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Minireview

MINIREVIEW

Cytokines IL-17 and IL-22 in the host response to infection

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One sentence summary: The review highlights the pivotal roles of IL-17 and IL-22 in host defense against microbes.

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ABSTRACT

Cytokines IL-17 and IL-22 play pivotal roles in host defense against microbes and in the development of chronic inflammatory diseases. These cytokines are produced by cells that are often located in epithelial barriers, including subsets of T cells and innate lymphoid cells. In general, IL-17 and IL-22 can be characterized as important cytokines in the rapid response to infectious agents, both by recruiting neutrophils and by inducing the production of antimicrobial peptides. Although each cytokine induces an innate immune response in epithelial cells, their functional spectra are generally distinct: IL-17 mainly induces an inflammatory tissue response and is involved in the pathogenesis of several autoimmune diseases, whereas IL-22 is largely protective and regenerative. In this review, we compare IL-17 and IL-22, describing overlaps and differences in their cellular sources as well as their regulation, signaling, biological functions and roles during disease, with a focus on the contribution of these cytokines to the gut mucosal barrier during bacterial infection.

Keywords: IL-17; IL-22; mucosal immunity

INTRODUCTION

Leukocytes constitute the second largest class of cells found within the intestine, second only to epithelial cells (Artis 2008; Ma *et al*. 2008). Within the intestinal mucosa, leukocyte types are segregated into two distinct anatomic areas: the lamina propria (LP) and the epithelium (Hooper and Macpherson 2010; Maynard *et al*. 2012). The LP harbors adaptive immune cells such as T cells and B cells, as well as innate immune cells, including dendritic cells (DCs), macrophages and eosinophils. In contrast, specific subsets of cells called intraepithelial lymphocytes (IELs) are found associated with the epithelial layer, in particular at the basement membrane between enterocytes (Cheroutre, Lambolez and Mucida 2011). Gut IELs are almost exclusively T cells, as originally estimated based on histological sections (Darlington and Rogers 1966). In addition, CX3C-chemokine receptor 1 (CX3CR1)$^{+}$ macrophages and DCs reside within the intestinal epithelial layer and have the capacity to sample antigens in the gut and promote appropriate T-cell responses (Bogunovic *et al*. 2009; Schulz *et al*. 2009).

The gastrointestinal (GI) tract is home to trillions of microbes, comprising thousands of species that reside within the lumen (Mowat and Agace 2014). These microbes, collectively referred to as the gut microbiota, vary in composition and number along the length of the GI tract (Mowat and Agace 2014). Although most intestinal microbes are beneficial and live symbiotically with the host, disruption of the epithelial barrier or invasion by pathogenic microbes elicits a complex immune response involving the intestinal epithelium and leukocytes. Restoration

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of epithelial integrity and eradication of invading microbes are orchestrated through the activity of cytokines and chemokines, which enable epithelial cells and leukocytes to communicate, and promote responses such as cell migration, differentiation, replication or activation of cell-intrinsic defenses (Matthews, Weight and Parkos 2014).

Intestinal cytokine responses comprise complex signaling networks, wherein cytokines regulate one another (Garlanda, Dinarello and Mantovani 2013; Manzanillo, Eidenschenk and Ouyang 2015). As such, disrupting one particular cytokine response can lead to different outcomes depending on the cell types and the intestinal regions involved, as well as on the gut microbiota. Recognizing the context of these signaling networks can help in understanding the various roles of intestinal cytokines under different conditions. In this review, we discuss recent findings on the interleukin (IL-) 17 and IL-22 pathways, focusing on their roles in intestinal homeostasis and in the host response to infection. Furthermore, we describe the various cell types that produce IL-17 and IL-22 during bacterial infection, and we discuss how these responses are activated and regulated by pattern recognition receptor (PRR)-dependent pathways. Finally, we examine the importance of IL-17 and IL-22 responses in mediating gut immunity to bacterial-induced colitis.

IL-17 and IL-22 are related, but distinct cytokines

Cytokines are secreted proteins that play an important role in intercellular communication. In addition to orchestrating the immune response to pathogens, cytokines also regulate wound healing, angiogenesis and physiological and pathological tissue reorganization (Zhu and Emerson 2002; Leoni *et al.* 2015; Kreuger and Phillipson 2016). Cytokines elicit biological effects by binding to the extracellular moiety of specific transmembrane receptor proteins on the outer membrane of cells. This binding triggers a signaling pathway, which leads to functional changes in these cells. Cytokines are grouped into families based on similarities in genome location, gene structure, structure of the secreted protein and the receptor(s) the cytokine engages. IL-17 and IL-22 are leukocyte-derived cytokines that primarily impact epithelial cells in tissues such as the gut, the lung and the skin (Blaschitz and Raffatellu 2010; Qu *et al.* 2013).

IL-17 belongs to the IL-17 cytokine family, whereas IL-22 is a member of the IL-10 cytokine family (Park *et al.* 2005). The *in vivo* effector functions of IL-17 and IL-22 are crucial to maintaining mucosal immunity against specific pathogens and include induction of antimicrobial proteins, recruitment of neutrophils to sites of bacterial invasion and enhancement of mucosal barrier repair and maintenance by stimulating epithelial cell proliferation and tight junction protein production (Ye *et al.* 2001a; Liang *et al.* 2006; Aujla *et al.* 2008; Raffatellu *et al.* 2008; Zheng *et al.* 2008; Conti *et al.* 2009; Pickert *et al.* 2009).

There are six members of the IL-17 family: IL-17A (commonly referred to as IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F (Kolls and Linden 2004; Iwakura *et al.* 2011). These cytokines are often co-expressed and can form homo- and heterodimers. In 1995, IL-17 receptor A (IL-17RA) was identified as a new cytokine receptor for IL-17A and was later found to be part of a new cytokine receptor family (Yao *et al.* 1995). The IL-17 receptor family now consists of five members (IL-17RA, RB, RC, RD and RE), all of which, like their ligands, share sequence homology (Aggarwal and Gurney 2002). IL-17RA is expressed on a wide range of tissues and cell types. Upon stimulation with IL-17, IL-17RA initiates the activation of downstream signaling pathways to induce the production of proinflammatory molecules. However, IL-17RA alone is insufficient to mediate IL-17 signaling. Further evaluation revealed that IL-17 signals through a heterodimeric receptor complex composed of IL-17RA and IL-17RC (Toy *et al.* 2006; Rickel *et al.* 2008; Song *et al.* 2011). It is proposed that the binding of ligand to the first IL-17 receptor subunit alters the affinity and specificity of the second binding event, thereby promoting the formation of a heterodimeric, rather than a homodimeric, receptor complex (Ely, Fischer and Garcia 2009; Liu *et al.* 2013). IL-17 receptors work through a pathway that depends on ACT1s (also referred to as CIKS) and activates NF-κB and MAP kinases for the induction of proinflammatory mediators such as IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), some chemokines (CXCL1, CXCL10, CCL2, CCL7, CCL20) and matrix metalloproteinase-3 (MMP3) and MMP13 (Fossiez *et al.* 1996; Gaffen 2009).

