Meeting Report: Innovations in Prostate Cancer Research

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Introduction

The incidence of prostate cancer has increased with serum prostate-specific antigen (PSA) screening. Although organ-confined prostate cancer can be cured by surgery and/or radiation therapy, metastatic disease cannot. Androgen ablation in this setting has long been recognized as effective, but tumors almost invariably relapse over time; unfortunately, outcome of patients with metastatic androgen-independent disease remains poor despite incremental improvements in chemotherapy. The purpose of this "Special AACR Conference in Prostate Cancer" was (a) to provide a specialized forum for presentation of state-of-the-art disease-specific research; (b) to attract innovative investigators from other fields; and (c) to introduce new cutting-edge technologies into prostate cancer basic, translational, and clinical investigation.

Opening Keynotes

Throughout the conference, the theme of androgen independence in prostate cancer was addressed. Howard Scher (Memorial Sloan-Kettering Cancer Center) focused on androgen-regulated gene expression and approaches to inhibiting the androgen receptor (1). Gene profiling revealed that androgen receptor expression persisted in all stages of hormonal treatment. Dr. Scher stated that many genes involved in androgen receptor signaling were found differentially expressed in androgen-dependent versus androgen-independent prostate cancer; some may be therapeutic targets in androgen-independent disease. Because DNA acetylation regulates androgen receptor expression, histone deacetylase inhibitors (such as vorinostat and LBH589) can influence prostate cancer cells. Indeed, such compounds down-regulate androgen receptor expression and inhibit prostate cancer cell growth. Clinical trials (LBH589 alone or in combination with docetaxel; vorinostat plus androgens) are ongoing.

Judah Folkman (Children's Hospital of Boston) galvanized the audience while broadly discussing angiogenesis as an organizing principle in medicine and biology (2). Based on the hypothesis that the growth of normal and neoplastic tissues is angiogenesis dependent, Dr. Folkman illustrated that blood vessel formation is not only closely related to development, wound healing, and cancer but also to certain nonmalignant eye and joint diseases. This paradigm has now been clinically validated with the Food and Drug Administration approval of bevacizumab. The advantage of the angiogenic endothelial cell as a therapeutic target was discussed in terms of accessibility and genetic stability compared with tumor cells. In closing, he proposed that, because compounds may interfere in different steps during angiogenesis, combination antiangiogenic therapy should be evaluated as a therapeutic approach.

Detection and Prediction

Otis Brawley (Winship Cancer Center) analyzed population-based PSA screening for prostate cancer detection; he questioned such programs regarding cost/labor intensity (3). Dr. Brawley emphasized that three kinds of prostate cancer must be distinguished: tumors that do not require treatment (proven to exist), tumors that require treatment but cannot be treated effectively and result in patient death (also proven to exist), and tumors that require treatment and can be sufficiently treated (may exist but uncertainty remains). Distinction among such phenotypes is mandatory to offer management options (3).

Marsha Moses (Children's Hospital of Boston) delivered a molecular account of the regulation of angiogenesis from an angiogenic switch through tumor progression and the resulting clinical implications. Identifying mechanisms that cause such tumor angiogenic switch might lead to novel diagnostic and therapeutic approaches. Dr. Moses proposed that, because proteolysis is among the earliest processes involved in the angiogenic switch, a critical step to be addressed is the degradation of the endothelial basement membrane and adjacent extracellular matrix proteins with the release of angiogenic factors (4). Thus, the study of matrix metalloproteases, cysteine and serine proteases, ADAM and ADAMTS families might yield mechanistic insights into the processing of growth factors and their receptors, and the influence on the equilibrium between angiogenic factors and their endogenous inhibitors.

A strategy to integrate microanatomic features and molecular biomarkers to predict prostate cancer progression was introduced by Carlos Cordón-Cardo (Columbia University). Dr. Cordón-Cardo presented a model that uses a combination of clinical data, histopathology, quantitative assessment of concentration and localization of relevant proteins, in situ transcriptional analysis, and computer-assisted data analysis. Such data can be used for a systems biology approach (5) to generate personalized outcome prediction of the response to different therapies against prostate cancer.

Nanotechnology applications are being rapidly developed for tumor imaging, predictive oncology, and targeted therapy. Jonathan Simons (Prostate Cancer Foundation) presented an overview about the promise of nanotechnology as tool in translational prostate cancer research (6). Dr. Simons showed that encapsulating luminescent quantum dots with amphiphilic block copolymers and linking the polymer to tumor-targeting ligands generated multifunctional nanoparticles with evident potential for detection of molecular targets in vivo.

Tumor Microenvironment

The vascular and peripheral nervous systems share a unique feature: Both are branched networks requiring guidance to ensure their proper positioning. Anne Eichmann (Institut National de la Sante
et de la Recherche Medicale) discussed her findings on the role of axon guidance molecules in angiogenesis (7). Dr. Eichmann showed that specialized endothelial cells (resembling axonal growth cones in neurons) locate at the tips of outgrowing capillaries to guide growing capillaries along vascular endothelial growth factor gradients.

