The 3rd Pacific Rim Meeting on Breast and Prostate Cancer: Progress in Hormonal Carcinogenesis and the Enduring Influence of Ron Ross

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Introduction

The 3rd Pacific Rim ("PacRim") meeting on breast and prostate cancer on Fraser Island (Queensland, Australia) brought together a cast of international experts from October 31 to November 4, 2006. The meeting highlighted the current progress in breast and prostate cancer in the context of the enduring legacy of Ronald K. Ross in hormone-dependent cancer research. The overall thrust of this meeting, attended by almost 200 delegates, was to highlight the current advances and novel concepts in hormonal cancers. Meeting details including the full program can be found at the conference web site³ and a full list of meeting registrants is included in the online supplementary materials. The meeting also acknowledged the untimely passing of Ron Ross who was an active participant and coorganizer of the first two PacRim meetings. Furthermore, Ron Ross made seminal contributions to the epidemiology and molecular epidemiology of hormonal cancers, especially breast and prostate cancers. He coauthored more than 245 peer-reviewed articles, of which 18 alone were in the journal. Ron Ross' research, hypotheses, generosity, and kindness influenced a number of studies, which were recognized in this journal. Ron Ross' research, generally outstanding mentor of students, postdoctoral fellows, and junior faculty. Further details on Ron Ross can be found at the University of Southern California web site.⁴

The Fraser Island meeting set out to identify the similarities and differences between breast and prostate cancer. Finally—and perhaps most importantly—this meeting focuses less on previously published data and more on novel and provocative concepts. Five overall themes emerged that cut across multiple disciplines, diseases, and sessions of the PacRim meeting:

- Emerging Themes in Epigenetics and Chromatin Remodeling
- New Advances in Animal Models
- New Therapeutic Strategies
- Novel Approaches to Prevention
- Responsibilities of the Modern Scientist. [Cancer Res 2007;67(10): 4550–2]

Emerging Themes in Epigenetics and Chromatin Remodeling

Michael Stallcup (Los Angeles, CA) gave a critical evaluation of the significance of coactivator-mediated histone modifications in gene regulation. To date, more than 200 coregulators have been identified and they are believed to assist in transcriptional activation using two principal mechanisms: recruitment and activation of the transcription initiation complex and remodeling of the local chromatin structure. The former involves recruitment of other coregulators and the basal transcription machinery including RNA polymerase, whereas the latter is dependent on unique intrinsic enzymatic activities. The coactivators are activated by DNA-bound activators such as nuclear receptors and initiate a series of tightly orchestrated events which have to happen in a specific succession. Coregulators are activated by their activators through signal input domains and transmit the signal to the transcriptional machinery with signal output or activation domains. Through multistep, rapid on-off, protein-protein interactions, and the combined action of various coregulators over time, a promoter region is progressively modified from an inactive to an active state, a phenomenon known as promoter progression.

Peter Jones (Los Angeles, CA) reported on the uses and limitations of DNA methyltransferase (DNMT) inhibitors as anticancer drugs. He first described classic DNMT inhibitors, such as 5-Aza2'-deoxycytidine and its deoxy analogue, 5-Aza-2'-deoxycytidine as the first generation of DNMT cancer chemotherapeutic agents. Zebularine, a novel inhibitor of DNA methylation, exhibits a greater stability in acidic and neutral solutions and minimal toxicity both in vitro and in vivo. Although it also functions as a nucleoside analogue and inhibits DNA methylation, cancer cells were found to preferentially incorporate this agent versus normal cells. This has dramatically minimized the bystander or nonspecific effects.

Furthermore, Jones also reported that his lab has recently developed technology that exquisitely maps the positions of nucleosomes on a given DNA sequence. The new method combines the novel use of Ss1 methylase treatment of chromatin followed by bisulfite chemistry, resulting in the deamination of only the cytosine residues that are protected by bound nucleosomes. Using this procedure, Jones was able to show that nucleosomes were depleted from actively expressing genes. Finally, Bernie Futscher (Tucson, AZ) presented data showing the epigenetic inactivation of the HOXA gene cluster in breast cancers. With a combined approach of CpG island microarrays to detect methylation differences from normal breast tissue and invasive breast cancer and gene expression arrays, his group identified a small neighborhood of contiguous methylation, localized to 100 kb, that correlated with transcriptional repression of the HOXA cluster in breast cancer. Futscher suggested that inactivation of the HOXA cluster may represent a new type of epigenetic lesion which he termed an epigenetic microdeletion.

