## Mitochondrial dysfunction in congenital heart disease

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Congenital syndromes involving defects of the heart and blood vessels comprise the most frequent form of birth defects and major cause of death in infants less than one year old in Australia. Mitochondrial defects particularly affect the heart as this organ has the highest density of mitochondria; followed by skeletal muscle and the central nervous system. As mitochondria are maternally inherited, the oocyte contains the entire mitochondrial progenitor pool available for a life time. Mitochondria, via oxidative phosphorylation, provide the primary source of ATP not only in myocytes of the myocardium (in mature form) but also in the oocyte, (even as primitive <1 μm diameter spheres lacking cristae). With development of the embryo, mitochondria progressively elongate and develop an extensive array of cristae which transect the matrix. As mitochondrial replication in humans does not commence until after blastocyst implantation, inherited genetic defects (mitochondrial and nuclear origin) that adversely impact embryogenesis and/or subsequent organogenesis may not be evident until after this stage. As anaerobic ATP synthesis assumes greater importance with increasing cell layer formation and hypoxia *in utero*, it is after the birth transition when glycolysis and lactate oxidation are superseded by fatty acid oxidation and oxidative phosphorylation defects become particularly overt.

Congenital defects causing primary cardiomyopathies more commonly occur only in the cardiac muscle, with abnormal cardiac metabolism apparent soon after birth or early infancy, however there is often a rapid onset of more complex clinical phenotypes involving multiple organs. Notable examples of this are the lysosomal storage diseases which result in toxicity from 50 different forms of lysosomal substrate accumulation (*i.e.* Pompe, Gaucher, Fabry, and Danon diseases). Although specific causes differ, hypertrophic cardiomyopathy, dilated cardiomyopathy, atrial and/or ventricular arrhythmia occur commonly with variable onset either at birth or in later childhood. Abnormalities (mutations/ knock out/ failed transcription) of mitochondrial DNA and/or nuclear genes encoding proteins involved in mitochondrial oxidative phosphorylation are also evident in cardiomyopathies. The mitochondrial respiratory chain enzyme complexes in the inner membrane of the mitochondria that generate ATP *via* oxidative phosphorylation are often involved, particularly complexes I, III and IV. In addition, deficiencies or modifications of the multiple assembly proteins that are crucial to the enzymic function of the numerous multi-subunit protein complexes may also underlie congenital defects. The severity and progression of the disorders depend on the variable tissue heteroplasmy and age of onset. However at least 1/5 of children affected by mitochondrial diseases present with overt cardiomyopathy and generally have poor prognosis and increased mortality. Other complex mitochondrial diseases such as Kearns-Sayre syndrome, MERRF syndrome and MELAS have also been associated with cardiomyopathies.

Mitochondria occupy between one and two thirds of cardiomyocyte volume and thus are, not surprisingly, critical to function and survival. Their highly plastic, dynamic and proliferative properties permit adaptive response to changing energy requirements and management of metabolism. Cardiomyocyte mitochondria are functionally linked to excitation contraction coupling and the sarcoplasmic reticulum *via* the intermediate filament protein desmin, thus altered integrity of the mitochondria or any component of their close milieu could lead to functional and structural impairment of myocytes. Learning more about the primary deficits in gene products and/or the secondary complex maladaptations that occur in mitochondria and connected signaling pathways, (ultimately giving rise to metabolic stress, loss of redox control, subsequent oxidative and other adduct post-translational structural protein modification and dysfunction, cell death and cardiac failure), will identify targets for specific therapeutic interventions. Recent examples of this are the direct targeting of complex I for Leigh's syndrome, desmin for Duchene muscular dystrophy, and frataxin in Friedreich's ataxia.