GM-CSF and Intestinal Epithelial Cell Survival in Ileal Crohn's Disease

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Crohn's Disease (CD) is believed to be caused by a complex interaction between genetic susceptibility and environmental triggers leading to chronic relapsing intestinal inflammation and epithelial apoptosis. Eighty percent of CD patients have involvement of the terminal ileum. Granulocyte-macrophage colony stimulating factor (GM-CSF) promotes epithelial barrier integrity, stimulates myeloid cell anti-microbial function, and reduces disease activity in CD and experimental colitis. Recent studies have shown that ileal CD patients exhibit high levels of neutralizing GM-CSF antibodies within the range which inhibits innate immune functioning.

Independently, a subset of CD patients exhibit a hyper-responsive increase in permeability in response to non-steroidal anti-inflammatory drugs (NSAIDS), due in part to selective inhibition of the COX enzymes. NSAID exposure is recognized clinically as a common trigger for flares of disease in individuals with CD.

This study specifically tests the link between environmental, genetic, and immune factors by testing whether GM-CSF promotes ileal barrier function in mice by increasing enterocyte survival in response to gut injury with NSAIDS. It was concluded that in the absence of GM-CSF function, IEC show increased histologic injury in addition to elevated markers for apoptosis, indicating an increase in cell death. It was also determined that the GM-CSF receptor beta chain is more highly expressed in the ileum than the colon, indicating that GM-CSF could play a role in the higher prevalence of ileal CD. Therapeutic agents for patients with CD are limited by a lack of animal models directly linking genetic, immune, and environmental factors. By linking these factors, this study can contribute to an overall research program that may afford an animal model appropriate for testing novel therapeutics specific to ileal CD, the largest subset of inflammatory bowel disease with the highest rate of hospitalizations, surgeries, and other morbidities.