAT3 (50). Indeed, IL-22 has recently been shown to have a strong ability to activate STAT3 as compared to IL-6 (51).

IL-22 and antibacterial proteins

IL-22 has been implicated in several important functions in innate cells, including the host defense against microorganisms and the wound healing (2–6). One of major functions played by IL-22 is the induction of antibacterial protein expressions. IL-22 stimulates kerationcytes to produce S100A7 and S100A8 (52). In collaboration with IL-17, IL-22 also synergistically promotes the expression of β-defensin 2 and S100A9 in kerationocytes (53).

Interestingly, even though the expression levels of S100A8 (also called MRP8), S100A9 (also called MRP14), regenerating gene (Reg) IIIγ and RegIIIβ are differerent, they are significantly enhanced and commonly observed in the colonic epithelial cells of different types of experimental “chronic” colitis models, including Th1-mediated and Th2-mediated colitis models (54). Alternatively, in DSS-induced “acute” colonic injury model, the expression pattern of these molecules differs in the acute versus recovery phases (54). RegIIIγ was initially thought to play a role in cell regeneration, but subsequent studies have identified the ability to serve as an antibacterial protein against gram (+) bacteria (55).

Interestingly, IL-22 stimulates epithelial cells to produce RegIIIγ and RegIIIβ in the context of infection with a gram (-) bacteria *C. rodentium*, (39), whereas *Listeria monocytogenes* stimulates the production of RegIIIγ in a MyD88-dependent manner (56). In DSS-induced colonic injury model, IL-22-dependent induction of RegIII γ and β expressions through STAT3 has been proposed (21), but a recent study suggests that IL-23 (the inducer of IL-22 expression) rather than IL-22 directly induces the expression of RegIII γ and β (57). An IL-17 family member IL-17C, which is produced by intestinal epithelial cells, has recently been shown to act in synergy with IL-22 to induce the expression of anti-bacterial proteins, including S100A8, S100A9, RegIIIβ, and RegIIIγ (58). Ability of IL-22 to promote the expression of β-defensin 2 has also been shown using a colonic cancer cell line HT29 (19). In CD patients, IL-22 induces the production of lipopolysaccharide (LPS)-binding protein by hepatocytes, which may contribute to the prevention of LPS-induced systemic responses (49).

IL-22 and intestinal mucus barrier

Intestinal mucus functions as a lubricant and a physiological barrier between luminal contents and mucosal surface (59). Mucin (Muc) 1, which is a heavily O-glycosylated membrane-bound mucin, represents one of the major components in the intestinal mucus (59). Bacteria-derived adenosine 5'-triphosphate (ATP) stimulates the development of intestinal Th17 T cells (60), and a segmented filamentous bacterium also leads to the appearance of intestinal Th17 cells (61). Interestingly, a recent study proposes the ability of Muc1 to suppress the expansion of both Th17 cells and IL-17-producing ILCs presumably by blocking the translocation of bacterial products from intestinal lumen into intestinal lamina propria (62).

Protective roles of Muc1 in both Th2-mediated colitis of T cell receptor (TCR) α knockout (KO) mice and Th1-mediated colitis of CD45RB model have recently been shown using loss-of-function systems (Muc1 KO mice) (62). Alternatively, forced overexpressions (Muc1 transgenic mouse system) of "hypoglycosylated" Muc1 make breaches in the static mucus barrier (63) and exacerbate Th1/Th17-mediated colitis in IL-10 KO mice (64), suggesting that complete glycosylation of Muc1 is required for eliciting the protective function in colitis. Indeed, impaired glycosylation in the mucus exacerbates or causes colitis (65,66). Interestingly, the ability of IL-22 to promote the production of functional Muc1 through activation of STAT3, but not STAT1, has been demonstrated using human colonic cancer cell lines (T84 and HT29) and primary colonic epithelial cells from mice (9,67). Consistent with these findings, binding of STAT3 within the promoter region of *muc1* gene has been demonstrated (68). Most notably, Muc1 expression is abolished in a patient with early onset form of IBD, who has a functional polymorphism within *il10rb*, a receptor for IL-22 (51).

