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The Journal of the International Society for Oncology and BioMarkers

TumorBiology

Tumor Markers, Tumor Targeting and Translational Cancer Research

The 36th Meeting of the International Society of Oncology and BioMarkers, ISOBM 2008

October 5–9, 2008, Tokyo, Japan

Abstracts

Development of New Molecular Tumor Markers for Diagnosis and Therapy

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TumorBiology

Tumor Markers, Tumor Targeting and Translational Cancer Research

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Plenary Lecture

PL1

Epigenetic Profiling and Epigenetic Therapy in Cancer

Jean-Pierre Issa

University of Texas MD Anderson Cancer Center

Epigenetics refers to stable changes in gene expression that cannot be accounted for by mutations or other genetic events. Epigenetic reprogramming, an essential component of embryogenesis, also has the potential to reverse the malignant phenotype in some cases. The myelodysplastic syndrome (MDS) has been used as a proof of principle disease for this approach. Preliminary studies using a panel of genes methylated in myeloid malignancies revealed frequent abnormal methylation in MDS, and classification of the disease into methylation high/low groups that correspond to shorter survival. In an effort to understand epigenetics of MDS in a global way, we have applied MCAM, a methylation microarray method that represents ~7,000 genes to several patients with MDS, including patients treated with the DNA methylation inhibitor decitabine. Overall, we identified hundreds of genes hypermethylated in MDS, with a rate of anomalies ranging from 5-15% of detectable loci. We identified ~200 genes concordantly methylated in the poor prognosis subset of MDS earlier described. Turning to therapy, we and others have shown that a certain degree of epigenetic reprogramming can be achieved by drugs that inhibit DNA methylation, and this leads to significant responses and prolongation of life in this disease. Using MCAM, we identified ~100 genes commonly hypomethylated after decitabine. Among the modified genes are several microRNAs, and we found that mir124a is frequently hypermethylated in MDS, which results in increased expression of its target, CDK6. The DNA methylation inhibitor decitabine leads to hypomethylation of mir124a in patients with MDS, along with upregulation of the miRNA and down-regulation of CDK6. Increased expression of mir124a correlates with response to decitabine in MDS. We conclude that aberrant methylation is very common in MDS, which may explain in part responsiveness of this disease to epigenetic therapy. These principles are now being translated in other leukemias and in solid tumors.

PL2

Large-scale Mutational Analyses of Human Cancers: Lessons Learned from Sequencing Cancer Genomes

DW Parsons[1,2], S Jones[1], RJ Leary[1], J Lin[1], X Zhang[1], LD Wood[1], T Sjöblom[3], N Papadopoulos[1], G Parmigiani[1], KW Kinzler[1], VE Velculescu[1], and B Vogelstein[1]

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[3]*Department of Genetics and Pathology, Uppsala University, SE-751 85 Uppsala, Sweden*

Human cancer is caused by the accumulation of mutations in oncogenes and tumor suppressor genes. In an attempt to comprehensively catalog the genetic changes that occur during tumorigenesis, we have developed techniques for genome-wide sequencing-based mutational analysis. These methodologies have been applied to a panel of 11 breast and 11 colorectal cancers. Based on analysis of exons representing ~20,000 transcripts from ~18,000 genes, we conclude that the genomic landscapes of breast and colorectal cancers are composed of a handful of commonly-mutated gene "mountains" and a much large number of gene "hills" that are mutated at low frequency. We have developed statistical and bioinformatic tools that help to identify single genes with a role in tumorigenesis, as well as to implicate pathways enriched for genetic alterations. These genome-wide analyses have provided us an unprecedented view of the spectrum and extent of somatic mutations in human tumors of similar and different histologic types. The results of these studies have profound implications for understanding the nature and heterogeneity of human cancers and for using personal genomics for tumor diagnosis and therapy.

PL3

The New Phase of Transcriptome Analysis

Yoshihide Hayashizaki

1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, 230-0045, Japan

Aim:

The international FANTOM consortium was organized in 2000 and established the *de facto* standard of the full-length cDNA banks of mouse, human and several other species. Now, it is entering a new scientific phase dealing with functional genomics of the gene networks.

