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Gut bacteria signaling to mitochondria in intestinal inflammation and cancer

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ABSTRACT

The gastrointestinal microbiome plays a pivotal role in physiological homeostasis of the intestine as well as in the pathophysiology of diseases including inflammatory bowel diseases (IBD) and colorectal cancer (CRC). Emerging evidence suggests that gut microbiota signal to the mitochondria of mucosal cells, including epithelial cells and immune cells. Gut microbiota signaling to mitochondria has been shown to alter mitochondrial metabolism, activate immune cells, induce inflammasome signaling, and alter epithelial barrier function. Both dysbiosis of the gut microbiota and mitochondrial dysfunction are associated with chronic intestinal inflammation and CRC. This review discusses mitochondrial metabolism of gut mucosal cells, mitochondrial dysfunction, and known gut microbiota-mediated mitochondrial alterations during IBD and CRC.

Introduction

Mitochondria are vital organelles for energy production in the cell. Emerging evidence suggesting that altered functioning of the mitochondria of mucosal cells is associated with intestinal diseases, including inflammatory bowel diseases (IBD) and colorectal cancer (CRC), has led to a renewed interest in the role of mitochondria in intestinal health. The intestinal microbiome, consisting of trillions of microorganisms such as bacteria, viruses, and fungi, plays a crucial role in intestinal homeostasis and disease. It is widely accepted that mitochondria were evolutionarily derived from a proteobacterium, resulting in common characteristics between eukaryotic mitochondrial and prokaryotic genomes. Due to these similarities, mitochondria can play a central role in triggering immune responses using mechanisms similar to bacteria. Additionally, bacteria can target mitochondria in host cells. Such cross-talk between gut microbiota and host mitochondria during health and disease is emerging as a significant area of research. Studies are beginning to elucidate the intricate molecular signaling between gut microbiome and mitochondria, but further studies are necessary to identify the mechanistic link between microbiome and host mitochondria in the pathogenesis of IBD or CRC. This review aims to present current evidence demonstrating the role of gut microbiome in signaling to the mitochondria of intestinal cells and the implications of this signaling in driving IBD or CRC.

Mitochondria structure, dynamics, and energy metabolism

Mitochondrial structure

Mitochondria are double membrane-bound organelles found generally in large numbers in the cytoplasm of eukaryotic cells. Mitochondria are important organelles due to their primary function to generate energy for the cell in the form of adenosine 5′-triphosphate (ATP). In 1957, Phillip Skiekevitz coined the phrase "powerhouse of the cell" for the organelle. In addition to ATP production, mitochondria are an important site of intracellular calcium storage and the induction of apoptosis during cellular stress predominantly by the release of cytochrome c into the cytosol. The outer mitochondrial membrane (OMM) is composed of a phospholipid bilayer separating the mitochondria and its contents from the cytosol. Ions and proteins smaller than 5 kDa diffuse into and out of the mitochondria freely via porins, and therefore, the concentration of small proteins and ions in the mitochondrial intermembrane space

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matches the cytosol. Proteins larger than 5 kDa possessing a 5′ mitochondrial localization sequence translocate across the OMM via binding to translocase of the outer membrane (TOM) transporters. Proteins transferred into the mitochondria include nuclear DNA encoded proteins such as those for oxidative phosphorylation and heat shock proteins.[1] The inner mitochondrial membrane (IMM) is also a phospholipid bilayer and houses electron transport chain (ETC) complexes which drive ATP production. Transporters called translocase of the inner membrane (TIMs) are required for all ions and proteins to enter the mitochondrial matrix[2] allowing formation of the protein gradient in the space between the OMM and IMM, driving electron flow through the ETC.[3] Inward folds of the IMM are called cristae, which increase the surface area for ATP production to match cellular demand.[4] Within the IMM is the mitochondrial matrix which houses ribosomes, mitochondrial DNA (mtDNA), and ATP synthase proteins that facilitate the catalysis from adenosine diphosphate (ADP) to ATP.[1]

Mitochondrial genome

Contrary to other eukaryotic organelles, mitochondria possess their own genome, mtDNA, located in the mitochondrial matrix.[5] mtDNA has been traced to a proteobacterial ancestor which is responsible for the first known case of ATP production in correlation to the ETC complex.[6] The bacterium-like protist *Reclinomonas americana* and the gram-negative, alphaproteobacteria *Rickettsia prowazekii* have been identified as potential ancestors of the eukaryotic mitochondrion.[6] Human mtDNA is ~16.6 kb long and contains 37 genes coding for two rRNAs, 22 tRNAs and 13 polypeptide mRNAs.[7] mtDNA is circular, double-stranded, and is exclusively transmitted from the female germline.[8] Circular molecules of DNA such as mtDNA are composed of two DNA strands consisting of the heavy, guanine-rich strand and the light strand. Majority of the mtDNA code is found in the heavy strand, including seven subunits of ETC complex I (NADH dehydrogenase), three subunits of ETC complex IV (cytochrome *c* oxidase), and two subunits of ETC complex V (ATP synthase) and ETC complex III.[9] Conversely, the light strand codes for eight tRNAs and a single polypeptide.[9] All the necessary transcription and translation machinery and protein folding chaperones are present in the matrix to facilitate production of functional proteins from the mitochondrial genome.[5] The majority of the proteins involved in this process are encoded by nuclear genes and not mtDNA and therefore, are transported from the cytosol into the mitochondrial matrix by TOMs/TIMs.[8] Unique features of mtDNA compared to nuclear DNA include circular structure, short introns, and lack of histone structures. The lack of histones and short intergenic regions contribute to mtDNA susceptibility to damage by oxidative stress and other noxious agents.[10] Mitochondria possess many of the same DNA repair pathways as found in the nucleus to repair DNA damage.[8]

Mitochondrial dynamics

Mitochondria are dynamic organelles which readily respond to environmental stimuli and cellular demands for energy.[11] Quality control of mitochondria is critical in maintaining cell homeostasis and consists of fission, fusion, and removal of damaged mitochondria by autophagy, known as mitophagy. In the event that these quality control pathways cannot restore the mitochondrial population, apoptosis of the cell ensues. Mitochondria exhibit high plasticity of structure with constant fission, fusion, and relocation throughout the cytoplasm. The process of mitochondrial fission and fusion are mediated by guanosine triphosphatases (GTPases) of the dynamin family.[11] These GTPases coordinate to divide (fission) and fuse (fusion) the two lipid bilayers of the mitochondria. A balance between fusion and fission events maintains the overall morphology of the mitochondrial population. An increased fusion/fission ratio generates elongated, tubular mitochondria, whereas an increased fission/fusion ratio results in fragmented mitochondria.

