Cleveland Clinic

Glickman Urological & Kidney Institute

Research Notes

Prostate Cancer Edition Spring 2014

Collaborative Research to Examine the Detrimental Impact of Endogenous Interferons in Prostate Cancer

Recipient of a Prostate Cancer Foundation Special Challenge Award

By George R. Stark, PhD

Endogenous interferons, whose production is triggered by exposure to viruses, bacteria and other infectious agents, are the innate immune system's major initial response to an invading pathogen. The antiproliferative, apoptotic and antiangiogenic effects of interferons, and their ability to modulate immune responses, have led to the administration of exogenous interferons as an adjunct therapy for some cancers.

Conversely, however, the increased expression of a subset of interferon-induced proteins in several different tumors correlates strongly with the tumors' ability to resist radiation and chemotherapy. In effect, the elevated expression of approximately 25 interferon-induced proteins — a response known as the interferon-related DNA damage resistance signature (IRDS) — appears to inhibit treatment of the cancer and predispose to a worse outcome.

Why this happens, and why the detrimental IRDS response is much more likely to

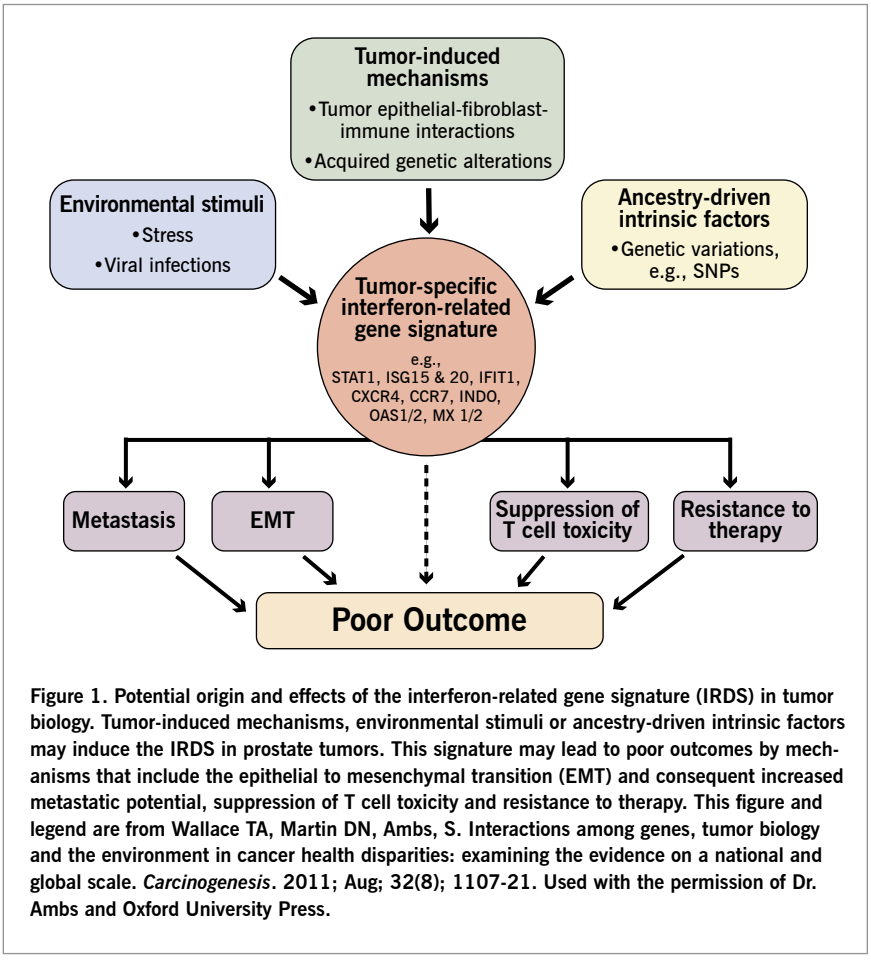

Figure 1. Potential origin and effects of the interferon-related gene signature (IRDS) in tumor biology. Tumor-induced mechanisms, environmental stimuli or ancestry-driven intrinsic factors may induce the IRDS in prostate tumors. This signature may lead to poor outcomes by mechanisms that include the epithelial to mesenchymal transition (EMT) and consequent increased metastatic potential, suppression of T cell toxicity and resistance to therapy. This figure and legend are from Wallace TA, Martin DN, Ambs, S. Interactions among genes, tumor biology and the environment in cancer health disparities: examining the evidence on a national and global scale. *Carcinogenesis*. 2011; Aug; 32(8); 1107-21. Used with the permission of Dr. Ambs and Oxford University Press.

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Welcome to the Prostate Cancer Edition of *Research Notes*!

