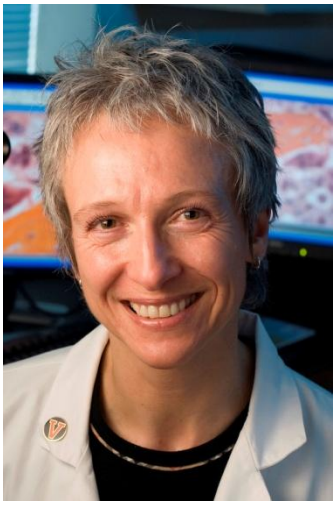
第207回　Bone Biology Seminar



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日時：平成20年6月24日（火）
17：30 ～19：30

演題：
Biology of Bone Metastases: Implications for Therapy

Bone metastases cause significant morbidity and once housed in bone, the tumors are incurable. Tumors produce factors which stimulate osteoclasts and osteoblasts to dysregulate normal bone remodeling. The bone microenvironment alters the behavior of metastatic tumor cells, driving a vicious cycle that makes skeletal metastases refractory to treatment and cure. Transforming growth factor beta (TGFβ) is a central factor in the vicious cycle. It is deposited into mineralized bone matrix by osteoblasts, is released and activated by osteoclastic bone resorption, and changes the phenotype of tumor cells.

In mouse models, TGFβ blockade inhibits osteolytic bone metastases due to breast cancer prostate cancer and melanomas by blocking tumor-produced osteolytic and prometastatic factors (PTHrP, IL-11, CTGF). It also increases bone mass, independent of effects on cancer cells, by increasing osteoblast activity and reducing osteoclast activity. These effects are potentiated with the use of a bisphosphonate, zoledronic acid.

Since the bone microenvironment is hypoxic, we tested the interaction between TGFβ and hypoxia signaling. We found that bone metastases are hypoxic and 1% O_2 increases hypoxia-inducible factor (HIF)1α in MDA-MB-231 breast cancer cells. Combined treatment with 1% O_2 and TGFβ additively increased mRNA expression and promoter activity of prometastatic factors VEGF and CXCR4, suggesting that HIF1α promotes bone metastasis via crosstalk with TGFβ. Our results show that hypoxia/HIF1α signaling promotes bone metastasis, which were inhibited when preventively HIF1α through genetic or pharmacologic approaches. Bone metastases development was further inhibited when targeting both HIF1α and TGFβ signaling. Combined targeting of HIF1α and TGFβ could treat bone metastases more effectively than single-agent interventions.

In summary, tumor bone microenvironment is rich in factors that cause cancer cells to thrive. Blockade of these factors have important implications for the skeletal health of cancer patients. The result can improve bone metastases, but may have differential effects which depend on the osteolytic or osteoblastic metastatic phenotype. Such therapy may alter bone remodeling at sites unaffected by tumor.

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