

Age-related changes in human periosteal derived stem cells: a matter for effective bone regeneration strategies

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Possible age-related changes in Mesenchymal Stem Cells (MSCs) are of great interest in view of their use for regenerative medicine approaches also in the elderly. Considering the primary role of periosteum in bone biology and to acquire data for a cell-based therapy stimulating graft osseointegration, we tried to identify specific aging markers or pattern of expression in human periosteal precursor cells (PDPCs). To this aim periosteal tissue was obtained from differently aged healthy subjects, gender matched with a mean age of 16, 28, 63 and 92 years. Immunohistochemical detection of Ki67 and p53, Nitric Oxide (NO) production and qRT-PCR of a selected gene panel for early osteoblastic differentiation (bmp2 and runx2) and bone remodelling (IL-6, RANKL and OPG) were evaluated. Our data evidenced that both Ki67 and p53 represent striking markers of cell-cycle arrest in these cells and that their expression correlates with NO production. In addition, age affects genes involved in bone remodelling, with a significant increase in IL-6 mRNA expression as well as in RANKL/OPG ratio. As far as NO release is concerned, our data showed higher levels in PDPCs isolated from the elderly and a good correlation with the immunohistochemical analysis. Moreover, mathematical modelling, *in silico* simulations and biochemical experiments were combined to investigate about possible underlying quantitative correlations. A clear one-term exponential relationship emerged from a comparison of involved marker trends against age of donors concerning measured NO concentration / Ki67 ratio. This analytical approach confirmed Ki67 as a senescence marker to be focused on. We believe that this study, taking into account age-related changes in human PDPCs, opens up new regenerative medicine strategies for aged bone and/or bone metabolic diseases.

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Keywords

Periosteal cells; ageing; Nitric Oxide; Ki67; p53; qRT-PCR; mathematical modelling.