IL-22 and epithelial regeneration

IL-22 has been demonstrated to promote the epithelial cell regeneration with goblet cell restitution under intestinal inflammatory condition, but it may play no obvious role in normal colonic epithelial homeostasis in the healthy state (9,21). Consistent with these observations, STAT3 activation through IL-22 enhances the transcription of anti-apoptotic and pro-proliferative genes such as *birc5, pla2g5, smo, myc*, and *mcl1* under inflammatory conditions (69). In addition, IL-22 stimulates a colonic cancer cell line to express a molecule termed "deleted in malignant brain tumor 1 (DMBT1)" that may play a role in epithelial cell differentiation (70). RegIα, which serves as a trophic and anti-apoptotic factor, is also reported to be induced in the inflamed colon of UC patients by IL-22 (20).

Protective versus proinflammatory roles of IL-22 in inflammatory responses

Recent accumulating evidence indicates dual abilities of IL-22 to serve as protective versus inflammatory mediators depending on several factors (Fig 2). Protective role of IL-22 has been shown in ConA-induced hepatitis (13), alcoholic fatty liver and liver damage (71), GVHD associated with heart allografts (72), autoimmune myocarditis (73), allergic airway inflammation (74), and uveitis (75). In contrast, proinflammatory role of IL-22 has also been demonstrated in collagen-induced arthritis (76). In skin, IL-22 causes psoriasis (15), but it may also suppress acne vice versa (77). IL-22 may play no role in experimental autoimmune encephalomyelitis (78). In infectious models, deficiency of IL-22 makes mice highly susceptible to broad-spectrum of pathogens, including *Klebsiella pneumoniae* (29), *Mycobacterium tuberculosis* (79), and cutaneous *Staphylococcus aureus* (80).

Roles of IL-22 in intestinal inflammations

In addition, IL-22 plays dual roles in intestinal infection presumably depending upon the type of pathogens. IL-22 provides protective role against *Citrobacter rodentium*-induced colitis (18,39,41,46), systemic infection with *Salmonella enterica* (81), and gastrointestinal *Candidasis* in absence of IL-17R (82). In contrast, IL-22 is required for the development of *Toxoplasma gondii*-induced immunopathology in the small intestine (35).

Potential role of IL-22 in IBD has also been explored using mouse model system (Fig. 2). In a Th2-mediated chronic colitis model (TCRα KO mice), supplementation of IL-22 expressions in the inflamed colon through a local gene delivery system improves the colitis by reinforcing intestinal mucus barrier function (9). In a Th1-mediated colitis model (CD45RB model), there is no significant difference in colitis severity when IL-22-deficient versus IL-22-intact $CD4^+$ $CD45RB^{high}$ T cells are transferred into recipient RAG1 KO mice that have endogenous IL-22 productions by innate cells (10,83). In contrast, IL-22-deficient $CD4^+$ $CD45RB^{high}$ T cells cause more severe colitis as compared to IL-22-intact $CD4^+$ $CD45RB^{high}$ T cells when IL-22-deficient and RAG1-deficient double knockout mice are used as the recipient (10). These findings suggest that both donor T cell-derived and recipient (NK cell)-derived IL-22 participate in the suppression of this colitis, but host innate cell-derived IL-22 has more prominent role in this regard (10). In contrast, proinflammatory role of memory $CD4^+$ T cell-derived IL-22 in a new colitis model has also been proposed (84). The authors propose that adoptive transfer of $CD25^+$ cell-depleted $CD45RB^{low}$ memory $CD4^+$ T cells can induce colitis in recipient RAG1 KO mice, but IL-22-deficient $CD25^+$ cell-depleted $CD45RB^{low}$ memory $CD4^+$ T cells are unable to do it.

