Diminished Proteolytic Shedding of Receptor Tyrosine Kinases Mediates MEK Inhibitor Resistance in Triple-negative Breast Cancer
Technology #16742

Applications

This invention diagnoses kinase inhibitor resistant cancer and also decreases resistance to kinase inhibitors for improved cancer treatments.

Problem Addressed

Molecular-targeted cancer therapeutics eventually fail due to cancer’s ability to become resistant to drugs. How carcinogenic cells achieve this resistance is poorly understood, with genetic and gene expression changes accounting for only a small percentage of their adaptability. This invention is a method to reduce cancer’s resistance to anti-cancer therapeutics, and may be used for triple-negative breast cancer (TNBC), melanoma, ovarian cancer, and other indications where MAPK pathway activation is prominent. The invention may also be used to aid in selecting patients for targeted combination therapies and in monitoring patients for treatment response and mechanisms of drug resistance.

Technology

This technology is based on the discovery that decreased proteolytic shedding of surface receptors, which provide negative feedback on signaling network activity thereby driving post-translational “bypass” signaling pathways, can be caused by anti-cancer kinase inhibitor treatments leading to resistance to those very same therapeutics. Inhibition of multiple signaling pathways, in particular MAPK signaling through MEK1/2, drives “bypass” signaling by causing diminished A Disintegrin and Metalloproteinase (ADAM)-mediated receptor tyrosine kinase (RTK) shedding including MET, HER2, HER4, and especially AXL RTKs. Targeted MEK inhibition (MEKi) has been identified as a promising therapeutic strategy since RAF/MEK/ERK mitogenic phospho-signaling is up-regulated in many cancers including TNBC. MEK, BRAF, p38, JNK and PI3K kinase inhibition have been shown to reduce RTK shedding and hence gives rise to the bypass signaling. This technology increases sensitivity of cancers under treatment with kinase inhibitors by blocking the bypass signaling pathways of RTKs and/or by encouraging RTK receptor shedding.

Advantages

- May be used in conjunction with kinase inhibitor cancer treatments to decrease resistance
- May be used to identify patients likely to respond to kinase inhibitor treatments and combinations thereof

Categories For This Invention:
Life Sciences
Biotechnology
Health
Clinical Applications
Oncology
Therapeutics
Chemotherapy

Intellectual Property:
Methods of reducing kinase inhibitor resistance
Copyright Other

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Publications:
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External Links:
Doug Lauffenburger Research Group
http://web.mit.edu/dallab/
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