Optimization of extracellular matrix for primary human hepatocyte cultures using mixed collagen-Matrigel matrices.

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Abstract

Loss of differentiation of primary human hepatocytes (PHHs) ex vivo is a known problem of in vitro liver models. Culture optimizations using collagen type I and Matrigel reduce the dedifferentiation process but are not able to prevent it. While neither of these extracellular matrices (ECMs) on their own correspond to the authentic hepatic ECM, a combination of them could more closely resemble the in vivo situation. Our study aimed to systematically analyze the influence of mixed matrices composed of collagen type I and Matrigel on the maintenance and reestablishment of hepatic functions. Therefore, PHHs were cultured on mixed collagen-Matrigel matrices in monolayer and sandwich cultures and viability, metabolic capacity, differentiation markers, cellular arrangement and the cells' ability to repolarize and form functional bile canaliculi were assessed by reverse transcription quantitative real-time polymerase chain reaction (RT-qPCR), functional assays and immunofluorescence microscopy. Our results show that mixed matrices were superior to pure matrices in maintaining metabolic capacity and hepatic differentiation. In contrast, Matrigel supplementation can impair the development of a proper hepatocytic polarization. Our systematic study helps to compose an optimized ECM to maintain and reestablish hepatic differentiation on cellular and multicellular levels in human liver models.