New identification of an Estrogen Receptor alpha (ERα) variant in Mesenchymal Stem Cells

S. Niada[1,2], C. Giannasi[1,2], L.M.J. Ferreira[1,2], A. Milani[1,2], A.T. Brini[1,2]

[1]Dept. of Biomedical, Surgical and Dental Sciences, University of Milan, Milan
[2]Galeazzi Orthopaedic Institute IRCCS, Milan

Estrogens confer multiple skeletal protective effects facilitating osteogenesis and suppressing osteoclast-induced bone resorption, and it is well known that their deficiency plays a pivotal role in the pathogenesis of postmenopausal osteoporosis (Compston 2001). In particular, 17 β-estradiol (E2) plays a multifunctional role in bone, exerting its function through the interaction with estrogen receptors alpha (ERα) and beta (ERβ). We have previously studied its effects on bone precursors, i.e. mesenchymal stem cells isolated from bone marrow and adipose tissue. We identified that E2 was able to induce a significant increase in the osteogenic potential of BMSCs only. This finding pushed us to investigate a cause of the different effect of E2 on these cell types. Since ERα rather than ERβ has been reported to be more involved in MSC estrogen response, we have investigated its expression in both ASCs and BMSCs. Surprisingly, we found that while the classical ERα-66 isoform of the receptor was faintly expressed, a variant of the receptor of about 37 KDalton was abundant in both cell populations. This ER-α variant has been detected with an antibody raised against an epitope located in the C-terminal domain of the receptor, suggesting it still contains the hormone binding domain. Therefore, we investigated its modulation during E2 treatment and differentiation induction. In details, we treated MSCs with 100nM E2 for 7 days, since our previous experiments identified this concentration as the most effective in increasing the osteogenic potential of BMSCs, and then either osteo- or adipo-induced ASCs and BMSCs for additional 7 days. Interestingly, osteogenic stimuli increased the expression of ERα-37 variant of about +37% and 46% in untreated and E2 treated BMSCs, respectively, while no effect was detectable in ASCs. Moreover we also observed a drastic reduction of the variant expression when both ASCs and BMSCs were cultured in the presence of adipogenic stimuli (about -70%). In contrast, 100nM E2 treatment did not modulate the receptor expression although, just in BMSCs, it slightly counteracted the downregulation induced by adipogenic stimuli.
Recently, several studies have led to the identification of ER-α variants in both normal tissues and tumour types (Herynk 2004, Barone 2010) but, up to now, nobody ever detected this isoform in MSCs. In conclusion, we have identified for the first time the presence of an ER-α variant of about 37 KDa in MSCs, whose expression appears to be variably modulated during differentiation; however, a full characterization of this isoform will be necessary to understand its possible role in progenitor cells.

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