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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Epithelial Reactive Oxygen Species and Risk for Very Early Onset Inflammatory Bowel Disease

Current evidence suggests that the inflammatory bowel diseases (IBD) Crohn's disease and ulcerative colitis (UC) are caused by a complex interaction between host genetic background, microbial shifts, and environmental cues leading to inappropriate chronic activation of the mucosal immune system. The development of antimicrobial seroreactivity and chronic Crohn's disease–like intestinal inflammation during the first decade of life in children with the inherited disorder of phagocyte function chronic granulomatous disease (CGD) has suggested that loss-of-function in phagocyte reactive oxygen species (ROS) production is likely to be a fundamental mechanism of very early onset (VEO, age <6 years at diagnosis) IBD pathogenesis.[1]

Dhillon et al[2] had previously reported that rare loss-of-function variants in the genes that comprise the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2) complex are associated with increased risk for VEOIBD. Although these variants do not reduce ROS production to the degree observed in CGD or cause overt immune deficiency, the functional defect may be sufficient to affect intestinal microbial responses. In the current study, the authors have now tested the hypothesis that genetic variants reducing function of the intestinal epithelial NADPH oxidases, *NOX1* and *DUOX2*, are also associated with VEOIBD.[3] They identified rare loss-of-function missense mutations in *NOX1* or *DUOX2* in five of 209 VEOIBD patients tested. Importantly, these missense variants were associated with reduced epithelial ROS production and defective host resistance to the bacterial pathogen *Campylobacter jejuni* (Figure 1). The study is the first to link *NOX1* variants to human disease, and establishes *NOX1* and *DUOX2* as risk genes for VEOIBD. The authors conclude that defective intestinal epithelial ROS production is therefore a risk factor for the development of VEOIBD, likely by impairing microbial defenses.

The profound reduction in phagocyte ROS production due to the NADPH oxidase genetic variants that cause CGD is associated with increased susceptibility to bacterial and fungal infections. In fact, the use of anti–tumor necrosis factor agents for CGD colitis is limited by a high risk for fungal infection. However, ROS also function as signaling molecules, and CGD myeloid cells have recently been shown to exhibit a hyperinflammatory phenotype.[1] The specific mechanisms remain under investigation, but this may involve monocyte inflammasome activation and preferential induction of proinflammatory T_H17 cells. Conversely, enterocyte NOX1 via ROS production has recently been shown to transduce the microbial signals that promote epithelial wound healing.[4] It will be of interest to determine whether the reduction in epithelial ROS production in VEOIBD patients with *NOX1* or *DUOX2* loss-of-function variants is also associated with impaired wound healing and/or enhanced production of inflammatory chemokines, which would promote mucosal ulceration and leukocyte recruitment.

The pediatric IBD collaborative research group, Pediatric Resource Organization for Kids with Inflammatory Intestinal Digestive Diseases (PRO-KIIDS), has recently reported the results of a combined clinical, genetic, and high-throughput mucosal transcriptomic and microbial community profiling at the time of IBD diagnosis in treatment-naïve pediatric Crohn's disease and UC patients.[5] A progressive increase in an ileal *DUOX2* gene coexpression signature was detected in association with expansion of *Proteobacteria* taxa across all forms of IBD (UC, colon-only Crohn's disease, and ileal Crohn's disease). These findings of substantially increased ileal expression of both *DUOX2* and its binding partner *DUOXA2* in IBD suggest a central role for the dual oxidase *DUOX2* in this setting. Indeed, *DUOX2* interacts with the Crohn's disease risk gene *NOD2* in generating intestinal epithelial cell responses to bacterial products, and susceptibility to spontaneous colitis in mice with deletion of antioxidant glutathione peroxidase function has been mapped to

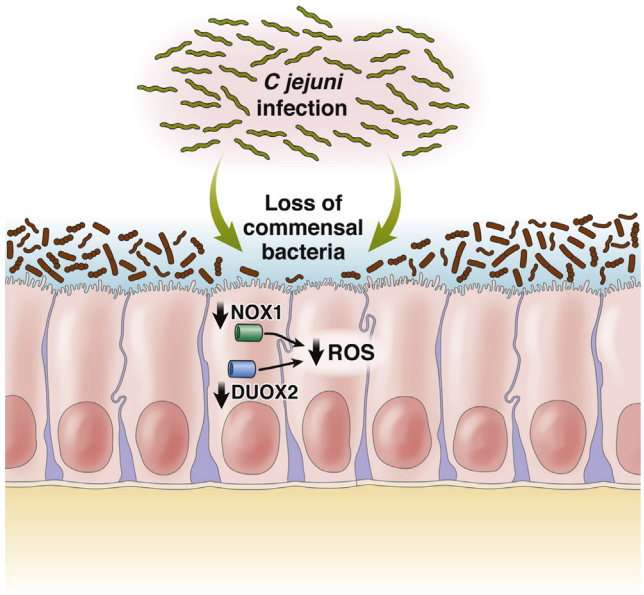

Figure 1. The article by Hayes et al[3] identifies novel mutations in two genes, *NOX1* and *DUOX2*, in patients with very early onset IBD. Functional analyses suggest that these mutations disrupt production of reactive oxygen species (ROS) and thereby impair host defense to enteric pathogens, including *Campylobacter* spp.

a locus containing *Duox2*. Collectively, these prior studies together with the current report place DUOX2 as a central mediator of mucosal immune responses, and suggest that precise control of DUOX2 expression and activity is required to maintain homeostasis.

The *NOX1* and *DUOX2* variants reported in the current study were discovered in an initial cohort of 59 VEOIBD patients, but they were not replicated in an independent cohort of 150 VEOIBD patients. Although it will be important to test for replication of these specific variants in larger VEOIBD cohorts, these results do suggest, as noted by the authors, that these and other variants in this pathway in VEOIBD are likely to be quite rare. Moreover, it is also likely that more comprehensive ongoing whole-exome sequencing efforts will identify multiple rare variants that will act together in individual patients to influence phagocyte and/or intestinal epithelial ROS production and host–microbe interactions. This understanding of an individual patient's composite genetic load for defects in ROS production and antimicrobial function will then likely provide a more focused approach to individualized therapeutics.

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Conflicts of interest
The author discloses no conflicts.

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