Unlike IBD models mentioned above, expression of IL-22 is not elicited in trinitrobenzene sulfonic acid (TNBS)-induced colitis model, and thus a strategy to induce the expression of IL-22 can be applied for the treatment of this colitis (45). Administration of an AHR agonist Ficz augments the colonic IL-22 expressions and suppresses the TNBS colitis (45). Neutralization of the IL-22 activity by treatment with anti-IL-22 mAbs abolishes the beneficial effect of Ficz on this colitis. Ficz also has therapeutic effect on Th1-mediated colitis of CD45RB model (45).

Role of IL-22 in intestinal wound healing

DSS-induced acute colonic injury spontaneously recovers after termination of DSS treatment, allowing us to closely examine the intestinal wound healing process (24,85). In this model, ability of IL-22 to promote intestinal wound healing has been well proven using different experimental approaches (9,10,21,45,57). IL-22 KO mice exhibit impaired recovery from DSS-induced acute colonic injury (21). Administration of neutralizing anti-IL-22 Abs also delays the recovery in WT mice (9). No recovery is observed in IL-22-deficient and RAG1-deficient double knockout mice lacking both T and B cells (10).

In addition to these loss-of-function systems, the role of IL-22 in the intestinal wound healing after exposure to DSS has been explored using gain-of-function systems that may be applicable for IBD patients. Supplementation of IL-22 expressions in the colon through a local gene delivery system promotes the recovery with enhanced goblet cell restitution (9). In addition, treatment with Ficz, which is capable of augmenting the IL-22 expression, suppresses the development of DSS-induced chronic colitis that is induced by repeated administrations of DSS with each interval (45). Interestingly, recovery from DSS-induced acute colonic injury is significantly impaired in IL-23R-deficient and RAG2-deficient double knockout mice that lack IL-22 expressions, and administration of recombinant IL-22 rescues the recovery in these mice (57).

Regulation of IL-22 function

The function of IL-22 is positively or negatively regulated by some other factors. In psoriasis, co-operative role of IL-22, IL-17, and IFN-γ may be required to fully establish the pathogenesis (86). IL-22 can induce psoriasis-like skin alteration, including acanthosis and hypogranularity, and IL-17 and IFN-γ are also necessary to induce the recruitment of inflammatory cells such as T cells and neutrophils into the region (86). In bleomycin-induced airway inflammation, IL-22 plays a proinflammatory role in the presence of IL-17A and, in turn, plays a protective role in the absence of IL-17A (87). This finding suggests that IL-17A governs the proinflammatory versus tissue-protective properties of IL-22 (87). In addition, lymphotoxin (LT) pathway, which is induced by the interaction of LTβR with LTβ but not with LIGHT, controls the protective function of IL-22 against *C. rodentium* (40).

Importantly, soluble class II cytokine receptor designated IL-22Ra2 (also called IL-22 binding protein, IL-22BP or CRF2-10) exists in our bodies (88-90). IL-22BP has high affinity binding capability to IL-22 and serves as an endogenous inhibitor of IL-22 activity (88–90). The cellular source of IL-22BP has not been fully established, but IL-22BP is highly expressed in placenta, spleen, skin and lung and to lesser extent in large and small intestine of humans (88). IL-22BP expressions are also detectable in normal colon of mice (9). Interestingly, distinct expression patterns of IL-22 versus IL-22BP are observed in DSS-induced acute colonic injury – IL-22 expressions increase whereas IL-22BP expressions decrease (9). Supplementation of IL-22BP expressions in the inflamed colon through a local gene delivery system significantly delays the recovery from the DSS-induced acute colonic injury and also suppresses goblet cell restitution (9). These findings indicate that IL-22 activity in the colon is controlled by its endogenous inhibitor IL-22BP.

