Osteosarcoma (OS) is the fifth most common cancer in children. Although cytotoxic chemotherapy and improved surgical approaches have increased the overall long-term survival rate to 70%, patients with metastatic disease have a survival rate lower than 20%. The biology of OS has become the focus of recent attention, and an improved understanding could lead to new pathways of treatment. The role of parathyroid hormone receptor (PTHR1) signaling in OS has never been defined, nor indeed has that of parathyroid hormone (PTH). Our recent findings suggest that PTHR1 acts to promote tumor invasion and proliferation in OS.

Induction of OS in rats by radiophosphorus injection yielded tumors that were markedly PTH-responsive. In that study, removing the source of PTH by parathyroidectomy had no influence on any aspect of OS, but that was many years before the existence of PTHR1 was appreciated. Subsequent studies in OS cell lines from several species have established PTH responsiveness as a common, if not universal, feature of OS. PTHR1, a G-protein coupled receptor linked to adenyly cyclase, is activated by the N-terminal regions of both PTH and PTHR1. Our recent findings suggest that PTHR1 acts to promote tumor invasion and proliferation in OS.

In osteosarcoma, knockdown of the parathyroid hormone-related protein (PTHR1) receptor reduces activation through cyclic AMP-dependent protein kinase A (PKA) and substantially decreases tumor differentiation, invasion, and proliferation in vivo. These findings complement other evidence supporting a central role of the PKA pathway in osteosarcoma biology and pathogenesis.

Keywords: osteosarcoma, PTHR1, PTHrP, PKA

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activity, an OS was identified with amplification of Prkaca, which encodes the catalytic component of PKA, and Prkaca RNA was shown to be overexpressed in that tumor. It seems that enhanced PKA signaling in OS might be mediated by later events in the PKA/CREB cascade, rather than strictly being ascribed to Prkar1a as a tumor suppressor. Figure 1 illustrates changes in the PKA pathway induced through these mechanism and through PTHrP/PTHR1.

Also of interest is the observation that loss of PRKAR1A increased the production of receptor activator of nuclear factor κB ligand (RANKL) in OS, whereas upon PTHR1 knockdown the expression of RANKL decreased and that of osteoprotegerin (OPG) increased. Two aspects of RANKL biology are significant in OS. It promotes both osteoclast formation, thereby favoring tumor establishment and proliferation, and the establishment and growth of metastatic cancers in bone. Importantly, however, there are also examples of osteoclastogenesis-independent effects of RANKL: blockade of RANKL/RANK can inhibit metastasis to bone by preventing cell migration, and RANKL can promote breast cancer metastasis to bone by a pro-migratory effect through its receptor, RANK, expressed on the cancer cells. Furthermore, in OS RANKL stimulated both invasion through matrigel and anchorage-independent growth, and each of these effects was prevented by blockade of the RANKL receptor.

Taken together, these findings provide a compelling case for a role of the PTHrP→PTHR1→PKA axis in the maintenance of OS. If the driver through this axis is indeed PTHrP, manipulating this upstream target, for example through small-interfering RNA or neutralizing antibodies, could be used to regulate OS behavior.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Author Contribution Statement
The content of this manuscript was discussed with all authors. The manuscript was written by T.J.M. and C.W. and reviewed by all authors.

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