

embedded within *PPARGC1b* which encodes PGC-1 β and that their expression is co-regulated by ERBB2 in breast cancer cells. We will show that miR-378 performs this function by inhibiting the expression of ERR γ leading to a reduction in tricarboxylic acid cycle gene expression and oxygen consumption as well as an increase in lactate production and in cell proliferation. *In situ* hybridization experiments also show that miR-378 expression correlates with progression of human breast cancer. These results thus identify a novel molecular mechanism governing the Warburg effect in breast cancer cells and demonstrate the important roles played by the ERRs in the etiology of cancer.

[5] A role for mutant p53 in promoting invasion

K. Vousden¹, P. Muller¹, P. Caswell¹. ¹The Beatson Institute for Cancer Research, Glasgow, United Kingdom

The p53 tumour suppressor protein restrains malignant progression through a number of mechanisms, and most cancers show loss of the normal functions of p53. In many cancers this is due to a mutation in the p53 gene that leads to the expression of a mutant p53 protein. Interestingly, these tumour associated mutant p53s not only lose wild type p53 activity but can also acquire the ability to promote cell motility and migration, and so contribute to the development of metastases. We have found that tumour associated mutant p53s can promote invasion and loss of directionality when cells migrate *in vitro*. These activities are independent of the loss of wild type p53 function, and reflect activation of integrin and EGFR trafficking that depends on Rab-coupling protein and which results in constitutive activation of EGFR/integrin signalling. These findings open the possibility that blocking $\alpha 5/\beta 1$ integrin and/or the EGF receptor will have therapeutic benefit in mutant p53 expressing cancers. We are now proposing to extended these observations by testing whether this activity of mutant p53 is restricted to the EGFR, or may also promote the activity of other cell surface receptors too. Simultaneous loss of p53 and p63 recapitulates the phenotype of mutant p53, suggesting that this function of mutant p53 reflects, at least in part, the inhibition of p63. However, mutant p53 is likely to have additional functions that contribute to the ability to induce an invasive phenotype, and we are presently investigating the activity of other mutant p53 binding proteins.

Saturday 26 June 2010

14:30–16:30

Symposium

Animal models

[6] Mouse models for lung cancer and mesothelioma

A. Berns¹, J. Calbo-Angrill¹, K. Sutherland¹, E. Van Montfort¹, N. Proost¹. ¹The Netherlands Cancer Institute, Department of Molecular Genetics, Amsterdam, The Netherlands

The mouse is used as a model organism for establishing the role of oncogenes and tumour suppressor genes in tumour development. By exploiting Cre/Lox mediated cell-type-specific switching and by taking advantage of somatic gene transfer methods, the expression of multiple oncogenes and tumour suppressor genes can be controlled in a tissue-specific and spatial-temporal fashion. This permits a more accurate modeling of tumorigenesis as it occurs in man, and therefore provides the opportunity for establishing more relevant genotype-phenotype correlations. These models also provide an excellent experimental tool to test prevention and intervention strategies especially when combined with sensitive *in vivo* imaging techniques. Finally, these models permit us to identify new oncogenes and tumour suppressor genes involved in tumour progression using a variety of techniques, such as array CGH, expression profiling and proviral and transposon-based insertional mutagenesis. Some of the gene families identified in our models are being studied in more depth.

We utilize mice carrying combinations of different oncogene and conditional tumour suppressor gene alleles to model a range of tumours. Our current focus is on several lung cancers subtypes and mesotheliomas. To achieve (sporadic) activation of oncogenes and inactivation of tumour suppressor genes we use Adeno-Cre or Lentivirus-mediated gene transfer to switch the conditional oncogenes and tumour suppressor gene alleles. Subsequently, tumour initiation and progression is monitored in longitudinal studies in which noninvasive imaging techniques are used.

Lung tumours: We focus on small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC). When *Rb* and *p53* are inactivated specifically in lung, SCLC ensues after a relatively long latency period. The marker profile of these tumours is very closely resembling that of human SCLC. The tumours also metastasize to the same organ sites as observed in human SCLC. Array CGH showed frequent amplification of *L-Myc* further supporting their resemblance with the human counterpart. The tumours are heterogeneous and are composed of different cell types. Cloning of the different cells from a single tumour showed very different marker profiles. Both cells with

neuroendocrine and progenitor marker profiles were found. Interestingly, these phenotypically highly diverse cell lines shared some highly distinct genetic aberrations indicating that they were derived from a common progenitor. We show by co-culture and co-grafting experiments that these clonally-related cells influence each other through paracrine mechanisms providing a basis for their maintenance during tumour progression.

