Why cholesterol-lowering statins might treat cancer

January 19 2012

Cholesterol-lowering statins seem to keep breast cancer at bay in some patients. Now researchers reporting in the January 20th issue of the journal *Cell*, a Cell Press publication, provide clues about how statins might yield those unexpected benefits. The findings also suggest that mutations in a single gene could be used to identify tumors likely to respond to statin therapy.

"The data raises the possibility that we might identify subsets of patients whose tumors may respond to statins," said Carol Prives of Columbia University. "Of course we can't make any definitive conclusions until we know more."

Prives said that a clinical trial of statins in breast cancer based on the mutation status of the tumor suppressor, p53, may be in order. The p53 tumor suppressor acts to regulate many aspects of cell proliferation, generally putting the brake on uncontrolled growth.

More than half of all human cancers carry mutations in the p53 gene. Many of these mutations don't simply disrupt the normal function of p53, they also endow p53 with new functions that promote, instead of inhibit, cancer formation. Mice lacking p53 develop cancer and die, Prives explained, but mice carrying tumor-derived mutant forms of the p53 gene suffer from more aggressive disease. What these mutant forms of p53 are actually doing is a big question in cancer research.

Prives' team designed experiments to sort this mystery out. By studying

cancer cells grown in an artificial system that resembles the three-dimensional structures in the human breast, the researchers learned that cells carrying mutant p53 grow in a disorganized and invasive manner, characteristic of human breast cancers. When the researchers lowered the levels of mutant p53, the 3D cell cultures grew more normally.

Further studies, led by study first author William Freed-Pastor, traced the structural changes to a cholesterol-building pathway (called the mevalonate pathway). This is the same pathway targeted by cholesterol-lowering statins. When the mutant p53 cells were treated with statins, they stopped their disorganized, invasive growth, and in some cases, even died. Importantly, the effects of the drugs were erased when intermediates of the mevalonate pathway were added back in, additional proof that the drug wasn't working in some other, off-target way.

With collaborators in Norway, Prives and Freed-Pastor analyzed breast cancer tissue taken from patients to find that mutations in p53 and elevated activity of mevalonate pathway genes tend to go together in human tumors too. While those findings are encouraging that the cell culture findings may have clinical relevance, Prives emphasizes that it will take considerably more work to confirm that.

"It is what it is," she says. "There are great implications, but nothing clinical yet. Perhaps one could do a clinical trial, and that may support these findings, or it may be more complicated."

Provided by Cell Press