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Hedgehog-targeted therapeutics uncouple the vicious cycle of bone metastasis

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Paracrine Hedgehog (Hh) signaling, in which tumor-derived Hh ligands activate stromal cells, has been implicated in the development and progression of many cancers. Recent data suggest that Hh-targeted therapeutics exert direct effects on host cells, thus interrupting a “vicious cycle” to bone metastasis that involves osteoblasts, osteoclasts, and tumor cells.

Hedgehog (Hh) signaling is recognized to contribute to the development and progression of many cancers.¹ During embryonic development, Hh signaling is critical for proper cellular differentiation. However, the Hh pathway is largely silenced postnatally, making it an attractive anticancer target. In its resting state, the receptor Patched (PTCH) inhibits the pathway transducer Smoothed (SMO). Binding of the ligands Indian, Desert, or Sonic Hh (SHH) to PTCH releases SMO, resulting in the activation of downstream signaling (which involves GLI transcription factors) that mediates increased cellular proliferation and survival.

To date, 7 small molecule inhibitors of SMO have entered clinical trials, while compounds targeting additional components of the Hh pathway are under preclinical development.¹ As targeted therapies, SMO antagonists have demonstrated safety and efficacy in tumors with ligand-independent Hh pathway activation due to mutations in PTCH or SMO. Following these encouraging clinical results, vismodegib has been granted FDA approval for the treatment of basal cell carcinoma, although it is important to note that even responsive tumors may develop resistance.² The clinical efficacy of SMO antagonists in other tumor types remains unclear, with some trials suspended due to the absence of clinical benefit. This apparent inefficacy may be attributed to the fact that the pro-tumorigenic effects

of Hh signaling in many settings is a result of enhanced paracrine stimulation of host components, rather than of direct effects on malignant cells.

For several years, paracrine Hh signaling between tumors and stroma has been recognized to support malignant growth.³ Our recent *Cancer Research* report⁴ and those of others^{5–8} suggest that Hh-targeted therapeutics may be particularly efficient for tumors that arise within the bone (i.e., multiple myeloma, osteosarcoma) or metastasize to bones (i.e., breast, prostate and lung cancer) due to effects on host cells within this microenvironment. The bone is a preferred site of tumor growth, containing abundant growth factors such as transforming growth factor β (TGF β) and bone morphogenic proteins (BMPs) stored within the mineralized matrix and released by bone-resorbing osteoclasts (OCs). In turn, tumor-derived factors such as osteopontin, PTHrP and interleukin-6 (IL-6) deregulate bone remodeling, resulting in excessive activation of OCs generating osteolytic lesions and/or bone-forming osteoblasts (OBs) causing osteoblastic lesions. This self-perpetuating cycle of tumor growth and bone abnormalities is known as the “vicious cycle.”⁹ Similar tumor-supporting cycles involving stromal and immune cells as well as components of the extracellular matrix have also been described for tumors developing in non-bone anatomical locations.

Our data suggest that paracrine Hh signaling can increase tumor growth through direct actions on stromal cells including OCs (Fig. 1).⁴ We first demonstrated that genetic deletion or pharmacological antagonism of SMO inhibited the differentiation and bone resorption function of OCs, revealing a previously undescribed cell-autonomous role for Hh signaling in cells of the OC lineage. Conversely, mice with constitutive Hh pathway signaling due to the heterozygous loss of the inhibitory receptor PTCH (Ptch^{+/-}) exhibited increased OC activity. Further, we demonstrated that the specific enhancement of Hh signaling in host cells resulted in increased subcutaneous growth and bone-metastatic potential in Ptch^{+/-} mice, attributed to both the mesenchymal and hematopoietic compartments. Together, these data demonstrate that regulated Hh signaling is critical for normal OC maturation and function and that enhanced Hh signaling in host cells promotes tumor growth.

Downstream activating mutations or alterations that prevent the binding of SMO to PTCH render a significant portion of tumors resistant to SMO antagonists, limiting their clinical use. As such, MDA-MB-231 human breast cancer cells are resistant to direct cytotoxic effects by SMO antagonists due to undetectable SMO expression. This system allowed us to precisely examine the effects of SMO