³ http://www.pacrimmeeting.com
⁴ http://www.usc.edu/~uscnews/stories/12354.html
New Advances in Animal Models

The emerging use of rodents as models for human diseases has brought with it a variety of questions, not the least of which is, whether this approach has relevance in hormone-related cancers. Diane Robins (Ann Arbor, MI) presented a timely study in which she generated an allelic series of mice with different glutamine tract [i.e., (CAG)n repeat] lengths in the human androgen receptor (AR), thereby replacing the endogenous mouse AR with human AR sequences. Crossing these alleles into the TRAMP mouse model of prostate cancer, Robins determined that the glutamine tract length affects the timing of disease onset and progression in intact mice, particularly with respect to duration of disease.

Priscilla Furth (Washington, DC) presented a mouse model system wherein she placed the estrogen receptor (ER) under the control of a tetracycline-regulated promoter. This conditional ER mouse model showed that alteration of ER expression in these mice is a rate-limiting factor for the initiation of ductal carcinoma in situ. This model closely represents the human case in which one might find misregulation and overexpression of ER during mammary gland development.

New Therapeutic Strategies

Lisa Butler (Adelaide, South Australia, Australia) presented her work on the use of histone deacetylase inhibitors in prostate cancer. She showed that the histone deacetylase inhibitor SAHA was synergistic with the AR antagonist casodex for growth inhibition, and the combination induced cell death. This synergistic effect was associated with reduced prostate-specific antigen levels, and might be an efficacious therapy for AR-positive prostate cancer.

Karen Knudsen (Cincinnati, OH) reported her finding that cyclin D1b–specific antibodies is currently an impediment, Knudsen’s work on the use of histone deacetylase inhibitors in prostate cancer. She showed that the histone deacetylase inhibitor SAHA was synergistic with the AR antagonist casodex for growth inhibition, and the combination induced cell death. This synergistic effect was associated with reduced prostate-specific antigen levels, and might be an efficacious therapy for AR-positive prostate cancer.

Karen Knudsen (Cincinnati, OH) reported her finding that cyclin D1b is expressed at high frequencies in prostate cancer and in prostatic intraepithelial neoplasia when compared with adjacent benign tissue. Cyclin D1b, like cyclin D1a, retains the ability to bind the AR, but significantly, it is impaired in its ability to down-regulate AR-mediated activation of the prostate-specific antigen promoter. Moreover, Knudsen reported that cyclin D1b stimulated proliferation in AR-dependent prostate cancer cells, whereas cyclin D1a inhibited cell cycle progression. Although the lack of cyclin D1b–specific antibodies is currently an impediment, Knudsen’s data supports the need to further examine the extent of cyclin D1b expression in preinvasive and invasive prostate.

Peter Jones described a study that uses zebularine (see Emerging Themes in Epigenetics and Chromatin Remodeling) in the prevention of colon cancer development in the APC(Min) mouse model. Zebularine was given to 1-week-old APC(Min) mice that would spontaneously develop colon cancer due to the inactivation of wild-type adenomatous polyposis coli (APC) gene functions. The drug had minimal toxicity and did not affect the growth of both male and female mice. Results showed that females were protected by the drug but not males. The strong gender difference was due to the higher levels of aldehyde oxidase metabolism of zebularine in male mice; however, this is not true for humans. Results confirmed demethylation of target genes in the target tissue, i.e., the colonic mucosa.

Stephen Birrell (Adelaide, South Australia, Australia) contrasted the effects of androgens on breast and prostate tissues and highlighted the potential for testosterone to counteract the deleterious side effects of systemic estrogen depletion in patients with breast cancer treated long-term with third-generation aromatase inhibitors. Mike Press (Los Angeles, CA) presented the BCIRG 006 adjuvant study interim analysis showing a more favorable outcome for Adriamycin/Cytoxin-based chemotherapy in those patients coamplified for HER2 and topoisomerase IIa, which are close-by. These results suggest that coamplification of topoisomerase IIa may be a useful biomarker for the selection of HER2-positive patients who are more likely to benefit from anthracycline combination chemotherapy.

Nigel Brooks from AstraZeneca (United Kingdom) described how translational science has grown over the past few years into a discipline that is now fully embedded in many academic and industrial organizations. For example, immunohistochemistry is used in tumor and non–tumor tissue to detect proof of mechanism and proof of principle biomarkers as an aid to dose and schedule decisions. Furthermore, cell line panels can be used to determine the molecular basis for response and resistance to drug therapies and in some cases can even predict, at least preclinically, which patients may be more or less likely to respond to such treatments.

