

Perspective

Role of GALNT14 in lung metastasis of breast cancer

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Aberrant expression of the polypeptide N-acetyl-galactosaminyltransferase (GALNTs) has been associated with cancer, but their function(s) in metastasis remains elusive. We have recently identified GALNT14, one of the O-GalNAc glycosylation-initiating enzymes, as a prognostic marker for pulmonary relapse in breast cancer patients. Furthermore, we showed that GALNT14 promotes lung metastasis by the following novel mechanisms: 1) enhancing metastasis initiation by inhibiting the anti-metastatic effect of BMP produced from the lung stroma, 2) exploiting growth signals (e.g. FGF) 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 the 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. [BMB Reports 2017; 50(5): 233-234]

Cancer metastasis is a multi-step process, which includes invasion, intravasation (entering bloodstream), survival in circulation, extravasation, and formation of new colonies in distant organs. While molecular mechanisms involved in the early stages of metastatic process have been extensively studied, those governing the later stages, such as formation of micro- and macro-metastases, remain to be further investigated. In order to form micro and macro-metastases,

cancer cells need to overcome the anti-metastatic signals present in the secondary organ, and also exploit growth signals provided by stromal components of the destination organ. Thus, the cancer cells with organ-tropic metastatic abilities exhibit distinct cellular properties. Corroborating this, it has been shown that organ-specific metastatic cells have differential gene expression profiles.

Glycosylation is a common post-translational modification known to regulate stability and activities of various secreted molecules, as well as cell surface receptors. Glycosylation is generally categorized into 5 groups, including N-linked and O-linked glycosylation. While glycan groups are attached to the Asn or Arg in N-linked glycosylation, O-glycosylation takes place at the Ser, Thr or Tyr residues of the target proteins. O-glycosylation regulates 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 galactosaminyltransferases (GALNTs) are enzymes that transfer the N-acetyl galactosamine (GalNAc) group to the target proteins. So far, 20 GALNT family members have been identified in humans. GALNTs are involved in the normal cellular processes, and its dysregulation is linked to various 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, the 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) 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

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<https://doi.org/10.5483/BMBRep.2017.50.5.055>

Received 28 March 2017

Keywords: Breast cancer metastasis, GALNT14, Microenvironment, O-GalNAcylation

Abbreviations: GALNT14, polypeptide N-acetyl-galactosaminyl-transferase; BMP, Bone morphogenetic protein; FGF, Fibroblast growth factor

Perspective to: Ki-Hoon Song (2016) GALNT14 promotes lung-specific breast cancer metastasis by modulating self-renewal and interaction with the lung microenvironment. Nat Commun. 7:13796. doi: 10.1038/ncomms13796.

lung metastatic breast cancer cells need to overcome their inhibitory effect. We found that GALNT14 blocks the anti-metastatic effect of BMPs by O-GalNAcylation of the BMP receptor 1A (ALK3) in breast cancer cells. As a consequence, GALNT14-expressing breast cancer cells efficiently 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 the lung environment. Specifically, our study suggested that GALNT14-expressing breast cancer cells recruit macrophages to the site of metastases. Furthermore, we showed that once macrophages are recruited, the breast cancer cells use macrophage-derived FGFs for their growth, and GALNT14 promotes this process by O-GalNAcylation of the FGF receptors in breast cancer cells.

In conclusion, our studies provide experimental evidence supporting the roles of GALNT14 in lung metastasis of breast cancer and suggest GALNT14 as a potential therapeutic target for breast cancer treatment.

ACKNOWLEDGEMENTS

This work was partially supported by KAIST Institute for the BioCentury, Cancer Metastasis Control Center (N11160071), the Intelligent Synthetic Biology Center of Global Frontier Project funded by the Ministry of Science, ICT and Future Planning (2011-0031955), the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2011-0020334, 2012-M3A9C705175, and NRF-2016M3A9B4915818).