S46-1 **Keeping Mitochondria in Shape: A Matter of Life, Death and Mitochondrial Diseases**

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Mitochondrial ultrastructural and morphological changes have been implied in the control of several physiological and pathological changes, including the progression of apoptosis. However, the role of mitochondrial dynamics in the control of complex cellular cues and in response to reversible and irreversible cellular damage is not clarified. Today I will overview the key experiments that shed light on the role of mitochondrial shape and ultrastructure in cell physiology and present our recent data obtained in genetic models of the key mitochondrial shaping protein Optic atrophy 1 (Opa1) in the mouse and in embryonic stem cells. The in vivo experiments of tissue damage by inducing atrophy, apoptosis, ischemia/reperfusion or nuclear defects in mitochondrial respiratory chain indicate that the master cristae biogenetic regulator Opa1 can prevent multiple forms of tissue damage by controlling mitochondrial cytochrome c release and metabolic efficiency. Ablation of Opa1 in mouse embryonic stem cells (ESCs), arrested mouse heart development and impaired differentiation of ESCs into cardiomyocytes. Gene expression profiling revealed roles for TGFβ/BMP, linked to increased Notch1 activity that, unexpectedly downstream of the Ca2+-dependent phosphatase calcineurin, impaired ESC differentiation. Orchestration of cardiomyocyte differentiation by mitochondrial morphology reveals how mitochondria, Ca2+ and calcineurin interact to regulate Notch1 signaling. Our data indicate that the mitochondrial shape and ultrastructure dictate organelle function and complex tissue responses ranging from death to differentiation.