618 Five vertebrate ChIP-seq reveals the evolutionary dynamics of transcription factor binding

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Mammalian transcription factor binding evolves rapidly, yet tissue-specific transcription is highly conserved. To explore this apparent paradox, we experimentally determined the genome-wide occupancy of two transcription factors (TF) CEBPA and HNF4A in livers of multiple vertebrates. Although each TF has highly conserved DNA binding preferences, most binding is species-specific and ultra-shared events are rare. Functional target genes are associated with an enrichment of shared TF binding, yet collectively, the binding events near functional targets show no increase in sequence constraint. Most lineage-specific lost TF binding can be explained by sequence mutations of the binding motif, and only half of the apparently lost binding events appeared to have turned over to a nearby location. Our results reveal the plasticity of vertebrate TF binding and the complex evolutionary dynamics of transcriptional regulation.

619 Blood based breast cancer molecular signatures

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Strategies to achieve personalized medicine and improve public health encompass assessment of an individual's risk for disease, early detection and molecular classification of disease resulting in an informed choice of the most appropriate treatment instituted at an early stage of disease development. A major contribution of proteomics in this field is the development of blood based tests to achieve the goals of personalized medicine. An integrated cooperative effort is currently under way for the identification of biomarkers of breast cancer risk, early detection of breast cancer and identification of altered signaling pathways based on serum and plasma analysis. The effort encompasses analysis of specimens collected before onset of symptoms for the identification of risk and early detection markers and elucidation of signatures in plasma for altered signaling pathways in tumours. This overarching effort also benefits from the availability of subject cohorts and from the availability of engineered mouse models and cell lines that inform with respect to proteins involved in altered signaling pathways. Such an effort requires and benefits from the availability of in-depth quantitative proteomics methods, bioinformatics resources and integration with other broad based molecular profiling technologies.

Tuesday 29 June 2010 10:20–12:20

Symposium
Chemoprevention & molecular epidemiology

620 Adjuvant diet to prevent cancer recurrence

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Background: There is increasing evidence that the same factors that influence cancer incidence may effect cancer prognosis. In the case of breast cancer, for instance, sedentary lifestyle, overweight, fatty diet, metabolic syndrome, and high serum levels of insulin and sex hormones, are associated with both incidence and the risk of recurrences. In the case of colon cancer the same is true for westerd dietary pattern, sedentary lifestyle, overweight, and serum levels of C-peptide.
Material and Methods: We carried out several dietary intervention trials to test the effect of a comprehensive dietary modification, aimed at reducing insulin levels, based on Mediterranean and macrobiotic dietary traditions, on metabolic and endocrine biomarkers of breast cancer incidence and progression. DIANA-1 randomized 104 healthy but hyperandrogenic postmenopausal women into a 5-month intervention and control group; DIANA-2 randomized 110 postmenopausal breast cancer patients into a 3-month intervention and control wroup, and subsequently offered the intervention to both groups for 9 months. DIANA-3 randomized 90 premenopausal healthy women to a 12-month insulin lowering intervention, with or without protein restriction, and to a control group.
Results: In postmenopausal women randonized in the intervention groups body weight, metabolic syndrome factors, serum insulin, testosterone, and estradiol decreased, while SHBG and IGFBP1 and 2 increased significantly. Before menopause we observed a decrease in IGF-I levels but no change in sex hormones.
Conclusion: Dietary intervention may improve breast cancer prognosis.

621 Individualized prediction of prostate cancer using genetic markers

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Background: Prostate cancer (PCa) has the highest heritability of all cancers. During the last 3 years over 35 risk-associated single nucleotide polymorphisms (SNPs) have been identified. Each SNP only confers to a 1.1−1.5 increased risk and the clinical used of these new genetic markers has been questioned. In PCa there are three possibilities to use these new markers:
1. To identify men at high risk before diagnosis.
2. To increase the sensitivity and specificity of the PSA test in the diagnosis of PCa.
3. To distinguish between men with aggressive and non-aggressive disease.

