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Hepatic repopulation capacity and advanced metabolic liver functions of adult human liver progenitor cells revealed their potential use for the treatment of liver metabolic diseases

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Abstract

The potential use of stem/progenitor cells as alternative cell sources to mature hepatocytes for liver disease treatment depends on their ability to exhibit advanced metabolic liver functions and hepatic repopulation capacity. In the current study, four major liver functions were investigated in adult derived human liver stem/progenitor cell (ADHLSCs) populations subjected to in vitro hepatogenic differentiation: gluconeogenesis, ammonia detoxification, and activity of phase I and phase II drug-metabolizing enzymes. Engraftment and hepatogenic regeneration capacity were evaluated seven, thirty and sixty days after intrasplenic transplantation of undifferentiated ADHLSCs into six to eight SCID mice without regeneration stimulus. We demonstrated that differentiated ADHLSCs displayed higher de novo synthesis of glucose, correlating to an increased activity of glucose-6 phosphatase and mRNA expression of key related enzymes. In addition, these differentiated cells were able to metabolize ammonium chloride and produce urea. This was correlated to an increase mRNA levels of relevant key enzymes. With respect to drug metabolism, differentiated ADHLSCs expressed mRNAs for all the major cytochromes. Such increased expression is correlated to an enhanced phase I activity as independently demonstrated using fluorescence based assays. The most important cytochrome CYP3A4 was pharmacologically modulated in differentiated ADHLSCs using activators (phenobarbital) and inhibitors (Naringin) in a similar way than mature hepatocytes. Phase II enzyme activity and amino acid levels also show a significant enhancement in differentiated ADHLSCs. The application of such hepatogenic differentiation protocol on cryopreserved/thawed ADHLSCs did not alter these acquired metabolic activities. Analysis of transplanted mice livers revealed that ADHLSCs engrafted as isolated cells or clusters of hepatocyte-like cells expressing both human albumin and human Alu sequences in the parenchyma of SCID mice mostly near vascular structures. Analysis of

serial sections revealed that these human albumin immuno-positive cells lost their initial mesenchymal marker vimentin and acquired the expression of ornithine transcarbamylase, suggesting in situ hepatic maturation of ADHLSCs. Displaying hepatic regeneration capacity in vivo as well as advanced liver metabolic functions after hepatogenic differentiation in vitro support the possibility to develop ADHLSCs as potential alternatives to primary hepatocytes for liver disease treatment.

⬆ Drug terms

messenger RNA	enzyme	cytochrome	human albumin	amino acid	marker	vimentin
ornithine carbamoyltransferase	phenobarbital	aurantiin	drug metabolizing enzyme	ammonia		
glucose	glucose 6 phosphatase	ammonium chloride	urea			

⬆ Disease terms

metabolic disorder	liver disease
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⬆ Other terms

liver	stem cell	liver function	adult	liver cell	in vitro study	regeneration
SCID mouse	drug metabolism	fluorescence	assay	enzyme activity	mouse	human
Alu repeat	parenchyma	engraftment	maturation	liver regeneration	gluconeogenesis	
detoxification	transplantation	stimulus	synthesis	cell population		

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