Epigenomic analysis of primary breast cancer tumors reveals novel tumor cell vulnerabilities and therapeutic targets

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Abstract

To date, a large portion of cancer research has focused on somatic mutations in protein coding regions to identify putative oncogenic drivers. Here, we have investigated the roles of genomic non-coding regions in defining oncogenic cell state drivers and pinpointing novel druggable targets. Abnormally large clusters of cis-acting enhancers, called super-enhancers (SEs), have emerged as regulatory features of oncogenes and other key tumor drivers in cancer cells. Mapping these features through H3K27ac ChIP-seq in primary patient samples and linking them to protein-coding genes provides an inroads to identify new therapeutic targets in cancer.

We have analyzed 43 primary breast cancer patient samples using H3K27ac ChIP-seq to map enhancers and SEs genome-wide. We find that these SE maps pinpoint known oncogenic drivers and recapitulate established clinical subgroups. Most samples classified as HER2+ contain a SE at the HER2 locus, most samples classified as ER+ contain a SE at the ERβ1 locus while neither tend to appear in TNBC samples. These findings strengthen the hypothesis that SE analysis can be used to discover breast cancer dependencies de novo, independent of somatic mutations. In order to validate novel targets that were revealed by SEs in primary patient samples, we used both CRISPR-mediated gene ablation as well as chemical validation in a panel of cell lines that either exhibit or do not exhibit the gene-associated SEs. Using the chemical validation approach, we identified a SE at the RARA locus that predicts sensitivity to a potent RARα agonist SY1425 in a panel of breast cancer cell lines. The sensitivity of these cell lines to SY1425 is correlated with enhancer size, identifying RARA as an enhancer-correlated vulnerability in breast cancer. We show that this correlation extends to in vivo xenograft models. Using the CRISPR-mediated validation approach, we discovered a number of novel targets that were identified by their association with SEs in primary samples and then validated in a panel of breast cancer cell lines.

Together, these studies indicate that super-enhancer analysis in primary patient samples can be used to define new biomarker-linked breast cancer vulnerabilities for therapeutic intervention.

Methodology: Super-enhancers (SEs) define key cancer drivers

Super-enhancer (SE) analysis of breast cancer tumors

SE analysis reveals key tumor dependencies in clinical subtypes

SE analysis reveals epigenomically defined subtype-selective patient subgroups

CRISPR-mediated validation of target genes

Overview: CRISPR-mediated ablation of SE-linked target genes

CRISPR-mediated transcript gain in breast cancer cell models

Novel breast cancer targets linked to patient enhancers

Gene essentially across breast cancer cell lines

SPDEF is a SE-correlated dependency gene

SPDEF is differentially occupied by SEs in patient tumors

RARA is a SE-associated target gene with subtype selective prevalence

ARARA is associated with a SE in some primary breast cancer samples

An immediately actionable enhancer-linked target: RARα

Model of RARα-mediated transcriptional control of differentiation and proliferation

SY1425 (Tamboglitane) is a potent and selective RARα agonist

RARα agonist SY1425 inhibits tumor cell proliferation

SY1425 anti-proliferative effect is highly dependent on RARα enhancer strength

CRISPR-mediated transcript gain in breast cancer cell models

Conclusions

- Super-enhancer analysis reveals both SE-linked novel drug targets and novel patient subtypes for existing drugs in breast cancer
- SE analysis in primary breast cancer samples revealed at least 14 potential new drug targets in TNBC, including 8 enzymes, 2 surface receptors, 1 signaling protein and 1 metabolism protein
- The RARα agonist SY1425 induces an anti-proliferative response in RARα-SE breast high cancer cell lines and slows tumor growth in RARA/high (not RARA-low) PDX models of breast cancer
- The use of a patient-selection biomarker, effectiveness of SY1425 in preclinical models of breast cancer, and prior human experience of SY1425 may provide a new therapeutic approach for breast cancer patients

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