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Mutations in gene promoters reveal specific pathway pathologies in pancreatic cancer

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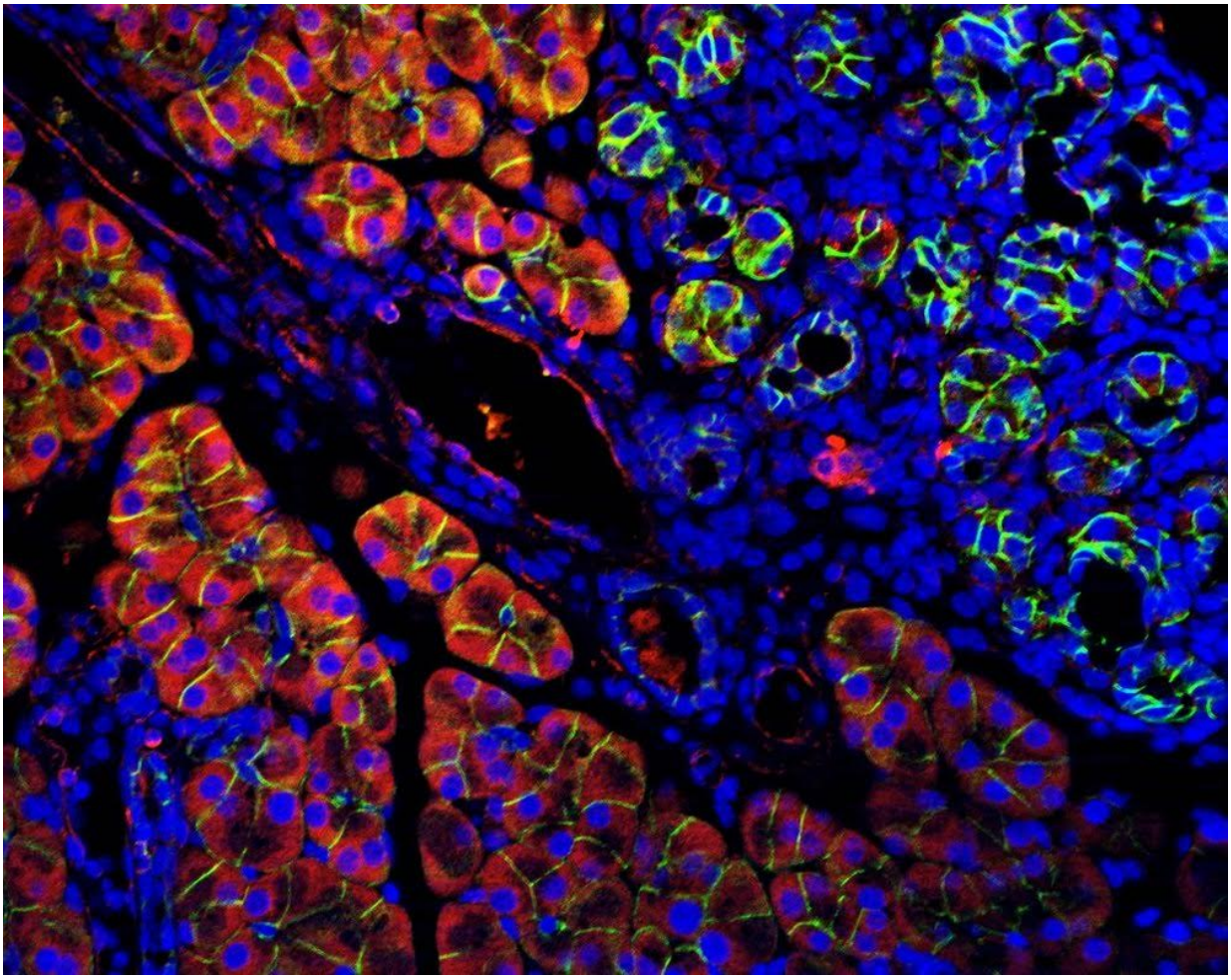

The cell adhesion pathway is among those affected by newly discovered mutations in gene promoter regions within pancreatic cancer cells. This image of cancerous pancreatic tissue shows how relatively healthy cells, stained red, remain clearly marked by junctions (stained green) at which adjacent cells adhere to one another. Much of the upper right side of the image is populated by

proliferating cancer cells (each blue dot represents an individual cell nucleus). Most of these cells have lost their ability to adhere to one another. This is a harbinger of metastasis. Credit: Michael Feigin, Tuveson Lab, CSHL

Over the last decade, it has made good sense to study the genetic drivers of cancer by sequencing a tiny portion of the human genome called the exome - the 2% of our three billion base pairs that "spell out" the 21,000 genes in our chromosomes. If cancer is a disease precipitated by changes in genes, after all, we need to know lots about how and when different genes change in the many distinctive subtypes of cancer.

