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Evaluating micronucleus frequency of circulating lymphocytes as a potential biomarker for oesophageal adenocarcinoma

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The late presentation of symptoms leads to poor prognosis in patients with Oesophageal adenocarcinoma (OAC). Patients with pre-malignant Barrett's oesophagus (BO) stay under surveillance to monitor level of cell dysplasia. Our group is interested in investigating lymphocyte micronucleus frequency (L-MN%) as a potential blood-based biomarker to prioritise patients for endoscopy. Previous work within our group involving blood samples obtained from healthy volunteers (n=34), patients with gastro-oesophageal reflux disease (GORD) (n=63), Barrett's oesophagus (BO) (n=34) and OAC (N=43) showed that OAC patients had significantly elevated lymphocyte micronucleus frequencies (L-MN%) than non-cancer controls ($p<0.001$) It is our current aim to investigate the mechanism behind the increased lymphocyte MN%(L-MN%) in patients with OAC.

To assess individual susceptibility to DNA damage, lymphocytes from healthy volunteers (n=15), patients with GORD(n=9), BO (N=9), and OAC(n=9) were stimulated with phytohemagglutinin and treated with hydrogen peroxide (H2O2), sodium deoxycholate (DCA) and vinblastine. L-MN% was assessed using the cytokinesis-block micronucleus assay.For H2O2 and DCA treatments there is no difference in L-MN% between patient groups, however there is a negative correlation (P value = 0.0005 and 0.0046 respectively) between MN% and MN% fold change. Plasma levels of reduced glutathione (GSH) were increased in patients with a higher L-MN% (P-value =0.0091). This suggests that the lymphocytes of some individuals exposed to higher levels of oxidative stress in-vivo have adapted to reduce further DNA damage. Following kinetochore staining of patient lymphocytes, it was observed that OAC patients have higher levels of centromere positive MNi, indicating an aneugenic mechanism behind the increase. This is further supported as the L-MN% fold change following treatment with vinblastine appears higher in cancer patients, compared to non-cancer controls.

Innate immune receptor cyclicAMP-AMP synthase (cGAS) recognises dsDNA from micronuclei, activating the Stimulator of Interferon Genes (STING) via cGAMP and leading to the upregulation of type 1 interferons e.g., IFN-B. OAC patients have significantly higher levels of IFN-B in their plasma, activation of this pathway with be evaluated following measurement of cGAMP in plasma. Whilst further work is required, the results are promising in the validation of L-MN% as a potential biomarker for risk of cancer progression.

Keywords:
Micronuclei, Lymphocytes, Biomarker, Oesophageal Cancer.