Juri Gelovani (M.D. Anderson Cancer Center) presented new techniques of noninvasive molecular imaging for in vivo detection and monitoring of therapy in preclinical models. Dr. Gelovani described [18F]FEAU positron emission tomography (PET) for imaging of Herpes simplex virus type-1 thymidine kinase expression in vivo (8). PET was also used with epidermal growth factor receptor (EGFR) kinase-specific radiolabeled tracers to image the heterogeneity of EGFR expression and signaling activity.

The unfolded protein response allows cells to adapt to adverse conditions affecting the endoplasmic reticulum. Amy Lee (University of Southern California/Norris Cancer Center) reported stress induction of glucose-regulated protein (GRP)-78 in tumor microenvironment. GRP-78 is overexpressed in many tumors (9) and Dr. Lee detailed its role in prostate cancer progression and drug resistance through blockade of Bax and caspase-7 activation. GRP-78 overexpression is associated with a poor prognosis and resistance to therapy.

In his presentation on microenvironmental control of prostate cancer growth via protein degradation, Bruce Zetter (Children’s Hospital of Boston) focused on the mechanistic role of ornithine decarboxylase antizyme in response to spermine in tumor cells (10). This response is suppressed during prostate cancer progression, which, in turn, may protect cancer cells from environmental restrictions on tumor growth. Dr. Zetter showed that the balance between antizyme and its endogenous inhibitor in the prostate cancer cell controls tumor proliferation.

Leland Chung (Winship Cancer Center) described the close interaction of prostate cancer cells and host stromal fibroblasts (11). The cancer cells can adapt to and mimic host stroma cells in the microenvironment. Dr. Chung proposed that “osteomimicry” in bone confers increasing malignancy to tumor cells. Osteomimicry is elicited or at least enhanced by soluble β2 microglobulin; this protein and downstream signaling are involved in growth, survival, and androgen responsiveness of prostate cancer.

Genetics and Epigenetics

The role of gene fusions in hematologic tumors is well known but much less established in prostate cancer. After introducing new high-throughput bioinformatics methodology, Arul Chinnaian (University of Michigan) described how a genetic fusion (between the TMPRSS2 and ETS transcription factors) plays a role in human prostate carcinogenesis. Dr. Chinnaian reported other ETS gene fusions by analyzing gene expression in prostate cancer (12).

Changes in DNA methylation occur early and extensively in prostate cancer. In particular, CpG island hypermethylation leads to silencing of many genes. William Nelson (Johns Hopkins University) presented studies aiming at the discovery of small molecules targeting DNA methyltransferases (DNMT) and methyl-CpG–binding domain proteins (MBD) for epigenetic reactivation of silenced genes in prostate cancer cells (13). Dr. Nelson showed that procainamide selectively inhibits DNMT1 at clinically relevant concentrations. In high-throughput screening, compounds interfering with MBD-mediated transcriptional repression were also found.

Colin Collins (University of California San Francisco) emphasized the importance of identifying genomic and associated transcriptional alterations that drive prostate cancer progression for the development of biomarkers and therapeutic targets. Dr. Collins profiled whole genome copy number changes in genomes of hormone-naive lymph node metastases from matched primary tumors with comparative genomic hybridization. Matched primary tumors and lymph node metastases showed very similar profiles but distinct from tumors that did not metastasize (14).

Tumor Progression and Metastasis

Warren Heston (Cleveland Clinic) originally cloned the gene encoding prostate-specific membrane antigen (PSMA). Dr. Heston discussed PSMA as a target in prostate cancer. PSMA expression increases in normal-to-neoplastic prostate epithelium transformation; it is expressed in a fraction of prostate cancers; and it is also a vascular target in other solid tumors. PSMA functions as an internalizing target; thus, radionuclide-conjugated PSMA antibodies resulted in antitumor responses and displayed enhanced sensitivity for bone metastasis detection. Antitumor effects were observed in preclinical models with an auristatin-linked toxin PSMA antibody as a vascular target (15).

Of any given primary tumor, only a minority of tumor cells eventually accrue the ability to disseminate, escape the immune system and biophysical barriers, and respond to growth stimuli or escape growth inhibition in distant sites. Thus, the molecular processes regulating tumorigenicity and metastasis are distinguishable. Carrie Rinker-Schaeffer (University of Chicago) reviewed work on discovery, molecular mechanisms, and potential applications of metastasis suppressor proteins. Dr. Rinker-Schaeffer discussed the functional roles of mitogen-activated protein kinase kinase (MKK)-4, MKK-6, and MKK-7 in prostate cancer (16).

Cell Growth and Apoptosis

John Isaacs (Johns Hopkins University) reported prostate-specific protease prodrugs as prostate cancer “smart bombs” (17). Thapsigargin—a cytotoxic molecule able to kill tumor cells independently of their proliferative state—was targeted to prostate cancer cells. It was linked to an inactivating peptide that can specifically be cleaved by PSA or PMSA. Several constructs were evaluated in vitro and in vivo with promising results.

