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Grant Title: Environmental and Pathogenic Triggers of Intestinal Inflammatory Disease
Abstract:

Intestinal inflammation is the basis of colitis and the human inflammatory bowel diseases (IBDs) that include Crohn's disease and Ulcerative Colitis (UC). These inflammatory syndromes arise primarily from unknown environmental triggers as deduced from studies of various human populations. Pathogen infection has been considered as a possible disease trigger, and seasonal infections have been associated with increased diagnoses of IBD. We considered that recurrent low-grade infections such as those that occur in mild cases of human food poisoning may represent an environmental trigger of chronic inflammation and colitis. We therefore previously developed a mouse model of human food poisoning using low–titer non-lethal gastric infections of the bacterial pathogen *Salmonella enterica* Typhimurium (*ST*). Gram-negative *ST* is widespread and remains a leading cause of human foodborne disease. We found that recurrent infections given after the host has cleared the pathogen nevertheless caused chronic inflammation and a progressive colitis similar to human UC. We determined that disease onset required the disruption by the *ST* pathogen of a protective mechanism in the host centered on the regulated expression of the anti-inflammatory enzyme Intestinal Alkaline Phosphatase (IAP) produced by enterocytes. Recurrent *ST* infection resulted in Toll-like-receptor-4 (Tlr4)-dependent induction of neuraminidase (Neu) activity resulting in IAP de-sialylation and internalization, thereby accelerating a normal mechanism of IAP protein aging and turnover. The resulting IAP deficiency with reduced de-toxification of the lipopolysaccharide-phosphate endotoxin produced by commensal bacteria of the colon thereby causing a persistent Tlr-4-dependent inflammation leading to colitis. Interestingly, similar alterations of IAP and Neu activity have been reported in studies of human IBD patients, and recombinant IAP is now in clinical trials for treating colitis and sepsis. We proposed herein to further investigate this disease mechanism by identifying the neuraminidase involved in disease onset, with host Neu3 as the hypothesized contributor based upon its Tlr-4-dependent induction as observed among enterocytes following *ST* infection. Research proposed herein will determine the role of Neu3 induction and its modulation in preventing and treating the debilitating and life-threatening symptoms of colitis.