Method:

A human monoblast cell line, THP-1, is used as a model for the development of a general-purpose pipeline for the elucidation of the gene expression regulatory network which consists of transcriptional factor proteins and functional RNA molecules. Large amounts of data such as promoter actitivites and RNA profiling by CAGE, chromatin structures and protein-DNA interaction by ChIP-Chip, small RNA profiling by sequencing and so on was obtained through PMA stimulation time coarse of THP-1, followed by extensive computational analysis.

Results:

The analysis has showed that the differentiation of the cell was precisely controlled by concerted regulation of gene expressions.

Conclusion:

We have recently introduced a new concept called "basin" for understanding cell function. The basin is defined as a steady state of a cell with specific gene expression profile to autonomously maintain the cell function.

Special Presidential Forum

SPF1

From Analbuminemic Rats to Pierisin, An Apoptogenic Peptide from Butterflies

Takashi Sugimura, Keiji Wakabayashi

National Cancer Center

In the1980's, I was fortunate in having opportunities to attend ISOBM meetings, or their precursors, and to interact with Prof. Hidematsu Hirai, who was once my mentor at University of Tokyo and a founder of the ISOBM. As I recall the meetings, I would like to start with one or three slides for each subject which I had the pleasure to present. The areas covered were: 1) analbuminemic rats and splicing infidelities induced in hepatic cells by treatment with carcinogens; 2) disdifferentiation and decarcinogenesis concepts deduced from findings of changes in isozyme patterns in tumors; and 3) the likely importance for carcinogenesis of epigenetic changes, in addition to genetic alterations, inferred from the modification of chromatin proteins by many carcinogens also producing DNA base adducts. I would like to also present our current and exciting information concerning an apoptogenic peptide, pierisin, isolated from the cabbage butterfly. Pierisin is rich in late phase larvae and pupae in the early phases of the cabbage butterfly life cycle. It exerts potent apoptogenic activity in cancer cells, and is able to ADP-ribosylate guanine bases of DNA. Pierisin seems to be important for metamorphosis of this species of butterfly and might be effective as a protective agent against natural enemies. The molecular biology, and phylogenic and ontogenic aspects of this compound are attracting increasing attention, and pierisin clearly could be a promising candidate for development as a lead compound for cancer drugs.

SPF2

From "Placental Alkaline Phosphatase" to "Oncodevelopmental Biology" to the "Burnham Institute for Medical Research" - A Success Story

José Luis Millán

Professor and Sanford Investigator, Sanford Children's Health Research Center, Burnham Institute for Medical Research, La Jolla, CA 92037 – USA

It started with a biochemical observation: a male patient with lung cancer had elevated plasma levels of placental-type alkaline phosphatase, an enzyme usually found in pregnant women. This discovery led William H. Fishman, Tufts University, Boston, to begin to formulate the concept that the re-expression of embryonic and/or developmental genes might be a mechanism evoked by cancer cells to gain a competitive advantage over neighboring normal cells in their quest to proliferate. Simultaneous and independent studies by Phil Gold on the expression of carcino-embryonic antigen and by Gary Abelev on alpha-fetoprotein, led to coining the term "Oncodevelopmental Biology" to define this new paradigm in cancer research. These scientists shared their views at the annual meetings of the "International Research Group for Carcinoembryonic Proteins", led by Prof. Hidematsu Hirai, Sapporo, Japan, and together decided to focus on this new paradigm and re-named that research group the "International Society for Oncodevelopmental Biology and Medicine" (ISOBM). Prof. Hirai, furthermore, encouraged Dr. Fishman to create an institution in the USA to sharply focus research at the interface of oncology and developmental biology. Thus, at the 4th ISOBM meeting organized by Bill Fishman at the Hotel del Coronado, San Diego, May 1976, the creation of the La Jolla Cancer Research Foundation, La Jolla, CA was announced. I had the privilege to join Bill Fishman's research group shortly after, in August 1977, when that new Foundation had less than 10 employees and I've had the unique opportunity to grow with and to contribute to the growth of that Institute that currently, known as the Burnham Institute for Medical Research (BIMR), counts with ~900 employees, ~70 principal investigators, NIH funding in the order of 90 million USD and conducts bicoastal operations with campuses in La Jolla and Santa Barbara in California and Orlando in Florida. BIMR has been ranked among the 10 most influential research institutes world-wide based on the impact of its research. Its motto is "From Research, the Power to Cure". It all started with an experimental observation, a supportive society, a dreamer like Bill Fishman and the will and perseverance to see that dream come true.

