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RNAi functional genome screens identifies novel breast cancer drug targets, combination therapies, and potential patient selection biomarkers

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We conducted a genome-scale RNAi screens using pooled-lentiviral approach to identify synthetic lethal or enhancer genes that interact with neratinib in a human breast cancer cell line (SKBR-3). Our study identified a diverse set of genes and mechanisms whose perturbation by RNAi selectively impaired or enhanced the viability of cancer cells in the presence of subeffective concentrations of neratinib. Examining the changes of these genes and their protein products also led to a rationale for clinically relevant drug combination treatments. Treatment of cells with either paclitaxel or cytarabine in combination with neratinib resulted in a strong antiproliferative effect. The identification of novel targets and pathways to neratinib could lead to the development of novel selective therapies and combination therapies that overcome therapeutic resistance to neratinib and other ErbB2-targeted therapies. Notably, our findings support a paclitaxel and neratinib phase III clinical trial in breast cancer patients.

In addition, we performed an RNAi screen to identify genes involved in resistance to lethal concentrations of neratinib under a long term selective pressure. The screen uncovered a set of novel genes whose silencing by RNAi caused long term chemoresistance to lethal concentrations of neratinib.

The identification of novel mediators of cellular resistance to neratinib could lead to the identification of new or neoadjuvant drug targets. Additionally, these resistant genes if confirmed in patient samples can be used as patient or treatment selection biomarkers to select individuals who will most likely benefit from neratinib and other anti-ErbB therapies.

Biography

Attila Seyhan is a Faculty at the Translational Research Institute (TRI) for Metabolism and Diabetes and a scientific advisor to Biomarker Discovery and Development Unit of TRI. He is also an Adjunct Professor at the Diabetes and Obesity Research Center, Sanford-Burnham Medical Research Institute, Orlando, FL and holds a position as a Research Affiliate in the Department of Chemical Engineering, Massachusetts Institute of Technology (MIT). Previously, he was a Senior Translational Medicine Leader in Inflammation and Immunology and Clinical R&D at Pfizer and was the Head of Functional Genomics at Wyeth Inc. He earned his Ph.D. in Biological Sciences from Michigan Technological University (MTU).

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