'Synthetic lethality' strategy improves molecularly targeted cancer therapy

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Molecularly targeted therapies can reduce tumors rapidly. However, not all tumors respond to the drugs, and even those that do often develop resistance over time. Looking for a way to combat the problem of resistance, researchers at Fox Chase Cancer Center hypothesized that hitting already weakened cancer cells with a second targeted agent could kill them—but only if it was the right second agent.

One well-validated molecular target for anti-cancer drugs is the epidermal growth factor receptor, or EGFR. Using a novel screening approach, investigators in the Fox Chase Developmental Therapeutics Program identified over 60 additional proteins that are necessary for cells to survive in the presence of an EGFR inhibitor. When they simultaneously blocked the EGFR inhibitors and any one of these other proteins, more of the cancer cells died. The researchers say this screening strategy to identify targets for effective combinations of cancer drugs will open the door for future therapies. Already, two clinical trials are under way to test innovative drug combinations suggested by the new tactic.

"We found that knocking out one or the other target doesn't have a major effect, but knocking out both increases tumor cell death," says Igor Astsaturov, M.D., Ph.D., an assistant professor and medical oncologist at Fox Chase. Astsaturov led the study, which will be published in the September 21, 2010 issue of *Science Signaling*.

To identify additional targets that would boost the effectiveness of

EGFR inhibitors against cancer, Astsaturov and colleagues screened only proteins that interact directly or indirectly with EGFR. The team mined the literature and built a candidate set of 638 EGFR-interacting proteins. They then used an experimental technique called small inhibitory RNA (siRNA) systematically to block activity of each of the genes in cancer cells that had been treated with an EGFR inhibitor. In doing so, the investigators demonstrated on three clinically relevant examples for which drugs are already available—PRKC, STAT3, and Aurora kinase A—that these proteins were necessary for cell survival in the presence of an EGFR inhibitor.

This two-hit strategy—where neither hit is adequate to kill the cells, but together they are—is called synthetic lethality. Geneticists have used synthetic lethal screens in experiments with model organisms, such as fruit flies and yeast, for decades, but cancer researchers have only recently adopted the approach.

"We knew from model organisms that there was a dense network of genes. Using bioinformatics tools to intelligently mine this network provided us with a rich source of hits," says Erica A Golemis, Ph.D., professor and co-leader of the Developmental Therapeutics Program at Fox Chase, and senior author on the new study. Golemis is also co-leader of the Keystone Initiative in Head and Neck Cancer at Fox Chase, and notes that EGFR inhibitors are already broadly used in the clinic for cancers affecting the head and neck.

"The most exciting hit is the Aurora kinase," Golemis says. Several Aurora kinase inhibitors are already being tested in the clinic and thus are available for testing in combination with EGFR inhibitors.

Based on the new data, Hossein Borghaei, D.O., director of the Lung Cancer Risk Assessment Program at Fox Chase is launching a trial testing the EGFR inhibitor erlotinib with an Aurora kinase inhibitor in

patients with non-small cell lung cancer. Astsaturov has started testing a drug called vandetanib—which simultaneously inhibits EGFR and RET (another protein in the EGFR-interacting network)—in patients with esophageal cancer.

In addition to providing a rich source of synthetic lethal hits, limiting the siRNA screen to a previously-defined network of interacting proteins had an important impact on the size of the project, according to Golemis. "A full genome siRNA screen is prohibitively expensive for many labs. This approach makes siRNA screens more accessible to smaller labs and academic institutions."

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