Sunday 27 June 2010 12:45–13:45

Young Cancer Researcher's Workshop: How to be effective in applying for fellowships

32 Applying for Fellowships

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Fellowships often carry significant prestige and can provide a valuable career transition between postdoctoral and independent investigator positions. This workshop will describe some of the fellowship opportunities that are currently available in Europe. Members of fellowship interview panels will also discuss what they are looking for in candidates and provide advice on how to increase the chances of an application being successful.

Sunday 27 June 2010 13:45–14:35

Special Session: Norwegian Pink Ribbon Lecture

33 Genomic analysis of inherited breast and ovarian cancer: a model for personalized medicine

No abstract received.

Sunday 27 June 2010 14:35–16:05

Presidential Session
Presidential Session I

34 Diacylglycerol kinase contribution to mTOR-mediated breast cancer progression

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Introduction: The mammalian target of rapamycin (mTOR) is a master regulator of cell growth, proliferation and survival. The two mTOR complexes, mTORC1 and mTORC2, differ in their mTOR partners and in the substrates they phosphorylate. mTORC1 contains the protein Raptor and phosphorylates many targets, including S6 kinase, whereas mTORC2 includes Rictor and is reported to phosphorylate AKT. Rapamycin and its analogs are mTOR inhibitors with potential to control cancerous states. Several transformed cell types are rapamycin resistant. Since rapamycin and phosphatidic acid (PA) compete for mTOR binding, high PA levels and/or activity of PA generating enzymes are thought to contribute to this resistance. Diacylglycerol kinases (DGK) belong to a family of lipid kinases that phosphorylate diacylglycerol to produce PA, and are promising therapeutic targets.
Methods: To determine how DGK modulates mTOR activity and contributes to tumour progression, we used a panel of human breast cancer-derived cell lines as models in which to downmodulate DGK activity with a pharmacological inhibitor (R59949) or by RNA interference (RNAi).
Results: In these cells, rapamycin did not inhibit AKT, whose phosphorylation was maintained or increased. In contrast, R59949 decreased AKT phosphorylation and counteracted rapamycin effects. Rapamycin had no effect on cell cycle progression and R59949 alone delayed S phase entry, which was potentiated by simultaneous use of both drugs. To determine the mechanism of R59949 action, we immunoprecipitated mTOR. R59949 treatment did not affect mTOR complex composition and rapamycin affected only mTORC1 assembly; combined, the drugs strongly reduced Rictor association to mTOR.
To test the specific contribution of DGKα and ζ isoforms, we measured their levels in our breast cell panel and found no difference in DGKζ expression, but DGKα levels correlated inversely with the degree of cell line malignancy. Whereas RNAi knockdown of either isoform impaired mTORC1 activity, only DGKα depletion reduced AKT activation during cell cycling. To confirm the DGK effect on tumour progression, we generated tumours with reduced DGKα or DGKζ levels in immunocompromised mice. While DGKζ depletion had no effect, a reduction in DGKα significantly impaired tumour growth.
Conclusions: Our data suggest that DGKα-derived PA is needed for mTORC2 complex integrity and its correct function, and thus for tumour progression. DGK inhibition could be tested alone or in combination with rapamycin to design effective anti-cancer therapies.

35 Adipocyte-derived fibroblasts contribute to the desmoplastic reaction in breast cancer: a new link between breast cancer and obesity?

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In a variety of tumours such as breast carcinomas, a desmoplastic response, characterized by the presence of dense collagenous stroma comprising fibroblast-like cells, is observed and is thought to contribute to tumour progression. Peritumoural fibroblasts are composed of several subpopulations that are morphologically undistinguishable and their origins remain debated. Most of the studies have focused on the activation of fibroblasts present in the interstitium (the so-called myofibroblasts) and very little attention has been given to adipocytes, although it is obvious that in breast, early local tumour invasion results in immediate proximity of cancer cells to adipose tissue. In this study we demonstrate that tumour cells modify mature adipocytes leading to the accumulation of an activated population with morphological features of fibroblast cells. Using an original 2D system, where an insert separates the two cell populations, we show that mature adipocytes cocultivated with breast tumour cells for 3 to 8 days exhibit loss of lipid content, decrease in differentiation markers and undergo morphological and functional changes into fibroblast-like cells associated to cytoskeleton reorganization. Interestingly, this population of adipocyte-derived fibroblasts (ADF) exhibits activated phenotype with enhanced migratory, invasive and profibrotic capacities (increase of fibronectin and collagen I secretions). Finally, we report that tumour cells profoundly inhibit the adipogenesis of pre-adipocytes, suggesting a role for precursor components of the adipose tissue in the establishment of ADF cells in breast tumour stroma. Ongoing experiments are performed in our laboratory to assess the presence of ADF in human breast tumours and in mouse tumour xenografts. Our results might provide an explanation for the poor prognosis observed in localised breast cancer in obese women, since the nature of the desmoplastic reaction and the secretion pattern of the ADF might be profoundly altered in this physiopathological condition.

36 Do breast cancers arise in areas of the breast that pre-diagnostically had high mammographic density?

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Background: Percent breast density (PD) is a strong marker of susceptibility to breast cancer, but it is not known whether PD is a generalised marker of susceptibility or a more localised one with tumours arising in dense breast areas. Two previous studies have produced conflicting results.
Methods: We conducted a study nested within the intervention arm of the Age Trial, in which ~54,000 women underwent annual mammography from age 40 to 48 (thereafter every 3 years). 794 women were diagnosed with breast cancer during follow-up. Diagnostic and pre-diagnostic mammograms from 232 cases of incident breast cancer were digitised. Radiologists identified the tumour location on diagnostic films and registration techniques were used to identify the corresponding area on pre-diagnostic films. For each woman, a square grid was drawn on the pre-diagnostic film and PD of the square that contained the eventual tumour ("case" square) was compared with PD in "control" squares on the same film. "Control" squares were chosen using various methods, e.g. use of all complete (i.e. excluding incomplete squares near the edge) squares or a random selection of 3 complete squares. We performed a matched case-control analysis to investigate whether pre-diagnostic localized square-specific PD was associated with eventual tumour location. The analysis was conducted 4 times, with square-grids of length 1, 2, 3 and 4 cm. We also analyzed the data using a previously published method that divided the breast into 2 regions to determine whether the results differed to our more localized density method.
Results: Mean (SD) age of diagnosis was 46.8 (3.1). Results are presented for pre-diagnostic images taken 4.9 (3.3, 5.1) (median (inter-quartile range) years prior to diagnosis. We consistently found that as square-specific PD increased the odds of the square developing into a tumour increased. For example, using all possible controls in a breast and a grid length of 2 cm, the odds of a region becoming cancerous was 2.1 (95% CI: 1.1–3.8), 4.9 (2.8–8.6) and 6.4 (3.7–11.1) higher, respectively, for the second, third and top quartiles in PD within a woman's breast relative to the bottom one. Results were similar for images taken 3 years before diagnosis. The published method yielded a borderline