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Impaired NRF2 inhibits the Recovery of ischemic reperfusion injury in Aging kidney

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Objectives: Decrease of kidney function is frequently observed in the elderly population, and vulnerability and inadequate recovery from acute kidney failure such as ischemic/reperfusion injury (IRI) is considered as one of the mechanisms. Potential factors in aging kidney may be suggested to mediate the progression of kidney dysfunction, but it has not been fully identified. We aimed to investigate the role of nuclear factor erythroid 2-related factor 2 (NRF2), a key regulator of cellular redox homeostasis, on the restoration of kidney function after IRI in aging kidney.

Methods: IRI in vivo murine model was established by clamping renal pedicle clamping for 45 min. To generate the senescent cells, long-term serial passaging was performed in Primary renal proximal tubule epithelial cells (RPTEC). For IRI injury *in vitro,* hypoxia/reoxygenation (H/R) model with senescent RPTEC was performed by incubation with serum-free medium in a hypoxic chamber containing 1% O_2 for 24 h and replaced to normoxia for 30 min. NRF knockdown deficiency were investigated using NRF2 knock-out (KO) mice *in vivo* and transfection of NRF2 siRNA *in vitro*. Immunohistochemical study using M-T, PAS, Sirius red, and TGF-β staining was used to utilized for the histological investigation.

Results: NRF2 expression was diminished and renal recovery after IRI was retarded in old mice than young mice. Persistent renal injury after IRI was aggravated in NRF2 KO mice compared to wild type (WT). Aggravation of oxidative stress was manifested in NRF2 KO mice along with decreased expression of mitochondrial OXPHOS related proteins. H/R injury was aggravated upon NRF2 knockdown in senescent RPTEC, which also elevated oxidative stress and mitochondrial dysfunction. Treatment with CDDO-Me, an activator of NRF2, in mice resulted in alleviation of injury.

Conclusions: Our research revealed that NRF2, a novel factor with the ability to attenuate renal damage, would contribute with the treatment and recovery of aging-related AKI.