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AMP-activated protein kinase regulates autophagic protection against cisplatin-induced tissue injury in the kidney

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ABSTRACT. Although the nephrotoxicity of cisplatin has been well documented as a major side effect of chemotherapy, the exact mechanism by which prosurvival and apoptotic pathways interplay to determine renal pathology remains elusive. Recent studies suggested that autophagy might serve as an adaptive mechanism to promote cell survival during acute kidney injury (AKI). We have used AKI as a disease model to investigate the mechanism regulating the cytoprotective role of autophagy in cisplatin-induced tissue damage. Pharmacological inhibitors such as chloroquine were used to manipulate autophagy during AKI, and DNA damage was evaluated by using the cellular marker γH2AX. Cisplatin induced extensive DNA damage during AKI. Autophagy activation served as a survival strategy to suppress cisplatin-induced DNA damage in the pathology of AKI both *in vitro* and *in vivo*. Interestingly, in the kidney, cisplatin treatment can activate AMP-activated protein kinase (AMPK), a signaling molecule that is also

critical for p53-mediated inactivation of mammalian target of rapamycin (mTOR) pathways. As a result, inhibition or knockdown of AMPK can lead to repressed autophagy in cisplatin-induced AKI, resulting in more DNA damage. Activation of AMPK regulates autophagy during cisplatin-induced AKI. Given the fact that p53 can regulate autophagy by inactivating mTOR via AMPK, our results suggest that the p53 pathway may also play a critical role in the pathogenesis of cisplatin-induced renal damage. This study may further our understanding of the physiological roles of autophagy in the pathogenesis of renal injuries, and thus may have pathological implications in the clinical setting.

Key words: Acute kidney injury; AMP-activated protein kinase; Cisplatin; Chloroquine; Autophagy; DNA damage

