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ALTERATIONS IN BIOLOGICAL CHARACTERISTICS OF HUMAN UMBILICAL CORD WHARTON'S JELLY-DERIVED MESENCHYMAL STEM CELLS DURING *IN VITRO* PASSAGING

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SUMMARY

Mesenchymal stem cells (MSCs) are promising sources for regenerative medicine. Known for their regenerative potential owing to high self-renewal and differentiation capacity, MSCs also secrete paracrine factors and possess immunomodulatory capacity, all of which contribute to their remarkable therapeutic outcomes. However, the acquisition of aging-like characteristics during long-term passaging to obtain sufficient cell number impairs their quality, thereby hindering MSC therapy translation. We aim to investigate the *in vitro* passaging-induced changes in biological characteristics of human umbilical cord Wharton's jelly-derived MSCs (WJMSCs). From Passage 2 (P2) to P10, proliferation (Alamar Blue assay and qRT-PCR), expression of stemnesss, senescence, cell cycle arrest and inflammatory markers (qRT-PCR) of isolated WJMSCs (Ethical Approval No: 2017315-5049) were assessed. Culturing WJMSCs was accompanied by morphological changes, featuring the loss of their characteristic spindled shape and the presence of stress fibres starting from P6, indicating senescence acquisition. There was a progressive decline in proliferation across the passages, with the first highest reduction observed at P6 - a 30%-reduction from P3, and molecularly shown through PCNA (proliferation marker) down-regulation. WJMSCs showed reduced expression of stemness markers (Oct4, Nanog, Sox2, Lin28, Klf4) during *in vitro* passaging, along with the up-regulation of senescence and inflammatory markers (IL-6, IL-8, IL-1β, MCP-1, ICAM-1, CXCL-2), and cell cycle arrest-related markers (p53, p21, TSAP6, especially p16 - a 15-fold increase at P9). Our results demonstrated that the cells undergo aging-like phenomena in culture, thereby sparking our interest in further investigating the effect of *in vitro* passaging on MSC migratory and stress resistance abilities, their low immunogenicity and secretome release. The knowledge acquired from this study would aid in developing effective approach to restore MSC therapeutic potential that is essential for their application in regenerative biology.

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