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Letter to the Editor

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Interleukin-18 Inhibition in Inflammatory Bowel Disease: A Delicate Balance

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To the Editors:

We read with great interest the study by Ikegami et al,[1] which addresses the inhibition of mature interleukin (IL)-18 in dextran sodium sulfate–induced mice models using a monoclonal antibody targeting a neoepitope of caspase-cleaved mature IL-18. The study analyzed several outcome parameters including inflammatory cytokines, intestinal epithelial permeability assays, goblet cell function, and gut microbiota alterations. The authors provide compelling data of beneficial effects of IL-18 inhibition using monoclonal antibodies to target mature IL-18, which might become novel therapeutic agents for patients with inflammatory bowel disease. However, the authors also aptly conclude that the precise mechanisms by which IL-18 regulates tight junction integrity and mucus production remain ambiguous. Here, we would like to emphasize and expand on the delicate balance between pro- and anti-inflammatory functions that IL-18 seems to fulfill within the intestinal mucosa.

Previous studies using murine models revealed anti-inflammatory and immune-protective properties of IL-18,[2,3] while others presented evidence supporting proinflammatory IL-18 signaling[4,5] in chemically induced intestinal inflammation. These diverging observations may arise from a disruption in the communication between gut microbiota, their metabolites, and inflammasome-mediated IL-18 production. For instance, bacteria-produced short-chain fatty acids can activate the inflammasome, thereby promoting IL-18 maturation and eliciting barrier-protective and immunoregulatory effects.[6,7] Our recent study proposed that IL-18 regulates intestinal homeostasis through activation of the HIF-1α (hypoxia-inducible factor 1α) pathway, facilitated by commensal short-chain fatty acid–producing bacteria (eg, *Faecalibacterium prausnitzii*) in a large inflammatory bowel disease patient cohort.[8] Moreover, taurine—a bile acid conjugate—has also been suggested to positively modulate inflammasome activation.[3,9]

Collectively, IL-18 seems to have a dual role in colitis: while it contributes to the maintenance of barrier integrity in homeostasis, during inflammation it may become implicated in goblet cell dysfunction and disrupted barrier integrity. The study by Ikegami et al offers compelling data of beneficial effects of IL-18 inhibition that are mainly targeted at the site of the intestinal epithelium. However, the nature of the effects of IL-18 inhibition may depend on the gut microbiota composition (eg, differing between homeostatic and dysbiotic microbiomes). Therefore, it remains challenging to discern the potential benefits and risks of therapeutically modulating this equilibrium. The specific cellular effects and interrelationships between IL-18, gut microbiota–derived metabolites, and mucosal immunity remain incompletely defined.[10] Finally, a temporal divergence may also exist, with anti-inflammatory effects of IL-18 observed in early stages of colitis-induced inflammation, while proinflammatory effects may manifest at later disease stages.[5]

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Conflicts of Interest

None declared.

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