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The Role for GALNT14 in the lung metastasis of breast cancer

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Original article

Ki-Hoon Song (2016) “GALNT14 potentiates organ-specific metastasis of breast cancer to the lung by mediating metastasis initiation and progression”
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Abstract

Aberrant expression of polypeptide N-acetyl-galactosaminyltransferases (GALNTs) has been associated with cancer, but their function(s) in metastasis remains elusive. Recently, we have identified GALNT14, one of the O-GalNAc glycosylation-initiating enzymes, as a prognostic marker for pulmonary relapses in breast cancer patients. Furthermore, we showed that GALNT14 promotes lung metastasis by novel mechanisms: 1) enhancing metastasis initiation by inhibiting anti-metastatic effect of BMPs produced from lung stroma, 2) exploiting growth signals (e.g., FGFs) supplied by macrophages for their growth into macrometastases in the lung environment. These multi-faceted roles of GALNT14 in lung metastasis are achieved by GALNT14-mediated inhibition and activation of BMP and FGF signaling pathways, respectively. The link among GALNT14, its downstream pathways and lung metastasis provides us with an opportunity to develop effective therapeutic intervention for breast cancer.

Cancer metastasis is a multi-step process including invasion, intravasation (entering bloodstream), survival in circulation, extravasation, and formation of new colonies in distant organs. While molecular mechanisms involved in early stages of metastatic process have been extensively studied, those governing later stages of metastasis such as formation of micro- and macro-metastases remain to be further investigated. In order to form micro and macro-metastases, cancer cells must not only overcome anti-metastatic signals present in the secondary organ but also exploit growth signals provided by stromal components of the destination organ. Thus, cancer cells with organ-tropic metastatic abilities exhibit distinct cellular properties. Supporting this, it has been shown that organ-specific metastatic cells have differential gene expression profiles.

Glycosylation is one of the common post-translational modifications and known to regulate stability and activities of various secreted molecules as well as cell surface receptors. Glycosylation can generally be categorized into 5 groups including N-linked and O-linked glycosylation. While glycan groups are attached to the Asp or Arg, O-glycosylation takes place in Ser, Thr or Tyr residues of the target proteins. O-glycosylation has been shown to regulate several cellular processes such as development, immune response, metabolism as well as homeostasis. In addition, several diseases have been associated with deregulated O-glycosylation.

N-acetyl galactosaminyl transferases (GALNTs) are enzymes that transfer N-acetyl galactosamine (GalNAc) group to the target proteins and 20 GALNT family members have been identified in human. GALNTs are shown to be involved in normal cellular process and its dysregulation is linked to and disease states such as cancer. The studies on GALNTs in cancer have mostly been focused on their roles in the early stages of metastasis including cancer cell growth and motility. On the other hand, function of GALNTs in the later stages of metastasis, which involves the interaction between incoming cancer cells and a microenvironment of the destination organ is unclear.

Our recent study (Song et al (2016) : Nat Commun. 7:13796. doi: 10.1038/ncomms13796.) has identified GALNT14 as a critical regulator in promoting breast cancer metastasis to the lung. By analyzing publically available microarray data, we found that GALNT14 expression is strongly associated with the risk of developing lung metastasis in breast cancer patients. This clinical analysis was

supported by xenograft assays, which demonstrated GALNT14 promotes lung metastasis in a catalytic activity-dependent manner.

Furthermore, we found two mechanisms underlying GALNT14-mediated pulmonary metastasis of breast cancer. Firstly, GALNT14 enables breast cancer cells to overcome anti-metastatic signals secreted by the lung. It has been shown that BMPs function as anti-metastatic signals in the lung and lung metastatic breast cancer cells must overcome their inhibitory effect. We found that GALNT14 blocks the anti-metastatic effect of BMPs by O-GalNAcylation of BMP receptor 1A (ALK3) in breast cancer cells. As a consequence, GALNT14-expressing breast cancer cells can initiate metastatic colonies in the lung microenvironment. ‘

Secondly, we showed that GALNT14 allows breast cancer cells to create a favorable microenvironment and exploit growth signals provided by lung environment. Specifically, our study suggested that GALNT14-expressing breast cancer cells recruit macrophages into the site of metastases by promoting CXCL1 production. Furthermore, we showed that once macrophages are recruited, breast cancer cells use macrophage-derived FGFs for their growth and that GALNT14 promotes this process by O-GalNAcylation of FGF receptors in breast cancer cells.

In conclusion, our study have provided experimental evidence supporting the roles of GALNT14 in lung metastasis of breast cancer and suggested GALNT14 as a potential therapeutic target for breast cancer treatment.

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