Characterizing the Extent of Cell Death in Innate Immune Mediated Colitis

Justin R Hendrix[1], Anne-Marie Overstreet[1], Antonia Boger-May[1], David Boone[1,2]

[1]Indiana University School of Medicine - South Bend IN, [2]University of Notre Dame, Department of Biological Sciences

Background and Hypothesis:

Intestinal epithelial cell (IEC) turnover occurs every four-to-five days. In inflammatory bowel disease (IBD), IECs undergo increased cell death due to inflammation of intestinal villi and colonic crypts. This cell death leads to increased permeability of the intestinal barrier. This study examined the pathogenesis of IBD, focusing on innate immunity using mice with spontaneous innate immune colitis. The objective was to observe if there is a significant difference in expression of apoptosis in colitic mice vs. control mice.

Experimental Design:

Mice expressing the NF-kB inhibitor TNFAIP3 in the villi of IECs were interbred with $RAG1^{-/-}$ mice. TNFAIP3 x $RAG1^{-/-}$ (TRAG) mice developed 100% penetrant colitis by 6 weeks of age that was not observed in TNFAIP3 or $RAG1^{-/-}$ littermates. The presence of activated caspase-3 in distal colons was detected using immunofluorescence and quantified using ImageJ to compare differences between 4- and 8-week-old RAG vs.TRAG mice.

Results:

Increased numbers of caspase-3^{+} cells were found in TRAG mice compared to RAG mice. After treatment with antibiotics, similar levels of capase-3 were detected in both groups.

Conclusion and Potential Impact:

This investigation suggests that cell death in TRAG mice were increased due to deficient innate immunity in IECs. Thus, bacteria play a direct role by killing IECs or an indirect role by causing inflammation. Understanding how innate immune activation drives cell death in IECs, may lead to a better understanding of the complex regulation of IBD, and improved therapeutic agents targeting novel cell types in the remission of chronic IBD.