by oncogene activation are restrained by cellular senescence. We have previously shown that expression of an activated oncogene in cultured normal human cells results in a permanent cell-cycle arrest caused by the activation of a robust DDR. Experimental inactivation of DDR abrogates senescence and promotes cell transformation. Oncogene-induced senescence is also associated with a global heterochromatinization of nuclear DNA. Senescence-associated heterochromatic foci (SAHFs) are enriched in heterochromatin markers and they have been proposed to enforce cellular senescence by suppressing the expression of proliferative genes.
We will discuss our most recent results on the interplay between DDR and heterochromatin formation, the differential repair of the human genome and the regulation of DDR in stem cells and its impact on their proliferation and viability.

22 DNA repair and cancer

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DNA is continuously being damaged by spontaneous decay and exposure to carcinogens. Such damage is cytotoxic and mutagenic. Spontaneous depurination alone accounts for more than 10,000 events per human cell per day, whereas some 100–200 DNA-cytosines are deaminated to mutagenic U:G mismatches per day. DNA repair processes eliminate cytotoxicity that would otherwise kill the organism, probably within few days, while preventing mutations is important to avoid cancer development. Inherited DNA repair deficiency is associated with strongly increased cancer risk, e.g. rare syndromes like Xeroderma pigmentosum and ataxia teleangiectasia and more common forms of cancer e.g. early onset breast cancer and hereditary nonpolyposis colorectal cancer (HNPCC). In addition, there is evidence that more common single nucleotide polymorphisms (SNPs) in DNA repair genes may increase cancer risk, e.g. lung cancer development, although relative risk increases are generally low. The degree of contribution of DNA repair deficiency arising in the life of somatic cells is less clear, but there is evidence that mutations, epigenetic silencing and imbalanced expression of DNA repair proteins may increase cancer risk. Using mice with targeted mutations in DNA repair genes, defects in each of the excision repair pathways have been found to increase cancer risk. However, in some repair pathways, e.g. base excision repair (BER) some defects do not increase cancer risk possibly due to overlapping functions of some of the repair proteins. Importantly, many DNA repair proteins, such as uracil-DNA glycosylase (UNG) and mismatch repair proteins are also essential for the adaptive immune responses somatic hypermutation (SHM) and class switch recombination (CSR) in B-cells. In mice, UNG-deficiency increases the risk of developing B-cell lymphoma ~20-fold. SHM is essential to generate high affinity antibodies. However, it is a risky process and dysregulated SHM may be an important contributor to B-cell lymphoma. In conclusion, DNA repair proteins may contribute to cancer prevention both via DNA repair and adaptive immunity.

23 Aging and tumour suppression: the double-edged sword of cellular senescence

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Background: Aging is the largest single risk factor for a host of chronic diseases, most of which are degenerative in nature. These degenerative diseases include cardiac failure, vascular degeneration, macular degeneration, sarcopenia, type II diabetes-associated disability, osteoporosis and others. The exception is hyperproliferative disease, of which cancer is the most important. Cancer is indubitably an age-related disease, but hardly degenerative in nature. For many mammalian species, including humans, both hyperproliferative diseases and degenerative diseases increase with approximately exponential kinetics after about the mid-point of the life span. Is there a common biology that links cancer to the other diseases of aging?
Results: Our research suggests the answer to this question is yes. Aging is most likely driven by somatic damage, which is also a major cause of cancer. Damage occurs to virtually all cellular components, but the genome is particularly vulnerable. Cells respond to severe genomic damage by undergoing cell death or permanent loss of proliferative capacity (cell senescence). These responses are tumour suppressive, and are required to prevent the development of cancer in young mammalian organisms. We find that genomic damage, when severe enough to cause cell senescence, also induces the secretion of a large number of cytokines and other proteins that promote inflammation. Inflammation underlies virtually all age-related diseases, including cancer. We now have molecular evidence to suggest a model by which somatic damage elicits an inflammatory response that drives many age-related pathologies, both degenerative and hyperproliferative.
Conclusions: Our findings not only provide insights into how diverse age-related pathologies might arise, but also provide strategies for rational interventions into the basic aging process, and hence multiple age-related diseases.

Sunday 27 June 2010 10:20–12:20

Symposium
Noncoding RNA

24 Cancerous microRNAs and regulatory RNA binding proteins

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MicroRNAs (miRNAs) are genes involved in normal development and cancer. They inhibit gene expression through interaction with 3′-Untranslated regions (3′UTRs) of messenger RNAs (mRNAs), and are thought to regulate a large proportion of protein coding genes. Patterns of mis-expression of miRNAs in cancer suggest key functions of miRNAs in tumourigenesis. We performed in the past genetic screens to identify cancer functions of miRNAs. Using a library of vectors expressing human miRNAs and we identified miRNAs that cooperate with oncogenes in cellular transformation, which stimulate cellular migration, invasion and metastasis, as well as key regulators of tumour suppressor genes.
In recent years, it is becoming apparent that the miRNAs themselves are subjected to intense regulation at various levels. miRNA biogenesis and activity can be kept in pace by RNA-binding proteins (RBPs). We show that interplay between RBPs and miRNA exists that affects gene expression and processes such as development and cancer.

25 Non-coding RNA production by RNA polymerase III is implicated in cancer

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RNA polymerase III is responsible for ~10% of nuclear transcription and makes a variety of short non-coding RNAs, including tRNA. Elevated expression of Pol III products has been observed in many types of transformed and tumour cells. This overexpression can be ascribed to three categories of molecular change [1].
(a) Release from repression by tumour suppressors. In untransformed cells the pol III-specific transcription factor TFIIIB is directly repressed by RB and p53 [2,3]. Inactivation of one or both of these tumour suppressors is frequent in cancer and releases TFIIIB from restraint, allowing pol III output to rise.
(b) Activation by oncogene products. Pol III transcription can be stimulated by many oncogene products. Perhaps the most important is c-Myc, which binds to TFIIIB and recruits GCN5 to pol III-transcribed genes [4,5].
(c) Pol III-specific transcription factors are produced at abnormally high levels in some types of tumour, such as prostate and ovarian carcinomas [6].
One of the key pol III products is the initator tRNAMet, which is required for production of new polypeptides. Levels of this tRNA are limiting for translation in fibroblasts. Mild overexpression of initator tRNAMet not only stimulates protein synthesis, but also promotes cell proliferation and oncogenic transformation [7]. Translational induction of c-Myc is implicated in this. Positive feedback may occur, with c-Myc stimulating pol III transcription of tRNA genes and then elevated tRNA selectively promoting translation of mRNA encoding c-Myc.

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26 Interweaving microRNA, inflammatory cytokine and p53 pathways in human cancer

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We and others have identified specific microRNAs and changes in their expression in human lung, colon, and esophagus cancers that are associated with diagnosis, prognosis, and therapeutic outcome. We have also identified expression profiles of inflammation-related genes that can be combined by COX regression hazard analysis to be prognostic classifies, i.e., inflammatory risk score (IRS). For example, IRS and miR-21 expression are independent predictors of prognosis and together may be clinically useful in identifying patients with early stage cancer at high risk of metastases. As our