DKK1 determines organotropism of breast cancer metastasis by regulating microenvironments

Supported by the National Natural Science Foundation of China, a collaborative study by the laboratories of Dr. Hu Guohong (**胡国宏**) from Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences and Dr. Yang Qifeng (**杨其峰**) from Shangdong University demonstrates that Dickkopf1 (DKK1) dictates breast cancer organ-specific metastasis by differentially regulating microenvironmental components, which was published in *Nature Cell Biology* (2017, 19: 1274—1285).

Metastasis is the leading cause of breast cancer mortality. The metastasis of breast cancer demonstrates a feature of organ-specificity, which means cancers from different patients show distinct preference of metastatic target organs. Though it is wildly observed that the most commonly visited target organs by breast cancer is the bone and lungs, the underpinning selective mechanism is still under-investigated, impeding the precise prediction of metastasis organ-tropism and the development of targeted therapeutic intervention.

The teams led by Dr. Hu and Dr. Yang discovered that the Wnt signaling inhibitor DKK1 played a key role in the decision of organ-specificity in breast cancer metastasis. Cancer cells with high levels of secreted DKK1 were prone to bone metastasis while low levels of DKK1 were correlated with lung metastasis. In lungs, DKK1 suppressed cancer cell metastatic colonization by inhibition of non-canonical Wnt signaling, which in turn alleviated myeloid cell recruitment and the bioavailability of TGFβ by cancer cells. In bone metastasis, DKK1 enhanced osteolytic colonization by suppressing canonical Wnt signaling pathway in osteoblasts. In pre-clinical trials, the administration of canonical Wnt signaling inhibitor marginally constrained lung metastasis but exacerbated bone metastasis. Alternatively, combinatory therapy against non-canonical Wnt downstream signaling pathways effectively mitigated both lung and bone metastasis.

In all, this discovery proved the existence of a Janus-faced club of genes with opposite functions in organ-specific metastasis of breast cancer, revealing the importance of microenvironmental modulation of metastatic colonization and the potential side effect of targeting canonical Wnt signaling. Moreover, the effective combinatory administration of non-canonical Wnt signaling inhibitors indicated a new therapeutic strategy against multi-metastasis in late-stage breast cancer patients.

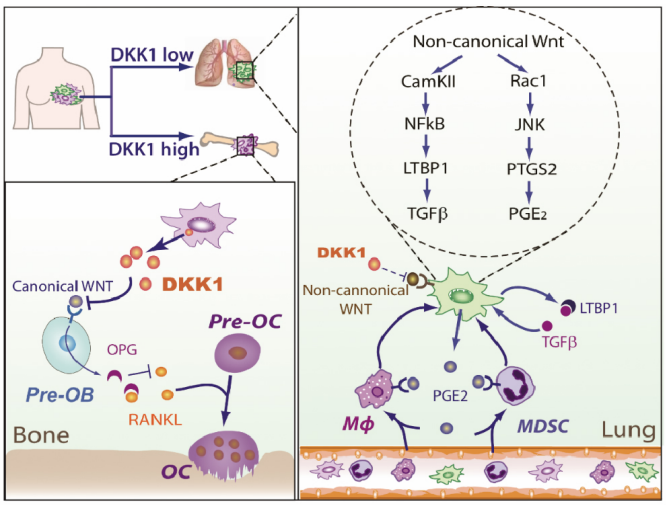

Figure The dichotomous roles of DKK1 in breast cancer organotropic metastasis.