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Monitoring RNA levels in blood yields dynamic picture of fetal development, disease

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Recent research has shown that tiny fragments of DNA circulating in a person's blood can allow scientists to monitor cancer growth and even get a sneak peek into a developing fetus' gene sequences. But isolating and sequencing these bits of genetic material renders little insight into how that DNA is used to generate the dizzying array of cells, tissues and biological processes that define our bodies and our lives.

Now researchers at Stanford University have moved beyond relying on the static information delivered by DNA sequences in the blood. Instead, they've generated a much more dynamic picture by monitoring changing levels of another genetic material—RNA—in the blood. It's the biological difference between a still photo and a video when it comes to figuring out what the body is doing, and why.

"We think of this technique as a kind of 'molecular stethoscope,'" said Stephen Quake, PhD, professor of bioengineering and of applied physics, "and it's broadly useful for any tissue you care to analyze. There are many potential practical applications for this work. We could potentially use it to look for things going wrong in pregnancy, like pre-eclampsia or signs of preterm birth. And we hope to use it to track general health issues in various organs."

Quake and his colleagues combined the use of high-throughput methods of microarrays and next-generation sequencing to analyze the sequences and relative levels of RNA in the blood of pregnant women, healthy volunteers and Alzheimer's patients. By focusing on RNA messages encoding proteins known to be produced only in certain tissues, they were able to track the development or health of particular organs throughout the body.

The Lee Otterson Professor in the School of Engineering and a Howard Hughes Medical Institute investigator, Quake is the senior author of a paper describing the research to be published online May 5 in the *Proceedings of the National Academy of Sciences*. Graduate students Winston Koh and Wenying Pan are lead authors of the study.

With a few exceptions, your genome, encoded by your DNA, is shared among every cell in your body. Specific tissues and organs are formed by expressing only certain subsets of genes from the thousands of options in your genome. This gene expression is accomplished in part through molecules called messenger RNAs, which carry instructions encoded in genes to the cell's protein-making factories. The proteins in turn do much of the work of the cell.

Specialized proteins and other regulatory molecules in each cell control which genes are expressed, when they are expressed and how much of each RNA message is made. As a result, the particular sequences of

messenger RNA used can vary widely among tissues and various biological and environmental conditions.

It's been known for decades that blood contains miniscule amounts of free-floating DNA and RNA released by dying or damaged cells throughout the body. Often this cell death represents natural cellular turnover; sometimes it's the result of disease processes. But, until recently, analyzing this genetic material has been difficult due to its scarcity.

New sequencing techniques capable of handling very tiny amounts of genetic material are opening broader vistas for researchers everywhere. Most efforts are focused on analyzing the DNA in the blood, either to determine its sequence or to compare the relative amounts of certain chromosomes. These techniques have applications in diagnosing cancers by looking for particular mutations not present in the patient's genome. Quake's lab pioneered an approach that allows clinicians to determine whether a fetus is likely to have conditions such as Down syndrome that are defined by abnormal chromosomal copy numbers. It is estimated that in 2013, more than 500,000 pregnant women used a version of Quake's noninvasive prenatal test to learn more about the health of their fetuses.

In the new study, the researchers used a technique previously developed in Quake's lab to identify which circulating RNA molecules in a pregnant woman were likely to have come from her fetus, and which were from her own organs. They found they were able to trace the development of specific tissues, including the fetal brain and liver, as well as the placenta, during the three trimesters of pregnancy simply by analyzing blood samples from the pregnant women over time.

Quake and his colleagues believe the technique could also be broadly useful as a diagnostic tool by detecting distress signals from diseased organs, perhaps even before any clinical symptoms are apparent. In

particular, they found they could detect elevated levels of neuronal-specific RNA messages in people with Alzheimer's disease as compared with the healthy participants.

Finally, in addition to monitoring messenger RNA levels, which encode protein-making instructions, the researchers were also able to detect other types of RNA—such as long, noncoding RNA and circular RNAs—that are likely to play significant regulatory roles within the cell. Further analysis of these molecules could yield additional insight into health and disease.

"We've moved beyond just detecting gene sequences to really analyzing and understanding patterns of gene activity," said Quake. "Knowing the DNA sequence of a gene in the blood has been shown to be useful in a few specific cases, like cancer, pregnancy and organ transplantation. Analyzing the RNA enables a much broader perspective of what's going on in the body at any particular time."

More information: Noninvasive in vivo monitoring of tissue-specific global gene expression in humans, *PNAS*, 2014. www.pnas.org/cgi/doi/10.1073/pnas.1405528111

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