Dynamic size and association profiles of tumour-derived dna during pancreatic cancer progression

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Abstract

Circulating tumour-derived DNA (ctDNA) is an increasingly important marker of minimal residual disease. Although generally referring to histone-bound fragments of <200bp, the term ctDNA can describe any length of DNA in various potential macromolecule complexes. To uncover which of these is most enriched in tumour-derived material, we used differential centrifugation to separate blood into eight cellular, vesicular and soluble components. Furthermore, we segregated long (>400bp) and short DNA fragments using ligation and tagmentation-based library amplification. To judge these dynamics at different stages of disease, we collected 53 samples from pancreatic cancer patients and separated these into 7 without progressive disease, 23 with advanced cancer and 23 at terminal stages. Using digital PCR and shallow whole genome sequencing, we find most short ctDNA associated with apoptotic bodies, which are removed in standard protocols. In contrast, the greatest overall enrichment of ctDNA is found as long fragments associated with small vesicles at earlier stages and soluble proteins in terminal disease. We further characterize the macromolecular complexes associated with these fragments using gel electrophoresis, serial centrifugation, nanoparticle flow cytometry and single particle profiling. This work suggests that ctDNA can be enriched based on its biological associations and that this may improve diagnostic sensitivity and clinical disease monitoring.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.