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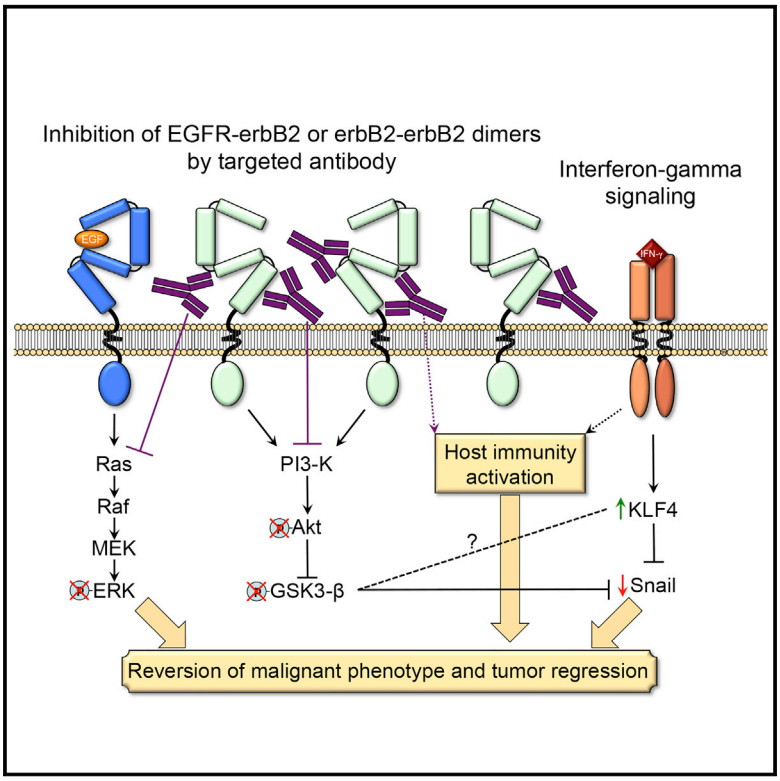
Disabling of the erbB Pathway Followed by IFN-γ Modifies Phenotype and Enhances Genotoxic Eradication of Breast Tumors

Graphical Abstract



Highlights

- IFN-γ and 4D5 act directly on erbB2-positive breast cancer cells
- IFN-γ, but not IFN-α or β, cooperates with 4D5 directly on erbB2+ breast cancer cells
- IFN-γ and 4D5 alters KLF4 levels and degrades Snail by the GSK3-β/proteasome pathway
- Sequential combination treatment with mAb and IFN-γ sensitizes for tumor eradication

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In Brief

Targeting erbB2-driven tumors with mAb-based targeted therapy benefits patient outcome in breast cancer; however, virtually all responders eventually relapse. Nagai et al. find that IFN-γ administration with an anti-erbB2 mAb inhibits certain intrinsic tumor-signaling pathways, limits transformed phenotypic properties, and induces host tumor immunity.

Nagai et al., 2015, Cell Reports *12*, 2049–2059
September 29, 2015 ©2015 The Authors
http://dx.doi.org/10.1016/j.celrep.2015.08.044

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Disabling of the erbB Pathway Followed by IFN-γ Modifies Phenotype and Enhances Genotoxic Eradication of Breast Tumors

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http://dx.doi.org/10.1016/j.celrep.2015.08.044
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SUMMARY

Reversion of the malignant phenotype of erbB2-transformed cells can be driven by anti-erbB2/neu monoclonal antibodies (mAbs), which disrupt the receptor's kinase activity. We examined the biologic effects of IFN-γ alone or after anti-erbB2/neu mAb treatment of erbB2-positive cells. IFN-γ had no effect on its own. Treatment of the tumors with anti-erbB2/neu mAbs followed by IFN-γ led to dramatic inhibition of tumor growth in vitro and in vivo with minimal mAb dosing. Sequential therapy enhanced the effects of chemotherapy. Moreover, IFN-γ with mAb treatment of mice with IFNγR knockdown tumors did not demonstrate marked synergistic eradication effects, indicating an unexpected role of IFN-γ on the tumor itself. Additionally, mAb and IFN-γ treatment also induced immune host responses that enhanced tumor eradication. Biochemical analyses identified loss of Snail expression in tumor cells, reflecting diminution of tumor-stem-cell-like properties as a consequence of altered activity of GSK3-β and KLF molecules.

INTRODUCTION

The erbB or HER family of receptor tyrosine kinases consists of erbB1 (the epidermal growth factor receptor [EGFR]/HER1), erbB2 (p185/neu/HER2), erbB3 (HER3), and erbB4 (HER4), all of which can form homomeric and heteromeric assemblies (Kokai et al., 1989; Qian et al., 1994a). These receptor tyrosine kinases participate in a variety of signal transduction cascades, including the Ras/Raf/MEK/ERK and PI-3K/Akt pathways. erbB2 is amplified in approximately 30% of breast cancer patients, and amplification is associated with poor prognosis and decreased survival (Riemsma et al., 2012). In various cancers, amplified or mutated forms of these kinases drive increased proliferation, migration, survival, evasion of apoptosis, metastasis, and resistance to chemotherapeutics and ionizing radiation.

Recognition that monoclonal antibodies (mAbs) could disable the $p185^{erbB2/HER2/neu}$ tyrosine kinase receptor complex and also lead to reversal of the malignant phenotype challenged dogma that transformed cells could only progressively become more abnormal (Drebin et al., 1985; Schechter et al., 1984). Reversal of the malignant phenotype by anti-erbB2 mAb begins rapidly within 24 hr of mAb binding (Drebin et al., 1986; Lee et al., 2012; O'Rourke et al., 1997; Qian et al., 1994b) and occurs with downregulation of $p185^{erbB2/neu}$ receptor tyrosine kinase proteins, causing diminished enzymatic activity (Drebin et al., 1986, 1988a; Furuuchi et al., 2007; Sliwkowski and Mellman, 2013; Wada et al., 1990; Zhang et al., 2007). These mechanistic events altering phenotype occur more dramatically with the inclusion of a second antibody, which more completely disables erbB2/neu kinase function (Drebin et al., 1988b; Furuuchi et al., 2007).

Tumor eradication that occurs in some partially syngeneic erbB2/neu models also displayed a role for $CD8^+$ T cells, macrophages, and natural killer cells (Park et al., 2010; Stagg et al., 2011). Cytokines derived from $CD8^+$ T cells and other cell types also contribute in certain tumor models (Park et al., 2010; Stagg et al., 2011). IFN-γ, a cytokine that plays diverse roles in innate and adaptive immune response, has been implicated in tumor immune responses. Stagg et al. (2011) demonstrated activity of both type I and II IFNs in mediating anti-erbB2 mAb functions in vivo in non-syngeneic tumor host systems.

Early biochemical studies indicated that IFN-γ could limit $p185^{erbB2/neu}$ expression at the mRNA level (Marth et al., 1990) in some tumor lines. Conversely, IFN-γ alone was thought to increase erbB1 (EGFR) levels (Hamburger and Pinnamaneni, 1991) and TGFα secretion through increased EGFR activity (Uribe et al., 2002) as well as to promote malignant growth of certain murine tumors (Beatty and Paterson, 2000). IFN-γ may also contribute to local environmental angiogenic effects (Coughlin et al., 1998). Historically, IFN-γ was one of the first recombinant

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