08 July 2008 08:00 - 08:50

EDUCATIONAL LECTURE

What is epigenetics?

459
What is Epigenetics?

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An altered pattern of epigenetic modifications is central to many common human diseases, including cancer. Many studies have explored the mosaic patterns of DNA methylation and histone modifications in cancer cells on a gene-by-gene basis, among them the seminal finding of transcriptional silencing of tumor suppressor genes by CpG island promoter hypermethylation. Epigenetic gene inactivation in transformed cells involves many "belts of silencing". We are in the process of completing the molecular dissection of the entire epigenetic machinery involved in methylation-associated silencing, such as DNA methyltransferases, methyl-CpG binding domain proteins, histone deacetylases, histone methyltransferases, histone demethylases and Polycomb proteins. The first indications are also starting to emerge about how the combination of cellular selection and targeted pathways leads to abnormal DNA methylation. In addition to classical tumor-suppressor and DNA repair genes, epigenetic gene silencing includes genes involved in premature aging and microRNAs with growth inhibitory functions. Recent technological advances are now enabling cancer epigenetics to be studied genome-wide. It is time to "upgrade" cancer epigenetics research and put together an ambitious plan to tackle the many unanswered questions in this field using genomics approaches to unravel the epigenome.

08 July 2008 08:00 - 08:50

EDUCATIONAL LECTURE

Promises, challenges and pitfalls in large data analysis

460
Biomarkers and surrogate endpoints in clinical research - some statistical challenges

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Recent developments in biostatistics and bioinformatics are reshaping clinical research. With the number of promising new molecules available for clinical testing, clinical trials need to detect a drug's benefit (and harm) as fast as possible. In parallel with the need for speed in clinical development, advances in molecular biology, high throughput technologies and imaging techniques provide investigators with an ever growing number of biomarkers which can be used for a variety of purposes: to inform go / nogo decisions in early clinical development, to stratify patients, to target subsets, to adjust treatments, or to replace / support clinical endpoints for drug approval. This talk will briefly cover all of these goals, and will discuss the level of evidence required for a biomarker to be useful in every case. The talk will mostly focus on the use of biomarkers as surrogates for clinical endpoints. It will be shown that two criteria need to be fulfilled before a biomarker can be considered a valid surrogate for a clinical endpoint: there must be a strong "individual-level" association between the biomarker and the clinical endpoint, and also a strong "trial-level" association between the effects of a treatment (or class of treatments) on the biomarker and the clinical endpoint.(1) The latter criterion is seldom looked at, and is (surprisingly) not implied by the former. Showing that both criteria are met usually requires a meta-analysis of randomized trials. When such data are available, the predictive value of potential surrogate biomarkers can be investigated, and the "surrogate threshold effect" can be estimated as the minimum effect on the surrogate biomarker that predicts a statistically significant effect on the clinical endpoint. (2) The talk will use actual datasets in oncology to illustrate all of these notions.

References:
1. Buyse M., Molenberghs G., Burzykowski T., Renard D., Geys H. The Validation of surrogate endpoints in meta-analyses of randomized experiments. Biostatistics 1: 49-68, 2000
2. Burzykowski T., Buyse M. Surrogate threshold effect: An alternative measure for meta-analytic surrogate endpoint validation. Pharmaceutical Statist 5: 173-186, 2006

08 July 2008 09:00 - 11:00

SYMPOSIUM

New targets

461
BRAF and RAS signalling in human melanoma

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The RAS-RAF-MEK-ERK signalling pathway is a critical player in human melanoma. This pathway is hyper-activated in the majority of human melanomas, largely because NRAS is mutated in ~15% of melanomas and BRAF is mutated in another 50-70% of cases. Signalling through this pathway stimulates proliferation and survival of melanoma cells and the pathway has been established as an important therapeutic target in this disease. We have developing mouse models of melanoma driven by oncogenic BRAF or oncogenic RAS. We find that inducible expression of oncogenic BRAF from the endogenous mouse gene stimulates a progressive disease that is characterized by the appearance of naevi followed by the induction of melanoma 6-12 months after the expression of oncogenic BRAF in the melanocytic lineage. Importantly, the tumours arise in the mice that have not been manipulated in any other manner and which have a wild-type genome. These data indicate that oncogenic BRAF is a powerful inducer of melanoma in mice. However, the long delay required for the appearance of the lesions indicates that oncogenic BRAF alone is not sufficient for complete progression from melanocyte to melanoma and that additional genetic events are required. We have also shown that expression of oncogenic KRAS in the melanocyte lineage leads to melanoma. Thus, we have developed a model of melanoma that are driven by oncogenic BRAF and oncogenic KRAS. The tumours appear to possess many of the features found in the human disease and these mice will therefore be powerful tools for the ongoing genetic analysis of melanoma.

462
PI3-kinases and cancer

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The phosphatidylinositol-3-kinase (PI3K) pathway plays a crucial role in cell growth and survival and is activated in cancer. Multiple components of the pathway are frequently targeted by amplification, mutation and translocation in cancer patients. Indeed, the breadth and frequency of genomic aberrations in the PI3K pathway in cancer patients indicates a critical role in tumor initiation and progression and further validate the pathway for targeted therapeutics. The frequency of aberrations in the PI3K pathway exceed that of any other pathway with the possible exception of the p53 pathway. However, crosstalk with the p53 and retinoblastoma pathways comprises a signalling network that promotes tumour initiation and progression. Further as the PI3K pathway is activated in tumors and consists of multiple kinases, it is a target rich environment. Despite major interest in this pathway for drug discovery efforts against cancer, no drugs have yet been approved that act specifically against PI3K or the downstream regulator, Akt. However, several drugs that were developed for other purposes either directly or indirectly target PI3K signaling, such as the rapamycin analogs, ether lipids such as perifosine and miltefosine, and inhibitors of the epidermal growth factor receptor (EGFR), HER2, c-kit, platelet-derived growth factor receptor and bcr–abl. Because of the crucial role of the PI3K pathway in normal cell growth and in response to stress, the main challenge to developing PI3K drugs is to identify inhibitors with a usable therapeutic index. Tumors with aberrations in the PI3K pathway may undergo "oncogene addiction" rendering them sensitive to inhibition of the PI3K pathway providing a potential therapeutic index. It is likely that PI3K inhibitors will need to be used in combination with other drugs that cause cell stress, such as other signaling inhibitors, radio- and chemotherapy. Points at which therapeutic intervention might be appropriate in the PI3K