**Regulation of PDH in health and disease**

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Mitochondrial morphology is uniquely linked to its functions - including the production of adenosine triphosphate (ATP) by oxidative phosphorylation (OXPHOS), cellular signaling, calcium homeostasis, regulation of programmed cell death and maintaining the delicate balance between generation and control of reactive oxygen species (ROS) – which are intricately controlled by the dynamic events of fusion and fission of the outer and inner membranes of the mitochondria (OMM and IMM). Here, we show that pyruvate dehydrogenase kinase 4 (PDK4) is genetically required for cells to undergo rapid mitochondrial fragmentation when challenged with ETC toxins. Moreover, PDK4 overexpression was sufficient to promote mitochondrial fission even in the absence of mitochondrial stress. Importantly, we observed that the PDK4-mediated regulation of mitochondrial fission was independent of its canonical function, i.e., inhibitory phosphorylation of the pyruvate dehydrogenase complex (PDC). Phosphoproteomic screen for PDK4 substrates, followed by nonphosphorylatable and phosphomimetic mutations of the PDK4 site revealed cytoplasmic GTPase, Septin 2 (SEPT2), as the key effector molecule that acts as a receptor for DRP1 in the outer mitochondrial membrane to promote mitochondrial fission. Conversely, inhibition of the PDK4-SEPT2 axis could restore the balance in mitochondrial dynamics and reinvigorates cellular respiration in mitochondrial fusion factor, mitofusin 2 (MFN2)-deficient cells. Furthermore, PDK4-mediated mitochondrial reshaping limits mitochondrial bioenergetics and supports cancer cell growth. Our results identify the PDK4-SEPT2-DRP1 axis as a regulator of mitochondrial function at the interface between cellular bioenergetics and mitochondrial dynamics.