A Novel Function of EGFR in Epigenetic Modulation via hMOF in Breast Cancer

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Public Abstract:

The epidermal growth factor receptor (EGFR) is aberrantly active in breast cancer, initiates and drives tumorigenic pathways, and has been implicated in multiple tumorigenic processes including hyperplasia, chemo-resistance and metastasis. Overexpression of EGFR is frequently linked to more aggressive tumor behavior. In particular, breast cancer patients that carry high EGFR expression survived poorly compared to those with little or no expression. Therefore, EGFR has been considered as an excellent target of anticancer therapy. Histone lysine modifications directly influence activation and repression of transcription. One example of histone lysine modification is acetylation, which is controlled by histone deacetylases (HDACs) and histone acetyltransferases. MYST family acetyltransferase, human males absent on the first (hMOF), plays an important role in transcription activity through histone H4K16 acetylation. Loss of hMOF and subsequently the absence of H4K16 acetylation have been shown to be a common feature in human cancer including breast cancer. Therefore, we hypothesize that hMOF plays an important role in breast cancer development and progression. However, the regulation of hMOF remains largely unknown. Recently, we and other groups have discovered the acetylation of EGFR in human breast cancer cells and porcine endothelial cells (Sorkin, A. and colleagues). We screened a set of EGFR-interacting acetyltransferases and found that EGFR directly interacts with and phosphorylates hMOF. Based on these interesting findings and existing literatures, we hypothesized that EGFR modulates histone acetylation status phosphorylating hMOF. The ultimate goal of this proposal is to understand the mechanism of EGFR-mediated hMOF regulation and further develop a rational strategy for breast cancer therapy. To this end, we proposed the following three Specific Aims: (1) To elucidate a functional change of EGFR-induced tyrosine phosphorylation of hMOF. (2) To identify target genes regulated by EGFR/hMOF/H4K16Ac axis and analyze the epigenetic changes of these genes. (3) To validate EGFR/hMOF/H4K16Ac axis in in vivo model and determine the clinical relevance of EGFR/hMOF/H4K16Ac axis in breast cancer. We anticipate our study of EGFR and hMOF to be of therapeutic relevance, possibly leading to novel discovery in drug development targeting the receptor tyrosine kinase and the acetylation process. Overall, I am very excited about this project because it carries an enormous potential for identification of new molecular regulators of breast cancer metastasis. I hope we will be able to expand our understanding of how EGFR modulates histone medication via hMOF and develop new strategies for improving the quality of life and the overall survival of breast cancer patients.