SBUR

SOCIETY FOR BASIC UROLOGIC RESEARCH, INC.

2021 Annual Meeting Program Book

November 4–7

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2021 Annual Meeting Program Book

November 4–7

Letter from the President and Program Chair

Welcome, Colleagues and Friends!

Welcome to the Society for Basic Urologic Research (SBUR) 2021 Annual Meeting. While we are not able to meet in person for the SBUR 2021 Fall Meeting, we are incredibly proud to bring together hundreds of SBUR members and non-members to showcase the latest advances in Basic Urology and present the extraordinary work of our specialty despite the COVID-19 pandemic.

The meeting will kick off with the Trainee Affairs Career Symposium on the afternoon of Thursday, November 4th, led by Drs. Daniel Frigo and Tanya Stoyanova. This will be followed with short presentations by the Eula and Donald S. Coffey Innovative Research Coffey Award finalists.

Friday morning will open with the keynote Leland W.K Chung lecture to be delivered by Dr. Padmanee Sharma, followed by six Plenary Sessions over the next two and half days covering the following topics: 1) Emerging Technologies and Models for Urological Research; 2) Endocrine and Genetic Regulations in Urological Biology;

3) Epigenetic Regulations of Urological Development and Diseases: 4) Infection, Inflammation, and Immune Response in Urological Biology; 5) Biomarkers, Environmental Factors, and Health Disparities in Urological Diseases; and 6) Urological Stem Cells, Lineage Plasticity, and Treatment Resistance. This year's American Urological Association (AUA)-sponsored lecture will be given by Dr. Martin Gleave, a clinician-scientist and urologic surgeon whose research focuses on mechanisms driving castration-resistant prostate cancer. In addition, a special highlight is the Panel Discussion on Health Disparities in Urological Diseases (moderated by Dr. Ganesh Raj) which will be presented from the perspective of patient advocates in addition to basic and clinician scientists. Following the Panel Discussion are the SBUR Awards Presentation Ceremony, Annual Business Meeting, and the Poster Hall Social on the evening of Saturday, November 6th.

Finally, we would like to thank the SBUR 2021 Annual Meeting Faculty and the Scientific Program Committee for their invaluable assistance in planning this meeting. We are also indebted to the National Institute of Health (NIH), in particular, the National Cancer Institute (NCI), for their generous support of this program. Furthermore, a special thanks goes to Dr. Li Xin (Chair) and the Abstracts Travel Award Selection (ATAS) committee members and to Dr. X. Sean Li (Chair) and the SBUR Awards Committee members for generously giving their time in reviewing many abstracts and award nominations, respectively.

Thank you for joining us at the SBUR 2021 Annual Meeting. We are excited about hearing novel concepts, cutting-edge research, and new technologies in Urology and anticipate that our discussions (even though they are still virtual this year) will translate to exciting new research opportunities and collaborations.

Enjoy the meeting!

Susan Kasper, PhD
President, SBUR

Jindan Yu, MD, PhD
2021 Scientific Program Chair

SBUR History

The Society for Basic Urologic Research (SBUR) was formed in 1986 and is the pre-eminent US-based urologic research society. Our members include molecular and developmental biologists, oncologists, immunologists, epidemiologists, andrologists, biochemists, bioinformaticians, and clinical urologic surgeonscientists from academia, industry and government. SBUR scientists' expertise includes the study of urologic cancers (prostate, bladder, kidney, testis, penis), the biology of benign diseases of the prostate, bladder and kidney, developmental biology, kidney and bladder function, autoimmune urologic diseases, infectious diseases, neuro-urologic diseases, male reproductive biology, infertility and erectile dysfunction.

SBUR was organized to:

- Provide a forum through the annual meeting for the presentation and discussion of basic, translational, and clinical scientific topics related to urology.
- Promote advocacy and the interests of urologic disease investigators with national funding agencies, industry representatives and academic institutions with regards to urology related research
- Promote collaborations among member scientists and exchange of expertise between clinical and basic scientists
- Develop educational forums concerning scientific advancements related to the field of urology
- Serve as a resource for research information and expertise to clinical urologists through the American Urological Association and Urological societies worldwide.

SBUR is proud to offer our members outstanding scientific meetings in the Spring and Fall each year, and discounts to other meetings. Members are eligible for prestigious awards that include the Young Investigator Award, Eula and Donald S. Coffey Innovative Research Award, Trainee Travel Awards, Distinguished Service and Meritorious Achievement Award. We offer access to our network of experts for mentoring and career advice. Members also receive early access to job and fellowship opportunities.

Members are encouraged to contribute to sustain these important programs. If you wish to learn more or donate, please contact SBUR at (630) 463 -9015 or **sbur@affinity-strategies.com**. SBUR Is granted taxexempt status by the Internal Revenue Service as a Section 501(c)(3) charitable/educational organization. All contributions are tax deductible. Tax ID# 36-3607930.

Meeting Overview

Target Audience

This activity is designed for urologists, pathologists, and medical oncologists with sub-specialization in treatment of patients with genitourinary pathologies.

Learning Objectives

At the completion of this activity, participants should be able to:

- Discuss recent advances in studying the cellular basis of urologic diseases with emphasis on bioengineering, organoid technology, novel animal models, cell-cell communication, immunology, genomics, epigenomics, transcriptomics, proteomics, metabolomics, immunology, and therapeutics.
- Identify critical knowledge gaps and stimulate approaches to address them.
- Disseminate and facilitate novel discoveries in urologic diseases.

Activity Goal

This activity is designed to address the following core and team competencies: *Medical Knowledge, Patient-based Learning, Interpersonal Communication, Professionalism, and Evidence-based Practice*.

Thank You to Our Sponsors!

