Generation of hepatocyte-like cells from stem cell sources

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Many of the regenerative technologies, for liver diseases include cellular components, which are either transferred into the target organs or utilized in extracorporeal devices. The primary hepatocytes, which can be isolated from adult liver organs, are still the most important cellular resource in clinical situations, in which specific liver functions need to be replaced. Due to the impossibility of maintaining hepatocytes in culture or to expand hepatocytes in vitro, the search for alternative cell sources, which can either be expanded in cell culture or can be easily harvested from the body in large quantities has been stimulated. It has been proposed that subpopulations of adult hematopoietic stem cells (HSC), mesenchymal stromal cells (MSC) and cord blood stem cells (CBSC) can transdifferentiate into hepatocytes after transplantation but the efficacy by which these cells form hepatocytes and liver tissue in animal experiments is still questionable. As an alternative concept, HSC, MSC and CBSC are being transplanted in patients with chronic liver disease with the therapeutic aim to induce liver regeneration and remodelling. High expectations have been attributed to embryonic stem (ES) cells and more recently to induced pluripotent stem (iPS) cells. These cells can be maintained in a state of pluripotency for long periods of time, grown in large quantities. Hepatocytes derived from ES cells may serve as an unlimited cell source unlike primary hepatocytes isolated from donor livers. In order to generate hepatocyte-like cells in vitro, the various differentiation protocols usually mimic the events occurring during embryonic development of the liver. Accordingly, the pluripotent ES cells are differentiated into the hepatocyte state by the formation of embryoid bodies, followed by the induction of definitive endoderm using Activin A. The endoderm cell population can be further induced toward the hepatocyte lineage by exposure to bone morphometric protein (BMP) 4 and fibroblast growth factor (FGF) 2, which represent important signals from the cardiac mesoderm in early liver embryogenesis. Last differentiation steps use hepatocyte growth factor (HGF) and oncostatin M. To date, most published ESC differentiation protocols generate hepatocyte-like cells, but not the fully functional, mature, and transplantable equivalents of hepatocytes that are isolated from adult liver. Recently several research groups have tried to improve the hepatocyte differentiation protocols by ectopic expression of liver enriched transcription factors. Hepatocyte-like cells with a mature phenotype could be differentiated from murine adult liver derived progenitor cells by ectopic expression of three transcription factors.