Editorial Commentary

The role of innate immune cells in post-hepatectomy liver regeneration

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The fame of regeneration has been attributed to the liver ever since the era of Greek mythology, in which Prometheus' liver could grow back overnight against the daily predation of Zeus' eagle. Hepatectomy is the very basis of liver surgery including liver transplantation, and post-hepatectomy liver regeneration remains the center of interest for both clinicians and scientists. Novel tools for structural and functional assessment of liver regeneration have been constantly developed and validated, laying the groundwork for clinical management and scientific analysis (1). The controversial role of liver regeneration, on the other hand, has been explored thoroughly in surgical outcome of tumorous diseases (2). Despite these, the intrinsic process of liver regeneration stays a mystery to human race with only part of it unveiled yet.

Innate immunity plays an important part in various human disease settings, and its participation in post-hepatectomy liver regeneration has been increasingly recognized. Since liver serves as a critical lymphoid organ focusing on innate immunity, the cellular and molecular components of innate immunity should be changed significantly after hepatectomy and contribute to liver regeneration process (3,4). Recent years witnessed the progressive understanding of innate immune cells, and the following will summarize known effects of innate immune cells in post-hepatectomy liver regeneration.

Briefly, surgical injury during hepatectomy somehow activates innate immune cells, which in turn secrete cytokines and other paracrine factors to stimulate the growth of hepatocytes directly, to promote transdifferentiation or dedifferentiation of hepatocytes and cholangiocytes (5), or to help with regeneration-associated neovascularization (6). Tissue-resident innate immune cells, including Kupffer cells, has been demonstrated to derive interleukin-6 upon injury-specific niche signal and inflammation-mediated transcription, which triggers the dedifferentiation of mature hepatocytes into liver progenitor-like cells (7). Type 1 innate lymphoid cells, other than myeloid cells, are reported to promote liver regeneration via sympathetic nervous stimulation-activated interleukin-22 secretion (8).

Circulating innate immune cells shall also be recruited to liver after hepatectomy and promote liver growth. Neutrophils, for instance, can be activated by apoptotic extracellular vesicles and then secrete various growth factors including fibroblast growth factor-2 and hepatocyte growth factor (9). Monocyte-derived macrophages release hepatocyte growth factor and other paracrine factors to boost liver regeneration as well, which can be influenced by endocrine and systemic inflammatory environment (10,11). Also, peroxisome proliferator-activated receptor alpha deficiency is reported to stimulate liver regeneration via macrophage polarization and consequent interleukin-6 release, which might serve as a drug target in the future (12).

In conclusion, both resident and circulating innate immune cells can be activated and recruited after hepatectomy, and help with hepatocyte expansion, transdifferentiation, and dedifferentiation via cytokine, growth factors and other paracrine mechanisms to promote

post-hepatectomy liver regeneration. The modulation of such processes should be explored further so that novel treatment strategies can be exploited accordingly.

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