Targeting EGFR as a Novel Strategy for Treating Acetaminophen Hepatotoxicity

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Introduction: Epidermal growth factor receptor (EGFR) is a well-established mediator of liver regeneration, driving hepatocyte proliferation after partial hepatectomy (PH). However, the role of EGFR in the clinically relevant acetaminophen (APAP)-induced liver injury (AILI) model which significantly differs from the PH model due to the presence of massive inflammation and necrosis has not been fully characterized. Our early explorations using a chemical EGFR inhibitor have found that, paradoxically, EGFR exacerbates AILI. Therefore, we aim to validate this unexpected role of EGFR in promoting liver injury using a hepatocyte-specific EGFR knockout (KO) mouse model, and test the therapeutic relevance using clinically-approved EGFR inhibitors.

Methods: Hepatocyte-specific EGFR-KO mice were generated by administering AAV8-TBG-CRE in $EGFR^{fl/fl}$ mice. EGFR-KO or wild-type (WT) mice were treated with a toxic dose of APAP and sacrificed at different timepoints to investigate liver injury and regeneration. Similarly, afatinib, osimertinib or erlotinib, three clinically-approved EGFR inhibitors, were administered post-APAP in C57BL6/J mice. A delayed dosing of osimertinib was also tested both alone and in combination with N-acetylcysteine (NAC), the primary treatment for AILI.

Results: Hepatocyte-specific EGFR deletion resulted in significantly decreased peak liver injury after APAP overdose, despite no observed changes in the key injury initiating events such as APAP metabolic activation and APAP-protein adduct formation. Mechanistically, EGFR deletion inhibited JNK activation and its mitochondrial translocation, resulting in reduced mitochondrial damage and release of cell death drivers. Consistently, clinically-approved EGFR inhibitors, osimertinib and afatinib, decreased AILI without impacting APAP metabolism, with osimertinib having a significantly stronger effect. Importantly, these inhibitors or EGFR deletion did not impair hepatocyte proliferation and liver regeneration. Notably, delayed osimertinib treatment with NAC tended to decrease AILI, when NAC alone is typically ineffective.

Conclusion: Our studies revealed that EGFR holds an unexpected death-promoting function in the AILI model, which has wide implications in liver biology. Further, clinically approved EGFR inhibitors which decrease liver injury without impairing liver regeneration may be able to be retooled for treating AILI patients.