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Umbilical cord matrix stem cells maintain a stable genotype after long-term in vitro culture

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Abstract

Introduction: Umbilical cord matrix stem cells demonstrated interesting properties and differentiation potential towards hepatic lineage. They therefore represent a promising stem cell based treatment for human liver inborn errors of metabolism. Aims: Therapeutic use of umbilical cord matrix stem cells (UCMSC) rely on the demonstration of their stabilized properties during long-term culture. During large scale ex vivo cell expansion, cell characteristics may be altered. In this study, we investigated in vitro and in vivo genetic stability of these cells cultured up to senescence. Methods: UCMSC were isolated from the Wharton's jelly of fourteen healthy at term newborns. Cells were characterized by measuring cytoplasmic and cell surface markers expression by flow cytometry, immunofluorescence and qPCR. Cell growth, morphology and anchorage dependance was followed at each passage. Hepatic differentiation potential was assessed analyzing key hepatic metabolic functions. Long-term genotype stability was investigated by performing karyotype, telomere length, measure of telomerase activity and gene expression related to tumorogenesis. Tumorigenic potential was investigated after subcutaneous injection of 1.107 cells in an immunocompromised xenograft model. Results: Proliferative capacity was similar between cell cultures. Cells reached senescence after 27.6 ± 1.6 cumulative population doublings corresponding to a culture period of 160.9 ± 6.9 days. Cells expressed high levels (>95%) of CD73, CD90, CD105, CD44 and CD29; and maintained their original phenotype up to senescence. UCMSC were able to acquire mature hepatic metabolic functions after differentiation, nearly reaching the potential of human hepatocytes concerning urea production and Cyp3A4 activity. UCMSC remained cytogenetically stable during long-term culture. The cells did not express telomerase activity or alternative telomere lengthening mechanisms. Human telomerase reverse transcriptase expression was not detected. Levels of cell cycle related genes such as p53, p16, p21 and pRb were typically correlated with

progressive cell senescence as shown by positive senescence associated beta-galactosidase staining. UCMSC did not display tumorigenic potential both in vivo or in vitro, as anchorage dependence was conserved in vitro and immunodeficient mice subcutaneously injected with UCMSC did not develop tumors. Conclusions: UCMSC is an unexhaustive, uncontroversial and easily accessible cell source. They can be expanded in vitro while maintaining a stable phenotype, genotype and differentiation capacity. UCMSCs therefore represent safe and effective candidates for liver regenerative medicine.

Drug terms

telomerase protein p53 beta galactosidase cell surface marker telomerase reverse transcriptase

Disease terms

liver disease neoplasm

Other terms

in vitro study **umbilical cord** **stem cell** **genotype** **liver** senescence human cell culture telomere phenotype staining mouse model metabolism drug therapy ex vivo study cell expansion genetic stability newborn flow cytometry regenerative medicine cell growth morphology karyotype gene expression subcutaneous drug administration xenograft population liver cell urea cycle cell cycle gene immunofluorescence

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