IL-22 signals through a heterodimeric receptor comprised of the broadly expressed IL-10R2 subunit and the more restricted IL-22R1 subunit (Dumoutier, Louahed and Renauld 2000; Dumoutier *et al.* 2000; Xie *et al.* 2000). IL-22R1 is mainly expressed on intestinal and respiratory epithelial cells, on keratinocytes and on hepatocytes, but not on cells of hematopoietic origin (Dudakov, Hanash and van den Brink 2015). IL-22 binds first to IL-22R1, and then the IL-22–IL-22R1 complex binds IL-10R2 to propagate downstream signals (Logsdon *et al.* 2002; Li *et al.* 2004). IL-22 signals through the JAK-STAT pathway, inducing phosphorylation of the kinases JAK1 and TYK2, as well as of the transcription factors STAT1, STAT3 and STAT5 (Dumoutier, Louahed and Renauld 2000; Dumoutier *et al.* 2000; Xie *et al.* 2000; Pestka *et al.* 2004). Triggering this signaling pathway allows IL-22 to induce the expression of various tissue-specific genes including those that encode proteins involved in tissue inflammation, immunosurveillance and homeostasis (Wolk *et al.* 2004; Liang *et al.* 2006, 2010; Zheng *et al.* 2008). By eliciting various innate defense mechanisms from epithelial cells, IL-22 is essential for host defense at mucosal surfaces against extracellular pathogens such as bacteria and yeast (Zheng *et al.* 2007, 2008; Aujla *et al.* 2008; Sonnenberg *et al.* 2012). In general, IL-22 acts to strengthen epithelial barrier functions and is involved in tissue homeostasis as well as in tissue repair and wound healing. However, excessive or prolonged production of IL-22 can cause pathology, such as psoriasis-like skin inflammation (Ma *et al.* 2008).

IL-17 was initially found to be secreted by a subset of $CD4^+$ T cells termed Th17 cells, which also secrete the cytokines IL-22 and IL-21 (Harrington *et al.* 2005; Langrish *et al.* 2005; Park *et al.* 2005; Korn *et al.* 2007; Zheng *et al.* 2007). However, recent studies identified several other cell types that contribute to IL-17 and IL-22 production (Wolk *et al.* 2002, 2011; Kondo *et al.* 2009; Ortega *et al.* 2009), including activated $CD4^+$ T cells (Harrington *et al.* 2005; Park *et al.* 2005; Wolk *et al.* 2011), $CD8^+$ T cells (Kondo *et al.* 2009; Ortega *et al.* 2009), as well as various innate lymphoid cells (ILCs) such as natural killer (NK) cells (Hughes *et al.* 2010; Pandya *et al.* 2011), NKT cells (Rachitskaya *et al.* 2008), lymphoid tissue inducer (LTi) cells (Cupedo *et al.* 2009; Crellin *et al.* 2010) and LTi-like cells (Luci *et al.* 2009; Kim *et al.* 2011) (Table 1). The role of these cells in secreting IL-17 and IL-22 is discussed in detail below.

Increasing evidence shows that IL-17 and IL-22 can be protective against infections, largely by the following two mechanisms. The first involves production of antimicrobial peptides, which is largely dependent on the synergistic action of IL-17 and IL-22 on epithelial cells (Wolk *et al.* 2004; Liang *et al.* 2006;

Table 1. Cell types that secrete IL-17 and/or IL-22.

Cell type	Cytokine secreted	Transcription factor	Surface phenotype	Human/mouse studies	Ref
Th17	IL-17, IL-22	RORγt	CD4$^+$, CCR4$^+$, CCR6$^+$, CXCR3$^-$, CD161$^+$, IL23R$^+$	Human and mouse studies	Cosmi *et al.* (2008), Kleinschek *et al.* (2009); Park *et al.* (2005)
Th22	IL-22	Unknown (AHR?)	CD4$^+$, CCR4$^+$, CCR6$^+$, CCR10$^+$	Human	Eyerich *et al.* (2009); Trifari *et al.* (2009)
Tc22	IL-22	Unknown	CD4$^+$, CD8$^+$, IL-21R$^+$	Human	Nograles *et al.* (2009)
Tc17	IL-17	Unknown	CD8$^+$, CD45RB$^+$, CD38$^+$, CD103$^+$, CCR6$^+$	Mouse	Yen *et al.* (2009)
γδ cells	IL-17, IL-22	AP1	CD27$^-$, CD28$^-$, NKP80$^+$, CD45RA$^+$, CD158$^+$	Human and mouse	Peng *et al.* (2008), Riera-Sans and Behrens (2007), Shibata *et al.* (2008)
NKT	IL-17, IL-22	ROR	CD3$^+$, CD56$^+$	Mouse	Rachitskaya *et al.* (2008)
LTi	IL-17, IL-22	RORC	CD3$^-$, CD56$^-$, CD161+, NKp44$^-$, CD117$^+$, CD127$^+$	Human	Cupedo *et al.* (2009)
NKp46$^+$	IL-17, IL-22	RORC	CD3-, CD56$^+$, NKp44$^+$ NKp46$^+$, NKG2D$^+$, CD117$^+$, CD127$^+$	Mouse	Satoh-Takayama *et al.* (2008)
NK22	IL-22	Unknown	CD3$^-$, CD56$^+$, NKp44$^+$ CD117$^+$, CD127$^+$	Mouse	Norian *et al.* (2009)

Zheng *et al.* 2008; Feng *et al.* 2009). The second mechanism involves IL-17 and IL-22 inducing gut and lung epithelial cells to express chemokines that attract granulocytes, particularly neutrophils, to sites of infection (Albanesi *et al.* 2000; Nograles *et al.* 2008). Despite their protective role against extracellular pathogens, IL-17 and IL-22 may also be detrimental when they are not tightly regulated. Indeed, these cytokines contribute to the pathology observed in several autoimmune and chronic inflammatory diseases, including psoriasis, asthma and inflammatory bowel disease (Teunissen *et al.* 1998; Andoh *et al.* 2005; Chan *et al.* 2006; Wolk *et al.* 2007; McKinley *et al.* 2008).

IL-17 and IL-22 are regulated by PRR-dependent pathways

The innate immune system is crucial for controlling infectious agents. By using a wide range of innate immune sensors termed pattern recognition receptors (PRRs), the host recognizes general pathogen-associated molecular patterns (PAMPs), initiating a response that limits the pathogen and alerts the adaptive immune system (Fig. 1). Two of the most important PRR protein families are the membrane-bound Toll-like receptors (TLRs) and the cytosolic Nod-like receptors (NLRs). Mammals have many TLRs, each of which recognizes certain PAMPs. For example, TLR4 recognizes lipopolysaccharide, a major component of the Gram-negative bacterial cell wall (Lu, Yeh and Ohashi 2008). TLR2, which is also located on the cell membrane, recognizes bacterial surface lipoproteins (Kang *et al.* 2009), whereas TLR9, which is located in the membrane of cellular organelles known as endosomes, recognizes non-methylated CpG sequences present in bacterial DNA (Latz *et al.* 2004). When a TLR binds to its ligand, host-cell adaptor proteins, such as Myeloid differentiation primary response gene 88 (MyD88), associate with the cytoplasmic part of the receptor, and downstream signaling is initiated (Medzhitov *et al.* 1998) (Fig. 1).

TLR-dependent pathways are important for host defense against bacterial pathogens (Charrel-Dennis *et al.* 2008; Kawai and Akira 2011; Wang and Liu 2016), including pathways that control IL-17 and IL-22 responses (Abt *et al.* 2016) (Fig. 1). For example, it was recently shown that TLR7 stimulation with the synthetic ligand resiquimod (R848) induces IL-23 expression followed by a burst of IL-22 secretion by ILCs, leading to expression of the antimicrobial lectin REG3γ and restoration of colonization resistance against vancomycin-resistant *Enterococcus* (VRE) (Abt *et al.* 2016).

