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Pi3k Pathway-Specific Inhibitors: New Hope for Patients with Er-Positive or Her2-Positive Breast Cancers

Pradip Kr De*

Department of Internal Medicine, University of South Dakota, USA

Research Interest

Broad objective of my laboratory

The De's laboratory seeks to investigate tumor suppressor and oncogene signaling pathways that are altered in breast tumors using a multidisciplinary approach that includes genetics, biochemistry, bioinformatics, and pathology. As a signal transduction research laboratory, we would like to understand how to phosphorylation and dephosphorylation of cellular proteins results in regulated and coordinated signal relay in ER+ and HER2+ breast cancers include all of the intrinsic molecular subtype. Furthermore, we are interested how the different oncogenic signaling pathways interact to dysregulate cell signaling (otherwise in fine tuned) in the context of genetic influences or when other membrane receptor tyrosine kinases are activated at the same time.

Specific Interest

• Identify genes/proteins dysregulated in different subset of breast cancers (especially ER+ and HER2+ breast cancers include all of the intrinsic molecular subtypes) and dissecting their signaling pathways for novel/combinatorial therapeutic intervention.

• Try to identifying a "signaling hub" as an enticing molecular target for subset-specific breast cancer therapy and overcome conventional targeted therapy resistance (like trastuzumab for HER2+ patients and tamoxifen or aromatase inhibitor for ER+ patients), with the intent to translate these important findings into future clinical trials.

• In particular, we are studying the role of aberrantly activated signaling pathways, such as PI3K-AKT-mTOR and RAS-MAPK pathways, as potential therapeutic targets in subset-specific breast cancers.

Molecular mechanisms of resistance to trastuzumab

The potential factors that can cause resistance to trastuzumab are i) hyper activation of PI3K pathway via different mechanisms, such as upregulation of upstream growth factor receptors such as IGF1R, cMET, HER3, p95HER2; loss of function of PTEN due to loss of heterozygosity, mutation and DNA methylation; and activating mutation of PIK3CA, which encodes the p110α catalytic subunit of PI3K (Figure 1). Three frequent PIK3CA mutations, E542K, E545K and H1047R activate AKT-mTOR signaling, ii) upregulation of HER-family receptors ligand such as heregulin, iii) dysregulation of Cyclin E, which can occur due to over expression of Cyclin E or downregulation of nuclear p27, iv) loss of binding of FcγR on immune effector cells to the Fc portion of trastuzumab due to FcγR polymorphisms and v) reduced endocytosis and lysosomal routing of HER2.

Estrogen receptor signaling and a reciprocal crosstalk between ER and growth factor (GFR) pathways

Binding of estrogen (E) to ER causes conformational changes in the nuclear E, which then binds to promoter/enhancer regions

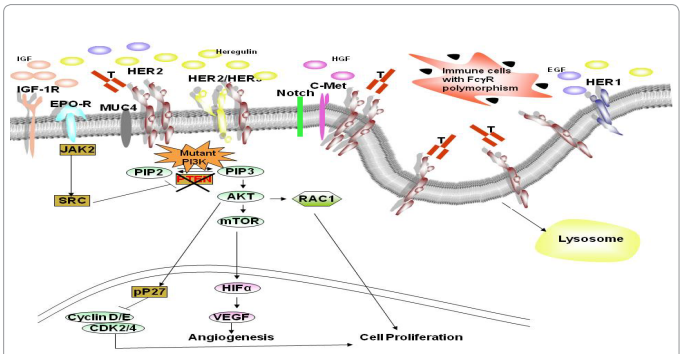

Figure 1: Molecular mechanisms of resistance to trastuzumab.

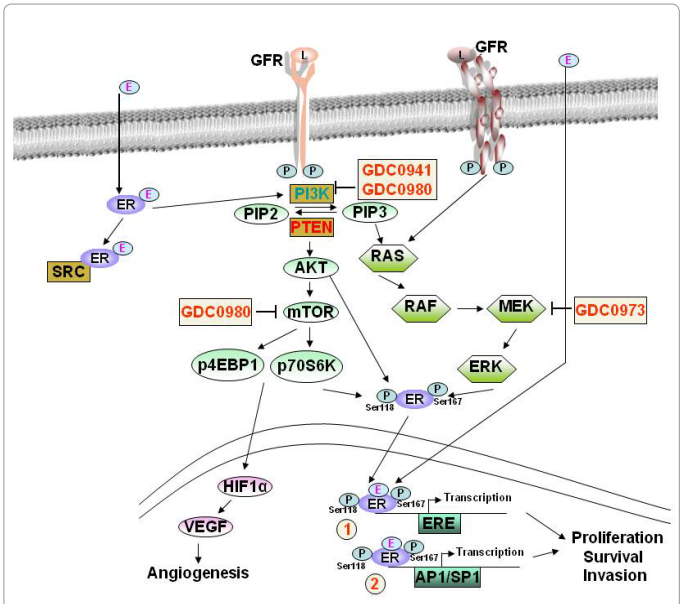

Figure 2: Estrogen receptor signaling, and a reciprocal crosstalk between ER and growth factor (GFR) pathways.

***Corresponding author:** Pradip Kr De, Department of Internal Medicine, University of South Dakota, USA, Tel: 605-312-602; Fax: 605-312-6071; E-mail: Pradip.de@sanfordhealth.org

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of target genes either directly at estrogen response elements (1) or indirectly via binding to other transcription factors such as AP1 or SP1 at the cognate DNA binding sites (2) Estrogen bound ER typically recruits co-activators to facilitate gene transcription of genes encoding growth factors, growth factor receptor tyrosine kinase (GFR) and others involved in cell proliferation, survival and invasion (Figure 2). Additionally, GFRs activate downstream PI3K-AKT-mTOR and RAS-RAF-MEK-ERK signaling pathways. Then downstream effectors of these respective pathways phosphorylate ER and/or co-activators to modulate ER transcription activity. ER also complexes with receptor tyrosine kinase (GFR) and non-receptor tyrosine kinase (SRC) to rapidly induce non-genomic signaling.

Cancer Cell Signaling

The cancer cell signaling study is required to assemble fundamental knowledge of the intra- and inter-cellular signaling pathways that control tumor cell proliferation, migration, and survival and to understanding how this information can be used to improve the diagnosis, prevention, and treatment of cancer. Our lab utilize this fundamental knowledge to study tumor cell responses to the microenvironment and to drug treatments, using *in vitro* cell culture models and in xenograft models (including patient derived xenografts) of individual cancers. Studying cell signaling in the context of pre-clinical cancer models provides relevant translation of cell signaling to the practical context of therapeutic intervention.

The research of the cellular signaling is organized around three themes:

1. Understanding fundamental properties of cancer cell signaling networks.
2. Identifying pathways that govern cell responses to the microenvironment.
3. Defining in vivo systems to study signaling networks and test preclinical therapeutic strategies for cancer treatment.

The long-term goals are to promote discovery science focused on the complex integration of signaling networks, on how tumors respond to the microenvironment, and how tumors evolve to survive anticancer therapies.