The differential effects of Sirtuin-3 in cardio-protection

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Background: A mitochondrial specific deacetylase, Sirtuin-3 has been reported to regulate oxidative phosphorylation, the activity of Cyclophilin D (a key component of the mitochondrial permeability transition pore, MPTP), and the ROS scavenger MnSOD. We hypothesised that Sirtuin-3 could be a potential therapeutic target for cardio-protection based its ability to prevent MPTP formation and inhibit ROS generation.

Methods and Results: In HL-1 cells (a murine cardiac cell line), over-expression of Sirtuin-3 reduced cell death following simulated ischemia-reperfusion injury (assessed by propidium iodide staining). Furthermore, Sirtuin-3 over-expression reduced MPTP formation (assessed by ROS-induced mitochondrial depolarization), and induced mitochondrial fusion (assessed by 3 blinded investigators and the PEG fusion assay). The catalytically inactive mutant form of Sirtuin-3 failed to mediate any of these beneficial effects. To investigate the role of endogenous Sirtuin-3 in the adult heart, Sirtuin-3 (whole body) KO mice and WT littermates were subjected to in vivo cardiac ischemia (30 min) followed by 24 hrs reperfusion. myocandial infarct (MI) was determined as a percentage of area at risk. Interestingly, no differences in MI size were observed between WT and KO mice under fed conditions. However, overnight fasting (to induce Sirtuin-3 expression and activity) resulted in a smaller MI size in the Sirtuin-3 KO when compared to WT mice.

Conclusions: We report that the role of Sirtuin-3 in cardio-protection differs between the HL-1 cardiac cell line and the adult heart. In the HL-1 cell, Sirtuin-3 over-expression had beneficial effects against acute IRI, suggesting that activating Sirtuin-3 in this cell-line may be cardio-protective. In contrast, fasted mice deficient in Sirtuin-3 had smaller MI following IRI, suggesting that inhibiting Sirtuin-3 in the fasted adult heart may be cardio-protective. This finding may have clinical implications in patients who are fasted before surgery.