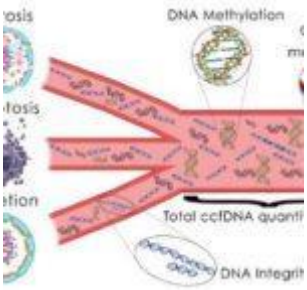
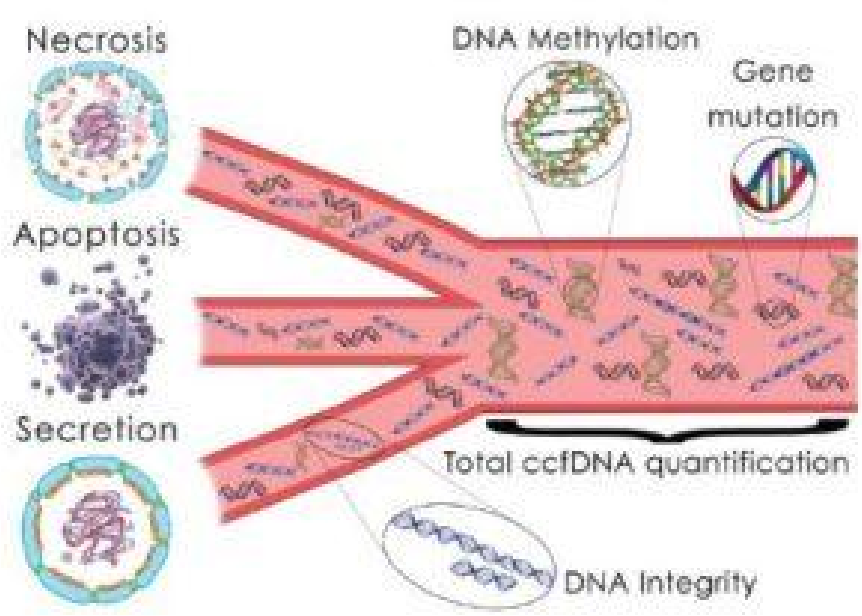
How DNA outside cells can be targeted to prevent the spread of cancer





Schematic mechanisms of release and ccfDNA characteristics. [Source: OLIVEIRA, Isadora Bernardo David de and HIRATA, Rosario Dominguez Crespo. Circulating cell-free DNA as a biomarker in the diagnosis and prognosis of colorectal cancer. Braz. J. Pharm. Sci. [online]. 2018, vol.54, n.1]

Cell-free DNA (cfDNA) is DNA found in trace amounts in blood, which has escaped degradation by enzymes. In 1994, a mutation

in a well-known cancer-associated gene, RAS, was found in cfDNA from the blood of cancer patients. This sparked interest in the potential use of cfDNA as a diagnostic marker for tumors. However, until now, exactly what gives rise to cfDNA was a question that was left unanswered. Is it derived from cells that undergo programmed death in the body (apoptosis) or is it derived from cells dying by injury or inflammation (necrosis)? What are the DNA-degrading enzymes involved? Watanbe *et al.*, 2019 led by Prof Mizuta, of the Research Institute of Biomedical Sciences at Tokyo University of Science, have now answered these questions.

Prior to this study, these scientists had already discovered an endonuclease, DNase1L3 (also called DNase γ), and found that it causes cellular DNA fragmentation during necrosis. Additionally, DNase1L3 plays "second fiddle" to caspase-activated DNase (CAD; the main degrading enzyme in apoptosis) during apoptosis. Indicating that DNase1L3 can breakdown extracellular DNA released during necrosis and/or apoptosis, into nucleosomes.

Watanabe et al., used genetically manipulated mice as study models to pinpoint the enzymes responsible for generating cfDNA. They showed that blood from DNase1L3-deficient mice had much lower concentrations of cfDNA than blood from CAD-deficient mice and normal mice, in both apoptosis- and necrosis-induced groups. The scientists thus concluded that during apoptosis, DNase1L3 is crucial as a "backup" enzyme for CAD in degrading condensed chromatin into fragments (single nucleosomes), thus giving rise to cfDNA. And in necrosis, DNaseIL3 is absolutely essential for generating cfDNA.

Additionally, Watanbe et al., showed that DNase1L3 can degrade neutrophil extracellular traphs (NETs) into cfDNA. NETs are small sticky fibers of chromatin released by neutrophils after infection or injury. Although NETs can stop harmful bacteria from spreading in the bloodstream, NET release can sometimes become uncontrolled; and cause clotting [thrombosis]. Thus

based on their discovery, Wantanbe et al., suggest that DNase1L3 can be used to treat thrombosis caused by NETs. NETs are also known to be the "seeding soil" for tumors. Tumor cells released in blood might latch onto NETs and grow on them and spread to other organs. Based on their results, Prof Mizuta suggest that, "[Since] DNase1L3 degrades NETs and generates cfDNA, we speculate that DNase1L3 treatment may also be useful to prevent tumor metastasis. We are now conducting experiments to test this speculation."

Journal Article: Wantanabe *et al.*, 2019. Cell-free DNA in blood circulation is generated by DNase1L3 and caspase-activated DNase. Biochemical and Biophysical Research Communications.

Article provided by Indrani Das, summarised by Cheleka Mpande

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