But a new wave of research, exemplified by a study published today in *Nature Genetics* by a team at Cold Spring Harbor Laboratory (CSHL), is significantly improving our ability to target cancer cells by studying "the other 98%" of DNA in human chromosomes, sometimes called the genome's "dark matter."

Research led by Michael Feigin, Ph.D., a postdoctoral researcher in the laboratory of CSHL Professor David Tuveson, M.D., Ph.D., looked closely at cells sampled from 308 people with pancreatic cancer, one of the most lethal malignancies, with a 5-year survival rate of only 8%. Importantly, the full genome of the sampled pancreatic cancer cells was sequenced, not just the 2% that comprises the exome.

This enabled Feigin and colleagues including computational biologist Tyler Garvin, Ph.D., formerly of Adjunct Associate Professor Michael Schatz's lab, to focus narrowly on genome segments called gene promoters. These segments of DNA typically lie adjacent to, but not within, the sequences of the genes that they regulate. Therefore, promoters are "invisible" when only the exomes of cells are sequenced, as has been commonplace in cancer genetics research.

"Promoters are important in determining when specific genes are turned on and off," says Feigin, "and I became interested in figuring out whether mutations within promoters - as opposed to within the genes they regulate -consistently affects the way cancers develop and sustain themselves."

The team "looked all across the genome," Feigin says, "and, interestingly, while we did find mutations in promoters, we never found clusters of these mutations near any of the genes that prior research had already told us were typically mutated in pancreatic cancer."

Genes called KRAS and p53 are mutated in the majority of pancreas cancer cells, for example. But mutations in promoters sifted out of mountains of data by the team's novel mathematical formula, or algorithm, called GECCO, lay in genes never before implicated in pancreatic cancer.

Feigin points out that mutations in a promoter can affect how much protein is generated by the gene its regulates. In this way these mutations are unlike those usually found in KRAS and p53, for example, which impair or otherwise alter the function of the proteins they encode.

While the promoter mutations were not near known pancreatic cancer genes, the team found that they affected some of the same biological pathways in cells. Most prominent among these were promoters affecting genes involved in cell adhesion and axon guidance. Both pathways involve cascades of interactions among dozens or hundreds of proteins, each one encoded by a different gene.

The new data thus "adds depth to our understanding of things that go awry in these critical pathways, sometimes promoting cancer formation, other times providing cancer cells with advantages that enable them to crowd out healthy cells," comments Dr. Tuveson, who in addition to

leading a lab at CSHL is the Director of CSHL's NCI-designated Cancer Center and Director of Research for the Lustgarten Foundation, the nation's largest philanthropic funder of pancreatic cancer research.

The cell adhesion pathway affected by newly discovered mutations in gene promoter regions is important for obvious reasons in cancer: cancer cells want to grow and proliferate, a process that can culminate in their migration from their tissue of origin. Once they have broken free, they can travel via the bloodstream to other places in the body, a process called metastasis that is often responsible for cancer fatalities.

The axon guidance pathway associated with promoter mutations has a less obvious but no less important role in pancreatic cancer. "In pancreas cancer, nerves are often attracted to or get attracted to the tumor," explains Feigin, "and sometimes they grow right through the tumor. This is one of the reasons pancreas cancer is so painful."

It's possible, Feigin says, that axon guidance signals - and indeed cell adhesion signals - "are actually being used by tumor cells" to gain advantages over healthy cells. "Tumors, for example, can actually spread via nerves; this is called peri-neural invasion."

A question naturally arises: if these and several other pathways were already implicated in pancreatic cancer, what is the advantage of the new knowledge about promoter mutations? The answer, the team explains, has to do with finding ways to fight pancreatic cancer, one of the major cancer types that remains profoundly resistant to all existing treatments. The more that is known about defects in specific pathways in specific cancer types, the more specific molecular targets - pathway components - appear in the sights of researchers trying to disable or enhance a given pathway.

More information: Recurrent noncoding regulatory mutations in

pancreatic ductal adenocarcinoma, *Nature Genetics* (2017). nature.com/articles/doi:10.1038/ng.3861