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Abstract

Mitochondrial metabolism modulates immune cell signaling, yet how individual electron transport chain complexes fine-tune dendritic cell (DC) function remains unclear. Here, we identify mitochondrial complex I (CI) as a critical metabolic checkpoint controlling antigen cross-presentation by DCs in mice. Deficiency of the CI subunit NDUFS4 in DCs led to the formation of a nonfunctional CI subcomplex, resulting in mildly impaired mitochondrial respiration without triggering a compensatory glycolytic shift. NDUFS4 deficiency limited endosomal escape of internalized antigens, thereby impairing antigen cross-presentation while largely preserving direct presentation. CI dysfunction lowered the NAD^+/NADH ratio, concomitant with decreased ATP levels, and diminished neutral lipid storage and lipid peroxidation. Restoration of the NAD^+/NADH ratio rescued cross-presentation in NDUFS4-deficient DCs. NDUFS2-deficient DCs showed similar defects in cross-presentation, which were also rescued by rebalancing the NAD^+/NADH ratio. Together, these findings reveal a link between mitochondrial CI integrity, NAD^+-driven redox metabolism, and antigen cross-presentation.