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EDITORIAL

A Pathobiont Fragments Mitochondrial Networks in Epithelial Cells: Implications for Crohn's Disease

It is well established that interactions between microbes and the intestinal epithelium are important in the pathogenesis of inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis. Although specific causative pathogens have not been identified, several pathobionts have been characterized in the intestinal microbiome that may play a facilitative role in disease progression.[1] One such pathobiont is adherent-invasive *Escherichia coli* (AIEC), which has been implicated specifically in Crohn's disease. Among other effects, AIEC induces the release of inflammatory mediators and disruption of epithelial barrier function, but the precise mechanisms are unknown. However, the original description of AIEC in Crohn's disease noted that mitochondria were disrupted in the epithelial cells with which the bacteria were associated.[2] Mitochondrial dysfunction also has been described in various types of intestinal inflammation, and mutations in genes that modulate mitochondria have been identified as IBD susceptibility loci.[3]

In the current issue of *Cellular and Molecular Gastroenterology and Hepatology*, Mancini et al[4] tested the hypothesis that AIEC may disturb epithelial barrier function, contributing to Crohn's disease pathogenesis, via an effect on mitochondrial networks. Specifically, they examined the possibility that AIEC causes an imbalance in the dynamic processes of fission and fusion that maintain the network and allow for epithelial homeostasis and appropriate energy balance. They began their study with an unbiased transcriptional screen to identify genes that were differentially regulated in the colonic epithelial cell line, T84, by an AIEC reference strain, LF82, compared with control strains of *E coli* (F18, HB101). There were numerous genes that were up-regulated or down-regulated by LF82 compared with control infections, but pathways related to mitochondrial function were notably and considerably overrepresented. Ultrastructural studies showed that these changes were associated with significant fragmentation of the mitochondrial network in LF82-infected cells. The impact of AIEC on mitochondrial homeostasis could be attributed, at least in part, to activation of the guanosine triphosphatase, dynamin-related protein1 (Drp1) and subsequent loss of the pro-fusion protein optic atrophy type 1 protein (long form) (OPA1-L). The effects also could be ameliorated by Mitochondrial Division Inhibitor (Mdivi1), a drug that inhibits mitochondrial fragmentation, at least at early time points after infection. Mdivi1 similarly reversed the increase in macromolecular permeability that occurs in T84 cells infected with AIEC, but not the decrease in transepithelial resistance. Mancini et al also showed that the ability of AIEC to disrupt mitochondria is likely not attributable to the production of reactive oxygen species. Rather, they speculated that reactive oxygen species production instead might be downstream of the effect of the bacteria on mitochondrial integrity.

The findings presented indicate an important role for an intact mitochondrial network in maintaining epithelial barrier function. When the dynamics of this network are disrupted, not only will the epithelium become leaky to potentially antigenic macromolecules, but also normally noninvasive commensals may gain access to the mucosa where they can trigger immune signaling and thereby perpetuate inflammation in a vicious cycle. Indeed, disruption of mitochondrial networks is a feature of infection with many gastrointestinal pathogens and may contribute to their ability to induce disease, and therefore is not limited to the pathobiont that was the focus of the present study.

The great value of the work reported is that it pulls together several previously largely disparate threads in IBD research: observations of mitochondrial disruption, an association of Crohn's disease with the specific pathobiont studied here, and the ubiquitous presence of epithelial barrier dysfunction in IBD. One might add another possible link, in that a bidirectional relationship has been described between the intestinal microbiota in general and the function of mitochondria.[5] In this vein, the dysbiosis that occurs in IBD and that may foster acquisition of pathogenic properties by AIEC similarly may potentiate the actions of the pathobiont on the integrity and function of the mitochondrial network. Ultimately, this would contribute to a degradation of the epithelial barrier and chronic disease. Studies in vivo, as well as using patient specimens, will be needed to flesh out this schema. Nevertheless, the work reported may suggest previously unidentified targets for the reversal of epithelial barrier dysfunction in IBD. Because of the widespread relevance of defects in mitochondrial dynamics in a whole host of diseases—cardiovascular disease, acute and chronic kidney injury, and Parkinson's disease, to name a few—there is intense pharmaceutical interest in identifying small molecules that can target the various players in the response, such as overabundant activity of Drp1, as studied here.[6] The work reported by Mancini et al holds out the intriguing possibility that some of these drugs may offer promise to avert relapses of IBD.

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Conflicts of interest
The author discloses no conflicts.

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