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The Role of IFN- γ Induced IL-10R1 Expression in Restitution of Epithelial Barrier Function during Intestinal Inflammation

Inflammatory bowel diseases (IBD) are debilitating diseases of unknown origin, but a combination of genetic and environmental factors are thought to be involved in disease pathology. Ongoing inflammatory responses are paralleled by significant alterations of epithelial cellular responses, including changes in barrier function and cytokine response. Preliminary studies indicate that epithelial IL-10 signaling plays a critical role in barrier function and tissue restitution. Importantly, during ongoing inflammation IFN- γ mediates the upregulation of IL-10R1 expression. Further, studies in a murine colitis model demonstrate that loss of epithelial IL-10R1 dramatically worsens inflammation and disease outcomes in vivo. Based on these preliminary studies, we hypothesize that epithelial IL-10R1 expression is crucial to tissue homeostasis and IFN- γ -induced upregulation of IL-10R1 primes the tissue for pro-resolving IL-10 signaling. To define these principles, two specific aims are being pursued. The first aim is to define the molecular mechanisms of epithelial IL-10-dependent maintenance of barrier function. Here we are focusing on the examination of apical junction proteins and the impact of IL-10 signaling on expression, protein level, and localization of these targets using a host of molecular biology techniques. The second aim is to further investigate the role that differentiation defects may play with regards to the barrier function of epithelial cells lacking IL-10R1. To this end we are investigating expression and protein level of factors critical to intestinal epithelia differentiation in vitro, as well as using staining techniques on tissues derived from colitis mouse models. A better understanding of these principles may lead to improved treatment for those suffering from IBD, controlling the inflammatory response and ultimately decreasing the severity of disease.