Proteomic insights in oncology: What have we learned from measuring millions of proteins?

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Abstract
We have assayed over 8400 blood samples from 10 different malignancies, generating over 8 million quantitative protein measurements using SOMAscan™, a new proteomic assay based on modified aptamers. It is capable of simultaneously measuring more than a thousand proteins from small volumes of biological samples such as plasma, tissues or cells. bioinformatic analysis has revealed biomarker panels for early detection, differential diagnosis or prognosis in 5 of these cancers: lung, mesothelioma, ovarian, pancreatic, and renal cell carcinoma. Individual classifiers have been built with 7-13 biomarkers and AUC ranges of 0.84-0.99. These analyses have revealed unique biomarkers for each cancer, as well as common markers.

Several themes emerge from our extensive survey of oncology proteomic profiles. Many of the proteins correlate with disease burden or histopathological grade, and thus have utility for diagnosis, prognosis and recurrence monitoring. Parallels between serum and lung tumor tissue protein measurements demonstrate that many of the blood biomarkers arise from the tumor environment. Inflammatory response proteins are identified in many cancers and reveal important connections between tumor development and host response. Patterns can be found for biological processes in tumor biology, including angiogenesis, apoptosis, inflammation, metabolism and tumor invasion.

With this new proteomics technology—which is fast, economical, highly scalable and flexible—we now have a powerful tool that enables proteome-wide proteomics, biomarker discovery and advancing the next generation of evidence-based, "personalized" diagnostics and therapeutics for oncology.

SOMAscan: Enabling Proteomic Discovery

Successful biomarker discovery through deep interrogation of the proteome

Precise quantification using SOMAmers (Slow Off-Rate Modified Aptamers)
- Sensitive and precise: LOD <1pM with <5% CV
- Highly multiplexed platform: >1000 analyses from 20 μL sample
- High throughput: >300 samples/day
- Broad coverage of cellular pathways and disease pathophysiology

Biomarker Discovery and Verification Studies for Diagnosis and Prognosis
- Assayed over 8400 blood samples and generated over 8 million protein measurements
- Discovered and verified biomarker classifiers for 5 cancers
- Panels include 42 unique proteins, 8 in more than one cancer
- Classifiers contain 7-13 biomarkers for each disease, AUC 0.84-0.99
- Performance supports clinical utility for surveillance, diagnosis, prognosis and recurrence monitoring

Oncology Portfolio

SOMAscan proteomic profiling provides a complete picture of hallmarks of disease
- Deep interrogation of the proteome enables quantification of altered of biological functions and provides of map of disease progression.
- Diagnostic, prognostic or mechanistic signatures have been discovered in a variety of cancers; the strength of the signal appears to relate to tumor progression and disease burden.
- Discoveries can translate rapidly into tools for probing drug mechanisms, pharmacologic effects, evidence-based biomarkers for personalized medicine and for clinical diagnostics.

Conclusions

References

Shared Malignant Mechanisms Signaled by Different Proteins

Functional analysis reveals hallmarks of processes altered in cancer
- Functional enrichment analysis using DAVID Bioinformatics Resources revealed clusters of protein annotations known to be associated with malignancy.
- Functional annotations significant (FDR P<0.05) relative to the SOMAscan menu as well as to the entire proteome
- Functions illustrate tumor growth strategies to deregulate cellular energetics, sustain proliferation, resist cell death, and activate invasion
- The supportive role of the tumor micro-environment is represented by proteins involved in avoiding immune destruction and inducing tumor-promoting inflammation
- Individual cancers may have different proteins mapping to these hallmarks, but most have at least one biomarker from each biological function
- Biomarker levels correlate with pathologic stage and are a measure of disease burden as tumors evolve from local to invasive systemic malignancy

SOMAscan data for one of the proteins in the renal cell carcinoma classifier. The measured value increases with pathologic stage and grade, indicating that this biomarker reflects disease burden and may be useful in diagnosis, prognosis and recurrence monitoring.