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Mesenchymal stem cell ageing: Tissue regeneration, repair and longevity

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Stem cells play an important role during development and their dysfunction is associated with a variety of diseases. Also the application of stem cells in medical therapeutics is a promising and emerging field. As organ repair and regeneration processes rely on the regulated activity of tissue-borne stem cells, and they may become increasingly compromised with advancing age, major issues in this context are to investigate the changes that occur in MSC with advancing age (1), and more than that whether these changes are causative for age-related deviations such as the accumulation of fat deposits in bone, impaired fracture healing, or de-regulated hematopoiesis. To analytically approach this question, we study primary MSC from bone of differently aged, yet systemically healthy human donors (2). We could demonstrate that MSC numbers barely decline with age. In contrast to that, long-term *in vitro* proliferation potential of explanted MSC was significantly diminished in cells derived from elderly donors. With advancing donor age, MSC raise the expression level of vascular cell adhesion molecule 1, also called CD106, which is also greatly boosted in response to proinflammatory stimuli. Increasing doses of interferon gamma exerted no immediate influence on the proliferative potential of MSC, but distinctly affected their respective commitment to either differentiate towards the adipogenic or osteogenic lineage. Moderately elevated levels of inflammatory stimuli support osteoblastogenesis and are thus instructive for healing processes, while excessive or chronic inflammatory insults promote adipogenic differentiation and adipose upgrowth (3). Besides this phenomenon, we also recognized large interindividual variation between MSC from different donors. Hence, instead of taking chronological donor age as a measure for MSC quality, we next defined age-matched pairs of primary MSC with largely differing proliferation potential in order to stipulate changes related to biological age. Working along this line, many genes were found to be differentially expressed with high statistical significance. Amongst others, one gene that encodes for a secreted product which can act systemically as a hormone with described functions on nerve and immune cells as well as in stress perception was further functionally tested with regard to enhancement of MSC stemness. Exogenous supplementation of the hormone to MSC cultures enhanced self-renewal of MSC and increased their proliferative capacity. Conclusively, MSC that for whatever reasons secrete more of the hormone are capable of maintaining stemness by autocrine cues. More than that, wholesomely fit MSC serve as potent systemic hubs for modulating neuronal and immunological activity.