Mitochondrial fusion is the merging of two or more damaged mitochondria, enabling mixing of contents within the mitochondrial population and subsequently diluting damaged components while preserving essential components.[11] Fusion proteins such as Mitofusin 1 (Mfn 1) and Mfn 2 as well as Optic Atrophy 1 (OPA1) are members of the dynamin GTPase family.[1,11] Mfn1 and

Mfn2 form homo- or heterodimers to fuse the outer membranes of adjacent targeted mitochondria together.[11] Subsequently, OPA1 that is located on the IMM coordinates with Mfn1 to facilitate IMM fusion.[11] Through these proteins, fusion facilitates the sharing of mtDNA between mitochondria thereby providing more support for critical functions such as oxidative phosphorylation, mitophagy, apoptosis, cell proliferation, and migration.[12]

Mitochondrial fission is the process by which mitochondria divide into smaller daughter mitochondria.[1] Mitochondrial fission is essential to generate adequate numbers of mitochondria for growing cells and is mediated by Dynamin-Related Protein1 (Drp1), Fission 1 (Fis1), Mitochondria Fission Factor (Mff), Mitochondrial Dynamics Protein (MID49) and MID51. The OMM protein Mff recruits Drp1 from the cytosol[13] to the OMM of mitochondria where it assembles into oligomeric complexes that compress the mitochondrial tubule to mediate fission.[11] This action leads to OMM constriction and cleavage.[11] Fis1 is located on the OMM as the receptor protein for Drp1 during its translocation from the cytosol.[14] The interaction of Drp1 with Fis1 can lead to the release of cytochrome *c* which can induce apoptosis.[11] MID49/51 are also found on the OMM and facilitate randomized screening of uncharacterized proteins whose expression cause changes in mitochondrial morphology.[13]

Autophagy is an evolutionarily conserved catabolic pathway that removes cytoplasmic components, including damaged organelles, through lysosomal degradation.[15] Autophagic flux is the dynamic process of autophagosome synthesis containing cargo to be degraded, fusion of the autophagosome with a lysosome, and degradation of autophagosome/cargo inside the lysosome. Selective autophagy of mitochondria, termed mitophagy, eliminates damaged mitochondria to prevent excessive mitochondrial reactive oxygen species (mtROS) generation and cell toxicity.[16] For detailed reviews, see refs.[17,18] Mitochondrial dysfunction (depolarization, excessive misfolded proteins, mtROS accumulation)[19,20] stimulates OMM-localized autophagy receptors to incorporate mitochondria into the autophagosome.[21] Some autophagy receptors are dependent on Parkin, which is recruited to dysfunctional mitochondria and targets OMM proteins for ubiquitination; polyubiquitinated chains are then recognized by the autophagy receptor, thereby incorporating the mitochondrion into the autophagosome via their LC3-interacting region.[21] Parkin-dependent autophagy receptors that target mitochondria include p62, NBR1, and AMBRA1. Other autophagy receptors that target mitochondria and act independently of Parkin include Bnip3, Nix/Bnip3L, FUNDC1, and BCl2L13. Parkin-independent autophagy receptors contain transmembrane domains and upon expression constitutively localize to the OMM.[16] Mitochondrial fission facilitates mitophagy by dividing mitochondria into fragments of small enough size to be engulfed by the autophagosome.[1]

Energy metabolism

Mitochondria provide efficient mechanisms for eukaryotic cells to generate ATP and produce building blocks for biosynthesis required for cell proliferation and differentiation. A key function of mitochondria is to produce ATP through oxidative phosphorylation. In the presence of oxygen, this process begins with cytosolic glycolysis of glucose to produce pyruvate, which is the main source of mitochondrial energy production and intermediate metabolism by conversion into acetyl-CoA. Acetyl-CoA is the initial molecule powering the citric acid cycle, also known as the tricarboxylic acid (TCA) cycle, in the mitochondrial matrix.[3] In addition, fatty acid β-oxidation (FAO) produces acetyl-CoA from fatty acids to feed the TCA cycle. The TCA cycle provides the required precursors for oxidative phosphorylation: 2 pyruvate molecules, 6 NADH, and 2 $FADH_2$ are produced from 1 glucose molecule. NADH and $FADH_2$ provide electrons to complexes I or II of the ETC, respectively, which in turn utilize the energy of passing electrons to translocate protons from the mitochondrial matrix to the intermembrane space. This accumulation of protons generates an electrical and chemical gradient across the IMM, that in turn drives transport of protons through the ATP synthase complex. This process transforms ADP and an inorganic phosphate into ATP.[22] During oxidative phosphorylation, 38 ATP molecules are made from one glucose molecule (two from glycolysis, two from the TCA cycle, and

approximately 34 from the ETC). When limited amounts of oxygen are available, anaerobic glycolysis occurs which produces lactate from glucose and generates two ATP molecules. Aerobic glycolysis is a well-documented phenomenon in cancer (called the Warburg effect). During aerobic glycolysis, cells ferment glucose to lactate even in the presence of oxygen. This produces only two ATP molecules but provides glycolytic intermediates to feed anabolic pathways necessary for rapidly dividing cells and is discussed further below. Importantly, through these metabolic pathways, mitochondria produce the majority of the acetyl-CoA and S-adenosylmethanione needed for protein acetylation and methylation, respectively.[23] Thus, alterations in mitochondrial biology and metabolism have profound outcomes on the epigenetic state of the genome.

Mitochondria and innate and adaptive immune responses

Dysfunctional mitochondria are emerging as key activators of the nucleotide binding domain and leucine-rich repeat pyrin 3 domain (NLRP3) inflammasome. Inflammasomes are multiprotein complexes in the cytosol that promote inflammation in response to pathogens and cellular distress. The NLRP3 inflammasome is the best-characterized inflammasome to date with known function to activate Caspase-1. Caspase-1 in turn cleaves and activates interleukin-1β (IL-1β) and IL-18 cytokines, thereby promoting inflammation and self-defense pathways. The NLRP3 inflammasome is most prominently expressed in myeloid cells. The NLRP3 inflammasome is activated by mitochondrial signals including mtROS, oxidized mtDNA, extracellular ATP efflux, loss of mitochondrial membrane potential, and alterations in cell metabolism.[24] Other inflammasomes including NLRP1, NLRC4, and NLRP6 also function to activate Caspase-1 but in response to distinct stimuli compared to NLRP3. Mice deficient in NLRP3 exhibited less severe experimental colitis with decreased production of pro-inflammatory cytokines.[25] Furthermore, recent findings suggested that IL-10 deficiency led to the accumulation of damaged mitochondria and dysregulated activation of the NLRP3 inflammasome in macrophages of mouse models of colitis and in IBD patients.[26] These studies imply that activation of the NLRP3 inflammasome is involved in IBD pathogenesis.

