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Local expression of insulin-like growth factor (IGF) signaling components during *in vitro* aging of mesenchymal stem cells

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Introduction:

Impairment of the proliferation potential of mesenchymal stem cells (MSCs) may account for age-related deficiencies in bone regeneration contributing to bone-related diseases like osteoporosis. As a model for cellular aging, extended *in vitro* passaging of MSCs results in replicative senescence that is associated with IGF signaling. Therefore, we aimed here to determine the expression of IGF signaling components as well as the effect of IGF supplementation during *in vitro* aging.

Materials and Methods:

MSCs were isolated from bone marrow and incubated in standard propagation medium. Additional MSC cultures were supplemented with 2 or 6 ng/ml IGF2 to check for a possible rescue of replicative senescence. For each incubation, monolayers were passaged as soon as they reached confluence and RNA was isolated in parallel with each passaging. Gene expression levels of IGF signaling components and putatively IGF2-responsive genes were evaluated by RT-PCR.

Results:

MSC populations of eight different donors were subjected to *in vitro* aging by cultivation for 6 - 11 passages. Independent from gender, IGF2 expression continuously decreased with progression of *in vitro* aging in most of the MSC populations. The expression of putatively IGF2-responsive genes like selenoprotein P (SeP) and collagen type 1 (COL1A1) decreased with advanced passaging. Supplementation with 6 ng/ml IGF2 decreased endogenous expression of IGF2, SeP, and COL1A1 already in earlier passages and enabled extended passaging for two out of three different MSC batches.

Discussion and Conclusions:

Reproducible down-regulation of IGF2 expression and some IGF2-responsive genes during *in vitro* aging of MSCs as well as the extension of the *in vitro* life span by IGF2 supplementation suggest an important role of IGF signaling for maintenance of the self-renewal potential of MSCs. Since IGF1 and IGF2 both mainly signal via the IGF1

receptor, their combined role in this regard remains to be examined. The decrease of endogenous IGF2 expression under IGF2 supplementation indicated an autocrine negative feedback of IGF2 signaling on local IGF2 production in MSCs. Examination of further components of IGF signaling, e.g. IGF binding proteins, will provide insight into the mechanisms regulating IGF2 and IGF2-responsive genes and therefore cellular aging. Prevention of replicative senescence via modulation of the IGF signaling pathway could stimulate MSC proliferation and hence osteogenic differentiation resulting in improved bone regeneration.

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