Novel mechanisms linking metabolic signaling and mitochondria to the pathophysiology of heart failure

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It is widely accepted that heart failure of diverse etiologies is associated with impaired mitochondrial bioenergetics (Doenst, Nguyen & Abel, 2013). However, recent evidence suggests that the relationship between mitochondrial dysfunction and heart failure extends beyond reduced ATP or high-energy phosphate generation. For example, heart failure is associated with reduced expression of the transcriptional co-activator PPAR gamma co-activator 1 alpha (PGC-1α), which is believed to account in part for the impairment in mitochondrial oxidative capacity that occurs in the failing heart (Riehle & Abel ED, 2012). Indeed mice, when mice with reduced expression of PGC-1α or PGC-1β are subjected to transverse aortic constriction, the transition to heart failure is rapidly accelerated (Arany *et al.*, 2006; Riehle *et al.*, 2011). However, when PGC-1α is sustained and mitochondrial bioenergetics preserved, heart failure was not ameliorated (Pereira *et al.*, 2014). Interestingly, in mice with inducible transgenic overexpression of the glucose transporter GLUT1, increasing glycolysis and utilization was associated with preservation of mitochondrial bioenergetics and attenuation of LV remodeling (Pereira *et al.*, 2013). Thus, the metabolic mechanisms linking mitochondrial dysfunction with heart failure likely transcends bioenergetics and ATP generation, but also includes novel signaling pathways that are regulated by metabolic intermediates (Karlstaedt *et al.*, 2016; Lee *et al.*, 2016; Nabeebaccus *et al.*, 2017) and may contribute to left ventricular remodeling.

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