

expected post-surgical course. In order to do so, we must demand the adequate means and sufficient complementary diagnostic resources of a certain quality.

With the severe economic crisis damaging the Spanish national healthcare system, it is true that the moment at hand is not precisely the best time for such demands. Thus, it is important to base our arguments on well-documented national data with sufficient statistical power to shine more light on this problem. In the meantime, it is necessary to strictly adhere to protocols and clinical pathways, progress in the sectorial organization of service portfolios and clearly regulate inter-hospital transfers and referrals.

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Hepatocyte Transplantation: Regenerative Potential and Limitations



Trasplante de hepatocitos: potencial regenerativo y limitaciones

Dear Editor,

We have read with interest the Paper published in your journal by Pareja et al.¹ about the future prospects of hepatocyte transplantation, in which they reported the results obtained in 4 children with inborn errors of metabolism and in 4 adult patients.¹

In both groups, a temporary improvement was observed in the biochemical parameters, without achieving a stable, long-lasting improvement,¹ which is why the authors reflect on the possible causes of the loss of viability of the transplanted hepatocytes as well as possible maneuvers aimed at promoting “nesting” or “engraftment” of the hepatocytes in the liver.¹ The results of Pareja et al. coincide with most of the clinical series published and contrast strikingly with experimental studies in rodents.^{2,3}

The temporary improvement and the inability to substitute the liver function is probably due to the altered proliferation of the transplanted hepatocytes, when on the other hand the evidence in rodents shows the extraordinary replicative capacity of hepatocytes to multiple stimuli.^{4,5}

Among the alternatives for improving engraftment, they mention 2 preconditioning techniques: radiation of the liver or portal embolization. These techniques induce a “liver injury” and stimulate cell division (transition of the G₀ phase until the cytokinesis of the cell cycle). In 1989, Pardee⁶ described the concept of competence acquisition by which the cells subjected to stress or mitogen factors evolve until the end of the G₀ phase of the cycle and surpass the critical point of control “R” when the cells are determined to divide irreversibly. It has been described that the isolation of the hepatocytes with collagenase represents a stimulus for them to divide more rapidly.⁷

Pareja et al., with their extensive experience in the isolation of hepatocytes, have reported that “some 70% of the hepatocytes are eliminated from the portal system” due to an inflammatory response and the overregulation of cytokines (TNF- α , IL-6).^{1,8} What is striking is that these cytokines induce the first phase of hepatocyte regeneration (hepatocyte purging or enrichment) by means of the transition of the hepatocytes of phase G₀-G₁ of the cycle.⁹

The proliferation of hepatocytes (requisite of hepatocellular transplant) is a process that is strictly regulated

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genetically, as is the cell cycle. When there is a “hyperproliferative stress”, there is an activation of p53, which induces cell apoptosis.¹⁰ This phenomenon could explain the effect described by Pareja et al.^{1,8}

The description of induced pluripotent stem cells (iPSC) by Nobel-prize winner Yamanaka and the recent creation of “organoid” structures with hepatic phenotype in mice by the infusion of iPSC cells with endothelial cells have opened new horizons for hepatocellular transplantation as a therapeutic alternative.

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