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Telomerase and telomeric repeat containing RNA at chromosome ends

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The ends of eukaryotic chromosomes, known as telomeres, play crucial roles as guardians of genome stability and tumor suppressors. Telomeric DNA is maintained by the ribonucleoprotein enzyme telomerase. Most normal human somatic cells express only very low levels of telomerase and telomeres shorten with continuous cell division cycles. Reactivation of telomerase is a key requisite for human cancer cells to attain unlimited proliferation potential. To study the mechanisms that control telomerase access and extension efficiency we developed for S. cerevisiae a system to measure telomerase activity at nucleotide resolution at single chromosome end molecules. Our results demonstrated for the first time that telomerase does not act on every telomere in each cell cycle. Instead, it exhibits an increasing preference for telomeres as their lengths decline. We identified two pathways that activate telomerase at short telomeres. In addition we discovered recently that telomeric heterochromatin, which had been accepted as being a transcription silencer, is in reality transcribed into telomeric repeat containing RNA (TERRA). TERRA is part of the telomeric heterochromatin and we suspect that it performs crucial roles in telomere structure and telomerase regulation.

08 July 2008 12:30 - 13:15

AWARD LECTURE

Carcinogenesis Young Investigator's Award

472A
Blueprint of the breast and colorectal cancer genomes

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It is generally accepted that cancer is a disease caused by accumulation of mutations in specific genes. These tumor-specific mutations provide clues to the cellular processes underlying tumorigenesis and have proven useful for diagnostic and therapeutic purposes. To date, however, only a small fraction of the genes has been analyzed and the number and type of alterations responsible for the development of common tumor types are unknown. The determination of the human genome sequence coupled with improvements in sequencing and bioinformatic approaches have now made it possible to examine the cancer cell genome in a comprehensive and unbiased manner. We have recently begun a systematic study of the cancer genome through analysis of the majority of protein coding genes in breast and colorectal cancers. These analyses have identified a wealth of new genes and pathways that had not been previously linked to human cancer. For example, we have found genetic alterations in the PIK3CA gene encoding the p110 alpha phosphatidylinositol 3-kinase and in related pathway genes in >30% of colon and breast cancers, providing rational targets for therapy in a large fraction of common malignancies. These studies define the genetic landscape of two human cancer types, provide new targets for personalized diagnostic and therapeutic intervention, and open fertile avenues for basic research in tumor biology. These analyses also provide valuable lessons for future large-scale genomic analyses in cancer and other human diseases.

08 July 2008 13:15 - 14:15

MIKE PRICE LECTURE

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Mike Price Lecture

No abstract received

POSTER SESSION

Cell and tumour biology 3

474 Poster
Diacylglycerol kinase contributes to the induction of HIF-1 by serum via mTOR activation in breast cancer cells

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The kinase mammalian target of rapamycin (mTOR) plays a major role in the regulation of cell growth by integrating nutrient and mitogenic signaling. mTOR is regulated by the lipid second messenger phosphatidic acid (PA). Noteworthy PA-binding site over mTOR is the same of rapamycin, a potent drug with anti-oncogenic properties. PLD, a PA-generator enzyme, has been described to activate mTOR during mitogenic signaling. Some breast cancers-derived cell lines display an elevated PLD activity that correlates with rapamycin resistance.

Diacilglycerol kinases (DGKs) are also PA generator enzymes and we have demonstrated previously that DGKζ contributes to mTOR activation. It is known that DGK activity is required to the induction of HIF-1α but the exact mechanism remains to be determined. In this study, using as a model the breast cancer derived cell line MDA mb231, we explore the role of DGKs over the HIF-1α induction elicited during mitogenic stimulation.

We found that DGKs are highly expressed in this cell line and that down-regulation of DGKζ by siRNA results in a reduction in HIF-1α levels upon mitogenic stimulation. The positive effects of DGKζ are dependant on mTOR activity, since silencing of this DGK augments the rapamycin sensitivity of this cell line. Then our results suggest that PLD and DGK could act in concert to activate mTOR and underscore the key function of DGKs over the induction of HIF-1α. Therefore DGKs constitutes potential diagnostic markers or pharmacological targets for the development of new anti-cancer therapies focused on cancer lipid metabolism.

475 Poster
CTCF regulates erythroid-related genes as revealed by genome-wide analysis

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CTCF is a multifunctional transcriptional regulator and a candidate tumor suppressor. CTCF, originally described as a negatively regulator of MYC gene, plays critical roles in the regulation of gene expression. CTCF has been characterized as a transcriptional repressor and activator, enhancer-blocker and boundary definer. CTCF is involved in several aspect of epigenetic regulation, including regulation of genomic imprinting and chromosome X inactivation. Its deregulation may contribute to epigenetic imbalance in cancer. CTCF biological functions include regulation of cell growth, differentiation and apoptosis.We have previously reported that CTCF inhibits proliferation and promotes erythroid differentiation of K562 myeloid cells (Torrano et al. JBC 2005, 280, 28152).The general aim of the present work was to elucidate the mechanisms underlying the effects of CTCF on erythroid differentiation. To identify CTCF target genes that could mediate such effects we performed genome-wide studies in transfectant K562 cells with ectopic expression of CTCF using the Affymetrix whole human genome expression Array (HG-U133 Plus 2.0). Microarray analysis showed 2061 differentially expressed genes (roughly half of them up-regulated and half of them down-regulated) by CTCF expression. Gene Ontology (GO) and Ingenuity Pathways Analysis programs used to analyze the cellular functions and interaction networks showed four very significant networks regulated by CTCF. Microarray analysis also reveals gene regulation consistent with the erythroid differentiation induced by CTCF. CTCF regulates erythrocytic transcription factors, hemoglobin components and erythroid differentiation markers. Validation of the microarray data has been performed by real-time RT-PCR. In conclusion, our microarray analysis in cells overexpressing CTCF revealed the importance of this transcription factor in the regulation of a broad spectrum of cellular functions and confirms our results on the role of CTCF in erythroid differentiation.