Liver Regeneration in the Acute Liver Failure Patient

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KEYWORDS

• Acute liver failure • Cytokines • Growth factors • Homeostasis • MicroRNAs
• Partial hepatectomy • Regeneration • Stem cells

KEY POINTS

- Liver regeneration is a tightly regulated process of coordinating cytokines, growth factors, inflammation, and cell fate.
- Emerging pathophysiologic mechanisms of this process include the gut-liver axis, microRNAs, the Hippo/Yap pathway, and stem cell function.
- Promising therapeutics include immunomodulation, microRNA technology, and stem cell therapy.

INTRODUCTION

The study of liver regeneration has evolved for decades, with the first experimental model of liver injury and regeneration, the two-thirds partial hepatectomy (PHx), described in 1931.[1] The majority of the understanding of liver regeneration stems from this surgical model of disease. Of interest in this review, as well as in much of the translational application of this topic, however, is liver regeneration in the setting of toxic and infectious insults as well as in the background of chronic liver dysfunction.

To understand the most recent data and findings as related to liver regeneration in acute liver failure (ALF), therefore, it is important to understand the historical context. Throughout this article, the two-thirds PHx model is referenced, providing a basis for understanding the pathways as well as a topic to contrast most recent findings as related to ALF.

BACKGROUND

The liver is an organ of homeostasis, with functions ranging from metabolism and detoxification to the balancing of glucose, lipid, and cholesterol levels as well as

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synthetic functioning. With such a far-reaching homeostatic role, it logically follows that the liver also has unique mechanisms to maintain its own normal cell function in times of injury. These unique characteristics of liver homeostasis include rapid initiation of mitosis from quiescent hepatocyte(s), a synchrony of this process, and a remarkable ability to regulate the final mass of the liver.

Early work in parabiotic models first suggested an extrahepatic, or humoral, factor initiating regeneration. In these studies, investigators found a significant increase in mitosis and DNA synthesis in the hepatocytes of a normal rat induced by cross-circulation with a recently hepatectomized rat.[2] Later work described a "synchrony" of regeneration, particularly noting a "wave" of mitoses, from periportal to pericentral regions.[3] Also, and interestingly, this synchrony was cell autonomous. Mouse hepatocytes implanted into the rat liver followed the same time course of regeneration as if they were in a mouse liver and did not take on the characteristics of the surrounding cellular millieu.[4] Early studies of the two-thirds PHx demonstrated the restoration of liver mass to preoperative weight and noted that the balance tipped toward massive necrosis and failed regeneration after a significantly greater percentage of resection.[1,5]

These findings, among many others, led to a search for the perfect mitogen, which would allow for initiation and synchronization of liver regeneration; withdrawal of this mitogen would cease regeneration when appropriate liver mass was obtained. This search has led to an ever-expanding list of contributors to this process, which has been explored in great detail in books and articles of significantly greater length and depth. This article hopes to highlight the basis of modern understanding of these mechanisms to apply them to the setting of ALF. First described is the classical pathway of cytokines and growth factors and then an alternative pathway and stem cells.

CLASSICAL PATHWAY(S)

This classical pathway of regeneration focuses on the extrahepatic and intrahepatic signaling cascades, which act rapidly and with precision on hepatocytes and the surrounding cellular milieu. This process has been described as "priming and progression," referring to the concept that regeneration is first preceded by a signal to hepatocytes priming them for mitosis and division, prompting the progression from G_0.[6] This signal alone, however, is not sufficient to direct hepatocytes through the cell cycle; a second factor, likely an extrahepatic mitogen, then tips the scales for cells to progress through G_1 and later divide. The data for this proposed mechanism are discussed throughout each topic.

IMMUNE REGULATION

The liver is the first checkpoint of portal blood returning from the gut; the gut-liver relationship is a complex balance of regulating inflammation and tolerance of this constant barrage of toxins and microbial input.[7] It is a reservoir for immune cells, notably the resident macrophages of the liver, also known as Kupffer cells. Kupffer cells make up the majority of all tissue macrophages as well as 30% of all sinusoidal cells.[8] This important interaction with portal blood makes the Kupffer cell an important signaling and filtering cell as well as an integral part of the regeneration process.

In response to liver injury, macrophage number and division are significantly upregulated, and recruitment of circulating monocytes is increased.[9] The decisive role of Kupffer cells and recruited macrophages in liver regeneration remains controversial, with a mix of outcomes after activation and depletion studies. Depletion studies have shown delayed regeneration and loss of nuclear factor (NF)-κB activation and