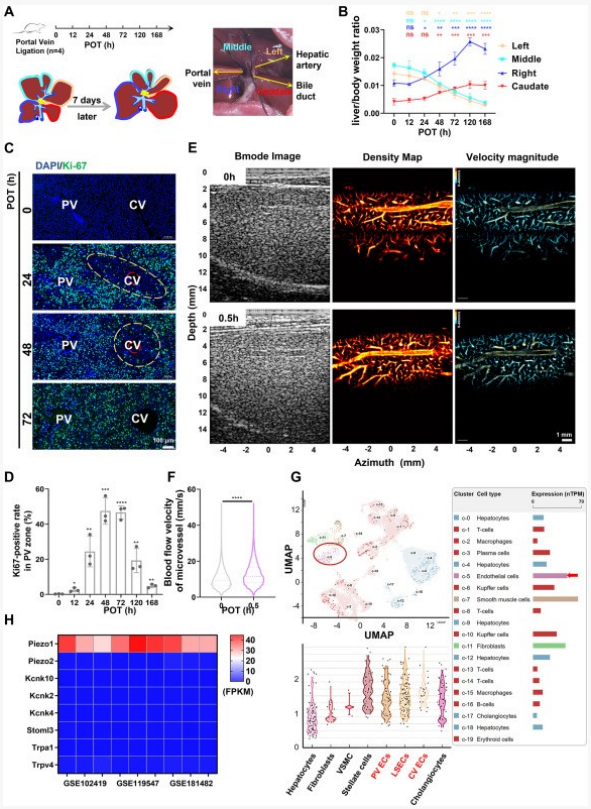
Delineating the Mechanisms Mediating Piezo-1- Induced Liver Regeneration

Theoretical basis for mechanical stimulation-mediated chemical signals-induced liver regeneration

CHINA, March 11, 2025 /EINPresswire.com/ -- Liver regeneration (LR) is a complex biological process involving the proliferation of parenchymal (hepatocytes) and non-parenchymal cells within the liver and is mediated by a complex interplay of inflammatory and growth factors. Hemodynamic changes following liver injury activate mechanosensing structures in vascular endothelial cells (VECs) to produce large amounts of cytokines, which play a crucial role in LR. Piezo-1 is a critical mechanosensory ion channel that can detect and convert mechanical forces into chemical signals to trigger downstream biological effects; however, its role in VECs, especially in regulating LR, remains unclear.



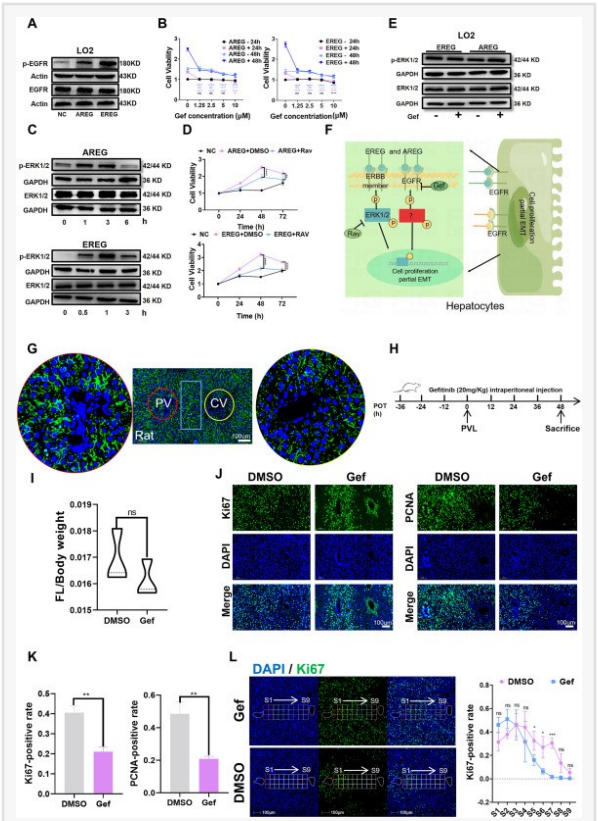
(A) Schematic diagram of the rat PVL model. (B) Changes in the ratio of liver weight to body weight in each lobe after 70% PVL in rats (the changes of each liver lobe were compared with 0 h). (C) Immunofluorescence staining analysis of Ki67 (in PV-CV) in

In this study, published in the Genes and Diseases journal, researchers from Jilin University, Chinese Academy of Medical Sciences, and Tsinghua University show that early changes in hepatic portal hemodynamics activate Piezo1 in VECs to promote hepatocyte proliferation during the LR process induced by portal vein ligation (PVL) in rats.