To gain more insight into the cell of origin of these tumours, we have designed a series of cell-type specific Adeno-Cre viruses that enable us to switch oncogenes and tumour suppressor genes in distinct lung cell types *in vivo*. Using promoters specific for Clara cells, Alveolar type I and II cells, and neuroendocrine cells to drive Cre expression upon Adeno-Cre infection we are defining the marker profile of cells in lung that give rise to SCLC and NSCLC.

[7] Signalling via the ALK receptor tyrosine kinase – insights from the fruitfly

No abstract received.

[8] Investigating the tissue specific functions of tumour suppressor genes and oncogenes *in vivo*

O.J. Sansom¹. ¹Beatson Institute of Cancer Research, Cancer Research UK, Glasgow, United Kingdom

Colorectal Cancer is the third most common cancer in the western world and the second most common cause of cancer mortality. Germline heterozygosity of the *Apc* (Adenomatous Polyposis Coli) gene leads to Familial Adenomatous Polyposis (FAP), a disease characterised by patients developing 1000's of colorectal adenomas by the time they are 30. Importantly, *Apc* loss is also the key initiating event in sporadic colorectal cancer with up to 80% of sporadic colorectal cancers having an *Apc* mutation.

I will discuss my groups latest attempts to find key regulators downstream of *Apc* loss *in vivo*. I will focus on the importance of mTOR and Rac1 on mediating hyperproliferation following *Apc* loss.

Moreover I will discuss our recent work on developing murine models of invasive and metastatic colorectal cancer and will focus on the role of p53 mutation.

[9] Studying the p53 pathway using Zebra fish models

D. Lane^{1,2}. ¹University of Dundee, Division of Molecular Medicine College of Life Sciences, Dundee, United Kingdom, ²p53 Lab A-Star, Singapore

While many thousands of studies on the regulation of the p53 pathway have been reported the majority use tissue culture cell systems and there are relatively few reports of the tissue specific nature of the response. To examine these questions we have begun to develop tools and reagents that allow an examination of the p53 response in the Zebrafish vertebrate model system. New monoclonal antibodies to Zebrafish p53 have established the tissue restricted nature of the p53 protein accumulation response to be measured. Reporter transgenic fish, where a GFP reporter gene is induced by p53 have allowed activity measurements in response to kinase inhibitors and DNA damaging drugs to be discerned and studies using p53 mutant fish have allowed the accumulation of p53 protein in response to stress to be shown to be independent of its transcriptional activity negating some feedback theories of p53 control. Mutations in p53 inactivate the apoptotic response to many agents to a dramatic extent underlining the importance of p53 in these whole tissue systems. Genetic experiments establish that mutant p53 is recessive to wild type p53 which helps to explain the Li-Fraumeni phenotype. Using a variety of approaches the clear role that p53 plays in inducing the phenotype of many developmental mutants has been established and finally the detection of p53 isoforms in this species confirms that these isoforms have been conserved through 400 million years of evolution supporting their biological importance. These early results suggest that the Zebrafish system could be a powerful addition to existing models for the study of the role of p53.

Saturday 26 June 2010

14:30–16:30

Symposium

Cancer systems biology

[10] The HER2 and EGFR alliance in cancer: defects in system control

Y. Yarden¹. ¹Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel

Growth factors and their transmembrane receptors contribute to all steps of tumour progression, from the initial phase of clonal expansion (cell proliferation), through recruitment of blood vessels to growing tumours (angiogenesis), and, eventually to migration and colonization of distant organs (metastasis). Hence, the information relay system involved in growth factor signaling provides potential site for signal interception and tumour inhibition.

A relevant example comprises the epidermal growth factor (EGF) and the respective receptor tyrosine kinases, namely ErbB-1/EGFR and HER2, which belong to a prototype signaling module that drives carcinoma development. The extended module includes two autonomous receptors, EGFR/ErbB-1 and ErbB-4, and two non-autonomous receptors, namely: a ligand-less oncogenic receptor, HER2/ErbB-2, and a kinase-dead receptor (ErbB-3). This signaling module is frequently involved in human cancer through autocrine loops involving co-expression of a receptor and one of the many EGF-like ligands, mutations and deletions within the *EGFR* gene (e.g., in lung and brain tumours), or amplification of either *HER2* (e.g., in breast cancer) or *EGFR* (e.g., in head and neck cancer). Moreover, both EGFR and HER2 serve as targets for several cancer drugs, such as monoclonal antibodies (e.g., Cetuximab and Trastuzumab) and tyrosine kinase inhibitors (e.g., Erlotinib and Lapatinib).

