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cMet agonistic antibody attenuates apoptosis in ischemia reperfusion induced kidney injury

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Objectives: Acute kidney injury (AKI) is a very common complication with high morbidity and mortality rates and no fundamental treatment. In this study, we investigated whether the hepatocyte growth factor (HGF)/cMet pathway is associated with the development of AKI and how the administration of a cMet agonistic antibody (Ab) affects an AKI model.

Methods: We measured cMet and HGF in plasma of patients with severe AKI requiring continuous renal replacement therapy. Bilateral ischemia-reperfusion injury was performed in wild-type (C57BL/6) mice. In addition, primary cultured glomerular endothelial cells and proximal tubular epithelial cells were treated with rHGF (10 ng/mL) or the cMet agonistic Ab (500 and 1000 ng/mL) and then incubated under hypoxic conditions for 24 hours.

Results: In the analysis using a human blood samples, cMet and HGF levels were found to be significantly increased in the AKI group, regardless of underlying renal function. The administration of a cMet agonistic Ab improved the functional and histological changes after bilateral ischemia-reperfusion injury. TUNEL-positive cells and Bax/Bcl-2 ratio were also reduced by cMet agonistic Ab treatment. In addition, cMet agonistic Ab treatment significantly increased the levels of PI3K, Akt, and mTOR. Furthermore, after 24 hours of hypoxia induction in hPTECs, treatment with the cMet agonistic Ab also showed dose-dependent antiapoptotic effects similar to those of the rHGF treatment. Even when the HGF axis was blocked with a HGF blocking Ab, the cMet agonistic Ab showed an independent dose-dependent antiapoptotic effect.

Conclusions: In conclusion, cMet expression is associated with the occurrence of AKI. cMet agonistic Ab treatment attenuates the severity of AKI through the PI3K/Akt/mTOR pathway and improves apoptosis. cMet agonistic Ab may have important significance for the treatment of AKI.

igure 1. cMet agonistic Ab attenuates the severity of AKI

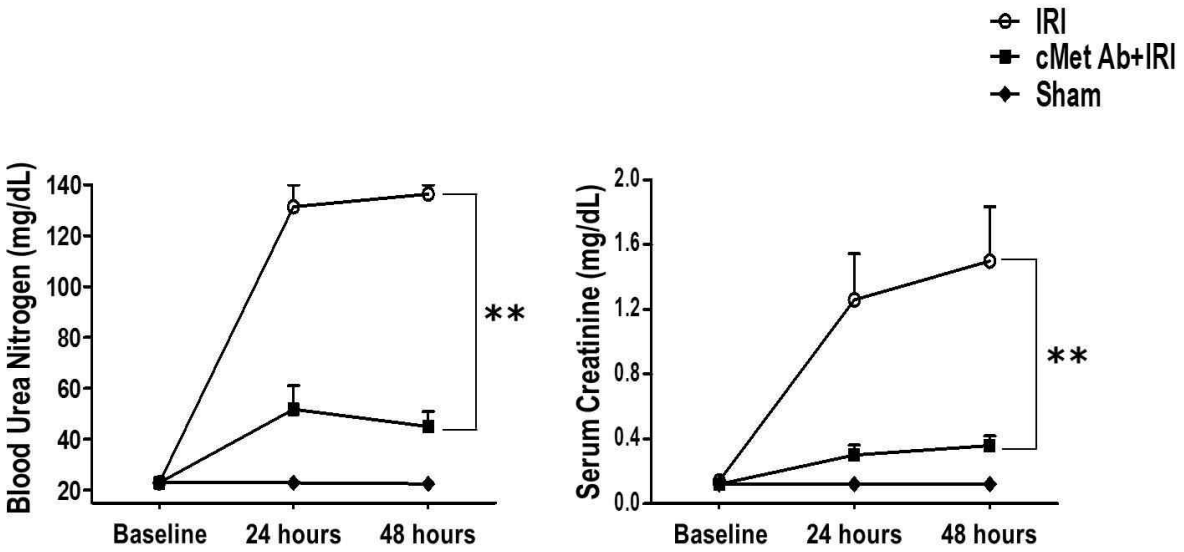

Figure 2. Antiapoptotic effect of cMet agonistic Ab in hPTECs