prioritize and focus on evolutionarily conserved events that are more likely to be biologically important. Examples of such approach will be described.

06 July 2008 12:45 - 13:45

YOUNG CANCER RESEARCHER'S WORKSHOPS

How to be effective in applying for fellowships

06 July 2008 13:45 - 14:35

AWARD LECTURE

Young Cancer Researcher's Award

37 Oral

SPAR1 is an anti-recombinase that impacts on genome stability and cancer

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DNA double-strand breaks represent a major threat to genome integrity and are predominantly repaired by homologous recombination (HR). Unscheduled or excessive HR can also lead to gross chromosomal rearrangements characteristic of cancer cells, but the mechanisms that restrain HR remain poorly understood.

Yeast Srs2 and E. coli UvrD are related helicases that suppress aberrant recombination by disrupting a specific step in HR, however functional homologues are not obviously conserved in higher eukaryotes. We therefore performed a genetic screen in C. elegans to identify uncharacterised helicases that are synthetic lethal in combination with C. elegans BLM mutants, based on the srs2 sgs1 (BLM) synthetic lethality observed in yeast. This screen identified a novel helicase, SPAR-1 that is conserved from C. elegans to humans and exhibits many of the genetic and biochemical hallmarks of yeast Srs2. Genetic analysis has revealed that C. elegans spar-1 mutants are also synthetic lethal with mus-81 and a distinct group of non-replicative helicases: BLM, FANCJ and RECQ5, but not with WRN. Additionally, the lethality in all four double mutant combinations results from an accumulation of toxic recombination intermediates. C. elegans spar-1 mutants and SPAR1 deficient human cells are also hyper-recombinogenic and exhibit exquisite sensitivity to interstrand cross-links (ICL) that block replication forks. SPAR1 knockout mice die between days 10 and 11.5 due to dramatic genome instability and rapid telomere loss and Human SPAR1 is over-expressed in gastric tumours. Collectively, our work suggest that SPAR1 acts as suppressor of aberrant recombination.

Further support for an anti-recombinogenic function for SPAR1 has come from biochemical studies. Human SPAR1 co-purifies with the critical recombinase Rad51, and is recruited to replication forks via interaction with PCNA. Purified Human SPAR1 can also actively disassemble post-synaptic recombination intermediates in an ATP-dependent manner. Our data indicate that the phenotypes observed in C. elegans, mice and human cells are caused by a failure to counteract inappropriate or persistent recombination intermediates. Furthermore, we suggest that promiscuous disassembly of recombination intermediates is the underlying cause of the genome instability of SPAR1 over-expressing cancers and propose a potential therapy for treating these cancers with a drug currently in clinical trials.

06 July 2008 14:35 - 16:05

PRESIDENTIAL SESSION
APPLIED BIOSYSTEMS – EACR 40TH ANNIVERSARY RESEARCH AWARDS

Signalling and tumour environment

31 Oral

Rac activation and inactivation control plasticity of tumour cell movement

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Background: One of the major discoveries of the last two decades has been the identification of Rho-family GTPases as key regulators of actin dynamics and cell movement. The activity of these GTPases is controlled by activators, guanine nucleotide exchange factors (GEFS) and inactivators, GTPase accelerating proteins (GAPs). How these GEFs and GAPs work together to regulate cell behaviour is a key issue in biology.

Materials and Methods: We carry out the first systematic screen of all known human GEFs and GAPs for Rho-family GTPases.

Results. We identify a GEF-GAP signalling module controlling Rac activity that controls the movement of metastatic melanoma cells. We show that a Rac-GEF interacts with an adaptor protein, that was recently shown to be up-regulated in human tumours and in metastases in a genetically engineered mouse model of melanoma. We show that the complex between the adaptor and the Rac GEF mediates the activation of Rac for cell movement. However, tumour cells can adopt two different modes of movement; a mesenchymal mode where cells have an elongated polarised morphology and an amoeboid mode where cells have a rounded morphology. We show that a series of human melanoma cell lines when cultured on a deformable collagen matrix consist of varying proportions of cells moving in mesenchymal and amoeboid fashions and importantly we show that individual cells within a culture convert between these two different modes. Significantly we show that this inter-convertibility is reciprocally controlled by Rac and Rho. Rac activation through the Rac GEF drives mesenchymal movement and suppresses amoeboid. Rho through activating Rho-kinase activates a Rac-GAP suppressing Rac activation and thereby permitting the high levels of actomyosin contractility required for amoeboid movement. Significantly we show that the expression of the GEF and the GAP determines the way in which different melanoma cells move.

Importantly the data we present is highly relevant to consideration of tumour cell movement in vivo. The biological properties of these different forms of movement provide cells with the ability to cope with different environments in vivo. Mesenchymal movement may be the most fit for rigid tissue environments that require extra-cellular proteolyisis while amoeboid movement in more deformable environments is rapid and its associated high actomyosin contractility provides cells with mechanical strength to deal with shear forces such as following entry in to the blood supply.

Conclusion: Our work leads to the important prediction that tumour cells that can exploit alternative modes of movement may be the most metastatic and that therapies targeting metastasis will have to block both forms of cell movement.

32 Oral

Tumorigenesis-promoting events and signaling by tenascin-C

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BACKGROUND: The ECM component tenascin-C is highly expressed in most solid tumors. Its high expression correlates with a bad survival prognosis in patients with several cancers. Results from cell culture experiments support a role of tenascin-C in enhancing tumor cell proliferation, promoting angiogenesis, invasion and metastasis. We showed that tenascin-C induces cell rounding, which may enhance proliferation and migration, by two mechanisms. Tenascin-C counteracts the tumor cell proliferation-suppressing effect of fibronectin by blocking the integrin alpha 5 beta 1/syndecan-4 complex. This caused cell rounding (Orend et al., 2003, Oncogene 22, 3917) and stimulated tumor cell proliferation (Huang et al., 2001, Cancer Res. 61, 8586) by activation of oncogenic Wnt and MAPkinase signaling (Ruiz et al., 2004, Cancer Res. 64, 7377). Tenascin-C also stimulated endothelin receptor type A (EDNRA) expression, and signaling through EDNRA maintained cell rounding (Lange et al., 2007, Cancer Res. 67, 6163). By using knockdown and over-expression studies, we identified paxillin, RhoA and TM1 as critical targets of cell rounding by tenascin-C downstream of syndecan-4 and EDNRA (Lange et al., 2007, Cancer Res. 67, 6163).

MATERIAL & METHODS: To determine a potential tumorigenesis-promoting effect of tenascin-C in vivo, we generated transgenic mice that ectopically express human tenascin-C in the pancreatic islets. Tenascin-C-transgenic mice, that are apparently healthy and fertile, exhibit normal development of the pancreas, but showed enhanced angiogenesis in the pancreatic islets. Next, we crossed RipTNC mice with tumor-prone RipTag2 (RT2) mice, that develop insulinomas due to ectopic expression of the SV40T-antigen and compared tumorigenesis in RT2/TNC and RT2 mice.

RESULTS: Double transgenic RT2/TNC mice experience more frequent and earlier death incidences than RT2 mice. RT2/TNC mice exhibit several signs of enhanced tumor progression, such as the appearance of local and distant metastasis.