

Preview

Mutant HER2 needs mutant HER3 to be an effective oncogene

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Hanker et al. reveal that co-occurring missense mutations in the human epidermal growth factor receptor 2 (HER2) and its catalytically inactive homolog HER3 synergize to promote oncogenic signaling by the HER2/HER3 complex.

The human epidermal growth factor receptors 2 (HER2) receptor gained its notoriety as an oncogenic driver of approximately a quarter of breast cancers in which its gene amplification leads to the accumulation of HER2 at levels 2-20-fold higher than those found in non-cancerous tissues.¹ HER2 hyperactivation is a hallmark of these cancers and renders them susceptible to HER2-targeted therapies. A number of breast cancers harbor HER2 missense mutations in the absence of *HER2* amplification.² These single amino acid substitutions are often moderately transforming on their own and only ~30% of metastatic cancers containing HER2 mutations respond to the HER2 kinase inhibitor neratinib.³ This suggests that in these tumors mutant HER2 cooperates with other oncogenes to drive tumorigenesis. Hanker and colleagues have previously found that HER2 mutations frequently co-occur with mutations in HER3.⁴ Cancers with these composite mutations have a poor response to the HER2-targeted small molecule inhibitor neratinib.^{3,5} The recent study by Hanker et al. sheds light on the molecular mechanisms of the co-dependence between HER2 and HER3 mutations in driving oncogenesis.⁶

HER2 and HER3 are closely related receptor tyrosine kinases (RTKs) that assemble into an active heterodimer upon binding to neuregulin (NRG) growth factors.⁷ The orphan receptor HER2 cannot undergo efficient homodimeriza-

tion and activation and is thus dependent on formation of heterodimeric complexes with other HER receptors. NRG-bound HER3 is a preferred dimerization partner of HER2.⁸ HER3 is an odd receptor itself because it lacks significant catalytic activity. While itself inactive, the HER3 pseudokinase plays an important role in the catalytic activation of the HER2 kinase within the HER2/HER3 kinase heterodimer.⁹ The HER2/HER3 complex robustly activates the PI3K/Akt pathway by recruiting PI3K to the phosphorylated tail of HER3 (Figure 1).

HER3 signaling is an obligatory aspect of oncogenesis in HER2-amplified breast tumors in which HER2/HER3 complexes are thought to stochastically form due to receptor crowding.⁷ However, co-occurring mutant HER2 and HER3 are found in tumors in the absence of HER2 amplification. Using molecular dynamics (MD) simulations, Hanker et al. show that the most common HER3 kinase domain mutation E928G, located at the active kinase dimer interface, significantly stabilizes the HER2/HER3 kinase dimer. This observation is consistent with the effect of the HER3 E928G on dimerization between HER3 and EGFR kinases.⁹ Hanker et al. show using MD simulations that HER2 mutations that co-occur with HER3 E928G lower the free energy barrier between the inactive and active HER2 kinase conformations.⁶ In EGFR, disease mutations that shift the equilibrium to an active kinase conformation promote receptor

dimerization.¹⁰ Thus HER2 mutations likely contribute to the stabilization of the active HER2/HER3 kinase heterodimers through a similar mechanism.

Using a spectrum of cell signaling and cell invasion assays, Hanker and colleagues provide evidence that the synergy between HER2 and HER3 mutations is essential to generate a sufficiently strong signal to transform cells in a growth factor-independent manner. The full extent of downstream signaling via the PI3K/Akt pathway is achieved only in the presence of both mutant HER2 and mutant HER3 as measured by invasive growth in 3D Matrigel cultures. Hanker and colleagues then investigate if the limited efficacy of neratinib in treating patients harboring HER2 mutations might be due to co-occurring HER3 mutations. They show that indeed neratinib is particularly ineffective when selected missense HER2 mutations co-occur with HER3 mutations. Based on MD simulations, they postulate that the dimerization of the HER2 kinase mutants with the HER3 E928G mutant increases the ATP binding affinity of HER2, which consequently interferes with neratinib binding.

A new vulnerability of cells co-expressing selected HER2 and HER3 mutants is their reliance on PI3K/Akt signaling, which makes them sensitive to a combination treatment with neratinib and PI3K inhibitors. Thus, an important conclusion of this study is the demonstration that mutant HER3 modulates the therapeutic



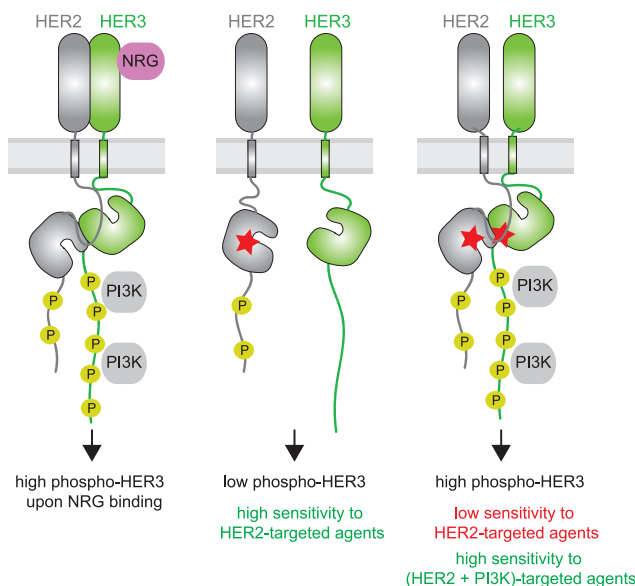


Figure 1. Co-occurring gain-of-function mutations in HER2 and HER3 promote their dimerization resulting in kinase activation and conferring resistance to HER2-targeting agents

Left, upon neuregulin (NRG) growth factor stimulation, HER2 and HER3 assemble into an active hetero-complex that is required for HER3 phosphorylation and efficient activation of the PI3K/AKT pathway. *Middle*, oncogenic HER2 missense mutations discussed by Hanker and colleagues shift equilibrium toward the active conformation of the HER2 kinase but are ineffective in driving formation of the stable complexes of mutant HER2 with wild-type HER3 in the absence of NRG. In this scenario, sensitivity to HER2-targeted agents is maintained. *Right*, co-occurring mutations in HER2 and HER3 receptors drive NRG-independent receptor association (only kinase domain mutations are depicted here), resulting in robust HER3 phosphorylation and activation of the PI3K/Akt pathway. This leads to cellular transformation, invasiveness, and resistance to HER2-targeted therapeutics, such as neratinib. Combination of HER2-targeted agents with PI3K inhibitors is effective in blocking oncogenic signaling in the presence of the composite HER2 and HER3 mutations.

efficacy of HER2-targeted agents in patients harboring HER2 mutations. Yet again, HER3 is identified as an important vulnerability of HER2 oncogenic signaling. This study reinforces the need for developing HER2/HER3-specific therapeutics and the importance of assessing HER3 mutational status in evaluating the efficacy of HER2-targeted therapies.

DECLARATION OF INTERESTS

N.J. is a member of the SAB and a shareholder of Turning Point Therapeutics, SUDO Biosciences, and Type6 Therapeutics. The Jura laboratory has received sponsored research support from Genentech. Other authors do not declare competing interests.

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