Metabolomic Differentiation of Thyroid Malignancies With Magnetic Resonance Spectroscopy of Tissue and Cytology Samples

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Introduction

Thyroid malignancies, despite low overall mortality rates, are cancers confounded by an inability to be accurately categorized. The majority of thyroid cancers are well-differentiated diseases arising from follicular cells. The main sub-types include papillary carcinoma, follicular carcinoma, and follicular adenoma; the latter two being clinically indistinguishable from one another prior to thyroidectomy. The main diagnostic tools for thyroid diseases include fine needle aspirations (FNA) producing cytological samples, and tissue biopsies. The accuracy of these methods relies heavily on the skill of the pathologists and surgeons involved in sample collection and analysis. In the era of personalized medicine new clinical tools are being explored that biochemically categorize tumors in order to direct individual treatment planning. This is especially relevant for diseases of the thyroid, which often result in unnecessary thyroidectomies. The high resolution magic angle spinning proton magnetic resonance spectroscopy (HRMAS 1HMRS) technique is utilized in the current study, which aims to determine if the methodology can provide clinically relevant information from samples of thyroid cytology and tissue.

Methods

Paired samples of cytology and tissue were collected from patients being treated for thyroid malignancy at the Massachusetts General Hospital. Tumors were classified prior to sample collection as: papillary carcinoma (n=4), follicular adenoma (n=4), or follicular carcinoma (n=2). When possible samples were also collected from the patient's non-involved thyroid tissue (n=5). Samples (intact tissue between 6 to 10 mg or 10 μl cytology) were placed in the MRS rotor for spectral measurements without any pre-treatment. A Bruker (Billerica, MA) AVANCE spectrometer operating at 600 MHz (14.1 T) was used for all spectroscopic experiments and spectra were processed with AcornNMR-Nuts (Livermore, CA). Following spectroscopic analysis, tissue samples were prepared as H&E sections for a pathologist to determine percent volume of different features; cytological pathology was conducted on smears prepared from the FNA material. Metabolomic profiles were independently constructed for tissue and cytology samples using principle component analysis on the most intense resonance peaks/regions (tissue = 35, cytology = 25). The resulting profiles and their correlations with pathology from the sample were analyzed statistically by JMP (SAS Inc).

Results and Discussions

The results of the current study indicate that the HRMAS 1HMRS method can metabolically characterize samples of both thyroid tissue and cytology. Principle component analysis of the tissue samples revealed PC 2 linearly correlated with the amount of cancer volume in the sample ($P<0.0026$) and could differentiate between samples of benign tissue, papillary carcinoma, follicular adenoma, and follicular carcinoma ($P<0.0335$). Furthermore, principle component analysis of the cytology samples revealed PC 3 linearly correlated with the amount of malignant cells in the smear ($P<0.0003$) and could also differentiate between the four cell types ($P<0.004$). These results not only establish the feasibility of conducting metabolomic studies on both tissue and cytology samples from the thyroid, they also indicate the impressive potential to metabolically distinguish between cell types present in a sample. This has potential clinical relevance given the dramatically different clinical outcomes among patients with the various thyroid malignancies, and the inability to accurately categorize patients' diseases without thyroidectomy, if at all. Interestingly if used clinically this study shows both the tissue and cytology samples can be used to categorize a patient's disease and can thus be impendent diagnostic tests.These results are entirely preliminary in nature and will need to be re-validated in a larger patient cohort. Further studies will refine the metabolomic profiles of the thyroid conditions studied and confirm if these profiles can be clinically useful as an adjunct to current diagnostic and prognostic measures.

Conclusion

We have demonstrated the potential of detecting and classifying tumors from either tissue or cytology samples from human thyroid cancer patients. We are encouraged by the current results, which provide information not currently clinically attainable with contemporary diagnostic tools. We are confident further studies will confirm if the highly reproducible HRMAS 1HMRS method, which is free of inter-observer reproducibility issues, can be implemented in today's thyroid cancer clinic.

Acknowledgements

Authors acknowledge support from CA115746 and CA095624, and MGH A. A. Martino Center for Biomedical Imaging.