TUDCA prevents cyclosporine-induced nephrotoxicity

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ER stress is linked to many disease states, including cancer, cardiovascular disease and neurodegenerative disease. Unfolded protein response (UPR) is a well-defined ER stress coping response composed of three signaling pathways; IRE1α, PERK and ATF6. Activation of ER stress coping responses have been associated with nephrotoxicity and kidney fibrosis.

Cyclosporine (CsA) is an immunosuppressant widely used in organ transplantation and in treatment of various autoimmune diseases. CsA binds to cyclophilin A and the complex associates with and inhibits calcineurin, a protein serine/threonine phosphatase, preventing de-phosphorylation of NF-AT and its nuclear translocation. CsA-dependent inhibition prevents activation of promoters of T-cell activation and overall immune response. Prolonged intake of CsA induces secondary side effects including fibrosis and chronic nephrotoxicity. The mechanism behind why CsA induces renal tubulointerstitial fibrosis is not completely understood. We discovered that CsA interacts with COX-2, an ER associated enzyme. Cyclooxygenases (COX) are members of a heme enzyme family that catalyze a cyclooxygenase and a peroxidase reaction to produce prostaglandins. COX-1 is ubiquitously and constitutively expressed in mammalian tissues and cells, whereas COX-2 is inducible and is present in mammalian tissues at variable levels. Both enzymes are localized at the membrane of the endoplasmic reticulum (ER) and the nuclear envelope. The CsA-COX-2 complex binds to IRE1α to enhance its activity and contributes, at least in part, to development of fibrosis. Increased COX-2 activity is associated with renal tissue damage and poor outcome for kidney transplant patients. COX-2 enzyme is also upregulated during cardiac allograft rejection and correlates with a poor outcome. CsA treatment also causes an increase in TGFβ secretion, induction of the fibrotic cascade and a disruption in the redox balance. Tauroursodeoxycholic acid (TUDCA) is a bile acid and proteostasis promoter that is shown to reduce the UPR and prevent cardiac fibrosis {Groenendyk, 2016 #15479}.

Here we show that application of TUDCA is able to prevent fibrosis in a nephrotoxic mouse model system. Mice were given 30 mg/kg/day CsA with or without 2 mg/ml TUDCA for 8 weeks followed by analysis of body fluids, Echo-MRI and several biochemical parameters. Animals receiving TUDCA showed reduced urine pH, reduced creatinine secretion and protein/creatinine ratio, all indicative of reduced kidney damage. CsA transiently induced the IRE1α arm of the UPR as monitored by XBP1 splicing. Abundance of molecular markers of fibrosis, collagen, periostin and TGFβ were monitored and all were reduced in TUDCA treated animals. We concluded that TUDCA, as a proteostasis promoter, provided relief from the kidney damage caused by CsA treatment, by inhibiting the IRE1α signalling arm of the UPR ER stress coping response. Application of TUDCA offers a new approach to prevent the ancillary side effects seen with prolonged CsA usage.