Activation, cell differentiation, and polarization of immune cells are dependent on metabolic reprogramming during bacterial infection. Neutrophils, dendritic cells, and CD4⁺ T cells undergo a metabolic shift from oxidative phosphorylation to glycolysis.[27] Elimination of activated neutrophils by mitochondria-induced apoptosis is crucial to preventing extended and exaggerated inflammation.[28] M1 macrophage polarization in response to lipopolysaccharide is dependent on activation of glycolysis to acquire bactericidal activity, while M2 macrophage polarization requires increased FAO and oxidative phosphorylation.[29] Shifts in mitochondrial metabolism play a central role in memory T-cell quiescence and activation responses during bacterial infection.[30] Stimulation of B lymphocytes induces glycolysis and oxidative phosphorylation to facilitate the production of IgG or IgA antibodies.[30] The signaling pathways mediating metabolic reprogramming in immune cells are not fully understood, but hypoxia-inducible factor-1α (HIF-1α) has been implicated as a master regulator of mitochondrial responses during bacterial infection.[31,32]

Mitochondria and the intestinal epithelium

Mitochondrial metabolism is distinct in intestinal epithelial cell types

The epithelial lining of the small intestine (SI) is regenerated in its entirety at a rapid pace of every three to five days. In tissues of high turnover such as the intestinal epithelium, stem cells are crucial regulators of tissue homeostasis. Crypt base columnar (CBC) stem cells, a population of rapidly dividing cells at the crypt base expressing leucine-rich-repeat containing G-protein coupled receptor 5 (Lgr5), give rise to all terminally differentiated intestinal epithelial cell (IEC) types (enterocytes, Paneth, goblet, enteroendocrine, tuft, and M cells).[33] CBCs divide into progenitor cells which move upward within the crypt into the transit amplifying zone.[34] It is here that the cells differentiate further and travel to the villus where their functions are required. At the villus tip, senescent IECs slough off through anoikis, a specific type of programmed cell death for

anchorage-dependent cells, and make room for newly formed cells to take their place.[34] Paneth cells are the exception as these cells are long-lived secretory cells that migrate to the crypt base and reside between Lgr5^{+} CBCs where they produce and secrete antimicrobial peptides and stem cell factors such as epidermal growth factor, Wnt3, and Notch ligand Dl14 that sustain the stem cell niche.[35-38] Local conditions in the stem cell niche regulate cell proliferation, differentiation, and stem cell self-renewal.[34]

Compared to other differentiated intestinal epithelial cells and relatively quiescent stem cell populations in the adult, such as hematopoietic stem cells and neural stem cells, Lgr5^{+} CBCs show higher mitochondrial oxidative phosphorylation activity.[37,39] Rodriguez-Colman et al. 2017 revealed that in support of increased demand for mitochondrial oxidative phosphorylation for Lgr5^{+} CBCs to maintain the immense amount of cell turn over in the small intestine, lactate from Paneth cells is fed into neighboring Lgr5^{+} CBCs fueling their oxidative phosphorylation processes.[40] Inhibition of glycolysis, and subsequently lactate production, in Paneth cells affects Lgr5^{+} CBC function and hinders crypt maturation.[40] Therefore, the glycolytic phenotype in Paneth cells is crucial for lactate production, which drives increased oxidative phosphorylation in Lgr5^{+} CBCs. Mechanistically, Rodriguez-Colman et al. demonstrated that mtROS produced in Lgr5^{+} CBCs during oxidative phosphorylation stimulate activation of p38 MAP kinase, which in turn regulates Lgr5^{+} CBC self-renewal and differentiation.[40] These results show that the glycolytic phenotype in Paneth cells and increased oxidative phosphorylation in Lgr5^{+} CBCs are required in supporting both stem cell niche and function. Provision of lactate from Paneth cells is therefore another critical aspect of the interdependent relationship between Lgr5^{+} CBCs and Paneth cells, essential to the maintenance and differentiation of SI epithelium.

Mitochondrial dysfunction and intestinal stem cell homeostasis

Mitochondrial metabolism, function, and biogenesis are all strictly regulated within intestinal stem cells (ISCs) as well as epithelial cells along the crypt-villus axis and in turn, play critical roles in the regulation and maintenance of ISCs. ISCs possess a large number of mitochondria, and crypt formation was shown to be dependent on an abundance of mitochondria.[41] IEC-specific deletion of the mitochondrial chaperone protein heat-shock protein 60 (HSP60) led to mitochondrial dysfunction, impairment of cell proliferation and loss of stemness of ISCs.[41] Furthermore, mitochondrial dysfunction impaired the ability of the ISCs to produce ATP, leading to altered ISC self-renewal and differentiation.[41] Therefore, a functioning mitochondrial population in ISCs is crucially important for intestinal epithelial regeneration and homeostasis.

ROS are well-established primary signaling molecules for downstream signaling from mitochondria and excessive mtROS not eliminated by mitophagy can lead to multiple cellular dysfunctions.[42] Intestinal organoids treated with buthionine sulfoximine to generate excessive mtROS, or intestinal organoids generated from mice with ISCs deficient in autophagy with subsequent mtROS accumulation, exhibited reduced number and self-renewal of ISCs.[43] Treatment with the antioxidant N-acetyl-L-cysteine, which dampens excessive ROS levels and restores ATP synthesis in mitochondria, restored the number of ISCs in intestinal organoids deficient in autophagy.[43] The role of mitochondrial function and ROS generation on stem cell fate and self-renewal is also important in relatively quiescent stem cell populations including hematopoietic stem cells[44] and neural stem cells[45,46] in addition to more active ISCs of frequent turnover tissues requiring more bioenergetics activity such as the intestinal epithelium.

Mitochondria–microbiota cross talk and implication in intestinal disease

Mitochondrial dysfunction and inflammatory bowel diseases

Inflammatory bowel diseases (IBD) are a group of idiopathic diseases of the gut characterized by recurring, chronic inflammation. The two predominant IBDs are Crohn's disease (CD) and ulcerative colitis (UC). These multifactorial diseases exhibit dysfunction of the intestinal epithelial barrier and dysregulated immune cell responses to gut microorganisms due to unknown environmental triggers in genetically

predisposed individuals.[47] IBD patients with colonic involvement exhibit an increased risk of developing colorectal cancer (CRC) dependent on disease severity and duration.[48]

