Publication

Activation of IGF1R/p110β/AKT/mTOR confers resistance to α-specific PI3K inhibition

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4373868
Author(s) Leroy, C.; Ramos, P.; Cornille, K.; Bonenfant, D.; Fritsch, C.; Voshol, H.; Bentires-Alj, M.
Author(s) at UniBasel Bentires-Alj, Mohamed ;
Year 2016
Title Activation of IGF1R/p110β/AKT/mTOR confers resistance to α-specific PI3K inhibition
Journal Breast Cancer Research
Volume 18
Number 1
Pages / **Article-Number** 41
Keywords Animals; Breast Neoplasms/drug therapy/*genetics/pathology; Cell Line, Tumor; Class Ia Phosphatidylinositol 3-Kinase/genetics/*metabolism; Drug Resistance, Neoplasm/drug effects/genetics; Female; Humans; Insulin Receptor Substrate Proteins/genetics/metabolism; Mice; Phosphatidylinositol 3-Kinases/*antagonists & inhibitors/genetics; Phosphorylation/drug effects; Protein Kinase Inhibitors/administration & dosage; Proto-Oncogene Proteins c-akt/genetics/*metabolism; Receptors, Somatomedin/genetics/*metabolism; TOR Serine-Threonine Kinases/genetics/*metabolism; Thiazoles/administration & dosage; Xenograft Model Antitumor Assays; Breast cancer; Phosphatidylinositol 3-kinase; Resistance; p110alpha; p110beta
Mesh terms Animals; Breast Neoplasms, pathology; Cell Line, Tumor; Class I Phosphatidylinositol 3-Kinases; Class Ia Phosphatidylinositol 3-Kinase, metabolism; Drug Resistance, Neoplasm, genetics; Female; Humans; Insulin Receptor Substrate Proteins, metabolism; Mice; Phosphatidylinositol 3-Kinases, genetics; Phosphorylation, drug effects; Protein Kinase Inhibitors, administration & dosage; Proto-Oncogene Proteins c-akt, metabolism; Receptors, Somatomedin, metabolism; TOR Serine-Threonine Kinases, metabolism; Thiazoles, administration & dosage; Xenograft Model Antitumor Assays
BACKGROUND: The PI3K pathway is hyperactivated in many cancers, including 70 % of breast cancers. Pan- and isoform-specific inhibitors of the PI3K pathway are currently being evaluated in clinical trials. However, the clinical responses to PI3K inhibitors when used as single agents are not as efficient as expected. METHODS: In order to anticipate potential molecular mechanisms of resistance to the p110alpha isoform-selective inhibitor BYL719, we developed resistant breast cancer cell lines, assessed the concomitant changes in cellular signaling pathways using unbiased phosphotyrosine proteomics and characterized the mechanism of resistance using pharmacological inhibitors. RESULTS: We found an increase in IGF1R, IRS1/IRS2 and p85 phosphorylation in the resistant lines. Co-immunoprecipitation experiments identified an IGF1R/IRS/p85/p110beta complex that causes the activation of AKT/mTOR/S6K and stifles the effects of BYL719. Pharmacological inhibition of members of this complex reduced mTOR/S6K activation and restored sensitivity to BYL719. CONCLUSION: Our study demonstrates that the IGF1R/p110beta/AKT/mTOR axis confers resistance to BYL719 in PIK3CA mutant breast cancers. This provides a rationale for the combined targeting of p110alpha with IGF1R or p110beta in patients with breast tumors harboring PIK3CA mutations.
ISSN/ISBN 1465-542X
URL https://doi.org/10.1186/s13058-016-0697-1
edoc-URL https://edoc.unibas.ch/61369/
Full Text on edoc No;
Digital Object Identifier DOI 10.1186/s13058-016-0697-1

PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/27048245
Document type (ISI) Journal Article