Myocardial insulin resistance, metabolic stress and autophagy

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Autophagy (’self eating’) is an intracellular lysosomal degradation process which involves vacuolar destruction of long-lived macromolecules and organelles - an essential cell recycling process to support energy homeostasis. Autophagy was first identified as prominent in the neonatal cardiac tissues during postnatal transition - a period of temporary nutrient deprivation stress. Similarly, upregulated myocardial autophagy in response to fasting is a recognized adaptive metabolic stress response. Various studies demonstrate a role for the class I PIK-Akt-mTOR pathway in negative regulation of autophagy. Cardiomyocyte autophagy induced by glucose deprivation is consistently associated with decreased Akt and mTOR activation, coincident with upregulation of the nutrient sensor AMPK.

Understanding the role of cardiac autophagy in settings of chronic metabolic stress represents a complex challenge. There is much debate about whether upregulated autophagy confers cellular protection or undermines cardiomyocyte survival in cardiac stress. In an acute situation (*i.e.* transient ischemia), a short-term increase in autophagic activity appears to be beneficial. In contrast, there is accumulating evidence that constitutive elevation of autophagy in response to maintained cardiac stress is deleterious and associated with a non-apoptotic form of programmed cell death.

Cardiac insulin resistance is characterized by a downregulation of the cardiomyocyte PtdIns3K-Akt pathway, associated with impaired GLUT4-mediated glucose uptake and a shift from glucose oxidation towards fatty acid metabolism. In a model of dietary fructose-induced insulin resistance we have provided the first evidence that in this type 2 diabetic setting, there is increased expression of autophagic markers (Mellor *et al.*, 2011). In mice fed a high fructose diet for a 12 week period this relative increase in autophagy induction was linked with elevated production of reactive oxygen species (ROS), interstitial fibrotic infiltration and evidence of myocyte attrition. A 4% reduction in cardiomyocyte number during the period of fructose treatment was determined - a rate of myocyte loss which could be expected to have marked cumulative functional impact with ongoing extended dietary exposure and maintenance of cardiac insulin resistance.

We have previously demonstrated that angiotensin II has the capacity to directly regulate cardiomyocyte autophagy through reciprocal actions mediated *via* the AT1 and AT2 receptor subtypes (Porrello *et al.*, 2009). Increased activity of the systemic and local cardiac renin-angiotensin system occurs in the diabetic state, and a role for ROS as a pathologic intermediary is indicated. Learning more about how the insulin-dependent (PI3K) and angiotensin II-dependent (G-protein coupled receptor) signaling pathways intersect and impact on autophagy regulation in the metabolically stressed heart will help to identify selective intervention targets appropriate for different cardiomyopathic states. Autophagy is emerging as a key target in a range of cardiac disease and stress states.

Mellor KM, Bell JR, Young MJ, Ritchie RH, Delbridge LMD. (2011) Myocardial autophagy activation and suppressed survival signaling is associated with insulin resistance in fructose-fed mice). *Journal of Molecular and Cellular Cardiology* **50**: 1035-43.

Porrello ER, D’Amore A, Curl CL, Allen AM, Harrap SB, Thomas WG, Delbridge LM. (2009) Angiotensin II type 2 receptor antagonizes angiotensin II type 1 receptor-mediated cardiomyocyte autophagy. *Hypertension* **53**: 1032-40