

Epigenetic Mechanisms Contributions to ERBB2 Positive Breast Cancer Development

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Breast cancer is the most common cancer among American women. According to American Cancer Society, there are about 231,840 new cases of invasive breast cancer will be diagnosed and about 40,290 women will die from breast cancer in 2015. ERBB2 gene amplification or overexpression occurs in 20-30% of breast cancer and such ERBB2 positive breast cancers are often associated with poor prognosis. Since ERBB2 plays critical roles in tumorigenesis, and resistance of radio- and endocrine therapy in breast cancer (Bca) patients. Many therapeutics targeting ERBB2 were developed, such as Trastuzumab or Lapatinib, and these therapeutics have shown clinical efficacy.

However, many tumors are resistant either *de novo* or following therapy. Long term exposure to antibodies and chemotherapies would change the genetic modifications of tumor cells and induce dramatic changes of gene expressions. These years, epigenetic mechanisms have emerged to play important roles in cancer development and drug resistance. DNA methylation on special sites could be used as clinical markers to predict cancer subtype and potential drug resistance phenotype. Chromatin regulators and non-coding RNAs have been increasingly targeted in developing cancer therapies. For example, targeting of the bromo domain and extra terminal domain (BET) protein by the inhibitor JQ1 has been shown to antagonize the proliferation of multiple myeloma cells, and to do so by repressing c-Myc and its downstream effectors. Similarly, targeting the histone demethylase KDM4 family member, NCDM-32B has been effective in reducing the cell proliferation and transformation in breast cancer. Thus, to understand the underlying epigenetic mechanisms, specifically, to identify novel druggable epigenetic factors, may provide a great opportunity to develop novel therapeutics in therapy resistant tumors involving ERBB2.

Epigenetic mechanisms play essential roles in cancers and are being targeted for cancer therapy. However, such mechanisms in ERBB2 signaling are largely unknown. Histone demethylase PHF8 (PhD finger protein 8) was discovered in 2010 and it serves as a transcription co-activator by demethylating H3K9me2 (di-methylated histone 3 lysine 9), H3K9me1, H3K27me2 and H4K20me1. PHF8 is overexpressed in prostate cancer, esophageal squamous cell carcinoma and lung cancer,

and has been proposed to contribute to cell proliferation and migration in these cancers. Although several papers have predicted PHF8 playing a role in breast cancer, and previous study of our lab found PHF8 protein level was significantly upregulated in breast cancer, the functions of PHF8 in breast cancers are not known.

Could PHF8 play a role in rapid growing of ERBB2 positive breast cancer cells? Histone modifier PHF8 plays co-activator role by demethylating several methylated histones including H4K20me1 (mono-methylated histone 4 lysine 20), which is critical for cell cycle progression, transcriptional regulation and genomic stability. We recently identified c-MYC/microRNAs/PHF8 regulatory axis, in which c-MYC upregulates PHF8 via repressing PHF8-targeting microRNAs. The axis involving miRs mediate the regulation of PHF8 in Bca cells and TGF- β induced EMT (Epithelial to Mesenchymal transition). Based on the essential function of MYC in ERBB2 signaling and the inverse correlation between these miRs and ERBB2, we hypothesize that ERBB2 regulates PHF8 through AKT/MYC/miRs axis. Moreover, we also found that positive correlation of PHF8 protein levels with ERBB2 status in hundreds of Bca samples and PHF8 is critical for the anchorage independent growth of ERBB2 amplified cells, the proliferation and EMT drive by ERBB2 in normal cells. Moreover, ERBB2 downstream signaling was affected by PHF8 inhibition in ERBB2 amplified cells. Furthermore, we found that ERBB2 therapeutics induces upregulation of PHF8 in drug sensitive and resistant ERBB2 positive cells. Thus, our central hypothesis is that PHF8 is upregulated by ERBB2/AKT/MYC/microRNAs axis and contributes to ERBB2-driven Bca development and anti- ERBB2 therapy resistance.

So our goal is to test this hypothesis and address these challenges by interrogating the role of novel epigenetic mechanisms in the tumor development and therapy resistance involving ERBB2. To establish the roles of histone demethylase PHF8 in tumorigenic functions of ERBB2 signaling and therapeutics resistance would help people understanding epigenetic mechanism underlying ERBB2 breast cancer development. Ultimately, such knowledge has the potential to confer PHF8 as a novel therapeutic target in cancers where ERBB2 plays a role.

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