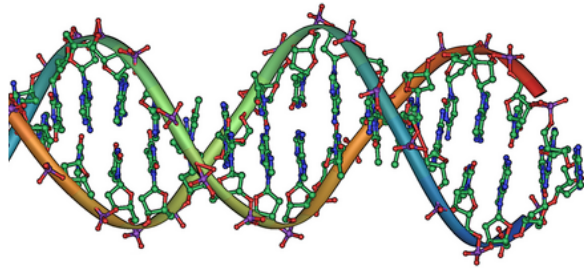


New method detects multiple diseases via DNA released from dying cells into blood

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DNA double helix. Credit: public domain

In a series of experiments involving 320 patients and controls, researchers developed a blood test that can detect multiple pathologies, including diabetes, cancer, traumatic injury and neurodegeneration, in a highly sensitive and specific manner. The novel method infers cell death in specific tissue from the methylation patterns of circulating DNA that is released by dying cells.

The findings are reported in a paper published in the *Proceedings of the National Academy of Sciences*, entitled "Identification of tissue specific [cell death](#) using [methylation patterns](#) of circulating DNA". The research was performed by an international team led by Dr. Ruth Shemer and Prof. Yuval Dor from The Hebrew University of Jerusalem, and Prof. Benjamin Glaser from Hadassah Medical Center.

Cell death is a central feature of human biology in health and disease. It can signify the early stages of pathology (e.g. a developing tumor or the beginning of an autoimmune or neurodegenerative disease), mark disease progression, reflect the success of therapy (e.g. anti cancer drugs), identify

unintended toxic effects of treatment and more. However to date, it is not possible to measure cell death in specific human tissues non-invasively.

The new blood test detects cell death in specific tissues by combining two important biological principles. First, dying cells release fragmented DNA to the circulation, where it travels for a short time. This fact has been known for decades; however since the DNA sequence of all cells in the body is identical, it has not been possible to determine the tissue of origin of circulating DNA, and simple measurements of the amount of circulating DNA is of very limited use. The second principle is that the DNA of each cell type carries a unique chemical modification called methylation. Methylation patterns of DNA account for the identity of cells (the genes that they express), are similar among different cells of the same type and among individuals, and are stable in healthy and disease conditions. For example, the DNA methylation pattern of pancreatic cells differs from the pattern of all other cell types in the body.

The researchers have identified multiple DNA sequences that are methylated in a tissue-specific manner (for example, unmethylated in DNA of neurons and methylated elsewhere), and can serve as biomarkers for the detection of DNA derived from each tissue. They then developed a method to detect these methylated patterns in DNA circulating in blood, and demonstrated its utility for identifying the origins of circulating DNA in different human pathologies, as an indication of cell death in specific tissues. They were able to detect evidence for pancreatic beta-cell death in the blood of patients with new-onset type 1 diabetes, oligodendrocyte death in patients with relapsing multiple sclerosis, brain cell death in patients after traumatic or ischemic brain damage, and exocrine pancreas cell death in patients with pancreatic cancer or pancreatitis.

"Our work demonstrates that the tissue origins of

circulating DNA can be measured in humans. This represents a new method for sensitive detection of cell death in specific tissues, and an exciting approach for diagnostic medicine," said Dr. Ruth Shemer of the Hebrew University, a DNA methylation expert and one of the lead authors of the new study.

The approach can be adapted to identify cfDNA derived from any cell type in the body, offering a minimally-invasive window for monitoring and diagnosis of a broad spectrum of human pathologies, as well as better understanding of normal tissue dynamics.

"In the long run, we envision a new type of [blood test](#) aimed at the sensitive detection of tissue damage, even without a-priori suspicion of disease in a specific organ. We believe that such a tool will have broad utility in diagnostic medicine and in the study of human biology," said Prof. Benjamin Glaser, head of Endocrinology at Hadassah Medical Center and another lead author of the study.

More information: Identification of tissue-specific cell death using methylation patterns of circulating DNA, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1519286113

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