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Stable isotope and *in situ* concentration measurements of Zn in breast cancer

DR. REBEKAH ET MOORE[1], ALEXANDER P MORRELL[2], ALEX GRIFFITHS[2], CHARLES COOMBES[1] AND MARK REHKÄMPER[1]

[1]Imperial College London
[2]King's College London
Presenting Author: rebekahetmoore@gmail.com

Zinc is an essential metal that has roles in most body systems as a structural or functional component of thousands of proteins and hundreds of enzymes. Zinc has been associated with breast cancer, but due to its many physiological functions, it is still unclear what its dominant roles in cancer progression are.

A recent study [1] found that there was significantly less Zn in 'normal' tissue adjacent (NAT) to both fibroadenomas (benign, BT) and invasive ductal carcinomas (malignant, MT) and that the Zn in both tumour types was isotopically lighter to that in NAT and healthy tissue taken from breasts with no tumours (HT). Interestingly, the Zn concentration in NATs of BTs was elevated compared to those in NATs of MTs and HTs. Despite the observed statistical differences in bulk Zn isotope compositions and concentrations, the results revealed much heterogeneity.

To investigate this further, a subset of tissue samples used in the isotope study, comprising malignant and benign tumours, their corresponding NATs and HTs, were selected for *in situ* concentration analysis. Sections of 5 µM thickness were taken from each sample. One slice from each was H&E (hematoxylin and eosin) stained, to highlight cell features, whilst adjacent, untreated slices were used for laser ablation (LA)-ICP-MS. Calibration pico-gels were analysed alongside the samples, to enable quantification.

This work used two spatial resolutions. A laser spot size of 35 µm was used to image entire tissue sections. Results showed that (i) Zn concentrates more in the cancerous regions and (ii) Zn distribution within benign and malignant NATs are different, as hypothesised based on the isotope data. Targeted sections were also chosen for ablation at 2-3 µm laser spot size and initial image analysis suggests that Zn may be particularly concentrated in the extracellular matrix. This work, which combines two ICP-MS techniques to investigate metal dyshomeostasis during cancer progression, represents a significant step forward for the field. In particular, more targeted data collection is planned with the aim of opening the doors for LA-ICP-MS analyses to be used to inform clinical decisions.

[1] Sullivan et al. (2021), *Metallomics* 13, mfab027.