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We also greatfully acknowlege support from:

The American Urological Association

The National Cancer Institute

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Tanya Stoyanova, Ph.D.

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Tanya Stoyanova, Ph.D.
Allen Gao, Ph.D.
David Degraff, Ph.D.
Dale Bjorling, Ph.D.
Carol Podlasek, Ph.D.
Hari Koul, Ph.D.
Hannelore Hemmers, Ph.D.

2021 Award Winners

Distinguished Service Award

Rosalyn Adam, PhD

I am a cell biologist and biochemist with interests in the molecular basis of urologic disease. I hold the David E. Retik Chair and am Director of Basic Urologic Research at Boston Children's Hospital. I am also Associate Professor of Surgery at Harvard Medical School, having completed postdoctoral training at the same institutions. I received my B.Sc. (Hons) from the University of St. Andrews and my PhD from the University of Southampton, both in the UK. My doctoral work focused on the mechanisms of tumor cell activation by the heparin-binding class of EGF-like growth factors, a theme continued during my postdoctoral training. Research in my laboratory, which has been funded by the NIDDK since 2004, is currently focused on two primary areas: (i) delineation of the molecular mechanisms that underlie urinary tract remodeling and detrusor overactivity following spinal cord injury; and (ii) investigation of novel mechanisms of smooth muscle contractility in hollow organs. In addition to my investigator-initiated funding, I serve as Program Director for the Boston Children's Hospital T32 program "Research Training in Pediatric Urology", funded by the NIDDK. I have served on multiple scientific review panels for the NIH, the Veterans Administration, the Department of Defense and the Canadian Institutes of Health Research. I have been an active member of the AUA since 2003 and the Society for Basic Urologic Research since 2001. I was Member-at-Large for the SBUR from 2010-2012, Secretary from 2013-2017, and will conclude as Immediate Past-President of SBUR in 2021.

Meritorious Achievement Award

Scott Dehm, PhD

Dr. Scott Dehm is Professor and Apogee Enterprises Chair in Cancer Research in the Departments of Laboratory Medicine and Pathology and Urology and the Masonic Cancer Center at the University of Minnesota. His research is focused on understanding how alterations in the genome, transcriptome, and proteome of prostate cancer cells underlie transition of prostate cancer to an advanced, castration-resistant phenotype. Dr. Dehm completed his PhD in 2003 at the Saskatchewan Cancer Agency at the University of Saskatchewan. He conducted postdoctoral training at Mayo Clinic with Dr. Donald Tindall from 2003-2008.

SWIU/SBUR Award for Excellence in Urology Research

Vinata B. Lokeshwar, PhD

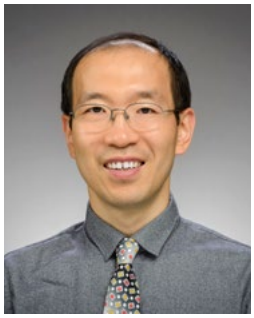
Dr. Vinata Lokeshwar, PhD is a tenured Professor and Chair of the Department of Biochemistry and Molecular Biology, Medical College of Georgia, Augusta University. Throughout her academic career she has collaborated with clinicians, clinical researchers, academic urologists and basic science researchers, within her institution and institutions within the US and abroad. Through these collaborations she has established extramurally funded research programs in urologic cancers and benign diseases. Her current research focus is in the areas of biomarkers and experimental therapeutics. This research has resulted in patented cancer diagnostic tests and novel glycosaminoglycan-based therapeutics. She has chaired and served on International Panels on Bladder Tumor Markers and was the President of the Society for Basic Urologic Research. She has served as a chartered or ad hoc member and have chaired numerous grant review panels for the NIH, Department of Defense and for other national and international agencies. Since she became the department chair five years ago, faculty retention has been > 90%, several received tenure and promotion and also new faculty were recruited. She enjoys didactic teaching to medical and graduate students and has won teaching awards. In her career, she has mentored over fifty-five graduate students, postdoctoral fellows, clinical fellows, urology residents and faculty. Her graduate students have received F30 and F31 graduate fellowship awards and several trainees received international fellowships to work in her laboratory. She has a good mix of trainees choosing either academia or industry for their career paths. While some of those who chose an academic career path have already become Professors and department chairs, the others choosing a career in industry have become project leaders. Research is her passion, as is teaching and mentoring.

2021 Award Winners

Young Investigator Award Recipients

Irfan Asangani, PhD

Research in my group focuses on studying the molecular, genetic, and epigenetic events associated with transcription-driven cancers with the ultimate aim of translating this knowledge into novel therapeutic strategies for treatment. In particular, I am interested in the role of chromatin-associated epigenetic regulator proteins in the context of transcriptionally addicted advanced castration-resistant prostate cancer (CRPC). With more than 50 research articles published in high-impact journals that include papers in Nature, Cancer Discovery, Molecular Cell, Cancer Research, Cell Reports, and greater than 10,000 citations, I have contributed significantly to the field of prostate cancer epigenetics. One of my most significant contributions is discovering therapeutic targeting of BET bromodomain proteins in CRPC, published in Nature 2014. This study led to the initiation of clinical trials with BET inhibitors in treatment-refractory CRPC. In a follow-up paper published in Cell Reports in 2018, my team revealed mechanisms of acquired resistance to BET inhibitors and potential new therapeutic opportunities in refractory disease. Recently, we showed that the AR driven transcriptional addiction in advanced prostate cancer could be targeted by CDK7 inhibition, published in Cancer Discovery in 2019. As cancer cells display an altered chromatin landscape, leading to broad changes in gene expression, I believe gaining insight into the mechanisms of transcriptional regulation will reveal novel approaches and targets for effective cancer therapeutics.



