MedicalXpress

By combining technologies, researchers rapidly hunt down and find new genes that lead to cancer

November 13 2008

Using a new approach that combines scientific technologies to hunt down genetic changes involved in cancer, researchers have discovered 13 tumor suppressor genes that, when mutated, can lead to liver cancers. Twelve of those genes had never been linked to cancer before, according to the report published online in the journal *Cell*, a Cell Press publication, on November 13th.

" It's important to understand all the genetic alterations that can give rise to cancer," said Howard Hughes Medical Institute Investigator Scott Lowe of Cold Spring Harbor Laboratory. "If we understand cancer, we can treat it better by going after the molecular causes or by categorizing cancers to better predict their behavior."

One of the challenges in identifying those mutations that are responsible for causing cancer is that, as Lowe puts it, cancers are often a mess. In other words, a given cancer may contain many mutations, some that drive the cancer and others that are just along for the ride. The challenge then is to sift through all the changes found in cancer to identify those that are functionally relevant to the disease.

Recent efforts to catalogue the cancer genome—all the genes that can play a role in cancer—have been stimulated by advances in genomics, Lowe said. But a genomic approach on its own can only identify genes that are, statistically speaking, more often altered, lost or amplified, in

cancer than they are in non-cancer. It doesn't tell you what those genes do.

In the new study, the researchers first identified genes that were recurrently deleted in 100 human liver cancers. The notion was that genes frequently lost in cancer likely include tumor suppressors that normally keep cancer at bay. That effort turned up 58 deletions, each including one to 46 genes, for a total of 362 genes.

They then identified mouse versions of 301 of those human genes and obtained so-called short hairpin RNAs (shRNA) corresponding to each of those. shRNA is a sequence of RNA that makes a tight hairpin turn and that can be used to silence genes in a process known as RNA interference. Those shRNAs were used to silence the cancer-linked genes one by one in liver progenitor cells that were then transplanted back into mice.

The mice they studied already had genetic changes known to occur in liver cancer but that aren't enough on their own to produce the disease. The idea, Lowe said, was to see which of the genes lost in human cancers could push those mice over the edge and into tumor development.

Their strategy quickly led them to 13 genes that, when silenced, could lead to cancer, most of them completely new. "Some of the genes make sense and suggest straightforward ways to follow up," Lowe said. "Others are completely unknown."

In fact, that's one of the big advantages of the new approach. It makes very few assumptions about the kinds of genes that are likely to play a role in cancer. "It allows the opportunity to tap into new and unappreciated areas of cancer biology we never would have looked at," he said.

The gene discoveries already suggest some possible new avenues to cancer therapy.

Indeed, two of the new tumor suppressors they identified represent secreted proteins. That may be good news in a practical sense since treatments designed to deliver those proteins systemically may hold promise for therapy.

" It's hard to put a gene back, but if it's a secreted protein, in theory you could inject the protein back," he said. They haven't yet validated that idea, but it's something he says his team intends to follow up on.

One of the other genes they found called XPO4, which encodes a nuclear export protein, may sensitize cells to drugs known as SMAD3 inhibitors that are now in clinical trials, they said. Since XPO4 loss is associated with poor survival in breast cancer patients, they noted that agents targeting this pathway may turn out to be clinically important.

The genes they uncovered also turned up a surprise, Lowe said. While most scientists imagine that deletion of a region containing multiple genes will have just one gene with relevance to cancer, they found multiple instances in which more than one gene within a deleted region can lead to cancer.

" Apparently, there is a high incidence of cancer genes that are physically next to each other in the genome," he said. The findings also show that there are just a lot of genes that can cause cancer. "It may explain why cancer is so heterogeneous; there are a lot of possible combinations to get there."

The same approach applied here to liver cancer can be applied to other forms of cancer, including leukemias, lymphomas, breast and some brain cancers, Lowe said. They also suspect that there will be more to find in

the case of liver cancer.

Source: Cell Press