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VIEWPOINT

Advances in Prostate Cancer Research: Part III

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We present here the last in a series of three groups of "Prospect Articles on Prostate Cancer" (see *Journal of Cellular Biochemistry* issues 91:1 and 91:3, 2004). This group of Prospects focuses on the basic mechanisms responsible for the establishment and growth of prostate cancer metastases.

The first study presented in this issue by Chunthapong and coworkers is an original article that describes the dual role of E-cadherin, a cell–cell contact molecule, in prostate cancer cell invasion. The authors show an innovative model in which E-cadherin is shown to be important for maintaining the poorly invasive phenotype but, upon cleavage, is also shown to promote invasion. This timely study elucidates the important role of E-cadherin in prostate cancer progression and has profound implications for metastatic prostate cancer therapy.

The second article is a Prospect by Lee and Tenniswood that elegantly reviews the molecular mechanisms involved in metastatic hormone-refractory disease with emphasis on anti-androgen therapy as a cause for a more aggressive phenotype. Anti-androgen therapy is known to initially block tumor growth, but eventually fails and leads to a drug-resistant stage, known as androgen-independent or hormone-refractory cancer. The authors propose that anti-androgen therapy alters several cellular functions as well as the interaction between stroma and epithelial cells and that a combination of intrinsic and extrinsic factors from the microenvironment contributes to the emergence of hormone-refractory metastatic cancer.

The third article, a Prospect by Evangelou and coworkers, provides a comprehensive analysis of the deregulation of growth factor and androgen signaling pathways and how they contribute to metastatic and androgen-independent cancer. The authors have generated a genetically engineered TRAMP mouse model for prostate cancer, and the article benefits from their experience with it; the Prospect highlights the spontaneous emergence of the neuroendocrine phenotype and discusses the pathological significance in this animal model.

Finally, given the fact that bone is one of the preferred sites for prostate cancer cells and that bone metastasis is associated with severe debilitating cancer symptoms and a negative impact on survival, we conclude our series with four articles that focus on cancer metastasis to bone. The first is an insightful Viewpoint article by Dr. Mohla that carefully highlights current NIH efforts to promote research on the cross-talk between prostate cancer cells and bone microenvironment and identifies areas that need to be developed. Dr. Mohla's Viewpoint offers an Introduction to the remaining three outstanding Prospects (by Edlund et al., Tantivejkul et al., and Keller and Brown) that focus on this problem and offer exciting discussions for their readers.

This group of Prospects concludes a comprehensive series of three groups of Prospect articles on prostate cancer. The authors have discussed recent progress in the basic mechanisms of prostate cancer (Part I, vol. 91:1); they have elucidated the translational and clinical aspects concerning the disease (Part II, vol. 91:3) and they have highlighted our current knowledge on prostate cancer bone metastasis

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(Part III, this issue). Overall, the key issues in this area of research pinpointed by the authors can be summarized as follows. In Part I, several Prospects urged the scientific community to focus on studies aimed at developing a deeper understanding of the unique molecular aspects underlying this disease. Other Prospects in this Part indicated that the basic and translational areas of research are not sufficiently integrated and interdisciplinary research should be promoted. In Part II, the Prospects raised serious concerns, both about current therapeutic modalities and about diagnostic tools, and stressed that these concerns must be addressed in the near future. This important message is supported by two recent studies that have also raised red flags regarding our current therapeutic modalities. The first study shows that finasteride, a drug that blocks conversion of testosterone to dihydrotestosterone, prevents or delays the detection of prostate cancer and also increases the risk of high-grade tumors [Thompson et al., 2003]. A second study by Chen et al. [2004] describes a surprising result that brings new insights into the mechanisms of resistance to anti-androgen therapy. This report shows that higher levels of androgen receptor cause resistance to anti-androgen therapy and may cause antagonists to become agonists. Finally, here in Part III, the authors point out the fact that the processes that support metastatic cancer growth are very complex and need further investigation.

Thus, in conclusion, the Prospects in this series bring to our attention the need for integrated studies in basic, translational, and clinical research, resulting in novel therapeutic modalities for primary as well as metastatic prostate cancer; more specifically, we are encouraged to devote future efforts to develop new anti-androgen therapeutic approaches as well as therapies to prevent and treat metastases to bone.

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