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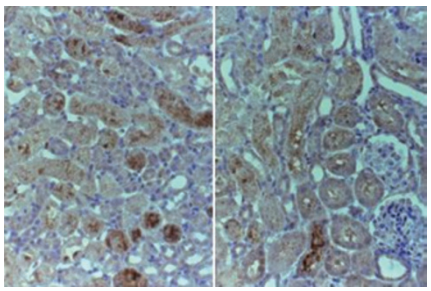
ACUTE KIDNEY INJURY

# Mechanism of AKI sensitivity in diabetic nephropathy

Patients with chronic kidney disease (CKD) are more susceptible to acute kidney injury (AKI) than are patients without CKD, but the mechanisms contributing to this increased susceptibility are unclear. A new study now suggests that hyperglycaemia, p53 and the mitochondrial pathway of apoptosis have key roles in this process.

Jianping Peng and colleagues first studied the effects of renal ischaemia–reperfusion (I/R) injury in two mouse models of diabetic nephropathy. They found that I/R injury induced more severe tissue damage in streptozotocin (STZ)-treated diabetic mice and hyperglycaemic Akita mice than in nondiabetic mice. The severity of AKI in these mice correlated with their blood glucose levels.



Insulin (right panel) attenuates renal apoptosis in STZ-treated diabetic mice following I/R injury, as assessed by caspase 3 staining. Permission obtained from Nature Publishing Group © Peng, J. *et al. Kidney Int*. doi:10.1038/ki.2014.226

The researchers then investigated the effects of glucose conditioning on cultured renal proximal tubular cells (RPTCs). Following ATP depletion or hypoxia, glucose-conditioned cells exhibited higher levels of apoptosis than did cells cultured in control media. This increased apoptosis was accompanied by the mitochondrial accumulation of Bax and cytochrome c release, suggesting activation of the intrinsic pathway of apoptosis.

On the basis of previous studies showing a link between p53 and ischaemic AKI, the researchers tested the involvement of p53 in the sensitivity of hyperglycaemic tissues to AKI. They found that p53 levels were markedly upregulated in glucose-conditioned RPTCs and in tissues from diabetic mice following injury. Administration of an inhibitor of p53, pifithrin-α, to Akita diabetic mice did not ameliorate tubular damage but did inhibit apoptosis following I/R injury. Injection of a p53 siRNA, however, suppressed the induction of p53 in Akita diabetic mice following I/R injury, and attenuated both renal apoptosis and AKI severity.

To investigate whether hyperglycaemia triggers AKI sensitivity, the researchers administered insulin to STZ-treated diabetic mice. Insulin treatment attenuated the severity of AKI induced by I/R injury, and suppressed the induction of p53 accumulation and mitochondrial cytochrome c release. "To our knowledge, this is the first report of the sensitization of the mitochondrial pathway of apoptosis by high glucose *in vitro* and by diabetic hyperglycaemia *in vivo*," say the researchers.

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