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VIEWPOINT

Androgen Action Series

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This new series of Prospect articles on prostate cancer reviews different aspects of the pathophysiological role of androgen and its receptor. The focus of the series is on the pathways that are likely to affect disease progression towards an androgen-independent phenotype. This progression is of profound medical significance because it causes treatment failure. The current therapy for prostate cancer involves androgen ablation or blockade of the androgen receptor (AR); however, a significantly high percentage of treated prostate cancers eventually grows despite either castration levels of androgen or the presence of anti-androgens.

In the first article, Dehm and Tindall reveal the prostate universe in a comprehensive analysis of the genes regulated by AR. The Prospect article by Dehm and Tindall focuses on the multi-functional activities attributed to androgen and surveys gene expression profile studies recently published in different systems. The authors succeed in reconciling the studies with a unifying hypothesis: the predominant effect attributed to androgen is largely due to changes in the levels of secretory proteins, cell proliferation, and survival.

The next six Prospect articles reveal the AR mystique by describing non-canonical mechanisms of AR activation. These mechanisms deserve further investigations since they offer new and promising therapeutic targets for androgen-refractory prostate cancer.

Miranti and Knudsen's article introduces the reader to the complexity of this system by pointing to the synergistic activity between integrins and growth factor receptors and by describing the differential expression of integrins, growth factor receptors, and AR in normal and neoplastic prostate. This article discusses how signals from integrins, growth factor receptors, and AR are integrated to regulate proliferation and survival of normal and malignant prostate epithelial cells. The authors stress that cell adhesion molecules (ligands and receptors) are likely to provide new targets for therapeutic approaches for metastatic prostate cancer, and that this area of research deserves further investigations.

Agoulnik and Weigel's article reviews non-canonical AR signaling pathways as a hallmark of advanced prostate cancer. These pathways are manifested as changes in expression levels and properties of the AR, as factors that potentiate the action of this receptor and as changes in cell signaling in recurrent prostate cancer. The mechanisms that mediate these changes include: gain-of-function mutations that permit "promiscuous" use of non-androgenic steroids and anti-androgens; upregulation of AR coactivators, such as SRC-1, RAC3, p300/CBP, TIF-2, huntingtin interacting protein 1, and Tip60; and activation of signaling pathways known to be deregulated in prostate cancer and to increase AR activity.

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As reviewed by Culig and Bartsch, the AR is critical for the growth of prostate cancer at the primary site as well as at various stages of cancer progression, including metastases at distant sites, independent of the androgen-responsiveness of the cancers. New evidence clearly shows that knockdown of AR by ribozyme or siRNA in AR-positive androgen-refractory prostate cancer cells blocks growth in vitro and in vivo. Thus, the AR is still a primary target for prostate cancer therapy. Culig and Bartsch have reviewed also mechanisms through which a host of growth factors or cytokines (EGF, IGF-1, KGF, TGF-α, TGF-β, HER-2/neu, oncostatin M, IL-4, and IL-6) could activate AR in the absence of a ligand by interacting with their cognate receptors and by activating the MAPK, ERK, and PI3K/Akt pathways.

The topic of the review by Ahmed and associates (Wang et al., pg 382) deals with protein kinase CK2, a signal active in both androgen-dependent and -independent prostate cancer. CK2 has multi-functional activity in these cancer cells including control of androgen-dependent or growth factor-dependent cell growth and is also a potent suppressor of apoptosis. Many effects of this kinase appear to be upstream of other signaling molecules in the cell. Accordingly, CK2 is emerging as a potential target for prostate cancer therapy as it can function in both androgen-dependent and -independent prostate cancer.

The review article by Wu et al. focuses on the cross-talk between insulin-like growth factor type I receptor (IGF-IR) and AR; the cross-talk has been suggested to play a role in AR-mediated prostate cancer progression to AI disease in the absence of androgen ligand. The IGF-IR is a promising target. Fully humanized antibodies targeting the IGF-IR are now in clinical trials. This Prospect article reviews some of the published data on the mechanisms of IGF-IR/AR interaction and presents new evidence that IGF-IR signaling may modulate AR compartmentalization and thus alter AR activity in prostate cancer cells.

Similarly, β-catenin, a critical molecular component of Wnt signaling is now known to act as a coactivator for AR. As reviewed by Buttyan and colleagues (Terry et al., pg 402), cytosolic interaction of β-catenin and the ligand-activated AR triggers nuclear translocation of β-catenin and enhances the ability of the liganded AR to activate transcription of androgen- regulated genes. In this regard, β-catenin enhancement of AR activation is of particular significance to genes regulated by the TCF family of transcriptional factors in various Wnt signaling pathways.

The reader will be stimulated by new hypotheses and by several major questions that remain unanswered. Will proteomic analysis of changes due to androgen action confirm the results of gene expression analysis? Will drugs that target integrins or growth factor receptors or both offer new therapeutic approaches for metastatic diseases? Which non-canonical AR signaling pathway will be "the" hallmark of advanced prostate cancer? Finally, it remains to be determined through which mechanisms the tumor microenvironment contributes to prostate cancer progression. Answers to these questions will open new horizons in the search for a therapeutic approach to aggressive prostate cancer.