Cleveland Clinic Ranked No. 2 in Urology and Nephrology

U.S. News & World Report "America's Best Hospitals"

Nima Sharifi, MD

Andrew J. Stephenson, MD, FRCSC, FACS

This is the second edition of Cleveland Clinic Glickman Urological & Kidney Institute's *Research Notes* to focus specifically on prostate cancer. In this issue, we feature active research projects that range from interrogation of basic mechanisms that drive prostate cancer growth and progression to the translation of insights developed from these studies into the clinic, and clinical trials that investigate the role of new treatment modalities for men with prostate cancer. We also provide updates on the projects highlighted in the 2012 inaugural prostate cancer edition of *Research Notes*.

Our approach to both the investigation and treatment of prostate cancer is multidisciplinary, involving close working relationships between basic biologists, urologists, radiation oncologists and medical oncologists. The prostate cancer research projects described here are the result of these complementary perspectives.

Specific projects highlighted here are focused on a gene expression profile induced by interferons and present in the tumors of African-American men that appears to adversely affect clinical outcomes in prostate cancer; the first identification of a mutation in an androgen-synthesizing enzyme that promotes resistance to hormonal therapy; and an adjuvant clinical trial of the potent androgen receptor antagonist enzalutamide for patients with high-risk disease treated with prostatectomy. Updates are provided on projects involving a genomic approach to active surveillance; radiosensitization strategies in prostate cancer; prostate cancer stem cells; and a viral-drug combination strategy for prostate cancer therapy.

As always, the patient is at the center of these projects and our work at Cleveland Clinic.

Sincerely,

Nima Sharifi, MD

Medical Editor,
Research Notes

Andrew J. Stephenson, MD, FRCSC, FACS

Director, Center for Urologic Oncology

Novick Center

The Novick Center for Clinical and Translational Research supports the research efforts of all members of the Glickman Urological & Kidney Institute. Headed by Daniel Shoskes, MD, and Sankar Navaneethan, MD, the center has 30 full-time employees, including a research manager, research nurses, study coordinators, database managers and IT support personnel. The center manages a number of clinical trials and 15 disease-specific databases that serve as a source for clinical projects and outcomes reporting. Biostatistical support is provided through the Department of Quantitative Health Sciences, led by Michael Kattan, PhD, and center personnel frequently collaborate with scientists in Cleveland Clinic's Lerner Research Institute.

To read the latest edition of Urology & Kidney Disease News, visit clevelandclinic.org/UKDNews.

Detrimental Impact of Endogenous Interferons Continued from Cover

occur in African-American men with prostate cancer than in their white counterparts, is the subject of a new collaborative research project involving Cleveland Clinic, the National Cancer Institute, the University of Chicago and Philadelphia's Thomas Jefferson University. The effort is funded by a $600,000 Special Challenge Award from the Prostate Cancer Foundation.

The IRDS collaboration resulted from the intersection of independent and seemingly unrelated studies at the member institutions. These studies involved how cells respond to interferon, the analyses of proteins expressed in radiation-resistant breast cancers, and the dramatic ethnic differences in the aggressiveness of prostate cancers. The prevalence of the IRDS genetic signal is 50 percent in African-American prostate cancer patients, compared with 20 percent in European-American patients, which may help explain the observed ethnic differences in mortality.

Key Points:

Endogenous interferons, which are a crucial component of our beneficial immune response to infections, have detrimental effects in many tumors.

A collaborative research project involving Cleveland Clinic, the National Cancer Institute, the University of Chicago and Thomas Jefferson University will explore the role of abnormally high expression of interferon-induced proteins in prostate cancer. The project also will examine these proteins' connection to resistance to chemotherapy or radiation therapy, and to the striking ethnic differences in tumor aggressiveness and disease mortality when African-American and white patients are compared.

The research project has received a $600,000 Special Challenge Award from the Prostate Cancer Foundation.

Interferon's Effects

Cells respond to interferons by inducing the expression of hundreds of proteins. But the laboratory of Ralph R. Weichselbaum, MD, at the University of Chicago showed that only a small subset of these proteins was constitutively expressed at a high frequency in several different cancers and, importantly, that IRDS expression correlated strongly with increased resistance to ionizing radiation and DNA-damaging chemotherapy.

Our laboratory discovered that expression of the same subset of genes was sustained in cells in tissue culture that were treated with a low concentration of interferon for many days. The mechanism depended upon the formation of a novel variant of ISGF3, the major transcription factor responsible for transmitting signals from the interferon receptor on the cell surface to genes in the nucleus. Our working hypothesis is that low steady-state levels of endogenous interferon in the tumor microenvironment are responsible for the IRDS signature.

The laboratory of Stefan Ambs, PhD, MPH, at the National Cancer Institute, in addition to demonstrating the striking ethnic difference in the prevalence of the IRDS in prostate tumors of African-Americans, also showed that these patients experience an excess mortality that is partly explained by an intrinsically aggressive disease.

