

The Search of New Cancer Biomarkers: Moving Forward

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Despite our recent strides in basic research and drug discovery, cancer continues to remain a leading cause for disease-associated mortality worldwide. The absence of effective treatment modalities for most advanced tumors has made the fight against cancer a daunting task. Although many cancers are treatable if detected early, the early detection of cancer has not been trivial due to the complexity and heterogeneity of various tumors. Our failures to control most advanced tumors have highlighted the urgent need to identify novel biomarkers that enable early diagnosis, staging and prognosis. Unfortunately despite our efforts the progress on this front has fallen short of expectations thereby warranting a need to revisit our extant biomarker discovery strategies.

An ideal biomarker should reliably predict the disease at an early stage with a low false-positive rate. Other factors such as ease of sample acquisition, cost of development, ease of deployment and processing also influence the success and commercial viability of a biomarker. It would be wrong to say that we have not progressed at all in our search for cancer biomarkers. However the progress has not been enough as reflected by the prevalent cancer-associated mortality statistics. Even among some established biomarkers the issue of increasing false-positives with increase in their usage is making them less appealing. For instance, Prostate-Specific Antigen (PSA) is widely used as a biomarker to detect prostate cancer. PSA-screening is sensitive, easy to perform and has been highly successful in detecting prostate cancer cases early. However, concerns are emerging regarding the higher than acceptable false-positive rate using standard PSA tests. It is now known that certain conditions other than prostate adenocarcinoma can also result in elevated serum PSA levels causing a false readout. Such concerns further emphasize the need to unravel newer detection standards.

Fortunately, due to the many advances in proteomics and genomics we are well poised today to tackle this issue. Using extant technology we can perform a far more extensive and exhaustive search to uncover novel diagnostic and prognostic markers. One exciting area is detection of circulating nucleic acids in serum. Circulating nucleic acids has been known to be present in human plasma and serum and their levels have been suggested to vary during cancer progression. For instance, quantification of ALU repeats in the serum of breast, and colorectal cancer patients reveal significantly higher values in sera of patients with cancer as opposed to those from healthy controls. However, lack of technology enabling reliable detection of such minute quantities of circulating nucleic acids had previously impeded their development as potential cancer biomarker. The technological robustness of the current sequencing technologies provides us the capability to monitor these minute yet consistent changes in quantities of circulating nucleic acids in blood serum of cancer patients.

As a tumor develops, it recruits many different cell types, growth factors, and inflammatory cytokines, which together form a complex tumor microenvironment. The interaction of these components with the tumor cells is key to progression of the tumor. The composition of the complex of tumor microenvironment changes as the tumor progresses. This ever-evolving tumor microenvironment contains a number of proteins, which are secreted into the serum. Thus, as a result of changes in the tumor microenvironment, the presence and levels of these secreted proteins in the serum also changes as the tumor grows in size and progresses from pre-malignant to malignant stage.

For many years, identifying these tumor-responsive changes in serum proteins has been the gold standard for cancer biomarker discovery. However, owing to the lack of sensitivity of the approaches used, many potential biomarkers might have escaped detection. Over the last decade, the field of proteomics and mass spectrometry has seen tremendous improvements in instrumentation and strategy thus making it possible to detect even femto-mol quantities of proteins from complex mixtures. These improvements in technology provide us the much-required impetus to discover novel biomarkers by revisiting some of the earlier studies.

An emerging theme in cancer biology is that many, if not, all cancers involve aberrant activation of protein kinases. Many protein kinases are secreted into the serum as ecto-kinases. Interestingly, the level of certain protein kinases such as cAMP dependent protein kinase (PKA) in serum has been shown to go up by several folds in cancer patients (Colon and Prostate Cancer patients). However, the physiological relevance of extra-cellular PKA has remained largely unknown due to the lack of many known substrates for these kinases in the serum. From a biomarker-discovery standpoint, the presence of these ecto-kinases provides a unique opportunity to detect and follow cancer progression in a far more comprehensive fashion than the currently employed. During cancer progression, the level of ecto-kinases and their substrates in the serum changes. New substrates emerge while some existing ones get cleared. Monitoring the phosphorylation-status of specific kinase-substrate pairs can be done during cancer progression using extant mass-spectrometry techniques. As the tumor progresses the phosphorylation status of different substrates of an ectokinase would change and which would give information about the stage and progression of the tumor. We could use this information to develop a phospho-antibody based platform to detect tumor initiation, progression, drug-response and prognosis. Since this approach using monitoring multiple variables at the same time, it would in theory provide a much reliable readout of the disease progression. Developing such a technology will have a profound impact on the current diagnostic and prognostic tools available for cancer detection and management. In addition, this work also has the potential to open up new avenues for therapeutic intervention and also helps determine the best treatment option for individual patients.

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