Medical Xpress

Innovative algorithm spots interactions lethal to cancer

September 3 2014

Despite the revolutionary biotechnological advancements of the last few decades, an ideal anti-cancer treatment—one that's immediately lethal to cancer cells, harmless to healthy cells, and resistant to cancer's relapse—is still a dream.

But a concept called "synthetic lethality" holds great promise for researchers. Two genes are considered synthetically lethal when their combined inactivation is lethal to cells, while inhibiting just one of them is not. Synthetic lethality promises to deliver personalized, more effective, and less toxic therapy. If a particular gene is found to be inactive in a tumor, then inhibiting its synthetic lethal partner with a drug is likely to kill only the cancer cells, causing little damage to healthy cells .

While this promising approach has been widely anticipated for almost two decades, its potential could not be realized due to the difficulty experimentally identifying synthetic lethal pairs in cancer. Now new research published last week in the highly prestigious journal *Cell* overcomes this fundamental hurdle and presents a novel strategy for identifying synthetic lethal pairs in cancer with the potential to bust cancer cells.

Tel Aviv University researchers have developed a computational data-driven algorithm, which identifies synthetic lethal interactions. In their comprehensive, multidisciplinary study, Dr. Eytan Ruppin of TAU's Blavatnik School of Computer Science and the Sackler School of

Medicine and Ms. Livnat Jerby-Arnon of TAU's Blavatnik School of Computer Science worked together with other researchers from TAU, The Beatson Institute for Cancer Research (Cancer Research UK), and the Broad Institute of Harvard and MIT.

Taking cancer personally

Analyzing large sets of genetic and molecular data from clinical cancer samples, the scientists were able to identify a comprehensive set of synthetic lethal pairs that form the core synthetic lethality network of cancer. They have demonstrated for the first time that such a network can be used to successfully predict the response of cancer cells to various treatments and predict a patient's prognosis based on personal genomic information.

"We started this research from a very simple observation: If two genes are synthetically lethal, they are highly unlikely to be inactive together in the same cell," said Dr. Ruppin. "As cancer cells undergo genetic alterations that result in gene inactivation, we were able to identify synthetic lethal interactions by analyzing large sets of cancer genetic profiles. Genes that were found to be inactive in some cancer samples, but were almost never found to be inactive together in the same sample, were identified as synthetically lethal."

The crux of the study, according to Ms. Jerby-Arnon, is the synergy between the computational research and the ensuing experiments, conducted at the Beatson Institute and the Broad Institute, to verify the predictive power of the new algorithm.

A road to new therapies

In addition to their promising role in tailoring personalized cancer

treatment, the synthetic lethal pairs discovered may also be used to repurpose drugs, which are currently used to treat other non-cancer disorders, to target specific cancer types. "We applied our pipeline to search for drugs that may be used to treat certain forms of renal cancer. We identified two such drugs, currently used to treat hypertension and cardiac dysrhythmia, that may be quite effective," said Dr. Ruppin. "Experiments in cell lines performed by the Gottlieb lab at the Beatson Institute support these findings, and we are now working on additional validations in mice."

The researchers are hopeful that their study will help boost the experimental detection of synthetic lethality in cancer cells and offer further insight into the unique susceptibilities of these pathological cells. "In this study, we have demonstrated the clinical utility of our framework, showing that it successfully predicts the response of cancer cells to various treatments as well as patient survival," said Ms. Jerby-Arnon. "In the long-run, we hope this research will help improve cancer treatment by tailoring the most effective treatment for a given patient."

The researchers are in the process of forming experimental and clinical international collaborations to test key emerging leads for novel drug targets and drug repurposing.

Provided by Tel Aviv University