

## The Many Tiers of Liver Repair: Prometheus Needed Them All

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Liver is the major site of many vital functions including synthesis, detoxification and metabolism, receiving its main blood supply from portal circulation. Due to its location and critical functions, liver is bestowed with multiple tiers of repair mechanisms that have been identified and validated using multiple and elegant models. While the ability of liver to regenerate through replication of remnant cells following surgical resection or after toxicant-induced liver damage has been well known, the molecular drivers of the process have been characterized more recently. It is now well appreciated that several signaling pathways work in tandem to ensure optimal hepatic growth following partial hepatectomy and disruption of one pathway is usually overcome by another pathway. Another important tier of repair is the innate process of metabolic zonation in a microscopic liver lobule. This phenomenon, which limits expression of certain metabolic genes to only specific zones in the liver lobule, allows compartmentalization of injury brought about by either toxins or metabolic stressors. This allows survival of liver cells in other zones thus providing a cell source for repair. Likewise, existence of polyploidy and aneuploidy in hepatocytes in a normal liver at baseline, also contribute towards survival of groups of cells which are resistant to injury or show growth advantage by virtue of presence of multiple copies or absence of specific genes due. Yet another mechanism by which liver repairs itself is via the process of fate-switch of hepatocytes and cholangiocytes, the two hepatic epithelial or 'hepithelial' cells. Hepithelial cells originate from the same precursors during development. Upon chronic or acute insult, if either of the hepithelial cells are unable to proliferate or keep up with the required proliferation, the other cell type has been shown to transdifferentiate and proliferate to aid in the repair of that cell type. Finally, during extreme cases of hepatic insults, the livers have shown to undergo metabolic reprogramming by which they can divert their energy to performing minimally required metabolic, synthetic and detoxifying functions, while also proliferating and thus maintaining the required hepatic mass to sustain life. Thus, liver possesses several tiers of repair that allow it to maintain its health.