Meeting report

Second International Workshop on the function of BRCA1 and BRCA2, Cambridge, UK, 9 to 10 September 1999

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Received: 22 September 1999
Accepted: 22 September 1999
Published: 27 September 1999

Important note about how to cite this article
This article is also available online in the *Breast Cancer Research* website. To avoid confusion, please ensure that only the online version of the article is cited in any reference, as follows:
Gabriel A, Kerr P, Warren M: Second International Workshop on the function of BRCA1 and BRCA2 [meeting report]. http://breast-cancer-research.com/vol1no1/27sep99/news/01

Introduction

Two years after the first international workshop in this field, scientists working on BRCA1 and BRCA2 re-convened to present and discuss their latest findings. The meeting, sponsored by Breakthrough Breast Cancer, was held in Cambridge, UK. It was apparent from this meeting that BRCA1 and BRCA2 may be multifunctional proteins involved in many different pathways and that, two years on, despite all the work discussed, there is still a lot to learn.

Epidemiology and pathology

Quantification of the prevalence, penetrance, carrier frequency and proportion of relative risk ascribed to BRCA1 and BRCA2 within an unselected population of breast cancer patients was addressed by Paul Pharoah [Cancer Research Campaign (CRC), Cambridge], who demonstrated that the mutation rates of BRCA1 and BRCA2 in the general population were similar to one another. He also observed that the ovarian cancer penetrance was lower than expected. Conversely, high risk populations (eg Icelandic) with single founder mutations provide material for studying the effect of modifying factors on BRCA2. Steinunn Thorlacius (Icelandic Cancer Society) informed us that there is evidence of anticipation and both interfamilial and intrafamilial variation in gene penetrance, cancer risk and even phenotype. One of the most intriguing aspects of this talk was the mutual exclusivity within families of male breast cancer and prostate cancer. This could lead to the identification of important modifier loci. Sunil Lakhani [University College London (UCL), London] concluded this session by discussing the specific histopathology, immunophenotype, and prognostic marker profile for BRCA1 and BRCA2 related tumours, and touched on the probable link between invasive lobular and familial breast cancer caused by putative high risk breast cancer genes, which remain to be identified.

The majority of the remaining talks concentrated on attempts to demonstrate functionality for BRCA1 and BRCA2.

Transcription and the cell cycle

Daniel Haber (Massachusetts General Hospital and Cancer Centre, Boston) and Jeff Parvin (Brigham and Women's Hospital and Harvard Medical School, Boston) presented evidence for a role of BRCA1 in transcriptional regulation. New technology in the form of high-density oligonucleotide arrays was exploited to identify BRCA1 target genes and Haber suggested a possible role for Gadd45 expression in BRCA1-induced apoptosis. However, Heinz Ruffner (Salk Institute, San Diego) did not observe a similar induction of Gadd45 following doxycycline-induced BRCA1 expression and the answer to this question remains to be resolved. Ruffner also presented new data on the nuclear localisation signals present in BRCA2, showing that the first of the three nuclear localisation signals at the carboxyl-terminus was sufficient to localise BRCA2 to the nucleus. This is relevant because most of the disease-causing mutations occur amino-terminal of this nuclear localisation signal, providing a neat explanation for loss of function since the mutant protein would be cytoplasmically localised. However, this would fail to adequately explain the differences in phenotype observed in the mouse models described to date [1–4]. Jeff Parvin insisted that size does matter, presenting evidence that during S-phase of the cell cycle BRCA1 exists in different-sized multiprotein complexes which make up the transcriptional machinery of the cell.

BRCA2 has been reported to interact with a number of proteins and Nicola Marston [Institute of Cancer Research (ICR), London] and Luke Hughes-Davies (CRC/Wellcome, Cambridge) described some of the more recently discovered partners. DSS1, DNA methyltransferase1, and

EMSY were discovered using yeast two-hybrid analysis. This implicated possible involvement of BRCA2 in cell cycle completion, methylation status of freshly replicated DNA in response to DNA damage, and in transcriptional regulation, respectively.

Paul Freemont [Imperial Cancer Research Fund (ICRF), London] concluded the meeting with a splendid demonstration of 3D computer modelling of the BRCA1 BRCT domains and demonstrated how two BRCT domains might interact. Intriguingly, disease-causing mutations that occur at high frequency, as reported in the Breast Information Core (BIC) database (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/index.html), tend to occur at residue locations that are probably involved in the interaction of two BRCT domains.

DNA repair

This session of the meeting concentrated on the role of BRCA1 and BRCA2 in DNA repair mechanisms. Stephen West (ICRF) spoke on double-strand break repair in mammalian cells and gave an excellent overview of this process and an insight into the mechanisms of homologous recombination, concentrating on Rad51 and Rad52. Having demonstrated the use of cell-free systems to analyse these processes *in vitro*, he suggested that they could be used to examine the currently obscure role of BRCA1 and BRCA2 in double-strand break repair.

Many breast tumours have an underlying genomic instability, the origin of which is still to be elucidated. Maria Jasin (Memorial Sloan-Kettering Cancer Centre, New York) has created a system that allows the visualisation of homologous recombination events following DNA double-stranded breaks. Using the enzyme I-Sce1 as an inducer of DNA damage and a linear molecule of DNA bearing homologous cassettes, she has shown that embryonic stem cells which carry a mutation in BRCA1 have an impaired ability to repair chromosomal double-strand breaks by homologous recombination. This may give us a clue to the initiation of chromosomal instability in tumours in response to mutations in BRCA1. Ashok Venkitaram (Cambridge Institute for Medical Research, Cambridge) and Andrew Tutt (ICR) demonstrated the role of BRCA2 in maintenance of genomic integrity. Venkitaram found that the mitotic spindle checkpoint gene Bub1 was mutated in the lymphomas that arise in the BRCA2 mutant mice. Work is underway to determine whether this gene is mutated in breast tumours.

Animal models

Anton Berns (Netherlands Cancer Institute, Amsterdam) provided a summary of the generation of conditional alleles of numerous tumour suppressor genes. He also exemplified the long-term nature of these projects in relation to generating mice with multiple genetic defects. Chuxia Deng [National Institutes of Health (NIH), Bethesda] spoke about the generation of a BRCA1 conditional knockout to result in a deletion of exon 11 and an in-frame splice into exon 12. These mice displayed a high level of genomic instability and, with time, 25% developed mammary tumours. Further investigation of the genetic makeup of the tumours revealed the acquisition of mutations in p53, many reminiscent of those observed in human tumours.

Ramon Parsons (Columbia University, New York) who recently cloned the gene PTEN, which is responsible for Cowden Syndrome, delivered the Plenary Lecture. PTEN is a dual specificity phosphatase that is mutated in sporadic breast cancers. PTEN deficiency in mice leads to the activation of AKT/protein kinase B, a molecule that regulates transcription, translation and apoptosis. The current focus of his laboratory is to identify target genes that are regulated by PTEN in sporadic breast tumours. The involvement of AKT in many cellular pathways has been quickly defined, compared to the relatively slow progress made in elucidating the function of BRCA1 and BRCA2. Whether this is a reflection of the large size of BRCA1 and BRCA2 or to do with their multifunctional nature remains to be seen.

Conclusion

The emerging consensus is that these molecules are involved in transcription and DNA repair. However, there is still a great deal to understand about the role of BRCA1 and BRCA2 in normal cellular mechanisms and what occurs once they are mutated. By the 3rd BRCA1/2 meeting, tentatively arranged for 2001, we will perhaps have a better idea about the function of these molecules. Who knows? We may even have BRCA3 by then.

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