

## Shedding LIGHT on bone cell differentiation and Multiple Myeloma-bone disease

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LIGHT/TNFSF14, a member of the tumor necrosis factor superfamily, is known to play a major role in T-cell homeostasis, whereas its effect on osteoclastogenesis is controversial. Here, we investigated LIGHT involvement in bone cell differentiation as well as in the bone-disease associated to Multiple Myeloma (MM), a plasma cell malignancies. We showed that LIGHT pro-osteoclastogenic effect can be exerted in a RANKL-independent and -dependent way. Regarding the last condition, at sub-optimal RANKL dose, the two molecules synergically increased osteoclastogenesis, due to an early and sustained Akt, NF- $\kappa$ B and JNK phosphorylation if compared with cultures treated with RANKL or LIGHT alone. Further, we found that LIGHT did not directly affect osteoblastogenesis in cultures of mesenchymal stem cells (MSCs). Conversely, LIGHT indirectly impaired osteoblasto-genesis in the co-culture of MSCs with monocytes plus T-cells, or with monocytes alone. Indeed in LIGHT treated co-cultures, we found significant lower levels of alkaline phosphatase (ALP) and Collagen-I mRNA than in untreated cultures. Surprisingly, we showed that the high sclerostin expression by monocytes can be related to LIGHT inhibitory effect on osteoblastogenesis. Regarding MM-bone disease patients, we found to express higher LIGHT levels on CD14<sup>+</sup> monocytes, CD8<sup>+</sup> T cells and CD16<sup>+</sup> neutrophils compared to the same cells from controls. Moreover, in bone marrow derived opportune cultures from MM-bone disease patients the addition of anti-LIGHT antibody dose-dependently inhibited osteoclastogenesis as well as it promoted osteoblastogenesis, as shown by the increase of CFU-OBs and by the up-regulation of Osterix, ALP, Collagen-I, Bone Sialoprotein and Osteocalcin expression. In conclusion, our data showed LIGHT involvement in bone cell differentiation and in MM-bone disease, highlighting it as a new promising target for the management of MM-bone disease and probably of other osteolytic pathologies.

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### Keywords

LIGHT / TNFSF14, Osteoclast, Osteoblast, Multiple Myeloma-bone disease.