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A targeted protein-based plasma biomarker approach demonstrates the feasibility of mass spectrometry to discriminate between patients with and without colorectal cancer

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Detectable variations in blood plasma proteins that signal cancer have long been sought as useful diagnostic and prognostic biomarkers. Studies have shown early detection from a routine colonoscopy can prevent colorectal cancer deaths, yet tens of millions of individuals in the US do not participate in a regular screening program. A simple blood based test that predicts colon cancer could be used to encourage participation. The objective herein is to identify blood plasma biomarkers with clinical utility that predicts colon cancer.

Mass Spectrometry, specifically, Multiple Reaction Monitoring (MRM) has the distinct advantage to rapidly measure hundreds of analytes with a high degree of sensitivity and specificity. A set of 188 proteins implicated in colorectal cancer were selected for MRM multiplex screening, with the potential for well over 150,000 molecular analytes. To reduce complexity, in-silico predictive methods identified approximately 5000 high responding MRM screening analytes, with experimental data reducing the final set to 674 final molecular analytes. The overall analyte down selection process followed the guidelines established by clinical and developmental standards.

In this study, three independent collections of age- and gender-matched patients were analyzed, totaling 137 procedure-confirmed colorectal cancer and 137 controls. Plasma samples were thawed and prepared for mass spectrometry analysis by filter-based lipid and particulate removal, abundant protein removal by column-based immunodepletion and enzymatic digestion to peptides by trypsin. Quantitative data on molecular analytes were collected on an Agilent 6490 ESI-QQQ platform and all mass spectrometry data were processed using custom methods and algorithms.

In an effort to further reduce feature complexity, exploration by maximal information-based nonparametric techniques provided a means to down select molecular analytes. The top 100 features resulting from this procedure were subjected to classifier construction by ten rounds of 10-fold cross-validation using an SVM (linear kernel) model for all possible four feature combinations. The best discovery 4 feature classifier, ROC performance of 0.82 AUC (+/- 0.05), was validated in an independent data set at an AUC of 0.87. This initial work shows great promise in distinguishing CRC patients from healthy controls, and continued work is in progress to further improve classification performance.

Biography

Jeff Jones is currently the Senior Bioinformatics Scientist at Applied Proteomics Inc. He received his PhD in Analytical Chemistry from the University of Arkansas, Fayetteville, in 2005. Immediately following, he did postdoctoral work at the Institute for Genomics and Bioinformatics at the University of Irvine. Jeff joined Applied Proteomics in 2007 and has worked to develop novel high throughput analytical methods and data mining algorithms for the identification of cancer biomarkers with potential clinical utility.

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