HUMANITAS UNIVERSITY

HUMAN GENOME AND BIOMEDICAL TECHNOLOGIES

Project title

"Dissecting the neglected link between RANKL cytokine and stemness features with high relevance in osteoporosis"

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Abstract

RANKL is a pleiotropic cytokine exerting many physiopathological functions1. In the bone tissue, it is the essential proosteoclastogenic signal. A monoclonal antibody against RANKL is used as an effective drug for diseases with excessive bone loss. In particular the first field of application was osteoporosis, a common multifactorial metabolic bone disease frequently affecting the elderlies2. In these subjects stem cell behavior may be altered in several relevant aspects: MSC are skewed towards the adipogenic at the expense of the osteogenic cell fate3 and HSC have altered myeloid and lymphoid lineage potential4. These considerations add to our recent data demonstrating a partial clonogenic and osteogenic defect in murine MSC lacking RANKL5, and preliminary results suggesting alteration of the HSC compartment. Here we aim to dissect the role of RANKL in relation to stemness features of murine and human cells, and to predict the possible impact of prolonged RANKL inhibition in this context.

Main technical approaches

i. Multicolor FACS analysis and gene expression profiling of murine HSC and progenitors in vivo.
ii. In vitro culture and transplantation assays of murine HSC and progenitor cells.
iii. Long-term co-culture of HSC and progenitors with MSC and/or MSC-derived osteoblasts.
iv. CFU and differentiation assays on Denosumab-treated human HSC and MSC.

Scientific references

1. Sobacchi C et al. The RANKL-RANK axis: a bone to thymus round trip. Front Immunol 2019 in press
2. Eastell et al. Postmenopausal osteoporosis. Nat Rev Dis Primers. 2016;2:16069.
3. Verma et al. Adipocytic proportion of bone marrow is inversely related to bone formation in osteoporosis. J Clin Pathol 2002;55:693-8.
4. Beerman et al. Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. Proc Natl Acad Sci USA 2010; 107:5465-70.
5. Schena et al. Murine Rankl-/- Mesenchymal Stromal Cells Display an Osteogenic Differentiation Defect Improved by a RANKL-Expressing Lentiviral Vector. Stem Cells 2017;35(5):1365-77.