Hepatocyte-Specific MET Deletion Exacerbates Liver Damage and Impairs Regenerative Response in Acetaminophen-Induced Hepatotoxicity Model

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Background: HGF receptor, MET, is considered one the most critical drivers of liver regeneration after partial hepatectomy (PH). Despite the well-known regenerative function of MET, its role in the clinically relevant acetaminophen (APAP)-induced liver injury (AILI) model remains unexplored, which markedly differs from the PH model due to the presence of massive liver necrosis and inflammation. The current study aim to delineate the role of MET in AILI, for the first time, using hepatocyte-specific deletion strategy.
Methods: Hepatocyte-specific MET-KO mice were generated by administering AAV8-TBG-CRE in $MET^{fl/fl}$ mice. MET-KO or WT mice were given a toxic dose of APAP (300 mg/kg) and subsequently assessed for liver injury and regeneration parameters at various time intervals.
Results: Deletion of MET led to a significant exacerbation of liver injury, and impaired liver regeneration culminating in significant mortality, while all the WT mice recovered spontaneously. Notably, the critical mechanisms initiating AILI such as APAP metabolic activation and APAP-protein adduct formation remained unchanged. However, JNK activation and its mitochondrial translocation were enhanced, and replenishment of antioxidant glutathione was impaired in MET-KO mice, resulting in excessive mitochondrial oxidative damage and subsequent release of cell death mediator, AIF, into cytosol. Excess JNK activation was attributed to increased phosphorylation of its kinase, MKK4, possibly resulting from reduced repressive activity of AKT on MKK4 in the absence of MET signaling. Impaired hepatocyte proliferation in MET-KO mice was linked to the suppression of ERK signaling. RNA-sequencing analysis not only showed repression of cell cycle/proliferation and survival (AKT) signalling but also activation pathways associated with cell death signaling and senescence (TGFβ), along with impaired unfolded protein response in MET-KO mice. Remarkably, HGF/MET signaling was strongly activated in APAP-induced acute liver failure (ALF) patients and vast majority (35%) of the genes altered in human ALF were found be regulated by MET in the mouse AILI model, indicating wider significance of MET signaling for human ALF.
Conclusion: Overall, our study demonstrates that MET is not only crucial for promoting regeneration/repair but also for restraining injury development after APAP overdose via inhibiting mitochondrial cell death signaling pathway.