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Activation of G-protein-coupled Receptor 40 Attenuates Cisplatin-induced Apoptosis in the Kidney

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Background: G-protein-coupled receptor 40 (GPR40) plays diverse physiological functions including cellular proliferation and inflammation. However, the localization of GPR40 and its physiologic function in the kidney have not yet been identified. We investigated the role of GPR40 in the cisplatin-induced kidney injury as well as its localization in the kidney.

Methods: The expression and localization of GPR40 in the kidney was investigated by semiquantitative immunoblotting and immunofluorescence staining. We examined the protein expression of GPR40 and apoptotic markers in rats with cisplatin-induced kidney injury and cisplatin-treated human renal proximal tubule (HK-2) cells. HK-2 cells were cultured with cisplatin in the absence or presence of GW9508, a selective GPR40 agonist. A human GPR40 (hGPR40) cDNA construct was stably transfected into the human embryonic kidney (HEK293) cells, which were also cultured with cisplatin. Then we examined the effects of GPR40 agonist or hGPR40 transfection on the cisplatin-induced apoptosis by semiquantitative immunoblotting.

Results: Immunoblotting revealed that GPR40 is abundantly expressed in the renal cortex and outer stripe of outer medulla. Immunofluorescence staining with tubule specific markers showed that GPR40 is highly expressed in S2 and S3 segments of the renal proximal tubules. After cisplatin treatment, the protein expression of GPR40 was significantly decreased, and the ratio of Bax/Bcl-2 expression was increased in the kidney of rats and HK-2 cells. In HK-2 cells, cisplatin treatment increased the ratio of Bax/Bcl-2 expression, expression of cleaved caspase-3 and the number of cells with condensed nuclei, which was ameliorated by the pretreatment of GW9508, a selective GPR40 agonist. The increased ratio of Bax/Bcl-2 expression by the treatment of cisplatin was also attenuated in the hGPR40 transfected HEK293 cells.

Conclusions: GPR40 is mainly expressed in S2 and S3 segments of the renal proximal tubule which has been known as vulnerable regions to cisplatin-induced injury. Cisplatin-induced kidney injury is ameliorated by activation of GPR40 through inhibition of pro-apoptotic factors.

Key Words: GPR40, Cisplatin, Apoptosis