Association of IL-22 with IBD susceptibility genes

An attractive biological property with IL-22 is the functional association with some major IBD susceptibility genes (Fig. 3). Interaction of IL-23 with IL-23R has been implicated in the maintenance of IL-22-producing Th17 cells (91,92) and in the development of IL-22-producing innate cells, including ILCs, LTi cells, and NK cells (10,37,38,41,43). Functional polymorphisms within *Il23r* gene are negatively associated with the development of both CD and UC (91,92). IL-22 binds to a heterodimeric receptor composed of IL-10Rβ and IL-22R1. Polymorphisms of *il10rb* are positively associated with both CD and UC (93). In addition, *il22* is located within a UC-risk locus on chromosome 12q15 (94). The receptor ligation by IL-22 induces rapid activation of STAT3 through JAK2 and TYK2. These *stat3*, *jak2* and *tyk2* all are well-defined susceptibility genes of CD and to lesser extent UC (91,92). The STAT3 activation then stimulates epithelial cells to produce Muc1 (9,67,68). A recent genome-wide association study proposes *muc1* as a potential candidate gene associated with CD (95)

Conclusion

Despite only ten years-history since the discovery, enormous efforts and rapid progression in the field of IL-22 have been seen. Indeed, as mentioned above, several unique biological properties with IL-22 have been defined. Importantly, the ability of IL-22 to promote intestinal wound healing in mice has been reproducibly confirmed by independent groups using different experimental approaches, and recent advance in genome-wide association studies has suggested the close association of IL-22 pathway with some major IBD susceptibility genes. These facts clearly highlight IL-22 as a promising target for IBD therapy. However, given the potential of IL-22 to serve as both protective and proinflammatory mediators depending on several factors, further extensive works on IL-22 would be necessary to bring novel and practical intervention for improving the lives of patients with IBD in effective and safety manner.

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Abbreviation used

AHR	aryl hydrocarbon receptor
DCs	dendritic cells
DSS	dextran sulfate sodium
IL-22R	interleukin-22 receptor
ILCs	innate lymphoid cells
JAK	Janus kinase
KO	knockout
LT	lymphotoxin
LTi	lymphoid tissue inducer
Muc1	mucin 1
RAG	recombination activation gene
Reg	regenerating gene
RORγt	RAR-related orphan receptor
STAT	signal transducer and activator of transcription
TCR	T cell receptor
Th	T helper
TNBS	trinitrobenzene sulfonic acid

