

QPRT DEFICIENCY TRIGGERS MITOCHONDRIAL DYSFUNCTION AND POTENTIATES STING-DEPENDENT INFLAMMATION IN INTESTINAL FIBROBLASTS

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STING activation in intestinal fibroblasts drives tryptophan degradation via the kynurenine pathway, and QPRT deficiency amplifies STING-mediated inflammation through mitochondrial dysfunction, which is attenuated by NAD precursor supplementation.

KEY POINTS

- STING agonists induced significantly higher IDO1 expression than established pro-inflammatory cytokines in human colonic fibroblasts, driving tryptophan into the kynurenine pathway, an effect inhibited by type I interferon receptor antagonist Anifrolumab and pan-JAK inhibitor Tofacitinib.
- QPRT knockdown, mimicking the metabolic block observed in IBD, resulted in spontaneous type I interferon activation that was further amplified by STING agonists, leading to pronounced inflammatory transcriptional responses.
- QPRT-deficient cells exhibited reduced intracellular NAD levels and mitochondrial dysfunction including mitochondrial permeability transition pore opening, release of mitochondrial DNA and RNA into the cytosol, and subsequent activation of cGAS-STING and RIG-I/MAVS pathways.
- Supplementation with nicotinamide riboside restored intracellular NAD levels and significantly attenuated the heightened inflammatory response induced by QPRT knockdown.
- This work reveals a novel mechanism linking STING signalling, tryptophan-NAD metabolism, and intestinal inflammation, relevant to researchers investigating metabolic targets in inflammatory bowel disease.

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