

Bone regeneration strategies in the elderly: the role of ageing and replicative senescence in periosteal-derived stem cells

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Periosteum contains resident progenitor cells (PDPCs) representing an attractive alternative source of mesenchymal stem cells (MSCs) for skeletal tissue engineering approaches based on cell recruitment (1). Increased in life expectancy point out the necessity for customized strategies to restore bone loss due to trauma and/or disease in elderly. Aim of the present research was the evaluation of the ageing impact on PDPCs isolated from differently aged subjects. Moreover, since long-term culture could lead MSCs to senescence, the effects of culture expansion method on young PDPC through sequential serial passages were examined. Age-related increase of p53 expression and impairment in proliferating capacity were observed; those findings were strictly related to nitric oxide (NO) release. Moreover, qRT-PCR analysis showed a greater expression of genes involved in bone remodelling in elderly donors. As far as replicative in vitro expansion was concerned, we observed that later PDPC passages exhibited the typical "replicative senescence" features (i.e. flattened and enlarged morphology, prolonged population doubling time and increased SA- β gal activity). In these cells, p16 rather than p53 seemed to be involved in senescence processes. Similarly to the elderly, the decrease in proliferating ability of in vitro senescent PDPCs was concomitant with a higher NO production, and the changes in the expression of genes involved in bone resorption and RANKL/OPG ratio were superimposable. Interestingly, the relationship between NO release and ageing could represent a cutting edge "replicative senescence index" as emerged by our System Biology approach. In conclusion, our findings suggest that in vivo cell ageing and in vitro subculturing must be taken into account when testing regenerative tissue strategies that use progenitor cells. Indeed, cells (e.g. MSCs and PDPCs) from the earliest subculture passages could be useful to validate any bone tissue engineering strategies, whilst the later ones could be used to test in vitro scaffolds for regenerative medicine approaches in elderly.

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References

- [1] Roberts et al. (2015) Uncovering the periosteum for skeletal regeneration: the stem cell that lies beneath. *Bone* 70: 10-18; doi: 10.1016/j.bone.2014.08.007.

Keywords

Periosteal cells; replicative senescence; aging; NO; tissue engineering.