Interleukin-23 is a heterodimeric cytokine comprised of the subunits p19 and p40 (Hunter 2005), and is a crucial upstream regulator of IL-17 and IL-22 expression *in vivo* (Dubin and Kolls 2007; Godinez *et al.* 2009; Gasse *et al.* 2011; Cox *et al.* 2012). In a mouse model of *Klebsiella pneumoniae* lung infection, bacterial stimulation of TLR4 on DCs results in IL-23 production (Happel *et al.* 2003). IL-23, in turn, triggers rapid production of IL-17 and IL-22 by T cells (Ye *et al.* 2001a,b; Happel *et al.* 2005; Aujla *et al.* 2008), which is required for efficient neutrophil recruitment in this model. Similarly, injection of *Escherichia coli* into the peritoneal cavity of naïve mice triggers IL-23 production in a TLR4-dependent manner, and the resulting secreted IL-17 largely originates from γδ T cells (Shibata *et al.* 2007). TLR4 also modulates IL-23 expression in mouse bone marrow-derived conventional DCs during *Salmonella enterica* serovar Enteritidis infection (Siegemund *et al.* 2007). In the presence of intestinal inflammation, IL-23 stimulates T cells in the murine intestinal mucosa to produce IL-17 and IL-22, promoting neutrophil recruitment in response to *S. enterica* serovar Typhimurium infection (Godinez *et al.* 2009). The TLR/IL-23/IL-17 axis is also an important player in vaccine-induced protection, wherein TLR4 signaling is required for vaccine-induced immunity to *Bordetella pertussis* in mice (Higgins *et al.* 2006). In this model, production of IL-23 and IL-1β by DCs contributed to Th17 cell differentiation, while increases in IL-17 levels led to enhanced bacterial clearance and macrophage bactericidal activity in a dose-dependent fashion (Higgins *et al.* 2006).

All TLRs except TLR3 require MyD88 as an adaptor to mediate signal transduction (Gay *et al.* 2014). MyD88 appears to be crucial for inducing maximal expression of IL-17 and IL-22 in

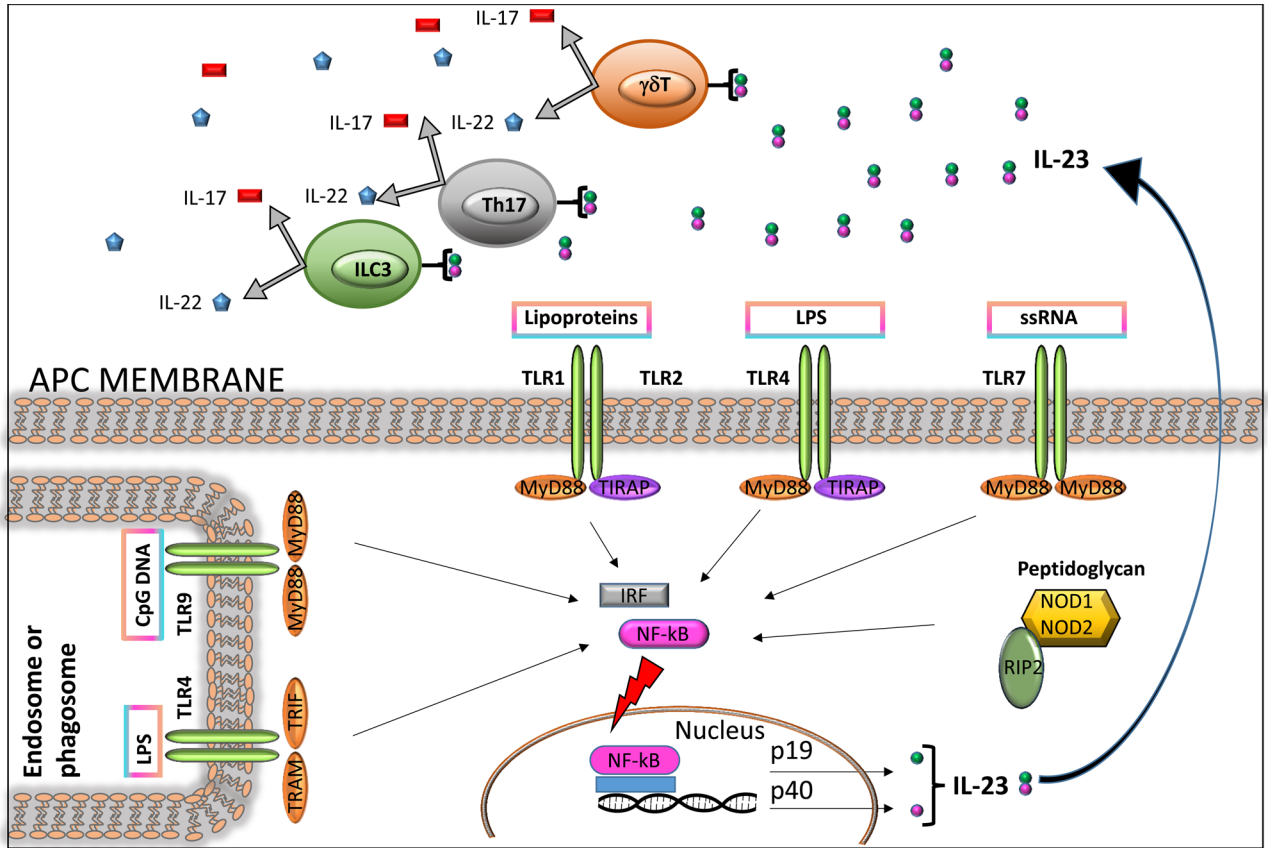

Figure 1. Bacterium-induced signaling in antigen-presenting cells (APCs) leads to IL-23 production and subsequent activation of IL-17 and IL-22-producing cells. APCs, for instance DCs and macrophages, express PRRs on their surface, such as TLRs, and intracellular receptors in their cytosol, such as NLRs. These PRRs recognize conserved microbial-associated molecular motifs and PAMPs, including LPS, lipoproteins, and CpG oligodeoxynucleotides. When a TLR binds to its cognate PAMP, host-cell adaptor molecules such as MyD88, TIRAP and TRIF are recruited, and downstream signaling is initiated. The resulting activation of nuclear factor-κB (NF-κB) promotes transcription of a range of genes coding for proinflammatory cytokines, including IL-23, which trigger the production of IL-17 and IL-22 in cell subsets including Th17, $\gamma\delta$ T and ILC3.

the gut and the lung (Lebeis *et al.* 2007; Gibson *et al.* 2008; Zhang *et al.* 2009; Keestra *et al.* 2011). In the *S.* Typhimurium colitis model, *Myd88*$^{-/-}$ mice exhibit a delayed mucosal inflammatory response and blunted IL-17 and IL-22 levels when compared to wild-type controls (Keestra *et al.* 2011). During gut infection with *Citrobacter rodentium*, *Myd88*$^{-/-}$ mice display increased mortality, intestinal pathology and systemic bacterial spread; whether this is associated with IL-17 and IL-22 responses has yet to be elucidated (Lebeis *et al.* 2007; Gibson *et al.* 2008). In the lung, *Myd88*$^{-/-}$ mice exhibit a reduced innate mucosal IL-17 response during infection with *Chlamydia muridarum* (Zhang *et al.* 2009). Moreover, in a T-cell transfer model of colitis, *Myd88*$^{-/-}$ CD4^{+} T cells express lower levels of IL-17 than wild-type CD4^{+} T cells, indicating a direct role for MyD88 signaling in modulating T-cell effector function (Fukata *et al.* 2008).