The authors showed that at 24–48 h post-portal vein ligation, hepatocyte proliferation, indicated by Ki67-positive cells, was mainly seen distributed in zone 1 and zone 2 of liver lobules, while only a few Ki67-positive hepatocytes were observed in zone 3. Subsequently, hemodynamic changes post-PVL enhanced the expression of Piezo-1 in liver VECs and sinusoidal endothelial cells. Additionally, the authors showed that Yoda-1 (a specific agonist of Piezo-1)-mediated Piezo-1 activation in VECs was associated with proliferation and EMT of the hepatocytes.

The study further showed that Yoda-1-mediated Piezo-1 activation was associated with the upregulation of ERBB and MAPK signaling pathways, along with a concomitant increase in the expression of heparin-binding epidermal growth factor (HBEGF), epiregulin (EREG), and amphiregulin (AREG)—proteins that promote hepatocyte proliferation and partial EMT via the PKC/ERK1/2 signaling pathways. It was observed that Yoda1 could promote the proliferation and partial EMT of hepatocytes through the EGFR signaling pathway. Further investigation revealed that AREG and EREG enhanced the phosphorylation of EGFR and promoted hepatocyte proliferation primarily via EGFR activation, while also inducing a partial EMT-like response through ERK1/2 activation.

In conclusion, this study demonstrates that Piezo1 activation in VECs leads to the up-regulation of HBEGF, EREG, and AREG gene expression in the ERBB signaling pathway through the PKCα-ERK1/2 axis, which in turn activates EGFR in hepatocytes, promoting cell proliferation and inducing a partial EMT-like response. The findings of this study provide mechanistic insights into how chemical signals mediated by mechanical stimulation regulate liver regeneration.



(A) WB revealed that EGFR was activated by recombinant proteins of AREG (50 ng/mL) and EREG (20 ng/mL) in LO2 cells. (B) The MTT assay at 24 and 48 h suggested that gefitinib could block the proliferation of hepatocytes induced by AREG (50 ng/mL) and EREG

Reference

Title of the original paper - EGFR-mediated crosstalk between vascular endothelial cells and hepatocytes promotes Piezo1-dependent liver regeneration

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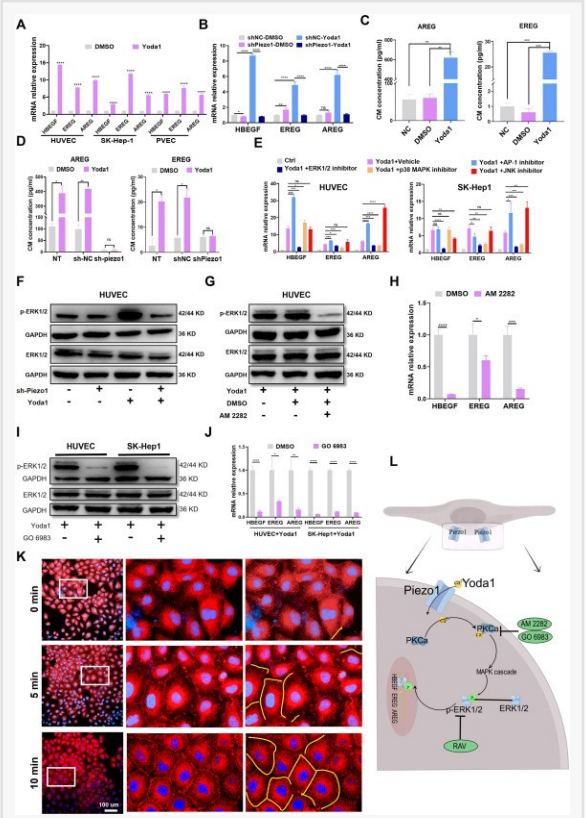

(A, B) The qRT-PCR results showed increased mRNA expression of HBEGF, EREG, and AREG induced by Yoda1 in endothelial cells and was reversed with Piezo1 knockdown in HUVEC cells. (C, D) the ELISA assay results showed that increased secretion of EREG and AR

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