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Mitochondrial Apolipoprotein A-1 Binding Protein Promotes Repolarization of Inflammatory Macrophage by Repairing Mitochondrial Respiration

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Abstract : Objective: Editing macrophage activation to dampen inflammatory diseases by promoting the repolarization of inflammatory (M1) macrophages to anti-inflammatory (M2) macrophages is highly associated with mitochondrial respiration. Recent studies have suggested that mitochondrial apolipoprotein A-1 binding protein (APOA1BP) was essential for the cellular metabolite NADHX repair to NADH, which is necessary for the mitochondrial function. The exact role of APOA1BP in the repolarization of M1 to M2, however, is uncertain. Material and method: THP-1-derived macrophages were incubated with LPS (10 ng/ml) or/and IL-4 (100 U/ml) for 24 hours. Biochemical parameters of oxidative phosphorylation and M1/M2 markers were analyzed after overexpression of APOA1BP in cells. Results: Compared with control and IL-4-exposed M2 cells, APOA1BP was downregulated in M1 macrophages. APOA1BP restored the decline in mitochondrial function to improve metabolic and phenotypic reprogramming of M1 to M2 macrophages. Blocking oxidative phosphorylation by oligomycin blunts the effects of APOA1BP on M1 to M2 repolarization. Mechanistically, LPS triggered the hydration of NADH and increased its hydrate NADHX which inhibit cellular NADH dehydrogenases, a key component of electron transport chain for oxidative phosphorylation. APOA1BP decreased the level of NADHX via converting R-NADHX to biologically useful S-NADHX. The mutant of APOA1BP aspartate188, the binding site of NADHX, fail to repair oxidative phosphorylation, thereby preventing repolarization. Conclusions: Restoring mitochondrial function by increasing mitochondrial APOA1BP might be useful to improve the reprogramming of inflammatory macrophages into anti-inflammatory cells to control inflammatory diseases.

Keywords : inflammatory diseases, macrophage repolarization, mitochondrial respiration, apolipoprotein A-1 binding protein, NADHX, NADH

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