Pathogen Resistance Mediated by IL-22 Signaling at the Epithelial–Microbiota Interface

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Abstract

Intestinal colonization resistance to bacterial pathogens is generally associated, among other factors, with mucosal homeostasis that preserves the integrity of the intestinal barrier. Mucosal homeostasis depends on physical and molecular interactions between three components: the resident microbiota, the epithelial layer and the local immune system. The cytokine IL-22 helps to orchestrate this three-way interaction. IL-22 is produced by immune cells present beneath the epithelium and is induced by bacteria present in the intestine. IL-22 stimulates the epithelial cells via the IL-22RA1–IL-10R2 receptor complex inducing changes in the expression of genes involved in the maintenance of epithelial barrier integrity, with a variety of functions in pathogen resistance such as mucus layer modifications and hydration, tight junction fortification and the production of a broad range of bactericidal compounds. These mechanisms of pathogen resistance, in turn, affect the microbiota composition and create an environment that excludes pathogens. Here we highlight the role of IL-22 as key mediator in the give-and-take relationship between the microbiota and the host that impacts pathogen resistance.

The Intestinal Ecosystem Contains the Microbiota, Epithelium and Immune Cells

The human intestinal tract is frequently challenged with potentially virulent bacteria during eating, drinking and environmental contamination, yet infection is relatively unusual. The first obstacle an invading pathogen would encounter when reaching the intestinal tract is a community of commensal bacteria, fungi, viruses and archaea collectively known as intestinal microbiota. The intestinal microbiota thrives in the lumen and within and around the nutrient-rich environment of the mucus layer in an intimate relationship with the host, taking part in many aspects of the host's physiology, from nutrition to development of its immune system [1,2]. A prospective pathogen would have to compete for nutrients and niches with the highly adapted local microbiota. This phenomenon is referred to as colonization resistance and serves as a conceptual framework for developing novel bacteria-based medicines to combat infections, as has been shown in the case of *Clostridium difficile* infection [3,4].

Acting as a filtering barrier, the mucus layer *per se* is the next obstacle an invading pathogen would encounter. The composition of the mucus layer, its thickness, its ability to exclude bacteria and its dependence on the microbiota for its genesis, represents long-term co--evolution between host and the commensal microbiota [5]. The mucus layer is a physical, gel-like barrier between the intestinal lumen and the underlying epithelium. The mucus layer is made mainly from Mucin-2 (MUC2), a glycoprotein secreted by epithelial goblet cells. In the large intestine, MUC2 forms two distinct layers. The first one, referred to as the inner layer, is in close contact with the epithelium and is tightly packed, virtually devoid of bacteria, partly due to the filtering capacity of the gel but also due to the presence of antibacterial molecules secreted by the epithelium. The second or outer layer is loosely packed and heavily colonized with microbiota. In contrast, the

