The A20 gene protects kidneys from ischaemia/reperfusion injury by suppressing pro-inflammatory activation.

Ischaemia followed by reperfusion (I/R) can induce inflammation and injury and is a risk factor for delayed graft function and rejection of transplanted kidneys. Inflammation is regulated by NF-kappaB transcription factors which induce pro-inflammatory molecules in endothelial cells (EC). We examined whether A20, a negative regulator of NF-kappaB, can protect kidneys from I/R injury. To mimic the fluctuations in endothelial oxygenation that occur during I/R we exposed cultured human umbilical vein EC (HUVEC) to hypoxia (1% O(2) for 4 h) followed by re-oxygenation (21% O(2) for 1 h-24 h). We observed transient expression of pro-inflammatory molecules (E-selectin, VCAM-1 and IL-8) and sustained expression of A20 in HUVEC exposed to hypoxia/re-oxygenation. The effect of A20 on endothelial responses to hypoxia/re-oxygenation was assessed. We observed that pre-treatment of HUVEC with an adenovirus containing A20 (Ad-A20) suppressed activation of NF-kappaB and induction of pro-inflammatory molecules by hypoxia/re-oxygenation, whereas a control adenovirus had little or no effect. Thus the induction of A20 may form a negative feedback loop in pro-inflammatory signalling in cells exposed to hypoxia/re-oxygenation.
To validate our cell culture experiments we examined the role of A20 in renal responses to I/R. We observed that A20 was induced in rat kidneys exposed to I/R. Moreover, pre-treatment of animals with Ad-A20 significantly reduced acute tubular necrosis, renal expression of VCAM-1 and NF-kappaB activation in response to I/R, whereas pre-treatment with control adenovirus did not. Our observations suggest that A20 maintains physiological homeostasis in kidneys exposed to I/R by protecting them from inflammation and injury.