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Breast Cancer

Major Finding: Estrogen receptor (ER) ligands' antagonism is dictated by their effects on intranuclear ER mobility.

Mechanism: Full ER antagonists immobilize ER and prevent ER-mediated increases in chromatin accessibility.

Impact: Screening for modulators of transcription factor mobility may be a useful avenue for drug discovery.

EFFECTS ON ESTROGEN RECEPTOR MOBILITY UNDERLIE ANTAGONIST ACTIVITY

The estrogen receptor (ER)–targeting agent tamoxifen's active metabolite, 4-OHT, competes with estrogen (E2) for ER's ligand binding domain (LBD), accounting for its therapeutic efficacy in ER$^+$ breast cancer. However, 4-OHT also weakly activates ER's N-terminal activation function 1 (AF1) domain, prompting a search for drugs that fully antagonize ER. Conventional wisdom is that ER degradation is a marker of strong antagonism, but Guan, Zhou, and colleagues found that ER degradation was not a reliable predictor in a study of six drugs and drug candidates. The effects of ER antagonists on the LBD did not determine their effects on cell proliferation, consistent with previous observations that the AF1 domain is also important for ER signaling. Each drug or drug candidate predicted to antagonize ER based on ER degradation altered the transcriptional profiles of cancer cell lines in distinct ways, with some activating canonical ER target genes normally induced by E2. In mice, greater transcriptional suppression of ER was associated with more powerful antitumor effects of ER antagonists. Contrary to the hypothesis that the reason the strong ER antagonists fulvestrant and GDC-0927 lack the weak ER-agonist activity of drugs like tamoxifen is that they prevent ER's binding to certain DNA sites, all E2-competitive ligands tested induced ER binding to canonical sites. Hinting at an alternative mechanism, fulvestrant and GDC-0927 binding had only a small impact on chromatin accessibility, whereas E2 and 4-OHT increased accessibility at ER binding sites. Live-cell imaging revealed that only the full antagonists fulvestrant and GDC-0927 uniquely immobilized ER by slowing intranuclear diffusion, and this immobilization dictated antagonism and ER turnover. Collectively, these results not only suggest that ER degradation capability alone should not be used as a proxy for ER antagonism, but also provide proof-of-concept that therapeutics targeting transcription-factor dynamics may be worth investigating. ■

Guan J, Zhou W, Hafner M, Blake RA, Chalouni C, Chen IP, et al. Therapeutic ligands antagonize estrogen receptor function by impairing its mobility. Cell 2019;178:949–63.e18.

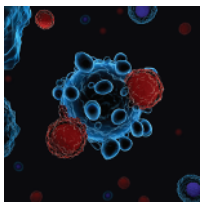
Immunotherapy

Major finding: Combining CAR-T cells with amph-ligand vaccination enhances CAR-T proliferation and activation *in vivo*.

Mechanism: Amph-ligands traffic to the LNs and insert in the membrane of APCs to boost CAR-T cell activation.

Impact: Vaccination with amph-ligands may improve the efficacy of CAR-T cell therapy.

AMPH-LIGAND VACCINE ENHANCES CAR-T CELL ACTIVITY AGAINST SOLID TUMORS



Chimeric antigen receptor-T (CAR-T) therapy specific to CD19 has shown clinical response in patients with B-cell malignancies. However, developing CAR-T therapy for solid tumors has been a challenge. To improve CAR-T efficacy in solid tumors, Ma and colleagues used a vaccination approach based on a recently developed method to link peptide antigens to albumin-binding phospholipid polymers. Binding of the amphiphile peptide (also called amph-ligand) to endogenous albumin enabled trafficking to the lymph nodes (LN), where it was inserted to the membrane of antigen-presenting cells (APC) and promoted activation and proliferation of CAR-T cells. First, fluorescein isothiocyanate (FITC)–conjugated peptide (amph-FITC) and anti-FITC CAR-T cells were used as a proof of concept to show the trafficking of amph-FITC to the draining LN, membrane binding, and proliferation of CAR-T cells *in vivo*. Blockade of a panel of costimulatory molecules expressed on APCs inhibited both proliferation and functional cytokine release of CAR-T cells *in vivo*. Next, a *bona fide* tumor antigen-specific CAR-T that targets EGFRvIII, in combination with amph-pepvIII (also called amph-vax) vaccination, was used in a tumor model of glioma cells expressing EGFRvIII. Treatment with EGFRvIII–CAR-T in combination with repeated amph-vax boosting significantly delayed tumor growth and prolonged survival, and surviving animals rejected tumor rechallenge. Rechallenge with parental cells that do not express EGFRvIII was also rejected, suggesting amph-vax activates endogenous T-cell responses against other tumor-derived antigens. Inclusion of both CD28 and 41BB domains further improved tumor control and increased survival when combined with amph-vax boosting. Lastly, a bispecific CAR platform was constructed by fusing anti–amph-ligand and a CAR targeting a tumor-derived antigen. Amph-ligand boosting improved the efficacy of the bispecific CAR-T cells in several models with low toxicity. Together, these results suggest a new vaccination approach to increase the efficacy of CAR-T cell therapy for solid tumors. ■

Ma L, Dichwalkar T, Chang JYH, Cossette B, Garafola D, Zhang AQ, et al. Enhanced CAR-T cell activity against solid tumors by vaccine boosting through the chimeric receptor. Science 2019;365:162–8.

AACR American Association for Cancer Research

CANCER DISCOVERY

Effects on Estrogen Receptor Mobility Underlie Antagonist Activity

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