Novel therapeutic targets in heart failure and atrial fibrillation

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Heart failure (HF) and atrial fibrillation (AF) often coexist and are associated with high mortality (Savelieva & Camm, 2004; Braunwald, 2013). Current treatment strategies are suboptimal making the treatment of HF and AF a major unmet need. We previously showed that reduced activity of phosphoinositide 3-kinase (PI3K; a critical mediator of physiological cardiac hypertrophy and cardiac protection) predisposes the mouse heart to AF and HF (Pretorius *et al.*, 2009). We have subsequently been exploring the regulation of PI3K-regulated microRNAs and lipid species in the heart as treatment strategies for HF and AF.

MicroRNAs. MicroRNA-34a (miR-34a) was elevated in the heart in a mouse HF model of dilated cardiomyopathy (DCM) and another model with HF and AF. Interestingly, inhibiting miR-34a with a locked nucleic acid-modified oligonucleotide (LNA-antimiR-34a) provided benefit in the DCM model but not the more severe disease model of HF and AF (Bernardo *et al.*, 2016). This may be due to the more complex regulation of other miRNAs in the HF and AF model.

Lipids. The lipid species GM3 ganglioside (GM3) was upregulated in the atria of a mouse model with HF and AF. A small molecule (BGP-15) which was associated with reduced levels of GM3 provided benefit in the HF and AF mouse model (improved heart function, reduced arrhythmia, lower cardiac fibrosis) (Sapra *et al.*, 2014). Another lipid species (plasmalogens) was identified as being differentially regulated in the healthy physiological heart *versus* the diseased heart. Plasmalogens were depressed in hearts of mice with reduced cardiac PI3K activity and mice with HF. The dietary supplement, batyl alcohol, was used to restore plasmalogens in the heart. This approach restored some plasmalogen species but not others, and may explain a lack of a therapeutic effect (unpublished data). In summary the regulation of PI3K-regulated miRNAs and lipid species may represent a potential therapeutic approach for HF and AF, but requires further examination.

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