Whether MyD88-dependent regulation of T-cell-induced colitis is due to TLR signaling or IL-1 family cytokine signaling remains unclear. Fukata *et al.* (2008) showed that CD4^{+}CD45Rb^{high} T cells express significant levels of TLRs, suggesting a role for TLR signaling by T cells in Th17 differentiation and in the development of inflammatory bowel disease. On the other hand, Chang *et al.* (2013) demonstrated that MyD88 mediates IL-1 signaling in CD4^{+} T cells for the upregulation of IL-23R by IL-23, which expands committed Th17 cells via mTOR activation.

The cytosolic NLRs are another class of PRRs activated during enteric infections, recognizing bacterial PAMPs in the cytosol (Fig. 1) (Inohara and Nunez 2001). NLRs are classified into several subfamilies on the basis of their amino-terminal domain (Ting *et al.* 2008), including the CARD-containing nucleotide-binding oligomerization domain proteins (e.g, NOD1, NOD2 and NLRC4), the pyrin domain-containing proteins (e.g. NLRP3) and the BIR-containing proteins (also known as NAIPs or BIRCs). NOD receptors recognize fragments of peptidoglycan; specifically, NOD1 recognizes γ-D-glutamyl-meso-diaminopimelic acid (iE-DAP), a molecule produced by Gram-negative bacteria (Chamaillard *et al.* 2003; Girardin *et al.* 2003a,b), whereas NOD2 recognizes muramyl dipeptide (MDP), which is present in both Gram-positive and Gram-negative bacteria (Girardin *et al.* 2003a,b). Several NLRs have been shown to have a role in inflammatory diarrhea. Mice deficient in *Nod1* and *Nod2* exhibit a delayed intestinal inflammatory response in colitis models employing *S.* Typhimurium or *C. rodentium* (Geddes *et al.* 2011). In the cecal tissue of these models, when compared to wild-type mice, absence of both *Nod1* and *Nod2* results in reduced amounts of IL-17 and IL-22, as well as the antimicrobial proteins RegIIIγ and lipocalin 2 (Geddes *et al.* 2011).

NLRP3 and NLRC4 trigger the formation of cytosolic protein complexes called inflammasomes, which in turn regulate the maturation of the cytokines IL-1β and IL-18 (Latz, Xiao and Stutz

2013). Inflammasomes are activated in response to a variety of signals that indicate injury to the host, including tissue damage, metabolic stress and infection. NLRP3 responds to a wide range of PAMPs and DAMPs, including bacterial messenger RNA, bacterial DNA:RNA hybrids, MDP, DNA and RNA viruses, fungi, protozoa, ATP, uric acid crystals, silica, aluminum hydroxide, asbestos and bee venom (Kanneganti *et al.* 2006; Dostert *et al.* 2008; Hornung *et al.* 2008; Marina-Garcia *et al.* 2008; Sander *et al.* 2011; Franchi *et al.* 2014; Kailasan Vanaja *et al.* 2014; Sha *et al.* 2014). The NLRC4 inflammasome is activated by flagellin (Franchi *et al.* 2006; Miao *et al.* 2006) and the inner rod proteins of type III secretion systems (Miao *et al.* 2010). The inflammasome is a key regulator of immune responses in the gut and inflammasome-dependent IL-17 production has been implicated in protection from bacterial and fungal infection. IL-1β produced by NLRP3 inflammasome activity has been shown to mediate a protective Th17 response against the *E. coli* heat-labile enterotoxin in mice, indicating that NLRP3 activation could regulate IL-17 responses (Brereton *et al.* 2011). Inflammasome-mediated IL-1β plays a critical role in promoting Ag-specific Th17 cells and in generating shielding immunity against *B. pertussis* infection (Dunne *et al.* 2010). It has also been demonstrated that caspase-1 and ASC are important in the defense against *Candida* through IL-1β and IL-18 expression and consequent induction of antifungal Th1 and Th17 responses (van de Veerdonk *et al.* 2011). Moreover, two recent studies (Levy *et al.* 2015; Nowarski *et al.* 2015) demonstrated that epithelial inflammasome activation and IL-18 secretion can control intestinal homeostasis or induce autoinflammation. ILC3 cells are triggered to secrete IL-22, regulating IL-18 expression in epithelial cells, in turn modulating homeostasis and inflammation. Finally, the IL-18 pathway seems to take part in the host's defense against *C. rodentium* infection downstream of IL-22 (Munoz *et al.* 2015).

IL-17 and IL-22-producing cells in response to acute infection

T helper cells

During the immune response to infection, IL-17A/F and IL-22 are often produced at the same time and at high levels in inflamed tissues. In general, a broad variety of T cells and other leukocytes secrete IL-17 and/or IL-22 (Table 1). The most characterized IL-17/IL-22-secreting cells are T helper 17 (Th17) cells (Korn *et al.* 2009). Th17 cells were first described as peripheral CD4$^+$ T cells that differentiate into a distinct lineage in a GATA-3 and T-bet-independent fashion (Harrington *et al.* 2005; Park *et al.* 2005). This T-cell population is abundant at homeostasis in gut-associated tissues, particularly in the LP, and is defined by expression of the transcription factor RORγt (Ivanov *et al.* 2006, 2008). Th17-cell differentiation depends on IL-6 and on transforming growth factor β (TGF-β) (Bettelli *et al.* 2006; Ivanov *et al.* 2006; Mangan *et al.* 2006). Signal transduction downstream of IL-6 and TGF-β, including STAT3 activation downstream of the IL-6 receptor, induces expression of RORγt, which promotes transcription of *Il17a* and *Il17f* (Ivanov *et al.* 2006; Harris *et al.* 2007; Yang *et al.* 2007).

In addition to IL-6 and TGFβ, commensal microbes are necessary for the development of Th17 cells (Atarashi *et al.* 2008; Hall *et al.* 2008), as Th17 cells are absent in germ-free mice (Ivanov *et al.* 2006). Monoassociation of germ-free mice with commensal microbes of the class Clostridiales known as 'Candidatus Arthromitus' or 'segmented filamentous bacteria' (SFB) is sufficient to induce Th17-cell development (Gaboriau-Routhiau *et al.* 2009; Ivanov *et al.* 2009; Wu *et al.* 2010). Colonization of mice with SFB results in rapid upregulation of serum amyloid A (SAA) proteins in intestinal epithelial cells, which is both necessary and sufficient to directly promote proliferation of RORγt$^+$ CD4$^+$ T cells and IL-17 production (Sano *et al.* 2015). Moreover, IL-22 derived from group 3 innate lymphoid cells (ILC3) seems to potentiate expression of SAAs by intestinal epithelial cells (Atarashi *et al.* 2015; Sano *et al.* 2015). CD11c$^+$ myeloid cells and adhesion-elicited epithelial cell production of reactive oxygen species also contribute to SAA-dependent production of Th17-promoting cytokines (Atarashi *et al.* 2015).

TLR, inflammasome and dectin signaling each appear to be required for SFB-mediated Th17-cell development, suggesting that there may be redundant innate signals (Ivanov *et al.* 2009). Additionally, a recent study suggests that intimate adhesion of SFB to the epithelium is important for Th17 development (Atarashi *et al.* 2015). As SFB have not been identified in the human gut, it is not clear yet whether microbes contribute to Th17 development in humans. Nevertheless, Atarashi *et al.* (2015) showed that Th17 cells develop in mice upon infection with the human pathogen Enterohemorragic *E. coli* O157:H7, as well as after administration of a mixture of adherent human commensal strains belonging to different species, including *Clostridium*, *Bifidobacterium*, *Ruminococcus* and *Bacteroides* isolated from fecal samples of a patient with ulcerative colitis.

