Abstract

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Interaction between bone marrow stromal cells and neuroblastoma cells leads to a VEGFA-mediated osteoblastogenesis.

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Abstract

The potential role of osteoblasts in bone and bone marrow (BM) metastases in neuroblastoma (NBL) remains unclear. In this study, we examined the effect of NBL cells on the osteoblastic differentiation of BM-derived mesenchymal stromal cells (BMMSC). We show that the presence of NBL cells enhanced the osteoblastic differentiation of BMMSC driven by bone morphogenetic protein (BMP)-4, in the absence of any effect on NBL cell proliferation. Expression profiles of BMMSC driven toward osteoblastic differentiation revealed an increase in vascular endothelial growth factor A (Vegfa) expression in the presence of NBL cells. We demonstrated that NBL cells increased BMMSC-derived VEGFA mRNA and protein and that this was enhanced by BMP-4. However, in similar conditions, neither the addition of an mVEGFA blocking antibody nor exogenous recombinant (r) mVEGFA affected osteoblastic differentiation. In contrast, siRNA- mediated knock-down of VEGFA in BMMSC prevented osteoblastic differentiation in BMP-4-treated cocultures, an effect that was not reversed in the presence of rmVEGFA. An analysis of murine bones injected with hNBL cells revealed an increase of mVEGFA producing cells near tumor cells concomitantly with an increase in Vegfa and Runx2 mRNA. This coincided with an increase in osteoclasts, in Rankl/Opg mRNA ratio and with the formation of osteolytic lesions. Thus NBL cells promote osteoblastogenesis in the BM by increasing VEGFA expression in BMMSC. Our study provides a new insight into the role of VEGFA in NBL metastases by pointing to the role of stroma-derived intracrine VEGFA in osteoblastogenesis.

KEYWORDS: VEGFA; mesenchymal cells; neuroblastoma; osteoblastogenesis

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