Role of ER stress in acute kidney injury

-Organelle stress network between the ER and mitochondria-

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Cells use an exquisite network of mechanisms to maintain the integrity and functionality of their protein components. In the endoplasmic reticulum (ER), the network of protein homeostasis regulates protein synthesis, folding and degradation via the adaptive unfolded protein response (UPR) pathway. Under the pathogenic conditions (e.g., hypoxia, metabolic disorder, uremia), maladaptive UPR activation due to defective ER function often occurs in glomerular or tubulointerstitial cells, which in turn leads to development or progression of kidney diseases, including acute kidney injury (AKI). Cell cycle arrest or apoptosis of tubular epithelial cells or fibrotic responses of the interstitial cells is closely associated with the maladaptive or proapoptotic UPR induction, estimated by ATF4-CHOP axis activation, in the damaged tubulointerstitium with hypoxia. ATF4 is a transcription factor of the UPR pathway, and recent findings demonstrate that the ATF4 activity is regulated by prolyl hydroxylase (PHD) 1, which also regulates the hypoxia inducible factor (HIF)1-α activity in a major adaptive response to hypoxia. Interestingly, we found that the microRNA, which suppresses PHD1 transcription, altered the activation of both adaptive UPR and HIF pathways as well as their down stream gene expressions (e.g., anti-oxidant enzymes), and thereby changed the tubular cell resistance against hypoxia-induced oxidative stress. These findings indicate 1) the impact of the stress signal network between UPR and HIF pathways and 2) its epigenetic regulation in the maintenance of entire tubular cell homeostasis.

Accumulating evidence also indicates the link between the ER stress and the mitochondrial dysfunction, namely mitochondrial stress. Not only ER stress, but also mitochondrial stress is a key issue for the progression of tubular damage in AKI. From the point of view that the organelle interaction between the ER and mitochondria contributes to the maintenance of mitochondrial structure (mitochondrial fusion and fission), it is reasonable that the mitochondrial stress is often exacerbated by ER stress. In fact, some ER stress inhibitors rescued the ER stress-induced tubular cell death

associated with mitochondrial dysfunction via suppression of UPR activation (CHOP activation) as well as normalization of mitochondrial membrane permeability. Restoration of normal UPR pathway and subsequent maintenance of mitochondrial homeostasis may hold promise in protecting the kidney from pathogenic stresses.

In this talk, I will focus on pathophysiological role of the ER stress and UPR pathway, the stress signal network between ER stress and hypoxia, and organelle stress between the ER and mitochondria in the tubular damages.

Inagi R. The gut-kidney connection in advanced chronic kidney disease. Kidney Res Clin Pract. 2015, 34:191-3.
Ishimoto Y, Inagi R. Mitochondria: a therapeutic target in acute kidney injury. Nephrol Dial Transplant. 2015, Sep 1 “in press”
Inagi R. Proteostasis in endoplasmic reticulum—new mechanisms in kidney disease. Nat Rev Nephrol. 2014, 10:369-78.

Key words: unfolded protein response (UPR), stress signal network, tubular homeostasis, mitochondrial stress