John Reed (Burnham Institute) presented a very comprehensive overview of apoptosis-based therapies against cancer (18). Dr. Reed illustrated how protease families regulate programmed cell death in prostate cancer. Alterations in the expression and function of these proteins have been described in prostate cancer, suggesting them as therapeutic targets. He also introduced other apoptosis-directed strategies such as the use of antisense oligonucleotides or protein kinase inhibitors and their corresponding signaling pathways.

Cancer Stem Cells

Paul Simmons (Institute of Molecular Medicine) talked about the bone marrow as a site of niches for normal and cancer stem cells. The process of stem cell lodgment that follows homing to the bone marrow was his focus. This process encompasses the migration of stem cells within the bone marrow to specific anatomic sites representing the putative stem cell niches; within such niches, stem cell proliferation and differentiation is regulated by a complex cellular interaction with the microenvironment, mediated by growth factors, adhesion molecules, and extracellular matrix proteins. Dr. Simmons described work on the key role of
Translational Research

Christopher Logothetis (M. D. Anderson Cancer Center) reviewed androgen-independent prostate cancer, which was discussed from a clinical investigator point of view. Dr. Logothetis used the proteasome inhibitor bortezomib as a drug development paradigm. Cancer cells seem to be particularly vulnerable to proteasome dysfunction and bortezomib is a very effective treatment for multiple myeloma. In a phase I trial, bortezomib dose correlated with proteasome inhibition, decreased serum PSA levels, and down-regulation of interleukin-6. Another drug example was the use of thalidomide to modulate tumor microenvironment in androgen-independent prostate cancer (21), in which hedgehog signaling is attenuated and the matrix metalloproteases to E-cadherin ratio shifts in favor of E-cadherin.

David Piwnica-Worms (Washington University) presented real-time molecular imaging of signal transduction in vivo. Dr. Piwnica-Worms showed that reporters such as firefly luciferase or green fluorescence protein could be engineered into distinct fusion proteins rather than cloned into constitutively active promoter contexts. Fundamental processes such as posttranslational modification, signal transduction or other protein-protein interactions, and even drug actions can be monitored in real time (22).

Wadih Arap (M. D. Anderson Cancer Center) highlighted combinatorial selection to discover/translate tissue-specific and angiogenesis-related receptors (“vascular ZIP codes”) into targeted therapies. Dr. Arap discussed mapping of protein-interacting sites and functional insights into the basis of recognition. Targeted AAV/phage (AAVP) for preclinical molecular imaging of prostate cancer was also presented (23).

New Therapeutic Approaches

A strategy to target tumor vasculature with peptide-guided cytokines was presented by Angelo Corti (San Raffaele Hospital and Research Center). Tumor necrosis factor (TNF) is a powerful antiangiogenic agent but cannot be used systemically due to toxicity. Peptides homing to tumor neovascularature (CNGRC and RGD4-C) were fused to recombinant TNF. In mouse models, picogram doses of these compounds had tumor-permeabilizing effects, whereas nanogram doses prevented this effect. This bell-shaped dose-response curve is mediated by counter-regulatory mechanisms blocking cytokine activity. Dr. Corti said that targeted TNF alone or in combination with chemotherapy is being evaluated in clinical trials (24).

Steven Libutti [National Cancer Institute (NCI)] reported another angiogenic approach: a tumor-targeted AAVP designed (25) to deliver a TNF transgene in vitro and in vivo. In unpublished work, Dr. Libutti reported preliminary results of a feasibility gene therapy trial of the NCI-sponsored veterinary consortium of dogs with naturally occurring tumors.

Martin Gleave (University of British Columbia) identified the secretory chaperone clusterin as an antiapoptotic protein up-regulated by androgen ablation and chemotherapy in prostate cancer. A clusterin antisense drug, OGX011, decreases the cytoprotective effects of clusterin and enhances antihormonal and chemotherapeutic effects in tumor xenograft prostate cancer models (26). Dr. Gleave indicated that a phase I clinical confirmed drug tolerability and dose-dependent knockdown of clusterin in tumors.

AACR Travel Award for Trainees

Immanuel Lerner (Michael Elkin Laboratory, Hadassah-Hebrew University) used DNA expression profiling in prostate cancer. Analysis in mouse models showed that secreted heparanase can be in prostate cancer cells enhances bone metastasis. Small interfering RNA–mediated heparanase knockdown inhibited prostate cancer growth in vivo, suggesting heparanase as a target.

Flip Jansen (Guido Jenster Laboratory, Erasmus University Medical Center) reported tumor xenograft-based discovery of candidate biomarkers in prostate cancer. Serum samples of tumor-bearing mice with human prostate cancer xenografts were analyzed by biochemical separation in tandem with mass spectrometry protein identification.

Closing Keynote

Vishva Dixit (Genentech) discussed the function of the E3 ligase constitutively photometric-1 (COP1). COP1 is an ubiquitin ligase that increases turnover of p53 by tagging it to be degraded by proteasomes. COP1 depletion up-regulates p53 and leads to cell cycle arrest. Tumor overexpression of COP1 mediates p53 inactivation and promotes cell survival. Another morphogenesis protein plant, de-etiolated (DET), promotes ubiquitylation of c-Jun. The role of the COP-DET axis in regulating growth and survival (27) in prostate cancer remains to be determined.

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References


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