Spotlight

By Caroline Seydel

Promising New Target in Drug-Resistant Breast Cancer

Yotsumoto et al.
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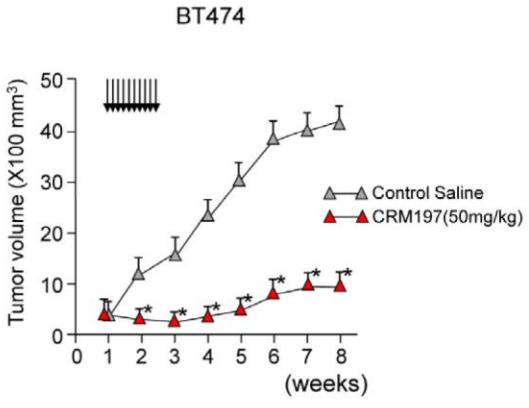
Breast cancer comes in many forms, some easier to treat than others. Yotsumoto, *et al.* investigated a potential target for treating certain drug-resistant types of breast cancer. They found that the difficult tumors expressed a particular ligand, HB-EGF, and that inhibiting that ligand could help fight the tumors.

Many aggressive breast tumors involve increased HER2 protein, and the drug trastuzumab inhibits the growth of these tumors by blocking the HER2 receptor. It works great – except that most patients develop resistance within a year. Previous work suggests that AKT signaling contributes to trastuzumab resistance; it also seems to be involved with so-called "triple-negative" breast cancers (TNBC), which carry no receptors for estrogen, progesterone, or HER2, making them hard to treat. Thus, researchers fervently seek new methods for beating back these drug-resistant tumors. One ligand emerging as a key player in cancer growth is the heparin binding epidermal growth factor (HB-EGF).

To pin down HB-EGF's role in TNBC and trastuzumab-resistant cancers, the team tested a compound, derived from the diphtheria toxin, that blocks HB-EGF. Treatment with the blocker stopped triple-negative cells from forming tumors and spurred trastuzumab-resistant cells to apoptosis. They also found that upping the HB-EGF induced AKT activation, while blocking HB-EGF thwarted AKT. The loop mediated by AKT and HB-EGF, which appears to foster more aggressive tumor behavior, can thus be broken using the modified diphtheria toxin that blocks HB-EGF. Developing HB-EGF inhibitors would seem a promising new approach for defeating these slippery cancers.



HB-EGF as a target molecule in trastuzumab-resistant breast cancer.

Weekly alterations in the tumor growth of BT474 or MCF7-HER2 cells in NOD/SCID mice (n=8). CRM197 (50 mg/kg) was injected intraperitoneally every day for 10 days after the tumor volume exceeded 100 mm^3. The data represent the means ± SD of the volumes in the 8 mice. *P<0.05, versus the tumor volume in nude mice without CRM197 treatment.