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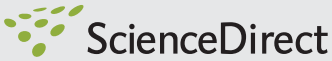

Saturday 26 June 2010

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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