

Two Fred Hutch Studies Identify Pancreatic Cancer Biomarker Driving Basal Disease

A key biological signature provides clinics a faster, cheaper way to tell pancreatic cancer subtypes apart—and might lead to therapies.

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The field of [pancreatic cancer](#) needs a measurable biological difference — a biomarker — to tell the difference between two subtypes of the disease with a timely and cost-effective clinical test.

Fred Hutch Cancer Center researchers have discovered this indicator in the form of two cellular building blocks, or proteins, operating in tandem that can tell the subtypes apart as distinctly as the red light and green light on a traffic signal.

Pancreatic cancer expert [Sita Kugel, PhD](#), and her colleagues in the [Human Biology Division](#) recently [published their results](#) in the journal Clinical Cancer Research.

“With our combination biomarker, you can now do that very quickly,” said Kugel, director of Basic and Translational Research in Gastrointestinal (GI) Oncology at Fred Hutch.

Pancreatic ductal adenocarcinoma, or PDAC, is projected to become the second leading cause of cancer-related death by 2030.

PDAC — one of the deadliest cancers in the United States, with a current five-year survival rate of 13% — strikes in two forms or subtypes: classical and basal.

The basal subtype is even more aggressive and lethal than classical, accounting for about 20% of PDAC.

Knowing whether PDAC is classical or basal could help doctors tailor chemotherapy and direct patients to [appropriate clinical trials](#).

But the subtypes vary by differences in gene expression that can’t be distinguished just by looking at tumor samples under a microscope.

The biomarkers Kugel's lab tested predict survival, how a tumor is likely to respond to specific treatments and whether it will become resistant to drugs.

In a separate study [recently published](#) in the journal Nature Communications, Kugel's lab found that expression of the biomarker not only correlates with the basal subtype, it is sufficient to define the basal version of the disease.

"It's actually orchestrating the creation of that subtype," Kugel said.

Understanding that orchestration could lead to potential therapies targeting that mechanism.

Finding a faster way to tell subtypes apart

In the past, researchers have distinguished the subtypes of PDAC using a sequencing method called RNA-seq that measures which genes are being expressed inside the tumor cell's nucleus and how often. But this kind of analysis is too costly and time-consuming to perform on all patient samples.

"We quickly realized that without a faster way of subtyping, it would not be actually feasible within the clinic," Kugel said.

Several labs have searched for a stand-in, a biomarker, that could quickly, cheaply and reliably distinguish classical tumors from basal.

The search has led to a few proteins that could distinguish the two subtypes.

None are ready for clinical use yet, but a few proteins look promising.

One of them, GATA6, regulates gene expression during embryonic development and in adult tissues. Classical PDAC tumors have much more GATA6 than basal tumors and respond better to chemotherapy.

The absence of GATA6 could indicate the basal subtype, but that inference isn't reliable enough for clinical use.

Kugel's lab focuses on another protein, HMGA2, which influences the structure of chromatin — DNA and the packaging materials that help cram it into a cell's nucleus. Their work has shown that the presence of HMGA2 closely associates with the basal subtype.

Co-authors Stephanie Dobersch, PhD, and Naomi Yamamoto, a graduate student, have explored various aspects of HMGA2's role in PDAC, helping each other on research studies in the Kugel Lab.

"They worked together very effectively, so between the two of them, this is really a very collective effort," Kugel said.

Combining biomarkers works best

For the Clinical Cancer Research study, the team analyzed hundreds of patient tumor samples using different techniques to establish the viability of HMGA2 as a biomarker for prognosis and the likelihood of the cancer developing resistance to treatment.

Because tumor samples were linked to detailed clinical treatment histories, the team could link high or low levels of HMGA2 with the disease progression for those patients.

The analysis revealed that HMGA2 was a more reliable biomarker for basal than merely the absence of GATA6.

However, HMGA2 paired with GATA6 did the best job of telling the samples apart and predicting what happened with each patient, including how they responded to different therapies.

Patients whose tumors had high levels of GATA6 and low levels of HMGA2 had better outcomes associated with the classical subtype.

Patients with tumors showing the reverse — high levels of HMGA2 and low levels of GATA6 — had poorer outcomes and responses to treatment, indicating the basal subtype.

The difference in median survival between those two groups was 10.5 months.

Because PDAC exacts a higher toll on Black patients than their share of the population, the team wanted to make sure they were well represented in the study.

Of the tumors the team analyzed for the study, 11.5% were from Black patients, a larger share than has been included in previous subtyping studies.

The combined biomarker worked for them as well.

Lighting up subtypes like a traffic signal

The best way to look for those biomarkers is RNA sequencing, which requires high quality samples.

However, a staining technique called [multiplex immunohistochemistry](#) can tag proteins with fluorescent dyes in a tissue sample that lights up under a special microscope.

Kugel's team tagged GATA6 proteins with green fluorescence and HMGA2 proteins with red and then used a special microscope to see if they could tell the subtypes apart.

The samples that glowed green were classical and the ones that glowed red were basal, just like a traffic signal.

That method not only distinguishes subtypes, it also defines critical features of the [tumor microenvironment](#) — the [surrounding normal cells, molecules, and blood vessels feeding tumor cells](#) — making it easier to anticipate how fast cancer will return after initial treatment.

It's an approach better suited for clinical use than RNA sequencing because it tolerates poorer quality samples and delivers much faster results (one to two days instead of up to 10 days).

Moving from correlation to cause

In the Nature Communications study, Kugel's lab found that HMGA2 isn't merely correlated with the basal subtype like an innocent bystander; it's the culprit creating the more lethal version of the disease.

"I'm super excited and proud about that connection because it really gives more gravitas to the finding," Kugel said.

Previous research has shown that HMGA2 and another protein, LIN28B — which normally are produced only in the earliest stages of life when embryos are growing— are re-activated in pancreatic cancer.

But it was unknown exactly how that re-activation promoted the initiation and progression of the disease.

Kugel's team solved the mystery by testing various ways that cells receive signals to grow, and they discovered a series of events involving HMGA2 that hobbles a cell's ability to suppress tumors.

The pathway they discovered works like this:

LIN28B regulates HMGA2, which in turn regulates the activity of a protein called PP2A that normally keeps cells healthy by turning off growth signals when growth is no longer needed.

When it's working properly, PP2A suppresses tumors, but to do that, it needs the help of yet another protein that adds a chemical tag to PP2A called a methyl group.

The team figured out HMGA2 messes up PP2A's function by interfering with that methyl tagging.

When PP2A can no longer suppress tumors, the cancer grows.

The team tested it two ways to make sure that HMGA2 was the culprit.

When they removed HMGA2 from basal cells, those cells became more like the classical, less aggressive subtype.

And when they added HMGA2 to classical cells, those cells became more basal.

“We could actually take the classical subtype, overexpress HMGA2, and drive basal identity,” Kugel said.

Kugel’s lab has created a genetically engineered mouse to model that basal biology.

“This K28C mouse is brand new to the field,” Kugel said. “It’s been hard to study the basal subtype in mouse models. This gives us the power to do that.”

They confirmed that the same mechanism driving the basal subtype in cells cultured in the laboratory also works in the K28C mice.

The mechanism that fuels the basal subtype may also provide the key to killing it.

When HMGA2 hobbles tumor suppression, those basal cells become [addicted to churning out a lot of proteins](#).

And that new dependency creates a vulnerability that could be exploited with drugs that inhibit protein synthesis or interfere in other ways with the growth signaling pathway the team identified.

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