Scientists show TAp63 suppresses cancer metastasis

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Long overshadowed by p53, its famous tumor-suppressing sibling, the p63 gene does the tougher, important job of stifling the spread of cancer to other organs, researchers at The University of Texas MD Anderson Cancer Center report in the Oct. 21 issue of *Nature*.

Not only does a specific form of p63 protein block metastasis, but it does so by activating the enzyme Dicer, which plays a pivotal role in the creation of micro RNAs, tiny bits of RNA that regulate a host of cellular processes.

"p63 is a master regulator of metastasis, an important role in its own right, but before now, no one understood how Dicer was regulated," said senior author Elsa R. Flores, Ph.D., associate professor in MD Anderson's Department of Cellular and Molecular Oncology.

Dicer's central role in miRNA regulation indicates the p63-Dicer connection likely has far-reaching downstream implications for many other cellular processes, Flores said. Dicer, as its name implies, slices up single pieces of non-coding RNA that then may suppress or alter coding RNA that tells the cell's protein production machinery what protein to make.

The team also demonstrated that p63 activates one miRNA that also suppresses tumor formation and metastasis. Metastatic disease accounts for about 85 percent of all deaths from cancer.

Previous studies have shown that mutant p53, commonly found in metastatic human cancer, inactivates p63. "Our findings indicate that reactivation of TAp63 in tumors lacking TAp63 expression or in those expressing mutant p53 could potentially benefit patients with metastatic disease," Flores said.

When TAp63 is missing, metastasis follows

A puzzling fact about p63 is that it's overexpressed in some tumors and underexpressed in others. Flores explained the difference depends on which form of the protein is produced. The TAp63 protein includes an area that is essential for activation of downstream target genes that protect cells from DNA damage. A second version that lacks this TA domain acts against p53, p63 and p73 genes and is associated with cancer progression.

The researchers examined the role of TAp63 by developing strains of mice lacking both copies of the TAp63 gene and others that had one intact and one knocked out version. They found:

- Mice lacking one or both copies of TAp63 spontaneously developed carcinomas (tumors that begin on the epithelium, or lining, of an organ, the most common type of solid tumor) and sarcomas, tumors of the bone, fat, cartilage. These tumors frequently metastasized to the liver, lungs and brain, as is frequently seen in human cancer.

- Mice lacking one or both copies of p53 develop non-metastatic tumors. Mice that have lost one copy each of p53 and TAp63 developed invasive and metastatic cancers.

- Mice with no copies of the p53 gene that lack one or both copies

of TAp63 developed highly metastatic carcinomas and sarcomas.

The team found that mice lacking only one copy of TAp63 had more aggressive tumors than mice that lack both copies. Their finding was similar to recent research by others indicating that loss of Dicer had the same effect - it is worse when one copy of the gene is inactive.

High-grade tumors have low levels of TAp63, Dicer and miR-130b

They compared expression levels of TAp63, Dicer, and the tumor-suppressing micro RNA miR-130b in a large number of samples of human head and neck, lung and breast cancers and found that high-grade tumors expressed low levels of all three.

Additional experiments showed that TAp63, but not p53, binds to the promoter region of the Dicer gene, where it can activate expression of the Dicer enzyme. Re-expressing Dicer in TAp63-deficient cells blocked the ability of tumor cells to migrate and invade, indicating that TAp63 suppresses invasion through regulation of Dicer.

Similarly, the researchers found that TAp63 binds to the miR-130b promoter and that re-expression of both Dicer and miR-130b in TAp63-deficient cells results in greater suppression of metastasis. "This indicates that TAp63 regulates both Dicer and miR-130 to suppress metastasis," Flores said.

Flores and colleagues are investigating how the other isoform of p63, deltaNp63, affects cancer development and metastasis. The goal is to understand the mechanisms of the p63 isoforms in cancer to improve targeted therapy for patients with alterations in the p53/p63 pathway.

Family of genes works together

Flores and colleagues study the p53, p63 and p73 genes. "Our main goal is to understand how the family works as a whole," Flores said. For example, p53 plays a vital role in monitoring cell replication and ordering irreparably damaged cells to kill themselves. When p53 is suppressed, as it is in many cancers, defective cells multiply, fueling the disease.

However, therapies designed to reactivate p53 don't work. "One reason therapies fail is they don't take into account the entire family," Flores said. In an earlier Nature paper, Flores and colleagues showed p53 can't order a bad cell to kill itself without p63 and p73 also being active.

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