serine 62, and thereby prevents c-Myc proteolytic degradation. Moreover, siRNA-mediated depletion of CIP2A, markedly increased PP2A activity in the c-Myc-PP2A complex. We also demonstrated that CIP2A is required for the malignant cellular growth and for *in vivo* tumour formation. In accordance with the oncogenic role of CIP2A, overexpression of CIP2A promotes Ras-elicited cell growth and transforms immortalized human cells (HEK-TERVs). In addition CIP2A was overexpressed in two common human malignancies, human head and neck squamous cell carcinoma (HNSCC) and colon cancer. Thus, our results demonstrated that CIP2A is a novel human oncoprotein that inhibits PP2A in human malignancies. More recently we have shown that in addition to its overexpression in HNSCC and colon cancer, CIP2A expression predicts poor prognosis in certain subtypes of human gastric cancers and correlates with breast cancer aggressivity. Together these results validate CIP2A as a clinically relevant human oncoprotein.

Reference(s)

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Khanna et al., J. Natl. Cancer Inst., 101, 2009.
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332 Dual-specificity protein phosphatases and the regulation of MAP kinase signalling

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DUSP5 and DUSP6/MKP-3 are members of a structurally distinct subfamily of ten dual-specificity (Tyr/Thr) protein phosphatases, which are responsible for the regulated dephosphorylation and inactivation of mitogen-activated protein kinases (MAPKs) in mammalian cells and tissues. DUSP6/MKP-3 is a cytoplasmic phosphatase, which is inducible in response to fibroblast growth factor (FGF) signalling during early embryonic development where it acts in a negative feedback loop to regulate the activity of the classical ERK1 and ERK2 MAPKs. DUSP5 is also a specific ERK phosphatase. However, it is a mitogen-inducible nuclear enzyme and can also act as a nuclear anchor for ERK1 and ERK2. Despite extensive knowledge of the biochemical and structural basis of their catalytic activity, until recently relatively little was known about the regulation and physiological functions of DUSP5 and DUSP6. In particular, it is unclear if these phosphatases play any role in the regulation of ERK activation in tumours where activated oncogenes drive high levels of signalling through the Ras/ERK pathway. Recent reports have identified DUSP6 as a gene, which is up regulated during the early stages of tumour development in lung and pancreatic cancers. However, its expression is lost as tumours become more advanced, suggesting that DUSP6 may be a candidate tumour suppressor. In order to test this hypothesis we have generated mice with targeted deletions of the genes encoding DUSP5 and DUSP6 and studied the effects of gene loss in both cultured cells and in mouse models of cancer. Our preliminary data would indicate that DUSP6 is an important regulator of ERK activity in tumours initiated by mutant ras and that DUSP6 loss results in increased levels of ERK activity which is associated with both an increased frequency and more rapid progression of ras-induced carcinogenesis.

333 Hedgehog signalling in skin and pancreatic cancer

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The Hedgehog (Hh) signalling pathway ending with activation of the GLI transcription factors is of central importance during embryo development and implicated in control of stem cell renewal and proliferation. When aberrantly activated the Hh pathway contributes to cancer development in several tissues such as skin and pancreas. To address the interaction with another key oncogenic pathway frequently activated in pancreatic cancer we have investigated the molecular crosstalk between RAS and Hh signalling and found that mutant RAS induces expression of the SHH ligand but at the same time potently inhibits autocrine Hh signal transduction. Mutant RAS functions in a cilium-independent manner upstream or at the level of Sufu and interferes with Gli2 activation and Gli3 processing. Mechanistically the cell-autonomous negative regulation of Hh signalling by mutant RAS is dependent on the dual specificity tyrosine kinase DYRK1B. Basal Cell Carcinomas (BCC) are the most common skin cancers and are dependent on deregulated Hh signalling. Using mouse models conditionally expressing GLI1 or with homozygous inactivation of the *Ptch1* gene we find that stem cells residing in the hair follicle represent a cell of origin. This stem cell population also contributes to wound healing and the wound environment alters stem cell lineage selection and accelerates BCC development providing a link between tissue injury and cancer risk.

Monday 28 June 2010 12:45–13:45

Young Cancer Researcher's Workshop

334-335 Career opportunities

No abstract received.

Monday 28 June 2010 13:45–14:35

Award Lecture: Anthony Dipple Carcinogenesis Award

336 Intricacies of BRCA1 genome integrity control and cancer suppression functions

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BRCA1 is a high penetrance breast and ovarian tumour suppressing gene. It encodes at least three, distinct products. The largest is p220, a multiphosphorylated, nuclear polypeptide that, when heterodimerized with a tightly binding partner protein, BARD1, operates as an E3 ubiquitin ligase. p220 has been much more extensively studied than the other known *BRCA1* products (BRCA1-IRIS and dl 11). It exerts tumour suppressing activity and is engaged in a variety of processes, each dedicated to the maintenance of genome integrity. These functions include: 1) support of error-free repair of DNA double strand breaks by homologous recombination (HR), a process performed coordinately with the major product of the other, known, high penetrance breast cancer gene, BRCA2; 2) suppression of illegitimate recombination between chromosomes; 3) support of key aspects of the process that leads to repair of bulky adduct-driven DNA damage; 4) participation in the building of mitotic spindle poles; and 5) a role in the regulation of centriole formation. Thus far, genetic studies strongly suggest that the contributions of p220 to HR and to mitosis control are linked to its breast cancer suppressing function, although how these two functions are linked to breast cancer suppression is not well understood. Moreover, whether the other functions operate in this regard is unknown.
Results are now emerging which suggest that a modicum of control is applied by certain BRCA1 binding proteins to the HR and illegitimate recombination suppression functions of p220. Breakdown in these functions can elicit major biological defects that have potential clinical significance. The nature of these controls, how they are executed, and the abnormal outcomes associated with failure of their function will be discussed.

Monday 28 June 2010 14:35–16:35

Symposium

Discovery based translational research

337 Biomarkers in early clinical development

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Current attrition rate of new oncology drugs is very high, this leading not only to an unsustainable budget in the pharmaceutical industry but a sense of great disappointment in the oncology community level. To curtail this rate of attrition, investigation leaders need to make confident decisions as early as possible during the drug development process and to ensure that only those drugs with an optimal safety/efficacy profile move to phase III development and only patients most likely to benefit from the drug are enrolled into the pivotal regulatory trials. A greater understanding of the biology of cancer coupled with major advances in biotechnology has resulted in the identification of rationally-designed targeted agents. Proof of principle and robust antitumour activity may be most efficiently demonstrated in phase II studies involving patients bearing tumours that are principally driven by aberrations of the specific target or dysregulation of related signal transduction pathways. The hope is that by identifying tumours that are dependent upon the targeted pathway and by demonstrating that the drug modulates the pathway (either abrogating or promoting the signal) it will be possible to identify the right population of patients for the pivotal trials and hence significantly increase the probability of success. Once a biomarker has been identified, the assay validated and its intended use defined, the challenge becomes how to incorporate the biomarker assay into the drug development program and design of the phase II and phase III development. At this time point several decisions have to be made regarding whether to evaluate the biomarker prospectively or retrospectively,