Here we present data in the ability to identify men at high risk and the impact of increasing numbers of SNPs and the predictive performance of family history of PCa and SNPs.
Methods: Absolute risk for PCa was estimated in a population-based case-control study in Sweden (2,899 cases and 1,722 controls) using family history and three sets of sequentially discovered PCa risk-associated SNPs. Their performance in predicting PCa was assessed by positive predictive values (PPV) and sensitivity.
Findings: SNPs and family history were able to differentiate individual risk for PCa and identify men at higher risk; ~18% and ~8% of men in the study had 20-year (55−74 years) absolute risks that were two-fold (0.24) or three-fold (0.36) greater than the population median risk (0.12), respectively. When predictive performances were compared at absolute risk cutoffs of 0.12, 0.24 or 0.36, PPV increased considerably (~20%, ~30% and ~37%, respectively) while sensitivity decreased considerably (~55%, ~20% and ~10%, respectively). In contrast, when increasing numbers of SNPs (5, 11 and 28 SNPs) were used in risk prediction, PPV approached a constant value while sensitivity increased steadily.
Interpretation: PCa risk-associated SNPs have better predictive performance for men at higher risk. SNPs discovered to date are suitable for risk prediction while additional SNPs discovered in the future may identify more subjects at higher risk. Men identified as high-risk by SNP-based testing may be targeted for PCa screening or chemoprevention.

622 Genetics of familial cancer

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Background: By early this year some 30 genes (high risk genes) have been linked to cancer syndromes and over 100 loci have been associated with cancer, mostly in unselected populations using genome-wide association studies (GWASs). These loci convey low risk but they are common and most of them have no known function. In this presentation I will review the population impact of these to types of gene variants by cancer type.
Material and Methods: Population attributable fractions (PAF) and familial relative risk (FRR) are calculated for the susceptibility genes/loci. PAFs have been used extensively for environmental risk factors of cancer in order to rank them and to assess the prospective gains in disease prevention. Their use in cancer genetics is relatively new, probably because the mutant variants of the 'classical' high penetrant cancer genes are so rare that their contribution to the population burden is low compared to the high individual risks.
Results: As an example on breast cancer, the nine established loci give a joint PAF of >60%, but explaining only some 8% of the empirical FRR. The GWASs on colorectal cancer include the chromosome 8 locus, represented by SNP rs6983267 and shared by prostate cancer, accounting for 0.4% of the empirical FRR of 2.7. Another locus close to *SMAD7* confer a marginally lower risk and it accounts for 0.3% of the empirical excess FRR. The joint PAF for these two loci is 27.8%; their FRR would be 1.01, accounting for 0.7% of the empirical excess FRR of colorectal cancer. Examples are given on several other cancers. Differences between high penetrant (relative risk some 5 or more) and low penetrant (relative risks below 1.5 or 2.0) genes have recently been illustrated by 'molecular landscaping'. The PAF of a gene variant integrates any unmeasured gene-gene and gene-environment interactions for the particular study population. With the current volume of genetic data on susceptibility genes, PAFs are useful in putting the findings into an etiologic perspective. The calculation of joint PAFs for several genes gives a progress report into the limits of understanding of the genetic basis of a disease.
Conclusions: The GWASs have identified a new repertoire of cancer susceptibility genes and loci which are characterized by a high frequency of the risk allele and a low relative risk, in line with the common disease-common variant paradigm. A reason for these apparent discrepancies is that the SNP platforms used have been built for relatively common variants (minor allele frequency >0.1) constraining the results to variants with high PAF and low FRR. However, once the true functional varaiants are found the FRRs

conveyed by them may be much higher balancing the explained PAFs and FRRs (Hemminki et al PLOS ONE 2008;3:e2504).

623 Integrating biomarkers of exposure, risk and outcome in epidemiology

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During the last two decades the use of biomarkers in cancer epidemiology has greatly increased. Several reasons explain this expansion. The identification of new carcinogens, characterized by complex exposure circumstances and weak effects, has become increasingly difficult with traditional epidemiological approaches. In parallel, increasing knowledge of mechanisms of carcinogenesis led to the proposal of models involving genetic and epigenetic events, as well as cellular and histological alterations. Furthermore, developments in molecular biology and genetics, such as the use of robots and the increasing throughput of automatic analytical equipments, allow the large-scale application of assays that would otherwise be very resource intensive.
A distinction has been made between markers of exposure, intermediate events, disease, outcome, and susceptibility. This distinction, however, is somewhat arbitrary, and any classification reflects the current understanding of a complex biological phenomenon such as carcinogenesis and the ability to measure events that are considered relevant to it. In fact, the increase in the understanding of the late steps in carcinogenesis, and the development of relevant and valid biomarkers, represents the main challenge to molecular cancer epidemiology.
If biomarkers are to offer new opportunities to overcome some of the limitations of epidemiology, then their added value over traditional approaches should be systematically assessed. Biomarkers should be validated and consideration of sources of bias and confounding in molecular epidemiology studies should be no less stringent than in other types of epidemiological studies. Similarly, other aspects of the study such as determination of required sample size, statistical analysis, reporting and interpretation of results should be approached with methodological rigor. One important goal is the integration of different types of biomarkers to derive risk and outcome profiles for healthy individuals as well as patients.

