HER2's outside help

By Lev Osherovich, Senior Writer

An international team has found that neurokinin 1 substance P receptor, a known player in nausea, pain and inflammation, enhances HER2 signaling in breast cancer.¹ The findings argue for combining antagonists against both receptors to treat cancer.

HER2 (EGFR2; ErbB2; neu) is a receptor tyrosine kinase (RTK) that promotes aggressive tumor growth in about 30% of breast cancers.

Four HER2 inhibitors and anti-HER2 mAbs are marketed for breast cancer, non-small cell lung cancer (NSCLC) and gastric cancer, and at least a dozen more are in Phase II and Phase III testing for a range of solid tumors.

Efforts to target HER2 and related receptors in the epidermal growth factor receptor (EGFR) family traditionally have focused on preventing receptor dimerization and kinase activation. However,

recent studies in cell culture and animals have pointed to an additional path to EGFR activation.

Cell culture studies have shown that HER2 and other EGFRs can be activated by a variety of GPCRs including protease-activated receptor 1 (PAR1),² KISS1 receptor (KISS1R; GPR54)³ and angiotensin II type 1 receptor (AGTR1).⁴

Now, a team led by Vanessa Almendro, group leader at the

Hospital Clinic of Barcelona and visiting scientist at the Dana-Farber Cancer Institute, has found that HER2 can be activated *in vivo* by another GPCR—neurokinin 1 substance P receptor (TACR1).

HER2 too

Last year, Almendro's team found that blocking substance P, the principal ligand of TACR1, reduced HER2⁺ breast cancer growth *in vitro*.⁵ In the new study, the team showed that TACR1 is responsible for substance P's effect on HER2 activity.

Almendro's team found that *TACR1* was overexpressed in 94% of 318 HER2⁻ and HER2⁺ patient-derived breast tumor samples. HER2⁺ tumors had even higher *TACR1* expression than HER2⁻ tumors.

In vitro, HER2⁺ tumor cells showed more rapid HER2 phosphorylation and activation upon treatment with substance P than untreated cells. Likewise, forced overexpression of *TACR1* increased HER2 signaling in tumor cells and small interfering RNA knockdown

or pharmacological inhibition of TACR1 decreased HER2 activation compared with what was seen in wild-type controls.

Pharmacological inhibition of TACR1 reduced growth of HER2⁺ but not HER2⁻ tumors in a mouse xenograft model of breast cancer.

Almendro told SciBX that she suspects chronic activation of TACR1 leads to upregulation of HER2, feeding tumor growth and reducing the efficacy of HER2 inhibitors. Indeed, cultured HER2⁺ cells chronically exposed to substance P had higher levels of HER2 and lower response to three small molecule HER2 inhibitors than untreated cells.

"Substance P and other signals that activate HER2 are likely to contribute to resistance to treatment," said Almendro.

The team did not examine how TACR1 activation affected response to HER2 mAbs.

Results were reported in *Cancer Research*.

Mechanism to therapy

Almendro's finding is the most clear-cut example to date for cross-activation of EGFR family members by GPCRs in cancer. Nevertheless, mechanistic questions remain about precisely how TACR1 and other GPCRs contribute to tumor growth.

One hypothesis is that GPCRs like TACR1 have distinct functions beside their normal role of turning on downstream G proteins. Binding to EGFR-family proteins could be one such function.

"GPCRs could act apart from their G proteins to interact with EGFRs and hijack their signaling," said Walter Thomas, a professor and chair of general physiology and head of the School of Biomedical Sciences at The University of Queensland.

Thomas noted that although previous cell culture studies have implicated other GPCRs in tumor growth, it has been difficult to draw a clear connection between specific EGFR-family proteins and GPCRs because of the complex downstream effects of modulating GPCR pathways.

"It's pretty definitive that knocking down *TACR1* causes loss of growth-promoting signaling by substance P," said Thomas. "This is good evidence of a direct link between HER2 and TACR1."

Last month, Thomas' team reported a genetic screen that identified a slew of downstream signaling components involved in the activation of EGFR signaling by AGTR1.⁶

Almendro favors the idea that TACR1 recruits other kinases to the plasma membrane, leading to phosphorylation and activation of HER2. She noted that substance P increased phosphorylation of HER2 by Src, an intracellular kinase that contributes to HER2 activation. She thinks that TACR1's ability to recruit Src to HER2 could contribute to resistance to conventional HER2 inhibitors.

"Pharmacological inhibitors of HER2 inhibit kinase activity, but they don't affect activation of other kinases like Src, which binds to HER2's cytoplasmic tail via TACR1," said Almendro.

For now, Thomas thinks that the best therapeutic prospects lie in combining HER2 inhibitors with TACR1 antagonists. He said that the ideal candidate would block TACR1's ability to interact with HER2 but would not interfere with TACR1's other functions in the nervous system.

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The University of Queensland

“This is an area for biased ligands,” said Thomas. “There may be distinct steps that affect HER2 activation that could be selectively modulated independently of other downstream effects.”

Without a side-by-side comparison in xenograft tumor models, it is not clear which—if any—existing TACR1 antagonist would be best suited to becoming a cancer therapeutic.

Merck & Co. Inc. markets the TACR1 antagonist Emend fosaprepitant dimeglumine to treat chemotherapy-induced nausea and vomiting (CINV). Three other TACR1 inhibitors are in Phase III testing for CINV, and at least five TACR1 inhibitors are in Phase I and II testing for a range of neurological and dermatological indications.

Almendo said that blocking TACR1 signaling may have the additional benefit of reducing pain and inflammation around tumors, and she is now conducting experiments to explore this in mouse models of breast, colon and prostate cancer, in which substance P levels are known to be elevated.

Although Almendo's current study focused on TACR1's direct effect on HER2, she nonetheless thinks that blocking substance P with antibodies will be more effective than inhibiting TACR1.

She said that there are at least two other receptors of substance P that are not likely to be affected by TACR1 inhibitors, so blocking TACR1 may not be enough, even in combination with HER2 inhibitors.

Almendo has been granted an EU patent on the use of antibodies against substance P for use in cancer. Negotiations with an undisclosed pharma to license that patent are ongoing.

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