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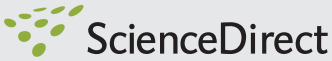

Saturday 26 June 2010

Saturday 26 June 2010 13:15–14:05

Mühlbock Lecture

1 Telomeres and telomerase: their roles in human health and disease

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Telomeres protect and stabilize the ends of chromosomes, ensuring genomic stability. Telomeres consist of simple DNA sequences, which bind cellular protein factors and make a "cap", thus securing every chromosome end. Without telomeric DNA and its specialized modes of replicating, chromosome ends dwindle away, eventually causing cells stop dividing altogether. For humans to live a long life, this erosion of telomeres is counteracted because the cellular enzyme telomerase replenishes telomeres, and protects them. Emerging understanding of telomeres and telomerase can potentially be exploited to improve health and combat cancer.

Telomerase, while present in a many normal cells in human adults, is often active there at only low levels. Throughout human life a minimal level of telomerase is required for replenishment of tissues, such as the immune system. Telomerase is influenced by both genetic and non-genetic factors. Our recent collaborative studies showed that the amount of telomerase activity in white blood cells of the body is diminished by chronic psychological stress, and inadequate telomere maintenance is associated with known major risk factors for cancer and cardiovascular disease.

Within the setting of malignant cancer cells, a very different setting from normal cellular contexts, telomerase promotes cancer. Telomerase is hyperactive in most advanced human cancers. We have begun ways of exploiting this abnormally high telomerase activity to kill cancer cells, by re-directing telomerase specifically in cancer cells to make "toxic telomeres". The challenge for cancer research is to develop the emerging molecular and cellular information about telomerase into rational cancer therapies and prevention strategies.

Saturday 26 June 2010 14:30–16:30

Symposium

Metabolism & cell death

2 Mitochondrial tumour suppressors: a genetic and biochemical link between metabolism and cancer

E. Gottlieb[1]. [1]*The Beatson Institute for Cancer Research, Apoptosis and Tumour Metabolism Laboratory, Glasgow, United Kingdom*

Both succinate dehydrogenase (SDH) and fumarate hydratase (FH) are tricarboxylic-acid (TCA) cycle enzymes that convert succinate to fumarate and fumarate to malate, respectively. SDH is also a functional member (complex II) of the Electron Transport Chain (ETC). Surprisingly, although SDH and FH are 'housekeeping genes' with key bioenergetic roles, germline mutations in these genes cause cancer. We demonstrated that succinate and fumarate, both TCA cycle metabolite (SDH and FH substrates, respectively), function as intracellular messengers between the mitochondria and the cytosol. When accumulated in the mitochondria due to the inactivation of SDH or FH, they leak out to the cytosol, where they inhibit the enzymatic machinery of oxygen sensing, mediated by a family of α-ketoglutarate-dependent Prolyl Hydroxylase enzymes (PHDs). PHD inhibition triggers the accumulation and activation of the hypoxia inducible factor (HIF) in the nucleus and the pseudohypoxic response that enhances tumour vascularisation and glycolysis. Nevertheless, it is inconceivable that cells which lost such fundamental metabolic machinery as the TCA cycle will not only survive the bioenergetic crisis, but actually will evolve into tumours. We hypothesised that a dramatic change in cellular metabolism must take place to keep those cells alive, and that pharmacologically targeting these alterations, will specifically kill cancer cells with dysfunctional TCA cycle (a synthetic lethal approach). To study this, we generated immortalized kidney cells from mice carrying conditionally-knockout FH alleles ($FH^{fl/fl}$) and infected them with Cre-encoding adenovirus to generate stable clones with stably knockout FH alleles ($FH^{-/-}$). We extensively studied these cells using transcriptomics and metabolomics approaches and applied these results to a computer model, generated specifically to study the cancer metabolome. We identified one important synthetically lethal pathway in FH-deficient cells which is crucial for the removal of excess TCA cycle metabolites (cataplerosis) in these cells.

3 Tumour suppression by BH3-only proteins, proapoptotic members of the Bcl-2 family

A. Villunger[1], V. Labi[1], A. Frenzel[1], A. Egle[2], J. Pinon[2]. [1]*Innsbruck Medical University, Division of Developmental Immunology, Innsbruck, Austria,* [2]*Salzburg Medical University, Internal Medicine III, Innsbruck, Austria*

Background: Apoptosis is considered as a critical barrier against tumour formation. BH3-only proteins are key-inducers of Bcl-2 regulated apoptosis and hence function as putative tumour suppressors.

Materials: We have used a series of gene-modified mouse models to investigate the impact of loss of individual BH3-only proteins on oncogene-driven as well as radiation-induced tumourigenesis and the development of possible drug-resistance phenotypes.

Results: Genetic ablation of individual BH3-only proteins such as Bim, Bad or Bmf all facilitated c-myc-driven B-cell lymphomagenesis, but only loss of Bim conferred drug-resistance. Noteably, Bmf expression was also lost in samples from Burkitt lymphoma patients and drug-treatment of Burkitt lymphoma cell lines restored Bmf expression correlating with the induction of cell death. On the other hand, Bmf, but not Bim or Bad deficient mice developed radiation-induced lymphomas faster than wt counterparts but most surprisingly, Puma-deficient mice resisted radiation-induced tumour formation.

Conclusions: BH3-only proteins are potent tumour suppressors and do so in a cell type and stimulus dependent manner. However, massive induction of apoptosis in response to DNA damage may be counterproductive and actually enhance malignant transformation.

4 Control of cancer cell metabolism by nuclear receptor-based transcriptional pathways

V. Giguère[1], L.J. Eichner[1], G. Deblois[1]. [1]*McGill University, Goodman Cancer Research Centre, Montreal QC, Canada*

Cancer cell metabolism is often characterized by a shift from an oxidative to a glycolytic bioenergetic pathway, a phenomenon known as the Warburg effect. The molecular mechanisms underlying this effect are complex and multifaceted and likely to be modulated at many levels. Members of the nuclear receptor superfamily are known to play important roles in metabolic control as they can translate hormonal, nutrient and metabolite signals into specific gene expression networks. Among them, the estrogen-related receptor (ERR) α, β and γ have been shown to vast gene networks involved in all aspects of energy homeostasis, including fat and glucose metabolism as well as mitochondrial biogenesis and function in both normal and cancer cells. Functional genomics and biochemical studies have shown that ERRα and γ operate as the primary conduits for the activity of members of the family of PGC-1 coactivators, a family of coregulatory proteins known to be essential for the control of energy homeostasis.

In this presentation, we will first review evidence that the identification of ERRα-dependent transcriptional network implicates ERRα signaling as an important determinant of breast cancer heterogeneity. We will then present data demonstrating that a specific miRNA can act as a molecular switch able to orchestrate the Warburg effect in breast cancer cells via interference with ERR-dependent transcriptional pathways. We will show that miR-378 is

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embedded within *PPARGC1b* which encodes PGC-1β 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 ERRγ 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. Vousden[1], P. Muller[1], P. Caswell[1]. [1]*The 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 alpha5/beta1 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. Berns[1], J. Calbo-Angrill[1], K. Sutherland[1], E. Van Montfort[1], N. Proost[1]. [1]*The 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 tumourigenesis 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. Sansom[1]. [1]*Beatson 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]. [1]*University of Dundee, Division of Molecular Medicine College of Life Sciences, Dundee, United Kingdom,* [2]*p53 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. Yarden[1]. [1]*Weizmann 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.