Emerging studies have begun to reveal the involvement of mitochondrial stress in the pathophysiology of IBD (Figure 1). Over 30 years ago, UC was thought to be an "energy deficient" disease of the epithelium.[49] Electron microscopy studies demonstrated that ultrastructural alterations to epithelial cell mitochondria, such as dissolved/irregular cristae indicative of impaired function, were evident in CD patients as an early event during inflammation, prior to alterations to the tight junctions controlling barrier function.[50] Decreased activity of ETC complexes has been observed in mucosal biopsies of CD and UC patients, which was restored by anti-TNFα treatment, suggesting TNFα regulates mitochondrial function during intestinal inflammation.[51–54] Induction of the mitochondrial-unfolded protein response (mtUPR) was evident in epithelial cells from CD and UC.[55] The mtUPR is activated upon an accumulation of unfolded or misfolded proteins in the mitochondrial matrix to upregulate protein folding chaperone proteins to return homeostasis.[41] In a recent study, it was demonstrated that mtDNA released into the serum in IBD patients was recognized as a damage-associated molecular pattern (DAMP) potentially by toll-like receptor 9 (TRL9), and could provide a biomarker of inflammation.[56] Paneth cell defects in CD patients, a phenotype shown to associate with early disease recurrence after resection,[57] were shown to correlate with dysbiosis of the microbiome and reduced expression of a large cluster of oxidative phosphorylation genes,[58] suggesting patients with Paneth cell defects may have altered mucosal mitochondrial function but
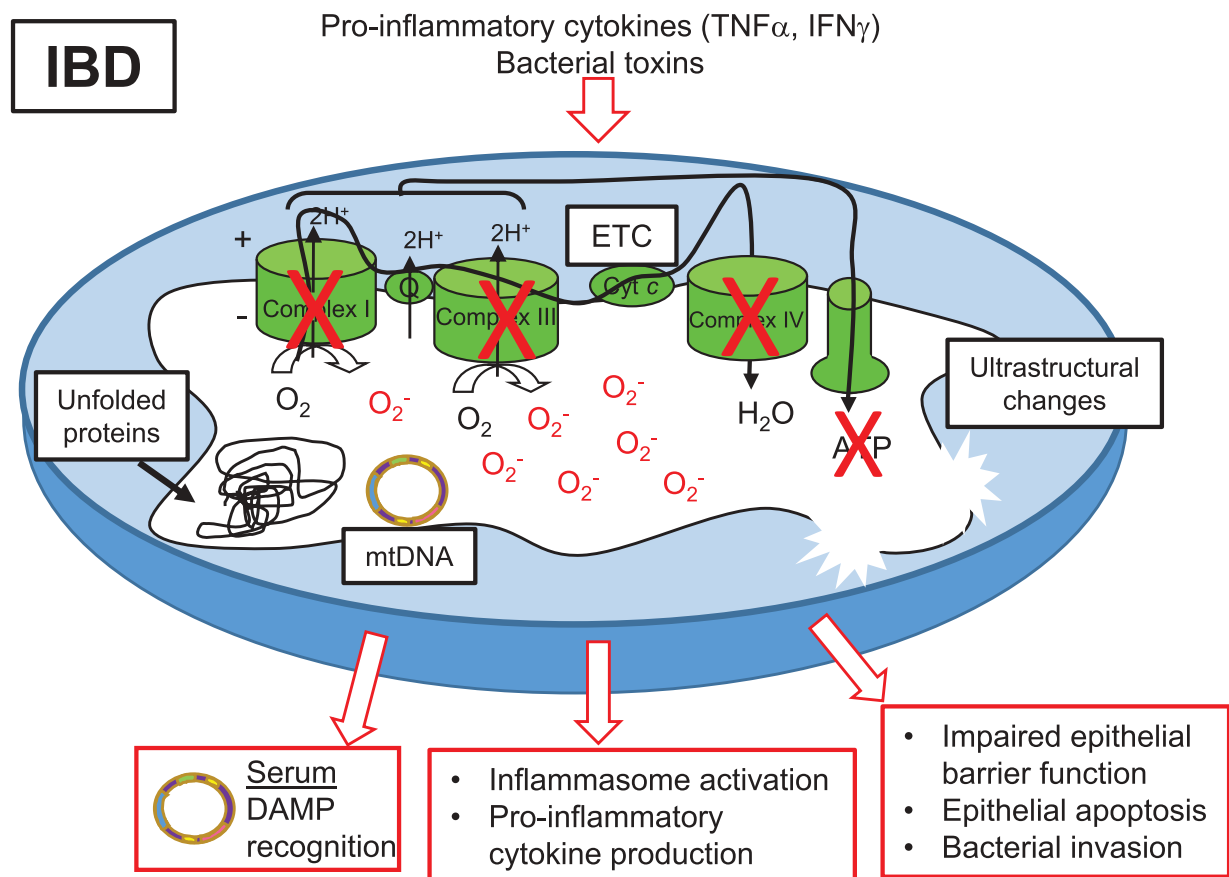

Figure 1. Mitochondrial dysfunction associated with IBD. Pro-inflammatory cytokines and bacterial toxins are implicated in mitochondrial alterations during IBD. Decreased activity of ETC complexes, decreased ATP levels, accumulation of mtROS, accumulation of misfolded or unfolded proteins in the matrix, and ultrastructural changes such as dissolved cristae have been reported in mitochondria of the epithelium of IBD patients. Subsequent loss of epithelial barrier integrity, epithelial cell apoptosis, and bacterial invasion have been demonstrated following mitochondrial dysfunction in the epithelium. mtDNA is released into the serum of IBD patients and serves as a DAMP for immune cell activation. Additionally, damaged mitochondria can signal inflammasome activation, leading to pro-inflammatory cytokine production.

this was not further elucidated. Recent reports on the pediatric RISK stratification study using RNA sequencing analysis on CD inflamed biopsies demonstrated that patients who were at risk of structuring, but upon follow-up through 36 months remained complication free, exhibited an enriched mitochondrial function gene signature compared to those patients who developed complications.[59] In a proteome study of pediatric CD patients with colonic involvement, impaired mitochondrial function was implicated and correlated with increased disease severity.[60] Importantly, mitochondrial-encoded DNA polymorphisms have been identified to be associated with UC in European cohorts.[61,62] Furthermore, 5% of genes highlighted by IBD genome-wide association studies were functionally linked to the maintenance of mitochondrial health, further underpinning the role of deregulated mitochondrial function in IBD.[63]

Multiple mouse models implicate mitochondrial dysfunction in the pathogenesis of intestinal inflammation. Mice treated with dextran sodium sulfate (DSS) to induce colitis exhibited swollen mitochondria, increased mtROS generation, decreased ETC activity and ATP level in the colonic mucosa that was ameliorated by anti-TNFα treatment.[54,64] Mice with deletion of IRGM, a CD susceptibility gene that affects mitochondrial fission and induces autophagy, exhibited increased susceptibility to experimental colitis.[65,66] Polymorphisms in *SLC22A5*, which encodes OCTN2 the carnitine transporter involved in mitochondrial FAO, are associated with CD risk.[67] Deletion of OCTN2 in mice caused spontaneous colitis.[68] Mice deficient in PGC1α, a master regulator of mitochondrial biogenesis, exhibited exacerbated intestinal inflammation associated with decreased mtDNA levels.[69] Deficiency of MDR1, which is an ATP-dependent efflux transporter, impaired mitochondrial homeostasis and promoted intestinal inflammation.[63] Bar et al. utilized conplastic strains of mice that have the same nuclear DNA but distinct mtDNA to demonstrate that strains of mice with increased ATP levels and increased mitochondrial oxidative phosphorylation were protected from experimental colitis. This protection was associated with enhanced IEC barrier function and epithelial proliferation.[70] Mice unable to mount a mtUPR due to deletion of PKR exhibited protection from experimental colitis, suggesting mtUPR is involved in the pathology of intestinal inflammation.[55] Genetic

overexpression in IECs or therapeutic delivery (via adenovirus or nanoparticles) of the mitochondrial protein Prohibitin 1, which provides chaperone function for proteins of ETC complexes, protected mice from experimental colitis.[71,72] Collectively, these mouse studies demonstrate the importance of mitochondrial health in protecting against intestinal inflammation.

