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LGR5 is a biomarker for stratification of HER-2 positive breast cancer patients and personalized treatment

Chan Chen [a], Cheng Zhang [b], Jun-Mei Xu [a,*], Yong Han [c,*]

[a] Department of Anesthesiology, Second Xiangya Hospital, Central South University, Anesthesiology Research Institute, Central South University, Changsha, Hunan, China
[b] Key Laboratory of Carcinogenesis and Translational Research Ministry of Education, Department of Biochemistry and Molecular Biology, Peking University Cancer Hospital & Institute, Beijing, China
[c] Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, United States

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ABSTRACT

VEGFR and HER2 are both important transmembrane proteins associated with several types of cancer. Overexpression of these 2 proteins had long been thought to contribute to cancer progression and poor outcomes, thus, therapies targeting HER-2 and VEGFA signaling pathways have been applied in recent years.

Herceptin is a HER-2 targeted antibody that being widely used for the management of HER-2 positive breast cancer, which demonstrate significant benefits in both the metastatic and adjuvant settings. However, acquired resistance develops in most treated patients despite treatment in as early as 10 months. Identification of subpopulations best suited for and most likely to respond to Herceptin is of utmost importance. We analyzed the signaling pathways of HER-2 and found that HER-2 shares a very similar downstream network with VEGFA, while LGR5 lies in the upstream of VEGFA and could promotes its expression through CTNNB1. This discovery suggests that the LGR5 directed VEGFA overexpression may activate downstream signals of HER-2 despite Herceptin treatment.

Here, we hypothesized that in LGR5 overexpressing breast cancer cases, activation of VEGFA-VRGFR bypass may account for the resistance to HER-2 directed therapies. Concurrent inhibition of VEGFR might enhance Herceptin sensitivity and moreover reverse the resistant phenotype in HER-2 positive breast cancer. Thus, we proposed alternate regimens to increase the efficacy of Herceptin-based therapy. Nevertheless, wet lab experiments and clinical trials are still required.

Introduction

HER2 and Herceptin

Human epidermal growth factor receptors (HER) belong to a transmembrane protein family, which share an extracellular ligand-binding domain, a short transmembrane domain, and an intracellular domain with tyrosine kinase activity. Activation of these receptors initiates signal cascades that involved in several phenotypes of cancer cell, including proliferation, differentiation, adhesion, migration and apoptosis [1]. HER-2, a critical HER family member, whose expression has been proved to be correlated with several types of human cancer, is a promising target for individualized treatment.

Herceptin is a HER-2 specific antibody being used in targeted therapies for the management of patients with HER-2 positive metastatic breast cancer and gastric cancer [2]. As a recombinant human antibody that directly binding to the extracellular domain of HER-2/neu protein, Herceptin is engineered by integrating the murine antibody's complementary determining regions with the scaffold of human IgG1. The binding of Herceptin to HER-2 blocks the dimerization of HER-2 with other HER-family members, which leads to the repression of downstream signal cascades [2,3].

About LGR5

The leucine-rich repeat containing G protein-coupled receptor 5 (LGR5), also known as GPR49, is a seven-transmembrane receptor and has been highlighted as an exquisite marker of wnt-regulated

Abbreviations: AKT, v-akt murine thymoma viral oncogene; CTNNB1, catenin (cadherin-associated protein), beta 1; HER-2, v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; IgG1, immunoglobulin G 1; LGR5, leucine-rich repeat containing G protein-coupled receptor 5; MAPK, mitogen-activated protein kinase; P27, cyclin-dependent kinase inhibitor 1B (p27, Kip1); PI3K, phosphoinositide-3-kinase; PTEN, phosphatase and tensin homolog; RER, rough endoplasmic reticulum; VEGFA, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor.

* Corresponding authors. Tel./fax: +86 73185295970 (J.-M. Xu). Address: Department of Biostatistics and Computational Biology, 11th Floor, 3 Blakfan Circle, Dana-Farber Cancer Institute, Boston, MA, United States. Tel.: +86 617 632 3012; fax: +86 617 632 2444 (Y. Han).

E-mail addresses: doctorjmxu@gmail.com (J.-M. Xu), Yong@jimmy.harvard.edu (Y. Han).

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cancer stem cells and adult stem cell populations in tissues such as intestine, stomach and hair-follicle [4]. Recent studies show that LGR5 plays a critical role in tumor progression and is associated with poor outcomes [5–8]. It is expressed downstream of Hedgehog signaling and could promotes cell proliferation and tumor formation in cases of basal cell carcinoma [9]. Studies also revealed that LGR5 is a receptor of R-Spondin (RSPO) [10,11] and could promote RSPO mediated wnt/beta-catenin and wnt/PCP signaling [12], which may lead to the Epithelial-Mesenchymal Transition (EMT) and in turn confers primary resistance to Herceptin [13–15]. Besides, the activation of wnt/beta-catenin signaling pathway might promote angiogenesis and therapeutic resistance by up-regulating VEGFA [16].

Disadvantages of present Herceptin regimens

Herceptin has been approved for clinical application for about a decade. However, there are 2 typical mechanisms through which Herceptin resistance could arise. The first is that Herceptin exhibits a low sensitivity: the response rate for HER-2 positive patient was only 30%, indicating a strong heterogeneity. This heterogenic resistance appears to correlate with the loss of nuclear expression or phosphorylation-induced repression of the cyclin-dependent kinase inhibitor, p27 [17], and further studies also revealed a more common relevance with inactivation of the tumor suppressor PTEN [18,19].