Research Goals

The first aim of the collaborative research project is to compare the frequency and magnitude of IRDS expression in archival samples of prostate cancers from African-American and European-American patients. This comparison will utilize samples from a database established by Cleveland Clinic Glickman Urological & Kidney Institute Chairman Eric A. Klein, MD. We also will investigate the correlation between IRDS expression and clinical outcomes.

The project's second goal is to determine the prevalence and consequence of IRDS in disease progression, a study that will be conducted by Karen Knudsen, PhD, of Thomas Jefferson University. Included will be an analysis of the impact of androgen receptor signaling and hormone therapy on IRDS expression and outcome.

In the project's third initiative, our laboratory and the Weichselbaum laboratory will investigate whether transient inhibition of the interferon response in prostate tumors will sensitize them to radiation or chemotherapy. Several inhibitors of the JAK-STAT pathway, which is essential for the ability of cells to respond to interferons, already are in clinical use in other diseases. An attractive possibility is that pretreatment with such an inhibitor will downregulate the tumor's response to endogenous interferon and thus downregulate the expression of IRDS genes, sensitizing the tumors to DNA damage inflicted by radiation or chemotherapy.

It will be of major benefit to patients if it is possible to reduce the amount of radiation or chemotherapy needed to achieve a given clinical effect.

Dr. Stark is the Distinguished Scientist of Cleveland Clinic and works in the Lerner Research Institute's Department of Molecular Genetics. He and Glickman Urological & Kidney Institute Chairman Eric A. Klein, MD, are principal investigators on the IRDS research project. Dr. Stark can be reached at starkg@ccf.org.

First Mutation Identified That Increases DHT Synthesis to Promote Hormone Therapy Resistance

By Nima Sharifi, MD

The development of castration-resistant prostate cancer (CRPC) occurs in large part by tumors acquiring the capability of synthesizing their own supply of 5αdihydrotestosterone (DHT) from non-gonadal sources, particularly from adrenal precursors. The role and requirement for intratumoral DHT synthesis in the development of CRPC is demonstrated by the efficacy of next-generation hormone therapies that have entered into clinical practice. This includes abiraterone acetate, which blocks androgen synthesis, and enzalutamide, which is a potent androgen receptor antagonist.

Despite the long-recognized phenomenon of elevated androgens in CRPC, no mutation has yet been described that is responsible for increasing DHT synthesis. Our group has identified the first such example of a genetic alteration that increases the conversion of precursor steroids to DHT, permitting tumors to grow in the absence of gonadal testosterone. The enzyme 3αhydroxysteroid dehydrogenase-isoenzyme-1 (3αHSD1) is required for the first and rate-limiting step in the conversion of adrenal dehydroepiandrosterone (DHEA) en route to DHT. A mutation occurs in 3αHSD1 in a subset of human CRPC tumors that blocks degradation of this enzyme, increasing the amount of enzyme available in the cell and resulting in an increase in the flow of precursor steroids to DHT. The essential consequence is that this mutation opens the floodgates to DHT synthesis, permitting tumors to grow in the absence of gonadal testosterone.

Key Points:

Our group has identified the first example of a genetic alteration that increases the conversion of precursor steroids to DHT, permitting tumors to grow in the absence of gonadal testosterone.

It is possible that this germline variant may play a part in upfront resistance to hormonal therapy.

