Review

Regulation of epithelial immunity by IL-17 family cytokines

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Cutaneous and mucosal epithelial cells function as both a physical barrier and as immune sentinels against environmental challenges, such as microbial pathogens, allergens and stress. The crosstalk between epithelial cells and leukocytes is essential for orchestrating proper immune responses during host defense. Interleukin (IL)-17 family cytokines are important players in regulating innate epithelial immune responses. Although IL-17A and IL-17F promote antibacterial and antifungal responses, IL-17E is essential for defense against parasitic infections. Emerging data indicate that another member of this family, IL-17C, specifically regulates epithelial immunity. IL-17C production serves as an immediate defense mechanism by epithelial cells, utilizing an autocrine mechanism to promote antibacterial responses at barrier surfaces.

IL-17 cytokines and receptors

The IL-17 cytokine family consists of six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F [1]. IL-17 cytokines display sequence conservation at the carboxyl terminus and contain five spatially conserved cysteine residues that mediate dimerization [2]. In addition to forming homodimers, IL-17A and IL-17F can be secreted as heterodimers [3,4]. Downstream immune responses are initiated following binding of IL-17 cytokines to receptor complexes composed of heterodimers of several IL-17 receptor subunits [5]. Five members of this family, IL-17 receptor A–E, have been identified through database searches (Figure 1). Structural studies indicate that IL-17 receptor A is a shared subunit that can pair with other members of the family [6]. Indeed, a requisite role for IL-17 receptor A has been demonstrated for IL-17A, C, E and F function [7–12]. However, although IL-17A, IL-17F, and IL-17A/F dimers induce antimicrobial responses through the IL-17 receptor A–receptor C complex, IL-17E and IL-17C utilize complexes composed of IL-17 receptor A–receptor B and IL-17 receptor A–receptor E, respectively [10–14], suggesting that cytokine specificity is dictated by the second subunit of the heterodimer. Although biochemical studies reveal that IL-17B can associate with IL-17 receptor B, the biological outcome of this interaction and whether IL-17 receptor A is also required is unclear [15]. Additionally, the receptors for IL-17D are unknown. The differences in receptor usage and cellular expression displayed by each family member shape their functional diversity and determine how they participate in host defense. Here, we focus the discussion on IL-17A, C, E and F and the interplay between epithelial cells and leukocytes during microbial challenges and inflammatory diseases. We review the recent data describing the biology of IL-17C, comparing the role of this pathway with other IL-17 family members in modulating the antimicrobial function of epithelial cells. Furthermore, we assess the emerging data describing how IL-17 family cytokines are regulated by epithelial cells during infection and autoimmunity.

Role of IL-17 cytokines in the regulation of epithelial responses during immunity

Although IL-17 family cytokines share the IL-17 receptor A chain as a common receptor, they can elicit different types of immune responses to deal with a variety of pathogens. IL-17A, IL-17C and IL-17F can directly target tissue epithelial cells to induce various antimicrobial responses against extracellular pathogens and promote tissue remodeling. By contrast, IL-17E primarily acts on leukocytes and induces type II immunity that is crucial for protection against parasites. IL-17E also negatively regulates IL-17A and IL-17F production from leukocytes.

IL-17 receptor A–receptor C complexes are expressed on a number of cell types found in the mucosa, including epithelial cells and fibroblasts. Although IL-17A and IL-17F homodimers and IL-17A/F heterodimers stimulate multiple overlapping pathways in target cells, their potency varies, with the IL-17A homodimer displaying greater potency than the heterodimer or the IL-17F homodimer [3,4,13,16]. The biological functions of IL-17A and its roles in diseases have been intensively reviewed [17]. In brief, activation of IL-17 receptor A–receptor C initiates innate defense and repair responses that include the induction of chemokines, in particular neutrophil chemoattractants such as granulocyte colony-stimulating factor (G-CSF) and chemokine CXC ligand (CXCL)8, cytokines such as IL-6, and antimicrobial peptides such as β-defensins and S100 proteins (Figure 2) [1]. The induction of antimicrobial proteins such as Regenerating islet-derived protein 3 γ (ReG3γ) in the gut helps to limit the dissemination of commensal bacteria that could penetrate a disrupted epithelial barrier [18]. Furthermore, IL-17A and IL-17F are instrumental in intestinal homeostasis. IL-17A has an important role in maintaining the mucosal barrier integrity; it enhances the synthesis of the tight junction protein claudin [19] to strengthen the connections between epithelial cells. Finally, both IL-17A and IL-17F synergize with