Xin Lu, PhD

Dr. Xin Lu is John M. and Mary Jo Boler Assistant Professor in Department of Biological Sciences at University of Notre Dame and a full member of Indiana University Simon Comprehensive Cancer Center. Dr. Lu received BA in Biology from Tsinghua University in 2004 and PhD in Molecular Biology from Princeton University (mentor: Yibin Kang) in 2010. His postdoctoral research was conducted with Dr. Ronald DePinho at MD Anderson Cancer Center (2011-2016). Dr. Lu's laboratory is focused on identifying cancer cell intrinsic and extrinsic mechanisms of tumor escape of immune surveillance, particularly in metastatic prostate cancer and breast cancer. Recent publications from Lu lab firmly establish that immunosuppressive myeloid cells, especially those of the granulocytic lineage, play the predominant role in inducing the exhaustion of cytotoxic T lymphocytes in the prostate tumor microenvironment. A number of mechanisms and targeting strategies of myeloid-elicited immunosuppression have been reported by the Lu lab, which may open new avenues to sensitize advanced prostate cancer to immune checkpoint blockade therapy. Dr. Lu also investigates therapeutic agents targeting newly identified targets in prostate cancer, breast cancer and rare cancers (e.g. penile squamous cell carcinoma). Dr. Lu's research at Notre Dame is supported by federal and foundation funding agencies, such as NIH/NCI, Department of Defense, Susan G. Komen Foundation, American Institute for Cancer Research, Elsa U. Pardee Foundation, and Mary Kay Foundation.

Coffey Research Finalists

Chengfei Liu, MD, PhD
UC Davis

Justin Hwang, PhD
Department of Medicine,
University of Minnesota-Twin Cities

Sean Li, PhD
Boston Children's Hospital

Jordan Vellky, PhD
University of Illinois at Chicago

Virtual Travel Award Winners

Shih-Bo Huang, PhD
Weill Cornell Medicine
Somatic point mutation in SPOP prevents N-Myc driven cancer progression to NEPC

Lourdes Brea, BD
Northwestern University Feinberg School of Medicine
FOXA1 regulates hypoxia and macrophage infiltration in prostate cancer

Shiv Verma, PhD
Department of Urology, Case Western Reserve University
Androgen deprivation therapy (ADT)-induced pro-inflammatory cytokines linked to cognitive impairment in patients with prostate cancer

Connor Forbes, MD
Vanderbilt University Medical Center
Clinically obstructive benign prostate hyperplasia tissue contains elevated glucocorticoid levels, which can induce prostatic growth

Shiqin Liu, MD, PhD
Stanford University
Shed Trop2 Extracellular Domain is a Regulator of Prostate Cancer Metastasis

Sarah Athans, BS
Roswell Park Comprehensive Cancer Center
STAG2 loss alters chromatin accessibility and invasiveness in MIBC

Mamatha Kakarla, PhD
Northshore University HealthSystem
Racial Differences in Prostate Stromal EphrinB ligands between African American and European American Populations and their role in Prostate Cancer tumorigenicity

Alexis Adrian, BA
University of Wisconsin, Madison
Mitochondrial dysfunction contributes to fibrosis in aging-associated benign prostatic hyperplasia (BPH)

Abstracts for the Virtual Travel Award Winners can be viewed starting on page 19

Distinguished Faculty

A. Lenore Ackerman, MD, PhD
University of California

Adam Murphy, MD, MBA
Northwestern University

Allen Gao, PhD
UC David School of Medicine

Amina Zoubeidi, PhD
University of British Columbia

Benyi Li, MD, PhD
University Of Kansas Medical Ctr

Carolyn Best, PhD
American Urological Association

Christina Jamieson, PhD
UC San Diego Health

Clayton Yates, PhD
Tuskegee University

Cory Abate-Shen, PhD
Columbia University

Daniel Frigo, PhD
University of Texas MD, Anderson Cancer Center

David DeGraff, PhD
Penn State University College of Medicine

Dolores J. Lamb, PhD
Baylor College of Medicine

Douglas Strand, PhD
UT Southwestern Medical Center

Gail Prins, PhD
University of Illinois Chicago

Ganesh Raj, MD, PhD
UT Southwestern Medical Center

Hansen He, PhD
University Health Network

Haojie Huang, PhD
Mayo Clinic Rochester MN

Hari Koul, PhD
Department of Biochemistry and Molecular Biology/ Urology and Stanley S Scott Cancer Center, LSUHSC-New Orleans

