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Renoprotective effect of carbon monoxide releasing molecule-2 against LPS-induced acute kidney injury

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Objectives: Acute kidney injury (AKI), which is defined as a rapid decline of renal function, is common and recently recognized to be closely intertwined with chronic kidney diseases. Current treatment for AKI is largely supportive. Since i) endoplasmic reticulum (ER) stress has emerged as a novel mediator of AKI, ii) Fyn, a member of Src family kinase (SFK), contributes to ER stress, and iii) carbon monoxide inhibits ER stress, the present study investigated the renoprotective mechanism of carbon monoxide releasing molecule2 (CORM2) focusing on Fyn-mediated ER stress using LPS-induced AKI model.

Methods: Male C57BL/6J mice or proximal tubular epithelial (mProx) cells were pretreated with CORM2 or PP2, a Src kinase inhibitor, and challenged with LPS. In addition, cells transfected with control, c-Src or Fyn siRNA were stimulated with LPS in the absence or presence of CORM2. Plasma creatinine and cystatin C were measured, and kidney tissues or cells were used for mRNA and protein analysis.

Results: Pretreatment of CORM2 effectively prevented LPS-induced ER stress and kidney injury including decreased glomerular filtration rate, increased oxidative stress, and inflammation in mice as much as PP2. LPS significantly increased p-Fyn and p-Src in the kidneys and mProx cells, which were effectively suppressed by CORM2 pretreatment. Interestingly, genetic inhibition of Fyn but not Src significantly attenuated LPS-induced ER stress in mProx cells.

Conclusions: These results demonstrate that CORM2 prevents AKI in mice through inhibiting Fyn-mediated ER stress.