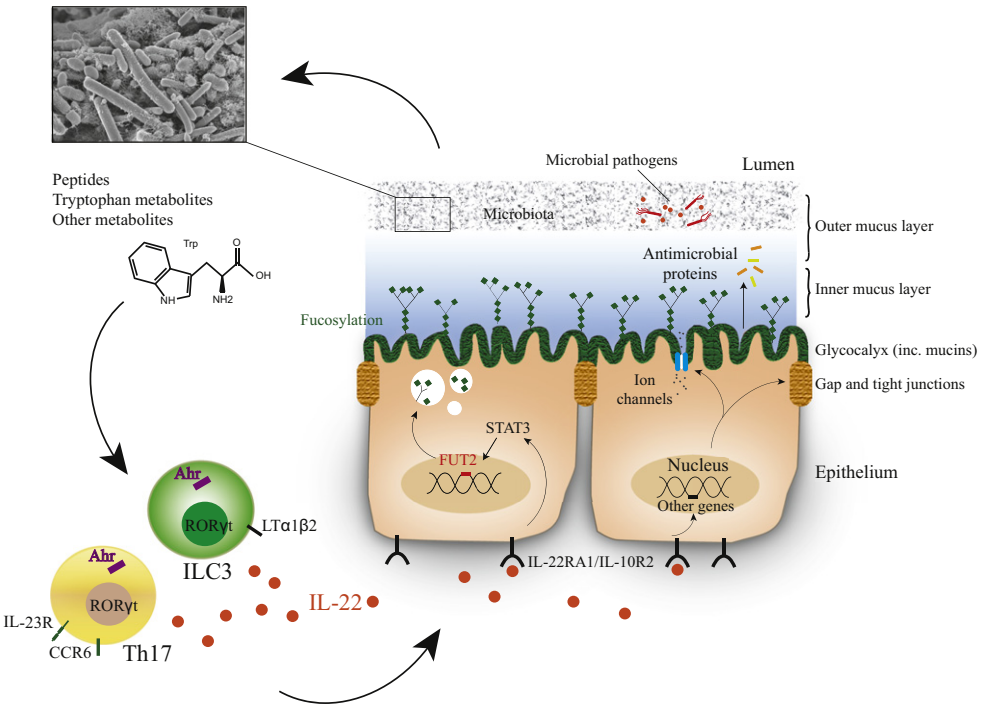

Fig. 1. IL-22, a key regulator linking the microbiota, the epithelium and the immune system. An intact intestinal epithelium is key to resistance against potential pathogens. A potential pathogen would have to compete for nutrients with the resident microbiota, fight its way through the mucus layer and survive the chemical attack by the epithelium in the form of antimicrobials and antibodies and avoid being detected by the underlying immune system. Maintenance of intestinal homeostasis requires the carefully balanced interaction of three main components: the microbiota, the epithelium and the underlying immune system. IL-22 sits at the center of this three-way interaction system, helping to maintain that balance. The microbiota and its products are necessary for the development of IL-22-producing immune cells, such as ILC3s and Th17 cells, and the induction of its expression. By acting on epithelial cells, IL-22 induces the expression of genes key to the maintenance of an intact epithelial barrier, such as mucins (involved in the formation of both the mucus layer and the glycocalyx), antimicrobials, glycoproteins (providing both a physical barrier and anchoring surface to bacteria), tight junction proteins (keeping the epithelial cells together as an unbroken barrier) and ion channels (regulating mucosal hydration, "flushing" potential pathogens and impairing their ability to colonize). In turn, many of these molecules will affect the composition of the microbiota, thus closing the circle.

small intestine contains only a layer of loosely packed mucin [6,7].

Below the mucus layers sits the epithelium, a cellular barrier that defines the border between our interior and the exterior, represented by the intestinal lumen. Across the epithelium, a constant exchange of nutrients and other molecules takes place. Depending on the area of the intestine in question, the epithelium is composed of several cell types with different functions: (1) mucus-secreting goblet cells, (2) antimicrobial-secreting Paneth cells, (3) hormone-secreting enteroendocrine cells, (4) lymphoid-associated epithelial microfold cells (M cells), (5) nutrient-absorbing enterocytes and (6) stem cells, which renew the intestinal epithelium every 4–6 days [8]. With the exception of Paneth cells, which are found solely in crypts of Lieberkuhn in the small intestine, other cell types are found throughout the intestinal tract at varying numbers depending on location, with enterocytes making up the majority of intestinal epithelium due to their role as nutrient-absorbing cells. The majority of goblet cells are located in the colon; individual enteroendocrine cells and stem cells are found throughout the intestinal epithelium with stem cells located at the bottom of crypts. Lymphoid-associated M cells are found in close association with gut-associated lymphoid tissue in both the small intestine (Payer's patches) and colon (colonic patches) [9]. The integrity of the epithelial barrier is maintained by tight and gap junctions between cells that prevent the microbiota and pathogens from invading deeper tissues and organs. The epithelial barrier integrity also regulates intestinal hydration through ion trafficking: an essential factor for nutrient absorption and clearance of potential pathogens, a process that will be discussed later on. The epithelium also acts as a sensor, keeping a constant surveillance on the microbiota through the expression of innate receptors, both membrane bound and cytosolic (Toll-like

