

**Curebound Discovery Spring 2022**

**Role of histidine phosphorylation in breast cancer invasion**

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**Scientific Abstract:**

Breast cancer (BCa) is a heterogeneous disease that can be divided into five different subtypes. Triple-negative breast cancer (TNBC) is the most aggressive subtype with no targeted therapy available, highlighting the need to identify new therapeutic targets in biologically relevant pathways in TNBC to improve patient survival. Phosphohistidine (pHis) is an emerging post-translational modification that is shown to play a functional role in cancers, such as liver cancer, where loss of the pHis phosphatase LHPP has been observed, and neuroblastoma where the NME1 His kinase is overexpressed. Whether LHPP phosphatase activity is involved in other cancer types remains to be elucidated. Overexpression of NME1/2 through its histidine kinase activity suppresses migration of breast cancer cells, and NME1 is poorly expressed in human invasive breast cancer tissue. In human breast tumors, the TNBC subtype exhibited higher levels of LHPP protein compared to the other subtypes. However, the molecular mechanism underlying the LHPP phosphatase activity in BCa cell metastasis remains to be determined. Here, we hypothesize that LHPP phosphatase activity, in conjunction with NME1, could impact TNBC invasion by promoting the formation of invasion structures (invadosomes), which have an essential role in metastasis. Therefore, we will determine if NME1 and LHPP localize and play a role in invadosome formation and function, identify their target pHis proteins through proteomic analysis in human breast cancer cell lines, and explore their spatial distribution in human breast cancer samples through immunostaining. Moreover, inhibition of invadopodia-mediated matrix degradation would be an effective way to block tumor invasion.

**Lay Abstract:**

Breast cancer is the most common type of cancer amongst women in the world with 684,996 deaths in 2020. This underscores the importance of developing new cancer therapies. In the last three decades, the addition of a phosphate (a process called phosphorylation) to certain proteins has been the focus of intensive efforts to create new cancer therapeutics. Phosphorylation can occur at 9 different amino acids in proteins. However, phosphorylation of only 3 of these 9 amino acids has been explored in efforts to develop cancer treatments. Phosphorylation of histidine (pHis), one of the neglected modifications, has recently been discovered to be relevant in liver cancer, but whether pHis is important in other types of cancer has yet to be examined in depth. Proteins that donate phosphates (kinases) to proteins or that remove phosphates (phosphatases) from phosphoproteins play essential roles in regulating phosphorylation of proteins to change their signaling activities. Previous studies showed that a histidine kinase called NME1 suppresses invasion to other tissues (metastasis) in breast cancer. Furthermore, our research has shown that a pHis phosphatase called LHPP is present at higher levels in triple-negative breast cancer (TNBC), which has the worst prognosis, and currently lacks an effective treatment. Combining cutting-edge molecular biology, cell biology and genetic techniques, we will investigate if pHis, the His kinase NME1 and the pHis phosphatase LHPP are important for breast cancer metastasis, aiming to identify key protein targets that are regulated by

histidine phosphorylation.