Glycogen synthase kinase controls autophagy during renal ischemia/reperfusion

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Autophagy occurs at basal level in most cells and contributes to the turnover of long-lived proteins and organelles to maintain intracellular homeostasis. In response to cellular stress, autophagy is up-regulated and can provide an adaptive strategy for cell survival, but may also directly or indirectly lead to cell demise. With the dual role in life and death, autophagy is involved in various physiological processes, and linked to the pathogenesis of a wide array of diseases. However, the defined role of autophagy is further complicated by the crosstalk and coordinated regulation between autophagy and apoptosis. In this study, we determined the contribution of autophagy and apoptosis in renal tubular cell injury (Jiang et al 2012) using different models of renal ischemia/reperfusion (I/R). C57BL/6 mice were anesthetized and subjected to 30 minutes of bilateral renal ischemia, followed by reperfusion (6 and 18 hrs) (Esposito et al 2011). On reperfusion a significant amount of LC3-II accumulated in renal tissues in a time-dependent manner, starting at 6 hours and further increasing after 18 hours (2.1-fold over control). Moreover, I/R increased mitochondrial cytochrome C release, nitrotirosine accumulation, Beclin-1 expression, Bax/Bcl-xL ratio, caspase 3 expression and poly-(ADP-ribose)-polymerase fragments. We found that I/R-induced damage was significantly decreased by administration of GSK inhibitor, the SB216763 (0.6 mg/kg i.p), given 5 minutes prior to reperfusion. A higher level of autophagy was also detected after SB216763 treatment. Moreover, in the Human Embryonic Kidney (HEK) 293 cell line following hypoxia and reoxygenization, SB216763 (5 μM) activated autophagy and suppressed inflammatory response.
Our results clearly demonstrate that GSK inhibitor significantly attenuated the degree of renal dysfunction and injury caused by IRI. Thus, these data show suppressed kidney damage by activating autophagy, offering a new target for prevention of kidney damage.

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