cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Mitochondrial Networks: A New Therapeutic Target in Colitis

Precise control of epithelial mitochondrial mass and function is required for maintenance of intestinal homeostasis.[1] Prior studies established a fundamental role for intestinal epithelial cell mitochondrial function in maintaining barrier function and tolerance of commensal microbes.[2] In addition, chemical depolarization of epithelial mitochondria was shown to be sufficient to trigger inflammatory responses to commensals.[2] In the current issue of *Cellular and Molecular Gastroenterology and Hepatology,* Mancini et al[3] have expanded on this work by testing for a role for altered mitochondrial dynamics (increased fission compared with fusion) in murine colitis and effects of dextran sodium sulfate (DSS) on intestinal epithelial cell or macrophage function in vitro. They show for the first time that DSS causes mitochondrial fragmentation in vitro, and that the small peptide P110, which was designed to block Fis1-Drp1 binding and thereby reduce mitochondrial fission, both ameliorated murine colitis and restored cellular energetics in the face of DSS exposure.[3] Importantly, the authors included endpoints in their murine models related to abnormal enteric nervous system function, such as hyperalgesia, which can be quite problematic for patients and are not always addressed by current anti-inflammatory therapies. Overall, data both highlight the role of mitochondrial network dynamics in colitis pathogenesis and support inhibition of mitochondrial fission as a novel therapeutic approach.

This study is an important addition to a growing literature regarding mitochondrial dysfunction in colitis, with a focus on the dynamics of mitochondrial fission not previously addressed. Prior studies have documented reduced mitochondrial membrane potential and cellular respiration in inflamed segments in patients with colitis and murine models and have implicated microbial products and oxidative stress in a reduction in mitochondrial biogenesis. In this regard, intestinal epithelial cell deletion of *PPARGC1A* (PGC1α), the master regulator of mitochondrial biogenesis, led to barrier dysfunction and more severe murine colitis.[4] A substantial suppression of PGC1α and each of the mitochondrial-encoded respiratory chain genes was identified in the inflamed mucosa in patients with ulcerative colitis, supporting a profound colonic mitochondriopathy.[5] These changes in colon gene expression were in turn associated with a decrease in the activity of Complex I of the electron transport chain, the rate-limiting step in oxidative phosphorylation. Similarly, proteomic analysis of the colonic mucosa of Crohn's disease patients identified suppression of mitochondrial proteins involved in hydrogen sulfide detoxification.[6] Microbial network analysis implicated *Atopobium parvulum* in microbial hydrogen sulfide production and severity of colitis in interleukin 10 deficient mice.[6] As improved imaging technology is developed, it will be of interest to determine whether there is direct morphometric evidence for dysregulated mitochondrial networks in colitis tissues in patients and animal models. It will also be important to determine whether alterations in mitochondrial biogenesis and dynamics are an intrinsic component of disease that may serve as a trigger for disease flares even when inflammation is controlled or are secondary to microbial signals and oxidative stress once inflammation is established.

An interesting and potentially clinically relevant finding from the current study was that the P110 small peptide inhibitor of mitochondrial fission restored epithelial butyrate oxidation in DSS treated intestinal epithelial cells in vitro. The microbial short-chain fatty acid metabolite butyrate regulates intestinal epithelial cell function via 2 primary mechanisms, as an energy source for oxidative phosphorylation and adenosine triphosphate production and as a regulator of gene transcription via histone deacetylase activity. These mechanisms play a critical role in maintaining epithelial barrier function in health and in regulating wound healing responses in the setting of colitis.[7] Inflammatory suppression of intestinal epithelial cell genes regulating butyrate transport, signaling, and mitochondrial oxidation is largely corrected by anti–tumor necrosis factor anti-inflammatory therapy.[8] However, complete healing only occurs in a minority of patients. When combined with the results of the current study, these data support the evolving concept that some patients may require both current anti-inflammatory biologic therapies and microbial or small molecule therapies targeting epithelial mitochondrial structure and function to achieve complete mucosal healing and more stable clinical remission. In terms of microbial targeted therapy, preclinical studies have shown that the human milk oligosaccharide 2′-fucosyllactose increased *Blautia*, *Roseburia*, and *Ruminococcus* abundance and cecal butyrate and ameliorated murine colitis. In a murine model of small bowel resection and undernutrition, 2′-fucosyllactose promoted microbial shifts and weight gain and induced intestinal epithelial genes regulating PGC1α dependent mitochondrial biogenesis. The current study provides strong support for further evaluation of the small peptide P110 as an adjunct therapy to restore mitochondrial network dynamics, suppress inflammation, and reduce complications of colitis including hyperalgesia.

