Development of a Metabolomic Profile for Fat-Poor Angiomyolipoma Using Magnetic Resonance Spectroscopy

Background

Fat-poor angiomyolipoma (AML) can be difficult to differentiate from renal cell carcinoma (RCC) radiographically and may lead to biopsy or unnecessary intervention. *In vivo* platforms with the ability to identify tumor histology based on metabolic profiles may avoid unnecessary procedures & their complications. The metabolomics of AML have not been characterized, & research into this area may provide targetable molecules for large AMLs. In this study, we investigate the metabolomic profile of AMLs compared to clear cell RCC (ccRCC) using high resolution magic angle spinning (HRMAS) magnetic resonance spectroscopy (MRS).

Methods

Tissue samples were obtained from radical or partial nephrectomy specimens that were fresh frozen & stored at -80°C. Tissue HRMAS MRS was performed by a Bruker AVANCE spectrometer. Metabolomic profiles of RCC & adjacent benign renal tissue were compared, and false discovery rates (FDR) accounted for multiple testing. Regions of interest (ROI) with FDR <0.05 were considered potential predictors of ccRCC rather than AML. The Wilcoxon rank sum test was used to compare median MRS relative intensities for candidate predictors. Logistic regression was used to determine odds ratios for risk of malignancy based on abundance of each metabolite.

Results

There were 16 ccRCC samples & 7 AML specimens. Candidate predictors of malignancy rather than AML based on FDR p-values include histidine, phenylalanine, phosphocholine, serine, alanine, glutamate, glutathione, glycerophosphocholine, & glutamine. While an abundance of these metabolites is associated with higher risk of malignancy, the odds ratio was particularly high in the 3.5-3.49 ppm spectral region (OR 2.99×10^{6}, 95% CI 3.27, 2.73×10^{12}, p=0.033) in ccRCC samples.

Conclusions

HRMAS MRS identified metabolites that may help differentiate fat-poor AML from ccRCC. In particular, metabolites in the 3.5-3.49 ppm spectral region increased the risk of harboring RCC. Our findings may contribute to future *in vivo* studies to help identify which patients require intervention for malignancy & which may be observed for benign AML without requiring biopsy.

Table 1: Summary of metabolites found to be significantly different between fat-poor AML and clear cell RCC, with odds ratios for risk of malignancy

	ccRCC (N=16)	AML (N=7)	P-value			
Median MRS relative intensities (IQR)				**FDR P-value**	**Odds ratios (OR, 95% CI)**	**P-value for OR**
4.67-4.66 (TBD)	1.22 (0.55, 4.62)	0.042 (0, 0.455)	0.007	0.00046275	4723.55 (1.54, $1.45x10^7$)	0.039
4.02-4 (TBD)	0.80 (0.56, 1.32)	0.46 (0.01, 0.67)	0.0299	0.03685893	17.89 (1.00, 319.6)	0.05
3.99-3.96 (Histidine, Phenylalanine, Phosphocholine, Serine)	1.80 (0.97, 2.61)	0.32 (0.03, 0.49)	0.0009	0.00052614	109.72 (1.25, $9.63x10^3$)	0.04
3.9-3.89 (TBD)	0.84 (0.56, 0.85)	0.10 (0.01, 0.42)	0.0019	0.00105305	674.29 (2.87, $1.58x10^5$)	0.019
3.84-3.81 (TBD)	1.51 (1.22, 1.89)	0.15 (0.03, 0.76)	0.0009	0.00055658	59.25 (2.15, $1.63x10^3$)	0.016
3.8-3.78 (Alanine, Glutamate, Glutamine, Glutathione)	2.34 (1.18, 3.23)	1.11 (0.02, 1.43)	0.0083	0.00293991	9.94 (1.08, 91.66)	0.043
3.77-3.74 Alanine, Glutamate, Glutamine)	2.75 (2.42, 3.31)	0.62 (0.03, 2.38)	0.0029	0.01004921	3.48 (1.26, 9.55)	0.016
3.57-3.56 (TBD)	1.83 (1.44, 2.45)	0.04 (0.02, 0.70)	0.0009	0.00046275	29.61 (2.23, 393.8)	0.01
3.5-3.49 (TBD)	0.53 (0.27, 0.63)	0.008 (0, 0.12)	0.0013	0.00052614	$2.99x10^6$ (3.27, $2.73x10^{12}$)	0.033
3.48-3.46 (TBD)	0.64 (0.36, 1.16)	0.01 (0.006, 0.35)	0.0045	0.0016087	1258.41 (3.2, $4.9x10^5$)	0.019
3.45-3.43(TBD)	1.31 (0.42, 2.13)	0.42 (0.03, 0.87)	0.0083	0.00418794	25.24 (1.21, 527.58)	0.037
3.42-3.39 (TBD)	1.73 (0.98, 2.81)	0.54 (0.02, 0.78)	0.0045	0.00534601	8.37 (1.14, 61.31)	0.037
3.22-3.21(Phosphocholine, Glycerophosphocholine, Histidine)	1.81 (1.03, 2.95)	0.03 (0, 0.19)	0.0003	0.00020209	888.36 (1.31, $6.04x10^5$)	0.041
2.38-2.37 (TBD)	0.22 (0.19, 0.28)	0.04 (0.008, 0.14)	0.0009	0.00052614	$2.44x10^{16}$ (0.73, $8.13x10^{32}$)	0.052
2.36-2.31 (Glutamate)	2.37 (1.67, 3.15)	0.90 (0.04, 1.33)	0.0015	0.00105305	15.05 (1.37, 165)	0.026
2.15-2.11 (TBD)	1.89 (1.43, 2.56)	0.68 (0.002, 1.27)	0.0009	0.00052614	62.62 (1.24, 3.12 $x10^3$)	0.038

TBD denotes that the specific metabolites characterizing this region remain to be identified