317 Is epigenetics the holy grail of cancer research?

Z. Herceg[1]. [1]*International Agency for Research on Cancer (IARC), Epigenetics Group, Lyon, France*

It is now widely accepted that cancer is also epigenetic disorder and that epigenetic changes play key roles in cancer development and progression. The fact that epigenetic alterations are, in contrast to genetic changes, reversible has an important implication for cancer treatment and prevention. Epigenetic inheritance include DNA methylation, histone modifications and RNA-mediate silencing all of which are essential mechanisms that allow the stable propagation of gene activity states from one generation of cells to the next. Epigenetic states are profoundly altered in human cancer and epigenetic deregulation have been observed in virtually all types of human cancers, although the precise underlying mechanisms remain poorly understood. Recent years have witnessed a remarkable pace of discoveries in epigenetics and epigenomics which will revolutionize our understanding of cancer and other complex diseases. This should help to elucidate the mechanism underlying tumourigenesis, identify specific epigenetic targets and the critical windows of vulnerability. The intrinsic reversibility of epigenetic changes represents a tremendous opportunity for the development of novel strategies for cancer treatment and prevention. Recent conceptual and technological advances in epigenetics and ongoing efforts aiming to identify epigenetic targets that could be exploited in cancer prevention and therapy as well as molecular epidemiology will be discussed.

Monday 28 June 2010 08:00–08:50

Educational Lecture
DNA damage response & novel targets

318 The ATM-mediated DNA damage response: the system and the pathways

Y. Shiloh[1], Y. Ziv[1], R. Elkon[2], S. Rashi-Elkeles[1], A. Kuperstein[1], A. Ben-Simon[1], A. Schmidt[3,4], R. Aebersold[3,4], R. Shamir[5]. [1]*Tel Aviv University, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv, Israel,* [2]*The Netherlands Cancer Institute, Division of Gene Regulation, Amsterdam, The Netherlands,* [3]*ETH Zurich, Institute of Molecular Systems Biology, Zurich, Switzerland,* [4]*ETH Zurich, Competence Center for Systems Physiology and Metabolic Diseases, Zurich, Switzerland,* [5]*Tel Aviv University, School of Computer Science, Tel Aviv, Israel*

The cellular DNA damage response (DDR) – a central axis in maintenance of genomic stability – is a complex system that is turned on most vigorously by critical DNA lesions such as double strand breaks (DSBs). The DSB response affects numerous cellular processes and involves marked changes in signaling pathways, in gene expression and RNA metabolism, and in protein turnover, location and post-translational modifications (PTMs). Following DSB induction, the nuclear protein kinase ATM mobilizes this intricate signaling web by phosphorylating many key players in its various branches. This complex mechanism requires many cellular resources and is prone to severe genetic defects that lead to genomic instability, tissue degeneration and cancer predisposition. For example, ATM loss or inactivation leads to the genomic instability syndrome ataxia-telangiectasia (A-T), characterized by neuronal degeneration, immunodeficiency, genomic instability, extreme radiation sensitivity, and cancer predisposition. The complexity of this system is, however, worth its cost: the system takes the cell safely through the DNA damage crisis and, within a few hours, leads it back to normal life cycle once the damage has been repaired. We are studying individual pathways in this network using an experimental approach aimed at isolating the effect of a single process against the noisy background of the entire network. Recently identified pathways will be presented. In parallel, high-throughput strategies to gain an overview of different DDR layers are being employed. One layer is the cellular transcriptome, which we explore by obtaining gene expression profiles and analyzing them using algorithms and software developed in our labs. This analysis has recently pointed out new transcription factors that are involved in the ATM-mediated DDR. Another layer of the DDR is protein PTMs. A major PTM that shows profound damage-induced dynamics is protein phosphorylation. We combined phosphopeptide isolation, advanced mass spectrometry and label-free quantitation to explore nuclear phosphoproteome dynamics following DSB induction and to determine quantitative changes in phosphorylation levels of specific sites. Hundreds of novel damage-induced phosphorylations and dephosphorylations were identified. Importantly, about 40% of damage-induced phosphorylations were ATM-independent. ATM was required not only for the initial phosphorylation of the ATM-dependent sites, but also for the maintenance of theses phosphorylations over time. We connected many of the phosphorylated and dephosphorylated proteins into functional networks. The data attest to the breadth of the cellular DDR and will aid in elucidation of novel signaling events in this ever expanding network.

