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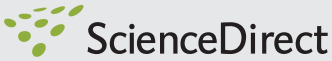

Tuesday 29 June 2010

Tuesday 29 June 2010 07:00–08:00

After Sunrise: Meet the Expert

606 Evolution of genetic and gene expression networks during tumour development

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Background: Quantitative genetics has identified polymorphisms within gene regulatory factors or their target genes which cause variation in phenotypes, such as inflammation and obesity, that influence disease susceptibility. Expression levels individual genes can also be regarded as "phenotypes" under genetic control, some of which may influence cancer susceptibility. Applying expression Quantitative Trait Locus (eQTL) approaches to mouse strains with differing susceptibility to diseases, such as obesity and cancer, has identified signaling hubs that may be important targets for drug development.
Methods: We used network construction methods to analyze the genetic architecture of gene expression in normal mouse skin in a cross between tumour-susceptible *Mus musculus* and tumour-resistant *Mus spretus*.
Results: We demonstrate that gene expression motifs representing different constituent cell types within the skin such as hair follicle cells, haematopoietic cells, and melanocytes are under separate genetic control. Motifs associated with inflammation, epidermal barrier function, cell cycle control and proliferation are differentially regulated in mice susceptible or resistant to tumour development. The intestinal stem cell marker *Lgr5* is identified as a candidate master regulator of hair follicle gene expression, and the Vitamin D receptor (*Vdr)* links epidermal barrier function, inflammation, and tumour susceptibility. These gene expression networks undergo substantial rewiring during development of benign and malignant skin tumours. The Lgr5 stem cell marker is expressed in skin tumours but is no longer linked to the expression of hair follicle genes, while the individual components of the susceptibility network associated with the *Vdr* locus are independently rewired in tumours.
Conclusions: The combination of genetics and gene expression approaches offers substantially greater power than classical methods for identification of genetic factors that contribute to cancer susceptibility and progression.

607 Exploring chemoresistance in vivo; are we making progress

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Chemoresistance remains the main obstacle to cancer cure. Contrasting prognostic factors, for which many are known in breast cancer as well as with respect to other solid tumours, few factors predicting sensitivity to chemotherapy are known. While HER-2/topo-II over expression is associated with enhanced anthracycline-sensitivity and recent evidence has linked KI67 levels to benefit of taxanes in ER+ breast cancer, so far predictive factors have not been implemented selecting patients for breast cancer chemotherapy. Notably, while gene expression signatures like the OncotypeDX has been associated with sensitivity to chemotherapy, it confers to a large extent the same information as has been covered by traditional parameters like histological grade and Ki67. Identification of the so-called basal cell-like breast cancer type has revealed a tumour sub-group with a gene expression profile resembling the bulk of tumours occurring in individuals harbouring BRCA1 mutations. Thus, current evidence propose these tumours may harbour defects in DNA double-strand repair resembling what has been revealed in BRCA1 and BRCA2 mutated tumours, and there is preliminary evidence suggesting these tumours like BRCA1/2 mutated ones may benefit from treatment with PARP inhibitors. Harbouring such defects, the potential exists that these tumours, similar to BRCA1 mutated ones may be sensitive to chemotherapeutic compounds like cis-platin, a drug not commonly used for breast cancer therapy in general. A major goal is to explore and understand the complete biology of chemoresistance. The fact that a limited number of genes seems to be critical to tumour development as well as growth (so-called "drivers", contrasting mutations in the bulk of genes considered to be "passengers") suggest chemoresistance may be due to defects affecting critical biological pathways executing processes like apoptosis or DNA repair. Now, with novel gene sequencing technologies open for complete genome sequencing of individual tumours we are facing an era allowing us, for the first time, to explore genetic alterations leading toward a full understanding of the processes guiding therapy response in breast cancer as well as in all forms of malignant disease.

Tuesday 29 June 2010 08:00–08:50

Educational Lecture
Developing targeted therapy

608 Systems approach to personalized molecular medicine

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The realization of the promise of personalized molecular medicine will require the efficient development and implementation of novel targeted therapeutics. The overall likelihood of response to particular drugs represents the interaction between predictors of sensitivity with predictors of resistance. The phosphatidylinositol 3′kinase (PI3K) pathway is aberrant at multiple levels across a wide variety of tumours making it the most common activating aberration in cancer. This has led to the development and now early clinical testing of drugs targeting multiple components of the pathway. The efficient utilization of these drugs will require the ability to accurately determine mutation and activation status in tumours as well as determining the interaction between the PI3K pathway and other pathways in driving tumour pathophysiology. The PI3K pathway is critically important to cellular function and is thus under exquisite homeostatic control. The feedforward and feedback loops in the pathway determine the response to perturbation of the pathway by mutation or therapeutic intervention. Strikingly inhibition of the pathway at the level of mTOR or AKT results in the activation of potent feedback loops resulting in activation of multiple cell surface tyrosine kinases, PI3K itself and AKT. This may contribute to the observation that mTOR inhibitors appear to make some patient tumours grow more rapidly an unexpected and disappointing consequence. Our preliminary systems biology-based mathematical and experimental models of the PI3K signaling network accurately predict these consequences as well as the biochemical processes involved. Further, the models suggest combinations of targeted therapeutics likely to reverse the negative effects of the mTOR inhibitors converting the outcome from negative to positive in terms of tumour growth.

Tuesday 29 June 2010 08:00–08:50

Educational Lecture
Cell cycle

609 In and out of G1

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The cell division cycle is a series of events that takes place in a cell leading to cell duplication. Checkpoints act at different points throughout the cell cycle overseeing that events in the proceeding cell cycle phase have been accurately completed.

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