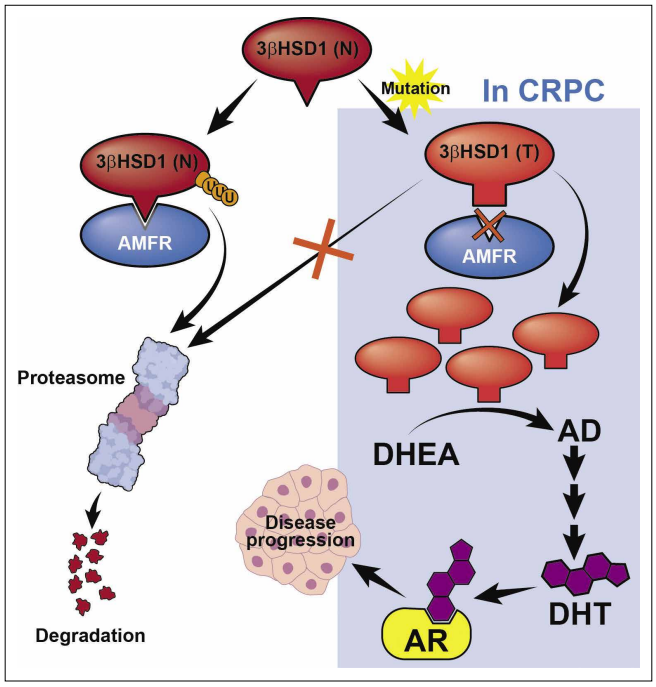

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Figure 1. The wild-type 3βHSD1 (N) enzyme normally undergoes ubiquitination by the AMFR protein, leading to rapid proteasome-mediated degradation, thereby blocking accumulation of this enzyme and DHT synthesis. When mutated to the 3βHSD1 (T) form, the association with the ubiquitinating AMFR protein is blocked (shown on the right-hand side). This allows the enzyme to accumulate and increase the conversion from the adrenal precursor steroid, DHEA, to androstenedione (AD) to DHT, promoting androgen receptor (AR) activation and castration-resistant prostate cancer (CRPC).

We found not only that this mutant 3αHSD1 occurs in human CRPC tumors, but also that it occurs in a mouse model of resistance to abiraterone acetate. Current studies are aimed at determining whether clinical resistance to abiraterone acetate and enzalutamide are attributable in part to 3αHSD1 mutations.

In addition to the 3αHSD1 mutation that occurs in tumors with the development of CRPC, the same genetic alteration exists as an inherited germline variant. In this form, it is possible that this germline variant may play a part in upfront resistance to hormonal therapy. Other ongoing studies will identify how germline variant inheritance regulates androgen metabolism in localized prostate cancer. It is conceivable that upfront genetic information on hormone therapy response/resistance may help determine the best treatment modality for a specific patient.

Dr. Sharifi holds the Kendrick Family Endowed Chair for Prostate Cancer Research in Lerner Research Institute's Department of Cancer Biology. He is an associate staff member of the Taussig Cancer Institute's Department of Solid Tumor Oncology, and of the Glickman Urological & Kidney Institute's Department of Urology. He can be reached at sharifn@ccf.org or 216.445.7434.

Adjuvant Systemic Therapy for Men with High-Risk Prostate Cancer

Andrew J. Stephenson, MD, FRCSC, FACS

By Jorge A. Garcia, MD, FACP

Prostate cancer remains the most common malignancy in American men. While a considerable percentage of men achieve cure with surgery or radiation therapy, some patients diagnosed with high-risk or locally advanced disease eventually develop local or systemic recurrence.

Existing risk-stratification criteria, including more contemporary tools, have permitted us to define this population at risk for systemic disease. To date, pathological stage, Gleason score and nodal disease after surgery remain the most common features used to determine the risk of recurrence after radical prostatectomy (RP).

According to the preoperative D'Amico criteria, RP alone in patients with high-risk prostate cancer leads to cure in about 50 percent of cases. Although quite heterogeneous, recurrence mostly is due to distant micrometastases and is often manifested first by an elevation in prostate-specific antigen (PSA). The goal of adjuvant therapy is to control and/or treat distant micrometastases, delay/avoid progression and ultimately improve survival.

Outside of postoperative radiation therapy (RT) for those with node-negative high-risk disease, no standard adjuvant systemic treatments after surgery exist. Existing data suggest that adjuvant androgen deprivation therapy (ADT) significantly improves survival in patients with positive lymph nodes.

The limitation of these data, however, is the lack of understanding of the appropriate timing to initiate ADT and the known long-term complications of testosterone suppression. In the case of negative lymph nodes, the survival advantage of adjuvant ADT has not been demonstrated. To date, no data supporting the role of chemotherapy in the perioperative setting exist.

For men with high-risk disease excluding those with positive lymph node disease, adjuvant RT has become the norm. Two large, randomized trials have demonstrated a reduction in biochemical recurrence, delay in time to metastases and overall survival improvement in those men who receive adjuvant RT.

With the recent development of novel agents in the castration-resistant state, a logical step is to move some of these agents to early-disease settings.

Key Points:

A significant number of high-risk prostate cancer patients eventually will develop local/systemic recurrence, despite primary treatment

Adjuvant therapy has the potential to delay progression and improve survival

Enzalutamide is a powerful oral AR inhibitor, with significant activity in men with castration-resistant prostate cancer that leads to survival improvement

Adjuvant enzalutamide has the potential to treat micrometastatic disease, which ultimately may lead to a reduced prostate cancer recurrence rate in this patient population

Enzalutamide, a novel oral androgen receptor inhibitor that has demonstrated significant activity in men with castration-resistant prostate cancer, is an ideal agent that can be moved to the perioperative setting. We are conducting a phase II trial evaluating the efficacy and safety of adjuvant enzalutamide in men with undetectable PSA values (PSA < 0.4) and high-risk disease features who have undergone RP.

Our main goal is to delay serologic progression (rising PSA), which often is the first manifestation of prostate cancer recurrence. Since adjuvant RT is a standard of care for some of these patients, RT will be allowed in the study, provided that patients already have started enzalutamide therapy.

