Molecular Cancer Therapeutics

Lapatinib: Functional Genomics Study Leads to Insights into Mechanism of Action

Tona M. Gilmer

Commentary on:
Priti S. Hegde, David Rusnak, Melissa Bertiaux, Krystal Alligood, Jay Strum, Robert Gagnon, and Tona M. Gilmer. **Delineation of molecular mechanisms of sensitivity to lapatinib in breast cancer cell lines using global gene expression profiles.** Mol Cancer Ther 2007;6:1629–40.

The epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2) have been intensely scrutinized as therapeutic targets in cancer because of the relationship between overexpression of these receptors and poor prognosis. In general, targeting EGFR or HER2 can be accomplished with antibodies directed against the receptor extracellular domains or with small-molecule inhibitors of the intracellular tyrosine kinase domains. Although both strategies have been clinically promising, considerable variability in efficacy has also been noted; this raises important questions about the molecular basis for drug responsiveness. Moreover, an improved understanding of the mechanisms of action of agents that target the HER family may open new avenues of research into therapeutic resistance and offer patients additional treatment options.

In breast cancer, for example, cross-talk between the growth factor receptors and hormone receptors offers a potential mechanism for therapeutic resistance. Estrogen receptor (ER) and progesterone receptor (PR) status is known to be a strong predictor for breast cancer prognosis. Antiestrogen-resistant breast cancers have also demonstrated both increased EGFR and HER2 expression. Clinical data also have shown reduced survival rates for breast cancer patients with both ER-positive and HER2-positive tumors compared with patients with ER-positive and HER2-negative tumors.

Based on these emerging data, our team sought to examine the effects of the dual EGFR/HER2 inhibitor lapatinib on cross-talk between growth factor receptor and hormone receptor pathways. We used microarray technology and targeted pathway analysis to establish gene expression profiles in breast cancer cell lines responsive or unresponsive to lapatinib. Our study yielded pivotal insights into the mechanism of action of lapatinib. First, lapatinib induced transcription of *ESR1* and *PgR* genes that regulate ER and PR expression, which provided a scientific rationale for clinical trials combining lapatinib with antiestrogens. Second, cell lines responsive to lapatinib showed strong differential effects on multiple genes that uniformly suggested AKT pathway inhibition and extended our previous studies that showed decreases in phosphorylated AKT in HER2-positive breast cancer cell lines. This finding was important because inhibition of the AKT pathway promotes apoptotic signaling, and ultimately cell death. Finally, lapatinib had differential effects on genes involved in cell-cycle control, glycolysis, and fatty acid metabolism, which may provide a mechanism for limiting growth of cells responsive to lapatinib.

These pathways continue to be promising and active areas of research with a number of approved agents as well as therapies under investigation. For example, the efficacy of small-molecule kinase inhibitors of the AKT pathway is currently under investigation as a viable therapeutic target in clinical trials. Directly related to the work reported in the cited article, lapatinib combined with the aromatase inhibitor letrozole was approved in 2010 for the treatment of postmenopausal women with hormone receptor–positive HER2-overexpressing metastatic breast cancer. Treatment with trastuzumab and anastrozole has also shown clinical promise. Ongoing studies examining the effects of lapatinib administered with other agents will further elucidate the importance of these pathways in breast cancer therapy.

Disclosure of Potential Conflicts of Interest

The author has an ownership interest with patents with GlaxoSmithKline.

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Author's Affiliation: GlaxoSmithKline, Research Triangle Park, North Carolina

Corresponding Author: Tona M. Gilmer, GlaxoSmithKline, Oncology Translational Research 17.1356I, 5 Moore Drive, Research Triangle Park, NC 27709-3398. Phone: 919-483-6335; Fax: 919-315-3749; E-mail: tona.m.gilmer@gsk.com

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