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987 Endoscopic Index of Disease Severity in Crohn's and Ulcerative Colitis

1035 Management of Anemia in Patients Treated for HCV Infection

1055 Role of Mitochondrial DNA Variation in Experimental Colitis

1133 MicroRNA, Autophagy, and Radioresistance in Pancreatic Cancer

ALSO:

- **REVIEWS: Fecal Transplantation 946 & Spectrum of Achalasia 954**
- **AGA CLINICAL DECISION TOOLS: HEP C Screening and Evaluation 1144 & 1146**

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14. Zeuzem S, Andreone P, Pol S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417–2428.
15. Burger D, Back D, Buggish P, et al. Clinical management of drug-drug interactions in HCV therapy: challenges and solutions. J Hepatol 2012;58:792–800.
16. Cacoub P, Bourlière M, Lübbe J, et al. Dermatological side effects of hepatitis C and its treatment: patient management in the era of direct-acting antivirals. J Hepatol 2012;56:455–463.
17. Hézode C, Fontaine H, Dorival C, et al. CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol 2013;59:434–441.
18. Sulkowski M, Reddy KR, Afdhal NH, et al. Anemia has no effect on efficacy outcomes in treatment-naive patients who received telaprevir-based regimen in ADVANCE and ILLUMINATE phase 3 studies. J Hepatol 2011;54:S195.
19. Poordad F, Lawitz E, Reddy KR, et al. Effects of ribavirin dose reduction vs erythropoietin for boceprevir-related anemia in patients with chronic Hepatitis C Virus genotype 1 infection—a randomized trial. Gastroenterology 2013;145:1035–1044.
20. Leroy V, Serfaty L, Bourlière M, et al. Protease inhibitor-based triple therapy in chronic hepatitis C: guidelines by the French Association for the Study of the Liver. Liver Int 2012;32:1477–1492.

Reprint requests

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Conflicts of interest

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The Other Genome: Mitochondrial DNA and Protection From Experimental Colitis

See "Mitochondrial gene polymorphisms that protect mice from colitis," by Bär F, Bochmann W, Widok A, et al, on page 1055.

Within each eukaryotic cell there are 2 genomes, one encoded by nuclear DNA and the other by mitochondrial DNA (mtDNA). Unlike nuclear DNA, mtDNA can be present in hundreds of copies per cell. mtDNA is replicated and transcribed independently of nuclear DNA to produce (in humans and mice) 22 tRNAs and 2 rRNA genes that function to translate an additional 13 protein coding genes (Table 1). These mtDNA genes encode components for 4 of the 5 respiratory chain complexes of the mitochondrial inner membrane that function in oxidative phosphorylation and thus the production of cellular ATP. Oxidative phosphorylation, and to a lesser extent glycolysis, are the major sources of energy in cells, with mitochondrial respiration producing large quantities of ATP from each molecule of glucose. Sperm are packed with mitochondria at the base of the flagella to provide sufficient ATP to travel around 200,000 times their own length to the ovum, the equivalent of a 6-foot tall human swimming 350 km without stopping. These sperm-derived mitochondria do not typically become part of the embryo and therefore mtDNA is maternally derived in a non-Mendelian fashion. Mutations in mtDNA cause maternally inherited diseases owing to defective oxidative phosphorylation that include Leber hereditary optic neuropathy, Leigh syndrome, encephalopathies, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and myopathies, including MERRF (myoclonic epilepsy with ragged red fibers) syndrome and Kearns–Sayre syndrome. Mutations in mtDNA may also contribute susceptibility to complex genetic disorders including macular degeneration, Alzheimer disease, type 2 diabetes, and the metabolic syndrome.[1] In this issue, Bar et al[2] find that genetic polymorphisms in mtDNA protect mice from chemically induced colitis, suggesting that inflammatory bowel diseases (IBDs) might be added to the growing list of diseases that involve mtDNA mutations.

Unlike genetic engineering of nuclear DNA, it is not currently possible to target and introduce mutations in mtDNA. Therefore, the study by Bar et al[2] employs conplastic strains of mice that have the same nuclear DNA but distinct mtDNA. These mice were generated by backcrossing different strains (using the female as the donor parent to provide mtDNA) for $\geq$10 generations. In this way, differential responses between conplastic mice can be attributed to differences in mtDNA and can help us to understand the contributions of mtDNA mutations and altered mitochondrial functions to models of IBD. Here, Bar et al[2] compare the responses of 4 conplastic strains and find that 2 strains have increased intestinal ATP levels along with increased mitochondrial oxidative phosphorylation activity and that these strains are protected from dextran sodium sulfate (DSS) and trinitrobenzene sulfonate–induced colitis. Although the 2 conplastic strains that were protected from colitis each had distinct mtDNA mutations, they shared a mutation in

Table 1. mtDNA-encoded Genes and Examples of Human Diseases Caused by Their Mutation