We estimate that the study will accrue 40 patients. Men enrolled in the trial will receive 24 months of therapy, with periodic evaluations for efficacy and safety. Enzalutamide is an oral agent, and the current standard dose is 160 mg PO daily.

Dr. Garcia is a member member of the Taussig Cancer Institute's Department of Solid Tumor Oncology, and of the Glickman Urological & Kidney Institute's Department of Urology. He can be reached at garciaj4@ccf.org or 216.444.7774.

Dr. Stephenson is Director of the Glickman Urological & Kidney Institute's Center for Urologic Oncology. He and Dr. Garcia, are co-principal investigators for the adjuvant enzalutamide clinical trial. Dr. Stephenson can be reached at stephea2@ccf.org or 216.445.1062

Update on a Genomic Approach to Active Surveillance

By Eric A. Klein, MD

In the Fall 2012 issue of Glickman Urological & Kidney Institute's *Research Notes*, we reported on developmental studies demonstrating that gene expression profiling can predict long-term clinical outcomes when measured in radical prostatectomy specimens. That work showed that gene expression measured even in the lowest Gleason grade present could predict for disease recurrence, and that the predictive ability was robust to heterogeneity in Gleason grade, and to tumor multifocality. The result was the definition of a 17-gene signature, including 12 cancer-related and five reference genes (Figure 1), which might have clinical utility for choosing men for active surveillance. In a follow-up study involving prostate needle biopsies, we demonstrated that this gene signature also can predict for the presence of adverse pathology as defined by dominant pattern 4 tumor or extraprostatic disease in a series of 167 men who had both needle biopsy and radical prostatectomy at Cleveland Clinic. In another study reported at the 2013 annual meeting of the American Urological Association, collaborators Matthew R. Cooperberg, MD, MPH, and Peter R. Carroll, MD, MPH, of the University of California, San Francisco, validated the ability of this gene signature to predict the presence of adverse pathology from needle biopsies in an independent contemporary cohort of 395 men who were candidates for active surveillance. The validation study demonstrated that use of this signature improves the accurate identification of men with low biologic risk who can confidently choose active surveillance as an initial management strategy. The gene signature also more accurately identifies those with a high risk of adverse pathology in whom immediate therapy is justified. This gene signature is now available commercially, marketed by Genomic Health Inc. as the Oncotype DX Prostate Cancer Assay.

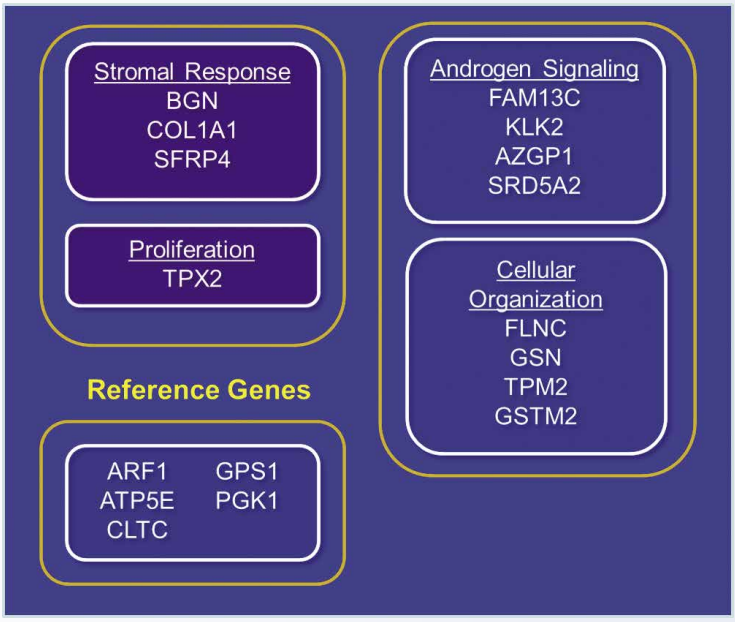


Figure 1. The 17 genes comprising the Genome Prostate Score

Dr. Klein is Chairman of the Glickman Urological & Kidney Institute. He can be reached at kleine@ccf.org or 216.444.5591.