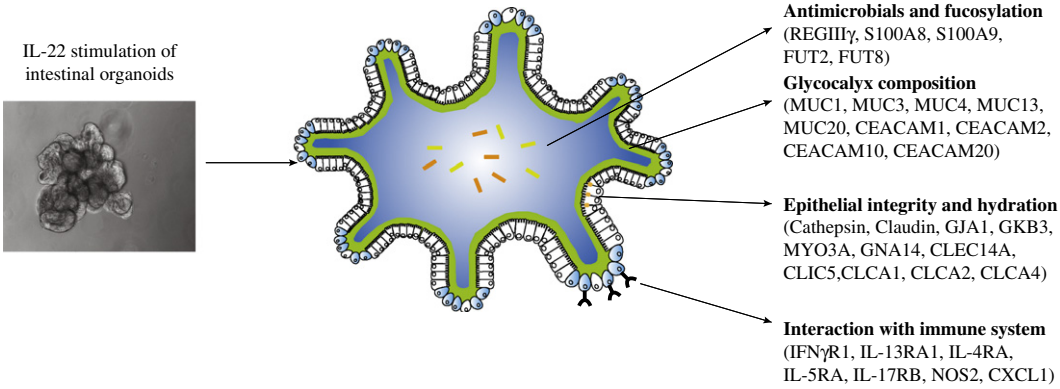

Fig. 2. IL-22 is involved in many aspects of maintenance of a healthy epithelial barrier. The development of new techniques in recent years, like the culture of intestinal organoids, coupled with advances in RNASeq and transcriptomics, has improved our understanding of IL-22 and its role in the intestinal epithelium. Primary murine intestinal organoids were stimulated with IL-22 and used for transcriptomic studies (Ref. [17]). Upon exposure to IL-22, there is an increased expression of genes related to most elements needed to keep the epithelium intact. This includes the mucus layer (presence of antimicrobials and fucosylation of mucins; regulation of mucosal hydration), glycocalyx (important in bacterial–epithelial cell interaction), tight and gap junctions (key to maintenance of an unbroken epithelial layer) and engaging the underlying immune system.

receptors and NOD-like receptors), which can detect microbe-associated molecular patterns (MAMPs). The MAMPs produced by the microbiota help maintain a basal activation level of the local immune system, which helps keep the microbiota at bay and also be "primed" and ready for action in case a pathogen manages to come in close contact to or even breach the epithelial [10,11].

The intestinal epithelium works in close proximity with the immune system to establish and regulate intestinal homeostasis. Immune cells, both innate and adaptive, accumulate beneath the epithelium in the lamina propria and also in between epithelial cells, constantly patrolling the area and scouting for pathogenic invaders. One of the first responder immune cell types are the innate lymphoid cells (ILCs). ILCs are members of the innate immune system but with similar functions as T cells and include natural killer cells (NK) and ILC1, ILC2 and ILC3. While NK cells are the innate equivalents of cytotoxic CD8+ T cells, ILCs (ILC1, ILC2 and ILC3) can be compared to CD4+ T helper (Th1, Th2 and Th17) cells. What distinguishes ILCs as innate rather than adaptive immune cells is their inability to express antigen receptors or to undergo clonal selection/expansion when stimulated. ILCs rapidly respond to signals from infected or injured tissues or as more recently discovered, the microbiota, to produce cytokines that modulate both the innate and adaptive immune responses. One of these cytokines is interleukin 22 (IL-22), which has been found to affect the expression of a wide range of effector molecules involved in epithelial barrier maintenance [12].

The IL-22 cytokine has emerged as a master regulator of intestinal homeostasis and pathogen resistance by linking together and maintaining a balanced microbiota, an intact epithelium and a functioning immune system (Fig. 1). This review will give an overview of IL-22 signaling at the epithelial–microbiota interface and its role in homeostasis and bacterial pathogen resistance.

