Meeting report

Reasons for Hope: Canadian Breast Cancer Research Conference, Le Concorde Hotel, Quebec City, Quebec, Canada, 3–5 May 2001

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Abstract

Canadian breast cancer researchers and international colleagues met recently to present and discuss their latest data. The conference, which was sponsored by the Canadian Breast Cancer Research Initiative, was held in Quebec City, 3–5 May 2001. The Research Initiative was founded in 1993 and is a unique partnership of groups from the public, private and non-profit sectors committed to funding a broad spectrum of breast cancer research. From this meeting, and others like it, it is becoming increasingly clear that basic research findings are rapidly being translated into tumor subtype and stage-specific therapeutic strategies that have the potential to impact significantly on disease outcome.

Keywords: breast cancer, genetics, epigenetics, microenvironment

Introduction

The Canadian Breast Cancer Research Initiative (CBCRI) sponsored its second 'Reasons For Hope' Conference, 3–5 May 2001, in Quebec City. This gathering brought together researchers, clinicians, healthcare providers and advocates to present and discuss some of the latest findings in breast cancer research, diagnosis and treatment. The multidisciplinary objective of the meeting's organizers was clearly illustrated by the initial reports from the CBCRI's recently instituted 'Streams of Excellence' program, which has brought together teams of researchers from across Canada to tackle large scale projects in a thorough and comprehensive manner. For example, Tim Whelan (McMaster University, Hamilton, Ontario, Canada) and Irene Andrulis (Lunenfeld Institute, Toronto, Ontario, Canada) outlined their group's conceptual framework for accelerating the discovery of clinically relevant molecular changes in breast cancer and rapidly translating these findings into novel treatment paradigms. Michael Pollak (Jewish General Hospital, Montreal, Quebec, Canada) and his group are taking a similar approach as it specifically relates to insulin-like growth factors in breast cancer development and progression. Both of these programs, and other CBCRI-funded ventures, have strong basic research components. The following is a sampling of the basic research highlights from this meeting.

Genetics versus epigenetics in breast cancer progression

In a plenary session entitled 'Genetic Approaches to Understanding the Conversion of Normal to Malignant Cells', Phil Leder (Harvard Medical School, Boston, MA, USA) and Mina Bissell (Berkeley National Laboratory, Berkeley, CA, USA) presented data and persuasive arguments for the importance of genetic and epigenetic change, respectively, in breast tumorigenesis. Leder's laboratory pioneered the use of transgenic mice to identify

CBCRI = Canadian Breast Cancer Research Initiative; HGF = hepatocyte growth factor.

the functional consequences of combinatorial oncogene overexpression in the mammary gland. This group has more recently used single oncogenes as genetic 'initiators' followed by mouse mammary tumor virus infection as an 'accelerator' to identify cooperativity between genetic pathways. Using this approach, they have demonstrated that FGF-3 and Wnt signaling, both of which normally regulate three-dimensional morphogenesis in the mammary gland, act cooperatively in progression to true malignancy. Bissell's laboratory has taken a very different approach. After first demonstrating that the tissue microenvironment regulates the emergence of the malignant phenotype, regardless of the genetic changes involved, the group has recently identified the molecular mediators of this epigenetic regulation. Bissell and her colleagues have now shown that cellular interactions with the extracellular matrix influence growth factor signaling, apoptotic pathways, nuclear structure and transcriptional activity. Importantly, the appropriate modulation of these epigenetic outputs occurs only when the three-dimensional architecture of the breast tissue is maintained.

As most pathologists are quick to point out, alterations in tissue architecture are a fundamental component of breast tumor staging. It is thus not surprising pathologists such as Olli Kallioniemi (National Institutes of Health, Bethesda, MD, USA) and Peter Watson (University of Manitoba, Winnipeg, Manitoba, Canada) have started to capitalize on the basic findings of researchers such as Leder and Bissell in their quest to identify the molecular cascades that regulate clinical breast tumor development. After first pointing out the inherent difficulties in assessing the masses of data being generated by gene profiling, Kallioniemi described the powerful potential of 'tissue chips'. In this procedure, serial sections of tissue are arrayed as the solid phase, which can then be probed for genetic or epigenetic changes. This technique allows precise correlations to be made between altered gene expression and specific architectural changes within heterogeneous tumor samples. As a proof of principle, Kallioniemi used fluorescent *in situ* hydridization to link erbB2 amplification with specific changes in tumor grade, a technique he called 'Fish' on 'Chips'. Watson, who maintains one of Canada's largest and most comprehensive breast tumor banks, has used microdissection together with array profiling to identify genes whose altered expression is associated with specific aspects of breast tumor progression. A number of these genes, and the biological functions of their products, were specifically reported on by other members of Watson's group throughout the meeting. These included psoriasin (S100A7), a calcium binding protein that interacts with centrosomal proteins and is upregulated in ductal carcinoma *in situ*; the hypoxia-regulated gene carbonic anhydrase IX, which is overexpressed in necrotic tumors; and the small leucine-rich proteoglycan lumican, which is upregulated in the stroma of invasive tumors. One conclusion that could thus be reached from observing this stimulating session is that genetic and epigenetic changes probably intersect at the microenvironmental level to facilitate architectural changes that ultimately result in the emergence of the malignant phenotype.