Loss of Cellular Cholesterol Efflux Transporter ABCA1 Is a Determinant in Prostate Cancer Aggressiveness

By Angela H. Ting, PhD

A pressing challenge in the clinical management of prostate cancer is to be able to accurately identify and treat aggressive tumors that will ultimately result in patient death, while at the same time sparing men with indolent cancers the morbidity of radical treatment. Our understanding of the molecular alterations responsible for the dichotomous behavior of prostate cancer is limited. This has hampered effective early risk stratification for appropriate management. Recently, my laboratory identified the cellular cholesterol efflux transporter, ATP-binding cassette, sub-family A, member 1 (ABCA1), as a determinant of prostate cancer aggressiveness through our efforts in mapping the genomic DNA methylation defects in prostate cancers. We demonstrated that reduction in cholesterol efflux, due to the loss of ABCA1, results in aberrant retention of intracellular cholesterol, which, among its many pro-cancer activities, is the substrate for de novo androgen synthesis in castration-resistant prostate cancers. We further determined that 71 percent of aggressive cancers have complete loss of ABCA1. Long-term use of statin, a cholesterol-lowering medication, is linked to decreased risks for aggressive prostate cancer. Our findings suggest that the true efficacy of statin on lethal prostate cancer development should be evaluated in the context of ABCA1 expression.

Dr. Ting is an assistant staff member in the Genomic Medicine Institute and in the Taussig Cancer Institute. She can be reached at tinga@ccf.org or 216.444.0682.

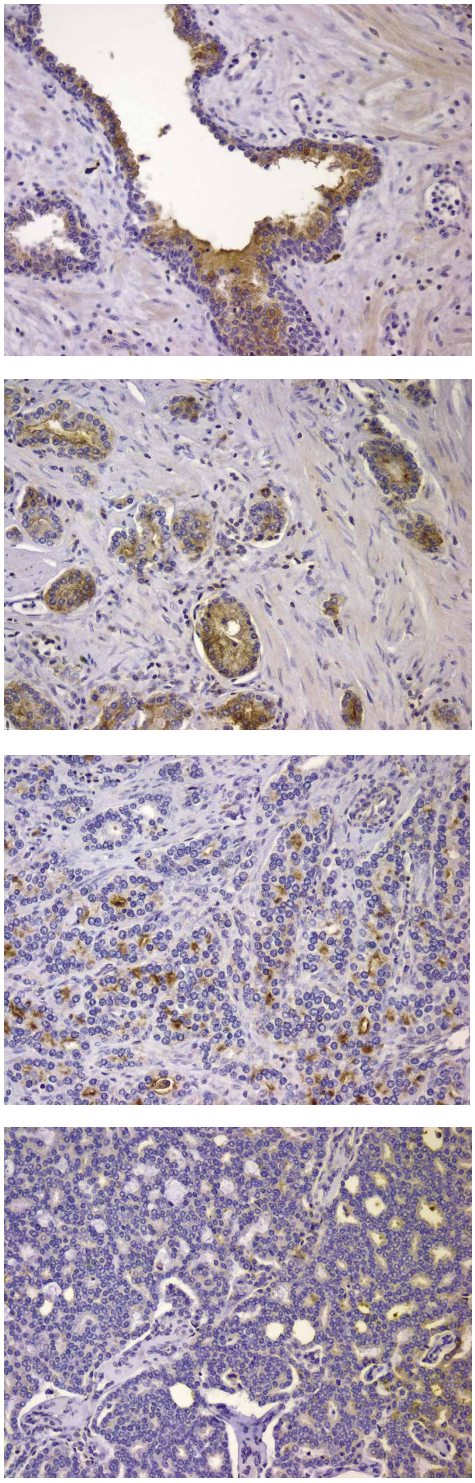


Figure 1. ABCA1 immunohistochemistry on benign prostate, GS 6, GS 7 and GS 8 prostate cancers.

Radiosensitization of Prostate Cancer Cells

By Alex Almasan, PhD

Our laboratory is interested in the response of prostate cancer cells to radiotherapy. The protein poly ADP ribose polymerase (PARP) is involved in repairing damaged cellular DNA. We previously reported on the synergistic response to a potent PARP inhibitor, rucaparib, when it is combined with radiation. Our studies show a synergistic interaction of rucaparib and radiation to treat tumors. Low dose-rate radiation mimicking brachytherapy was more effective than a radiation dose equivalent to that used clinically for conventional radiotherapy. Our data support the effectiveness of PARP inhibition for radiosensitizing prostate cancer cells, particularly those that express the *TMPRSS2-ERG* gene fusion and are *PTEN*-deficient. This finding indicates a potential clinical application for brachytherapy in patients with intermediate- and high-risk prostate cancer. Radiation produces double-strand breaks, repaired predominantly by nonhomologous end-joining (NHEJ). We identified the cellular damage-repairing protein Ku70 as an interacting partner of p18CycE, a Cyclin E fragment. The expression of p18CycE sensitizes human prostate cancer cells to radiation because of ineffective NHEJ. A profound influence of p18CycE on NHEJ was through its interference with DNA-PKcs, the kinase required for effective NHEJ. These studies provide unique mechanistic insights into NHEJ misregulation in tumor cells, in which defects in NHEJ core components are rare. We are now investigating similar effects regarding the inactivation of NHEJ by *TMPRSS2-ERG*, which is expressed in the majority of prostate cancer patients.

