MAYO CLINIC

Liver Renewal: Detecting Misrepair and Optimizing Regeneration

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CME Activity

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Abstract

Cirrhosis and liver cancer, the main causes of liver-related morbidity and mortality, result from defective repair of liver injury. This article summarizes rapidly evolving knowledge about liver myofibroblasts and progenitors, the 2 key cell types that interact to orchestrate effective repair, because deregulation of these cells is likely to be central to the pathogenesis of both cirrhosis and liver cancer. We focus on cirrhosis pathogenesis because cirrhosis is the main risk factor for primary liver cancer. Emerging evidence suggests that the defective repair process has certain characteristics that might be exploited for biomarker development. Recent findings in preclinical models also indicate that the newly identified cellular and molecular targets are amenable to therapeutic manipulation. Thus, recent advances in our understanding about key cell types and fundamental mechanisms that regulate liver regeneration have opened new avenues to improve the outcomes of liver injury.

Trial Registration: clinicaltrials.gov Identifier: NCT01899859

 ■ Mayo Clin Proc. 2014;89(1):120-130

The tremendous regenerative capabilities of the liver have been suggested since the ancient Greek myth of Prometheus. Today, we know that the myth closely resembles actual physiology because the liver can fully regenerate after removal of 70% of its mass, even after repeated hepatectomies.[1] However, it is equally true that regeneration sometimes fails, resulting in misrepair of liver injury and consequent progressive scarring (cirrhosis) and/or development of liver cancer. In this article, we focus on misrepair that results in liver cirrhosis, the main risk factor for primary liver cancer,[2,3] because recent reviews have been written about the pathogenesis of primary liver cancer and the association

Mayo Clin Proc. ■ January 2014;89(1):120-130 ■ http://dx.doi.org/10.1016/j.mayocp.2013.10.009
www.mayoclinicproceedings.org ■

between deregulated regeneration and hepatocarcinogenesis.[4,5] At present, therapies for most types of chronic liver disease focus on eliminating the causes of liver injury while relying on inherent hepatic repair capabilities to restore liver structure and function. When these approaches fail, either the diseased liver is replaced by transplant or complications resulting from liver damage are palliated until death ensues.

The burden of liver damage is increasing worldwide owing to recent epidemics of viral hepatitis[6] and obesity-related fatty liver disease[7] that have been superimposed on endemic liver diseases caused by alcohol, other toxins, and relatively rare inherited conditions. Even in countries with robust resources for—and social acceptance of—organ transplant, the demand for liver replacement now far outstrips the availability of transplantable organs.[8] This situation is compounded by the social and economic forces that stifle organ donation and transplant. Thus, health care delivery systems are confronted by a growing demand for palliative liver care, which is expensive and only somewhat successful in reducing liver-related morbidity but incapable of preventing ultimate mortality from advanced liver damage. Thus, there is a definite need to develop effective therapeutic approaches to improve repair and regeneration of injured livers. Another key challenge is to improve the detection of individuals with defective liver repair before overt, life-threatening manifestations of liver damage emerge. This detection is important so that pro-regenerative treatments can be implemented when they have the greatest chance of efficacy. Success in both diagnosis and treatment necessitates improved understanding of the mechanisms that regulate effective liver regeneration.

SCIENTIFIC OVERVIEW

Liver Regeneration Is Nothing More (or Less) Than a Wound-Healing Response

Liver regeneration is nothing more (or less) than a wound-healing response. As such, it is a precisely orchestrated, multifaceted process that involves inflammation, vasculogenesis, matrix remodeling, and the growth and differentiation of liver progenitors. It has long been believed that the wounded liver is superior to other adult organs in regenerating its functional epithelia mainly because surviving mature hepatocytes are able to reenter the cell cycle and replicate repeatedly.[9] Until recently, this dogma substantially curtailed research about liver progenitors. Thus, relatively little is known about these cells in adults. However, knowledge in this area is improving owing to growing evidence that stem/progenitor cells are generally required for effective wound-healing responses in liver, as in other organs.[10] Indeed, the progenitor compartment appears to be the main source for the replacement of dead liver epithelial cells during most types of chronic liver disease because chronic exposure to injury-related stresses typically triggers replicative senescence in mature liver cells that are able to survive.[11] That said, it is not known why mammalian liver is much more effective than other vital organs at regenerating its parenchyma because many aspects of wound healing are highly conserved in organs and across species. Solving this puzzle might suggest new interventions to optimize regeneration not only of wounded livers but also of other organs.

Effective Wound Healing Involves Constrained Scarring

One of the most highly conserved components of the wound-healing response is scarring. Scarring describes a tissue remodeling response that is typically triggered by "deep" injury. It involves accumulation of cell types that are fairly inconspicuous in the healthy tissue, including myofibroblasts (MFs), various immune system cells, activated endothelial cells, and progenitors. These cells interact to initiate the reconstruction of the injured tissue via a process that involves removing cellular debris, remodeling existing stroma vasculature, and marshaling the growth and differentiation of cells that will ultimately replace damaged parenchyma while attempting to maintain the viability of surviving parenchyma until fully functional replacement cells become available. In its entirety, scarring is an essential component of effective regeneration. However, it is often maligned because tissue architecture becomes variably disrupted by the accumulation of "abnormal" matrix during much of this rebuilding response, and remodeling the matrix back to its "healthy" configuration is easily thwarted if injury recurs. Thus, fibrosis is often considered to be synonymous with scarring. In