Irfan Asangani, PhD
University of Pennsylvania

Isla Garraway, MD, PhD
University of California, Los Angeles

Jan Manarite
CancerABCs

Jelani Zarif, PhD
Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine

Jennifer Anger, MD
Cedars Sinai Medical Center

Jiaoti Huang, PhD
Department of Pathology, Duke University School of Medicine

Jindan Yu, PhD
Northwestern University

Joshi Alumkal, MD

Jung Wook Park, PhD
Duke University

Karen Sfanos, PhD
Johns Hopkins School of Medicine

Kexin Xu, PhD
University of Texas Health Science Center at San Antonio

Kosj Yamoah, MD, PhD

Larisa Nonn, PhD
College of Medicine, University of Illinois At Chicago

Leah Cook, PhD
University of Nebraska Medical Center

Leigh Ellis, MD
Cedars-Sinai Medical Center

Lin Xin, PhD
University of Washington

Maria Hadjifrangiskou, PhD
Vanderbilt University School of Medicine

Martin Gleave, MD
The University of British Columbia

Distinguished Faculty

Mehdi Mollapour, PhD
Suny Upstate Medical University

Michael Freeman, PhD
Cedars-Sinai Medical Center

Michael Crosby
Veterans Prostate Cancer Awareness Inc

Natasha Kyprianou, PhD
Icahn School of Medicine at Mount Sinai

Padmanee Sharma, MD, PhD
MD Anderson Cancer Center

Pavlos Msaouel, MD
MD Anderson Cancer Center

Petros Grivas, MD, PhD
WU Medicine

Ping Mu, PhD
UT Southwestern Medical Center

Praveen Thumbikat, PhD
Northwestern University

Rosalyn Adam, PhD
Boston Children's Hospital & Harvard Medical School

Sarki Abdulkadir, MD, PhD
Northwestern University

Scott Dehm, PhD
University of Minnesota

Shafiq Khan, PhD
Clark Atlanta University

Shuk-Mei Ho, PhD
University of Cincinnati

Stanley Qi, PhD
Stanford University

Susan Kasper, PhD
University of Cincinnati College of Medicine

Tanya Stoyanova, PhD
Stanford University

Tim Ratliff, PhD
Purdue University

Travis Jerde, PhD
Indiana University

Wei-Qiang Gao, PhD
Shanghai Jiao Tong University

Xin Lu, PhD
University of Notre Dame

Yan Dong, PhD
Tulane University School of Medicine

Yuanyuan Zhang, PhD
Wake Forest University

Zhou Wang, PhD
University of Pittsburgh Medical Center

Zongbing You, PhD
Tulane University

SBUR
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2021 Annual Meeting
November 4–7

NOW MEETING VIRTUALLY!

2021 SBUR Fall Meeting Program Committee

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Scott Dehm, PhD, University of Minnesota

Larisa Nonn, Ph.D., University of Illinois at Chicago

Shawn Lupold, Ph.D., John Hopkins University

Li Xin, Ph.D., University of Washington

Daniel Frigo, Ph.D., University of Texas MD Anderson Cancer Center

Susan Kasper, Ph.D., University of Cincinnati College of Medicine

Rosalyn Adam, Ph.D., Boston Children's Hospital & Harvard Medical School

Shu-Yuan Yeh, Ph.D., University of Rochester Medical Center, Department

LaMonica Stewart, Ph.D., Meharry Medical College

Guiting Lin, MD, Ph.D., University of California, San Francisco

Karen S. Sfanos, Ph.D., Johns Hopkins School of Medicine

Adam Murphy, MD, Northwestern University

Will Ricke, Ph.D., University of Wisconsin School of Medicine and Public Health

Program Schedule

All times listed are Central Daylight Time

Thursday, November 4th

2:00–4:30pm	Trainee Affairs Career Symposium	Chairs: Daniel Frigo, PhD and Tanya Stoyanova, PhD
5:00–7:00pm	Coffey Nominee Poster Presentations	Li Xin, PhD and Jindan Yu, PhD

Friday, November 5th

9:00–9:05am	Welcome and Introduction	Susan Kasper, PhD, SBUR President
9:05–9:10am	Tribute to Leland Chung	Michael Freeman, PhD
9:10–10:10am	**Leland W. K. Chung Lecture** Immune Response and Immunotherapy in Urological Diseases	Padmanee Sharma, MD, PhD *MD Anderson, TX*
10:10–10:20am	Leland W. K. Chung Lecture Discussion	Discussion Leaders: Gail Prins, PhD and Jindan Yu, PhD

Friday, November 5th

Plenary Session I: Emerging Technologies and Models for Urological Research		Session Discussion Leaders: Natasha Kyprianou, PhD and Allen Gao, PhD
10:20–10:40am	Genetically Engineered Mouse Models of Urological Cancers	Cory Abate-Shen, PhD *(Columbia University, NY)*
10:40–11:00am	PDX and PDO Models to Study Bone Metastatic Prostate Cancer	Christina Jamieson, PhD *(UCSD, CA)*
11:00–11:20am	Programmable Genome Engineering for Chromosome Diseases and Gene Therapy	Stanley Qi, PhD *(Stanford University, CA)*
11:20–11:30am	Travel Award Presentation #1 Clinically Obstructive Benign Prostate Hyperplasia Tissue Contains Elevated Glucocorticoid Levels, Which Can Induce Prostatic Growth	Connor Forbes, MD
11:30–11:40am	Travel Award Presentation #2 Mitochondrial Dysfunction Contributes To Fibrosis In Aging-Associated Benign Prostatic Hyperplasia (BPH)	Alexis Adrian, BA
11:40am–12:00pm	Plenary Session I Discussion	Natasha Kyprianou, PhD and Allen Gao, PhD
12:00–12:30pm	Lunch Break	

Plenary Session II: Endocrine and Genetic Regulations in Urological Biology		Session Discussion Leaders: Zhou Wang, PhD and Scott Dehm, PhD
12:30–12:50pm	Androgen Signaling, Luminal Epithelial Permeability, and Prostatic Inflamation in Glandular BPH	Zhou Wang, PhD *(University of Pittsburgh, PA)*
12:50–1:10pm	Tumor Suppressor FLCN Mediated Inhibition of Lactate Dehydrogenase-A and Regulation of the Warburg Effect in Kidney Cancer	Mehdi Mollapour, PhD *(Upstate Medical Univ, NY)*
1:10–1:30pm	Androgen Receptor Splice Variants In Prostate Cancer	Yan Dong, PhD *(Tulane University, LA)*
1:30–1:50pm	Understanding and Targeting Therapy-Induced Androgen Receptor Pathway Loss in Prostate Cancer	Joshi Alumkal, MD, *(University of Michigan, MI)*
1:50–2:10pm	Plenary Session II Discussion	Zhou Wang, PhD and Scott Dehm, PhD

