Breast Cancer RESEARCH

EDITORIAL

Breast cancer: current state and future promise

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Over the past 50 years, deaths from cardiovascular disease, stroke and pneumonia have plummeted as a result of new therapies and preventive strategies based upon a detailed understanding of the causes and pathogenesis of these diseases. Over this same period, deaths from cancer have changed relatively little. Consequently, we have now reached a tipping point in history at which deaths from cancer will soon surpass those from cardiovascular disease. In this regard, breast cancer holds the dubious honor of having become the leading cause of cancer mortality among women worldwide.

The enormous commitment of resources to research on breast cancer, and the dedication of the thousands of researchers focused on this problem, is predicated on the belief that the prevention, detection and cure of this disease will ultimately depend upon a greater understanding of the biology of breast cancer than we hold today. Equally important, however, is the recognition that translating the fruits of basic research to the clinic is an extraordinarily challenging task that requires intellectual cooperation amongst individuals spanning a broad range of expertise and understanding.

For this reason, success in translational research requires the confluence and engagement of multiple disciplines. Accordingly, the cell biologist, the epidemiologist, the molecular biologist, the pathologist, the radiologist, the molecular geneticist and the clinical researcher have all become inextricably linked in their shared quest for progress towards reducing breast cancer mortality. Achieving this goal challenges each of these specialists to assemble and integrate knowledge from diverse fields with which they are relatively unfamiliar.

It was to address precisely this need that *Breast Cancer Research* was launched 12 years ago. Guided by an editorial board possessing a wide perspective of specialist fields, and supported by scientists actively engaged in the laboratory and clinic, *Breast Cancer Research* has aimed - in the words of its founding Editor-in-Chief Sir Bruce Ponder - 'to integrate and interpret biologically based research across the whole spectrum relevant to breast cancer, to make it accessible to the breast cancer community, and to keep in view the goal, however distant, of practical application.'

It is with this goal in mind that we present the accompanying special review series. With reviews spanning breast cancer susceptibility, the molecular genetics and cell biology of breast cancer development and progression, and the validation of new cellular biomarkers for clinical trials, this collection reflects the focus and commitment of *Breast Cancer Research* to report on all areas of biology and medicine relevant to breast cancer.

In our first review, Boyd and colleagues [1] address a fascinating aspect of breast cancer susceptibility as they summarize current understanding and future prospects regarding the relationship between mammographic density and breast cancer risk. Over the past decade, mammographic density has emerged as a major risk factor for breast cancer, with odds ratios generally in the range of 3.5 to 4.5. Indeed, among endocrine, reproductive and familial risks of breast cancer, only age, gender, and *BRCA1* and *BRCA2* carrier status are associated with larger relative risks of breast cancer than mammographic density. Moreover, since high mammographic density is common in the population, if the association with breast cancer risk is causal, the proportion of the disease attributable to this risk factor is likely to be substantial. Intriguingly, age, parity and menopausal status account for only a small proportion of the observed variation in mammographic density in the population; in contrast, twin studies suggest that much of the residual variation in mammographic density is the result of heritable - presumably polygenic - factors. In light of the strong association between mammographic density and breast cancer risk, the genetic factors that influence mammographic density may represent a treasure trove of currently unappreciated genes and pathways that contribute to breast cancer incidence. As such, the identification of factors that influence mammographic density may lead to a greater understanding of the causes of breast cancer as well as new approaches to preventing this disease. In their review, Boyd and colleagues survey critical aspects of the biological underpinnings of

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mammographic density, and discuss clinical implications for mammographic screening, individual risk prediction, and breast cancer prevention.