IL-22, an Epithelial-Activating Cytokine

IL-22 belongs to the IL-10 family of cytokines, sharing a similar secondary protein structure with other members of this family. The IL-22 receptor complex is composed of IL-22RA1 and IL-10R2 and initiates a signaling cascade through the activation of STAT3 [13,14]. IL-22RA1 is the receptor component specific for IL-22, which gives the signaling specificity and restricts the action of IL-22 to epithelial cells due to its expression pattern. Although IL-10R2 is expressed by multiple cells types, the IL-22RA1 can be found only on epithelial cells but not on immune cells, therefore limiting the existence of a functional IL-22 receptor complex to the epithelium [15].

IL-22 is produced by a variety of innate and adaptive immune cells. These include T cells (Th1, Th17 and Th22) and ILC3, also known as NK22 or NKp44 cells [13,16].

Upon binding its receptor on target epithelial cells and engaging the STAT3 signaling cascade, IL-22 induces the expression of many genes. Previous work carried out in our laboratory, using primary colonic organoids derived from wild-type and IL-22RA1 knockout mice, showed differential expression of genes involved in diverse protective functions: the epithelium and its protective mucus layer, ion channels, antimicrobials, tight and gap

junctions and certain immune functions. All of these elements work together in the maintenance of the epithelial barrier (Fig. 2) [17].

When homeostasis is breached, IL-22 plays a key role during both infection and chronic inflammation in the gut. IL-22 is highly up-regulated during infection with pathogens such as *Citrobacter rodentium* [18], *Salmonella* Typhimurium [19] and *C. difficile* [20], although its role is different in each case. Whereas IL-22 has a protective function during *Citrobacter* and *Clostridium* infections, it fails to prevent dissemination and promotes colonization by *Salmonella* due to increased gut inflammation.

Inflammatory bowel disease (IBD) is a chronic inflammatory disease linked to host genetic predisposition. For example, human genome-wide association studies (GWAS) have identified single nucleotide polymorphisms in the IL-22 promoter region that are linked to IBD, implying a more general role between IL-22 expression and the intestinal microbiota structure [21,22]. Several other genes linked to IBD, also identified by GWAS, are induced by IL-22 and relate to several aspects of maintenance of an intact epithelial barrier, again suggesting a critical role for IL-22 both in the homeostasis of the epithelial barrier and in the pathogenesis of IBD [12].

IL-22 Interaction with the Microbiota

The microbiota lives in a mutually beneficial relationship with its host and its composition is influenced by age, diet, disease, antibiotics and genetics [23–25]. As mentioned previously, the microbiota helps in host defense by competing with potential pathogens for resources, but it is also important for the correct development of the immune system [23,26]. Indeed, there is a close relationship between the microbiota and IL-22 production: the microbiota is required for proper development of IL-22-producing cells, as indicated by the reduction in the number of ILC3s in germ-free mice [27]. During bacterial infection, ILC3s have been shown to respond mainly to IL-1β and IL-23 produced by myeloid cells [28,29]. Moreover, direct effects of bacterial compounds on ILC3s have also been shown; for example, exogenous tryptophan metabolites produced by the microbiota act as aryl hydrocarbon receptor agonists controlling the maintenance, survival and function of ILC3s, including IL-22 production. Furthermore, ILC2s and ILC3s isolated from human tonsils produce IL-5, IL-13 and IL-22 when stimulated with pattern recognition receptor Toll-like receptor 2 ligands such as Pam3CYS or Pam2CYS. When co-stimulated with IL-23, this response was limited to ILC3s and resulted in the production of IL-22 [30].

