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EDITORIAL

Harnessing the UDP-G/P2Y₁₄R axis to promote liver regeneration in acute liver failure



KEY WORDS

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Liver regeneration

Acute liver failure (ALF) is a life-threatening condition characterized by severe liver dysfunction¹. It is primarily caused by bacterial invasion, viral infections (*e.g.*, hepatitis B or E), or hepatotoxic drugs, notably acetaminophen overdose. Despite its high mortality rate, the liver's innate regenerative capacity can potentially restore liver function^{1,2}. However, in cases where spontaneous regeneration is insufficient, liver transplantation remains the only curative option in clinic. Therefore, developing strategies to promote liver regeneration and restore liver function in ALF patients holds significant clinical value. In acute liver failure, hepatocyte death is rampant, and the liver's regenerative capacity is often overwhelmed. Advances in understanding the pathophysiology of ALF have focused on promoting hepatocyte proliferation, as well as mitigating oxidative stress, inflammation, and apoptosis, to promote liver regeneration.

Research on liver regeneration has consistently been a key focus in the field of regenerative medicine. The process is highly complex and tightly regulated, with many underlying mechanisms yet to be fully elucidated^{3,4}. So far, key signaling pathways, including yes-associated protein (YAP), β -catenin, and hepatocyte growth factor (HGF)/c-Met, have been revealed to play critical roles in liver regeneration³. For instance, we have shown that nuclear receptors, such as pregnane X receptor (PXR), constitutive androstane receptor (CAR), and peroxisome proliferator-activated receptor α (PPAR α), activate the YAP pathway to enhance liver regeneration^{5–8}. Despite significant advances in basic research, effective clinical interventions to stimulate liver regeneration remain unavailable.

The study by Hu et al.⁹ provides novel insights into the role of the UDP-glucose (UDP-G)/P2Y purinoceptor 14 (P2Y₁₄R) axis in ALF and liver regeneration. The authors demonstrated that hepatic P2Y₁₄R was significantly upregulated in ALF models, and hepatocyte-specific deletion of P2Y₁₄R, but not hepatic stellate cell (HSC)-specific deletion, exacerbated liver failure by inhibiting β -catenin-mediated liver regeneration. Mechanistically, they showed that P2Y₁₄R induction regulated the methylation of Dact-2, a stabilizer of the β -catenin degradation complex, through CREB/DNMT3b signaling in hepatocytes. This inhibition of Dact-2 expression activated β -catenin-mediated liver regeneration, a critical pathway for liver recovery. Importantly, administration of exogenous UDP-G, the endogenous ligand of P2Y₁₄R, accelerated liver regeneration and functional recovery after partial hepatectomy in mice with hepatocellular carcinoma. These findings demonstrate that the UDP-G/P2Y₁₄R axis plays a crucial role in the liver's response to injury and targeting the UDP-G/P2Y₁₄R axis could be a promising therapeutic strategy for promoting liver regeneration in ALF and other liver diseases.

P2Y₁₄R is a widely expressed G protein-coupled receptor that plays roles in epithelial, immune, and other cell types. A previous study showed that P2Y₁₄R was highly enriched in hepatic stellate cells, while its ligand UDP-G was abundant in hepatocytes and released upon hepatocyte death. The UDP-G/P2Y₁₄R axis then activated extracellular signal-regulated kinase (ERK) and YAP signaling in HSCs, resulting in stellate cell activation and liver fibrosis in multiple mouse models of liver injury^{10,11}. However, until recently, the role of the UDP-G/P2Y₁₄R axis in hepatocytes remained unexplored. A study published in *Science* firstly showed that UDP-G was transported to the Golgi apparatus, where it bound to site-1 protease (S1P) and inhibited S1P-mediated cleavage of sterol regulatory element-binding proteins (SREBPs), thereby reducing lipogenesis in hepatocytes¹². Consistent with this mechanism, UDP-G administration effectively ameliorated non-alcoholic fatty liver disease (NAFLD) in mouse models¹¹. In their study, Hu et al.⁹ uncovered a new role for the UDP-G/P2Y₁₄R axis in hepatocytes and elucidated its significance in ALF and liver regeneration. They demonstrated that

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hepatic P2Y₁₄R was markedly elevated in ALF models and that hepatocyte-specific knockout of P2Y₁₄R exacerbated liver failure by inhibiting β -catenin-mediated liver regeneration. Furthermore, exogenous UDP-G administration accelerated liver regeneration and recovery after partial hepatectomy. Together, these studies provide comprehensive knowledge on the UDP-G/P2Y₁₄R axis's function in liver disease treatment. Notably, given the pro-fibrotic role of the UDP-G/P2Y₁₄R axis in hepatic stellate cells¹¹, caution should be exercised when evaluating the risk of liver fibrosis associated with UDP-G-based therapies for ALF and liver regeneration.

Moreover, understanding the mechanisms by which the UDP-G/P2Y₁₄R axis influences liver regeneration can provide insights into the development of novel therapeutic agents. Despite the potential pro-fibrotic effects in hepatic stellate cells, developing effective P2Y₁₄R agonists or exogenous UDP-G supplementation remains a promising therapeutic approach for ALF. Harnessing the UDP-G/P2Y₁₄R axis provides a novel and potentially effective strategy for enhancing liver regeneration in acute liver failure. For example, developing drugs that specifically target the P2Y₁₄ receptor or modulate the release of UDP-G ligands could enhance liver regeneration. Harnessing the UDP-G/P2Y₁₄R axis offers several potential advantages. First, UDP-G administration is likely to be safe due to its endogenous presence in the body. Second, since ALF patients often present with metabolic disturbances, including impaired glucose metabolism, exogenous UDP-G may aid in restoring glycogen synthesis. Third, UDP-G supplementation might also help prevent NAFLD progression, a rapidly increasing contributor to advanced liver diseases such as fibrosis and hepatocellular carcinoma. These advantages highlight the potential of UDP-G or P2Y₁₄R agonists as novel therapeutic strategies to promote liver regeneration and address both ALF and NAFLD in clinical settings.

Collectively, this work by Hu et al. enhances our comprehension of the mechanisms underlying liver regeneration and harnessing the UDP-G/P2Y₁₄R axis could be a novel and promising strategy for enhancing liver regeneration in ALF and other liver diseases. Further research is needed to fully explore the therapeutic potential of this axis in clinical settings.

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