Colonic IL10Ra deficient macrophages at the apex of colitis initiation

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Cytokines maintain intestinal health, but precise inter-cellular communication networks remain poorly understood. Macrophages are immune sentinels of the intestinal tissue and are critical for gut homeostasis. Intestinal macrophages reside in the connective tissue underlying the gut epithelium, which separates them from the diverse microbiota populating the gut lumen. This complex and dynamic environment necessitates intimate and precise inter-cellular communication.
We established a murine colitis model based on a macrophage-restricted IL10 receptor deficiency (CX3CR1Cre:IL10rafl/fl mice). IL10Ra deficient gut macrophages are pro-inflammatory, causing severe colitis that resembles the pathology of children carrying IL10Ra mutations. To investigate the initial steps of inflammation in our model, we dissected the interaction of IL10Ra-deficient macrophages with their immediate environment in the original animals and in bone marrow chimeras. We found that production of IL23 by IL10Ra-deficient colonic macrophages is critical for disease initiation, since ablation of macrophage-specific IL23 expression in our system (CX3CR1Cre:IL10rafl/fl: p19fl/fl mice) prevented colitis development. Increased IL23 levels allow recruitment of Th17 cells that secrete IL22, stimulating an IL22 induced gene signature in colonic epithelial cells. Specifically, IL22 stimulated epithelial cells express elevated levels of neutrophil recruiting chemokines Cxcl1 and Cxcl5, causing neutrophil infiltration to the colonic tissue. Upon ablation of IL22 induction, either by gene deletion (CX3CR1Cre:IL10rafl/fl: IL22-/- mice) or antibody mediated depletion of T cells which produce IL22, colitis symptoms were found ameliorated. Hence, we describe a novel pro-inflammatory role for IL22 in colitis initiation, specific for this colitis model. Further, we elucidate the impact of neutrophil recruitment to the colonic tissue, establishing the pathogenic role of neutrophils and their importance in disease progression. Finally, we investigate how disease progression affected colonic macrophages that initiate inflammation. By analyzing transcription profiles of IL10R deficient colonic macrophages in the presence or absence of neutrophils we dissect the response of disease initiating macrophages to severe inflammation of the colon.

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