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Gene changes in breast cancer cells pinpointed with new computational method

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Computer scientists at Carnegie Mellon University, working with high-throughput data generated by breast cancer biologists at Lawrence Berkeley National Laboratory, have devised a computational method to determine how gene networks are rewired as normal breast cells turn malignant and as they respond to potential cancer therapy agents.

This method for analyzing how genes interact with each other in laboratory-grown cells is described in a report published today by the online journal *PLOS Computational Biology*.

The method could provide new insights into cancer and identify the most promising molecular targets for drug therapy. In their study, for instance, the researchers were able to show how changes in these gene networks led breast cancer cells to develop resistance to several different agents being evaluated as drugs for targeted therapy.

"With our system, pharmaceutical developers wouldn't need to go to expensive clinical trials to discover that a drug isn't going to work," said Wei Wu, associate research professor in CMU's Lane Center for Computational Biology. "It could save them a tremendous amount of money and a tremendous amount of time."

The approach also might be used to detect differences in gene regulation between individuals, helping physicians select which treatment will be most effective for each patient, she added.

Wu and Eric P. Xing, associate professor of machine learning, worked with Mina Bissell, a renowned breast cancer researcher at the Berkeley Lab, to investigate whether distinctly different gene regulatory networks could be identified within cells as normal cells become malignant and as the malignant cells respond to various drug treatments. The researchers studied these breast cancer cells using a 3D cell culturing technique developed by Bissell's laboratory.

These networks can be inferred based on microarrays, which measure the expression levels of tens of thousands of genes in a cell. But the number of microarrays that investigators can afford to run for each cell state—normal cells, malignant cells and malignant cells that have reverted to normal-looking cells that also are organized normally—is limited. So researchers often pool microarray data from several cell states in hopes of gaining enough samples to draw solid conclusions about networks, Wu said.

That approach wouldn't work in a study that sought to differentiate between the various cell states. But Xing's research group had developed a computational method called Treegl that can detect multiple networks by examining the relationships between the cell types. The method pools microarray data to build statistical power in similar samples in which the gene regulatory networks appear similar while also taking the differences into account.

In this way, the researchers were able to identify different signaling networks with just three microarrays for each of five cell states—normal, malignant and three types of reverted cells.

Though the reverted cells looked physically normal in culture, Wu said their signaling pathways differed not only from the malignant cells, but also the normal cells. In fact, each had distinctly different signaling pathways depending on what drug had been used to treat them, as each

compensated for the effects of the drugs in different ways.

In the case of cells that had been treated with MMP inhibitors, the researchers could see how the rewired signaling pathways had created compensatory signaling which would cause them to resist the drug—an effect that would explain why cancer patients receiving MMP inhibitors in clinical trials show either poor survival or no survival benefit, Wu said.

Wu also said by using this approach for studying cancer cells, it should be possible to eliminate drugs that appear promising but are ultimately flawed earlier in the development process. It also might result in clinical trials that require fewer patients and less time to complete, she added. Differences in gene regulatory networks in patients also might be used as the basis for personalized medicine.

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