Metabolomics of Head and Neck Cancer

Progress Report

Jim Higginson

March 17, 2019

Summary

This project is still in progress: we anticipate that the project will be completed and submitted for publication within 6 months.

Using the generous grant from BAOMS, we have performed a full lipidomic analysis of primary tissue samples and both wild-type and cetuximab resistant oral cancer cell cultures, to provide insights into the metabolic behaviour of this disease. For both arms of the project, we used liquid-chromatography mass spectrometry to provide a comprehensive breakdown of the lipid molecules present within the tissue, giving information on their solubility, molecular mass and relative abundance.

Both sets of samples will shortly undergo further analysis, this time using next generation sequencing of messenger RNA (RNASeq) to identify whether up- or down-regulated transcriptional pathways can be correlated with the observed changes in metabolism, as a a hypothesis-generating exercise for druggable targets or potential biomarkers.

Patient Data

Samples from a pilot cohort of head and neck cancer patients (n = 8) and a subsequent validation cohort of oral cancer patients (n = 22) underwent lipidomic analysis. Samples were analysed from tumour core, tumour margin and matched contralateral normal mucosa.

Our results suggest that malignancy is strongly associated with lower abundance of lipid storage species, particularly triacylglycerol (TAG), and higher abundance of functionally active lipid species, notably phosphatidylserine (PS, an important cell membrane immunosuppressive signal), ceramides (a class of lipid previously associated with head and neck cancer, poor prognosis and tumour progression) and cholesterol esters (associated with cancer proliferation and aggression in breast and prostate cancers.

Cell Culture Data

Using the same methodology, we have used reliabile, validated lines of oral cancer cell cultures to investigate the mechanisms underlying cetuximab resistance. The resistant cell lines were cultured in the presence of cetuximab, then both lines were challenged with cetuximab. Cell viability was assessed at pre-treatment, immediate post-treatment and 24 hours post-treatment using AlamarBlue assays.

Our results have confirmed the cetuximab-resistance of our cell culture line, and has demonstrated subtle but significant metabolomic differences between these and the parental cell line. It does not appear that there are substantial changes in metabolism following challenge with cetuximab. Analysis is ongoing, and as with the patient data, our findings will be correlated with transcriptomic data from RNASeq.

Conclusion

We are taking an multi-omics approach to investigating changes to the lipid phenome of head and neck cancer, with evaluation of underlying transcriptional changes that may contribute to these changes. We anticipate that this will contribute to the knowledge of the biology of head and neck cancer, and further expect hypotheses to be generated regarding potential biomarkers or druggable targets.

We intend to submit for publication towards the end of 2019.