Novel Approaches to Prevention

David Feldman (Stanford, CA) reported that—given the anti-inflammatory properties of vitamin D—in vitro studies were undertaken to determine if there was a role for vitamin D in prostate cancer. It was also proposed that there could be synergy between calcitriol and nonsteroidal anti-inflammatory drugs (NSAID), as calcitriol can inhibit the action of prostaglandin by down-regulating the expression of cyclooxygenase-2, and NSAIDs could also act in part by inhibiting the action of prostaglandin by affecting the cyclooxygenase enzyme activity. It was found in two cell lines that combinations of calcitriol and NSAIDs did reduce the growth of both cell lines.

Geoff Green (Chicago, IL) reported that green tea is widely used in Asia and the active ingredients are polyphenol catechins. In a proof of principle study, 60 volunteers with high-grade prostatic intraepithelial neoplasia were randomized to either placebo or green tea. In those receiving placebo, 30% were shown to be positive for prostate cancer at the end of 12 months, whereas only 3.3% were shown to be positive in those receiving green tea. The dose of green tea administered per day was equivalent to that obtained in 12 to 15 cups of green tea infusion. Furthermore, studies were reviewed on the effect of green tea in a transgenic mouse model of mammary carcinoma. In this study, it was possible to show that the green tea catechins significantly delayed the onset of invasive mammary tumors and mitosis was suppressed whereas apoptosis increased in tumor cells. Therefore, it seemed from both the human and the animal studies that green tea may have a preventive role in both breast and prostate cancer.

John Forbes (Newcastle, New South Wales, Australia) presented an overview of prevention trials in breast cancer. He first focused on the IBIS 1 trial in which breast cancer incidence was reduced by 32% in women receiving tamoxifen; however, the effect was confined to ER-positive tumors. A meta-analysis of four tamoxifen prevention trials was presented showing that the greatest benefit from tamoxifen was in very high risk ER-positive breast cancers in women who had no risk of thrombosis and had had a previous hysterectomy and in whom tamoxifen was well tolerated.

Responsibilities of the Modern Scientist

An award in Ron Ross’ name was established to honor his memory and contributions to this and future PacRim meetings.
The winner of the inaugural Ron Ross award was Malcolm Pike, the Flora L. Thornton Chair in Preventive Medicine at University of Southern California (Los Angeles, CA), who received the award from Ron’s wife, Karen. Pike was cited for his seminal contributions to breast, ovarian, and prostate cancer. His talk was entitled “Breast Cancer and Hormone Replacement Therapy: Lessons and Challenges from the Debacle.” He credited Ron Ross and himself as the authors as they had worked so closely together on this issue for decades. The Women’s Health Initiative randomized trial of EPT (estrogen-progestin therapy) showed quite clearly in 2002 that over a period of 5 years, breast cancer risk increased by at least 25%. In the U.S., this resulted in thousands of additional cases of breast cancer every year. The publicity surrounding the announcement of the results persuaded most women to cease using EPT and forced physicians to alter their prescribing habits. Importantly, Ross, Pike, and their colleagues had predicted, based on the epidemiology and biology of breast cancer, just such an added risk of breast cancer from the use of EPT in two articles as early as 1988. Furthermore, radiologists had published instances of greatly increased mammographic densities in women on EPT in the early 1990s, and finally, a small epidemiologic study from Scandinavia published in 1992 had found a greatly increased risk from EPT. The lessons to be learnt from this sobering trial are many and include: (a) that the regulatory authorities need to take into account potential long-term effects when considering the licensing of hormonal preparations. Because these effects can only be predicted on the basis of biomarkers, such biomarkers (such as mammographic density changes) must be considered and the authorities’ actions should be guided by them. It is not permissible to act as if biomarker evidence was irrelevant, which is what unfortunately happened with the evidence on increased mammographic densities and increased breast cell proliferation. (b) Breast cancer researchers must also take responsibility. They failed to distinguish between what was required for proof of the effect of EPT and what was required for action from the regulatory authorities, and thus, no warnings from them to the regulatory authorities was forthcoming. (c) Epidemiologists (and other scientists) did not take their responsibilities seriously enough. In summary, Pike embraced the informal spirit of the meeting by highlighting past mistakes, especially in breast and ovarian cancer research and public policy drawn from his own decades-long experience in hormonal cancer research. Pike encouraged the audience not to repeat these mistakes and to be fully engaged with the public and specialists in the relevant medical disciplines to make evidence-based policy decisions for everybody’s benefit.

Conclusion

Significant progress has been made in breast and prostate cancer, which was highlighted on Fraser Island. However, many challenges still remain, such as effective presymptomatic risk assessment, effective and rational disease prevention, personalized treatment strategies, truly relevant animal models for human disease, and stem cells (if any). Many of these questions will be explored at the next meeting in Vancouver in 2008.

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