Mitochondrial fatty acid oxidation orchestrates alveolar epithelial immunity

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Type 2 alveolar epithelial cells of the lung are fundamental in regulating alveolar inflammation in response to injury. In acute respiratory distress syndrome, the expression of carnitine palmitoyltransferase 1a (CPT1a), a rate limiting enzyme regulating mitochondrial long-chain fatty acid β-oxidation, in type 2 alveolar epithelial cells is significantly decreased. While mitochondrial fatty acid β-oxidation in type 2 alveolar epithelial cells is assumed to regulate alveolar inflammation, the importance of CPT1a and mitochondrial fatty acid β-oxidation to type 2 alveolar epithelial cell function needs to be defined. In mice, *Cpt1a* deficiency in type 2 alveolar epithelial cells impairs mitochondrial long-chain fatty acid β-oxidation without reducing ATP production and alters surfactant phospholipid abundance in the alveoli. Impairing mitochondrial long-chain fatty acid β-oxidation through deleting *Cpt1a* or *Acadl* (acyl-CoA dehydrogenase long-chain) restricts alveolar inflammatory cascade by hindering the production of the neutrophilic chemokine CXCL2 from type 2 alveolar epithelial cells, leading to profound neutrophilic dysfunction and impaired alveolar inflammatory cascade. The findings thus highlight mitochondrial long-chain fatty acid β-oxidation as an immunometabolism signature in type 2 alveolar epithelial cells and suggest altered mitochondrial fatty acid β-oxidation in type 2 alveolar epithelial cells reshapes alveolar inflammatory responses in acute lung injury and acute respiratory distress syndrome.