Researchers identify new mechanism used by cells to reverse silenced genes

June 30 2011

Scientists at Fox Chase Cancer Center have discovered a new mechanism used by cells in the body to turn on silenced genes. This process is critical in preventing the development of cancer -- suggesting the possibility of new therapies that might target the specific changes underlying the disease. The findings will be published online in the journal *Cell* on June 30, 2011.

The process investigated by Alfonso Bellacosa, M.D., Ph.D., Associate Professor at Fox Chase, and his colleagues, is called methylation, in which the cell chemically tags genes to turn them off. More specifically, the cell silences a gene by adding a chemical compound known as a methyl group; without that methyl group, the gene remains active.

It's a process of great interest to scientists, Bellacosa explains, because methylation is a key part of normal gene regulation – but, when it silences the genes that normally suppress tumors, it results in cancer. Indeed, some cancer drugs work by demethylating—meaning, removing methyl groups from DNA. But those drugs will demethylate DNA non-specifically, he says, causing side effects and other problems.

Scientists have been investigating for years how the cell adds methyl groups to genes to turn them off, but have been less clear about the process of demethylation. For instance, some have suspected that demethylation only occurs passively, such as when DNA with an attached methyl group replicates, creating new DNA without a methyl group.

Now, Bellacosa and his team present the first direct evidence that demethylation can be, in fact, an active process, controlled by a specific protein – along with clues about how to act on it in a targeted way.

The researchers found that one protein called thymine DNA glycosylase or TDG—known to help repair DNA—is also responsible for removing methyl groups from DNA. Studies with mice that lacked TDG activity indicated the gene was needed for survival. Looking closer at the mouse embryos that didn't survive, they saw that the methylation was all awry – genes that would normally be demethylated weren't, and remained silenced.

TDG needs a second protein to demethylate DNA, says Bellacosa - so future therapies might be devised to direct this machinery to turn on specific anti-cancer genes, for instance. "Since we now know there are proteins that actively affect demethylation, then we can imagine a new type of cancer therapy that demethylates specific genes. We would have a more precise and more targeted type of therapy."

What's also exciting, explains Bellacosa, is the discovery that the cell uses tools that normally repair DNA for a very different purpose: reversal of gene silencing by demethylation. "It's a totally new concept – that DNA repair has this additional new function."

Beside cancer, this knowledge may also be applied to other diseases with alteration of methylation. He cautions, however, that scientists still have not figured out how to target therapy to specific genes, so any benefits to this discovery are years away. "This is a very fundamental study that gets at the process by which genes are turned on or turned off," he says. "We may be several years away from taking full advantage of this new knowledge. But we will get there."

Provided by Fox Chase Cancer Center