Propagating factor IX-producing hepatocytes for haemophilia B therapy

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Developing effective cell-based therapies to treat severe haemophilia B remains attractive for several reasons. On-demand and prophylactic factor IX replacement using plasma-derived or recombinant factor IX are both safe and effective (1). However, the cost of either replacement product for lifelong therapy is a significant barrier for patients with limited access to health insurance to cover the ongoing cost of treatment. Further, long-term, cell-therapy-based factor IX replacement could probably materialize if a reliable delivery at ~10% of the normal factor IX plasma levels in treated patients could be assured, as consistent delivery in vivo of factor IX at this level would essentially prevent spontaneous bleeding in the individuals thus treated (2). Prior studies using viral vectors have shown long-term therapeutic efficacy in experimental animals (2–6). Thus far, however, viral vectors-based approaches have been essentially ineffective in patients due to the very low levels and short-term delivery of factor IX in the patients thus treated (7, 8). Concerns associated with the short-term delivery of factor IX via viral vectors include antibody-mediated destruction of the delivery system and/or inactivation of factor IX (8, 9). Another concern associated with the use of viral vectors is the transient elevation of liver transaminases. Generation of humoral and cellular immune responses to both the delivery system and the factor IX delivered in vivo are potential concerns, regardless of the delivery system employed as an alternative to factor IX concentrate infusion.

A proven effective and long-term cure of severe factor VIII or factor IX deficiency is successful liver transplantation (10–12). Since factor IX is synthesized by hepatocytes, effective transplantation and long-term survival of isolated hepatocytes have the potential to reduce or even eliminate the need for whole liver transplantation or periodic infusions of plasma-derived or recombinant factor IX into severe haemophilia B patients. Tatsumi et al. have demonstrated the therapeutic potential of hepatocyte transplantation in a patient with congenital factor VII deficiency and the therapeutic effectiveness of human hepatocytes transplanted under the kidney capsules, in delivering human factor VIII into the plasmas of severe haemophilia A mice (13, 14). The present study by Tatsumi et al. (15) in this issue of Thrombosis and Haemostasis is an extension of the authors’ previous work that has the long-term goal of ensuring both the reliability and robustness of hepatocytes engineered to deliver therapeutic levels of proteins ably synthesized by isolated primary hepatocytes. This study employed canine and human primary hepatocytes that were propagated into the well-described immunodeficient mouse model over-expressing urokinase (uPA) that confers an acquired selective growth disadvantage on the endogenous mouse hepatocytes of the uPA-SCID mice. The study demonstrates an effective propagation and engraftment of both canine and human hepatocytes in uPA/SCID mice. Importantly, the engrafted hepatocytes maintained their capacity to synthesize albumin and factor IX (canine or human as appropriate) at acceptable levels. One obvious advantage of primary hepatocyte-mediated factor IX delivery is that the factor IX delivered would likely have all the functional attributes of factor IX arising from all the post-translational modifications factor IX and other vitamin K-dependent clotting factors normally undergo. The limited volume of plasma available did not allow the authors to assess whether the transplanted hepatocytes also synthesized prothrombin, factor VII, factor X, protein C or protein S.

The authors recognize several important drawbacks that must be tackled before hepatocyte transplantation could become an acceptable routine clinical procedure. Acceptable methods for conferring selective growth and engraftment advantages on the transplanted hepatocytes relative to the endogenous livers of the transplant recipients remain to be established. Immunosuppressive or immune modulation regimens will probably be mandatory to assure the long-term survival of engrafted hepatocytes, as well as the survival of the factor IX delivered. Use of SCID mice in this study clearly highlights this concern. In addition, acceptable methods for large scale culture of primary human hepatocytes in vitro or in vivo and the harvesting of pure human hepatocytes for transplantation must also be found. Possible engraftment of hepatocytes at sites other than the liver may have undesired clinical
consequences and must therefore be rigorously ruled out. A final question that has yet to be sufficiently answered is whether the transplanted hepatocytes can synthesize adequate levels of the proteins and carry out all the other metabolic functions the endogenous livers performed prior to their deliberate impairment. In spite of all these obstacles, hepatocyte transplantation offers a potential cell-based approach for treating or moderating the spontaneous haemorrhagic or thrombotic tendency associated with congenital vitamin K-dependent clotting factor deficiencies.

References