pathway responds by initiating a process of cell cycle arrest, senescence or apoptosis which either permits repair of these errors or kills the clone of cells that contain these mutations. Central to this pathway are a series of proteins that respond to the stress signals and regulate the levels and activity of the p53 pathway. We have identified a number of single nucleotide polymorphisms (SNP) in those genes that regulate p53 activity and functions and these SNPs can play a role in the incidence of cancers in a population, the age of onset of cancers and the response to therapy. Some of the haplotypes containing these SNPs appear to be under positive evolutionary selection pressures in some human populations. The reason for this appears to be the role of p53 in the implantation of embryos into the uterus and the impact of some of these SNPs upon the fecundity of mice and humans. This process is mediated by the p53 regulated gene, Leukemia Inhibitory Factor or LIF, a cytokine that is essential for the implantation of embryos. SNPs in the p53 gene, the MDM-4 gene and the LIF gene regulate the efficiency of implantation of embryos in humans. It could well be that the p53 protein is also involved in the surveillance of developmental abnormalities.
The p53 transcription factor also regulates the synthesis of glutaminase-2, an enzyme that converts glutamine to glutamate in the mitochondria of both the liver and the brain. In the liver glutamate is converted to alpha-keto glutamate and this helps promote oxidative phosphorylation. In liver cancers glutaminase-2 is not produced and these cancers produce energy via aerobic glycolysis. Returning the glutaminase-2 gene to liver tumour cells increases glutamate levels and inhibits the growth of these cells. It appears that a metabolic regulator that restores oxidative phosphorylation can inhibit this type of cancer. In the brain glutamate is a neurotransmitter and five different glutamate receptors are also regulated by p53 in response to stress signals. In the brain the stress signals that activate p53 are communicated throughout the body by these glutamate receptors. Interestingly three of the genes that can cause Parkinsons Disease and the Huntington gene are also regulated by p53 in the brain. The role of p53 in the central nervous system remains to be explored.

Monday 28 June 2010 10:20–12:20

Symposium
Epigenetics: from DNA methylation to stem cell differentiation

322 Mechanisms of DNA methylation in mammals

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DNA methylation plays an important role in cancer and is associated with gene silencing of tumour suppressor genes. The methylation of CpG sites is established by the DNA methyltransferases – the DNMTs. One main interest in our lab is to better decipher the mechanisms by which these enzymes function and participate to cancerogenesis.
In recent years, we have contributed to show that the DNA methylation machinery brings about transcriptional repression through recruitment of histone modifying enzymes. In particular, a close connection was found between DNMTs and histone methyltransferases (1–5), with for exemple an impact on PML-RAR-mediated leukemia.
A key question still poorly understood is how are the DNMTs, and in particular their enzymatic activity, regulated. Data will be presented that suggest a new mechanism for the regulation of DNA methylation by post-translational modification.

Reference(s)

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323 Human cancer epigenetics: from DNA methylation to microRNAs

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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 tumour 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 tumour-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.

324 Understanding the origins of aberrant DNA methylation in cancer

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The conversion of normal cells to cancerous cells typically involves several steps resulting in the acquisition of unlimited growth potential (immortality). Both genetic and epigenetic changes have been detected in a number of different cancer cell types. Generally, these changes lead to the activation of oncogenes and the inactivation of tumour suppressor and pro-apoptotic genes. Although a number of tumour suppressor genes have been shown to be silenced by promoter DNA methylation, the following questions still remain: Do epigenetic changes contribute directly to cancer and if so when, where and how do they co-operate with genetic changes during the transformation process? To try to address these questions we have generated a human cancer cell model with defined genetic elements to study the global epigenetic changes associated with cellular immortalisation and transformation. We will describe the generation and characterisation of this cancer cell model and will provide preliminary evidence for progressive changes in promoter DNA methylation.

325 The role histone methyl transferases and demethylases in stem cell differentiation and cancer

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A major goal of our research is to identify and characterize genes involved in the regulation of normal proliferation and differentiation that also contribute to the development of human disease. Consistent with an essential role of histone modifying enzymes in controlling cell-fate decisions, several of these are causally linked to the development of diseases, such as cancer and CNS-associated disorders.
Histone methylation regulates chromatin structure and gene regulation. Histone methylation patterns define the state of chromatin and it is regulated by histone methyl transferases and demethylases. The Polycomb group proteins (PcGs) were until few years ago best known for their essential role in development, however, several reports have established that PcGs are frequently deregulated in human tumours. Others and we have demonstrated that the PcG protein and histone methyl transferase EZH2 is an oncogene, which regulates the expression of a large number of genes dictating cell-fate decisions.
Recently, others and we have discovered a group of proteins that catalyze the demethylation of methylated lysines. Members of this Jumonji demethylase family are overexpressed in human cancer and mutated in neurological disorders. At the meeting, results will be presented describing the functional characterization of some of these very exciting proteins – that also present strong candidate targets for drug development.

Monday 28 June 2010 10:20–12:20

Symposium
Hypoxia & angiogenesis

326 Targets of "angioprevention": from inflammatory angiogenesis to hypoxia

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Background: The complex cancer microenvironment cooperates with tumour and endothelial cells to promote malignancy. We propose to identify molecules and pathways involved in cancer progression in order to prevent tumour development by targeting the microenvironment and inflammatory angiogenesis.