

MICROGRAVITY MAINTAINS STEMNESS AND ENHANCES GLYCOLYTIC METABOLISM IN HUMAN HEPATIC AND BILIARY TREE STEM/PROGENITOR CELLS

LA MICROPESANTEUR MAINTIENT LA SOUCHITUDE ET AMÉLIORE LE MÉTABOLISME GLYCOLYTIQUE DES CELLULES HÉPATIQUE ET DES CELLULE SOUCHES/PROGÉNITRICES DE L'ARBRE BILIAIRE HUMAIN

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Introduction: Liver diseases represent a major public health problem affecting 5-15% of the inhabitants worldwide. The final manifestation of chronic liver diseases is cirrhosis. When a successful etiologic approach is unavailable or has failed, progressive, extensive fibrosis, with concurrently impaired hepatocyte regeneration, leads to irreversible cirrhosis and then liver failure. Resident stem cells play a key role in driving the process of liver repair and, indeed, they are currently taken into consideration for the cell therapy of terminal liver diseases and for the liver regenerative medicine. Gravity plays a key role in regulating cell processes such as proliferation, differentiation and cell function. The aim of our research was to evaluate the effects of microgravity on differentiation and exo-metabolomic profile of human hepatic and biliary tree stem/progenitor cells.

Method: Simulated weightless conditions were obtained by using the Rotary Cell Culture System (RCCS, Synthecon). Primary cultures of human biliary tree stem cells (hBTSCs) and immortalized human hepatic cell line (HepG2) were cultured in microgravity or in normogravity conditions. Self-replication and differentiation toward mature cells were determined, respectively, by culturing in Kubota's Medium and hormonally defined medium tailored for hepatocyte differentiation. RT-qPCR was used to evaluate gene expression and NMR to analyze the cell exo-metabolomic profile.

Results: Microgravity determined an increase of stemness genes (OCT4, SOX17, PDX1) in hBTSCs ($p < 0.05$ vs normogravity). hBTSCs cultured in microgravity showed an impaired capacity to differentiate toward mature hepatocytes, since the expression of hepatocyte lineage genes (ALB, ASBT and CYP3A4) was significantly lower with respect to normogravity ($p < 0.05$). In HepG2, the microgravity caused a lower ($p < 0.05$ vs normogravity) expression of CYP3A4, a terminal differentiation gene expressed in lobular zone 3. The NMR PCA of the exo-metabolomic cell profile evidenced that, in microgravity, both cell lines presented higher glucose consumption and lower consumption of pyruvate and glutamate with respect to normogravity ($p < 0.05$), with formation of fermentation.