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Title: Liver Regenerative Medicine and In Vivo Molecular Imaging for the Study of In Vivo Liver Organogenesis, Liver Disease and Development of New Diagnostics and Therapeutics

The emerging field of liver (hepatic) regenerative medicine encompasses understanding hepatic stem cell biology, organogenesis, tissue regeneration, and tissue homeostasis for the study of liver disease and development of new diagnostic and therapeutic strategies. The liver, the largest internal organ in the body, performs critical metabolic, endocrine, and synthetic physiological functions. As such, it displays elaborate cellular phenotypes and intricate tissue architecture, including hexagonal, lobular structure, complex vascular spaces with specialized endothelial cells, tissue specific fibroblasts and macrophages, complex blood supply (hepatic artery and portal vein) and heterogeneous billiary duct cells which line billiary duct drainage systems. With respect to capacity for organ regeneration, the liver is unmatched. For example, preclinical, rodent studies have indicated acute hepatocellular loss results in compensatory replication of neighboring adult hepatocytes. In contrast, chronic hepatocellular injury, which often leads to end-stage disease, is compensated for by small, liver stem/progenitor cells lying at the junction of intrahepatic bile ducts and the Canals of Hering. Furthermore, circulating and immune cells, like bone marrow mononuclear cells, mesenchymal stem cells, and tissue macrophages, all have major roles in orchestrating repair in liver injury. These repair mechanisms have been translated to established treatments, like human liver transplantation, and promising therapies, such as human hepatocyte, human bone marrow-derived, and human liver stem/progenitor cell transplantation. However, current and new therapies require harvesting of human tissue, underlying mechanisms of tissue homeostasis remain elusive and hard to decipher in vitro, in animals and humans, and new approaches and techniques are needed answer critical scientific questions and take steps towards new diagnostics and therapeutics aimed towards regeneration.

A deeper understanding of human, three-dimensional (3D) liver organogenesis would naturally advance liver regenerative medicine. Unfortunately, crucial steps of liver organogenesis take place in utero, and most research has been focused on making functional hepatocytes rather than re-creating liver organogenesis. Nevertheless, this would lead to more accurate studies of acute and chronic regenerative capacity, metabolic, detoxification, and synthetic functions, and disease modeling. A second point is the need for being able to assess 3D liver organogenesis while it is occurring. Current techniques rely on removing tissue, treating the tissue and analyzing it in a static fashion. However, techniques are also needed to assess dynamic molecular events in real time, in the intact living subject, during organogenesis or regeneration. These needs are addressed by techniques in the field of molecular imaging, which aims to study biological events and pathways in the intact living subjects. Thus the combination of studying 3D liver organogenesis, and applying current techniques and developing new techniques in molecular imaging, will likely further the field of hepatic regenerative medicine.