

第207回 Bone Biology Seminar



講師 : Theresa A. Guise, M.D.

Professor of Medicine

Gerald D. Aurbach Professor of Endocrinology

Department of Internal Medicine

Division of Endocrinology & Metabolism

University of Virginia

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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 (TGF β) 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, TGF β 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 TGF β and hypoxia signaling. We found that bone metastases are hypoxic and 1% O₂ increases hypoxia-inducible factor (HIF)1 α in MDA-MB-231 breast cancer cells. Combined treatment with 1% O₂ and TGF β additively increased mRNA expression and promoter activity of prometastatic factors VEGF and CXCR4, suggesting that HIF1 α promotes bone metastasis via crosstalk with TGF β . Our results show that hypoxia/HIF1 α signaling promotes bone metastasis, which were inhibited when preventively HIF1 α through genetic or pharmacologic approaches. Bone metastases development was further inhibited when targeting both HIF1 α and TGF β signaling. Combined targeting of HIF1 α and TGF β 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.

(公開講座、来聴自由)

場所 : 東京医科歯科大学

難治疾患研究所 (駿河台地区2階)

第2ゼミナール室 (参加費:無料)

第1回GCOE 海外研究者招聘講演会

東京医科歯科大学グローバルCOE プログラム

「歯と骨の分子疾患科学の国際教育研究拠点」

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問い合わせ先: 難治疾患研究所分子薬理学 野田政樹 TEL : 03-5280-8066