Unlocking More Information From Liquid Biopsies

Gavin Ha explains his research on liquid biopsies—blood samples with traces of DNA that provide molecular details about cancer.

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Fred Hutchinson Cancer Center computational biologist Dr. Gavin Ha received a 2022 National Institutes of Health Director's New Innovator Award to fund his work aimed at unlocking new and useful information from cell-free tumor DNA in cancer patients' blood. Ha is working to enhance the information that scientists and cancer doctors can glean from liquid biopsies—blood samples with traces of DNA that provide molecular information about tumors—to improve cancer diagnosis, treatment selection and disease monitoring.

New Innovator Awards are part of the NIH's High-Risk, High-Reward program and support exceptionally creative early-career investigators carrying out innovative, high-impact projects. The $1.5 million, five-year award will support Ha's efforts to develop novel computational tools and cutting-edge assays that provide new information about tumor cell state from cell-free DNA circulating in the blood.

Both healthy and cancerous cells release DNA into the bloodstream. Most liquid biopsy strategies focus on cancer-associated changes to DNA sequence that can reveal the presence of cancer or potential treatment targets. But DNA sequence isn't the whole story, Ha said.

Instead, he focuses on what allows these DNA fragments to persist in the blood: protection from DNA packaging proteins. All six feet of our DNA is neatly bundled into each cell, and this packaging also helps our cells regulate which genes are turned on and off. Gene expression, in turn, affects how a cancer cell responds to or resists treatment, and even how it may change into a different type of cancer cell.

"We're looking at a whole other, important layer of information about tumor cells that we believe can be more directly related to cells becoming resistant or responding to treatment," Ha said. "This is still a nascent field. The New Innovator Award will allow us to get a better understanding of how these footprints of DNA packaging can be captured from the blood and ultimately used to benefit patients."

Liquid Biopsies: A Non-Invasive Window Into Cancer

The blood sample-based biopsy that Ha is working to develop would give scientists a new window into the inner workings of tumors. Understanding tumors at the level of gene regulation could help doctors select more effective treatments, identify tumors by subtype and recognize when a cancer begins to respond (positively or negatively) to treatment.

Liquid biopsies have the potential to be much more than just a less-invasive replacement for surgically based biopsies. Assessing tumors through blood could allow doctors to monitor disease over time, or in cases (like advanced, late-stage disease) where surgery isn't an option. Researchers are also working to develop strategies that could be used to detect early-stage cancer or tumor recurrence, or how treatment itself reshapes a patient's disease.

When a patient's cancer recurs, it can be different from the original tumor in a significant way.

For example, a patient whose estrogen receptor-positive breast cancer initially responded to treatment may see that her tumor is ER-negative when it recurs. A prostate cancer driven by the androgen-receptor may morph into different type of prostate tumor after exposure to androgen receptor-targeted therapies. Tumors that undergo these changes won't respond to the original course of treatment.

Ha's strategy would give doctors a new way to detect changes in a cancer that dictate a different treatment strategy.

What drives a tumor and how it responds to treatment comes down to its proteins, and the genes that encode them. Our cells use DNA packaging to help regulate how genes are turned on and off. DNA loops around protein spools called nucleosomes. A gene or gene-regulating DNA region that's turned on will have a looser, more "open" conformation. A gene or DNA region that's turned off will have a tighter, more "closed" conformation.

Ha's work focuses on locating nucleosomes and figuring out what their placement can tell us about what's going on inside a cancer cell. Which genes are turned on? Which are turned off? What can that tell us about the subtype of tumor a patient has, or how it might respond to treatment? The innovation comes from answering these questions from tiny amounts of cell-free DNA in the blood.

Ha sees a lot of potential for liquid biopsies helping to guide treatment and improve patient monitoring in the clinic as well as in the research setting, as scientists test new treatments in clinical trials. His New Innovator Award will allow his group to partner with research and clinical collaborators to apply his approaches to a various adult and pediatric cancers.

New Computational Tools and Assays to Highlight Cancer DNA

Ha's New Innovator Award will help him develop new assays to better pinpoint the location of

nucleosomes on cell-free DNA fragments in our blood, and the computational tools that will help him separate important information from nucleosome noise.

Because, it turns out, there's a lot of noise. Cancer cells aren't the only cells that leak DNA. Most cell-free DNA in our blood comes from non-cancerous immune cells.

"That's a major challenge," Ha said. "Oftentimes the amount of tumor DNA [in the blood] is quite low. So you need, one, better assays to capture the DNA molecules you're looking for, and two, better computational approaches so you can interpret that signal coming from cancer cells. Because it's a mixture, it's a pool of all the DNA released from healthy and tumor cells into the blood."

Ha's new computational methods will allow him to separate the key gene activity data that's coming from cancer DNA from uninformative data that's coming from non-tumor cells.

As a tumor progresses, recurs or reacts to treatment, which genes are open and which are closed will shift.

"Nucleosomes have to reorganize and reshuffle [when a cell changes gene activity]," Ha said. "We want to be able to detect that dynamic nucleosome organization."

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