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mTOR Signaling Controls Mitochondria Activity by Regulating Nitric Oxide Production in mouse Dendritic Cells

Dendritic cells (DCs) are innate immune cells. They are important for recognizing and degrading pathogens and inducing the adaptive immune system. When DCs are activated, they interact with T-cells to initiate and shape the adaptive immune response. Lipopolysaccaride (LPS) is found in the outer membrane of Gram-negative bacteria and is a potent stimulator of DC activation. LPS activation induces the expression of inducible Nitric Oxide Synthase (iNOS) which produces the toxic gas nitric oxide (NO). NO blocks mitochondrial function and prevents mitochondria from producing cellular energy in the form of ATP. The PI3K/Akt signaling pathway is activated upon LPS stimulation of DCs and further activates mammalian Target of Rapamycin (mTOR), a central regulator of cell metabolism. We have found that this signaling axis regulates DC metabolism upon activation. We inhibited mTOR by using two different pharmacological inhibitors, Rapamycin and KU, to block LPS activation of this pathway. Our data show NO levels are regulated by the two different mTOR inhibitors. From this we conclude, that mTOR is important for NO production in response LPS and that by blocking mTOR that we can reduce NO levels. We hypothesize that mTOR-dependent nitric oxide production blocks mitochondrial function and we show that by inhibiting mTOR signaling, DCs retain mitochondrial function and energy-producing pathways.