IEC culture and enteroid models have provided important mechanistic insight suggesting that decreased mitochondrial function in epithelial cells drives a loss in barrier integrity and subsequent bacterial invasion of the underlying intestinal tissue. Loss of barrier function can manifest from epithelial cell death or leakiness of paracellular epithelial cell-cell junctions. DSS-induced colitis is associated with epithelial barrier dysfunction and mechanistic studies using Caco-2 cell monolayers demonstrated that mtROS plays a key role in loss of barrier integrity during DSS via stimulating the redistribution of Occludin and ZO-1 from intercellular junctions into intracellular compartments causing leakiness of the tight junctions without altering cell viability.[73] Many forms of ROS have been implicated in disrupting tight junctions through the rearrangement of the actin cytoskeleton to decrease its interaction with tight junction proteins Occludin and ZO-1 and interaction with myosin heavy chain.[74] Additionally, hydrogen peroxide alters phosphorylation of Occludin, disrupting the tight junction, and phosphorylation of β-catenin, disrupting the adherens junction due to the redistribution of E-cadherin preventing interaction with β-catenin.[74] The role of ROS specifically derived from mitochondria in inducing intestinal epithelial barrier dysfunction was demonstrated by rescue experiments using a mitochondrial-targeted ROS scavenger called mitoquinone (MitoQ).[75] Indeed, dysfunctional mitochondria and accumulation of mtROS during deficiency of the autophagy protein ATG16L1 induced epithelial barrier defects and the transcellular passage of bacteria that perpetuated intestinal inflammation.[75,76]

In addition to epithelial barrier integrity, intestinal epithelial mitochondria serve as both targets and facilitators of inflammatory pathways. Cultured colon epithelial cells with reduced mitochondrial activity (p0 cells) exhibited activation of

pathways associated with inflammation through an AMPK-mediated mechanism.[54] Since colonic p0 cells are unable to produce mtROS but actively induce inflammatory pathways, decreased oxidative phosphorylation likely plays a role in triggering intestinal inflammation.[54] TNFα, a pro-inflammatory cytokine that plays a central role in IBD inflammation, inhibited mitochondrial function in cultured IECs, inducing mtROS accumulation and subsequently leading to impaired barrier function.[54,77] Infliximab, an anti-TNFα biologic therapy for IBD, was shown to be beneficial to reduce mitochondrial dysfunction in cultured IECs and IBD patients.[54,78] The role of microbiome in mitochondrial alterations driving epithelial barrier dysfunction will be discussed in the following section.

Gut microbiome signaling to mitochondria – IBD

The interface between the IECs and intestinal luminal contents stimulates a variety of immune and metabolic activities, with the mucosa armed with mechanisms able to sense nutrients, microbes, and microbial metabolites.[79] The gut microbiome actively interacts and shapes the host mucosal immune system and regulates intestinal homeostasis. Bacteria lead the microbial ecosystem in terms of abundance inside the GI tract, at over 90% of the healthy gut microbiome belonging to the *Bacteriodetes* and the *Firmicutes* phyla. However, inter-individual variation can be more than an order of magnitude in their *Fimicutes/Bacteriodetes* ratios. Typical gut bacterial families found in healthy individuals includes Bacteroidaceae, Clostridiaceae, Prevotellaceae, Eubacteriaceae, Ruminococcaceae, Bifidobacteriaceae, Lactobacillaceae, Enterobacteriaceae, Saccharomycetaceae, and Methanobacteriaceae.[80–82]

Bacterial metabolites, including short-chain fatty acids (SCFAs) and hydrogen sulfide (H_2S), serve as messengers to colonic epithelial and immune cells, impacting their metabolism, epigenetic modifications, and gene expression. SCFAs are currently the most studied bacterial metabolites and are beneficial to colon homeostasis. The three major SCFAs, acetate, propionate, and butyrate, are produced in the colon by bacterial fermentation of carbohydrates and are an important source of energy for colon epithelial cells. SCFAs

are ligands for free fatty acid receptors 2 and 3, which modulate glucose metabolism and FAO. Additionally, SCFAs regulate PGC1α, a master regulator of mitochondrial biogenesis.[83] These responses to SCFAs result at the organelle level in increased glucose uptake, FAO, oxidative phosphorylation, and mitochondrial biogenesis. In terms of intestinal homeostasis, these responses to SCFAs in colon epithelial cells facilitate the development of a tolerant mucosal immune system, promote epithelial barrier integrity, promote "physiologic hypoxia", and suppress colitis.[83–87] In addition, steady-state NLRP3 inflammasome activation in the colon is mediated by SCFAs, which produces basal IL-18 levels, regulates the microbiome composition, and dampens overt inflammatory responses.[88]

H_2S is largely produced by colonic enteric bacteria such as *Escherichia coli* (*E. coli*) and *Salmonella* through degradation of sulfur amino acids. Some studies report anti-inflammatory activity of H_2S in the intestine, while others demonstrate detrimental effects, suggesting that these results are likely context dependent.[89] In IECs, H_2S exhibits detrimental responses. Relative levels of H_2S in the colon directly regulate oxidative phosphorylation in epithelial cells, with elevated H_2S levels inhibiting complex IV of the ETC.[90] Additionally, H_2S induces genotoxic damage to the epithelium, inhibits metabolism of SCFAs, and induces breaks in the mucus barrier allowing exposure of luminal contents to the underlying tissue.[91]

IBD is associated with disruption of commensal bacteria and their downstream genes, which has been extensively reviewed elsewhere.[92] IBD patients exhibit decreased overall diversity of the microbiome and alterations in the gut microbiota (Table 1), but it is not understood if these changes to the microbiota initiate disease pathogenesis or are secondary to inflammation. Commensal bacteria, such as mucosa-associated *E. coli* and *Mycobacterium avium paratuberculosis*, are thought to serve a pathogenic role in the development of IBD. Mucosal-associated microbiota is 50% less diverse in the colon of patients with active CD and 30% less diverse in UC patients.[93] A large-scale study describing the microbiome in 447 newly diagnosed CD pediatric patients prior

Table 1. Alterations to gut microbiome during IBD and CRC.

IBD	CRC
Dysbiosis	Dysbiosis
Barrier defects leading to bacteria-activated inflammation	Pathogenic involvement of commensal bacteria
Loss of microbiome diversity	Loss of microbiome diversity
Decreased SFCA production	Decreased SFCA production
	Increased sulfide production

to anti-inflammatory treatment reported dysbiosis of the microbiome with increased abundance of Enterobacteriaceae, Pasteurellaceae, Fusobacteriaceae, Neisseriaceae, Veillonellaceae, and Gemellaceae, and decreased abundances of Bifidobacteriaceae, Erysipelotrichaceae, Clostridiales, and Bacteroidales.[94] Some reports suggest that increased amounts of sulfate-reducing bacteria, enhancing the capacity to elevate H_2S levels, are present in the gut microbiome of IBD patients.[91] Additionally, IBD patients exhibit decreased levels of SCFA-producing bacteria (*Clostridium* and *Faecalibacterium prausnitzzi*) and increased levels of mucolytic bacteria that degrade the mucus layer (*Ruminococcus gnavas* and *Ruminococcus torques*).[95] The central involvement of gut microbiota in the development of intestinal inflammation is further identified in studies demonstrating that genetically altered mice that manifest spontaneous intestinal inflammation fail to do so in a germ-free environment.[96]

