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Alteration of bone remodeling in multiple myeloma bone disease: role of Sclerostin

Silvia Colucci[1], Giacomina Brunetti[1], Angela Oranger[1], Giorgio Mori[2], Matteo Centonze[1], Rita Rizzi[3], Vincenzo Liso[3], Maria Grano[1]

[1] Department of Human Anatomy and Histology "Rodolfo Amprino", University of Bari, Italy
[2] Department of Biomedical Science, University of Foggia, Italy
[3] Hematology Section, Department of Pathology, University of Bari, Italy

Multiple myeloma (MM) is characterized by osteolytic bone lesions, adiacent to tumor foci within bone, that arise as a consequence of osteoblast inactivation and osteoclast activation. Canonical Wnt signaling is central to normal bone homeostasis, and secretion of Wnt signaling inhibitors by MM cells contributes to MM-related bone destruction and disease progression. In this study, we investigated the effects of MM cells on osteoblast differentiation and the potential role of Sclerostin, a Wnt signaling antagonist, in the inhibition of osteoblastogenesis in MM. In our study, we first showed that MM cells expressed Sclerostin at mRNA and protein levels. Moreover, using a co-culture system between human bone marrow stromal cells (BMSCs) and MM cells we demonstrated that MM cells induce an inhibitory effect on alkaline phosphatase, collagen I and AP-1 transcription factor expression in BMSCs. This inhibition was reverted by the addition of the anti-Sclerostin neutralizing monoclonal antibody. In the co-culture system, this antibody also partially rescued the inhibitory effect on BMSC mineralization. Moreover, knowing that the Wnt signaling activation affect the RANKL/OPG axis, we studied in our co-colture system the effect of the anti-Sclerostin monoclonal antibody on the expression of these two cytokines. In particular, we found that human MM cells up-regulated RANKL expression, but strongly down-regulated OPG production by BMSCs at mRNA and protein levels. The presence in the co-culture of the neutralizing antibody reduced RANKL and increased OPG expression. Thus, our data indicate that Sclerostin could be one of the factors inducing the uncoupling between formation and resorption in MM patients by the direct inhibition of osteoblast differentiation and the indirect stimulation of osteoclast activity.

Key words
Multiple myeloma, sclerostin, osteolysis, osteoblasts