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Acute liver steatosis signals the chromatin for regeneration via MIER1

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ABSTRACT

During liver regeneration, especially after a hepatectomy, hepatocytes experience significant lipid accumulation. These transiently accumulated lipids are generally believed to provide substrates for energy supply or membrane biomaterials for newly generated hepatocytes. Remarkably, a recent study found that acute lipid accumulation during regeneration can act as a signal for chromatin remodeling to regulate regeneration. Chen, Y.H., et al. identified MIER1 (mesoderm induction early response protein 1) as a crucial inhibitor of liver regeneration through *in vivo* CRISPR screening. MIER1 binds to and restrains cell cycle genes' expression. During liver regeneration, acute lipid accumulation suppresses MIER1 translation via the EIF2S pathway, resulting in transient down-regulation of MIER1 protein, which promotes cell cycle gene expression and liver regeneration. Interestingly, the researchers also found that the dynamic regulation of MIER1 was impaired in fatty and aging livers with chronic steatosis, while of knockout of MIER1 in these animals improved their regenerative capacity. In conclusion, this study provides valuable insights into the complex mechanisms underlying liver regeneration and highlights the potential therapeutic applications of targeting MIER1 for improving liver regeneration in disease states associated with impaired lipid homeostasis.

Healthy mammalian liver tissue possesses remarkable regenerative capacity following injury. After hepatectomy or acute toxic injury, liver cells (mainly hepatocytes) in the resting phase will re-enter the cell cycle to proliferate, generating new liver cells, which is able to restore full liver quality and function in less than two weeks [1]. However, the regenerative capacity of liver is significantly weakened in tissues with lipid metabolism disorders, such as alcoholic or non-alcoholic fatty liver and aging liver [2–7]. As a result, the liver is unable to fully restore the number of cells and normal function after liver injury. This promotes the development of end-stage liver diseases like fibrosis and cirrhosis [8]. In addition, in clinical liver transplantation, donor livers with abnormal lipid metabolism (such as fatty liver) sometimes cannot proliferate adequately in the recipient, resulting in "small-for-size syndrome" and transplantation failure [9–11].

It is widely acknowledged that maintaining hepatic lipid homeostasis is critical for preserving the liver's regenerative capacity. During liver regeneration, hepatic lipid accumulation peaks 12–24 hours after 70% partial hepatectomy [12–14]. Triglyceride content can reach up to three to four times the pre-surgery level, gradually decreasing to basal levels by 72 hours post-surgery. Several studies have demonstrated that impaired liver regenerative capacity can result from disruptions in lipid accumulation [2,15–19]. However, the mechanisms through which lipid homeostasis regulates liver regeneration and the reasons behind the decreased regenerative potential in livers with lipid metabolism disorders remain unclear.

In a recent study published in *Nature Communications*, Chen et al. discovered that the transient accumulation of liver lipids during liver regeneration serves as a signal for regeneration and repair, promoting liver cell proliferation [20]. The researchers constructed an *in vivo* large-scale CRISPR screening platform for liver regeneration to identify potential key regulators. They found that *Mier1* is a key regulator during liver regeneration. *Mier1* encodes the mesoderm induction early response protein 1, which was previously identified as a transcriptional repressor via the recruitment of histone deacetylase 1 and 2 [21,22]. However, there have been limited functional studies of MIER1 in the liver or liver regeneration. Through 70% partial hepatectomy experiments, researchers found that MIER1, as an epigenetic regulator, plays an epigenetic "brake" role during liver regeneration. MIER1 binds to a large number of transcriptional initiation regions of genes related to cell proliferation and inhibits their expression. Knocking out MIER1 can significantly promote chromatin remodeling, increase the expression of cell proliferation-related genes, and enhance liver regeneration.

The researchers also discovered a transient downregulation of MIER1 protein levels after hepatectomy, suggesting a dynamic regulatory mechanism of MIER1 during liver regeneration. Further studies revealed that MIER1 responds to acute lipid accumulation during liver regeneration, performing an important epigenetic regulatory function by modulating the protein levels of MIER1. Acute liver lipid accumulation induces a transient stress response in hepatocytes, resulting in the acute inhibition of the ribosomal translation process, thereby affecting MIER1 translation and causing dynamic downregulation of MIER1. This downregulation of MIER1 further promotes chromatin opening, cell cycle gene expression and liver regeneration. Interestingly, this physiological regulatory process is significantly impaired in aging and high-fat diet-induced fatty livers, resulting in a consistently high expression status of MIER1, which continuously suppresses cell cycle gene

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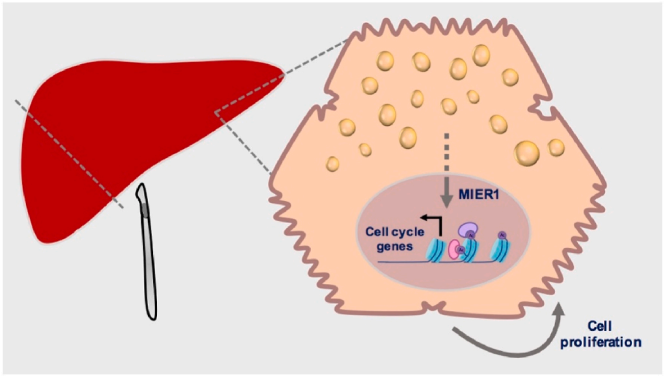

Fig. 1. Lipid acute accumulation after hepatectomy promotes cell cycle gene expression and liver regeneration via regulating the epigenetic factor MIER1.

expression. Knocking out MIER1 can recover the regeneration capacity of aging and fatty livers.

In summary, this study introduced a novel *in vivo* screening strategy, revealed an interesting underlying mechanism by which lipid homeostasis regulates liver regeneration, and identified the epigenetic factor MIER1 as a key "bridge" factor in mediating the transition from lipid signals to repair and regeneration capacity (Fig. 1).

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