The Th17 response is a crucial arm of mucosal immunity against bacterial pathogens in the lung and the intestine. These cells mediate protection in a number of models of lung infection, including *K. pneumoniae*, *Pseudomonas aeruginosa*, *Shigella flexneri* and several *Mycobacterium* species (Khader *et al.* 2007; Umemura *et al.* 2007; Aujla *et al.* 2008; Priebe *et al.* 2008). In the GI tract, Th17 cells increase host resistance against *Helicobacter pylori*, *C. rodentium* and *S.* Typhimurium (Wu *et al.* 2007; Raffatellu *et al.* 2008; Ivanov *et al.* 2009; Velin *et al.* 2009; Sellge *et al.* 2010). For instance, in a simian immunodeficiency virus infection model in macaques, depletion of gut CD4$^+$ Th17 cells led to increased systemic dissemination of *S.* Typhimurium (Raffatellu *et al.* 2008). Similarly, depletion of CD3$^+$ T cells in the streptomycin-treated mouse model of *S.* Typhimurium colitis resulted in a blunted innate IL-17 response and an associated decrease in mucosal protection against the pathogen (Raffatellu *et al.* 2008; Godinez *et al.* 2009). A subset of LP CD4$^+$ T cells that express IL-17 and IL-22 during the innate phase of infection with *S.* Typhimurium and *C. rodentium* has subsequently been identified and termed innate Th17 (iTh17) cells (Geddes *et al.* 2011). Finally, two novel subsets of Th17 cells have recently been identified: a proinflammatory subset that produces GM-CSF (Codarri *et al.* 2011; El-Behi *et al.* 2011) and a regulatory subset that produces IL-10 (Esplugues *et al.* 2011). The role of these cell subsets in response to infection is unknown.

Beyond the mucosa, SFB also trigger development of systemic Th17 cells, which can be detrimental; for example, by triggering spontaneous arthritis in a mouse model (Wu *et al.* 2010). Similarly, monoassociation of mice with SFB exacerbates the course of experimental autoimmune encephalomyelitis (Lee *et al.* 2011), a paralytic autoimmune disease induced by immunization with myelin protein and mediated by Th17 cells. Thus, depending on the setting, Th17 cells can be protective, but they can also initiate or exacerbate autoimmunity.

In addition to Th17 cells, a second T helper cell population was recently described as a major source of IL-22 in human tissue. Named Th22 cells, this population expresses the CCR4 and CCR10 chemokine receptors, and is enriched for during inflammatory skin diseases (Nograles *et al.* 2008; Duhen *et al.* 2009;

Eyerich *et al.* 2009; Trifari *et al.* 2009). In contrast to Th17 cells, which are able to secrete both IL-17 and IL-22, Th22 cells do not secrete IL-17. A third group of adaptive immune cells that produce IL-17 and/or IL-22 are $CD8^+$ T cells (Kondo *et al.* 2009; Ortega *et al.* 2009). Similar to Th17 cells, a population of $CD8^+$ T cells produces IL-17, but it is unclear whether these cells coproduce IL-22 and whether they represent a functionally distinct subset (Tc17 cells) of $CD8^+$ T cells (Shin *et al.* 1999). Furthermore, there is evidence for a subgroup of $CD8^+$ T cells that produces IL-22, but not IL-17 (Tc22 cells) (Nograles *et al.* 2009). The discovery of these distinct lineages of leukocytes that produce different subsets of cytokines emphasizes that production of IL-17 and IL-22 is regulated by distinct processes, underlining the potential complexity of these responses in different models of infection and autoimmunity.

$\gamma\delta$ T cells

$\gamma\delta$ T cells are an innate immune cell population that plays important roles at the mucosal barrier. These cells are predominantly found in the intestinal epithelial lymphocyte compartment of the intestinal mucosa and they can be classified into an IFN-γ-producing subset or an IL-17 and IL-22-producing subset (Cua and Tato 2010). $CD27^-$ $ROR\gamma t^+$ $\gamma\delta$ T cells secrete IL-17 and/or IL-22 when stimulated with IL-23, IL-1β, or with a cocktail of phorbol 12-myristate-13-acetate (PMA) and ionomycin (Jensen *et al.* 2008; Ribot *et al.* 2009). Relatedly, IL-23 is sufficient to induce IL-17A production in $\gamma\delta$ T cells purified from the peritoneum of infected mice (Shibata *et al.* 2007). Of particular note, $\gamma\delta$ T cells can rapidly produce IL-17A upon TLR and/or cytokine stimulation. Early production of IL-17A was observed during *E. coli* infection, where peritoneal IL-17A was found as early as 1 h after infection (maximal production at 6 h), and large amounts of neutrophils were recruited by 24 h post-infection (Shibata *et al.* 2007). Similarly, IL-17A production by peritoneal $\gamma\delta$ T cells is rapidly induced after injection of heat-killed mycobacteria (Martin *et al.* 2009) or after sepsis due to cecal puncture (Flierl *et al.* 2008).

In the skin, IL-17A-producing $\gamma\delta$ T cells can promote the formation of abscesses and granulomas to help mediate containment of microbial infections (Cho *et al.* 2010). In cutaneous *Staphylococcus aureus* infections, IL-17A-producing skin cells play a critical role in the immune response against this pathogen. In this setting, IL-17A helps to recruit neutrophils into skin abscesses, to limit the size of abscesses and to reduce the number of *S. aureus* bacteria contained in these abscesses (Cho *et al.* 2010).

In *Listeria monocytogenes* infections, IL-17A-producing $\gamma\delta$ T cells contribute to bacterial clearance by containing the bacteria within granulomas in the liver and by promoting the recruitment of neutrophils and other myeloid cells (Hamada *et al.* 2008). In the absence of $\gamma\delta$ T cells or IL-17A, bacterial numbers in the liver are more than 100-fold higher than in wild-type mice (Hamada *et al.* 2008). Moreover, *L. monocytogenes* infection in $\gamma\delta$ T-cell-deficient mice is associated with large inflammatory lesions in the liver with necrotic hepatocytes (Mombaerts *et al.* 1993; Fu *et al.* 1994) that are similar to those seen in IL-17A-deficient mice (Hamada *et al.* 2008). IL-17RA and IL-23 are required to control *L. monocytogenes* systemic infections and $\gamma\delta$ T cells are the principal source of IL-17A early in infection (Meeks *et al.* 2009), although $CD4^-8^-$ $\alpha\beta$ T cells also produce IL-17A in the peritoneum (Riol-Blanco *et al.* 2010).

$\gamma\delta$ T cells can also be pathogenic. As with many T-cell populations, inappropriate or sustained production of a proinflammatory cytokine can have negative consequences. Several autoimmune disease models have identified IL-17A-producing $\gamma\delta$ T cells as being important in disease progression. For example, in a model of collagen-induced arthritis, oligoclonal IL-17A-producing $\gamma\delta$ T cells accumulate in the lymph nodes and joints of collagen-injected mice (Roark *et al.* 2007). Depletion of Vγ4 $\gamma\delta$ T cells greatly reduces disease severity consistent with a significant reduction in pathogenic anticollagen IgG2a (Roark *et al.* 2007). Moreover, in different models of neuroinflammation, $\gamma\delta$ T cells play an important role in early activation and recruitment of cells through the release of IL-17A. In experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis, $\gamma\delta$ T cells producing IL-17A accumulate in the brain (Jensen *et al.* 2008; Sutton *et al.* 2009). Although $\gamma\delta$ cells alone are not sufficient to reconstitute disease ($\alpha\beta$ T cells are also required), $\gamma\delta$-deficient mice exhibit reduced EAE severity (Sutton *et al.* 2009). In addition to producing IL-17A, $\gamma\delta$ T cells also inhibit $CD4^+$ Treg responses in EAE and reverse Treg suppression of $\alpha\beta$ T cells *in vitro* (Petermann *et al.* 2010).

