

A new biomarker for early cancer detection? Research reveals that 'microRNA' may fit the bill

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Scientists at Fred Hutchinson Cancer Research Center have discovered that microRNAs – molecular workhorses that regulate gene expression – are released by cancer cells and circulate in the blood, which gives them the potential to become a new class of biomarkers to detect cancer at its earliest stages. Muneesh Tewari, M.D., Ph.D., and colleagues describe their findings in the July 28 issue of the *Proceedings of the National Academy of Sciences*.

MicroRNAs, which act as brakes on different parts of a cell, keeping genes in check, have some advantages over protein-based early-detection systems, including that they can be detected potentially in smaller quantities and that the technology exists to rapidly develop microRNA-based early-detection tests, said Tewari, an assistant member in the Hutchinson Center's Human Biology and Clinical Research divisions. His work is focused on understanding why the brakes fail – allowing unchecked cell growth – in prostate and ovarian cancer.

"Current technology for developing tests to measure microRNAs in clinical samples is quite advanced, whereas the bottleneck for developing protein-based biomarkers is the slow process of generating assays for measuring specific proteins," he said.

The next steps, now that a proof of principle has been established, are to identify specific microRNAs that can signal the presence of a variety of

solid-tumor cancers at an early stage, and to further develop the technology to detect the microRNAs in minute quantities.

For the study, Tewari and colleagues tested blood from mice and humans with advanced prostate cancers, as well as that from healthy controls. They measured microRNAs made by the tumors in both cases and controls, and they could distinguish which individuals had cancer based on blood microRNA measurement.

"This research shows that microRNAs, which weren't previously thought of as markers of cancer in the blood, are a worthwhile class of molecules to study for the purpose of early cancer detection," Tewari said.

The research that led to the surprising finding of microRNAs in plasma and serum resulted from a combination of observations and a hunch, he said.

MicroRNAs play a key role in a wide range of normal cell processes, including embryonic development and cell differentiation. The tiny regulatory molecules modulate the activity of specific messenger-RNA targets, which in turn give rise to proteins. Humans have 30,000 genes that can make messenger RNAs. There are more than 500 known microRNAs encoded by the human genome and each is thought to target up to hundreds of messenger RNAs.

That microRNAs existed in humans is in itself a recent discovery. Tewari's group initially was studying their role in cancer development and maintenance because microRNAs are often dysregulated in cancer. During the course of those experiments, the scientists found that microRNAs circulate outside of cells and are remarkably stable.

"We were surprised to discover that there are microRNAs in plasma and serum that are not associated with cells and that are not being degraded

by enzymes in the blood that would degrade regular RNA," Tewari said. It isn't fully known how the microRNAs are protected from degradation or how they get into the blood.

This in turn led the researchers into a new direction of determining whether cancer-associated microRNAs could be found. Earlier studies in model organisms such as worms and flies showed that some microRNAs have specific expression in certain kinds of cells and not anywhere else.

The paper details the step-by-step approach that led to discovering microRNAs in plasma and serum components of blood, that microRNAs remain stable even after incubation at room temperature for 24 hours and after eight freeze/thaw cycles, and finally that tumor-derived microRNAs enter the circulation at levels sufficient to be measured as biomarkers for cancer.

"The results presented here establish the foundation and rationale to motivate future global investigations of microRNAs as circulating cancer biomarkers for a variety of common cancers," the authors wrote.

The availability of existing, powerful tools to characterize and measure microRNAs, such as polymerase-chain reaction technology for DNA amplification, "suggests that the discovery-validation pipeline for microRNA biomarkers will be more efficient than traditional proteomic biomarker discovery-validation pipelines, which typically encounter bottlenecks at the point of antibody and quantitative assay development for validation of biomarker candidates," the authors wrote.

Source: Fred Hutchinson Cancer Research Center

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