MedicalXpress

Study finds potential to match tumors with known cancer drugs

February 5 2013

When it comes to gene sequencing and personalized medicine for cancer, spotting an aberrant kinase is a home run. The proteins are relatively easy to target with drugs and plenty of kinase inhibitors already exist.

Now in a new study, University of Michigan Comprehensive Cancer Center researchers assess the complete landscape of a cancer's "kinome" expression and determine which kinases are acting up in a particular tumor. They go on to show that those particular kinases can be targeted with drugs – potentially combining multiple drugs to target multiple kinases.

"We have a small but effective inventory of 'druggable' mutations that we know play a role in cancer. As we are doing more sequencing, we're coming to realize just how small that inventory is. On the one hand, it's a limitation. On the other hand, there are numerous oncogenic kinases, and there are a lot of kinase inhibitors. Our goal is to determine how to match more of these therapies with the right patients," says senior study author Chandan Kumar-Sinha, Ph.D., research assistant professor at the Michigan Center for Translational Pathology.

The researchers looked at RNA sequencing data from 482 samples of both cancerous and non-cancerous tissue and identified the most highly expressed kinases in individual breast cancer and pancreatic cancer samples. They found certain common themes.

"A lot of samples showed one or two kinases that showed an outstandingly high 'outlier' expression," says Kumar-Sinha. It wasn't that the researchers always found a mutation – just that one or more kinases were expressed at a far higher level than all other kinases.

"We don't always know what's causing it to be overexpressed. But since it's there, we know that somehow the high expression of oncogenic kinases is advantageous to the cancer, and so we can therapeutically exploit that dependency," Kumar-Sinha says.

Results of the study appear online in the journal *Cancer Discovery*.

In breast cancer, the researchers spotted outlier expression of ERBB2 kinase in HER2-positive tumors, which would be expected. HER2-positive tumors can be treated with Herceptin. But they also found another kinase, called FGFR4 – and they found that adding a drug that blocks FGFR4, in combination with Herceptin, improved the anti-cancer effect. This was done only in cells in the laboratory, but the FGFR4-inhibitor continued to be effective in cells even after they became resistant to Herceptin.

In the pancreatic cancer samples, the researchers found several different kinases that have drugs that work against them, including MET, AKT and PLK. Pancreatic cancer is one of the most deadly types of cancer, often diagnosed in its late stages when treatments are not very effective. The main driver of pancreatic cancer, a mutation in a gene called KRAS, has proven difficult to target with treatments.

In the lab, researchers blocked the outlier kinases and found it had an effect against the cancer cells. They then blocked KRAS – something that can be done in the lab but has not been achieved in patients with pancreatic cancer – and found an even larger effect.

"If in the future we could target KRAS in patients and also hit the outlier kinases, it could have a huge impact on treatment of pancreatic cancer," Kumar-Sinha says.

These findings must still be tested in patients, but researchers are hopeful that targeting specific kinases expressed in an individual patient's tumor could make a difference.

The U-M Comprehensive Cancer Center is currently using gene sequencing techniques to help match advanced cancer patients with potential clinical trial opportunities based on the make-up of their tumor.

"We hope kinases will represent another available avenue with whole genome sequencing. If we can identify rational multiple targets for treatment, it's more effective. This gets us one of those targets," Kumar-Sinha says.

More information: *Cancer Discovery*, "Outlier Kinase Expression by RNA Sequencing as Targets for Precision Therapy," published online Feb. 5, 2013, doi:10.1158/2159-8290.CD-12-0336

Provided by University of Michigan Health System