Summary

Because of the increasing shortage of livers for transplantation, liver cell therapy has become an exciting alternative for the management of liver fibrosis and HCC.

The liver is an organ with extensive regenerative capacity based on two distinct mechanisms. After limited hepatocellular damage, mature hepatocytes expand extensively. After more serious damage, or when hepatocyte-based tissue regeneration is severely impeded, tissue is replaced through the proliferation and maturation of a phenotypically defined pool of primitive precursor cells. These stem cells have been characterized as oval cells because of their distinct morphology, and they possess the capacity for bi-directional differentiation to hepatocytes and bile duct epithelium.

The concept that the oval cell is the most primitive stem cell in liver was challenged by recent experimental models showing that bone marrow-derived stem cells had sufficient maliability to contribute to hepatic regeneration. These observations left unexplored the phenotypic and functional inter-relationships between marrow- and liver-derived hepatic progenitor cells. This knowledge is critical if marrow and hepatic stem cells are to be effectively utilized in therapy for liver disorders.

Under proper experimental conditions, marrow, umbilical cord, embryonic and fetal stem cells have been shown to be able to differentiate into hepatocytes. At present, most biotechnology industries and research laboratories are working to optimize the differentiation protocols. Also, useful stem cell-derived hepatocytes will need to not only express the genes found in mature hepatocytes, but the levels of expression will need to be at or near those found in the normal liver.

In a number of clinical trials, transplantation of marrow stem cells-derived hepatocytes has been met with success in treating liver cirrhosis or augmenting the liver remnant volume after resection of a liver with HCC. Although the small number of patients and lack of a control group, these results seem to confirm, at least in part, the results obtained in the many experiments performed in rodents showing some role of BM-derived stem cells in liver repair.

To be useful for transplant purposes, marrow or liver stem cells must be reproducibly made to: differentiate into the desired cell type(s), proliferate extensively and generate sufficient quantities of liver tissue, survive in the recipient after transplant, integrate into the surrounding tissue after transplant, and function appropriately for the duration of the recipient's life.

Liver failure occurring in patients with chronic liver disease, namely cirrhosis, is not only due to the lack of healthy cells, but also to the disruption of tissue architecture and progressive accumulation of inflammatory cells and fibrosis. While "brand new" hepatocytes derived from stem cells may temporarily support the impaired liver function, they would hardly be able to restore the original liver structure and eliminate collagen deposition. Thus, further strategies are needed. A better understanding of the mechanisms leading to collagen deposition and re-adsorption, and the development of new antifibrotic agents, combined with effective antiviral agents for patients with viral hepatitis, will be critical for the success of cell-based therapy in chronic liver failure.

Chronic viral hepatitis and alcohol abuse are the main causes of liver cirrhosis among humans worldwide. These conditions are not present in rodents and are not completely reproducible experimentally. Thus, using the data obtained from experiments carried out in rodent models of liver injury to design human studies can be complex.

Is it fruitful to add hepatocyte-like cells to an already cirrhotic liver, where the environment is extremely harsh, and even professional hepatocytes find the going tough, or should one seek to modify the cellular and extracellular milieu, to allow the endogenous hepatocytes and progenitor cells to regenerate the liver? The latter may well be a more realistic medium-term goal for cell therapy. In other words, spending some time improving the soil may bring forth more regeneration than simply throwing more seeds onto rocky ground. In the end, the humble rake may be a better tool for this job than that fancy double-edged sword. There is a growing realization that many, if not all, cancers contain a minority population of self-renewing stem cells, the cancer stem cells (CSCs) which are entirely responsible for sustaining the tumour as well as giving rise to proliferating but progressively differentiating cells that are responsible for much of the cellular heterogeneity that is so familiar to histopathologists. Targeting these cancer stem cells will be the key to defeating many forms of cancer in geneal and HCC in particular.
Liver repopulation with transplanted cells offers unique opportunities for treating a variety of liver diseases and for studies of fundamental mechanisms in cell biology. In the future, stem cell-derived hepatocytes mey be used for treatment of patients with liver failure replacing whole organ transplantation.

The confluence of insights in stem/ progenitor cells, transplantation immunology, cryobiology and liver repopulation in specific models of human diseases indicates that the field of liver cell therapy will begin to reap the promised fruit in the near future.