In turn, it has been shown in mice that IL-22 expression can change the composition of microbiota, regulating the expansion of segmented filamentous bacteria (SFB) [31,32]. In the absence of IL-22, the number or SFB increases. Since animals colonized with SFB are resistant to infection by the intestinal pathogen *C. rodentium*, this appears to be detrimental for the host [33]. However, having elevated SFB is not enough for protection, and IL-22 expression is required to fend off *Citrobacter* infection [31]. Furthermore, studies on the probiotic effects of *Bifidobacterium lactis* BB12 have indicated that this bacterium may activate ILC3 cells through production of a low-molecular-weight peptide [34].

Other microbial metabolites such as short-chain fatty acids (SCFAs), which are by-products of bacterial fermentation in the large intestine, have been shown to promote gut barrier function through inducing the production of mucin [35]. The effect of SCFAs on IL-22-producing ILC3 cells have not been studied, but they may have indirect effects on these cells by acting on leukocytes in the gastrointestinal tract. For example, SCFAs such as butyrate have been shown to inhibit histone deacetylases in regulatory T cells and increase their proliferation, which in turn may affect the activity of ILC3s [36].

IL-22 Role in the Maintenance of Epithelium Integrity

An intact epithelium consists of a continuous wall of epithelial cells tightly adhered to each other by tight junctions and covered by a protective mucus layer. IL-22 regulates the expression of many genes involved in the maintenance of an intact epithelium (Fig. 2).

Firstly, there is a link between IL-22 production and the presence of a healthy mucus layer. The intestinal mucus layer is formed by complex multimers of secreted MUC2. Although there is no report of IL-22 regulating the production of MUC2, mice lacking MUC2 show an increased expression of genes belonging to the IL-22 pathway; probably, these genes were induced due to the resulting close contact of the microbiota with the epithelial surface [37]. The mucus layer not only does provide a filtering mechanism that prevents microbes to come into close contact with the epithelium but also contains an arsenal of antimicrobials such as RegIIIγ, β-defensins and S100A proteins. The expression of these compounds by epithelial cells and neutrophils is regulated by, although not exclusively, IL-22, helping control the microbiota and creating an effective defense mechanism against pathogens.

Maintenance of mucosal hydration is a key process in the formation of a protective barrier and one of the primary physiological roles of epithelial cells. When this hydration balance is broken, a pathological state ensues as exemplified by cystic

fibrosis (decreased hydration) or cholera (increased hydration). This water exchange occurs via chloride channels and potentiates the role of the mucus layer as a mechanical barrier by "flushing" the luminal surface. This "flushing" mechanism affects the translocation of pathogens, such as *Escherichia coli* and *Salmonella* Typhimurium. It also causes a shift in microbiota, affecting mostly Firmicutes and Bacteroidetes, in particular, the genre *Coprobacillus* (over-represented after "flushing"), *Parasporobacterium* and *Sporobacterium* (under-represented after "flushing") [38]. During inflammation, there is an inhibition of Ca^{+}-dependent chloride channels, reducing mucosal hydration [39]. IL-22 induces the expression of several chloride channel proteins (CLIC5, CLCA1, CLCA2 and CLCA4), in keeping with its anti-inflammatory role [17].

Underneath the MUC2 mucin layer and firmly attached to the cell membrane lies the glycocalyx. Like the mucus layer, the glycocalyx, the glycosylated cover on epithelial cells, is mainly formed by mucins, in this case, membrane-bound mucins (MUC1, MUC3, MUC4, MUC12, MUC13, MUC15, MUC17 and MUC20) [7,40]. Other glycosylated structures, like the carcinoembryonic antigen-related cell adhesion molecules (CEACAM), also form part of the glycocalyx. The glycocalyx can have a dual role during bacterial infection: on one hand, the glycosylated proteins can act as recognition molecules for bacterial pathogen adhesins (CEACAM1 serves as receptor for both *E. coli* and *Salmonella* spp [41]) but they can also provide a physical barrier that can protect against infection (the presence of the glycocalyx is important in the defense against *Shigella flexneri* infection [42]). Cell surface mucins can also act as sensors, initiating intracellular signaling cascades in response to bacteria and can even act as decoy ligands, by cleaving and releasing the extracellular domain [40]. IL-22 stimulation promotes the up-regulation of several membrane-bound mucins (MUC1, MUC3, MUC4, MUC13 and MUC20), as well as CEACAM molecules (CEACAM1, CEACAM2, CEACAM10 and CEACAM20), highlighting its role in the maintenance of this barrier [17].

