

**Molecular mechanisms of estradiol attenuating renal ischemia-reperfusion injury**

Yan-Feng WANG

Females show a better tolerance in renal ischemia-reperfusion (I/R) injury compared with males in both animals and humans. Many studies have demonstrated that estradiol (E2) plays a key role in protection from IRI in female, but the underlying molecular mechanism remains unknown. The latest research shows that female rats exhibited less extensive apoptosis, kidney injury, and fibrosis compared with male rats, these effects were worsened in ovariectomized (OVX) rats and ameliorated upon E2 supplementation. Furthermore, the levels of TGF- $\beta$ RI were significantly increased in OVX rats, accompanied by phosphorylated SMAD2/3 activation. Furthermore, dual luciferase reporter and chromatin immunoprecipitation assays showed that ER $\alpha$  could bind to the promoter region of TGF- $\beta$ RI and negatively regulate its mRNA expression. Moreover, an in vitro study using NRK-52E cells showed that ER $\alpha$  knockdown blocked E2-mediated protection, while TGF- $\beta$ RI knockdown protected cells against hypoxic insult. The study suggests that renal IRI is closely related to the TGF- $\beta$ RI-SMAD pathway in females and that E2 exerts its protective effect via the ER $\alpha$ -mediated transcriptional inhibition of TGF- $\beta$ RI expression. Other study indicated that estradiol protects against I/R-induced AKI through peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) stimulated eNOS activation in rats. Meanwhile, another study discovered that phosphorylation of Akt and eNOS protein was significantly increased 30–60 min after reperfusion in estradiol-treated compared to vehicle-treated rats, which were reversed by the PI3K inhibitor wortmannin or the ER antagonist tamoxifen. The E2-induced renoprotective effects were not seen in eNOS knockout mice with renal injury, suggesting that the E2-induced renoprotective effect is due to activation of the PI3K/Akt pathway followed by increased eNOS phosphorylation in the post-ischemic kidney. Furthermore, E2 exhibits protective effects against renal IRI possibly through the suppression of endothelin-1 overproduction in postischemic kidneys, this effect was probably mediated by ER $\beta$  and G protein-coupled estrogen receptor 1 (GPER1) in the kidney.

**Key Words** estradiol; renal; ischemia-reperfusion injury; molecular mechanism