

Metabolomic Analysis of Tissue-Serum Pairs for Human Lung Cancer

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Introduction

Responding to the urgent clinical need and issues surrounding the early diagnosis of lung cancer, the goal of this project is to develop a blood serum-based metabolomic screening test that may provide biochemical information indicating the risk of lung cancer and direct patients to further radiological tests for disease detection at clinically asymptomatic stages. This project is based on our hypothesis that serum metabolomic profiles measured by magnetic resonance spectroscopy (MRS) have sufficient sensitivity and specificity to detect lung cancers at early stages. If used as a screening test in general and high-risk populations, patients displaying suspicious serum metabolomic profiles may have the opportunity to seek immediate additional clinical tests including imaging evaluations such as chest CT, MRI and PET, all of which are too costly to be included in annual physical exams. We measure and establish tissue metabolomic profiles according to their quantified pathologies for squamous cell carcinoma (SCC) and adenocarcinoma, and apply these profiles to serum data to evaluate the sensitivity and specificity of the obtained serum profiles for differentiation between the two analyzed cancer groups, as well as from serum results of healthy controls.

Methods

Human SCC and adenocarcinoma tissue and serum paired samples from 14 patients, as well as seven serum samples from healthy controls, were analyzed by high-resolution magic angle spinning (HRMAS) MRS. Samples of intact tissue between 6 to 10 mg and 10 μ l of serum, without pre-treatment, were placed in the MRS rotor to measure spectra. Following HRMAS spectroscopic analyses, tissue samples were subjected to quantitative pathological analyses. Tissue metabolic changes analyzed by principal component analysis (PCA) were used in accordance with their quantitative pathologies to generate metabolomic profiles that can differentiate the two tested cancer types in terms of canonical analysis; the profiles obtained were applied to serum spectral data and the resulting values of serum profiles in differentiating cancer types as well as from controls were evaluated by ANOVA. In addition, serum data were also evaluated independently to generate additional metabolomic profiles.

Results and Discussions

In the analysis of tissue samples alone, PCs 1, 2, 7, and 12 showed potential to differentiate SCC from adenocarcinoma and correlate with pathological features. Canonical analysis involving these PCs and the volume % of cancer revealed potential discriminants and a resulting canonical score that can differentiate tissue profiles of the two tested cancer types with an overall accuracy of 96%. Applying the coefficients from this analysis to the spectral data of serum samples demonstrated a statistically significant differentiating power of ANOVA $p < 0.0001$ among the three serum groups SCC, adenocarcinoma and healthy controls, and an overall accuracy of 89% between the two cancer types (Figure 1).

In addition to developing lung cancer serum profiles through tissue profiles, serum spectroscopic data was analyzed with PCA independently from tissue results to discover cancer-specific profiles. Seven PCs were used for canonical analysis, resulting in a score that can separate SCC from adenocarcinomas with statistical significance of $p < 0.0001$. We tested the utility of the resulting score obtained from these 14 serum samples from cancer patients on the seven control sera. We calculated the scores for these controls with coefficients of PCA and canonical analysis obtained from cancer sera and obtained a much better differentiation, i.e. less overlaps, between controls and adenocarcinomas ($p < 0.0005$). More interestingly, by combining the lung cancer tissue-derived serum profile with the independent serum profile, we obtained differentiation among the three tested serum groups on a two dimensional plot with statistical significance ($p < 0.0001$) based on nominal logistic regression analysis (Figure 2).

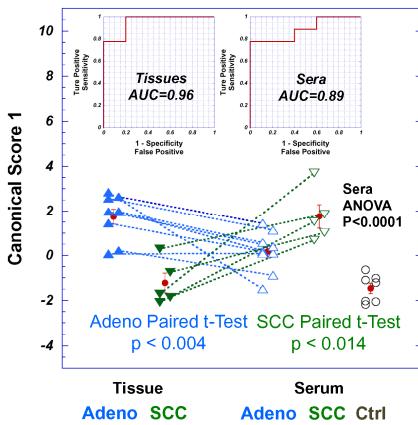


Figure 1

Adeno SCC Adeno SCC Ctrl

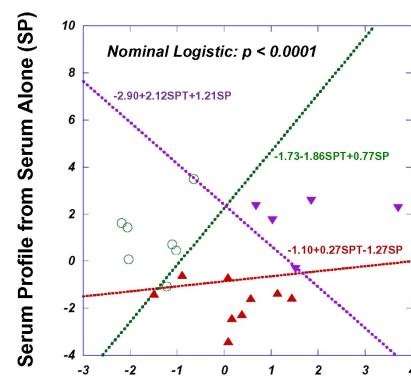


Figure 2.

Serum Profile Based on Tissue (SPT)

Conclusion

We have demonstrated the potential to assess risk of cancer in our testing pairs of human lung tissue and serum samples presented above. Based on our previous success in HRMAS spectroscopy studies of human tumor tissue specimens, we are extremely confident we can generate data that will be used to plan future trial studies investigating the clinical utility of the proposed screening tests for lung cancer based on the achieved serum metabolomic profiles.

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