IRCC-QIB Seminar

International Research Collaboration Center, NINS
Quantitative and Imaging Biology

Tumor-Stromal Interactions in Breast Cancer Bone Metastasis

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Time: 12:00-13:00 (Lunch time seminar)

Date: March 3 (Fri), 2023

Place: Main Conference Room, Yamate 3rd building, 2F west wing, Yamate Campus

Abstract: During cancer metastasis, disseminated tumor cells often hijack existing physiological cellular interactions to facilitate their seeding, survival and outgrowth in distant organs. Bone metastasis is a frequent occurrence in breast cancer, causing severe complications such as fracture, bone pain, and hypercalcemia. The pathogenesis of osteolyitc bone metastasis depends on cross-communications between tumor cells and various stromal cells residing in the bone microenvironment. We used advanced imaging techniques and molecular biology approaches to prove the signaling interactions between metastatic tumor cells and various stromal cells in bone, in order to identify potential new therapeutic targets for bone metastasis. We identified Jagged1 as a TGFβ target genes in tumor cells that engaged bone stromal cells through the activation of Notch signaling to promote tumor growth and to activate osteoclast differentiation. Using mouse models, we revealed a surprising role of Jagged1 in promoting chemoresistance of bone metastasis. Chemotherapy of bone metastasis induced elevated expression of Jagged1 in osteoblasts, which provide a pro-survival niche for tumor cells in the bone. We show that an adhesion molecule E-selectin functions as an essential component of the endothelial niche for bone metastasis, wherein glycosylated E-selectin ligands expressed by metastatic breast cancer interact with endothelial E-selectin to promote metastatic seeding in bone by simultaneously inducing mesenchymal-to-epithelial transition and activation of stemness-enhancing Wnt signaling. We further found that Dact1 is induced by TGF-β signaling and forms dynamically regulated biomolecular condensates that induce Wnt suppression via sequestration of Casein Kinase 2. Induction of Dact1 by TGF-β likely contributes to the switching of bone metastasis from a Wnt-active status during initial seeding in the bone vascular niche to a TGF-β active and Wnt-suppressed stage during dormancy, outgrowth and ostelytic expansion of bone metastasis. These findings support the notion that development of organ-specific metastasis depends on the interactions between tumor cells and various stromal niche components in a given organ. Importantly, therapeutic targeting of Jagged1 and E-selectin significantly reduce bone metastasis and sensitize them to chemotherapy, suggesting possible avenues to dramatically improve the treatment of metastatic bone disease.

Additional Information:

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