Regulation of EGFR signaling by SEPT9_v1 in inflammatory and triple-negative breast cancers

Inflammatory breast cancer (IBC) is the most aggressive and lethal form of breast cancer. IBC accounts for 10,000 new cases of breast cancer each year and it is responsible for 4,000 deaths from this disease in USA.[1] IBC is a very aggressive type of breast cancer with distinct characteristics that make it hard to diagnose and treat as compared to other breast cancer subtypes[1]. Due to its fast development, aggressive spread and lack of effective targeted therapies, it has the worst prognosis compared to other breast cancer subtypes. This calls for more research in the area, most importantly at the molecular level aiming to advance treatment options. It has been found that about 50% of patients with IBC overexpress the epidermal growth factor receptor (EGFR)[1]. This receptor is a transmembrane protein activated by specific ligands. Upon EGFR activation, many downstream effectors proteins are stimulated and can elicit different cellular functions including cell proliferation, survival, migration and remodeling of the cytoskeleton. SEPT9 is part of a family of cytoskeletal proteins that was recently found to interact with EGFR. In addition, SEPT9 was found to stabilized EGFR in the membrane by downregulating its degradation.[2] Importantly, SEPT9 isoforms dysregulation has been found to be associated with the development of pro-oncogenic phenotypes and tumorigenesis in models of breast cancer.[1,3,4] However, the molecular mechanisms responsible for the cell biological functions of SEPT9 remains to be fully elucidated. Thus, SEPT9 interaction with EGFR provides the first link of SEPT9 molecular function to a cell biology process in IBC. Because of this, we will explore the possible pro-oncogenic role of SEPT9 isoforms, particularly SEPT9_v1, in Inflammatory Breast Cancer. Our hypothesis is that the SEPT9_v1 isoform contributes to oncogenesis partially due to regulation of the ErbB receptors family in IBC. Thus, the functional relationship between SEPT9_v1 and EGFR will be evaluated in two different IBC cell lines SUM149, SUM190 and triple negative breast cancer (TNBC) cells. The goal is twofold, to determine if SEPT9_v1 isoform interacts and regulate EGFR activation and second to characterize which downstream effectors proteins are affected by this interaction. This study will help us to characterize further the molecular signature of IBC and to identify new potential therapeutic targets for the better management of this form of breast cancer.

[1] Kleer, C.G., K.L. van Golen, and S.D. Merajver, Molecular biology of breast cancer metastasis. Inflammatory breast cancer: clinical syndrome and molecular determinants. Breast Cancer Res, 2000. 2(6): p. 423-9.

[2] Gonzalez, M. E., Peterson, E. A., Privette, L. M., Loffreda-Wren, J. L., Kalikin, L. M., & Petty, E. M. (2007). High SEPT9_v1 expression in human breast cancer cells is associated with oncogenic phenotypes. *Cancer Research*, *67*(18), 8554-8564.

[3] Gonzalez, M. E., Makarova, O., Peterson, E. A., Privette, L. M., & Petty, E. M. (2009). Up-regulation of SEPT9_v1 stabilizes c-Jun-N-Terminal Kinase and contributes to its pro-proliferative activity in mammary epithelial cells. *Cellular Signalling*, *21*(4), 477–487. http://doi.org/10.1016/j.cellsig.2008.11.007

[4] Diesenberg, K., Beerbaum, M., Fink, U., Schmieder, P., & Krauss, M. (2015). SEPT9 negatively regulates ubiquitin-dependent downregulation of EGFR. *J Cell Sci*, *128*(2), 397-407.