Novel Non-Invasive Biomarker Signature Predicts Pilocytic Astrocytoma both in vitro and in a Pediatric Neurosurgical Clinical Setting

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Introduction

We report our initial experience with sensitive and disease-specific urinary biomarkers as a novel method of disease detection and potential follow-up of pilocytic astrocytomas (PA). Furthermore, patient samples in an in vitro setting support the reproducibility of this approach, important for future refinement of other biomarkers and putative therapeutic targets.

Methods

Urine was collected from 75 pediatric patients (0-21 years of age), focused on pilocytic astrocytoma (n=20), then compared to children with medulloblastoma, glioblastoma, arteriovenous malformations and age- and sex-matched controls (n=21), following an IRB-approved protocol. Diagnoses were pathology-confirmed and correlated with multiplanar MRI. ELISA quantified levels of an established panel of 20 putative urinary biomarkers and normalized to protein concentration using Bradford assays. Matched tissue was subjected to immunohistochemistry to correlate source tissue expression with biomarker levels. Results were subjected to univariate and multivariate statistical analyses. Primary cell culture was derived from same-patient JPA tumor tissue and in vitro validation of urinary biomarkers was performed.

Results

Statistical analysis revealed PA-specific biomarker fingerprints capable of discerning PA both from controls and also from other types of neurosurgical disease. Compared to controls, elevation of bFGF (4.56 pg/ug vs. 0.45pg/ug, $p<0.001$) and TIMP3 (8.86pg/ug vs. 1.71pg/ug, $p<0.01$) identified PA. Specific to tumors, multiplexing bFGF elevation with decreased MMP-13 distinguished PA from medulloblastoma ($p<0.001$). Similar multiplexing of TIMP-3 and MMP-13 successfully discerned GBM from PA ($p<0.01$). Independent elevation of bFGF identified PA with an AUC=0.914 and generated clinically relevant cutpoints. Tissue culture of patient samples allowed serial passage with concordant biomarker profiles in both media and cell-staining.

Conclusions

These data suggest potential utility of urinary biomarkers as diagnostic tools for clinicians treating children with PA and demonstrates proof-of- principle results supporting the concept of biomarker “fingerprinting” for unique disease and tumor subtypes relevant to clinical practice and reflective of tumor cell secreted protein.

Learning Objectives

By the conclusion of this session, participants should be able to:

1) Describe the importance of urinary biomarkers as novel diagnostic tools.

2) Discuss, in small groups, the advantages and shortcomings of non-invasive methods of central nervous system disease diagnosis and follow-up.

3) Identify an effective panel of molecules able to assist in the diagnosis of central nervous system disease.

References

Smith ER, Zurakowski D, Saad A, Scott RM, Moses MA.

Urinary biomarkers predict brain tumor presence and response to therapy.

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