The gut microbiome has emerged as a dynamic central regulator of mitochondrial function in intestinal cells, including immune and epithelial cells.[97] Studies have reported mitochondria to be the most responsive organelle to microbiotic signaling.[98] mtROS produced in immune cells plays an important role in the eradication of invading pathogens via direct bactericidal effects or via indirect effects to activate the NLRP3 inflammasome and produce pro-inflammatory cytokines. Invading bacteria as well as fermentation products of the gut microbiome such as SCFAs induce mtROS production in immune cells via upregulation of mitochondrial respiration and enhanced oxidative phosphorylation. Activation of Toll-like receptors (TLRs) 1, 2, or 4 at the plasma membrane or endoplasmic reticulum membrane occurs upon bacterial or viral infection and subsequently induces mtROS accumulation in macrophages and neutrophils.[99] This was shown

to be dependent on TRAF6-induced accumulation of evolutionarily conserved signaling intermediate in Toll pathways (ECSIT), a protein important for ETC complex assembly and activity.[99] Immune-Responsive Gene 1 (Irg1) is a mitochondrial enzyme induced in macrophages during inflammation that regulates FAO and is required for enhanced oxidative phosphorylation and mtROS production during infection.[100] Such increased mtROS via enhanced oxidative phosphorylation is crucial in macrophage- and neutrophil-mediated eradication of invading pathogens.

Microbial signaling to mitochondria is also emerging in key regulation of intestinal epithelial function. Studies suggest that commensal bacterial-induced mitochondrial signaling potentiates epithelial homeostasis, while pathogenic bacterial-induced mitochondrial responses are detrimental to the function of gut epithelial cells. Colon epithelial metabolism of the SCFA butyrate promoted "physiologic hypoxia" via mitochondrial O_2 consumption to stabilize HIF and induce HIF-targeted barrier-protective genes, linking microbe, epithelial metabolism, and mucosal homeostasis.[87] Generation of ROS in epithelial cells induced by commensal bacteria promoted restitution of damaged epithelium and wound healing.[101] Furthermore, mtROS produced by IECs was shown to protect mice from experimental colitis dependent on the recruitment and polarization of intestinal macrophages to the M2 anti-inflammatory phenotype.[102] The ability of the epithelium to be tolerant of commensal bacteria was lost when epithelial cells exhibited mitochondrial dysfunction and was dependent on the expression of TNFα and IFNγ.[103] When treated with *E. coli* to mimic bacterial invasion during IBD, human colonic epithelial cells exhibiting mitochondrial dysfunction were more susceptible to impaired barrier function, suggesting that during mitochondrial stress, epithelial cells sense commensal bacteria as a pro-inflammatory threat.[103] Mitochondria are important targets of bacterial pathogens to manipulate eukaryotic cellular machinery and exploit apoptotic pathways. Pathogenic bacteria produce toxins that directly damage IEC mitochondria, including the suppression of critical mitochondrial ATP-sensitive potassium channels, initiating mitochondrial membrane

hyperpolarization and apoptosis and subsequently impairing epithelial barrier function.[104] Epithelial barrier defects mediated by pathogenic *E. coli* involve relocalizing Occludin from the peri-junctional region to the cytosol, thereby disrupting tight junctions.[105] This was mechanistically shown to be mediated by two effector proteins, called EspF and Mitochondrial-Associated Protein (MAP), released into the cell by pathogenic *E. coli*. MAP is targeted to the mitochondria where it interferes with mitochondrial function and induces loss of mitochondrial membrane potential via pore-forming activity.[106] Mitochondrial depolarization leads to mtROS accumulation, which in turn, disrupts tight and adherens junctions.[74] In a mouse model of IBD induced by murine norovirus, accumulation of damaged mitochondria during loss of the autophagy protein ATG16L1 induced epithelial cell death via necroptosis, driving barrier dysfunction and inflammation,[76] suggesting that disruption of autophagy and mitochondrial function can confer susceptibility to epithelial cell death and subsequent inflammation. These mechanisms whereby the microbiota elicits alterations to epithelial cell mitochondria play crucial roles in intestinal homeostasis and disease pathogenesis.

Gut microbiome signaling to mitochondria – CRC

CRC is the third most common cause of cancer-related deaths worldwide.[107,108] 90% of CRCs are adenocarcinomas originating in the epithelium via sporadic DNA mutations or as a consequence of chronic inflammation.[109] Patients with chronic IBD affecting the colon have increased risk for developing CRC, accounting for nearly 10–15% of deaths in IBD patients.[110,111] It is well established that mitochondrial alterations are associated with all stages of tumorigenesis, including oncogenic transformation, tumor progression, and metastasis (Figure 2). However, the contribution of mitochondria to cell transformation and tumor progression are not completely understood. The Warburg effect, first postulated in the 1950s, suggested that mitochondrial dysfunction causes cells to undergo aerobic glycolysis, a characteristic of cancer cells.[112] However, more recent studies convey that cancer metabolism is not the consequence

of mitochondrial dysfunction, but the result of mitochondrial reprogramming by loss-of-function mutations in tumor suppressor genes or proto-oncogenic-directed gene modulation.[113] Mitochondrial reprogramming alters cellular metabolism to enhance anabolic pathways critical in supplying the increased requirements of tumor growth.[114] Alteration of cellular metabolism is fundamental to transformation, selected for during tumorigenesis, and does not occur passively as a response to damaged mitochondria or reduction in ATP concentration.[113] The assumption that cancer cells do not utilize mitochondria to derive ATP through oxidative phosphorylation is a misconception; oxidative phosphorylation yields a significant amount of ATP in cancer cells. However, these cells concurrently alter use of mitochondrial enzymes to create anabolic precursors such as reduced carbon, reduced nitrogen, and cytosolic NADPH for macromolecular synthesis of nucleotides, proteins, and lipids necessary for cell proliferation.[114] It has recently been proposed that cancer cells exhibit a hybrid metabolic state, utilizing both oxidative phosphorylation and glycolysis allowing adaptation to changing microenvironments.[115] In a dynamic process, the function of tumor mitochondria is complemented to the metabolic needs necessary to achieve rapid cell growth and enhance metastatic potential.