In our second review, Arteaga and colleagues [2] address the role of mutations in the phosphatidylinositol 3-kinase (PI3K) pathway in breast cancer progression and response to therapy. PI3K serves as a major signaling hub downstream of HER2/neu and other receptor tyrosine kinases and mutations in the genes constituting this pathway occur in >70% of breast cancers, making it the most frequently mutated pathway in this disease. Moreover, PI3K pathway activation is now recognized as an important molecular determinant of resistance to anti-estrogen therapies in estrogen receptor-positive breast cancers, as well as resistance to HER2/neu-targeted therapies in HER2/neu-amplified breast cancers. Arteaga and colleagues review alterations in the PI3K pathway in breast cancer, their association with therapeutic resistance, and the state of clinical development of PI3K pathway inhibitors. In doing so, they describe an exemplary model for the integration and translation of fundamental molecular genetics research to clinical oncology.

Next, Davidson, Oesterreich and colleagues [3] report on recent developments in epigenetics and breast cancer, an area that has witnessed an explosion of new knowledge. Their review emphasizes advances in our understanding of histone methylation and demethylation as an example of the remarkable progress that has been made in recent years towards a basic understanding of how various epigenetic changes, such as DNA methylation, histone modification, microRNA expression, and higher order chromatin structure, affect gene expression. Their review focuses on exciting and rapidly evolving areas within epigenetics research, with an emphasis on opportunities for clinical application, including its promise for prognosis, prediction, and therapeutic intervention.

Turning to cell biology, Ford and colleagues [4] examine the complexities and nuance of the so-called epithelial-to-mesenchymal transition (EMT) in breast cancer. The EMT is a critical developmental program of cellular behavior that has recently come center stage in attempts to understand the aggressive behavior of human breast cancers. The ability of some breast cancer cells to acquire a mesenchymal-like phenotype is strongly associated with a host of properties associated with tumor progression, including increased motility, invasion, anoikis resistance, cancer stem cell characteristics and therapeutic resistance. This transition appears to be reversible with a plasticity that may explain the remarkable ability of breast cancer cells to disseminate and adapt to new environments. Their review addresses the molecules and pathways that mediate EMT in breast cancer, the impact of EMT on breast cancer behavior, and the implications of this new-found knowledge for breast cancer therapy.

In our fifth review, Polyak and associates [5] address those factors outside of cancer cells that so profoundly affect their behavior. Beginning with the prophetic assessment that 'tumors are wounds that do not heal' [6], the tumor microenvironment is now widely recognized as a critical determinant of, and participant in, breast cancer progression and the response to anti-neoplastic therapy. Consequently, there is enormous interest in developing new therapies that target the microenvironment with a particular aim towards affecting the course of invasion and metastatic progression. Their review summarizes recent advances in our understanding of the breast cancer microenvironment, as well as the challenges of translating this knowledge into clinical practice.

Finally, Pantel and colleagues [7] describe recent advances pertaining to the biology and clinical relevance of circulating tumor cells (CTCs). The detection of CTCs in peripheral blood and disseminated tumor cells (DTCs) in the bone marrow of breast cancer patients has become an extremely active area of translational research with more than 200 clinical trials incorporating CTC counts as a biomarker in patients with various types of solid tumors. As the authors of this review highlight, breast cancer has played perhaps the most prominent role in elucidating the biology and meaning of CTCs in cancer patients. While the clinical relevance of DTCs is well-established, the biology and relevance of CTCs is at present much less clear. Pantel and colleagues summarize key findings with regard to current technologies for CTC detection, the biology of CTCs, the relationship between CTCs in the bloodstream and DTCs in the bone marrow, the clinical relevance of CTCs, and their potential utility as predictors of response to therapy. These advances in understanding pave the way for what could be a promising new test in the arsenal of clinical oncologists.

When taken together with the highly referenced recent research publications in *Breast Cancer Research*, whose abstracts are also included in this issue, we anticipate that this series of reviews will both intrigue and enlighten. In doing so, we hope to have succeeded in presenting these recent advances in a manner that is accessible, accurate, and engaging for the entire breast cancer community.

Abbreviations

CTC, circulating tumor cell; DTC, disseminated tumor cell; EMT, epithelial-to-mesenchymal transition; PI3K, phosphatidylinositol 3-kinase.

Competing interests

LAC is Editor-in-Chief of *Breast Cancer Research* and receives an annual honorarium.

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