

New Technique Could Help Make Precision Medicine More Widely Available

Simple CUT&Tag adaptation gives information about genetic regulatory elements in formalin-fixed tumor samples

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Precise, tailored cancer diagnosis and treatment, known as precision oncology, is gaining steam. But most methods able to look deeply at the molecular characteristics of a patient's tumor rely on fresh or frozen cells—and it's rare that surgically removed tumor tissue gets this treatment.

Tumor samples usually get soaked in formalin and then embedded in paraffin wax, ready for a pathologist to examine under a microscope. Unfortunately, it's difficult to look for DNA mutations or changes in how genes are regulated in formalin-fixed, paraffin-embedded, or FFPE, tissue samples.

Now that may be changing. Fred Hutchinson Cancer Center scientists recently published a method in Nature Communications that [adapts a technique called CUT&Tag](#) to allow investigators to examine key gene regulatory elements in FFPEs.

"The data we get is so good that we can use it to identify the key genes that are involved [in tumors]," said Fred Hutch molecular biologist [Steven Henikoff, PhD](#), who led development of the original CUT&Tag method and modified it for use on FFPEs.

Henikoff initially developed his new strategy, dubbed [CUTAC](#), during the COVID-19 pandemic. CUTAC works around DNA packaging proteins to reveal regions that are important for regulating transcription, the process of turning information stored in DNA into RNA. Henikoff's latest modifications enable its use on FFPEs.

Using CUTAC on mouse FFPEs, Henikoff and his collaborators were able to reveal previously unknown patterns of gene regulation in cancer. This included highlighting certain small, non-protein coding RNAs (called microRNAs) that may play a role in cancer and are difficult to detect using other methods.

The ability to mine molecular information from FFPEs "could allow us to do retrospective studies

that link tumor biology with patient outcomes using samples already collected and stored,” said co-author and Fred Hutch brain cancer researcher [Eric Holland, MD, PhD](#), who heads the Human Biology Division and holds the Endowed Chair in Cancer Biology.

The new method could help scientists explore biological processes beyond cancer, the researchers said. They are working with EpiCypher, Inc., the commercial provider of CUT&Tag that holds the licenses for CUT&Tag and adapted methods, to commercialize the newest method for use in FFPEs.

FFPEs: Potential Treasure Trove of Tumor Molecular Information

Many patients with cancer receive surgery or biopsies as part of their care. To preserve them for long-term storage and review by pathologists, it’s standard practice to soak these tissue samples in formalin and then embed them in paraffin. Scientists and physicians have been creating formalin-fixed, paraffin-embedded tissue samples, or FFPEs, since the late 19th century.

“Every pathology department in every hospital is full of these,” Holland said.

In the past decade or two, technological advances have made it possible for scientists to go far beyond a microscope-based look-see at tumor tissue. They can get detailed peeks inside individual cells, learning about gene sequences, which genes are turned on and off, and even how the DNA is packaged and bundled to regulate gene expression—all of which can have powerful influences on cancer development and progression.

But these technologies work on fresh or frozen cells—leaving the wealth of tumor molecular information stored in FFPEs nearly unreadable.

“But if you want a future in which we sequence everyone’s tumor and do something with that information, we can’t change everything. We need to start with what oncologists are using,” Holland said. “A group of us [at Fred Hutch] have been trying to get sequencing to work out of paraffin.”

Henikoff was interested in getting information that goes beyond the DNA sequence. The DNA packaging proteins that help it fit within a cell, and the molecular modifications that help regulate gene activation are called chromatin. Chromatin works like a computer program, helping orchestrate which genes are turned on and off.

CUT&Tag, for [Cleavage Under Targets & Tagmentation](#), reveals chromatin patterns in DNA. Henikoff and his team developed the method to map chromatin in single cells. During the pandemic, he simplified the protocol to allow researchers to map more loosely packaged “accessible” chromatin areas at home. This adaptation was dubbed CUTAC, for Cleavage Under Targeted Accessible Chromatin.

Henikoff discovered that with a couple of simple changes to CUTAC, he could map regions of

compacted chromatin and also where RNA-building enzymes (RNA polymerase II) are paused on DNA in FFPEs. These enzymes pause at regions that regulate transcription, the process of using a DNA sequence to build an RNA molecule. The pattern of active regulatory regions in a tissue can give important clues about the biological processes occurring — and whether they’ve changed in the tumor.

“It gives you the ultimate checkpoint for gene regulation. So if something goes wrong in cancer, it’s going to go wrong at the transcriptional level. It’s going to go wrong here,” Henikoff said. “We’re using RNA pol-II to tell us about regulatory elements and how they change in cancers.”

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