Mitochondrial alterations are evident early in cancer progression in both sporadic and IBD-related tumorigenesis. Emerging evidence suggests an early loss of mitochondrial function during pre-neoplasia and restoration after malignant transformation. UC-associated progression to tumorigenesis demonstrated early loss of mitochondria and increased glycolysis followed by restoration of oxidative phosphorylation and positive-selection of mitochondria in cancer cells to further growth.[116] This was further corroborated by a recent study demonstrating frequent mtDNA mutations contributing to early UC tumorigenesis that were no longer evident in cancer, suggesting functional mitochondria are required for transformation.[117] The same phenomenon has been observed in sporadic CRC tumorigenesis with increased mtDNA mutations demonstrated in adenomas that decrease in CRC.[118] This supports a model in which mtDNA mutations clonally expand in the colon epithelium during pre-neoplasia,
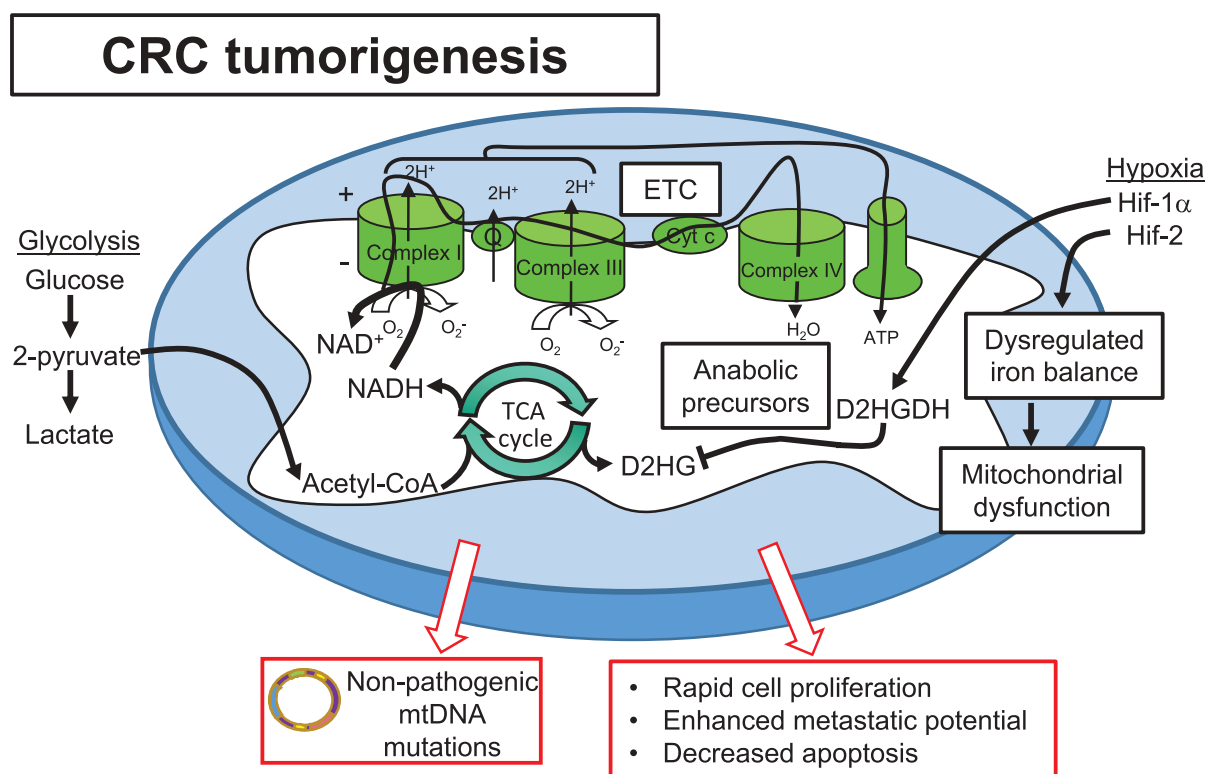
Figure 2. Mitochondrial alterations play a central role in CRC tumorigenesis. Cancer cells exhibit hybrid metabolism, utilizing both glycolysis and oxidative phosphorylation to drive ATP production and adapt to ever-changing microenvironments. Acetyl-CoA produced by glycolysis feeds the TCA cycle to produce cofactors NADH and $FADH_2$ that donate electrons to the ETC and drive oxidative phosphorylation. Altered use of mitochondrial enzymes generate anabolic precursors necessary for rapid cell proliferation. Hypoxia is implicated as a driver of progression to CRC, with Hif-1α providing protection via enhanced D2HGDH production to inhibit the oncometabolite D2HG produced by the TCA cycle. Hif-2α directly targets STEAP4 which modulates mitochondrial iron balance and function. Although mtDNA mutations are demonstrated early in neoplasias, progression to malignancy selects for non-pathogenic mtDNA mutations and functioning mitochondria. These mitochondrial alterations enhance proliferation and metastatic potential and decrease apoptosis, driving CRC tumorigenesis.

exacerbated by increased epithelial cell proliferation as an injury response during inflammation. Progression to malignancy involves selection of clones carrying fewer and/or non-pathogenic mtDNA mutations.[117] Interestingly, methylation and silencing of DNA polymerase γ (POLG), which is the only mtDNA polymerase tasked with mtDNA repair and replication and maintenance of mitochondrial numbers, occurs early during a mouse model of colitis-associated CRC. This was associated with reduced mitochondrial levels, altered mitochondrial metabolism, and resistance to oxidative stress.[119] Studies using ρ0 cells, which are deficient in mitochondrial energy function, suggest that multiple established regulators of CRC depend on reduced mitochondrial function for their expression and are linked to lower patient survival.[120] CRC cells exhibit remodeling of intracellular calcium homeostasis characterized by increased mitochondrial calcium storage.[121] This increased mitochondrial calcium storage was dependent on aerobic glycolysis metabolism and contributed to enhanced cell proliferation, invasion, and resistance to cell death. Further studies are needed to gain an understanding of the role of mitochondrial metabolic reprogramming, mtROS accumulation, and mitochondrial biogenesis in this progression of mitochondrial alterations during tumorigenesis.

Recent studies suggest that hypoxia plays an important role in mediating early mitochondrial alterations during the progression of colitis to cancer. Hypoxia is present during both inflammation and cancer and there are similar metabolic reprogramming pathways affected in both states.[64] HIF-1α and HIF-2α are transcription factors responsive to hypoxia (Figure 2). HIF-1α is beneficial to reduce

intestinal inflammation and regulate epithelial barrier function, in contrast to HIF-2α that has been shown to promote colitis.[122] A recent quantitative proteomics study demonstrated that mitochondrial iron dysregulation occurred early during colitis via upregulation of the mitochondrial iron reductase, six-transmembrane epithelial antigen of prostate 4 (STEAP4).[64] Mechanistically, STEAP4 was shown to be a direct target gene of HIF-2α in a hypoxia-dependent manner, that led to a dysregulation in mitochondrial iron balance, mitochondrial dysfunction, tissue injury, and potentiated colon cancer.[64] Another recent study implicated HIF-1α in the elimination of the mitochondrial oncometabolite D-2-hydroxyglutarate (D-2-HG) in colonic epithelial cells, thereby protecting against colitis-associated cancer.[123] D-2-HG, which is normally produced in the TCA cycle and quickly converted to α-ketoglutarate by D-2-HG dehydrogenase (D-2-HGDH), was highly elevated during colitis and directly correlated with the severity of tumorigenesis in a mouse model of colitis-associated cancer. Elevated D-2-HG enhanced the progression to cancer and conferred a hyper-proliferative, non-apoptotic phenotype in cultured IECs, which are prone to neoplastic progression in the setting of chronic inflammation. The colonic expression of D-2-HGDH was decreased in UC patients at baseline who progressed to cancer. HIF-1α was shown to directly induce transcription of D-2-HGDH, suggesting hypoxia associated with inflammation regulates mitochondrial TCA metabolites that can drive progression of colitis to cancer.[123]

