A REVIEW

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Role of hematopoitic stem cells in liver injury

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Stem cells can be defined as cells capable of unlimited self-renewal, multilineage differentiation, and *in vivo* functional reconstitution of a given tissue with flexibility in the timing of this differentiation Loeffler and Roeder (2002). Until relatively recently, pluripotent stem cells were thought to derive only from embryonic sources. Embryonic stem (ES) cells derive from totipotent cells of the early postimplantation embryo and are capable of unlimited, undifferentiated proliferation *in vitro* while maintaining the potential to form cell types of all three germ layers Loeffler and Roeder (2002).

In the adult, many tissues are known to contain lineage-restricted stem cells that possess the ability for lifelong renewal and functional maintenance (Scharenberg *et al*. (2002). The most widely studied example of adult stem cells is hematopoietic stem cells (HSCs), which sustain formation of the blood and immune systems throughout life. The bone marrow compartment is largely made up of committed progenitor cells, non-circulating stromal cells that have the ability to develop into mesenchymal lineages (termed mesenchymal stem cells), and HSCs (Shimano *et al.*,2003).

This latter group has been the predominant focus of research examining the stem cell compartment of bone marrow, its identification relying largely on the expression of cell-surface markers to define a subpopulation enriched for HSCs. Although this method of identification can be easily performed in the laboratory, there are several caveats, most notably that there is no assessment of stem cell function inherent to it. However, complete characterization of HSCs before their use invokes the biological equivalent of Heisenberg's uncertainty principle; by the time the cell has been isolated and demonstrated to differentiate down multiple lineages, it is no longer a stem cell Loeffler and Roeder (2002).

Adult stem cell plasticity raised expectations regarding novel cellular therapies of regenerative medicine after findings of unexpected plasticity were reported. In this review, reports of hematopoietic stem cells (HSCs) contributing to hepatocytic lineages are critically discussed with reference to rodent and human models. In particular, the role of liver injury and the potential contribution HSCs make to hepatic regeneration in both injury and physiological maintenance is reviewed. The relative contributions of genomic plasticity and cell fusion are studied across different model systems, highlighting possible factors that may explain differences between often conflicting reports. Insights from experimental studies will be described that shed light on the mechanisms underlying the migration, engraftment, and transdifferentiation of HSCs in liver injury. Although it appears that under differing circumstances, macrophage fusion, HSC fusion, and HSC transdifferentiation can all contribute to hepatic epithelial lineages, a much greater understanding of the factors that regulate the long-term efficacy of such cells is needed before this phenomenon can be used clinically.

Presently, orthotopic liver transplantation is the major therapeutic option for patients with acute and chronic end-stage liver disease. However, a shortage of suitable donor organs and requirement for immunosuppression restrict its usage, highlighting the need to find suitable alternatives.A novel and exciting approach could be offered through the current developments in the field of stem cell biology. In the past few years, multiple studies have demonstrated that adult stem cell plasticity is far greater and complex than previously thought, raising expectations that it could lay the foundations for new cellular therapies in regenerative medicine. In this review, the evidence for adult stem cell plasticity will be discussed with respect to hepatology, covering experimental models in animal and human tissues along with a discussion of the factors, putative mechanisms involved, current controversies, and potential clinical implications

Nevertheless, surface marker expression is used in standard experimental practice to identify a population that is enriched for HSCs. Although expression of the CD34 antigen is generally used in human studies as a surrogate marker for these progenitors (Ros *et al.*,2003), there is a population that lacks this surface marker that acts as a more primitive form of HSCs (Ros *et al.*, 2003). Although the $CD34^+$ population is used in clinical practice for patients undergoing stem cell transplantation, it should be noted that in murine settings, $CD34^+$ expression is a

dynamic phenomenon and may not truly reflect stem cell content (Ros *et al.* (2003). In humans, within the $CD34^{+}$ population, the monoclonal antibody AC133 identifies a $CD34^{bright}$subpopulation that has greater hematopoietic-reconstituting properties in xenotransplantation models (Taylor *et al.*,2000) (compared with the $CD34^{dim}$ population).

By staining HSCs with Hoechst 33342 dye, a selection of side population (SP) of cells with the highest efflux capacity has been demonstrated to identify a primitive population (Ros *et al.*, 2003). Furthermore, it is the expression of the ATP-binding cassette (ABC) transporter, ABCG2 that mediates the SP phenotype Taylor *et al.* (2000). Notably, ABC transporters have been shown to be up regulated in rodent hepatic oval cells (Osawa *et al.*, 1996), and human hepatic oval cells (Ros *et al.*, 2003), implying an overlap with this lineage-restricted stem cell compartment. This overlap of putative surface markers across different stem cell populations is a common feature and can result in difficulties discerning respective cellular populations when they admix in end organs such as liver and muscle.

Hepatic stem cells have been identified in adult liver. Recently, the origin of hepatic pro-genitors and hepatocytes from bone marrow was demonstrated. Hematopoietic and stems share the markers CD 34, c-kit, and Thy1. Little is known about liver stem cells during liver development. In this study, we investigated the potential stem cell marker Thy1 and hepatocytic marker CK-18 during liver development to identify putative fetal liver stem.

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