Daniel Neiman et al., Biol syst Open Access 2016, 5:2 (Suppl)
http://dx.doi.org/10.4172/2329-6577.C1.006

Identification of tissue specific cell death using methylation patterns of circulating DNA

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Minimally-invasive detection of cell death could prove an invaluable resource in many physiologic and pathologic situations. Cell-free circulating DNA (cfDNA), released from dying cells is emerging as a diagnostic tool for monitoring cancer dynamics and graft failure. However, existing methods rely on DNA sequence differences in source tissues, so that cell death in tissues with a normal genome cannot be identified. We developed a method of detecting tissue-specific cell death in humans, based on tissue-specific methylation patterns in cfDNA. We interrogated tissue-specific methylome databases to identify cell type-specific DNA methylation signatures and developed a method to detect these in mixed DNA samples. We isolated cfDNA from plasma or serum of donors, treated with bisulfite, PCR-amplified and sequenced to quantify cfDNA carrying the methylation markers of the cell-type of interest. Pancreatic beta-cell DNA was identified in the circulation of recently diagnosed type-1 diabetes patients and islet graft recipients, oligodendrocyte DNA in patients with relapsing multiple sclerosis, neuronal/glial DNA in patients after traumatic brain injury or cardiac arrest and exocrine pancreas DNA in patients with pancreatic cancer or pancreatitis. This proof-of-concept study demonstrates that the tissue origins of cfDNA and thus the rate of death of specific cell types can be measured in humans. 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.

Biography

Daniel Neiman is a Phd Student under Prof Aharon Razin &prof Yuval Dor lab & Ruth Shemer in The Hebrew University-Hadassah Medical School.

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