Breast Cancer

Major finding: The 1q21.3 amplification can be detected in cfDNA from most patients with recurrent breast cancer.

Mechanism: 1q21.3 harbors S100A7/8/9 which promote IRAK1 phosphorylation and cell growth.

Impact: 1q21.3 amplification may serve as a biomarker of recurrence and confer sensitivity to IRAK inhibitors.

CHROMOSOME 1q21.3 AMPLIFICATION IS LINKED TO BREAST CANCER RECURRENTCE

In patients with breast cancer, biomarkers are needed to determine which patients are at high risk of recurrence. A better understanding of the molecular drivers of tumor recurrence may lead to the identification of biomarkers and development of targeted therapies. Using integrative genomic analyses Goh, Feng, Wang, and colleagues found that a 1q21.3 chromosomal amplification is enriched in tumor-initiating cells and associated with recurrent tumors in breast cancer. The 1q21.3 amplification was present in both ER+ and ER− tumors and, although the amplification was present in approximately 10% to 30% of primary tumors, it occurred in more than 70% of recurrent tumors. Droplet digital PCR was able to detect the 1q21.3 amplification in cfDNA from patient blood, with a sensitivity of 93.3% and a specificity of 97.5%, suggesting the feasibility of a liquid biopsy to identify patients with breast cancer with a high risk of recurrence. The 1q21.3 locus encodes members of the S100A calcium binding protein gene family, which act upstream of Toll-like receptor signaling to activate IRAK-NFκB. Accordingly, S100A7, S100A8, and S100A9 were upregulated in 1q21.3-amplified breast cancer cells, and their depletion reduced IRAK1 phosphorylation and cell growth in tumorspheres. Conversely, IRAK1 depletion downregulated S100A8/9, indicating a reciprocal regulation. In 18 of 25 sets of paired primary and recurrent breast tumors, IRAK1 phosphorylation and S100A8 expression were elevated in the recurrent samples. Further, 1q21.3 amplified cells were sensitive to the JAK2 inhibitor pacritinib, which has also been reported to inhibit IRAK1, both in vitro and in vivo. Moreover, in mice pacritinib was effective and well tolerated in combination with chemotherapy. Altogether, these findings suggest that 1q21.3 amplification may serve as a biomarker to identify patients with breast cancer at risk of recurrence and identify IRAK1 as a potential therapeutic target in these tumors, supporting further investigation of IRAK inhibitors, such as pacritinib, in breast cancer.


Drug Discovery

Major finding: A virtual ligand screen led to generation of A-485, a potent selective p300/CBP catalytic inhibitor.

Mechanism: A-485 competes with acetyl-CoA for p300/CBP active site binding to inhibit H3K27 and H3K18 acetylation.

Impact: Targeting p300/CBP may be effective in some transcription-driven malignancies.

INHIBITION OF p300/CBP SUPPRESSES CASTRATION-RESISTANT PROSTATE CANCER

The paralogous histone acetyltransferases (HAT) p300 and CREB-binding protein (CBP) are transcriptional coactivators that have been implicated in cancer. However, selective potent inhibitors of p300 and CBP have not been developed, although the tool compound C6-46 has suggested the potential for therapeutic targeting of HATs in cancer. To identify small-molecule inhibitors of p300/CBP, Lasko, Jakob, and colleagues conducted a virtual ligand screen of 800,000 compounds in silico and evaluated 1,300 commercially available compounds in a direct radioactive p300/CBP HAT assay. Hydantoin emerged as a compound class and further optimization yielded A-485, a selective small-molecule inhibitor that was at least 1,000-fold more potent than C6-46 in inhibiting p300. Determination of the X-ray crystal structure of the p300 HAT domain in complex with A-485 at 1.95 Å demonstrated that A-485 competed with acetyl coenzyme A (acetyl-CoA) for binding to the catalytic active site of p300. A-485 reduced acetylation of H3K27 and H3K18, but not H3K9, in prostate cancer cells, indicating a specificity for p300/CBP over other HATs. Further, A-485 suppressed proliferation of a number of cancer cell lines, including multiple myeloma, acute myeloid leukemia, and non-Hodgkin lymphoma. Most solid tumor cell lines were less sensitive, but A-485 potently suppressed the growth of androgen receptor (AR)-positive, but not AR-negative, prostate cancer cell lines. The A-485-mediated reduction in H3K27Ac deposition led to a reduction in AR transcriptional activity. In vitro, A-485 suppressed the growth of AR-positive castration-resistant prostate cancer xenografts. In addition to developing a highly potent and selective p300/CBP small-molecule inhibitor, these findings suggest that inhibitors of HAT catalytic activity may have antitumor activity in multiple tumor types including AR-positive castration-resistant prostate cancer.


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Chromosome 1q21.3 Amplification Is Linked to Breast Cancer Recurrence

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