The involvement of IL-17A-producing $\gamma\delta$ T cells in models of microbial, autoimmune and inflammatory diseases underscores their importance in the initiation and resolution of acute inflammatory responses in a variety of settings. Despite their small numbers, $\gamma\delta$ T cells can have large effects on the type of immune response and the disease outcome.

Innate lymphoid cells

The importance of a non-T-cell source for IL-22 was first demonstrated in a *C. rodentium* infection model, in which wild-type mice and mice that lack B and T cells ($Rag2^{-/-}$) exhibited comparable IL-22 production and normal host defense during the early phase of infection (Zheng *et al.* 2008). These newly identified cells were termed ILCs, then later categorized in human tonsils and intestinal LP as ILC3 based on their production of IL-17 and IL-22 (Montaldo *et al.* 2014).

ILC3s can secrete IL-17 and IL-22 in response to IL-1β and/or IL-23 due to their constitutive expression of IL-1R and/or IL-23R (Spits and Cupedo 2012). ILCs, like B and T cells, are derived from a common lymphoid progenitor. However, they represent a very heterogeneous group of cells. All IL-17/IL-22-producing ILCs are dependent on $ROR\gamma t$ for their development, including LTi cells (Takatori *et al.* 2009), LTi-like ILCs (Buonocore *et al.* 2010), $NKp46^+$ ILCs (Satoh-Takayama *et al.* 2008; Cella *et al.* 2009; Luci *et al.* 2009; Sanos *et al.* 2009), invariant NKT cells (Doisne *et al.* 2011) and mucosal-associated invariant T cells (Le Bourhis *et al.* 2011). Unlike Th17 cells, antigenic priming is not required for activation of LTi, LTi-like, $NKp46^+$ ILCs and probably $\gamma\delta$ T cells; IL-23 stimulation is often sufficient for inducing IL-17 and IL-22 secretion by these cell types (Cua and Tato 2010; Cua and Sherlock 2011; Le Bourhis *et al.* 2011).

The lineage of $NKp46^+$ cells was first identified as a major source of IL-22 in the intestine (Satoh-Takayama *et al.* 2008; Cella *et al.* 2009; Luci *et al.* 2009). These cells do not co-express IL-17, lack typical NK cell effector functions, and may or may not express NK1.1. Interestingly, some of these NKp46+ cells also express CD11c, an intergrin highly expressed by DCs. Surprisingly, mice deficient in NKp46 are still capable of secreting IL-22 and are fully resistant to *C. rodentium* infection (Satoh-Takayama *et al.* 2009). In the spleen and in the mesenteric lymph nodes, another cell type, $CD4^+$ LTi-like cells, produce IL-17 and IL-22 upon IL-23 stimulation (Takatori *et al.* 2009; Sonnenberg *et al.* 2011). LTi cells are also the building blocks of cryptopatches, which are lymphoid structures found in both the small and

large intestine. During *C. rodentium* infection, LTi cells are major sources of IL-22 in the mesenteric lymph nodes (Sonnenberg *et al.* 2011). In contrast to NKp46$^+$ ILCs, the development of LTi cells is regulated by the lymphotoxin (LT) pathway (Eberl *et al.* 2004; Satoh-Takayama *et al.* 2011). LT is a member of the TNF core family and plays a critical role in regulation of mucosal immune responses (Fu and Chaplin 1999; Tumanov, Christiansen and Fu 2007) and contributes to effector immune responses (Ware 2005; Wang *et al.* 2010). LT also regulates DCs and CD4$^+$ T-cell homeostasis in the steady state, as well as determines the functions of these cells during pathogenic challenge (Lewis *et al.* 2011; Upadhyay and Fu 2013).

Consistent with a role for LTi cells during *C. rodentium* infection, mice deficient in the LT pathway are also more susceptible (Spahn *et al.* 2004; Ota *et al.* 2011). Specifically, wild-type mice treated with either an anti-IL-22 antibody or with LTβRFc fusion protein show similar degrees of susceptibility to *C. rodentium* infection, suggesting a connection between the LT and IL-22 pathways. Indeed, IL-22 induction in the colon during *C. rodentium* infection is blocked when the LT pathway is deficient (Tumanov *et al.* 2011). Taken together, these studies suggest a redundant role for different ILC subsets during *C. rodentium* infection, and the specific contribution of each cell type needs to be further elucidated.

In addition to the aforementioned cell types, a pathogenic population of Thy1$^+$Sca1$^+$ ILCs has been identified in the inflamed colon of mice in a *H. hepaticus*-induced colitis model (Buonocore *et al.* 2010). These cells are negative for both NKp46 and CD4, but they are able to produce IL-17 and IL-22 upon stimulation with IL-23, and drive the development of colitis (Buonocore *et al.* 2010).

NON-LYMPHOID SOURCES OF IL-17 AND IL-22

Other potential sources of IL-17 and IL-22 include neutrophils that are recruited to the site of infection (Zindl *et al.* 2013; Taylor *et al.* 2014; Lee *et al.* 2015). In the dextran sodium sulfate colitis model, IL-22-producing neutrophils were shown to be protective (Zindl *et al.* 2013). Intestinal pathology was alleviated in DSS-treated *Il22*$^{-/-}$ mice transplanted with neutrophils from wild-type mice, whereas neutrophils from *Il22*$^{-/-}$ mice had little effect on disease progression (Zindl *et al.* 2013). During fungal infection, IL-17-producing neutrophils are recruited to the site of infection (Taylor *et al.* 2014), but whether neutrophils produce IL-17 or not appears to be dependent on the infection model (Huppler *et al.* 2015). Proposed mechanisms for activation of IL-17 and IL-22 production by neutrophils include stimulation with cytokines such as IL-6 and IL-23, activation of dectin-1 and 2, and through regulation of RORγt and aryl-hydrocarbon receptor (AhR) via activation of mTOR (Werner *et al.* 2011; Zindl *et al.* 2013; Taylor *et al.* 2014; Chen *et al.* 2016). Future studies are needed to further elucidate whether IL-17 and IL-22 production by neutrophils contributes to the host response to infection.

HOST DEFENSE AND PROTECTIVE FUNCTION OF IL-17 AND IL-22 DURING INTESTINAL INFECTION

In the gut mucosa, IL-17 and IL-22 have synergistic effects on the induction of antimicrobial proteins by GI epithelial cells, which have an important role in limiting dissemination of pathogens and of commensal bacteria that could penetrate a disrupted epithelial barrier (Zheng *et al.* 2008; Ismail, Behrendt and Hooper 2009). IL-17 and IL-22 act in concert to orchestrate the mucosal barrier, but the biological effects of these cytokines differ in many aspects. IL-22 appears to be a novel type of immune mediator that increases the immune defenses of tissue cells, protects tissues from damage and enhances their regeneration, whereas IL-17A and IL-17F are typical proinflammatory mediators. Below we discuss the effects of IL-17 and IL-22 primarily in the context of gut infection.

