

New Role for Tumor Suppressor Gene in Pancreatic Cancer

Mutations in the p53 gene contribute to many cancers. A Damon Runyon scientist explores the gene's ability to suppress pancreatic cancer.

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P53, the most frequently mutated gene across all human cancers, is mutated in the majority of pancreatic cancers. But despite the overwhelming evidence that p53 mutations contribute to cancer progression, therapies targeting mutant p53 have had limited success, suggesting an incomplete understanding of the protein's function. In order to understand what goes wrong when p53 mutates, researchers need a clearer picture of how normal p53 prevents tumor development in the first place.

P53 protein binding to DNA
Courtesy of Damon Runyon Research Foundation

Like p53 mutations, the stages of pancreatic cancer development have been the subject of intensive study. The pancreas contains acinar cells, which synthesize and store digestive enzymes, and ductal cells, which deliver those enzymes to the small intestine. Acinar cells are highly plastic, meaning they can differentiate into other cell types. This is a useful property for pancreatic tissue regeneration after injury. In response to certain genetic or environmental stressors, however, acinar cells can morph into ductal-like cells, an event known as acinar-to-ductal metaplasia (ADM). This, in turn, can give rise to precancerous lesions called pancreatic intraepithelial neoplasias (PanINs), which ultimately develop into pancreatic cancers.

So when does p53 normally swoop in to save the day? The working theory has been that p53 interferes at the end of this pathway, preventing the transition from PanINs to cancer cells. But [new findings](#) from former Damon Runyon Scholar Laura D. Attardi, PhD, and her lab at Stanford University School of Medicine indicate that the tumor suppressor protein actually plays multiple earlier roles.

Rather than inhibit p53 in order to deduce its function, the team observed a mouse model with a

hyperactive version of the protein. They found that, with p53 on overdrive, fewer acinar cells underwent acinar-to-ductal metaplasia and fewer PanIN cells accumulated than in mice with normal p53. The hyperactive p53 also more effectively suppressed the activity of mutant KRAS proteins, which trigger rapid cell growth and are found in 90% of pancreatic cancers.

With this study, Dr. Attardi and her team have uncovered two new mechanisms by which p53 suppresses pancreatic tumor growth. Together, their findings support the exciting idea that boosting p53 activity may work as a preventative therapy for patients at risk of developing pancreatic cancer. Therapies that target mutant p53 continue to hold promise, but to paraphrase Bing Crosby, drug developers might consider “accentuating the positive” in addition to “eliminating the negative” in this case.

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<http://beta.docker.cancerhealth.com/blog/new-role-tumor-suppressor-gene-pancreatic-cancer>