Mitochondrial Gene	Encoded Protein	Function	Human Disease (Examples)
MT-RNR1	None (12S RNA)	mtDNA translation	Nonsyndromic deafness
MT-RNR2	Humanin? (16S RNA)	Prosurvival factor?	
tRNAs (22 of these)	None	mtDNA translation	MELAS; MERRF syndrome; deafness
MT-ND1	NADH dehydrogenase subunit 1	ETC Complex I	LHON; MELAS
MT-ND2	NADH dehydrogenase subunit 2	ETC Complex I	LHON
MT-ND3	NADH dehydrogenase subunit 3	ETC Complex I	Leigh syndrome
MT-ND4	NADH dehydrogenase subunit 4	ETC Complex I	LHON; MELAS
MT-ND4L	NADH dehydrogenase subunit 4L	ETC Complex I	LHON
MT-ND5	NADH dehydrogenase subunit 5	ETC Complex I	LHON; Leigh syndrome; MELAS
MT-ND6	NADH dehydrogenase subunit 6	ETC Complex I	LHON; MELAS
MT-CYB	Cytochrome b	ETC Complex III	LHON; myopathies
MT-CO1	cytochrome c oxidase subunit 1	ETC complex IV	LHON
MT-CO2	Cytochrome c oxidase subunit 2	ETC complex IV	cytochrome c oxidase deficiency
MT-CO3	Cytochrome c oxidase subunit 3	ETC complex IV	LHON; complex IV deficiency
MT-ATP6	ATP Synthase F0 subunit 6	ATP synthesis/hydrolysis	LHON, Leigh syndrome
MT-ATP8	ATP Synthase F0 subunit 8	ATP synthesis/hydrolysis	

LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; NADH, reduced nicotinamide adenine dinucleotide.

one of the mitochondrial tRNA genes ($tRNA^{Arg}$), suggesting that this mutation could account for the increased ATP, oxidative phosphorylation, and protection from colitis observed in these 2 strains. Precisely how altered mitochondrial function might lead to protection from IBD is not yet known, but the work by Bar et al[2] suggests that increased respiratory capacity of mitochondria might facilitate epithelial cell proliferation and thus better barrier function.

Although this field of inquiry is understudied, some lines of evidence point to a role for altered mitochondrial function in IBD. The levels of mitochondrial respiratory complex protein activity are reduced in IBD patient mucosa.[3,4] The mitochondrial translocator protein TSPO is increased in enterocytes in human IBD and after DSS treatment of rodents.[5] Treatment with TSPO ligands modulates DSS-induced colitis and cytokine expression.[5] Case reports of mitochondrial dysfunction in IBD have been reported. In one case, a pediatric patient with functional defects in mitochondrial respiration displaying muscle weakness, respiratory insufficiency, and seizures developed Crohn's disease that responded to anti-tumor necrosis factor (TNF) therapy.[6] A mutation in mtDNA was also found in a 46-year-old woman with ischemic colitis.[7] Polymorphisms in mtDNA previously identified in multiple sclerosis were found to affect risk of Crohn's disease, ulcerative colitis, and other autoimmune disorders.[8] Mutations in mtDNA were found to be reduced in the active lesions of ulcerative colitis compared with unaffected tissues, suggesting that active inflammation may affect the relative rates of replication of mitochondria with different polymorphisms or may alter the survival or proliferation of cells with mutant mitochondria.[9] Last, polymorphisms in the autophagy-related gene IRGM have been implicated in IBD. IRGM localizes to mitochondria and affects autophagy, cell death, and resistance to *Mycobacterium tuberculosis*.[10]

Bar et al[2] provide evidence of increased activity of nuclear factor (NF)-κB in the intestinal epithelium of conplastic strains that were more resistant to chemically induced colitis. The role of NF-κB activity is typically to transactivate genes involved in inflammation and cell survival. However, the function of NF-κB is cell and context dependent. In innate immune cells, NF-κB activation is predominantly proinflammatory, whereas in B lymphocytes NF-κB activity is predominantly prosurvival. In the intestinal epithelium, NF-κB activity is essential to prevent TNF-induced cell death, and mice lacking NF-κB activity in intestinal epithelial cells (IECs) develop severe colitis owing to TNF-induced IEC death.[11] Conversely, NF-κB activity in IECs can be proinflammatory, because constitutively active NF-κB in IECs leads to colitis, especially when accompanied by concurrent mitogen-activated protein kinase activation.[12] In addition, NF-κB activity in IECs can alter the course of colitis by increasing IEC tight junction integrity and by the production of antimicrobial peptides. Thus NF-κB activity in IECs is cytoprotective, but also potentially proinflammatory; therefore, context is everything when considering how NF-κB activity might impact the course of IBD. For this reason, other models of IBD, such as the $IL\text{-}10^{-/-}$ mouse will be important to examine to more fully understand the role of mtDNA mutations and NF-κB activity in IBD.

