Transient suppression of the ECM1 gatekeeper is essential for HGF/c-MET-driven liver regeneration

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Authors

Ye Yao Yujia Li Chenjun Huang Jiayi Ma Liang Xu **Stephanie D. Wolf** Julian Gilljam Haifeng Zeng Stefan Munker Xioachun Cao-Ehlker Ruochan Li Bernhard Renz Hanno Nieß **Seddik Hammad** **Elisa Holstein** Laura Danielczyk Roman Liebe Honglei Weng **Ursula Klingmüller** Matthias P. A. Ebert Chunfang Gao **Johannes Bode** Donato Inverso **Peter ten Dijke** Shanshan Wang **Stefan Höhme** Weiguo Fan **Steven Dooley** Sai Wang

Abstract

Hepatocyte growth factor (HGF) is a multifunctional cytokine stored in the extracellular matrix as an inactive precursor and is essential for tissue repair. How HGF activity is dynamically regulated during regeneration remains unclear. Here, we identify extracellular matrix protein 1 (ECM1) as a physiological inhibitor of active HGF during liver regeneration. Following 70% partial hepatectomy, active HGF rapidly increases in parallel with a sharp decline in ECM1, and preventing this downregulation delays liver mass recovery. Mechanistically, ECM1 directly binds the active HGF α-subunit through a mechanism dependent on residue R392, thereby suppressing c-MET–ERK–MYC signaling and hepatocyte proliferation. Loss of ECM1 permits activation of this pathway, whereas MYC overexpression rescues ECM1-mediated growth inhibition. In patients, proliferative hepatocytes localize to ECM1-negative regions. Supported by transcriptomic analyses and computational modeling, these findings identify ECM1 as an extracellular gatekeeper whose transient downregulation enables HGF-driven tissue repair.