Hitting cancer where it hurts

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Two studies in the May 29th issue of *Cell,* a Cell Press publication, have taken advantage of new technological advances to search for and find previously unknown weaknesses in a hard to treat form of cancer. The discoveries lend new hope in the fight again tumors that are today considered "undruggable."

The tumors in question are driven by a particularly widespread alteration in the gene known as KRAS. Mutations in the KRAS gene account for some 30 percent of human cancers, including leukemias, pancreatic and lung cancers, and have so far proved exceedingly difficult to tackle with targeted cancer drugs.

"It's been a real frustration," said Gary Gilliland of Harvard Medical School, who led one of the studies with his colleague William Hahn. "We know the mutation, but we haven't been able to do a thing about it."

Rather than going after KRAS itself, the researchers who led the new studies took an entirely different tack. They asked a simple question, explained Stephen Elledge of Howard Hughes Medical Institute and Harvard Medical School, leader of the companion study. What is it that KRAS-driven cancers need to live?

Despite their reputation, "cancer cells aren't super cells," Elledge explained. "They are very sick cells that have needed to make a lot of compromises." Those compromises represent sources of vulnerability. Once found, those vulnerabilities can be exploited as new avenues for drug therapy.

Most targeted cancer therapies today take aim at the cancer-causing oncogenes themselves. However, cancer cells can also develop secondary dependencies or "addictions" to other genes that are not themselves cancer-causing. Disruption of those genes can result in what the researchers refer to as "synthetic lethal interactions." In other words, loss of those secondary genes can prove fatal to cancer cells with a specific disease mutation but not to normal cells.

In search of those synthetic lethals, the teams used a method known as high-throughput RNA interference (RNAi), in which small bits of RNA are used to drastically reduce the activity of genes of interest throughout the human genome. "This method allows us, in a systematic way, to identify many more targets," Hahn added. The approach will also aid in the development of combination therapies that take aim at multiple molecular targets in rational ways, he said.

Elledge's group screened the entire genome using RNAi, which landed them a diverse set of proteins that KRAS cancers depend on to survive. They focused their attention on one pathway in particular including the enzyme known as PLK1. PLK1 is part of a family of enzymes known as kinases, which are generally recognized as good drug targets.

They report evidence that patients with KRAS tumors are more likely to survive if they also have reduced expression of genes in the PLK1 pathway. It suggests that drugs designed to target this pathway may come with a benefit to survival, Elledge said.

In the other report, Gilliland and Hahn focused their RNAi efforts from the outset specifically on the kinases. Those screens revealed that KRAS-driven human cancer cells derived from several tumor types are sensitive to suppression of the serine/threonine kinase STK33. This is true irrespective of their tissue of origin, suggesting that STK33 may be a therapeutic target in many types of cancers. They further found evidence

that STK33 keeps the cancer cells alive through its effects on a cell death pathway.

"The beauty of the strategy is that it would take only 50 to 70 percent knockdown of STK33 to kill a cancer cell," Gilliland said. "It relies on a unique frailty of the cancer cell that normal cells don't have."

Both studies demonstrate a new and powerful strategy in the fight against cancer that can now be applied to other forms of the disease as well.

In the history of cancer research, "the modus operandi is to find the gene involved and to use that to try and 'cure cancer' in some way," Elledge said. "That hasn't always worked out because those mutations aren't necessarily the best targets. This strategy allows us to ask what the best targets are, with no preconceived notions."

Source: Cell Press (news : web)