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P163 -The role of SIRT5 in acute kidney injury

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Introduction. Acute kidney injury (AKI) is a global health concern and is associated with high morbidity and mortality.1 In the UK, AKI accounts for up to 18% of emergency hospital admissions and is a key risk factor for the development of kidney failure.2 The most common cause of AKI is renal hypoperfusion (90% of cases) leading to ischemia/reperfusion injury (IRI). Accumulating evidence has identified mitochondrial dysfunction as a central pathologic feature of IRI.3 The mitochondrial NAD+-dependent lysine de-malonylase/-succinylase sirtuin 5 (SIRT5) has emerged as key regulator of metabolic pathways including fatty acid oxidation, the citrate cycle and glycolysis but its role in IRI in the kidney remains unknown.4,5
Methods. Male C57Bl/6J mice underwent renal IRI or sham-surgery. Tissues were screened for SIRT5 by immunohistochemistry. A combined oxygen/nutrient-deprivation (OND) model using the human proximal tubular cell line HKC-8, was developed as an in vitro model of renal ischemia and analysed by qPCR and Western blot (WB). A SIRT5 RNA interference (RNAi) strategy was applied followed by metabolic characterization (ATP assay and WB), assessment of the mitochondrial membrane potential by Fluorescence-Activated Cell Sorting analysis (TMRM) and determination of mitochondrial structure by confocal microscopy (Mitotracker).
Results. IRI induced SIRT5 expression in murine kidneys. Furthermore, OND increased SIRT5 expression and induced mitophagy in HKC-8 cells. Knockdown of SIRT5 by RNAi impaired ATP production (glycolysis and oxidative phosphorylation) and resulted in a reduction of the mitochondrial membrane potential indicating a role for SIRT5 in the regulation of the cellular energy metabolism. SIRT5 RNAi also induced mitochondrial fragmentation as determined by confocal microscopy. Subsequent WB analysis revealed that SIRT5 RNAi directly affected the levels of mitochondrial proteins involved in mitochondrial dynamics (fusion and fission): SIRT5 RNAi reduced protein levels of the mitochondrial pro-fusion proteins optic atrophy 1 (OPA1) and mitofusin 2 (MFN2); and, promoted the serine 616 phosphorylation on dynamin-related protein 1 (DRP1) (DRP1-S616) which is an established mechanism driving mitochondrial fission. Finally, combining the OND model with SIRT5 RNAi showed SIRT5 is key to protecting mitochondria from degradation.
Conclusion. Taken together, these findings suggest that SIRT5 is a central component of the endogenous stress response required to maintain energy homeostasis as well as protect mitochondria from fragmentation during ischemia and therefore, might be a promising target for therapy in AKI.