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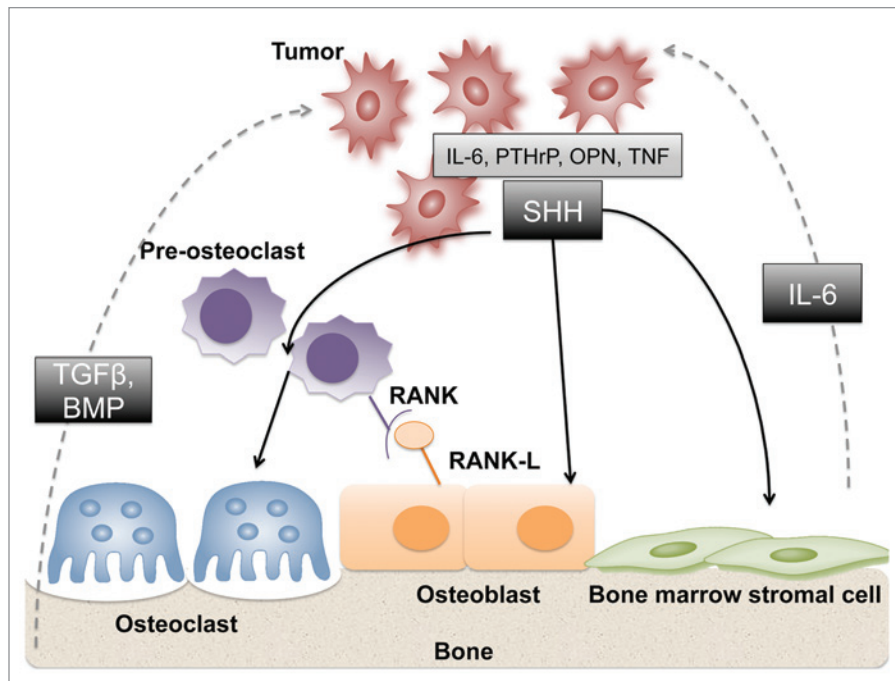


Figure 1. Tumor cell production of the Hh ligand SHH stimulates the vicious cycle of bone metastasis. Tumor-derived SHH acts in a paracrine manner to stimulate Hh signaling in host cells within the bone microenvironment. Hh signaling in bone marrow stromal cells augments production of factors that promote tumor growth including, but not limited to, interleukin-6 (IL-6). SHH also induces osteoblastic commitment. Osteoblasts express RANKL ligand (RANKL), which binds to RANK on myeloid progenitors leading to the formation of multinucleated, bone-resorbing osteoclasts. Hh signaling also exerts cell-autonomous effects on osteoclast differentiation and function. Finally, osteoclastic bone resorption releases growth factors such as transforming growth factor β (TGF β) and bone morphogenic proteins (BMPs) from the mineralized matrix, further enhancing tumor growth and survival. This creates a ‘vicious cycle’ in which tumor-derived factors such as SHH, along with other known osteolytic factors (gray box), deregulate bone remodeling (solid black lines), while stimulating the production of pro-tumorigenic factors (dashed gray lines). This self-perpetuating cycle results in increased tumor burden and bone destruction.

inhibitors on the tumor microenvironment. Interestingly, MDA-MB-231 cells express high levels of the ligand SHH, yet cannot respond to it in an autocrine fashion. We hypothesized that the production of SHH by tumor cells would promote a paracrine signaling pathway and stimulate Hh signaling in host cells. Therefore, targeting SMO specifically within stromal cells would effectively block the supply of pro-tumorigenic growth factors. Indeed, the SMO inhibitor LDE225 (which is currently being tested in Phase II clinical trials) decreased the growth of resistant MDA-MB-231 cells in vivo. We demonstrated that tumor-derived SHH induced paracrine signaling in bone marrow stromal cells, resulting in increased expression of the pro-tumorigenic

cytokine IL-6. Accordingly, knockdown of SHH in MDA-MB-231 cells resulted in decreased tumor growth in vivo. Taken together, these data provide evidence that Hh-targeted agents may offer a clinical benefit even in the context of Hh resistant tumors. In this scenario, SMO inhibitors would act on host cells, rendering them unresponsive to tumoral Hh ligands and changing the microenvironment into one that is less supportive of tumor growth.

Our data, along with that of several other groups,^{5–8} underscore the beneficial effects resulting from Hh inhibition in host cells. The Hh pathway has also been implicated in the maintenance of a “cancer stem cell” compartment, implying that Hh inhibitors may exert substantial effect specifically on this rare, long-lived

sub-population.¹⁰ Altogether, these observations suggest that the benefits of Hh inhibition may be most apparent in an adjuvant setting, in which the prevention of recurrence or metastasis follows the eradication of the primary tumor with conventional or targeted therapeutics. We propose that Hh-targeted therapeutics may be particularly attractive for the treatment and prevention of bone metastasis, as they effectively interrupt the “vicious cycle” of pro-tumor interactions between OB, OC and tumor cells. In ongoing preclinical and Phase II clinical studies, we are exploring the effects that SMO antagonists exert in preventing the survival and expansion of residual bone-marrow disseminated tumor cells (DTCs) in patients with high-risk localized breast cancer.

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