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Abstract 1973: HER2 promotes super enhancer formation in breast cancer

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Abstract

Background. HER2 positive (HER2+) breast cancer (BCa) occurs in 25-30% of cases and is associated with an aggressive phenotype. Multiple HER2-stimulated pathways are known but the genes that are specifically controlled by HER2 are poorly understood. We previously used RNA polymerase II (POL II) immunoprecipitation (ChIP) to identify 737 genes that bind POL II in HER2+ but not in HER2- BCa cell lines. 51 of these genes were differentially expressed in a HER2+ dependent manner and 113 genes were differentially expressed in a HER2-dependent manner in breast tumors from 812 patients. The 113 genes are not differentially expressed in cell lines but expressed in BCa cases can be considered “poised” for expression, and activated when in the context of a breast tumor.

Methods. The 737 genes were examined using pathway finding tools and the MIT database for Super-enhancers and the dbSUPER database (2). The expression of certain genes in attached cell cultures and in mammosphere cultures were examined by qPCR.

Results. Some of the 113 genes that are “poised” for expression in cell lines in a HER2-dependent manner, and then expressed in breast cancers in a HER2-dependent manner, encode proteins that commonly occur in Super-enhancers, which are a variety of DNA regulatory structures formed by looping that associate multiple bound transcription and DNA-modifying factors in proximity to target promoters. Examples include Mediator12 (MED12) and the Bromdomain protein 2 (BRD2), and DNA binding factors such as HDAC and CREB1-cofactors. Moreover, many pluripotency genes are also found in the list of 113 genes; NANOG, OCT3/4, and SOX2 (NOS genes). These genes commonly interact with SEs as associated factors and as targets. We confirmed by qPCR that the three NOS genes exhibit increased expression in mammosphere of HER2+ MCF7 cells but not in control cells.

Using the MIT and dbSUPER (2) database we determined that 70 genes of the 113 genes (62%) that are located in or near SEs, including some present in the HER2+ BCa cell line HCC1954. Similarly, 33 (65%) of the 51 differentially expressed genes in HER2+ cell lines were associated with SEs in many diverse cell types. For comparison, the class of 573 genes that are bound to POL II in HER2+ cell lines, but are not differentially expressed in cell lines or breast cancer tissues, have a much lower fraction of genes, 213 or 37%, that encode potential members or targets of SE. The difference is highly significant, $p = 0.008$.

Pathway analyses of the 113 genes indicates that major pathways enriched in these genes ($p < 0.001$) include EGFR and Map Kinase signaling, notch pathway signaling, hedgehog, Wnt, Integrin-mediated cell and cytokine signaling Interleukin 1 and Interleukin 14.

Conclusion. These results suggest that the pathways associated with HER2 over-expression in BCa include genes associated with Super-enhancer assembly, as well as many genes encoded close to the location of Super-enhancers.

1.Rahmatpanah et al,. (2015) Oncotarget

2. Aziz Khan, Nucleic Acids Res., 2015

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