Combination cancer therapies to circumvent induced resistance pathways

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Technology description

Summary

MARKETS ADDRESSED:
The invention developed in Dr. Brugge's laboratory includes a platform for identification of co-activated oncogenic pathways, and particular drug combinations targeting these pathways.Unfortunately, some tumors eventually relapse, typically by activating an alternative pathway, not impacted by the treatment. Thus, single agent therapies may not be the most potent and effective treatments, since alternative pathways may be activated and lead to drug resistance.
Combination therapy kills drug-resistant cancer cells: Dr. Brugge and Dr. Mills, experts in cancer cell biology, collaborated to identify co-activated oncogenic pathways using protein microarrays. They identified synergies between PI3K/mTOR inhibitors and inhibitors of alternative oncogenic pathways activated upon treatment with PI3K/mTOR inhibitors. A 3D culture system was then used to test combinations of inhibitors targeting these co-activated pathways. They demonstrated that specific combination therapies killed drug-resistant cancer cells, suggesting that these dual-agent therapies may lead to a more effective cancer treatment and reduce the risk of cancer relapse:
â€¢ Identification of co-activated oncogenic pathways using protein microarrays: Researchers in Dr. Mill's laboratory developed a reverse-phase protein microarray assay. This high throughput technology allows rapid and reliable quantification of protein levels in cell lysates. This assay was used to track the activation of particular signaling pathways upon drug treatment.
â€¢ Treatment with PI3K/mTOR inhibitor activates alternative oncogenic pathways: Protein microarrays revealed that cancer cells treated with a PI3K/mTOR inhibitor increase the activity of several key signaling proteins. The proteins identified by the Brugge laboratory are known to be overexpressed or mutated in aggressive drug-resistant cancers. Their findings suggest that cancer cells may rely on these alternative signaling pathways to survive drug treatment.
â€¢ 3-D culture system protects cells from drug induced cell death: To reconstitute the in vivo tumor environment, the Brugge laboratory developed a 3D culture system in which ovarian cancer cells formed spherical colonies. After adding a PI3K/mTOR inhibitor to the 3D cultures, the inner cells of the spheroid died, while the outer, matrix-attached cells, survived.
â€¢ Combination therapy kills drug-resistant, "matrix-attached" cells: In striking contrast, the

combination of the PI3K inhibitor with inhibitors of co-activated oncogenic pathways identified by the lab, killed all cells in ovarian cancer spheroid colonies, including those attached to the matrix.
â€¢ Preliminary in vivo data: There is also exciting, new animal data just coming out of the lab that we would be happy to share under CDA.

Application area

Possible applications might include:
â€¢ Identifying novel combination cancer therapies: Many inhibitors of PI3K kinases have entered into clinical trials. Dr. Brugge's laboratory identified oncogenic pathways activated by treatment with PI3K inhibitors which may rescue these cells. Many of these signaling proteins have been extensively studied. A combination therapy that includes inhibitors of PI3K/mTOR and co-activated oncogenic proteins may be a more effective cancer treatment that reduces the risk of cancer relapse. In addition, the screening platform can be used to identify additional combination therapies for cancer treatment.
â€¢ Therapeutic prediction / Profiling cancer cell lines in clinical settings and R&D: In drug development, the ability to identify possible mechanisms of cancer relapse will allow researchers to better optimize drug candidates and increase success rate in clinical trials. In hospitals, biopsy samples can be profiled to identify the need to supplement an ongoing therapy with additional targeted therapeutics.
â€¢ Biomarker profiling: Finally, the protein microarray screening platform may lead to the identification of novel cancer biomarkers which can serve as novel drug targets.

Advantages

Tumor cells contain mutations in cell signaling pathways that drive uncontrollable cell proliferation, survival, and invasion. Recent advances in cancer biology and rational drug design gave rise to targeted therapeutics which selectively inhibit a particular mutated molecular switch and block tumor progression. Some of the most promising groups of targeted anti-cancer drugs are inhibitors of PI3K, a lipid kinase, and mTOR, a downstream protein kinase. The specificity of drug action greatly reduces the side effects and leads to rapid regression of the disease.

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