Factors regulating stem cell behaviour – P29

Hypoxia enhances proliferation and attenuates differentiation capacity of human mesenchymal stromal cells - and prolongs their lifespan

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Low oxygen tension is thought to be an integral component of the human mesenchymal stem cell (MSC) native bone marrow microenvironment. MSCs (n=9) were maintained under hypoxic atmospheres (1%O₂ and 5%O₂) for up to ten in vitro passages. This resulted in approximately 3,000 (1%O₂) and 1,800 (5%O₂) fold higher cumulative cell numbers after five passages compared to MSCs cultured at normoxic (20%O₂) conditions. When compared with MSCs expanded at normoxic atmospheres, sixfold (1%O₂) or fourfold (5%O₂) higher number of colony-forming units were found; MSCs also expressed higher levels of stem cell markers (STRO-1, Oct-4, SSEA-1, SSEA-4 and NANOG). However, under 1%O₂ adipogenic and osteogenic differentiation was suppressed, while chondrogenic differentiation was inducible but diminished compared to standard in vitro conditions. Using 5%O₂ tension attenuated differentiation capacity was detected for osteogenic and adipogenic pathway while chondrogenesis was enhanced. In turn, with the exception of chondrogenesis (5%O₂), MSCs obtained from hypoxic cultures offered a better differentiation capacity and also expressed higher levels of osteogenic and adipogenic differentiation markers when subsequently were differentiated under normoxic conditions. Additionally, in vitro proliferation lifespan was significantly increased with about 7 additional passages (1%O₂) before reaching terminal growth arrest. Thus, the low oxygen tension is a key parameter that influences in vitro characteristics of MSCs by providing a micromilieu for extension of lifespan and enhanced proliferation capacity. Simultaneously the maintenance of stemness and differentiation capacity was improved.