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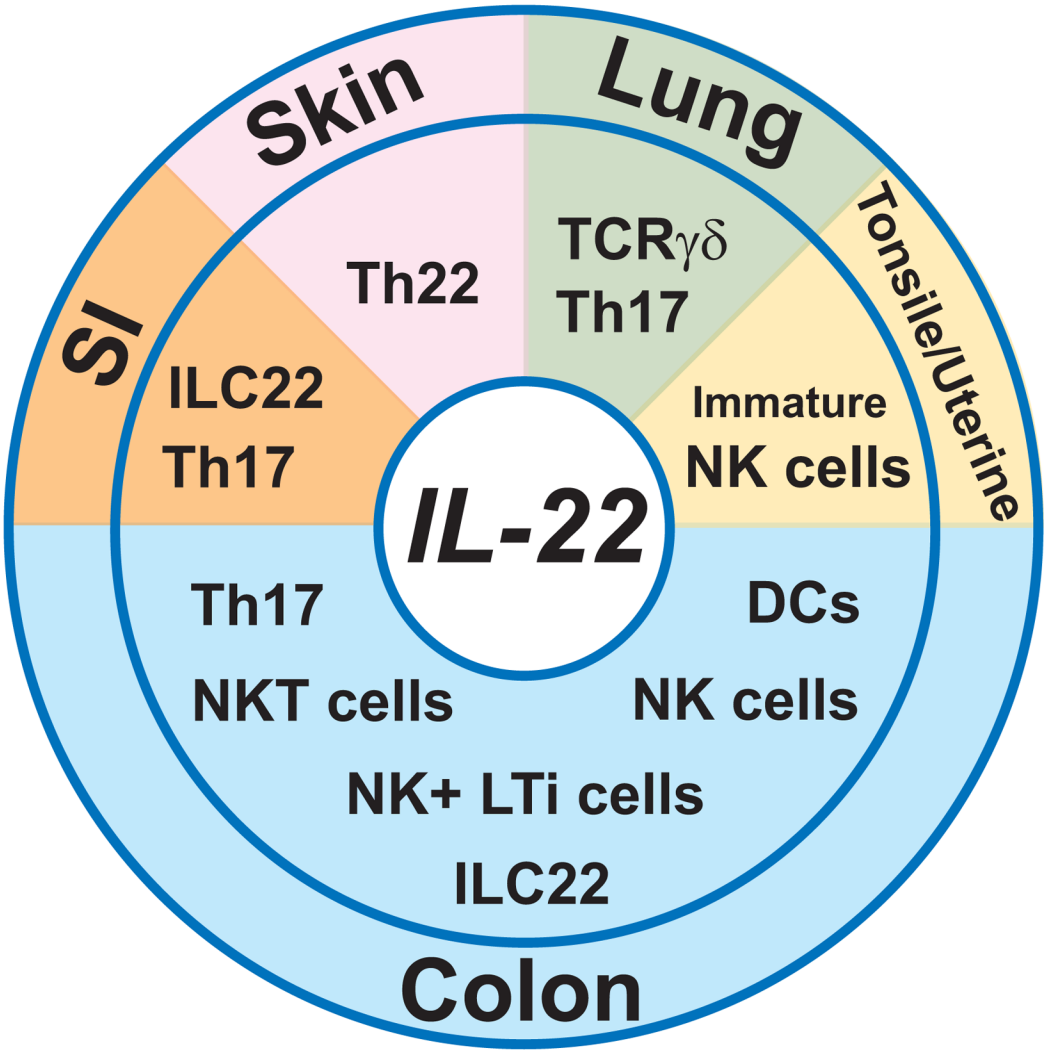

Figure 1. Cellular sources of IL-22

Potential major cellular sources in the small intestine (SI, orange), skin (pink), lung (green), tonsile and uterine (yellow), and colon (blue) are shown. Some innate cells in the colon may represent a same linage with different differentiation stages.

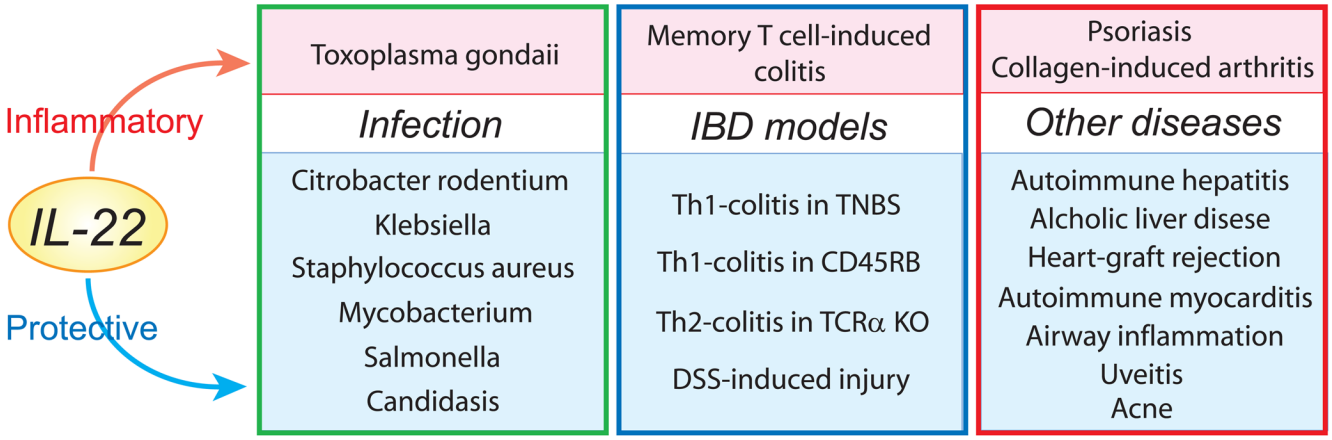

Figure 2. Role of IL-22 in inflammatory responses

Experimental diseases, in which IL-22 has been shown to play a proinflammatory role, are indicated in pink boxes. Experimental diseases, in which IL-22 has been demonstrated to play a protective role, are listed in blue boxes.