To explain the remarkable oncogenic potential of HER2/ErbB-2, a ligand-less receptor that forms heterodimers with the other three ErbB proteins, we proposed a network configuration: through a layered organization of ligands, receptor dimers, downstream pathways and transcription factors, the ErbB network tunes and diversifies signal transduction, with HER2 operating as a signal amplifier. The network achieves robustness by adopting universal features common to engineered and natural systems: a modular architecture, a common core process, and a dense web of feedback control circuitry. My presentation will concentrate on system controls, which can be divided into two categories: the immediate loops are the domain of post-translational protein modifications, such as receptor phosphorylation, ubiquitinylation and neddylation. One consequence of this phase comprises endocytosis of ligand-receptor complexes, a process evaded by several oncogenic mutants of EGFR. In my presentation I will describe our screens, which identified the DEP-1 tyrosine phosphatase, a putative tumour suppressor, as a regulator of EGFR. The late category of system control depends on newly transcribed messenger RNA and micro-RNA molecules. Through coordinated functions, inducible mRNAs and miRNAs terminate expression of the highly oncogenic, immediate early genes, such as *c-FOS* and *c-JUN*. My lecture will highlight examples of tumour evasion from system control. In addition, I will focus on the inevitable fragility of robust signaling networks, as well as propose that system level understanding may help identify Achilles heels amenable for therapeutic intervention.

11 From benchside to byteside: what we can learn from computational modelling

W. Kolch¹, M. Birtwistle¹, B. Kholodenko¹, J. Grindlay², O. Sturm³, R. Orton⁴, D. Gilbert⁵, A. von Kriegsheim¹. ¹University College Dublin, Systems Biology Ireland, Dublin, Ireland, ²The Beatson Institute for Cancer Research, Signalling and Proteomics Lab, Glasgow, United Kingdom, ³St Jude Children's Research Hospital, Department of Immunology, Memphis TN, USA, ⁴University of Glasgow, Institute of Comparative Medicine, Glasgow, United Kingdom, ⁵Brunel University, School of Information Systems Computing and Mathematics, Uxbridge, United Kingdom

Background: On the molecular level cancer can be perceived as a disease that deregulates signal transduction networks (STNs). This is reflected in the increasing number of anti-cancer drugs that are targeting signal transduction proteins. However, we have an insufficient understanding how the design properties of STNs can be exploited to gain insights into pathogenetic processes and improve drug therapies.

Materials and Methods: A combination of proteomics, biochemical measurements and mathematical modelling was used to generate computational models that can be used to analyse emergent network behaviour.

Results: Here, we show that the intrinsic design properties of STNs give rise to emergent functions that can specify the biochemical and biological behaviour of STNs. Thus, they are critical to determine the genuine behaviour of cancer cells as well as the response to drugs. We will discuss selected examples of STN design principles as revealed by computational modelling. They include the (i) modelling of drug responsiveness in the Ras-Raf-MEK-ERK pathway; (ii) switchlike changes between apoptosis and proliferation responses determined by the dynamics of the formation of competing protein complexes; and (iii) migration and invasion determined by the ERK pathway.

Conclusions: Emergent properties resulting of the design of STNs are crucial determinants of robustness, adaptation and dynamic response behaviour of STNs both in respect to physiological cues and drug therapies.

12 A systems approach to identification of therapy response subsets in breast cancer

No abstract received.

13 How genomics has reshaped our view of cancer

D. Botstein¹. ¹Princeton University, Lewis-Sigler Institute, Princeton NJ, USA

The sequence of the human genome, the primary goal of the Human Genome Project, was achieved just a few years ago. The ability to obtain genomic sequences depended on revolutionary progress not just in DNA chemistry but also on the equally revolutionary advances in speed, capacity and versatility of digital computers. Among the many benefits to society provided by our knowledge of genomic sequences has been the identification, through their inheritance in families, of thousands of genes that cause inherited diseases. Among them are genes that cause inherited predispositions to breast cancer, colon cancer, and kidney cancer, among others. Study of how these genes cause relatively rare forms of cancer has informed our understanding cancer generally, because so many of these genes are homologs of genes better understood in model organisms, where experimental determination of their biological functions has been massively accelerated by genomic technology. More recent progress, driven by rapidly increasing productivity in sequence technology, has not only confirmed these relationships but also allowed the discovery of new mutations affecting previously unsuspected genes that contribute to cancer.

A quite different benefit of the genomic sequences is that they allow us to study the activities of all the genes simultaneously, using once again a combination of DNA chemistry and computational methods. With these methods it has become possible to study, at a comprehensive (genome-wide) level, the differences in gene activity that accompany the transformation of tissues from normal to cancerous, and to classify different subtypes of cancers by their "molecular signatures". We now can distinguish, for example, several kinds of breast cancer, some of which are more aggressive and lethal than others, and some of which are uniquely sensitive to new classes of unusually effective drugs directed specifically at these subtypes.