Friday, November 5th

Plenary Session III: Epigenetic Regulations of Urological Development and Diseases		Session Discussion Leaders: Amina Zoubeidi, PhD and Jelani Zarif, PhD
2:10–2:30pm	Regulation and Function of the Epigenetic Modulator EZH2 in Kidney Cancer	Haojie Huang, PhD *(Mayo Clinic, MN)*
2:30–2:50pm	Regulation of AR Signaling by NSD2 Histone Methyltransferase in Prostate Cancer	Irfan Asangani, PhD *(University of Pennsylvania, PA)*
2:50–3:10pm	Epigenetics In Chronic Pelvic Pain	Praveen Thumbikat, PhD *(Northwestern, Chicago)*
3:10–3:20pm	Travel Award Presentation #3 Shed Trop2 Extracellular Domain is a Regulator of Prostate Cancer Metastasis	Shiqin Liu, MD, PhD
3:20–3:40pm	Plenary Session III Discussion	Amina Zoubeidi, PhD and Jelani Zarif, PhD
3:40–3:50pm	Break	

Plenary Session III continued: Epigenetic Regulations of Urological Development and Diseases		Session Discussion Leaders: Leigh Ellis, PhD and Benyi Li, MD, PhD
3:50–4:10pm	Regulation of Genomic Integrity by m6A in Prostate Cancer	Kexin Xu, PhD *(UT Health San Antonio, TX)*
4:10–4:30pm	Distinct Genomic And Immune Hallmarks Of Renal Medullary Carcinoma	Pavlos Msaouel *(MD Anderson, TX)*
4:30–4:40pm	Travel Award Presentation #4 STAG2 Loss Alters Chromatin Accessibility And Invasiveness In MIBC	Sarah Athans, BS
4:40–4:50pm	Travel Award Presentation #5 Somatic Point Mutation In SPOP Prevents N-Myc Driven Cancer Progression To NEPC	Shih-Bo Huang, PhD
4:50–5:10pm	Plenary Session III Discussion	Leigh Ellis. PhD and Benyi Li, MD, PhD
5:10–5:25pm	AUA Office of Research: Update on Urologic Research Support Opportunities	Carolyn Best, PhD *(American Urological Association)*
5:25–5:30pm	Discussion	

SBUR
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2021 Annual Meeting
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Saturday, November 6th

Plenary Session IV: Infection, Inflammation, and Immune Response in Urological Biology		Session Discussion Leaders: Shafiq Khan, PhD and Zongbing You, PhD
9:00–9:20am	MYC, Microbes and the Prostate Tumor Immune Microenvironment	Sarki Abdulkadir, MD, PhD *(Northwestern University, IL)*
9:20–9:40am	Infection and Inflammation in Prostate Cancer Initiation	Karen Sfanos, PhD *(Johns Hopkins University, MD)*
9:40–10:00am	Prostate Cancer and Penile Cancer: Similarity in Immunosuppression?	Xin Lu, PhD *(University of Notre Dame, IN)*
10:00–10:10am	Travel Award Presentation #6 FOXA1 Regulates Hypoxia And Macrophage Infiltration In Prostate Cancer	Lourdes Brea, BS
10:10–10:20am	Travel Award Presentation #7 Androgen Deprivation Therapy (ADT)-Induced Pro-Inflammatory Cytokines Linked To Cognitive Impairment In Patients With Prostate Cancer	Shiv Verma, PhD
10:20–10:40am	Plenary Session IV Discussion	Shafiq Khan, PhD and Zongbing You, PhD
10:40–10:50am	Break	

Plenary Session IV continued: Infection, Inflammation, and Immune Response in Urological Biology		Session Discussion Leaders: Douglas Strand, PhD and Travis Jerde, PhD
10:50–11:10am	Host-Microbe Interactions in Lower Urinary Tract Disorders	A. Lenore Ackerman, MD, PhD *(UCLA, LA)*
11:10–11:30am	How Bacteria Co-Opt Respiration During UTI	Maria Hadjifrangiskou, PhD *(Vanderbilt University, TN)*
11:30–11:50am	Tumor Heterogeneity: Implications for Immunotherapy in Bladder Cancer	David DeGraff, PhD *(Penn State University, PA)*
11:50am–12:10am	Immunotherapy in Urothelial Carcinoma	Petros Grivas, MD, PhD *(University of Washington, WA)*
12:10–12:30pm	Plenary Session IV Discussion	Douglas Strand, PhD and Travis Jerde, PhD
12:30–1:00pm	Lunch Break	
1:00–2:00pm	**AUA Lecture** Targeting Adaptive Stress Pathways in Advanced Prostate Cancer	Martin Gleave, MD *(UBC, Canada)*
2:00–2:10pm	Discussion	Discussion Leaders: Hari Koul, PhD and Shuk-Mei Ho, PhD

Saturday, November 6th

Plenary Session V: Biomarkers, Environmental Factors, and Health Disparities in Urological Diseases		Session Discussion Leaders: Hari Koul, PhD and Shuk Mei Ho, PhD
2:10–2:30pm	Regulation of Prostatic Androgen Import by Vitamin D and MEGALIN	Larisa Nonn, PhD *(University of Illinois at Chicago, IL)*
2:30–2:50pm	Clinical Implications of Genomic Classifiers for African American Men with Prostate Cancer	Kosj Yamoah, MD *(Moffitt Cancer Center, FL)*
2:50–3:00pm	Plenary Session V Discussion	Hari Koul, PhD and Shuk-Mei Ho, PhD
3:00–4:00pm	**Panel Discussion** Health Disparity in Urological Diseases	Moderator: Adam Murphy, MD Patient Advocates: Mr. Michael Crosby and Mrs. Jan Manarite Clayton Yates, PhD *(Tuskegee University, AL)* Rosalyn Adam, PhD *(Harvard University, MA)* Jennifer Anger, MD *(Cedars Sinai, CA)*
4:00–4:10pm	Break	
4:10–4:45pm	**SBUR Awards Presentation** • Meritorious Achievement Award • Distinguished Service Award • Young Investigators Awards • Eula and Donald Coffey Innovative Research Award • Travel Awards	
4:45–5:15pm	SBUR Annual Business Meeting	
5:15–7:15pm	Poster Hall Social	