Dr. Almasan is a staff member of the Lerner Research Institute's Department of Cancer Biology and of the Taussig Cancer Institute's Department of Radiation Oncology. He can be reached at almasaa@ccf.org or 216.444.9970.

Virus-Drug Therapy for Late-Stage Prostate Cancer

By Robert H. Silverman, PhD

The high toll of lives lost to prostate cancer reflects the lack of an effective therapy for an advanced form of the disease known as castration-resistant prostate cancer (CRPC). Therefore, there is a critical need for innovative and novel approaches for the treatment of CRPC.

In the past year, our laboratory team (including lead author Babal Kant Jha, PhD) has advanced the development of a highly effective therapeutic approach for CRPC and other solid tumors, involving therapeutic infection with an oncolytic virus combined with oral delivery of an FDA-approved drug, sunitinib. Oncolytic viruses infect and replicate in cancer cells, leading to elimination of tumors.

A study published in September 2013 in the peer-reviewed journal *Molecular Therapy* demonstrated that prostate, breast and kidney tumors were eliminated from mice by this novel treatment strategy.

There are genetic changes in the cancer cell that enhance susceptibility to viral infections. The team showed that sunitinib was able to temporarily disable the innate immune response to the virus by blocking two antiviral enzymes present in the cancer cells (called RNase L and PKR), proteins that normally counteract viral infections.

The drug has the added benefit of suppressing the tumor cells' ability to grow their own blood supply, thus starving the tumor and preventing its growth. Sunitinib allowed the virus to spread through and kill the tumor cells while sparing normal cells. A remarkable recovery of the tumor-bearing animals was observed.

Virus therapy is generally considered safe for humans. The virus-drug approach could lead to an effective treatment for a range of advanced and difficult-to-treat forms of cancer. Our research is expected to lead to clinical trials within the next few years.

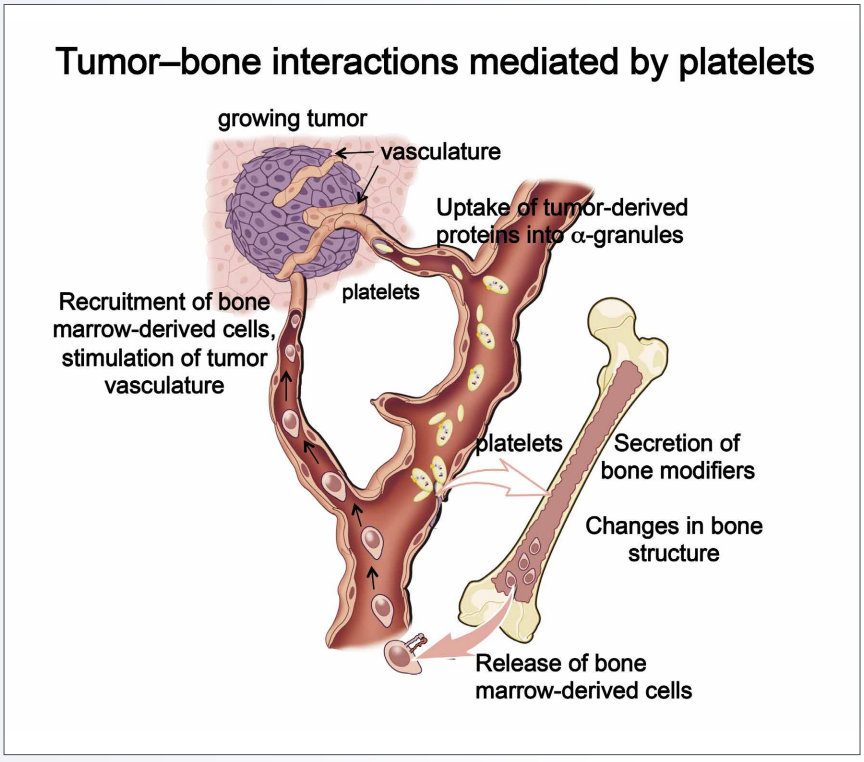
Dr. Silverman holds the Mal and Lea Bank Chair in Cancer Biology in the Lerner Research Institute, where he is a professor in the Department of Cancer Biology. He can be reached at silverr@ccf.org or 216.445.9650.

