Discovery Raises Questions About Some Therapies Designed to Treat Half of all Human Cancers

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Biologists at the University of California, San Diego have uncovered a new way by which common mutants of a critical human tumor-suppressing gene can promote tumor progression, a finding which may explain why some cancer treatments targeting human cancers with these mutants have proven ineffective.

Their discovery, detailed in a paper published in this week's early online issue of the journal *Nature Cell Biology*, also raises questions about the effectiveness of certain cancer therapies that may be unintentionally enhancing rather than retarding the progression of human cancers by expressing the mutated cancer-promoting tumor suppressor.

"Our findings could explain the resistance of human cancer cells expressing the mutants of this important tumor suppressing gene, p53, to current cancer therapies," says Yang Xu, an associate professor of biology at UCSD who headed the research team, which included Hoseok Song, a postdoctoral fellow at UCSD, and Monica Hollstein, a collaborator at England's University of Leeds.

Scientists have long known that the p53 gene is critical in suppressing the formation of tumors in the human body. Over the past 20 years, researchers have also discovered that when the p53 gene is mutated, which occurs in about half of all cancer cases, the p53 mutant protein not only loses its tumor suppressing properties, but can promote the progression of cancer and the resistance of cancer cells to drug therapies.

"The expression of p53 mutants is correlated with the poor prognosis of cancer patients," notes Xu. "Therefore, it is critical to understand the gain of function of p53 mutants in promoting cancer and resistance to current cancer therapy."

Using mutant mice that express the most common forms of human p53 mutants, Xu's team found that the mutant proteins affected a multi-protein complex called Mre11complex that attaches to double-stranded breaks in DNA, the key genetic material of the cell, and participates in its repair. This prevented cells in the mice, as well as human cancer cells, from recognizing DNA damage, the scientists discovered, and led to genetic instabilities such as the translocation of chromosomes that can significantly increase genetic mutations in the cells, eventually promoting the growth of cancer cells.

"Current cancer treatments, including radiotherapy and many forms of chemotherapy, kill cancer cells by inducing DNA double-stranded break damage in their genomes," says Xu. "Our findings could explain why cancer cells with p53 mutants are resistant to such therapies."

In addition, because such treatments attempt to kill cancer cells by inducing genetic mutations through DNA strand-break damage, the findings suggest they may lead to genetic mutations if the DNA damage is not repaired efficiently and properly. In other words, they may be unintentionally enhancing rather than retarding cancer progression by inducing genetic mutations of the mutant cancer-promoting genes.

"These cancer treatments may be further promoting genetic instability in p53 mutant-expressing cancer cells because they lack the ability to recognize DNA damage," says Xu.

Source: University of California San Diego