Sunday, November 7th		
Plenary Session VI: **Urological Stem Cells, Lineage Plasticity, and Treatment Resistance**		**Session Discussion Leaders:** **Jiaoti Huang, PhD and Leah Cook, PhD**
9:00–9:20am	Investigation of Bladder Regeneration and Tumorigenesis by Application of Single Cell RNA-seq	Weiqiang Gao, PhD *(International Scholar)*
9:20–9:40am	Defining Cells of Origin and Oncogenic Drivers for Urologic Cancers	Jung Wook Park, PhD *(Duke University, NC)*
9:40–10:00am	Germ Cells And Male Infertility	Dolores J. Lamb, PhD *(Weill Cornell University, NY)*
10:00–10:20am	Human Urine-derived Stem Cells for Urological Applications	Yuanyuan Zhang, PhD *(Wake Forest University, NC)*
10:20–10:40am	Plenary Session VI Discussion	Jiaoti Huang, PhD and Leah Cook, PhD
10:40–10:50am	Break	
Plenary Session VI continued: **Urological Stem Cells, Lineage Plasticity, and Treatment Resistance**		**Session Discussion Leaders:** **Tim Ratliff, PhD and Susan Kasper, PhD**
10:50–11:10am	The cfDNA Methylome Captures Distinction Between Primary and Metastatic Prostate Tumors	Hansen He, PhD *(University of Toronto, Canada)*
11:10–11:30am	A Tale of Two Evasions: Lineage Plasticity and Tumor Heterogenity	Ping Mu, PhD *(UT Southwestern, TX)*
11:30–11:50am	Features of Benign Prostate Stem-Like Cells that May Emerge in Metastasis	Isla Garraway, MD, PhD *(UCLA, CA)*
11:50am–12:00pm	Travel Award Presentation #8 Racial Differences In Prostate Stromal EphrinB Ligands Between African American And European American Populations And Their Role In Prostate Cancer Tumorigenicity	Mamatha Kakarla, PhD
12:00–12:20pm	Plenary Session VI Discussion	Tim Ratliff, PhD and Susan Kasper, PhD
12:20–12:30pm	Closing Remarks	Susan Kasper, PhD, SBUR President

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2021 Travel Awardees – Podium Presentation Abstracts

19 – Androgen deprivation therapy (ADT)-induced pro-inflammatory cytokines linked to cognitive impairment in patients with prostate cancer

Dr Shiv Verma PhD[1], Dr Eswar Shankar PhD[1], Dr Sanjay Gupta PhD[2,3,4]

[1]Department of Urology, Case Western Reserve University, Cleveland, Ohio, USA. [2]The Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA. [3]Department of Urology, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio, USA. [4]Department of Urology, Case Western Reserve University, School of Medicine, Cleveland, Ohio, USA

Abstract

Androgen deprivation therapy (ADT)-induced pro-inflammatory cytokines linked to cognitive impairment in patients with prostate cancer

Background

Androgen deprivation therapy (ADT) is a commonly used clinical treatment for non-metastatic and metastatic hormone-sensitive prostate cancer. Long-term ADT treatment results in adverse side effects in patients including depression, cognitive impairment, and dementia. Studies have reported increased levels of proinflammatory cytokines and inflammatory markers in older cancer patients, however, the relationship between inflammatory biomarkers and the severity of cognition in prostate cancer patients under ADT has not been investigated. We sought to identify peripheral biomarkers that could provide links between the mental changes and major pathological mechanisms responsible for the development of cognition in these patients.

Methods

Gene expression data (GSE69223) of 30 matched malignant and non-malignant prostate tissue samples from 15 prostate cancer patients receiving neoadjuvant antiandrogen therapy before prostatectomy, were compared in parallel with postmortem brain tissue samples of Parkinson's and Alzheimer patients as an additional neurological diagnosis. IPA analysis was performed in the context of known biological responses and regulatory networks. Fisher's exact test for each network was converted to a score of −log10 (p-value). Further validation was performed in BT142-neural cells and M059K-glial cells by qRT-PCR with and without antiandrogen (enzalutamide) treatment.

Results

A total of 1952 DEGs were identified in postmortem brain tissue specimens, and 101 DEGs were identified in prostate cancer patients receiving ADT before surgery. IPA analysis revealed 33 commonly expressed genes with changes in cytokine-cytokine signaling network overlapped in both patient cohorts. Pathway analysis showed that the IL17 signaling pathway, regulation of cytokine production, and changes in T-cell subsets by IL-17A and IL-17F were overrepresented. Furthermore, lipopolysaccharide (LPS), TNF, and toll-like receptors were identified as upstream transcriptional regulators of these signaling pathways. Furthermore, gene expression of pro-inflammatory cytokines viz. LIFR, IL1RN, IL6, IL10, and LIF were increased in both neural and glial cells treated with enzalutamide, compared to non-enzalutamide treated cells.

Conclusion

Our results suggest that changes in cytokine signaling under the influence of ADT in prostate cancer patients may be linked with cognitive impairment presenting new areas for diagnostic and therapeutic development in combating brain deficits.

