Editorial

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Hepatocyte transplantation, a step forward?

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Hepatocyte transplantation emerged a few decades ago as a possible strategy to overcome some of the limitations of liver transplantation, among them the availability of organ donors and the functional quality of grafts. Nowadays, allogenic cell transplantation is still to be confirmed as a viable therapeutic option for patients with hereditary metabolic liver diseases. Although we have now overseen 5 decades of basic and animal research in the field, the number of successfully treated patients remains low. Limitations in cell engraftment and selective proliferation of transplanted cells remain a constraint to the generalized use of this therapeutic approach. The discrepancy between the results of cell transplantation in animals, where different strategies have been successfully used (*i.e.*, partial hepatectomy, irradiation, drugs to enhance cell engraftment and decrease cell losses, *etc.*), and the outcomes in patients is somewhat disappointing. Animal experiments are conducted to achieve the best possible outcomes, using animal models that enable a selective growth advantage for high quality transplanted cells (*i.e.*, freshly isolated autologous hepatocytes). The clinical scenario, however, relies on the use of allogenic hepatocytes, often isolated from marginal liver donor organs, repeated cell transplants (occasionally combined with previous partial hepatectomy or liver irradiation) and the drawbacks of immunosuppression, which explain the mismatch between the experimental scenarios and the clinical reality. Attempts to substitute primary isolated allogenic hepatocytes with autologous induced pluripotent stem cell-derived hepatocytes have remained elusive; conclusive results to confirm the broader clinical applicability of this procedure are still awaited.

In this issue, Barahman, Guha and colleagues have studied the use of focal radiation combined with hepatic cell growth stimuli, as a clinically feasible therapeutic modality to increase engraftment and repopulation of a host liver with transplanted hepatocytes.[1] The apolipoprotein E "knock out receptor deficient mouse model", which they have used, does not provide a selection advantage for transplanted cells and has thus rarely been used in earlier studies. The therapeutic outcome was analysed not only histochemically by calculating the number / percentage of successfully engrafted cells, but also by monitoring increases in ApoE levels and reductions in cholesterol, low-density lipoprotein and very low-density lipoprotein levels in serum. Infusion of hepatocytes via the portal vein or into the spleen usually results in less than 2% engraftment and would not significantly change lipid serum levels in this mouse model. The authors of the study explored a strategy based on regional high dose irradiation of mouse liver combined with hepatic cell growth stimulation and analysed the effects on engraftment and functionality of hepatocyte transplantation. Previous studies by this group and others had already shown a dose-dependent inhibitory effect on proliferation of liver hepatocytes with maintenance of liver function and only a slow clearance of the irradiated cells.[2] Radiation therapy (50 Gy) was restricted to the median and right lobes of the mouse liver. Although this focal radiation of the host liver might diminish the effectiveness and therapeutic effects of transplanted cells, in turn, it reduces the risk of liver failure in unsuccessful cell transplants, especially in children.

With this approach the number of transplanted cells was significantly, but not impressively increased, compared to control animals (transplanted without irradiation). Initially engrafted hepatocytes would probably increase their number over a long period of time, since the irradiated host hepatocytes slowly die after the previous high dose irradiation. To accelerate the process of liver repopulation, Barahman *et al.* used growth stimulators such as adenovirus encoded hepatocyte growth factor (HGF), or GC1, a selective agonist of the T3 thyroid hormone β receptor, which elicits a strong hepatic mitogen stimulus but does not have the impact on cardiac function that thyroid hormones have. Four months after hepatocyte transplantation the number of engrafted hepatocytes had dramatically increased and serum cholesterol, low-density lipoprotein and very low-density lipoprotein levels reduced to almost normal levels. Based on these observations, the authors conclude that focal radiation in combination with a hepatic growth stimulus improves the therapeutic outcome of hepatocyte transplantation and successfully corrects this hereditary liver disease in the absence of a selection advantage for transplanted cells. Side effects were acceptable with no long-term safety concerns, although these issues were not the focus of this study.

Preparative radiation in the context of hepatocyte transplantation was already explored in a pioneering study by

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Soltys *et al.*, in a small number of non-human primates, as a basis for the *first-in-man* trial published in this *Journal*.[3] In that study, 3 patients with hereditary liver diseases were transplanted after prior focal irradiation of the liver. The results demonstrated clear positive effects of the previous liver irradiation, although detailed data on long-term outcomes and safety issues were not reported. The study by Barahman *et al.* shows convincingly that radiation therapy combined with hepatocyte growth stimuli can improve engraftment of transplanted hepatocytes, even if there is no selective advantage for them, providing an efficient therapeutic correction of an inborn error of the liver. The work provides detailed analysis on a cellular and molecular level and gives support for further clinical development. Whether the administration of HGF or the agonist GC1 is safe and efficient in humans, remains to be determined. The eventual use of adenoviral vectors to deliver HGF, could be problematic in clinics, based on the pre-existing clinical information and, consequently, other strategies (*i.e.*, GC1) might be preferred. Furthermore, few data currently exist on the long-term safety of using radiation to precondition the liver, especially in children. Although no long-term consequences have been reported in one retrospective study,[4] careful monitoring of patients treated with radiation therapy and hepatocyte transplantation is mandatory.

Partial hepatectomy has been used as a clinical procedure to increase the number of successfully engrafted hepatocytes; it has also been applied in 2 patients with Crigler-Najjar syndrome, but it did not result in complete correction of the disease.[5] Other alternative therapeutic approaches to correct hereditary metabolic liver diseases are currently being explored. Adeno-associated virus vectors have been used in clinical gene therapy protocols (*i.e.*, haemophilia B) with promising results[6] and are being explored in liver diseases as well.[7] Whether this type of gene therapy can be successfully applied to newborns and small children remains to be verified, since episomal adeno-associated virus vectors may be lost in a growing liver. More recent studies point at the potential of CRISPR/Cas9 based homology directed repair and base editing methods for the correction of genetic liver diseases, such as familiar hypercholesterolemia in patient-derived induced pluripotent stem cells,[8] and phenylketonuria in mice *in vivo*.[9] Currently, we cannot anticipate which of these advanced therapies will be the treatment of choice to correct hereditary metabolic liver disease in the near future, but Barahman and co-workers[1] have clearly shown that hepatocyte transplantation, together with focal radiation and growth stimuli, is a promising candidate.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.022.

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Author names in bold designate shared co-first authorship

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