Inflammatory Macrophages Contribute to Gut Inflammation through Continuous Notch Signaling

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Inflammatory Bowel Disease (IBD) is the general term used to characterize chronic inflammation of the gastrointestinal tract. In spite of the extensive research efforts, the precise pathogenic factors that cause IBD remain unclear. However, immune dysregulation and intestinal barrier defects are believed to be two major factors contributing to IBD pathogenesis. In attempt to understand the biological factors contributing to immune dysregulation and intestinal barrier defects, we utilized two animal models of IBD: i) the chronic DSS-induced colitis model and ii) the spontaneous enterocolitis development in IL-10-deficient mice. We found in these animal models of IBD, the inflamed colonic epithelium have increased Notch targeted gene hairy and enhancer of split-1 (Hes1) expression and a decrease in atonal homolog 1 (Atoh1) expression when compared to B6 mice. Additionally, ex vivo analysis revealed the inflamed colon harbored intestinal macrophages with increased Notch ligand expression. Furthermore, the conversion of macrophages into inflammatory macrophages resulted in the upregulation of Notch ligands. Lastly, we found inflammatory Notch ligand-positive macrophages reduced secretory cell differentiation and barrier integrity in a co-culture system with colonic organoids. Based on these findings, we conclude that chronic intestinal inflammation is maintained by inflammatory macrophages through continuous Notch signaling.