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Understanding blood cell mutational biomarkers for biomonitoring and disease purposes.

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Micronuclei (Mn) form from mitotic errors during the telophase stage of mitosis. Mn are easily measured in isolated human lymphocytes stimulated to grow ex vivo by using microscopy-based approaches. Mn can be caused either by systemic genotoxic exposure or by underlying disease states in vivo. Another easily measurable blood cell mutation employs the PigA mutation locus. Erythrocytes with mutated PigA can rapidly be identified by flow cytometry coupled to fluorescent antibodies for GPI anchored proteins (e.g. CD55, CD59), with mutated cells losing fluorescence.

We have been assessing the combined use of Mn and PigA as endpoints to comprehensively study human mutation. We have collected blood from over 500 patients and volunteers and assessed lymphocyte Mn and erythrocyte PigA. We have observed that both mutational endpoints are elevated in older participants and have shown associations with modifiable lifestyle factors such as BMI, smoking status, diet, medication and other factors. We have also noted increasing levels of both Mn and PigA mutations in the blood cells of patients with oesophageal cancer.

In an effort to better understand the origin of these blood cell mutations, we have explored underlying causative genotoxic factors. We have shown that lymphocyte Mn from cancer patients are more likely to contain whole chromosomes and that lymphocytes from cancer patients are more sensitive to aneugen exposure (vinblastine) in a “challenge assay”. We have shown that patient lymphocytes show an adaptive response to oxidative stress, with those bearing high Mn levels being resistant to ROS induced Mn in a ex vivo challenge assay. We also show that patient plasma samples show markers of oxidative stress (GSH), activation of the cGAS-STING pathway (IFN-b) and that human plasma can ultimately induce Mn in TK6 cells in an ROS dependent manner in some patients. Further efforts are needed to better understand the underlying cause of these blood cell mutational events in populations.

In conclusion, this kind of multi-mutation approach may be useful in both biomonitoring studies and in understanding the role of internal secondary mutations induced by various diseases including cancer.