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Umbilical cord matrix stem cells: A new model to study the role of hepatogenic differentiation and its association with the susceptibility to hepatitis B virus infection

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Abstract

The discovery of HepaRG cell line shed light on cell differentiation state as a possible explanation of HBV liver tropism. A non-transformed cell model would be needed to better elucidate the role of hepatogenic differentiation on cell susceptibility to HBV infection. Methods: Umbilical cord matrix stem cells (UCMSCs) have been isolated by collagenase digestion of Wharton's jelly, and then cultivated, characterized and differentiated as described before (Campard, Gastroenterology 2008). To standardize infection conditions, HBV was obtained from a culture of HepAD38s, and concentrated by PEG precipitation. After infection, HBV DNA was quantified by real time qPCR using a specific TaqMan probe. cccDNA was specifically measured following digestion with a Plasmid-Safe DNase. Differentiated UCMSCs (D-UCMSCs) were compared to undifferentiated cells (UD-UCMSCs) and to primary human hepatocytes (PHH). Results: UCMSCs' mesenchymal stem cell identity was confirmed by the expression of CD90, CD73, CD105, the absence of CD45, CD133 and CD117, and by their ability to accomplish adipogenic and osteogenic differentiation. Following hepatogenic differentiation, D-UCMSC showed an increased expression of Cyp3A4, albumin and HNF4, and acquired functions typical of mature hepatocytes, such as Cyp3A4 and glucose- 6-phosphatase activity. To study HBV binding to cell membrane, cells were incubated with 2.4±1.5 x 104 IU/cell of HBV for 2 hours (h) at 4°C. After extensive washing, 7.3, 27.5 and 26.5 HBV gen.eq./cell were bound to PHH, UD-UCMSC and D-UCMSC respectively. After 1 h at 37°C, PHH, UDUCMSC and D-UCMSC were able to uptake 5%, 2.5% and 6.3% of membrane-bound HBVs, respectively. The proportion of virus uptake increased after 4 and 24 h for both PHH (12.1%, 19%) and D-UCMSC (10.8%, 25.8%), but it remained stable for UD-UCMSC (4.2%, 3.7%). Susceptibility to viral replication was studied by measuring intracellular HBV DNA at 3, 7 and 10 days post-infection (pi), as compared to 24 h pi. HBV DNA levels increased in both

PHH (165%, 314%, 958%) and D-UCMSC (105%, 135% and 769%), suggesting viral replication. cccDNA was measured in D-UCMSCs 7 days pi and shown to increase 7 times as compared to 24 h pi. HBsAg and HBeAg levels in culture supernatant confirmed viral replication in D-UCMSCs. Conclusions: UCMSCs are non-transformed, easy-to-obtain, human cells that proved to be resistant to HBV infection in their undifferentiated state and to acquire susceptibility to HBV uptake and replication after hepatogenic differentiation. They constitute a new in vitro "physiological" model to study the role of differentiation on HBV-cell interactions. Note: original work - confidential.

Drug terms

DNA deoxyribonuclease glucose 6 phosphatase hepatitis B surface antigen hepatitis B(e) antigen collagenase albumin

Disease terms

virus infection **liver disease** infection

Other terms

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