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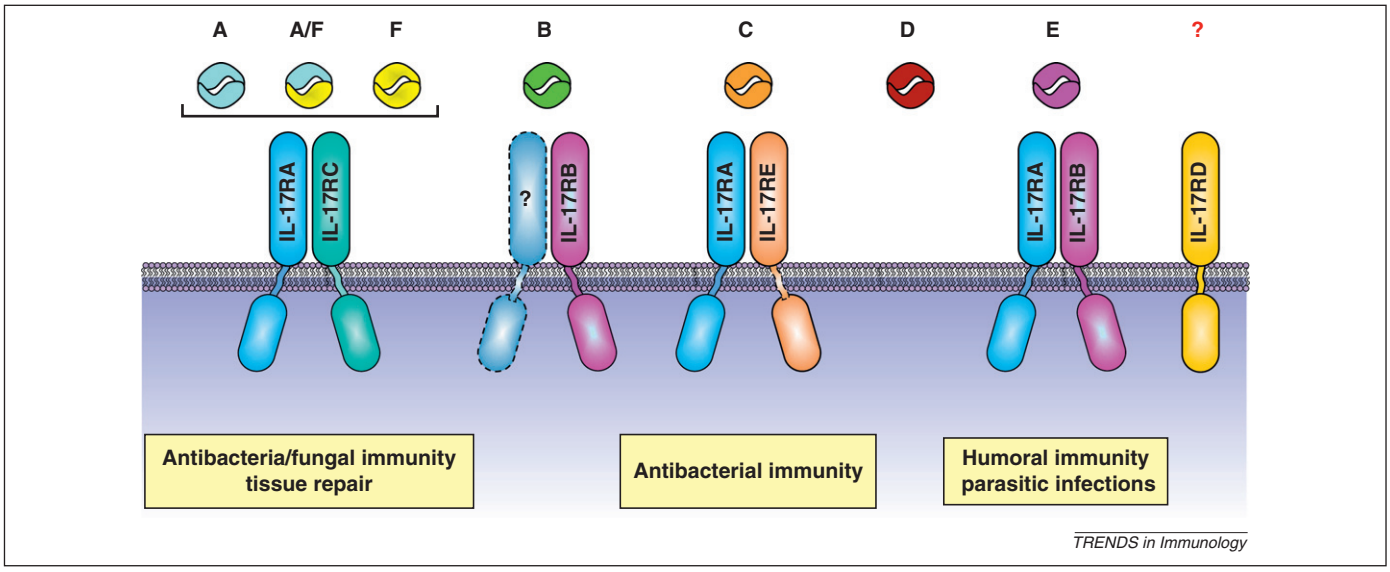

Figure 1. IL-17 family cytokines and receptors. Six members of the IL-17 family of cytokines have been identified (IL-17A–F). Cytokines function as homodimers, with IL-17A/F also forming heterodimers. Each cytokine uses a specific receptor complex composed of the IL-17 receptor subunits **(A–E)**. IL-17A, A/F and F dimers bind to IL-17 receptor A–receptor C to promote antibacterial/fungal immunity and tissue repair. IL-17C binds to the IL-17 receptor A–receptor E complex to mediate antibacterial responses, however, the role in antifungal defense and tissue repair is unclear. IL-17E interaction with the IL-17 receptor A–receptor B complex induces humoral immune responses, which are required for protection from parasites. Although IL-17B can associate with IL-17 receptor B biochemically, the function of this interaction is unclear. Likewise, it is unknown whether IL-17B behaves like the other family members and uses IL-17 receptor A. The receptor for IL-17D is unknown, and IL-17 receptor D is an orphan receptor.