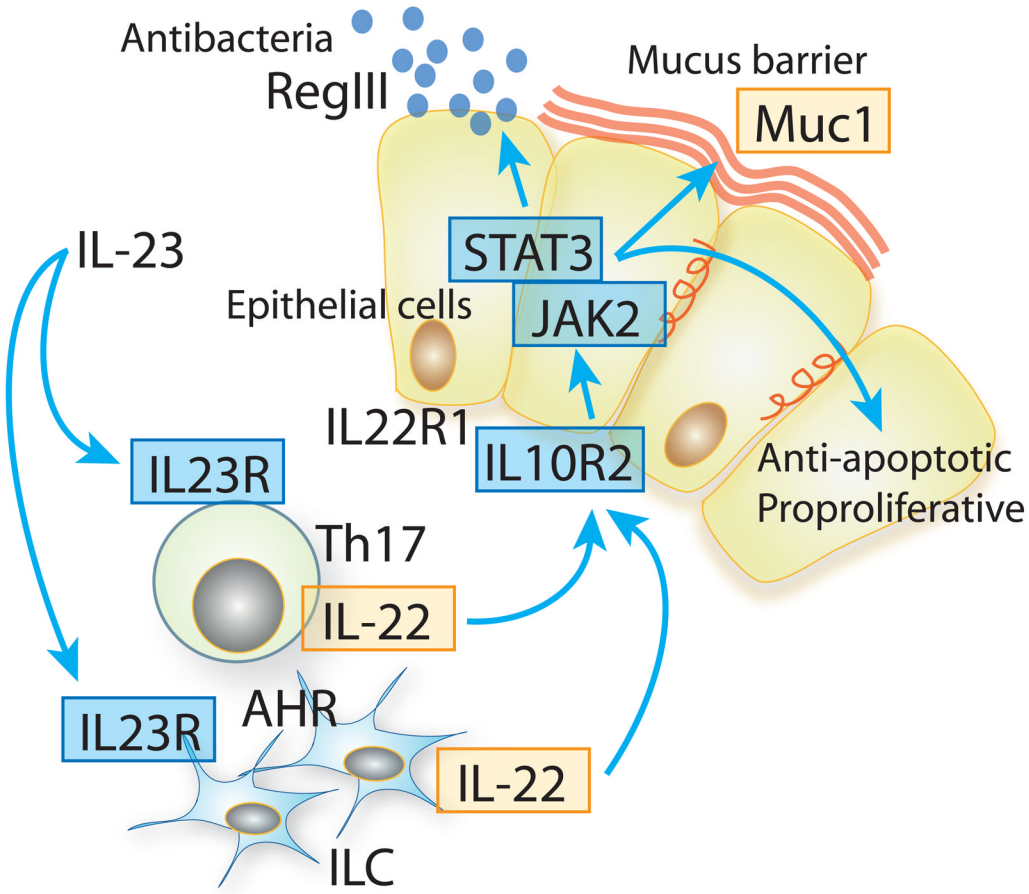

Figure 3. Functional linkage of IL-22 to some IBD susceptibility genes

Ligations of IL-23R by IL-23 maintain the expansion of IL-22-producing Th17 cells and induce the development of IL-22-producing ILCs. Subsequent ligation of IL-10R2/IL-22R1 receptor complex by IL-22 activates JAK2/STAT3 pathway in epithelial cells. The activated STAT3 then stimulates epithelial cells to produce RegIII and Muc1 and also promotes epithelial cell regeneration. Well-defined IBD-association genes are indicated in blue boxes, and potential IBD-association genes indicated in yellow boxes.