Another bad news is that even for breast cancer patients who achieve an initial therapeutic response to Herceptin, the majority of those would show disease progression within 1 year. Since acquired resistance develops in such high frequency, identification of the scenarios in which Herceptin resistance could arise remains a critical goal. Among the reasons that lead to Herceptin resistance, abnormal activation of downstream signaling pathways is the most important one. Thus, our efforts were dedicated to this area.

Our discoveries and hypothesis

By data mining from KEGG pathway database [20], we discovered an interesting phenomenon: HER-2 shares a very similar downstream signal cascades with VEGFA (Figs. 1 and 2). Long been recognized as an important angiogenesis-inducing factor, it is quite possible that VEGFA–VEGFR pathway parallelize and interplay with HER-2 signaling pathways in caner progression. This means if VEGFA–VEGFR bypass is activated, cancer would keep progressing and show no clinical response even when HER-2 pathway was blocked by Herceptin. Conversely, HER-2 may also play the same role as VEGFA–VEGFR does.

Further analysis shows that LGR5 lies in the upstream of VEGFA and could enhance VEGFA expression by stabilizing CTNNB1 [16,21] (Fig. 2), raising the possibility that VEGFA–VEGFR bypass is activated in patients with LGR5 overexpression and this activation may play a hostile role against Herceptin's efficacy. Besides, LGR5 might also promote Herceptin resistance through wnt-EMT signaling pathway [13–15]. These discoveries suggest that LGR5 could be used as a predictive marker for Herceptin resistance and help direct therapies.

Suggested regimens

New therapeutic options for patients whose tumors have become refractory to HER-2 directed therapy is one of the key challenges facing physicians today. In light of the potential of VEGFA–VEGFR signaling bypass in Herceptin's antitumor action, we propose 2 improved regimens for HER-2 positive breast/gastric cancer: for HER-2 positive and LGR5 overexpression patients, both LGR5 activated VEGFA–VEGFR bypass and HER-2 could promote cancer progression through the same downstream signaling pathways, therefore, a combination therapy is a necessity. Considering the drug-specific resistance of CTNNB1 and VEGFA (Fig. 3), we suggest applying Herceptin in combination with two other chemo-

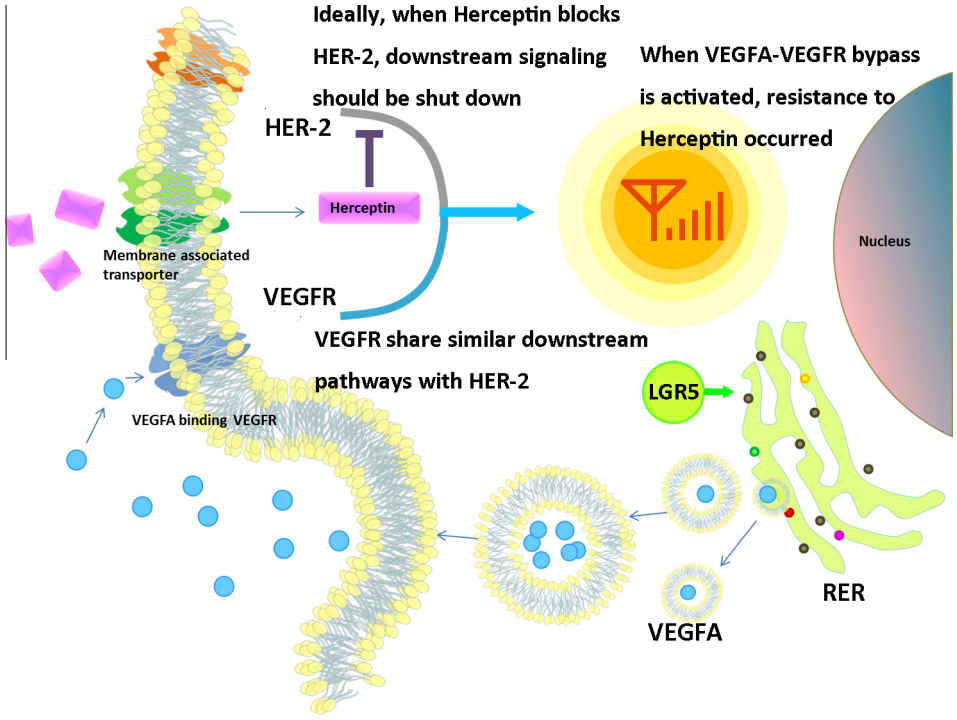

Fig. 1. Key concepts of our hypothesis. High expression of HER-2 promotes cancer progression through downstream signaling pathways. Ideally, when Herceptin blocks HER-2, downstream signals should be shut down, which would lead to clinical response. However, bioinformatics analysis indicates that HER-2 shares several critical downstream signaling pathways with VEGFA, which means high expression of VEGFA could still activate those downstream pathways, even when HER-2 was blocked by Herceptin. This might account for Herceptin resistances. Since LGR5 can up-regulate the expression of VEGFA, the overexpression of LGR5 may play a hostile role against Herceptin's efficacy.