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Study finds key to calling back-up help when tumor-fighter p53 goes down

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Tumor suppression, the family business of the sibling genes p53, p63 and p73, is undermined from within by the split personalities of p63 and p73, which each produce protein forms that not only block the work of the other two genes but also shut down its own cancer-stifling fraternal twin.

In a presentation at the AACR Annual Meeting 2013, scientists from The University of Texas MD Anderson Cancer Center demonstrate that tumor suppression can be restored in mice that lack p53 by knocking out the ΔN isoforms of p63 and p73 that interfere with tumor suppression. Isoforms are proteins made from the same gene that are often produced by alternative gene promoter usage or splicing.

"In many cancers, the tumor-suppressor p53 is inactivated by genetic mutations or is deleted outright, damage that is exploited by cancer to develop and grow," said study senior author Elsa Flores, Ph.D., associate professor in MD Anderson's Department of Biochemistry and Molecular Biology.

"We can use the other family members to compensate for the loss of p53 as we learn more about them and how they function," Flores said. Attempting to restore p53 expression in tumors has so far been largely ineffective in cancer treatment.

The youngest of the three genes, p53, was the first discovered in 1979. It controls the activity of dozens of other genes that detect abnormal cells

during cell division, attempt to repair the damage and order the defective cell to kill itself if it can't be fixed.

Two protein forms: TA version inhibits cancer, ΔN version thwarts TA

The Human Genome Project identified p63 and p73 in 1997, Flores said. Both genes have a longer evolutionary history than p53 and can perform the same cancer-blocking function. Or rather, one isoform of each gene can do the job.

Research by Flores and others has shown that p63 and p73 come in two major isoforms: the transactivation versions (TAp63 and TAp73) that act like p53, and the Delta-N versions (ΔNp63 and ΔNp73), which appear to act as oncogenes, helping tumors form and grow by blocking suppressors.

Flores, study first author and presenter Avinashnarayan Venkatanarayan and colleagues knocked down ΔNp63 and ΔNp73 in a thymic lymphoma mouse model that lacked p53. Mice with ΔNp63 and ΔNp73 blocked had a lower incidence of lymphoma, and greater expression of genes usually targeted by p53 that regulate the cell cycle and promote death of abnormal cells.

"This suggests that ablating the ΔN isoforms facilitated increased activity by genes that induce cell cycle arrest and apoptosis that are downstream targets of p53," Venkatanarayan said.

Knocking out ΔNp63 and ΔNp73 shrinks tumors in mice that lack p53

To further demonstrate the effect, the researchers then deleted ΔNp63

and ΔNp73 by injecting adenoviral-CRE in the thymus of ΔNp63 and ΔNp73 conditional knockout mice with p53 knocked out. With the two inhibiting isoforms blocked, treated mice had significant tumor shrinkage within three weeks.

The team also found that ΔNp63 and ΔNp73 hinder tumor suppression by binding to the promoter sites of TAp63 and TAp73; further supporting the thesis that blocking the ΔN isoforms frees the TA versions to repress tumors.

A test in human cancer cell lines showed that knocking down ΔNp63 and ΔNp73 led to cell cycle arrest and apoptosis when p53 was completely deleted. In cell lines with mutated p53, TAp63 and TAp73 were prevented from activating tumor-killing genes by the mutated p53.

"Mutant p53 actually hinders its family members from taking up the tumor-suppressing cause when p53 is dysfunctional," Flores said. "Our research now focuses on overcoming the mutant p53 effect in these cancer cell lines.

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