IL-17

The most prominent function of IL-17 is the recruitment of neutrophils to the site of infection, which is necessary for clearing microorganisms (Ishigame *et al.* 2009). IL-17 stimulates target cells to produce neutrophil chemoattractants such as the CXC chemokines IL-8 (CXCL8), CXCL1 and CXCL2, as well as growth factors, including G-CSF and GM-CSF (Fig. 2). Neutrophil recruitment is required for a rapid response (i.e. within 4–8 h) against bacterial and fungal pathogens such as *Citrobacter rodentium*, *Salmonella* Typhimurium and *Candida albicans* (Raffatellu *et al.* 2008; Saijo *et al.* 2010; Geddes *et al.* 2011). IL-17 also synergizes with other cytokines, such as IL-1, IL-6 and TNF-α, which together promote activation of tissue infiltrating neutrophils to effectively eliminate extracellular pathogens (Awane *et al.* 1999; Dong 2008). Mice infected with *C. rodentium* mount protective IL-17 responses, and disruption of IL-17 or its receptor leads to exacerbated bacterial burden and dissemination, increased disease susceptibility resulting from defective induction of CXC chemokines and impaired neutrophil recruitment (Happel *et al.* 2005; Mangan *et al.* 2006). Importantly, administration of recombinant IL-17 into IL-17-deficient mice infected with *C. rodentium* restored neutrophilia at sites of inoculation (Happel *et al.* 2005), demonstrating the critical importance of the IL-23/IL-17 axis in host defense against extracellular bacterial infections. Neutrophils are also an important first line of mucosal defense against *S.* Typhimurium. In patients affected by primary neutrophil immunodeficiency (e.g. chronic granulomatous disease), *S.* Typhimurium often disseminates from the gut, resulting in bacteremia (Mouy *et al.* 1989; Winkelstein *et al.* 2000). In accordance with these observations, *Il17ra*$^{-/-}$ mice exhibit reduced neutrophil accumulation in the gut, and increased translocation of *S.* Typhimurium to the mesenteric lymph nodes and spleen (Raffatellu *et al.* 2008).

In addition to neutrophil recruitment, the IL-17 cytokine family targets epithelial cells to induce antimicrobial responses against extracellular pathogens and to promote tissue remodeling (Ouyang, Kolls and Zheng 2008). An important mechanism of host defense in the intestine against bacterial pathogens is the presence of tight junctions that maintain the integrity of the intestinal epithelium, thereby preventing bacterial translocation (Macdonald and Monteleone 2005). In the gut epithelium, IL-17 stimulates the secretion of claudin 1 and claudin 2, proteins that are involved in the formation of tight junctions, ultimately forming a large, interconnecting network and maintaining intestinal integrity (Moran *et al.* 2009; Dungan and Mills 2011). Although IL-17 is largely considered proinflammatory, the cytokine may also promote restoration of the mucosal barrier and further control microbial translocation through the induction of tight junction proteins.

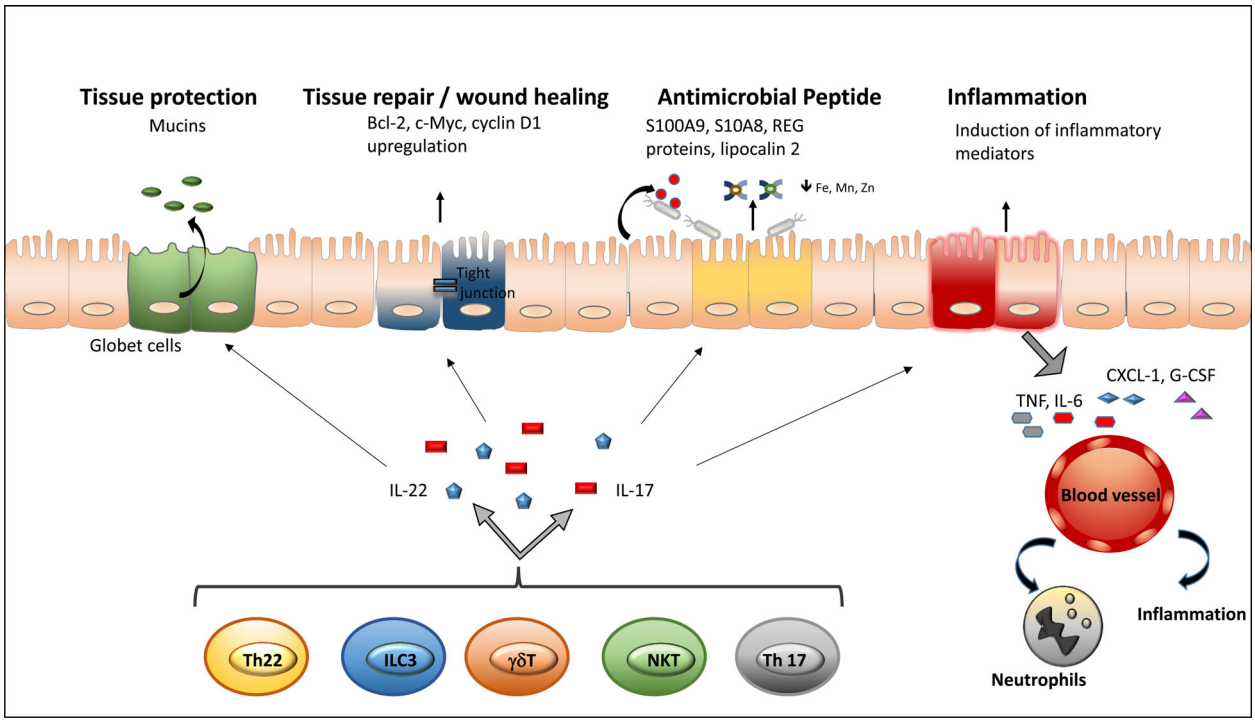

Figure 2. Functions of IL-17 and IL-22 at epithelial surfaces. IL-17 and IL-22 are upregulated in response to infection with a variety of pathogens. These cytokines are produced by subsets of cells, including $\gamma\delta$ T cells, ILC3 and Th17 cells, and elicit innate responses from mucosal epithelial cells. These responses include production of mucins by goblet cells, upregulation of genes involved in wound healing (e.g. Bcl-2, c-Myc, cyclin D1), the secretion of antimicrobial molecules (e.g. S100A8, S100A9, REG proteins, lipocalin-2) and the induction of proinflammatory mediators (e.g. TNF-α, IL-6, CXCL1, G-CSF) that contribute neutrophil recruitment at the site of infection. The functions of both cytokines are overlapping and in part synergistic. While IL-22 is more potent in tissue protection, repair and induction of antimicrobial peptides, IL-17 mediates stronger inflammatory responses by inducing other proinflammatory cytokines and the recruitment of neutrophils.

IL-22

The beneficial role of IL-22 during host defense has been studied in several models of intestinal infection, including *C. rodentium* (Ota *et al.* 2011) and *Clostridium difficile* (Hasegawa *et al.* 2014), as well as during infection with VRE, a gut commensal bacterium that causes bacteremia and endocarditis (Abt *et al.* 2016).