SPF3

From the Study of Carcinoembryonic Proteins to Molecular Medicine

Sabine von Kleist

Univ. Freiburg, Germany

Not only anniversaries lend themselves for reflections and critical evaluations of the years that have passed. A change of name of a scientific society existing now for 36 years under the same name provides also a welcome opportunity to have a look on its past and to dare a look into the future. If it needs to count the milestones of success of this society, the first is surely its foundation as International Society of Oncodevelopmental Biology and Medicine (ISOBM) by the eminent and farsighted researcher Prof. H. Hirai, whose wisdom, reputation and outstanding leadership attracted right from the start (Oct. 23, 1972) a rapidly growing audience around renowned colleagues from all over the world. They all were highly interested in this new field of research of fetal proteins and a phenomenon already observed by Hirszfeld in 1932 of common traits between embryonal and tumor tissues. In less than ten years purely basic fetal research had developed into molecular biology and medicine. Clinical implications were found most everywhere thanks to a close collaboration between basic scientists and clinical oncologists fostered since the beginning by ISOBM's president. He was also at the origin of many life-long friendships beyond any what so ever boundaries. Let us henceforth revive the thought that a society is made of human beings, who -although having common interests- still need personal attention and individual contacts testifying the esteem of the presidency for the members of the society.

SPF1

From Analbuminemic Rat to Organic Anion Transporting Polypeptides and Molecular Medicine

Takeshi Sugiyama, Keiji Wakabayashi

National Cancer Center

SPF2

From "Placental Alkaline Phosphatase" to "Oncodevelopmental Biology" to the "Burnham Institute for Medical Research" - A Success Story

José Luis Millán

Professor and Sanford Investigator, Sanford Children's Health Research Center, Burnham Institute for Medical Research, La Jolla, CA 92037 – USA

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ISOBM Abbott Award

Clinical Aspects of α-fetoprotein and Its Sugar Chain

Kazuhisa Taketa

Emeritus Professor Okayama University, Japan

Serum α-fetoprotein (AFP) has been widely used for the early detection of hepatocellular carcinoma (HCC) and its follow-up after intervention. The positive rate of AFP in HCC in the period of 1980-1981 was 63.1% for cases with AFP>200 ng/ml and 25.1% for those with AFP>10,000 ng/ml and the rate in the period of 2002-2003 decreased to 27.1% for those with AFP>200 ng/ml and to 15.7% for those with AFP>10,000 ng/ml. The decrease in positive rate of AFP was correlated with the decrease in tumor size. This is probably related to the fact that HCC became detected earlier while the tumor size was small as a result of the development of imaging modalities. Thus, the setting of cut-off level for AFP is less meaningful. Another difficulty in interpreting the rise in serum AFP level lies in the fact that serum AFP level rises not only in HCC but also in hepatitis and cirrhosis, which are the underlying pathogenetic conditions of HCC. In order to circumvent the difficulty in differentiating benign and malignant conditions, microheterogeneity of AFP sugar chain was determined in HCC and compared with that in hepatitis and cirrhosis. AFP having sugar chains with fucosylated core *N*-acetylglucosamine, namely, AFP-L3, was more specific to HCC when it was expressed by the percentage of total AFP. AFP-P4, which was separated by affinity electrophoresis with erythroagglutinating phytohemagglutinin (E-PHA), had a monosialylated biantennary oligosaccharide with an exposed β-D-galactose of the α-D-mannose α1→6 antenna and increased in HCC even in cases with negative AFP-L3. Therefore, the combined use of different glycoforms of AFP increases both the specificity and sensitivity in diagnosing HCC. Two-dimensional isoelectric forcusing and lectin affinity electrophoresis with E-PHA further revealed additional microheterogeneity forms of AFP in HCC. This new separation technique would facilitate the marker diagnosis of HCC in view of the fact that the microheterogeneity of epigenetic expression is the fundamental feature of malignancy in addition to dedifferentiation.