Similar to IBD, CRC increased risk has been associated with dysbiosis of the gut microbiome and decreased production of SCFAs (Table 1). Several studies have demonstrated CRC patients exhibit increased abundance of *F. nucleatum*, *E. coli*, *Bacteriodes fragiles*, and *Enterococcus faecalis*, and decreased *Clostridiales*, *Faecalibacterium*, *Blautia*, and *Bifidobacterium*.[124] It has been proposed that abundance of *Butyricicoccus*, *E. coli*, and *Fusobacterium*, may provide potential biomarkers for normal, adenomatous, and cancerous colon mucosa, respectively.[125] Bacterial targeting of mitochondria is considered a risk factor for carcinogenesis but the mechanism underpinning this association has not been elucidated.[126] Computational prediction models suggest that 87

E. coli proteins target host cell mitochondria that contribute to the etiology of CRC.[127] SCFAs exhibit anti-tumorigenic properties in colon epithelial cells through homeostasis of mitochondrial metabolism and cell proliferation.[128] Gut bacteria have been shown to generate mutations of mtDNA and to modulate DNA repair pathways of the mitochondria.[126] Additionally, bacteria-to-mitochondrial signaling can inhibit the inherent apoptotic pathway in the gut epithelium.[129] Future studies are needed to gain further understanding of whether direct bacterial toxins or bacterial metabolites are involved in the mechanism whereby bacterial-to-mitochondrial signaling enhances colon tumorigenesis.

Mitochondrial targeting by potential therapeutics

Mitochondrial-targeted therapeutics for intestinal inflammation have thus far targeted elimination of mtROS via antioxidant function. The mitochondrial-targeted antioxidant mitoTEMPO is a key example of experimental drugs being used in preclinical research moving towards the elucidation of mitochondrial-based therapeutic approaches for intestinal disorders. Prophylactic mitoTEMPO treatment in DSS-induced colitis demonstrated less severe inflammation and barrier dysfunction.[130] Furthermore, mitoTEMPO decreased metabolic stress in human CD biopsies.[130] TEMPO not targeted to the mitochondria has been shown to affect microbiota, but this has not been investigated for mitoTEMPO.[131] The mitochondrial-targeted antioxidant MitoQ protected against murine ileocolitis in glutathione peroxidase (GPx) −1 and −2 knockouts.[132] Moreover, DSS-induced colitis was ameliorated by MitoQ in mice.[133] These accounts suggest that the targeting of mitochondrial mechanisms, namely mtROS production, assist in quelling inflammation as it relates to IBD. However, future translational studies using mitochondrial-targeted antioxidants in IBD biopsies or patients are necessary. Use of mitochondrial-targeted antioxidants during inflammation in pancreas, arterial blood vessels, liver, and brain also demonstrate beneficial results.[134–137]

With mitochondria as inducers of apoptotic activity and providers of ATP and intracellular ROS, they have been heavily implicated in affecting cancer cell activity.[138] Mitochondria targeting therapeutics for CRC stimulate mitochondrial-induced apoptosis or inhibit ETC complexes, curbing necessary ATP production for cancer cells. Pro-apoptotic factors such as Bcl-2 homology domain 3 (BH3) mimetics, Bcl-2-associated X protein (BAX) and Bcl-2 antagonist/killer protein (BAK) are potential therapeutics for cancer – namely ABT-263, ABT-737 and GX15-070 (obatoclax) for example.[139–141] In addition, voltage-dependent anion channel blockers for the triggering of apoptosis and ROS regulators which are geared towards increasing oxidative stress, and thereby cytotoxicity, are also being used in the clinical setting to decrease tumor progression via mitochondrial targeting.[141] Inhibition of glycolysis, thereby decreasing ATP sources of energy for progressing tumors, can also be initiated via 2-deoxy-D-glucose (2DG).[142] Additionally, numerous studies suggest the mechanism by which the diabetic drug metformin inhibits cancer cells might correlate with its mitochondrial-targeting activity to inhibit the ETC.[143] Population studies such as that of Seo et al. have shown that diabetic patients treated with metformin, which inhibits ETC Complex I, present an approximately 30% reduced overall cancer incidence and mortality rate.[144] Therefore, mitochondrial-targeted therapeutics are emerging as an exciting opportunity for cancer therapy.

The usage of nutraceuticals such as prebiotic molecules and probiotic bacterial species, as well as an alternative diet, can help maintain intestinal homeostasis, thereby providing therapeutics for intestinal diseases. Although controversial in terms of effectiveness, the usage of prebiotics and probiotics in some studies have been shown to ameliorate dysbiotic characteristics of the gut microbiome.[145] Human CRC cell lines treated with butyrate, an SCFA, exhibited decreased cell proliferation and increased apoptotic cell death, suggesting that SCFAs may be capable of CRC inhibition.[146] Westernized diets consisting of increased ingestion of saturated fats, red meat, refined carbohydrates, and decreased dietary fibers not only potentiate dysbiosis of the microbiota but have also been implicated in increased CRC incidence.[145] Evidence of invoking a modified diet and nutritional management has been presented in some cancers as beneficial. Ketogenic diets (KD), in which 90% of the calories source is from fat coupled with sufficient protein and low carbohydrates, produces ketone bodies by metabolic changes that imitate those during starvation.[147] This mechanism forces cells to rely on fat oxidation and mitochondrial respiration in lieu of glycolysis that is a major source of ATP for cancer cells.[147,148] Given these findings, implementing KD based nutritional adjustments could potentially reduce tumor size and progression rates that are dependent upon glucose as an energy source during anaerobic glycolysis.[147] In this way, KD can provide a rationale for therapeutic strategies via tumor growth inhibition.

Conclusions/perspectives

As the powerhouse of the eukaryotic cell, mitochondria play an imperative role in intestinal homeostasis. Mitochondria invoke innate and adaptive immune responses, thereby promoting inflammation and self-defense pathways. Mitochondrial function is crucial to proper epithelial barrier integrity during inflammation and plays a central role in tumorigenesis. The gut microbiome plays an important role in modulating mitochondrial signaling in intestinal mucosal cells, but the involvement of microbiota-mitochondrial cross-talk in driving intestinal diseases such IBD and CRC is not fully understood. Mitochondrial-targeted therapies provide an exciting novel strategy for intestinal diseases. Additionally, therapies aimed at altering the intestinal microbiome may in turn drive mitochondrial responses in intestinal cells. Future studies elucidating the molecular mechanisms linking the gut microbiome and host mitochondria in the pathogenesis of IBD and CRC will be fundamental in advancing mitochondrial-targeted therapies for these intestinal diseases.

Abbreviations

CD	Crohn's Disease
CRC	Colorectal cancer
CBC	crypt base columnar
DAMP	damage associated molecular pattern
ETC	electron transport chain
FAO	fatty acid oxidation

HIF	hypoxia inducible factor
IBD	inflammatory bowel disease
IMM	inner mitochondrial membrane
IECs	intestinal epithelial cells
ISCs	intestinal stem cells
KD	ketogenic diet
mtDNA	mitochondrial DNA
mtROS	mitochondrial reactive oxygen species
NLRP	nucleotide binding domain and leucine rich repeat pyrin
OMM	outer mitochondrial membrane
SCFAs	short-chain fatty acids
SI	small intestine
TCA	tricarboxylic acid
UC	ulcerative colitis

Acknowledgments

Disclosure of Potential Conflicts of Interest

The authors have declared that no conflict of interest exists.

Funding

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