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Mitochondria in Control of Cell Fate
Clifford D.L. Folmes, Petras P. Dzeja, Timothy J. Nelson, Andre Terzic

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genes and transcription factors, and promoting stem cell cardiac differentiation.20–22 Such cardiogenic effects appear to be concentration-dependent, as high levels of ROS can delay cardiac differentiation.23,24 The work of Hom et al indicates that the redox status might control cardiogenesis in a temporal fashion, with early commitment of cardiac progenitors occurring in a highly oxidized environment, while subsequent cardiomyocyte differentiation proceeding under reduced ROS load.1,25 The intimate effects of permeability transition on mitochondrial function and downstream pathways involved in differentiation, including ROS as well as associated energy metabolism and calcium signaling, would require further examination.

Transient mPTP openings may control mitochondrial ionic status to match oxidative metabolism with myocardial workload. In fact, mitochondria-dependent energetic circuits are critical regulators of de novo cardiogenesis.2 Transient mPTP opening directly regulates cellular energy metabolism as it uncouples oxidative metabolism from ATP synthesis, a mechanism that operates in concert with ROS flashes to promote cardiomyocyte differentiation.12,13 Knockout of the mPTP component cyclophilin D results in elevated mitochondrial matrix calcium, which enhances the activation of Ca2+-dependent dehydrogenases reducing metabolic flexibility.16 The early embryonic heart is primarily dependent on anaerobic glycolysis for ATP generation, as a potential consequence of low substrate supply and oxygen availability.3,26 With growing oxygen supply following the e10 stage, oxidation of substrates, in particular lactate, increases as the heart requires more oxygen to maintain contraction.27,28 Hom et al demonstrate a reliance on complex II for electron entry at day e9.5 with increasing importance of complex I at e13.5, supporting bioenergetic remodeling during differentiation.1 Much of the evidence for metabolic remodeling during cardiogenesis is derived from in vitro differentiation of stem cells.2,4,5,7–9 Like the early embryonic heart, pluripotent stem cells rely on glycolytic metabolism, with increased oxygen consumption and cellular respiration concomitant to the upregulation of tricarboxylic acid cycle and electron transport chain components associated with mitochondrial maturation during differentiation.5,7,12,29,30 Disruption of mitochondrial respiration impairs the ability of pluripotent stem cells to differentiated into cardiomyocytes and to maintain stemness.2,31 A growing body of literature has implicated a deterministic role for energy metabolism in driving cellular fate.6,12,32 Indeed, the differentiation potential of cardiac progenitors into cardiomyocytes relies on mitochondrial content and the capacity for oxidative metabolism.13 The necessary shift from glycolytic to oxidative metabolism during differentiation of pluripotent stem cells is dependent on the regulation of mitochondrial substrate entry, including by downregulation of uncoupling protein 2 and changes in hexokinase isoforms.6,34–36 The reverse of this process, dedifferentiation of somatic cells back to the pluripotent state also requires metabolic remodeling, which precedes the expression of pluripotency markers.6,12 Thus, beyond match-
ing bioenergetic supply and demand, the regulation of energy metabolism is central to fueling specification of cell fate.\textsuperscript{5,12,32–36}

The interconnectivity of mPTP, mitochondria maturation and embryonic development has significant implications for the understanding of normal cardiac differentiation, and heart vulnerability to injury. Opening of the mPTP is largely associated with dissipation of mitochondrial membrane potential, release of proapoptotic stimuli and induction of cell death, associated with pathological conditions.\textsuperscript{37} Inhibition of pore opening using a variety of techniques, including pre- and postconditioning, promotes cardioprotection.\textsuperscript{13,37} Therefore, future studies to identify mechanisms regulating mPTP behavior during embryogenesis may provide novel targets against cardiac injury. In addition, embryonic hearts tolerate transient mPTP openings, suggesting the presence of prosurvival pathways early in development, offering potential avenues for targeted protection. In contrast, sustained mPTP opening and the associated impairment in mitochondrial and cardiomyocyte maturation may impede the developing heart from matching the energetic demands of the mature embryo and could ultimately lead to congenital defects or embryonic lethality. Beyond disease pathogenesis, regulation of mitochondrial maturation and myocyte differentiation by permeability transition has the potential to impact lineage specification. Indeed, targeting master regulators of cell fate plasticity offers an innovative technology for purposes of tissue regeneration.\textsuperscript{38} Case in point, cyclosporine A, a mPTP inhibitor, can augment the in vitro production of cardiac progenitor cells capable of integrating into the infarcted heart.\textsuperscript{39} Moreover, the mPTP associated peripheral benzodiazepine receptor has been implicated in cell proliferation and differentiation with related ligands affecting stem cell fate.\textsuperscript{40} Manipulation of mPTP and its downstream signaling pathways may thus be considered to promote differentiation of resident cardiac stem cells for facilitated heart repair. Deciphering mechanisms underlying the role for mPTP and mitochondrial signaling in heart development offers implications for cardiac embryology and pathology, and more broadly may refine stem cell specification for regenerative applications.

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References


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