Stanford technique pinpoints the 'partners in crime' of cancer genes

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Batman and Robin. Sherlock Holmes and Dr. Watson. Fiction is full of dynamic duos that work together to accomplish amazing feats. When one partner is out of commission, the other steps in to make sure the job gets done. But if both are missing in action, the outcome is likely to be dire.

Cancers also often rely on pairs of complementary genes to keep their cells plugging along as they spin increasingly out of the bounds of normal cellular control. If one partner is mutated, the other springs to the rescue; if both are compromised, the cell dies. Genes that work in this way are called synthetic lethals, and cancer researchers' ears perk up when one member of the pair is a known cancer-associated mutation. Blocking its partner could be an attractive therapeutic target that would specifically kill cancer cells while sparing normal cells without the mutation. But until now it's been difficult to identify these partners in crime.

Now researchers at Stanford University have devised a new computer algorithm to churn through piles of existing data to suss out and target these genetic understudies in primary human tumors. Doing so is likely to lead to new, less-toxic treatments for many cancers, they believe. They are now collaborating with oncologists at Stanford and at M.D. Anderson Cancer Center in Texas to use the algorithm, which they've called MiSL, to find new, mutation-specific therapies for patients with a variety of cancers.

"We're entering a new era of precision health," said associate professor of medicine Ravi Majeti, MD, PhD. "Using data from real human tumors gives us important, fundamental advantages over using cancer cell lines that often don't display the same mutation profiles. We've found that, although many known cancer-associated mutations are difficult to target clinically, their synthetic lethal partners may be much more druggable."

The researchers tackled 12 different types of cancers and over 3,000 cancer-associated mutations to identify thousands of new genetic partnerships that could be amenable to drug treatment. In particular, they found that 17 of the 89 potential synthetic lethal partners for a well-known, leukemia-associated mutation are likely to be susceptible to drugs that are either already clinically available or are under development.

Majeti and professor of computer science David Dill, PhD, share senior authorship of the study, which will be published online May 31 in *Nature Communications*. Research associate Subarna Sinha, PhD, and postdoctoral scholar Daniel Thomas, PhD, share lead authorship.

The collaboration between the Majeti and Dill labs developed through Stanford's Center for Cancer Systems Biology, which aims to identify broad biological patterns in the methods cancer cells use to evade the immune system.

Sifting through the mess

The researchers capitalized on the fact that cancer cells are often a genomic hot mess. As they proliferate out of control, they play fast and loose with the normal rules for DNA duplication and

cellular division. It's not uncommon for genes to be summarily deleted from the genome or, conversely, to be "amplified" so that they occur two, three or more times in the cells' DNA.

In this study, the researchers taught the computer a simple "if this, then that" concept to help them identify pairs of genes whose expression levels were co-dependent—a hallmark of synthetic lethals.

"We were looking for situations in which, if gene A is mutated, gene Y is amplified to compensate for the loss of function of gene A," said Dill, who is the Donald E. Knuth Professor in the School of Engineering. "Conversely, gene Y is only ever deleted in cells in which gene A is not mutated." In other words, these genetic partners have each others' backs.

The researchers applied their technique to data stored in a national human cancer database called The Cancer Genome Atlas. The software sifted through DNA sequences and gene expression levels to identify situations in which genes were either more highly expressed in the presence of particular cancer-associated mutations than when the mutation was absent, or genes that were rarely or never deleted in the presence of the mutation. Because the analysis was computerized, it could be conducted without any preconceived notions about what genes might be working together in the cancer cells.

"We found these strong relationships much more often than we had expected, even among seemingly unrelated genes," said Dill.

The researchers analyzed more than 3,000 known cancer-associated genes and identified more than 140,000 potential synthetic lethal partners through a study of the DNA sequences of the cells. They winnowed this number down by limiting the prospects to only those that displayed a true difference in gene expression levels of the partner based on whether the first gene was mutated. In most cases, this narrowed the contenders down to 50 or fewer for each mutation.

Powerful tool

They found that MiSL pinpointed some synthetic lethals that had previously been identified by other means—confirming that their approach was working. But they also identified some new relationships, including one between a mutation in a gene called IDH1 that's associated with the development of leukemia and another gene called ACACA. They validated this synthetic lethal partnership by a variety of tests in laboratory grown cells and human tumor tissue.

"We have just scratched the surface of what we think we can learn with MiSL," said Majeti. "It's an incredibly powerful way to analyze large amounts of data to quickly identify relationships of potential interest, and it's likely to make drug development much more efficient and quick."

Interestingly, the researchers found that some synthetic lethal pairs predicted by MiSL were found in multiple human cancers. In particular, the genes tended to be involved in pathways of broad biological significance, including the Krebs cycle, which releases energy stored in carbohydrates, fats and proteins; the DNA repair machinery used by cells to correct genetic mistakes; and the Wnt signaling pathway, which has been shown to be critical in normal development and many human cancers,

The team's work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

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