The link between altered mitochondrial respiration and protection from colitis remains unanswered. One possibility, raised by the authors, is that altered levels of ATP impact AMPK activity in cells, leading to a potentially wide array of signaling pathways that help the cell respond to stress. Mitochondria, in addition to providing cellular supplies of energy, also participate in a wide array of

cellular functions, making it difficult at present to model exactly how altered mitochondrial function could prevent inflammation. Mitochondria are platforms for innate immune signaling, including responses to viruses and for activation of the NLRP3 inflammasome.[13] These effects are mediated by a receptor called MAVS (also called CARDIF, VISA, IPS1) found on the outer mitochondrial membrane and MAVS expression and activity can be altered by the degree of mitochondrial polarization, an effect that is directly related to mitochondrial respiration.[14] Nonetheless, further exploration of the link between mtDNA mutations, altered NF-κB activity, IEC proliferation, and protection from colitis will certainly provide a rich and interesting new framework for understanding the pathogenesis of IBD.

If mtDNA mutations contribute to IBD, we may be able to manipulate this effect to provide treatments for this disease. A limited number of proteins are directly encoded by mtDNA and all of them are involved in mitochondrial respiration. Known regulators that decrease mitochondrial respiration include reactive oxygen species generated by the respiratory chain, suggesting that targeted antioxidants could be beneficial to reduce chronic inflammation. Increasing the rate of mitochondrial replication or deleting defective mitochondria with agents that target mutant mtDNA in IECs might also provide some benefits in IBD. Defective mitochondria are cleared from cells by a specialized form of autophagy, called mitophagy, and increasing this activity might help to improve the overall mitochondrial activity of cells. This might be of particular interest given that IRGM, which is genetically associated with IBD, is a mitochondrial protein involved in autophagy. One interesting question is whether and how current useful therapies might act in part by altering mitochondrial function, or whether mtDNA mutations impact the response of patients to certain therapies. For example, it would not be surprising to learn that azathioprine or 6-mercaptopurine impact mitochondrial function and that such an effect could contribute to the efficacy of these drugs. Because defective mitochondrial function has been implicated in many human disorders, including Parkinson disease, type 2 diabetes, and other age-related diseases, we should be cognizant of the work by our scientific and clinical colleagues in those research areas to better develop new therapies and understanding of the contribution of mtDNA mutations to IBD.

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References

1. Ruiz-Pesini E, Lott MT, Procaccio V, et al. An enhanced MITOMAP with a global mtDNA mutational phylogeny. Nucleic Acids Res 2007; 35:D823–D828.
2. Bär F, Bochmann W, Widok A, et al. Mitochondrial gene polymorphisms that protect mice from colitis. Gastroenterology 2013; 145:1055–1063.
3. Sifroni KG, Damiani CR, Stoffel C, et al. Mitochondrial respiratory chain in the colonic mucosal of patients with ulcerative colitis. Mol Cell Biochem 2010;342:111–115.
4. Santhanam S, Rajamanickam S, Motamarry A, et al. Mitochondrial electron transport chain complex dysfunction in the colonic mucosa in ulcerative colitis. Inflamm Bowel Dis 2012;18:2158–2168.
5. Ostuni MA, Issop L, Peranzi G, et al. Overexpression of translocator protein in inflammatory bowel disease: potential diagnostic and treatment value. Inflamm Bowel Dis 2010;16:1476–1487.
6. Restivo NL, Srivastava MD, Schafer IA, et al. Mitochondrial dysfunction in a patient with crohn disease: possible role in pathogenesis. J Pediatr Gastroenterol Nutr 2004;38:534–538.
7. Hess J, Burkhard P, Morris M, et al. Ischaemic colitis due to mitochondrial cytopathy. Lancet 1995;346:189–190.
8. Yu X, Wieczorek S, Franke A, et al. Association of UCP2 -866 G/A polymorphism with chronic inflammatory diseases. Genes Immun 2009;10:601–605.
9. Fukushima K, Fiocchi C. Paradoxical decrease of mitochondrial DNA deletions in epithelial cells of active ulcerative colitis patients. Am J Physiol Gastrointest Liver Physiol 2004;286:G804–G813.
10. Singh SB, Ornatowski W, Vergne I, et al. Human IRGM regulates autophagy and cell-autonomous immunity functions through mitochondria. Nat Cell Biol;12:1154–1165.
11. Nenci A, Becker C, Wullaert A, et al. Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature 2007; 446:557–561.
12. Guma M, Stepniak D, Shaked H, et al. Constitutive intestinal NF-kappaB does not trigger destructive inflammation unless accompanied by MAPK activation. J Exp Med;208:1889–1900.
13. Tait SW, Green DR. Mitochondria and cell signalling. J Cell Sci 2012; 125:807–815.
14. Koshiba T, Bashiruddin N, Kawabata S. Mitochondria and antiviral innate immunity. Int J Biochem Mol Biol;2:257–262.

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Conflicts of interest
The author declares no conflicts.

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