Tuesday 29 June 2010 12:20–13:45

Workshop: Grant opportunities

624 The role of the Marie Curie Actions in Cancer Research

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Europe needs world-class research and world-class researchers, their creativity and skills. Our future depends critically on society's ability to inspire, motivate and train high quality researchers.
The European Commission's Marie Curie Actions scheme is a set of initiatives that aim to help researchers to fulfil their potential and develop their careers. The way that Marie Curie Actions work not only benefits the researcher themselves but also promotes research excellence and international collaboration, which bring benefits to society as a whole.
Marie Curie Actions promote the development and skills of researchers across Europe. The scheme helps researchers to broaden their career prospects, boosts the transfer of knowledge between researchers in different sectors and countries, and advances European excellence in research.
'Marie Curie Actions' follow a "bottom-up"-approach, hence they are open to researchers in any field of research, at all stages of their career and wherever they choose to do their research – in academia or industry.
During the session an overview of all funding schemes will be given and the role of the Marie Curie Actions in Cancer Research will be presented.
More information:
http://ec.europa.eu/research/mariecurieactions/

625 Not available

No abstract received.

Tuesday 29 June 2010 12:20–13:45

Workshop: Women in Science

626-627 Progress and promise

No abstract received.

Tuesday 29 June 2010 13:45–14:35

Plenary Lecture: AICR Lecture

628 The microenvironment and the genome in breast cancer: how tissue architecture informs

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That development, differentiation and cancer are fundamentally connected has been appreciated for decades. How and why, however, still need much exploration. In the last three decades, we have developed a number of concepts and assays to study how a normal mammary gland conducts the processes of forming, branching, producing milk proteins, remodeling and maintaining steady-state and homeostasis. We have modeled the formation of the unit structure of the mammary gland, a polar 'acinus', and have followed the consequences of loss of its structural integrity. We show myoepithelial cells are crucial regulators of homeostasis and functional differentiation by their ability to make laminin111 (Ln-1) an extracellular matrix molecule (ECM) essential for formation of the acini, homeostasis and functional differentiation; both Ln1 and myoepithelial cells are virtually lost in breast cancer. We have evidence to show that the mechanisms that maintain polarity of the acini are important in preventing cancer, and the restoration of the unit structure can 'reverse' malignant progression.
In the last decade, we have used some of these concepts to understand also the nature of the breast stem and precursor niche. Further more, taking a leaf from invasion and branching of the normal gland in virgin mice, we have developed new models and techniques for understanding invasion and metastasis. Finally, such models have helped us define the plasticity of both normal and malignant cells and the possibility of using microenvironmental therapies to treat breast and other forms of cancer.

Tuesday 29 June 2010 14:35–16:35

Symposium

Cancer stem cells

629 The molecular portraits of breast cancer and their relationship to mammary stem cells

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Background: Breast cancer is a heterogeneous disease in terms of histology, dissemination patterns, therapeutic responses, and patient outcomes. Gene expression analyses using DNA microarrays have helped to explain some of this heterogeneity and provided important new clues as to the cellular origins of many breast tumours.
Material and Methods: Genomic studies using DNA microarrays have established five major breast cancer intrinsic subtypes (Luminal A, Luminal B, HER2-enriched, Claudin-low, Basal-like) and a Normal Breast-like group. FACS analysis of normal human mammary epithelial cells, mouse models, and cell lines, have identified a mammary luminal cell developmental pathway starting from a bi-potent stem cell, to a luminal progenitor, and ending in a mature ER+ luminal cell.
Results: We compared the genomic profiles of each intrinsic subtype to that of profiles coming from FACS isolated mammary epithelial cell populations in order to determine if any relationships might exist. We also present the most recent therapeutic data on the intrinsic subtypes of breast cancer with a special focus on the Claudin-low subtype; this unique subtype shows many mesenchymal and stem cell-associated features, and by genomic analyses it appears to be the most related to the bi-potent normal mammary stem cell fraction. In addition, recent evidence also suggests that the typically triple-negative Basal-like tumour subtype may represent a committed luminal progenitor, with the Luminal A/B tumours showing a mature luminal cell profile.
Conclusion: The observed intrinsic subtypes of breast cancer appear to mimic normal mammary development with each subtype representing a distinct stage of development. These findings also have important implications for the potential cell type of transformation of each subtype, which may be a stem cell for some subtypes (Claudin-low and Basal-like) and a differentiated cell for others (Luminal A).

630 Prospective cloning of functionally distinct breast cancer cells by use of markers from a normal human breast lineage hierarchy

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Tumour heterogeneity is a hallmark of cancer and it is responsible for tumour progression and resistance to therapy. According to Nowell's classical theory