Acknowledgments

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2021 Travel Awardees – Podium Presentation Abstracts

28 – STAG2 loss alters chromatin accessibility and invasiveness in MIBC

Ms. Sarah Athans BS[1], Ms. Nithya Krishnan MS[1], Dr. Swathi Ramakrishnan PhD[1], Ms. Sofía Lage-Vickers MS[2], Ms. Zara Kazmierczak BS[1], Mr. Eduardo Cortes Gomez MS[1], Dr. Jianmin Wang PhD[1], Dr. Kristopher Attwood PhD[1], Dr. Monika Rak PhD[3], Dr. Ania Woloszynska PhD[1]

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Abstract

Background
STAG2 (Stromal Antigen 2) functions in chromatid cohesion, DNA damage repair and genome organization, but its impact on chromatin and gene regulation in muscle invasive bladder cancer (MIBC) remains unknown. We found that in MIBC STAG2 is frequently mutated, and its loss is associated with better clinical outcomes. This study aims to determine how STAG2 affects chromatin structure and gene transcription to alter cell phenotype and therapy response in MIBC. We hypothesize that STAG2 loss in MIBC slows disease progression by reducing chromatin accessibility and transcription of genes promoting invasion, rendering tumor cells more sensitive to epigenetic drugs.

Methods
To determine effects of STAG2 loss, we used a combination of short hairpin RNA and CRISPR-Cas9 to knock down (KD) or knock out (KO) STAG2 in T24 MIBC cells, respectively. We identified altered chromatin regions using Assay for Transposase-Accessible Chromatin. We determined transcriptomic changes employing RNA-seq to identify STAG2-mediated biological pathways. Utilizing time lapse microscopy and invasion assays we quantitively determined cell movement over time. Finally, we used drug screening to determine if STAG2 loss alters response to an array of anticancer agents including epigenetic and DNA damaging drugs.

Results
STAG2 KD in T24 MIBC cells led to an overall reduction in chromatin accessibility. Since changes in chromatin accessibility can alter gene transcription levels, we investigated if this reduction was associated with transcriptional changes. RNA-seq revealed a downregulation of extracellular matrix (ECM) related gene transcripts. Reduced ECM gene expression corresponded with reduced displacement (78 vs 114 μm, $p<.05$), speed (0.30 vs 0.41 μm/min, $p<.05$) and invasion (137 vs 190 cells/field, $p<.001$) of T24 cells *in vitro*. Screening revealed that combining STAG2 KO with several epigenetic drugs, including histone deacetylase and methyltransferase inhibitors, reduced cell viability up to 19% vs the inhibitors alone.

Conclusion
STAG2 loss alters chromatin accessibility and downregulates ECM gene transcripts, leading to a less invasive phenotype. This may explain how loss of STAG2 can alter cell behavior leading to slower disease progression and positive outcomes in MIBC. The mechanism by which STAG2 alters chromatin, transcription, and invasiveness in MIBC will be dissected by integrating co-immunoprecipitation and chromatin immunoprecipitation results that identify STAG2 binding partners and sites. MIBC patients with known STAG2-null status may benefit from treatment with epigenetic drugs in addition to standard of care.

2021 Travel Awardees – Podium Presentation Abstracts

34 – Clinically obstructive benign prostate hyperplasia tissue contains elevated glucocorticoid levels, which can induce prostatic growth

Dr Connor M Forbes MD[1], Dr Nicole L Miller MD[1], Mr Thomas Case BSc[1], Dr Douglas Strand PhD[2], Dr Qi Liu PhD[1], Ms Marisol Ramirez-Solano MS[1], Dr Justin M Cates MD PhD[1], Dr Ned A Porter PhD[3], Dr Hye-Young H Kim PhD[3], Dr Philip Wages PhD[3], Dr James L Mohler PhD[4], Dr Robert J Matusik PhD[1], Dr Ren Jie Jin PhD[1]

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Abstract

Background

Other than androgens and the androgen receptor, disease-altering pathways in benign prostate hyperplasia (BPH) have not been well established. 5-alpha reductase inhibitors (5ARI) reduce synthesis of the active androgen metabolite dihydrotestosterone. Treatment failure is common, and progression despite medical management is not well understood. We evaluated the glucocorticoid receptor and glucocorticoids in the progression of BPH.

Methods

Tissue was collected from patients with clinically obstructing BPH requiring surgery (S-BPH) and from controls were incidentally harvested benign tissue collected from patients undergoing radical prostatectomy for localized prostate cancer treatment (I-BPH). Steroid levels were compared between groups. Based upon elevated tissue glucocorticoid levels in S-BPH, 3D organoid culture of BPH cell lines (BHPrE1, NHPrE1, RWPE-1 and PZHPV-7) were assessed for branching/budding morphology with and without dexamethasone (Dex), a synthetic glucocorticoid. Bulk RNA sequencing was performed for S-BPH, I-BPH, and cell lines +/- dexamethasone. Upregulated genes which overlapped in S-BPH and branching/budding cell lines were identified.

Results

Higher testosterone levels and lower dihydrotestosterone levels in S-BPH on 5-ARIs confirmed the success of the 5ARI compared to controls. Corticosterone levels were higher in S-BPH patients on 5ARI compared to I-BPH. Branching/budding morphology was induced in all four cell lines in 3D culture with the addition of Dex compared to controls. On RNA-sequencing, there were 3375 genes upregulated in S-BPH (n=30) compared to I-BPH (n=14). There were 368 genes upregulated in the budding/branching cells treated with Dex. Overlapping genes were narrowed further by proximity to YAP1/TEAD/AR adjacent binding sites based on previous research, and a signature of 9 genes was identified and expanded based on biologic principles.

Conclusion

In clinically obstructive BPH refractory to treatment with 5ARI, glucocorticoidslevels in tissue are elevated. 3D organoid culture showed morphologic induction of branching/budding with synthetic glucocorticoids. An RNA signature identifying candidate genes was developed using bulk RNA-sequencing of patient and *in vitro* benign cell lines.