Circulating Proteins and CD117-Expressing Stem Cells Can Predict Aggressiveness of Prostate Cancer

By Bethany Kerr, PhD, and Tatiana V. Byzova, PhD

The inability to accurately predict which patients are likely to experience future disease recurrence has resulted in the overtreatment and overdiagnosis of clinically insignificant prostate cancer. Our research focuses on finding new markers to identify prostate cancer patients likely to progress to bone metastases. Our previous work focused largely on progenitor cells circulating between primary tumors and metastatic sites in the bone. We found that CD117, a stem cell factor (SCF) receptor, was a possible marker for prostate cancer stem cells in the circulation of patients with advanced prostate cancer. CD117 also correlated with higher tumor stage. After tumor removal, the number of CD117-positive cells in the circulation of patients decreased. Interestingly, in patients who experienced a recurrence of cancer, the number of CD117-positive cells in circulation did not decrease after surgery, indicating that CD117 may also be a marker for prostate cancer recurrence. In a parallel study, we found that protein levels of SCF, which stimulates CD117, were increased in the platelets of patients with advanced prostate cancer. Our ongoing work focuses on SCF and other proteins controlling tumor progression in the platelets of prostate cancer patients. These platelet proteins may be additional markers for diagnosis and prognosis in developing prostate cancer.

Dr. Kerr is project staff in the Lerner Research Institute's Department of Molecular Cardiology. She can be reached at kerrb2@ccf.org or 216.445.8206. Dr. Byzova is Director of the Lerner Research Institute's Angiogenesis Research Center. She can be reached at byzovat@ccf.org or 216.445.4312.



Nima Sharifi, MD, Honored for Cancer Research

Cleveland Clinic medical oncologist and prostate cancer researcher Nima Sharifi, MD, is the winner of the 2014 American Association for Cancer Research (AACR) Award for Outstanding Achievement in Cancer Research.

The award, presented annually since 1979, honors investigators younger than 40 who have made meritorious accomplishments in cancer research. Recipients are chosen by an international panel of cancer experts and by the AACR's executive committee. Dr. Sharifi received the award April 7 at the AACR's annual meeting in San Diego, where he presented the lecture "Androgen Metabolism Drivers in Prostate Cancer: From Mechanism to Therapy."

Dr. Sharifi's research focuses on metabolic and molecular mechanisms of resistance to hormonal therapy in prostate cancer.

Castration-resistant prostate tumors gain their resistance to androgen-deprivation therapy by reactivating the androgen receptor. Tumors accomplish this in large part by acquiring the ability to synthesize their own 5αdihydrotestosterone (DHT) from adrenal precursor steroids.

Dr. Sharifi's research demonstrated the involvement of a previously underappreciated intermediate steroid metabolite — 5αandrostanedione — in prostate tumors' synthesis of DHT. More recently, Dr. Sharifi's lab identified the first example of an enzymatic mutation that increases the conversion of precursor steroids to DHT, permitting tumors to grow in the absence of gonadal testosterone. (For details, see Page 4 in this edition of *Research Notes*.)

As in other cancers, the discovery of a disease-driving mutation in prostate cancer may create opportunities for novel therapies that pharmacologically inhibit these altered enzymes.

In addition to the AACR award, Dr. Sharifi previously received the Howard Hughes Medical Institute Physician-Scientist Early Career Award, the American Cancer Society Research Scholar Award and the Prostate Cancer Foundation Young Investigator Award.

Dr. Sharifi holds the Kendrick Family Endowed Chair for Prostate Cancer Research in Lerner Research Institute's Department of Cancer Biology. He is an associate staff member of the Glickman Urological & Kidney Institute's Department of Urology and of the Taussig Cancer Institute's Department of Solid Tumor Oncology. He received his medical degree from the University of Pittsburgh School of Medicine. He completed his internal medicine residency at Yale-New Haven Hospital and his medical oncology fellowship at the National Cancer Institute.

Upcoming Events – Save These Dates

October 10-11, 2014

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October 24, 2014

Kidney Stones: Medical, Surgical and Dietary Approaches

Course director: Edmund Sabanegh Jr., MD

Research Notes Prostate Cancer Edition

Spring 2014

Research Notes is a publication of Cleveland Clinic's Glickman Urological & Kidney Institute. It is intended to provide highlights of our clinical, translational and basic science research in urology and nephrology. In part because of the groundbreaking research initiatives underway at Cleveland Clinic, both urology and nephrology specialties are ranked No. 2 in the country in 2013-14 by *U.S. News & World Report*.

Research Notes is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

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The Glickman Urological & Kidney Institute is a world leader in treating complex urologic and kidney conditions in adults and children. Our physicians have pioneered medical advances including partial nephrectomy, laparoscopic and robotic urologic surgery, and the bioartificial kidney, while serving tens of thousands of patients annually.

The Glickman Urological & Kidney Institute is one of 27 institutes at Cleveland Clinic, a nonprofit academic medical center ranked among the nation's top hospitals (*U.S. News & World Report*), where more than 3,000 physicians in 120 specialties collaborate to give every patient the best outcome and experience.

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Cleveland Clinic Urology and Nephrology Ranked No. 2 in the U.S. — *U.S. NEWS & WORLD REPORT*

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