The functions of IL-22 during host defense against pathogens can be summarized into three major categories (Fig. 2). First, by promoting epithelial proliferation, IL-22 helps to maintain and restore epithelial barrier function after infection. Second, IL-22, together with other cytokines such as IL-17 or TNF-α, induces the expression of antimicrobial proteins involved in host defense in the skin, the airways and the intestine. Some antimicrobial proteins induced by IL-22 include lipocalin-2 and calprotectin, which is a heterodimer of S100A8 and S100A9 (Behnsen *et al.* 2014). These antimicrobial proteins sequester essential metal ions from pathogens (Corbin *et al.* 2008; Liu *et al.* 2012), a process known as nutritional immunity (Kehl-Fie and Skaar 2010). Therefore, IL-22-mediated induction of metal sequestration is an essential process in limiting growth and translocation of commensal microbes from the gut (Flo *et al.* 2004; Berger *et al.* 2006; Raffatellu *et al.* 2009). IL-22 also promotes the production of inflammatory mediators such as IL-1β, SAA and LPS-binding protein (Wolk *et al.* 2007; Dalmas *et al.* 2014; Sano *et al.* 2015). During *Klebsiella pneumoniae* infection, IL-22 is essential for the release of chemokines such as CXCL1, CXCL5 and CXCL9, as well as IL-6 and G-CSF from airway epithelial cells (Aujla *et al.* 2008). Overall, the primary function of IL-22 is to promote mucosal barrier integrity, thus limiting bacterial replication and dissemination.

During *C. rodentium* infection, IL-22 stimulates the production of protective mucins from goblet cells (Sugimoto *et al.* 2008; Turner, Stockinger and Helmby 2013) and induces the release of the C-type lectins REG3β and REG3γ from intestinal epithelial cells in the colon (Cash *et al.* 2006; Zheng *et al.* 2008). REG3γ is a soluble C-type lectin produced by Paneth cells and epithelial cells, which exerts its antimicrobial activity by interacting directly with the bacterial cell wall (Cash *et al.* 2006). Mice lacking IL-17 and IL-22 have reduced amounts of antimicrobial peptides and are highly susceptible to *C. rodentium* infection; however, they can be rescued by treatment with recombinant REG3γ (Zheng *et al.* 2008). Microbiota-derived LPS maintains basal expression of REG3γ in intestinal epithelial cells and Paneth cells. Indeed, REG3γ is not detected in germ-free mice (Cash *et al.* 2006; Mukherjee *et al.* 2014), and even short-term antibiotic treatment impairs its expression, rendering mice susceptible to VRE infection, a defect that can be reverted by oral administration of LPS (Brandl *et al.* 2008). Similarly, flagellin from commensal bacteria sensed by TLR5 expressed on CD103$^+$ CD11b$^+$ DCs found in the LP contributes to the maintenance of REG3γ expression. Upon TLR5 activation, DCs produce IL-23, promoting IL-22 release by ILCs, and therefore REG3γ expression in intestinal epithelial cells (Kinnebrew *et al.* 2010; Kinnebrew *et al.* 2012). The importance of the IL-22-REG3γ axis against bacterial infections has been recently demonstrated by Abt *et al.* (2016). Briefly, these authors showed that Resiquimod (R848), a synthetic ligand for TLR-7 that stimulates antiviral innate immune defenses, induces IL-22 expression, restoring REG3γ and reestablishing colonization resistance against VRE in antibiotic-treated mice.

Another mechanism by which IL-22 controls opportunistic gut pathogens is by facilitating the binding of complement component C3 to bacteria (Hasegawa *et al.* 2014). When the intestinal mucosa is infected with *C. difficile*, this organism is capable of translocating to other tissues, contributing to *C. difficile*-induced mortality. However, IL-22 induces an increase of C3 expression and secretion in the liver, which is mediated by the STAT3 pathway. This process leads to a substantial increase in systemic serum levels of C3, which in turn mediates enhanced opsonization of translocated commensals and pathogens, and their subsequent killing and clearance by neutrophils and macrophages (Hasegawa *et al.* 2014).

Although IL-22 plays a beneficial role in many infection models, recent studies have shown that IL-22 production may also be detrimental to the host. For instance, during S. Typhimurium infection, IL-22 does not play a protective role, but is instead exploited by the pathogen to colonize the gut to high levels (Behnsen *et al.* 2014). IL-22 favors S. Typhimurium colonization by inducing antimicrobial proteins that sequester metal ions. As the pathogen is able to overcome metal starvation, it outcompetes related commensals such as *Escherichia coli* (Behnsen *et al.* 2014). During *Helicobacter pylori* infection, IL-22 also contributes to the development of gastric pathology. Both *H. pylori*-infected humans and mice exhibit an overabundance of IL-22 (Zhuang *et al.* 2015), which stimulates gastric epithelial cells to secrete CXCL2. CXCL2 then recruits myeloid-derived suppressor cells that produce the proinflammatory proteins S100A8 and S100A9 and inhibit Th1 cell responses, thereby contributing to the development of *H. pylori*-associated gastritis (Zhuang *et al.* 2015).

CONCLUSIONS

The intestinal tract is home to commensal bacteria and fungi that have coevolved with the mammalian host. In order to maintain intestinal homeostasis, the mucosal immune system must balance between an appropriate response to dangerous pathogens and an inappropriate response to commensal microbiota that breach the epithelial barrier. IL-17 and IL-22 have been shown to play a critical role in maintaining barrier homeostasis against intestinal pathogens and commensal bacteria. It is becoming increasingly apparent that bacterial pathogens trigger a rapid IL-17 and IL-22-dependent innate defense in the gut mucosa. In turn, intestinal production of these cytokines seems to be regulated homeostatically by interactions between the host and the intestinal microbiota (e.g. SFB).

IL-17 and IL-22 enhance basic innate barrier defenses at mucosal surfaces, such as antimicrobial peptide production and neutrophil recruitment, i.e. rapidly occurring events that precede adaptive immunity. Although the functional spectra of these cytokines overlap with regard to inducing an innate immune response in epithelial cells, they are generally different. IL-17 is largely proinflammatory and can be pathogenic, whereas IL-22 primarily exhibits regenerative and protective roles. Nevertheless, IL-22's proinflammatory effects might contribute to pathology, as could be the case in psoriasis (Zheng *et al.* 2007) or IBD (Brand *et al.* 2006). Altogether, cytokines IL-17 and IL-22 provide barrier integrity against extracellular pathogens by (i) instructing innate immune responses in tissue cells, (ii) inducing the recruitment of adaptive immune cells via epithelial-derived chemokines and (iii) inducing regeneration of epithelial surfaces after inflammation.

The IL-17 and IL-23 (i.e. the cytokine upstream of both IL-17 and IL-22) pathways are clinical targets for multiple inflammatory diseases. For example, the antibody ustekinumab, which neutralizes the p40 subunit of IL-23 and IL-12, is approved to treat psoriasis and is showing benefit in clinical trials for Crohn's disease (Sandborn *et al.* 2008). Clinical data on the use of antibodies specific to the IL-23 p19 subunit are beginning to emerge in IBD and also show efficacy (Sandborn *et al.* 2008). IL-23-specific antibodies are also highly efficacious in psoriasis, suggesting that the efficacy achieved with p40 inhibition is largely a result of IL-23 inhibition (Leonardi *et al.* 2008; Papp *et al.* 2008; Croft, Benedict and Ware 2013). Antibodies to IL-17A or IL-17RA are also highly effective in psoriasis (Papp *et al.* 2012; Langley *et al.* 2014), but surprisingly, they exacerbated Crohn's disease in a subset of patients (Hueber *et al.* 2012). Thus, although IL-23 is important for production and maintenance of IL-17A and IL-17F, inhibition of IL-17A or IL-17RA in patients with Crohn's disease does not phenocopy the effects observed with a p40 or p19 inhibitor. As such, the mechanism(s) underlying the differential efficacy observed in Crohn's disease with inhibition of IL-17 versus IL-23 is an important unanswered question.

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