other proinflammatory cytokines, including tumor necrosis factor (TNF)-α and IL-1β, to amplify proinflammatory responses from tissue epithelial cells and fibroblasts. The indispensable roles of IL-17A and IL-17F in host defense are supported by various *in vivo* infection models [1]. Uncontrolled IL-17 responses can augment inflammation and cause tissue damage in many autoimmune diseases, such as psoriasis and rheumatoid arthritis [1].

Although IL-17C signals through a receptor complex different from that used by IL-17A/F, data from our group and others have revealed that IL-17C shares many functional similarities with IL-17A/F. IL-17C preferentially targets epithelial cells due to the selective expression of IL-17 receptor E on these cells. IL-17C triggers similar pathways as IL-17A and IL-17F in epithelial cells, including the induction of neutrophil chemoattractants, proinflammatory cytokines and antimicrobial peptides (Figure 2) [10,11]. Furthermore, akin to IL-17A/F, IL-17C displays synergism with other proinflammatory cytokines to augment the immune response [10,11]. Likewise, IL-17C displays a protective role in the immune response to bacterial infections. IL-17C has been found to have an essential role in the intestinal immune response to *Citrobacter rodentium* [11]. IL-17-receptor-E-deficient mice display marked weight loss, greater bacterial burden and increased mortality following challenge with *C. rodentium*. This phenotype resembles the early mortality observed in infected *Il22*$^{-/-}$ mice [18]. Although IL-17C does not regulate IL-22 expression, the ability of these two cytokines to synergize *in vivo* may explain the functional overlap. A similar mucosal protective function of IL-17C has been observed in dextran sulfate sodium (DSS)-induced colitis, which mimics a bacterial infection, because DSS disrupts the intestinal epithelial barrier, exposing host tissue to commensal bacteria, initiating an immune response and tissue inflammation. IL-17C is rapidly induced in colon tissues of wild-type mice following DSS treatment, with expression detectable several days before that of IL-17A/F [10]. DSS-treated *Il17c*$^{-/-}$ and *Il17re*$^{-/-}$ mice display more severe inflammation, revealing a role for IL-17C in controlling the intestinal microflora and maintaining intestinal homeostasis. In addition, a proinflammatory function of IL-17C has also been found in an inflammatory skin disease model. Wild-type mice treated topically with imiquimod, a Toll-like receptor (TLR)7/8 agonist, develop noninfectious cutaneous lesions characterized by epidermal proliferation and leukocyte infiltration, histologically resembling human psoriasis. However, mice deficient in IL-17C or IL-17 receptor E display reduced disease activity, demonstrating that, analogous to IL-17A, this pathway plays a pathogenic role under nonhomeostatic conditions [10]. In summary, these studies have confirmed similar roles for IL-17C and IL-17A in both host defense and in tissue inflammation. However, the extent to which IL-17C, like IL-17A, contributes to human autoimmune diseases needs further investigation.

Despite the similarity between the IL-17A and IL-17C pathways, there are notable differences between these cytokines that are attributed to their distinct regulation and cellular targets. First, due to the broad expression of IL-17 receptor C, IL-17A and IL-17F target many cell types, particularly tissue fibroblasts. Conversely, IL-17 receptor E expression is limited, and thus IL-17C does not trigger detectable downstream responses from primary fibroblasts. Second, IL-17A acts on epithelial cells with much higher potency than IL-17C. Third, in addition to the role in epithelial cells, a role for the IL-17C pathway in mediating T helper (Th)17 responses has been demonstrated [12]. IL-17 receptor E expression is upregulated on Th17 cells, indicating this population is another target of IL-17C. The significance of this observation is highlighted in studies examining the effect of IL-17C deficiency in