Speaker Summaries

SP140

Gene methylation biomarkers for lung cancer risk, recurrence, and prognosis

S. Belinsky. *Lovelace Respiratory Research Institute, USA*

The involvement of gene methylation in carcinogenesis has led to studies focused on establishing the utility of methylation as a biomarker in screening for cancer risk, prevention, treatment, and prognosis. Our group was the first to establish that gene-specific methylation could be detected in sputum from lung cancer patients prior to clinical diagnosis of lung cancer. This observation led to the initiation of studies focused on identifying a panel of genes whose methylation in sputum would predict the presence of early lung cancer. Those studies conducted through the Johns Hopkins Lung SPORE and in collaboration with the Colorado Lung SPORE initially identified a panel of six genes whose concomitant methylation in sputum was associated with a 6.5-fold increased risk for lung cancer. Studies have now been extended to identify additional genes associated with lung cancer risk, to assess whether methylation can predict tumor recurrence, and survival.
The nested, methylation-specific PCR (MSP) assay was used to detect gene promoter methylation in sputum, while standard MSP assayed for methylation in primary tumors.
An additional 46 genes have been evaluated for their association to lung cancer using the case-control design within the Colorado Cohort. We have now identified 14 genes associated with a 2-fold or more increased lung cancer risk. These studies were extended to evaluate the performance of the top 17 genes in a study of prevalent Stage I cases and controls. Similar associations of genes to lung cancer were observed. The ability of gene methylation to predict tumor recurrence was also assessed in sputum from resected Stage I lung cancer patients participating in a Phase III trial of selenium supplementation. Findings indicate both individual and composite methylation of a gene panel were associated with recurrence. Finally, the methylation status of SULF2, a heparin sulfate 6-O-endosulfatase enzyme that promotes the release of growth and angiogenic factors, was defined in lung tumors. Survival following tumor resection and in patients undergoing chemotherapy was reduced in tumors with an unmethylated SULF2 gene. These studies highlight the promise of gene promoter methylation as a biomarker for early detection, recurrence, and prognosis for lung cancer patients.
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SP139

Leukemic stem cells

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An emerging concept in cancer biology is that a rare population of cancer stem cells exists among the heterogeneous cell mass that constitutes the tumour. Based on this notion, tumours are thought to be driven by a cellular subpopulation that retains key stem cell features. Yet, despite their critical importance, much remains to be learned about the developmental origin of cancer stem cells and the mechanisms responsible for their emergence in the course of the disease.
The adaptation of xenotransplantation assays to examine the propagation of AML in vivo has allowed the phenotypic identification of the AML-IC. Transplantation of primary AML cells into NOD/SCID mice led to the finding that only rare cells, termed AML-initiating cells (AML-IC), are capable of initiating and sustaining growth of the leukemic clone in vivo, and serial transplantation experiments showed that AML-IC possess high self-renewal capacity, and thus can be considered to be the leukemic stem cells.
The development of an in vivo model that replicates many aspects of human AML had provide a mean to identify leukaemic stem cells. This in vivo assay provides the foundation of an assay to define the biological and molecular properties of such leukaemic stem cells (LSC).
Since the early studies, further heterogeneity in the LSCs has been identified. Using cell-tracking analysis, the Dick's group identified different sub-clone of SL-ICs. Recently, we also show phenotypic heterogeneity of the SL-ICs between patients and also within the same patients. This heterogeneity not only indicates a potential differential origin or progression of the disease but also have important implications in the development of new therapies to eradicate these cells.
Existing cancer therapies have been developed largely against the bulk population. The lack of durable response in most cases, suggests that the treatment used may not effectively target the CSC population. Indeed, the failure of the current therapeutic regimens is likely related to the resistance and persistence of CSC. Thus, the identification of CSC has important implications for future research as well as for the development of novel therapies.
The seminar will summarise our knowledge of Cancer Stem Cells notably in AML and will try to propose few new avenues that might be taken to eradicate these population of cells.

SP149

Validation of statistically reliable biomarkers

M. Buyse. *IDDI, Belgium*

Background: The clinical literature is replete with the use of biomarkers, but in many cases these have not been properly validated, resulting in a large number of false claims, inappropriate trial designs, and sub-optimal patient management. Yet biomarkers hold great potential for the development of new and more effective cancer treatments by targeting patients who benefit and by providing early signals of efficacy.
Definitions: A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". The term biomarker covers characteristics measured at baseline as well as those measured repeatedly over time, before, during or after treatment. Clinical data, laboratory data, imaging data, gene expression and proteomic data can all be considered biomarkers.
Types of biomarkers: Biomarkers can be useful as prognostic factors that predict the outcome of individual patients in terms of a clinical endpoint, predictive factors that predict the effect of a specific treatment on a clinical endpoint in groups of patients, or surrogate endpoints that replace a clinical endpoint of interest. Biomarkers can be used to stratify the patients at entry in clinical trials, to select the patients eligible for clinical trials, to monitor patients and guide treatment decisions, or to substitute for a clinical endpoint in the evaluation of the effects of new treatments.
Study designs: Different study designs are required for the identification and validation of biomarkers. Case-control or cohort studies are sufficient to validate prognostic biomarkers, large randomized trials are needed to validate predictive biomarkers, and multiple randomized trials are needed to validate surrogate biomarkers. In all cases, the biomarker should be validated either through cross-validation (internal validation in the discovery set) or in different trials (external validation in a confirmatory set).
Validation criteria: The criteria used to validate biomarkers include classification measures (sensitivity and specificity, ROC curves), treatment effect measures (odds ratios, hazard ratios) association measures (correlation coefficients, information theory based measures), and prediction measures (the surrogate threshold effect). These various criteria all have advantages and limitations that will be illustrated in this presentation.

SP141

Serum proteomics in lung cancer

D. Carbone. *Vanderbilt University, USA*

Unlike some tumor types, the majority of the common solid tumors appear not to be driven by single dominant targetable pathways. DNA sequence analysis will likely yield small subgroups with direct therapeutic implications, and expression arrays are beginning to identify others, but analysis of the proteome has many theoretical advantages, for a complete knowledge of the proteome would encompass all known mechanisms of functional dysregulation associated with the development of cancer, including DNA mutations, rearrangements, transcriptional alterations and promoter methylation, but also post-translational modifications.
Using the simple, inexpensive, and rapid technology of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI MS) we studied unfractionated, pretreatment sera to identify NSCLC patients with improved survival after treatment with the EGFR TKIs gefitinib and erlotinib.
Mass spectra, independently acquired at two institutions, gave highly concordant results, and were used to generate an algorithm predictive