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Mitochondria and Inflammatory Bowel Diseases: Toward a Stratified Therapeutic Intervention
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Supplemental Figure 1. Characteristics that set the stage for mitochondrial dysfunction to be a key factor in IBD

Why mitochondrial dysfunction in IBD?

1. The gut and its interphase with the luminal content is a hostile environment for the mitochondria
    a. Injurious metabolic products of the microbiota
    b. Potential specific mitochondrial xenotoxins
    c. Mitochondria are directly involved in bacterial killing

2. IBD patients have increased susceptibility to gut mitochondrial damage:
    a. Genetics (e.g. autophagy defects, *ATG16L1, PARK7* and *LRRK2*)
    b. Usual protective mechanisms overwhelmed (e.g. efflux of xenotoxins by Multidrug-Resistance 1 Gene [*MDR1*] and ROS-detoxification by Superoxide Dismutase-2 [*SOD2*])
    c. Changes in gut microbiome with metabolic products that are toxic to mitochondria (nitric oxide and hydrogen sulphide)

3. Intrinsic cellular properties within the gut enterocyte populations are predisposed to the effects of mitochondrial dysfunction:
    a. Gut enterocytes received 70% of energy from gut microbiota
    b. Crypt base cells and intestinal stem cells have high bioenergetic demands
    c. Crypt stem cell fission can propagate damage mitochondria to ‘daughter’ enterocytes
    d. Long-lived Paneth cells have limited capacity to counter the effects of mitochondrial damage

Pathogenic mitochondrial mechanisms in IBD

1. Epithelial energy deficiency
    a. Impaired physical barrier function or higher susceptibility to damage
    b. Reduced secreted barrier function by Paneth and Goblet cells
    c. Reduced capacity to regenerate and repair following inflammation

2. Alteration of cell phenotypes to favor inflammation
    a. Mitochondrial ROS promotes pro-inflammatory metabolism and inhibit autophagy
    b. Mitochondrial ROS potentiates NLRP3 inflammasome and NFκB activation

3. Mitochondrial DAMPs acting as direct inflammatory triggers
    a. Oxidized mitochondrial DNA is NLRP3 activator
    b. Mitochondrial formylated peptides are ligands for Formylated Peptide Receptor-1 (FPR1)
    c. ATP