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Iressa inhibits growth of HER-2-overexpressing cells

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Keywords

Breast cancer, HER-2, Iressa

Context

ZD1839 or Iressa is a quinazoline tyrosine kinase inhibitor selective for the epidermal growth factor receptor (EGFR). Due to its oral bioavailability and antitumor activity against a broad range of mouse xenograft models, it was selected for clinical development and has now reached phase II-III clinical trials. Although it selectively inhibits EGFR, the molecular bases for the sensitivity to this compound are not fully understood. EGFR overexpression alone does not seem to be neither sufficient nor indispensable for tumor sensitivity to Iressa.

Significant findings

The authors found that within a panel of human breast cancer and other epithelial tumor cell lines, HER-2-overexpressing tumors were the most sensitive to ZD1839 (even more than EGFR-overexpressing cell lines). The growth inhibition of these tumor cell lines was associated with the dephosphorylation of EGFR, HER-2, and HER-3, the downregulation of Akt activity, and with the loss of association between HER-3 and PI3K (phosphatidylinositol 3-kinase). Furthermore, downregulation of the PI3K/Akt pathway was found to be the best correlate of tumor sensitivity to Iressa, and could be used as a marker of response to this drug. A preliminary *in vitro* evaluation of the efficacy of the monoclonal antibody anti-HER-2 trastuzumab (HerceptinT) in combination with ZD1839 was performed; the growth inhibitory activities of these two agents were found to be additive.

Comments

These results indicate that the clinical potential of Iressa is not limited to tumors with EGFR overexpression, and that this agent may represent a novel treatment option for patients with HER-2-overexpressing tumors. Clinical studies exploring the feasibility and antitumor activity of combinations of Iressa and other agents that target the EGFR-family, particularly HER-2, are warranted.

Methods

Tumor cell lines, western blot, immunoblot analysis, autoradiograms, immunoprecipitation

Additional information

References

1. Moasser MM, Basso A, Averbuch SD, Rosen N: The tyrosine kinase inhibitor ZD1839 ("Iressa") inhibits HER2-driven signaling and suppresses the growth of HER2-overexpressing tumor cells. *Cancer Res.* 2001, 61: 7184-7188.