Microenvironmental mediators of breast cancer progression

The characterization of structural, growth factor and signaling molecules that facilitate microenvironmental change in the normal and malignant breast was a theme that cut across many sessions at the meeting. At the level of tissue structure, Dale Laird (University of Western Ontario, London, Ontario, Canada) has demonstrated that gap junctional subtypes may play a role in the functional segregation of the myoepithelial and luminal epithelial compartments in the normal mammary gland and that the loss of these structures plays a role in breast tumor progression. In an interesting twist, however, Laird's latest data indicate that forced expression of gap junctional connexin proteins in aggressive tumor lines does not lead to functional communication, at least in two-dimensional monolayer culture. Instead, the connexins were targeted to the lysosomal pathway for degradation in these cells. Despite this novel and potentially significant *in vitro* finding, connexin expression did decrease the tumorigenicity of these cells *in vivo*, which led Laird to speculate that the tumor microenvironment may facilitate transitory channel formation that could affect cell–cell adhesion.

Decreased adhesion between cells probably facilitates migration at the invasive front of malignant tumors. One microenvironmental factor that can initiate such a decrease in cell–cell adhesion, at least transiently, is hepatocyte growth factor (HGF). HGF is normally produced in the mammary stroma and acts in a paracrine fashion to stimulate epithelial ductal morphogenesis by activating the c-Met tyrosine kinase receptor. Interestingly, Bruce Elliott (Queens University, Kingston, Ontario, Canada) has shown that HGF can act as an autocrine factor at the invasive front in mammary tumors and has presented new data implicating c-*src* tyrosine kinase signaling in this process. Specifically, it appears that c-*src* activity, which is commonly upregulated in breast tumors, impinges on STAT-3 signaling to increase HGF expression. The chronic upregulation of c-*src* activity in breast tumors has a strong epigenetic component. For example, work from Donald Fujita (University of Calgary, Calgary, Alberta, Canada) indicates that the protein tyrosine phosphatase 1B upregulates c-*src* activity by dephosphorylating the negative regulatory C-terminal Tyr530 residue of the kinase molecule.

Morag Park's group (McGill University, Montreal, Quebec, Canada) has identified a number of signaling events that contribute to the morphogenic responses elicited by the HGF-mediated activation of the c-Met receptor. At this

meeting, Hanane Khoury (from Park's group) presented data demonstrating that a constitutively active form of the ErbB2 receptor tyrosine kinase disrupts cell–cell junctions and initiates an invasive program by coopting pathways that are also utilized by c-Met. Specifically, the oncogenic form of ErbB2 acts via the Gab1 docking protein to initiate a sustained activation of Erk signaling that is necessary for cell junction disruption. Interestingly, this does not occur when the regulatable wild-type ErbB2 receptor is transiently activated. These data go a long way towards reconciling the apparently paradoxical finding that ErbB2 signaling plays critical roles in both differentiative alveolar morphogenesis and neoplastic progression in the breast. Coupling findings such as these together with the combinatorial signaling pathway data being generated by laboratories such as that of Bill Muller (McMaster University, Hamilton, Ontario, Canada) will contribute greatly to the development of the second generation of rational chemotherapeutic agents that is being accelerated by the significant, but still limited, success of the upstream ErbB receptor modulators.

Finally, Evelyn Voura, who is working in the laboratory of Rama Khokha (Ontario Cancer Institute, Toronto, Ontario, Canada), used an elegant *in vitro* tissue reconstitution approach to show that focal proteolysis initiated by the action of microenvironmentally regulated matrix metalloproteases facilitates the migration of breast tumor cells across endothelial cell membranes. This transendothelial migration is a critical step in tumor extravasation. Specifically targeting this process may therefore lead to the development of another class of rational therapeutic tools that could be used in combination anti-proliferative and anti-migratory therapies to halt the progression of invasive carcinomas attempting to leave the primary tumor – the ultimate architectural disruption that signals the onset of metastasis.

Conclusion

This meeting offered an interesting mix of basic, translational and clinical research. As many investigators presented overviews as well as their latest findings, I found that many sessions gave me an appreciation, in some depth, for topics outside my specific field. In addition, it was clear from the data presented that the CBCRI has been successful in fostering meaningful multidisciplinary interactions across fields – an accomplishment that is certain to improve breast cancer prevention, diagnosis and treatment.

Acknowledgement

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