LEE A. DENSON, MD
Pediatric Gastroenterology, Hepatology, and Nutrition
University of Cincinnati College of Medicine and
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

References

1. Novak EA, Mollen KP. Mitochondrial dysfunction in inflammatory bowel disease. Front Cell Dev Biol 2015; 3:62.
2. Nazli A, Yang PC, Jury J, Howe K, Watson JL, Söderholm JD, Sherman PM, Perdue MH, McKay DM. Epithelia under metabolic stress perceive commensal bacteria as a threat. Am J Pathol 2004;164:947–957.
3. Mancini NL, Goudie L, Xu W, Sabouny R, Rajeev S, Wang A, Esquerre N, Al Rajabi A, Jayme TS, Bernandes ET, Nasser Y, Ferraz JGP, Shutt T, Shearer J, McKay DM. Perturbed mitochondrial dynamics is a novel feature of colitis that can be targeted to lessen disease. Cell Mol Gastroenterol Hepatol 2020;10:287–307.
4. Cunningham KE, Vincent G, Sodhi CP, Novak EA, Ranganathan S, Egan CE, Stolz DB, Rogers MB, Firek B, Morowitz MJ, Gittes GK, Zuckerbraun BS, Hackam DJ, Mollen KP. Peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α) protects against experimental murine colitis. J Biol Chem 2016;291:10184–10200.
5. Haberman Y, Karns R, Dexheimer PJ, Schirmer M, Somekh J, Jurickova I, Braun T, Novak E, Bauman L, Collins MH, Mo A, Rosen MJ, Bonkowski E, Gotman N, Marquis A, Nistel M, Rufo PA, Baker SS, Sauer CG, Markowitz J, Pfefferkorn MD, Rosh JR, Boyle BM, Mack DR, Baldassano RN, Shah S, Leleiko NS, Heyman MB, Grifiths AM, Patel AS, Noe JD, Aronow BJ, Kugathasan S, Walters TD, Gibson G, Thomas SD, Mollen K, Shen-Orr S, Huttenhower C, Xavier RJ, Hyams JS, Denson LA. Ulcerative colitis mucosal transcriptomes reveal mitochondriopathy and personalized mechanisms underlying disease severity and treatment response. Nat Commun 2019;10:38.
6. Mottawea W, Chiang CK, Mühlbauer M, Starr AE, Butcher J, Abujamel T, Deeke SA, Brandel A, Zhou H, Shokralla S, Hajibabaei M, Singleton R, Benchimol EI, Jobin C, Mack DR, Figeys D, Stintzi A. Altered intestinal microbiota-host mitochondria crosstalk in new onset Crohn's disease. Nat Commun 2016;7:13419.
7. Martin-Gallausiaux C, Marinelli L, Blottière HM, Larraufie P, Lapaque N. SCFA: mechanisms and functional importance in the gut. Proc Nutr Soc 2020. https://doi.org/10.1017/S0029665120006916.
8. De Preter V, Arijs I, Windey K, Vanhove W, Vermeire S, Schuit F, Rutgeerts P, Verbeke K. Impaired butyrate oxidation in ulcerative colitis is due to decreased butyrate uptake and a defect in the oxidation pathway. Inflamm Bowel Dis 2012;18:1127–1136.

Conflicts of interest
The author has received research support from FrieslandCampina, Glycosyn, and Janssen.

Most current article

2352-345X
https://doi.org/10.1016/j.jcmgh.2020.05.008