Myocardial responses to metabolic stress – myocyte attrition and adaptation

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A variety of myocardial pathologies are characterized by energy stress states - in particular cardiac hypertrophy and diabetic cardiomyopathy. There is a growing appreciation that adult pathology states have their origins in (and may indeed recapitulate) pathologies evident relatively early in development – especially in the perinatal period. We have previously shown that excess neonatal occurrence of autophagy in the neonatal heart is linked with increased stress induction of autophagy in the adult heart in response to ischemia. More recently we have investigated the possibility that a specific form of glycogen autophagy ('glycophagy') may be also involved in neonate and adult cardiopathology.

In several contrasting myocardial 'stress scenarios' we have characterized features of the metabolic and cell signalling responses. In a novel in-bred model of primary cardiac hypertrophy which we have developed, the 'Hypertrophic Heart Rat', the loss of cardiac myocytes in the growth-stressed neonatal heart is associated with angiotensin-II promoted induction of autophagy evidenced by increased LC3BII and beclin-1 levels (Porrello *et al.*, 2009). In a state of insulin resistant metabolic stress induced in rodents by feeding a high fructose diet, the elevation of expression of autophagy markers occurs in association with loss of cardiomyocytes. In this situation suppressed signalling through the Akt-PI3K pathway is linked with autophagy induction (Mellor *et al.*, 2011). Most recently, investigations of nutrient restriction stress *in vivo* and *in vitro* have revealed that a specific form of phagosomal glycogen handling is involved in the cardiac myocyte response to substrate deprivation. In this setting, we have shown that in addition to the relatively well characterized machinery of 'macro' (protein) autophagy associated with LC3B and p62 mobilization, a process of glycogen degradation involving the markers GABARAPL1 and STBD1 can be demonstrated. Most intriguingly, there is evidence of a sex-specific 'glycophagic' response in glycogen handling mediated by differential AMPK activation and altered phosphorylation responses of glycogen handling enzymes (Reichelt *et al.*, 2013).

The demonstration that myocardial stress responses can manifest as macro- and/or glyco-phagic activity, and that there is sex-specificity in these responses, suggests the potential for highly targeted therapeutic interventions appropriate for different stress states. This may be of relevance to hypertrophic and diabetic cardiopathologies.

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