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Editorial

The expansion and advancement of cancer biomarkers

Protein biomarkers of malignancy have been an engaging focus of investigation for nearly half a century. Commonly utilized biomarkers of this type include PSA, AFP, CA 125, EGFR, CEA, and Her2/neu. While these proteins and others have been utilized extensively as indicators of disease development, progression, prognosis, sensitivity to specific therapeutics and treatment response, the search continues for a biomarker test which is truly diagnostic of cancer. Underlying this challenge is the observation that the vast majority of cancer biomarkers do not represent novel pathological entities, but merely dysregulated aspects of normal physiology. Therefore, any test based on single biomarker measurements is inherently burdened by limited sensitivity and specificity. Many investigators have attempted to overcome this obstacle through the use of multianalyte biomarker panels which incorporate complementary information derived from multiple protein factors into a single discriminatory index. While a number of groups have been relatively successful in these efforts, the divergent and often complex bioinformatic algorithms employed in multianalytical analyses are commonly a hindrance to reproducibility and clinical acceptance. Protein biomarkers, measured by immunoassay, immunohistochemistry, proteomics or other methods, represent the myriad factors whose production is altered in tumor cells or in response to those cells. The unifying concept underlying this complex network of protein interactions is genetic alteration. The ability to detect tumorigenic genetic alterations in a noninvasive manner presents an opportunity to definitively distinguish pathology from physiology. The emergence of cell-free nucleic acids (cfNA) as cancer biomarkers may offer such an opportunity.

Cellular necrosis and apoptosis within the tumor microenvironment including circulating tumor cells (CTC) are believed to be responsible for the release of nucleic acids, including genomic and mitochondrial DNA along with a spectrum of RNA species, into the circulation. cfNAs can be analyzed from serum or plasma sample through a variety of techniques including PCR, microarray analysis and direct sequencing. Potential applications include targeted mutation screening, analysis of epigenetic alterations (e.g. methylation patterns), microsatellite analysis, gene expression and miRNA profiling. Through the use of these methods, genetic material released directly by the tumor can be utilized as a potential biomarker for early detection, prognosis, and the design and evaluation of treatment regimens. In this issue of *Cancer Biomarkers*, Xu et al. describe the significant correlation of mutation rates in four genes: *EGFR*, *KRAS*, *BRAF*, and *PIK3CA* with gender, histology and smoking history in a large group of Chinese patients diagnosed with non-small cell lung cancer (NSCLC). Reports such as this not only add to our understanding of the tumorigenic mechanisms at work in NSCLC, but also allow us to begin to assemble a molecular profile of the disease which may be correlated with epidemiological parameters and treatment response rates in order to hasten the development of personalized medicine. Non-invasive mutation screening through the analysis of cfNAs will be a crucial aspect of such advances. Recent studies have also demonstrated that cfNA testing may allow detection of the presence of residual disease following surgical removal of the primary tumor including CTC and disseminated tumor cells. As Zheng et al. demonstrate in this issue, CTC may represent an important source of cfNA, aiding in the accurate staging of disease. The use of cfNAs as biomarkers is likely to result in enhanced levels of specificity in comparison to protein biomarkers, however the standardization of extraction and analysis methods across the multiple platforms currently employed in their analysis represents a significant hurdle at the current stage of development.

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In this issue of *Cancer Biomarkers*, Zheng et al. report on the use of miR-21 as a biomarker of circulating tumor cells in gastric cancer, tapping into perhaps the most promising avenue of cfNA research. In this study the use of a single miRNA provided a high level of discrimination between cases and controls, albeit in a sample of limited size. Several characteristics of circulating miRNAs have led to their attractiveness to biomarker researchers. Perhaps foremost among these is their remarkable stability in bodily fluids, a factor which greatly enhances their efficacy as laboratory analytes. miRNAs are also highly relevant to oncology related endeavors. Several large studies have demonstrated their expression in nearly all evaluated human cancers, including both solid tumors and hematologic malignancies. miRNA expression signatures also show a high degree of cancer specificity and have been successful in the identification of primary sites in cancers of unknown origin. Functional analyses of miRNAs have indicated that they are capable of functioning as both oncogenes and tumor suppressors and that the role of an individual miRNA may fluctuate in response to its cellular environment. miRNAs do appear to be an important component of normal human physiology, and as such, face obstacles similar to those of protein biomarkers with regard to specificity. Therefore, it seems unlikely that individual miRNA biomarkers will provide a diagnostic and/or prognostic capacity sufficient for clinical applications. Rather, the continued emergence of cancer-specific miRNA signatures is likely to make the most significant impact.

Several other research articles in this issue highlight the diversity associated with the current state of cancer biomarker research. Paratore et al. and McCall et al. employ immunohistochemical analyses to predict brain metastases in NSCLC and treatment outcome in prostate cancer, respectively. The diagnostic and prognostic potential of anterior gradient-2 protein is evaluated in lung cancer by Chung et al. Niu et al. utilize proteomic methods to investigate the carcinogenic mechanisms at work in bladder cancer. Clearly the field of cancer biomarkers is expanding at a rate equal to its advancement. The goal of this expansion is the synergistic incorporation of multiple types of biomarkers, including proteins, cfNAs, miRNAs and possibly others into informative and easily implemented clinical tests.

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