Free Session

Tissue and organ models

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Three Dimensional Multicellular Hepatic Organoid Model For In Vitro Biomaterial Risk Assessment

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Introduction: Effective preclinical screening of drugs, chemicals and biomaterials safety is of critical importance in drug development and environmental toxicology research. A major limitation of the currently used *in vitro* models is related to inadequate tissue model functionality. In commonly used simple 2D monolayer cultures, human hepatocytes rapidly lose their phenotype due to de-differentiation, restricting their use to simple acute toxicity studies. Cultivation of hepatic cells in 3D configuration as spheroids has been shown to better preserve the mature hepatocyte phenotype during long-term cultivation, due to their extensive formation of cell-cell contacts, the re-establishment of cell polarity and production of extracellular matrices. Information on hepatic metabolic clearance is indispensable for the safety assessment of xenobiotics or other degradation products from biomaterials implanted/in contact with human tissues/organs. Therefore, development of such a platform could be beneficial as an *in vitro* screening platform for biomaterial risk assessment. Within PANBioRA project one major focus is the prediction of hepatotoxicity of biomaterials and development of an *in vitro* screening platform to reliably identify potentially hepatotoxic agents. Herein, we describe the development, optimization and characterization of a novel 3D hepatic spheroids model using differentiated hepatocytes and stellate cells.

Experimental methods: Human cell lines representing hepatocytes (HepaRG) and stellate cells (LX-2) were co-cultured using the Aggrewell technology to generate 3D spheroids. Gelatin hydrogels crosslinked by microbial transglutaminase were used to encapsulate 3D spheroids for static and perfused systems. 3D encapsulation provides an attractive tissue-like environment that better mimics what cells observe *in vivo,* compared to standard tissue culture methodologies. Those systems were treated with various compounds and the spheroids behaviour was evaluated up to 14 days in both conditions. The biocompetency and biomaterials evaluation over the spheroids was assessed by determining cell viability, multiparametric liver metabolites, cytokines expression and cytochrome activity

Results and discussions: The results indicate that 2D cultures have a higher variation in readouts compared to a 3D system where the readouts are more stable and represent a profile pattern close to the physiological range. Moreover, the cytokine and liver metabolites values for the 2D culture could be attributed to several facts such as high substrate stiffness, forced apical-basal polarity and continuous matrix deposition. Based on encapsulation of the spheroids, this approach demonstrate that the multicellular 3D spheroids setup could be maintained in a non-activated status, based on the low expression levels of activation markers. This *in vitro* model can be used to study the effects of various insults over the functional characteristics of the liver hepatotoxicity.

Conclusions: 3D hepatic spheroids cultured in microfluidic devices are good models to maintain hepatocyte-like features, showing applicability for toxicological studies and integration with *in silico* models. The human liver 3D organoid model here presented, can be classified as a valuable, simple and efficient tool to investigate biomaterial risk assessment.

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