High resolution mutagen adduct signature mapping using nanopore sequencing

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Abstract

About half of all cancers are caused by exposure to environmental mutagens. Mutagens leave signatures in the form of patterns and spectrums of mutations in cancer cell DNA that reflect the chemical properties of the carcinogen, mechanisms of metabolic activation, repair pathways, genetic selection, epigenetic state and perhaps even the microbiome. About 50 such signatures have been identified in cancer cells. Some signatures have been shown to reflect specific exposures such as smoking or sunlight, but about half of the signatures do not have a known cause. Less is known about assessing if early signs of DNA damage stress occur in individuals. Telomeres are believed to be particularly sensitive to such stress, which can contribute to cancer and other diseases, but assays to measure telomere damage are cumbersome. Evaluating levels of stress would be aided by a rapid test of DNA damage. We propose here to develop a novel rapid DNA test for mutations as well as environmental DNA damage, using newly invented nanopore DNA sequencing. Though nanopore is primarily a DNA sequencing tool, we believe the technology can be modified to detect damaged DNA and locate it on the genome. We will validate it using known chemical damage.