Regulation of essential hepatocyte functions and identity by super-enhancers in health and disease

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Abstract

Physiologically, hepatocytes perform an estimated 500 essential liver functions to ensure systemic homeostasis. The mechanisms how hepatocytes maintain these numerous crucial functions in response to physiological and pathophysiological challenges are largely unknown. In this study, we found that vital liver function genes (e.g., HNF4A, ALB, coagulation factors, and SLC2A2) in hepatocytes possess super-enhancers. Interfering with the super-enhancers by dCas9-sgRNA remarkably decreases the expression of these genes. Quiescent liver progenitor cells (LPCs) do not have active super-enhancers in vital liver function genes. In acute liver failure (ALF) caused by massive hepatic necrosis, activated LPCs perform liver function and differentiate into hepatocytes to rescue patients' lives. We show that activated LPCs gradually form super-enhancers in liver function genes (e.g., HNF4A, ALB, and coagulation factors) during proliferation and differentiation. These super-enhancers are regulated by FOXA2 through the recruitment of HNF4 a, p300 and Mediators in most liver function genes, such as ALB and coagulation factors. However, super-enhancers in some genes (e.g., SLC2A2) are FOXA2-indenpendent. Hepatic FOXA2 expression is closely associated with the clinical outcome of ALF. In a cohort of ALF patients, robust FOXA2 is observed only in the surviving patients. Collectively, super-enhancers represent a critical epigenetic regulatory mechanism that enables rapidly enhanced transcription of liver function genes in response to pathophysiological challenges. In urgent clinical syndrome such as ALF, LPCs rescue liver function by rapid formation of super-enhancers in vital genes.