IL-22-IL-18 signaling initiates an epithelial response circuit against *E. coli* infection

Research associate Hung-Yu Chiang and Hsueh-Han Lu, led by associate research fellow Dr. Jr-Wen Shui at Institute of Biomedical Sciences, address a novel anti-bacteria circuit in the gut with animal disease models and publish in *Nature Communications* on Feb 15, 2022. The group shows the protective cytokine IL-22 could initiate an IL-18-dependent epithelial response circuit to enforce intestinal host defence. The finding of this immunological pathway provides new insights about the therapeutic strategy of using IL-22/IL-18 as a potential anti-inflammatory target.

Impaired host defence to intestinal pathogens is associated with increased susceptibility to inflammatory bowel disease (IBD). Gram-negative bacteria, such as *Yersinia enterocolitica* or *adherent-invasive Escherichia coli* (AIEC), are described as a pathogenic trigger for IBD. Indeed, high prevalence of AIEC in patients with Crohn's disease (CD) has been frequently reported. In the small intestine, while dysfunction of Paneth cells, a type of anti-microbial epithelial cells located at the crypt base, is a common feature of Crohn's disease, evidence of how Paneth cells are regulated or how host-derived cytokines regulate Paneth cells during AIEC infection is missing.

IL-22 is widely known as a tissue-protective cytokine which exclusively targets IL-22R$^+$ epithelial lineages such as the gastrointestinal system. Clinical relevance of IL-22 to IBD is well-established and IL-22 therapy is considered as a promising strategy for IBD treatment because of its key role in gut epithelial barrier such as the capability to promote epithelial repair and induce production of anti-microbial peptides (AMP). In IL-22-mediated signaling cascade, IL-18 is recently emerging as an IL-22-induced and epithelium-derived cytokine. Together with inflammatory IL-1β, IL-18 is an effector cytokine when inflammasome is activated in myeloid cells such as macrophages. While increased IL-18 levels in serum and mucosal biopsies are correlated to inflammatory Crohn's disease, it remains largely unexplored whether and how epithelium-derived IL-18 contributes to barrier function. Specifically, while IL-22 promotes stem cells and Paneth cells, however; a role for IL-18 in epithelial stem cells or Paneth cells has not been studied. In the milieu of IL-12, IL-18 is a potent IFNγ inducer in Th1 cells, suggesting that the IL-18-IFNγ axis could potentially contribute to the pathogenesis of CD. While the interplay between IL-22 and IL-18 appears cross-regulated, evidence of a specific role for IL-18 in gut epithelial barrier during inflammation or host defence is missing.

Here, using a clinical isolate AIEC from CD patients, we report a well-coordinated and IL-22-initiated IL-18 response circuit during mucosal host defence against Crohn's AIEC. At the cellular level, we identify that loss of *Il-22* or *Il-18* in mice causes compromised Lgr5$^+$ stem cells and Ki67$^+$ transit-amplifying cells (i.e. reduced tissue repair), as well as Lysozyme$^+$

Paneth cells (i.e. reduced anti-microbial immunity). Moreover, both IL-22 and IL-18 stimulate Goblet cells to produce mucins and we identify that the IL-22-IL-18 axis has a key role in promoting mucin secretion. Therefore, similar to IL-22, we conclude that IL-18 is a bona fide gatekeeper for epithelial barrier at the steay state and during AIEC infection.

At the molecular level, we first reveal that IL-22 induces the transcription factor Stat3 binding to the *Il-18* promoter that subsequently triggers an IL-18 response circuit. Secondly, we report that both IL-22 and IL-18 regulate Paneth cells for AMP induction via a Stat3-dependent manner. Furthermore, while IL-22 inhibits stem cell genes via Stat3-independent pathway, IL-18 promotes Lgr5^{+} stem cells via Akt-Tcf4 signaling for tissue regeneration instead of Stat3. At the global level in mice, we reveal that, during AIEC infection, IL-22 links IL-18 for boosting innate immunity by upregulating Lysozyme^{+} Paneth cells and that IL-22 links IL-18 for connecting to adaptive immunity by inducing IFNγ^{+} T cells for AIEC clearance at the later stage of infection.

Therefore, we show that IL-22-Stat3 signaling triggers an IL-18 response circuit at the frontline barrier during host defence against AIEC infection. This response circuit involves an IL-18-Stat3 signaling to boost Paneth cells for anti-microbial response, an IL-18-Akt-Tcf4 signaling to promote Lgr5^{+} stem cells for tissue repair, and an IL-18/IL-12 signaling to promote IFNγ^{+} T cells for AIEC clearance.

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