in Drosophila for signaling pathways that regulate autophagy under hypoxic conditions – a state associated with many solid tumours. This identified a cell autonomous mechanism in human tumour cells which selectively promotes hypoxia associated autophagy and cell survival. Theses findings therefore represent a paradigm for the targeting of cancer-associated autophagy to cause tumour cell death.
The mechanism of action and context-specific nature of this and other factors identified from our screens will be described and the potential implications for the development and treatment of cancer will be discussed.

Sunday 27 June 2010 17:55–18:45

Radium Hospital Foundation Lecture: Genetic instability

52 Early epigenetic and genetic events in breast carcinogenesis

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The active acquisition of epigenetic changes is a poorly understood but important process in development, differentiation, and disease. Our work has recently demonstrated that repression of the p16/pRb pathway in human epithelial cells, a condition common to stem cells and many tumour cells, induces dynamic epigenetic remodeling resulting in the targeted methylation of selected CpG islands. We hypothesized that cells in this epigenetically-plastic state can be programmed by the microenvironment to acquire epigenetic changes that promote tumourigenesis. Normal human mammary epithelial cells (HMEC), and HMEC with repressed p16 were first transduced with constitutively active Ha-rasV12. In order to mimic the secretory aspects of the extracellular environment, the cells were subsequently cultured in a serum-rich environment. When p16-repressed cells were challenged with oncogenic stress, they failed to undergo the classic proliferative arrest as documented in normal cells. When further stressed by being cultured in a serum-rich environment, they spontaneously immortalized and exhibited phenotypic changes indicative of epithelial to mesenchymal transition (EMT). The EMT was accompanied by *de novo* methylation of the E-cadherin promoter and increased motility. These data demonstrate that signals from the microenvironment can induce phenotypic and gene expression changes that result in *de novo* epigenetic alterations important in tumour progression.

Sunday 27 June 2010 09:45–17:30

Poster Session

General, Molecular and Genetic Epidemiology

53 Assessing interaction between established breast cancer genetic susceptibility loci and selected non-genetic risk factors using data from the Breast Cancer Association Consortium

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Background: Breast cancer is known to have both a genetic and non-genetic etiology. A number of common genetic susceptibility variants has recently been identified by predominantly genome-wide approaches, but it is not known whether the loci involved act independently of established non-genetic risk factors. We aimed to assess interaction between genetic and non-genetic risk factors in the Breast Cancer Association Consortium. We focused on age at menarche, ever having had a live birth, number of live births, age at first birth and body mass index and their interaction with single SNPs within each of 10 established susceptibility loci (CASP8, FGFR2, 8q24, TOX3, MAP3K1, LSP1, 2q35, 5p12, SLC4L1 and COX11) and two additional SNPs (TGFB1 and ESR1) with less clear evidence of association.
Material and Methods: Per-allele odds ratios (OR) for SNPs were estimated by categories of non-genetic variables using logistic regression adjusted for study, and two-way gene-environment interaction was tested for by fitting a single-parameter interaction term for departure from log-additive effects. These analyses were applied to data from 14,600−29,991 cases and 16,188−30,990 controls from the Breast Cancer Association Consortium.
Results: No statistical evidence of interaction was observed beyond that expected by chance, given the number of tests carried out. The analyses were repeated using data from 11 population-based studies only, with similarly null results for interaction.
Conclusions: This is by far the largest study to assess interaction between established common genetic risk factors for breast cancer and age at menarche, parity-related variables and body mass index. Further studies of very even larger samples are required to determine whether these common susceptibility variants are associated with different risks of breast cancer depending on other non-genetic factors.

54 Screening for large genomic rearrangements of the BRIP1 and CHK1 genes in Finnish breast cancer families

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Background: In search for susceptibility genes that could explain a portion of familial breast cancer clustering in Finland, we set out to evaluate the presence of large genomic rearrangements in two candidate genes. BRIP1 (alias FANCJ or BACH1) is a BRCA1 associated protein mutated in a fraction of familial breast cancer and Fanconi anemia (FA) cases. The role of large *BRIP1* deletions in breast cancer predisposition is not well-characterized. CHK1 is a critical maintainer of cell cycle checkpoints and genomic stability, and is also involved in the BRCA1 and FA signaling pathways. Although CHK1 is an essential protein for cell cycle and DNA integrity maintenance control, no mutations in this gene has yet been associated with predisposition to cancer. To our knowledge, this is the first report to determine the existence of large *CHK1* deletions in familial breast cancer or in any disease with hereditary background.
Material and Methods: Blood DNA from affected index persons of 111 northern Finnish breast cancer families was assessed for possible constitutional exonic deletions or amplifications in the *BRIP1* and *CHK1* genes by using the multiplex ligation-dependent probe amplification (MLPA) method.
Results: Neither of the genes examined showed any large genomic rearrangements.
Conclusions: Our current results raise the possibility that germline exonic deletions or amplifications do not serve as a significant inactivating mechanism of the tumour suppressive functions of *BRIP1* and *CHK1* in breast tissue. Together with a PCR-based mutation analysis of the *BRIP1* gene, we conclude that pathogenic germline alterations in *BRIP1* appear not to contribute to breast cancer susceptibility in Finland.

55 Association of mammographic density with selected nutrients in Norwegian women

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Background: Mammographic density has been strongly associated with breast cancer risk. The determinants of mammographic density have been shown to be similar to those of breast cancer risk. Investigating the association between diet and mammography density could shed light on the possible relationship between diet and breast cancer risk.
Material and Methods: In this study we analyzed data of 2250 postmenopausal Norwegian women aged 50−69 years residing in the three largest Norwegian counties who participated in the Norwegian Breast Screening Programme in 2004. We estimated intake of selected nutrients and vitamins using a previously validated 200 item food frequency questionnaire. Mammographic density was assessed on scanned mammograms using a computer assisted method. We used multivariate linear regression to determine the least square mean of percent and absolute mammographic density adjusting for potential confounders. Because of the strong confounding effect of body mass index (BMI) on mammographic density we used different adjustments for BMI, analyses were also carried out for different BMI strata.
Results: The mean percent and absolute mammographic density were 19.2% and 24.5cm^2 respectively. Overall, we observed no strong association between mammographic density and total caloric intake or intake of proteins, carbohydrates, total fat, monounsaturated and polyunsaturated fat, cholesterol or dietary fiber. There was a positive borderline statistically significant association (p for trend=0.07) with saturated fat, which became stronger when the analysis was restricted to women with a normal BMI (23–25.9) (p for trend=0.01).