**Microenvironmental IL1β promotes breast cancer metastatic colonisation   
in the bone via activation of Wnt signalling**

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**Presenter:** Yu-Hao Kuo                     **Date/Time:** 2020/9/10, 16:10-17:00

**Commentator:** Hung-Chi Cheng, Ph.D.             **Location:** Room 601, Med College Building

**Background**

In breast cancer, dissemination of tumor cells to the bone marrow is an early event, however cells may lie dormant for many years before bone metastases develop. The current treatment of bone metastases is not curative, thus new adjuvant therapies which prevent the disseminated tumor cells (DTCs) into metastatic lesions are required. There is evidence that a small subset of cancer stem cells (CSCs) with an aggressive phenotype are capable of undergoing metastasis. However, it is still not clear about the colonisation of disseminated CSCs aiding by microenvironmental factors after reaching the bone marrow. Recently, IL1β has been proposed as an important cytokine for metastasis. However, the mechanism of IL1β promoting metastasis has not yet been defined, limiting the use of inhibitors for anti-metastasis therapy.

**Objective/Hypothesis**

In order to determine the mechanism of IL1β’s contribution to metastatic growth and provide the inhibitors for anti-metastasis therapy.

**Results**

 Conditioned media from normal bone marrow cultured for 5–17 weeks (termed CM) significantly increased CSC colony formation and mammosphere self-renewal; however it did not induce migration. In cell lines and PDX models, the bone microenvironment specifically induced breast CSCs to form colonies following arrival. Furthermore, CSC colony formation in bone marrow was mediated by Wnt signaling. Besides, high expression of Wnt signalling in tumors had poor prognosis. Then, by cytokine arrays, the authors found that it was IL1β to promote Wnt-dependent breast CSC colony formation. Luciferase reporting for the NFκB and CREB pathways were increased after IL1β treatment, which meant that CREB and NFκB were important cellular pathways downstream of IL1β and upstream of Wnt signalling. Finally, the authors tested that systemic inhibition of either IL1β or Wnt signaling could prevent bone metastasis.

**Conclusion**

IL1β promotes the ability of breast CSCs to form colonies through activation of NFKB and CREB signalling, inducing Wnt ligand secretion and autocrine Wnt signalling in breast cancer cells. Furthermore, inhibition of this pathway prevents both metastasis of breast cancer cells to bone *in vivo*, and CSC colony formation in the bone environment *in vitro*, which means inhibiting IL1β-NFKB/CREB-Wnt signalling can be an important adjuvant therapeutic strategy in bone metastases.

**References**

1. Hosseini, H. et al. Early dissemination seeds metastasis in breast cancer. *Nature*, (2016).
2. Husemann, Y. et al. Systemic spread is an early step in breast cancer. *Cancer Cell* 13, 58–68 (2008).