Sunday 27 June 2010 08:00–08:50

Educational Lecture
Molecular imaging

17 Intravital microscopy of cancer progression, regression and resistance to therapy

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Molecular programs controlling metastatic cancer progression are diverse in different cancers as well as within the microenvironment of a single lesion. These include amoeboid, mesenchymal and collective invasion processes, followed by different mechanisms to seed and condition the metastatic site for secondary survival and growth. Cancer plasticity may further be supported as side-effect of therapeutic interference, prompting cellular and molecular adaptation programs. Examples for unexpected adaptation programs suited to overcome molecular interference are the mesenchymal-amoeboid transition after the interference with surface proteases or surface integrins, the amoeboid-mesenchymal transition after interference with Rho/ROCK pathways, and the collective-to-amoeboid transition leading to the dissociation of multicellular lesions followed by amoeboid single-cell dissemination. Thus, an understanding of cellular plasticity of invasion programs will be important to better target cancer progression.
Multiphoton microscopy (MPM) has become the method of choice for investigating cell structure and function in tissues and organs, including the invasion and progression of cancer lesions. Using a novel approach of infrared-excited (IR-)MPM at wavelengths above 1080 nm that enhances deep tissue microscopy in orthotopic fibrosarcoma xenografts, we here show deep collective invasion strands of several hundred connected cells. These multicellular units proliferate and simultaneously move with velocities of up to 200 μm per day along pre-existing blood vessels but not tumour-induced neovessels and proliferate ("invasive growth"). These perivascular tumour cell strands further maintain invasion and robust survival during otherwise regression-inducing experimental radiation therapy. Both, primary growth and survival and increased resistance to experimental therapy were ablated by interfering with beta1 and beta3 integrins, implicating integrin-mediated signals as microenvironmental denoinators of response to therapy. In conclusion, intravital deep tumour imaging by IR-MPM identifies the tumour-vessel interface as preferred niche of invasive growth, radioresistance and enhance preclinical anti-cancer therapy.

Sunday 27 June 2010 08:00–08:50

Educational Lecture
Bioinformatics

18 Analyzing functional genomics data and networks to understand disease

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Background: Understanding complex disease at the molecular level requires cataloguing and modeling specific molecular-level changes that lead to disease. Modern genome-scale experimental techniques (including expression, sequencing, interaction, SNP data) enable monitoring of these molecular events, and their integrative analysis holds the promise of generation of specific, experimentally testable hypotheses, paving the way for a systems-level molecular view of carcinogenesis. The complexity and scale of human biology make it challenging to integrate such a large body of data, model them on a systems level, and use these models to study specific pathways, genetic disorders, acquired disease, and therapeutic responses.
Results: I will describe how these challenges can be addressed through the development of integrative bioinformatics frameworks that enable cancer researchers to effectively explore and analyze the entirety of functional genomics data in a way driven by their biological question of interest. Specifically, I will present HEFalMP, a regularized Bayesian integration system we developed that provides maps of functional activity and interactions in over 200 areas of human cellular biology and disease, each including information from ~30,000 genome-scale experiments pertaining to ~25,000 human genes. HEFalMP allows prediction of protein function and functional modules, cross-talk among biological processes, and association of novel genes and pathways with known genetic disorders. I will also describe our work in starting to model these systems-level processes in a cell-type/tissue specific context, starting with accurate predictions (and experimental confirmation) of tissue-specific expression. Gene expression and high throughput copy number data are perhaps the most widely used functional genomics approaches for the study of cancer. I will describe a software package we developed for probabilistic analysis of these data to identify phenotypically/clinically relevant aneuploidies.
Conclusions: The presentation will be accessible to those with biology or computational background and will be focused on using these methods to analyze functional genomics data and discovery novel biology. For more information, please explore: http://function.princeton.edu/ and function.princeton.edu/hefalmp

Sunday 27 June 2010 09:00–09:50

Radium Hospital Foundation Lecture: Epigenetics

19 Epigenetic therapy

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The abnormal methylation of CpG islands located near the transcriptional start sites of human genes plays a major role in carcinogenesis. The methylation of cytosine residues in these regions is associated with alterations in chromatin structure including changes in the state of modification of histone residues in nucleosomes and the positioning of these nucleosomes with respect to the transcription start site. These alterations serve to reinforce each other and may lead to the heritable silencing of genes which can have profound implications for human cancer development. Unlike mutational changes, epigenetic alterations are acquired in a gradual process which is associated with cellular division. Thus, these progressive alterations are potentially susceptible to interventions to reverse silencing. Epigenetic changes can be observed in premalignant tissues so that understanding what causes the alterations and development of potential strategies to reverse them could have an impact on carcinogenesis. The mechanisms underlying progressive methylation of CpG islands leading to altered chromatin configuration are now beginning to be understood. Drugs such as 5-aza-2′-deoxycytidine can reverse DNA methylation changes and reactivate gene expression by changing not only the methylation, but also the nucleosomal occupancy of the promoter. Further understanding of epigenetic changes in cancer and the mechanisms by which they are acquired may therefore help in the search for new therapeutics.

Sunday 27 June 2010 10:20–12:20

Symposium
Senescence & aging

20 Roles and regulation of cellular senescence

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Cellular senescence was originally described as the process that accompanies replicative exhaustion in cultured human fibroblasts, and is characterized by a series of poorly understood markers. Our laboratory previously showed that deregulated mitogenic oncogenes could drive cells into a senescent state thereby preventing transformation, and that senescence could contribute to the outcome of chemotherapy *in vivo*. Based on the hypothesis that senescence is an important tumour suppressive mechanism, we continue to study the roles and regulation of senescence during cancer and other types of pathologies. Recently, we performed a series of genome wide gene expression profiling and chromatin binding experiments to identify genes controlled by the retinoblastoma tumour suppressor (RB) that are uniquely targeted as cells exist the cell cycle into senescence. These studies imply that RB acts, primarily, to suppress genes involved in DNA replication, particularly in cells undergoing cell cycle exit into senescence. These same processes are redundantly controlled by the RB family as cells exit cell cycle into quiescence. We believe this may be crucial to its tumour suppressive role and continue to work on the mechanism of this effect. We also study the biology of senescence and, recently, have shown that senescent cells can be targeted and cleared by the immune system in vivo. These results have implications for the role of senescence in tumour suppression and other human pathologies, and hence we continue to explore the factors underlying senescent cell clearance. Recent studies support a role for inflammatory programs, as well as the perforin/granzyme B pathway, in this processes. Current efforts to characterize molecular mechanisms of senescence the behavior of senescent cells in vivo will be discussed.

21 Molecular mechanisms of cellular senescence

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Early tumourigenesis is associated with the engagement of the DNA-damage checkpoint response (DDR). Cell proliferation and transformation induced