Monday 28 June 2010 08:00–08:50

Educational Lecture
Statistical analysis

319 Analysis of complex datasets with descriptive and predictive models – application to biomolecular pathways

K. Sachs[1], S. Itani[2], G.P. Nolan[3]. [1]*Stanford University, Department of Microbiology and Immunology, Stanford CA, USA,* [2]*Berkeley, Electrical Engineering, Berkeley CA, USA,* [3]*Stanford University, Molecular Biology and Immunology, Stanford CA, USA*

Background: Datasets produced in today's molecular biology laboratories provide a bewildering amount of data and a wealth of opportunity to probe the underlying biological systems. This instructional talk will discuss various approaches for tackling biological questions that can be approached with some high throughput datasets. The focus will be on proteomic data but the approaches presented are applicable more generally in various biomolecular contexts.
Materials and Methods: We will handle a classic experimental scenario in which various states or experimental conditions are subjected to high throughput measurement techniques, e.g. protein measurements following cytokine stimulus, potentially with an outcome measurement as well (e.g. percent apoptosis). For these, we will discuss the types of questions that can be asked, including predictive tasks ('Can we predict the degree of apoptosis') and mechanistic questions ('By what molecular pathway does TNF induce apoptosis'). We will briefly discuss regression models and classifiers, followed by a more detailed discussion of Bayesian network models.
Results: Applications in molecular biology and examples from a clinical setting will be presented.
Conclusions: Some remaining challenges and future directions for algorithmic development will be discussed.

Monday 28 June 2010 08:00–08:50

Educational Lecture
Novel diagnostics

320 Elucidation of pathomechanisms in human brain tumours by molecular profiling

P. Lichter[1]. [1]*Deutsches Krebsforschungszentrum, Division of Molecular Genetics, Heidelberg, Germany*

Identification of genomic and transcriptomic alterations have greatly contributed to revisions of tumour classification schemes and the identification of pathogenically relevant molecular pathways. We performed comprehensive molecular profiling on the level of the genome, the transcriptome and the epigenome, employed to the same samples of human brain tumours. Subsequently, these data were integrated and related to clinical parameters. Emerging candidate genes have been subjected to functional tests in dedicated cellular systems by means of ectopic expression as well as gene knock-down strategies and subsequent assays for cell viability, proliferation, apoptosis and cell migration. This approach allowed us to further elucidate pathomechanisms in human astrocytoma and oligodendroglioma and to uncover novel factors relevant to cell cycle control and cell migration. Notably, we identified (i) signatures distingiuishing two subgroups of primary glioblastoma, (ii) a pathogenic pathway downstream of TP53 regulated by DNA methylation in astrocytoma, (iii) selective pathway activations in glioblastoma of long term survivors, and (iv) genetic alterations in paediatric low grade astrocytoma that affect targeted molecular therapy procedures. Furthermore, novel algorithms to classify and to stratify paediatric and adult medulloblastoma patients will be presented. Possible consequences of these findings for the management of brain tumour patient will be discussed.

Monday 28 June 2010 09:00–09:50

Pezcoller – EACR Lecture

321 The p53 pathway: cancer, fertility, metabolic control and the central nervous system

A. Levine[1]. [1]*Institute for Advanced Study and Cancer Institute of New Jersey, Simons Center for Systems Biology, Princeton, USA*

The p53 protein and the signal transduction pathway controlled by that protein responds to a wide variety of stress signals which can disrupt the fidelity of DNA replication and cell division. To prevent these errors or mutations the p53