Another gene regulated by IL-22 and also related to both mucus layer and glycocalyx is *Fut2*, encoding for α(1,2)-fucosyltransferase, the enzyme that catalyzes the addition of fucose residues to glycoproteins. Fucosylated carbohydrates expressed on epithelial cells are involved in generating an environmental niche for the microbiota, as many bacteria use them for attachment and as an energy source [43,44]. Fucose can function as mediator between the host and the microbiota, as signals from the microbiota are needed for fucosylation and, in turn, lack of FUT2 modifies the composition and diversity of the microbiota [17,45]. Defective FUT2 results in susceptibility to candidiasis and other metabolic, infectious and inflammatory diseases [46–48].

Finally, tight junctions and gap junctions maintain the intestinal barrier by keeping epithelial cells together while at the same time regulating permeability of ions, nutrients and water. Considering their importance, it is not surprising that proteins involved in the formation of tight and gap junctions have been associated with IBD [12,49]. IL-22 can also increase the expression of genes involved in tight and gap junction formation (cathepsin, claudin, GJA1, GJB3, MYO3A, GNA14 and CLECL14A), therefore playing a role in the maintenance of an intact epithelial barrier.

IL-22 Role in Modulating the Immune Response

Activated ILC3s produce membrane-bound lymphotoxin (LT) $\alpha_1\beta_2$ and IL-22, which promote local tissue protection and repair responses [50]. $LT\alpha_1\beta_2$ activates dendritic cells, which in turn produce high levels of IL-23 that feeds back to promote the activity of ILC3s and the differentiation of Th17 cells [51]. It is also worth mentioning that, in addition to $LT\alpha_1\beta_2$ and IL-22, ILC3s and Th17 cells also produce IL-17 and GM-CSF (granulocyte-macrophage colony-stimulating factor, recently renamed Csf2) and exert other immune modulatory effects through these pro-inflammatory cytokines, for example, antimicrobial production and neutrophil recruitment [52,53]. Despite its lack of a direct effect on immune cells, IL-22 engages the immune system by inducing the expression of cytokines such as IL-10 by epithelial cells, as only epithelial cells express IL-22RA1 [54]. Moreover, IL-22 plays a dual role in controlling inflammation on the one hand and promoting it on the other hand. In one study, human colonic sub-epithelial myofibroblasts were subject to a high concentration of IL-22 (100 ng/ml) and cDNA microarrays were used to identify altered gene expression. These showed an increased production of anti-inflammatory compounds such as Follistatin and IL-11 and the expression of pro-inflammatory IL-6 and many chemokines (CCL7, CXCL1, CXCL2, CXCL3, CXCL6 and CXCL8) [55]. Consistent with these results, when intestinal organoids were stimulated with IL-22, a number of antimicrobials and chemokines such as RegIIIγ, RegIIIβ, CXCL1, CXCL3 and CXCL5 were up-regulated. Interestingly, no cytokines were induced by IL-22 but a number of cytokine receptors were up-regulated (IL-4RA, IL-5RA and IL-13RA1) and IL-17RB was down-regulated [17].

Conclusions

In recent years, technical advances in the fields of microbial sequencing, transcriptomics and the culture of organoids have allowed great advances in our

understanding of the complex relationship between host and the microbiota. IL-22 showcases this intimate cross-talk: produced by the host but driven by the microbiota, it plays a key role in the maintenance of a healthy gut, allowing both the host and the microbiota to thrive.

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Abbreviations used:
ILC, innate lymphoid cell; IBD, inflammatory bowel disease; SFB, segmented filamentous bacteria; SCFA, short-chain fatty acid.

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