2021 Travel Awardees – Podium Presentation Abstracts

39 – Mitochondrial dysfunction contributes to fibrosis in aging-associated benign prostatic hyperplasia (BPH)

Ms. Alexis Adrian BA[1], Dr. Teresa Liu PhD[1], Ms. Emily Ricke MS[1], Dr. Donald DeFranco PhD[2], Dr. William Ricke PhD[1]
[1]University of Wisconsin, Madison, Madison, WI, USA. [2]University of Pittsburgh, Pittsburgh, PA, USA

Abstract

Background
Benign prostatic hyperplasia (BPH) is characterized by proliferation, smooth muscle changes, and fibrosis of the prostate. The single greatest risk factor for BPH is age, with 90% of men in their eighties impacted. Many men with BPH will develop lower urinary tract symptoms, which reduce their quality of life as disease severity progresses. Given the multifactorial nature of the disease, treatments have thus far been limited. While aging has been clearly linked to BPH, the molecular mechanisms involved with aging have yet to be fully elucidated. In this study, we specifically examine how mitochondrial dysfunction caused by aging may contribute to fibrosis in BPH.

Methods
To evaluate how mitochondrial dysfunction may contribute to fibrosis, we used both *in vivo* and *in vitro* models. We examined the complex I protein, NDUFS3 and a mitophagy associated protein, PINK1, via immunohistochemistry in prostate tissue from young (2 months) and old (24 months) C57Bl/6J mice. Additionally, we quantified collagen using picrosirius red as an indicator of prostatic fibrosis. We also assessed loss of complex I function *in vitro* using complex I inhibitor, rotenone, on prostate stromal cells (BHPrS1) and determined collagen gene expression. Complex I rescue experiments using idebenone, a CoQ10 analog, were also tested.

Results
IHC staining of mouse prostate tissue showed decreased levels of NDUSF3, suggesting a decrease in mitochondrial function, specifically associated with complex I of the electron transport chain. Furthermore, PINK1 was also decreased by IHC, suggesting parkin-dependent mitophagy is reduced. qPCR experiments on the rotenone treated BHPrS1 cells revealed increased gene expression for both *Col1a1* and *Col3a1*, suggesting complex I dysfunction can contribute to increased collagen production, and therefore fibrosis. Furthermore, treatment with idebenone was able to rescue this effect.

Discussion
Collectively, these *in vivo* and *in vitro* data suggest that mitochondrial dysfunction originating from complex I contributes to the production of collagen, hence the promotion of fibrosis and BPH in men. These data provide new molecular mechanisms and therefore therapeutic targets for the treatment of BPH/LUTS. U54DK104310 (WAR) and K01AG059899 (TL)

2021 Travel Awardees – Podium Presentation Abstracts

41 – Racial Differences in Prostate Stromal EphrinB ligands between African American and European American Populations and their role in Prostate Cancer tumorigenicity

Dr Mamatha Kakarla PhD, Dr Sathyavati ChallaSiva Kanaka PhD, Ms Mary F Dufficy B.S., Dr Renee E Vickman PhD, Ms Victoria Gil MS, Dr Susan E Crawford PhD, Dr Simon W Hayward PhD, Dr Omar E Franco MD; PhD
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Abstract

Background
African American (AA) men are at a higher risk of developing and dying from prostate cancer (PCa) compared to European American (EA). Members of the Ephrin family (receptors and ligands) not only regulate a variety of normal biological processes, but are also implicated in cancer. Although there are prominent differences in the tumor microenvironment between AA and EA population, the role of Ephrin ligand (EFN) activation in stromal cells on PCa tumorigenicity is unknown. In this study, we evaluated whether increased EFNB ligands in carcinoma associated fibroblasts (CAF) exert an enhanced pro-tumorigenic microenvironment.

Methods
Expression (mRNA and protein) of Ephrin ligands were assessed in primary prostate fibroblasts of patient samples and compared between two racial (AA vs EA) cohorts. Altered ligand-expressing fibroblasts (benign and CAF) were engineered and their biological effects studied in vitro and in vivo.

Results
Higher expression of Ephrin B1, B2 and B3 (EFNB1, EFNB2 and EFNB3) were found in prostate fibroblasts from peripheral zones (PCa) of AA compared to EA. Overexpression of these ephrin ligands in the benign human prostate stromal cell line (BHPrS1) changed the levels of markers associated with myofibroblast activation (a-SMA, vimentin, TNC) and also increased in vitro cell proliferation of human prostate epithelial cells in a paracrine manner. BHPrS1EFNB1 and BHPrS1EFNB3 significantly increased the tumorigenicity of a premalignant prostate epithelial cell line BPH1 in vivo. Interestingly in the presence of BHPrS1EFNB2, we observed tumor suppressive effects. We also tested the metastatic properties of EA PCa cell lines LnCaP and PC3 and AA PCa cell line MDA Pca 2B in vivo in presence of stromal cells overexpressing the ephrin ligands. Ephrin-B ligands promoted a pro-tumorigenic secretome in BHPrS1 cells, which had various effects on neovascularization, collagen deposition, enhanced inflammation, cancer cell proliferation, and motility, all of which increased PCa tumorigenicity.

Conclusion
Chronic activation of ephrin ligands, especially EFNB1 and EFNB3 in the stroma of prostate cancer have direct implications in tumor progression. Because expression of ephrin ligands shows racial diversity, future research will determine the translational clinical utility in PCa for the AA population.

2021 Travel Awardees – Podium Presentation Abstracts

46 – Somatic point mutation in SPOP prevents N-Myc driven cancer progression to NEPC

Postdoctoral Associate Shih-Bo Huang Ph.D., Instructor Nicholas Brady Ph.D., Research Associate Deli Liu Ph.D., Associate Professor David Rickman Ph.D., Associate Professor Christopher Barbieri M.D., Ph.D.
Weill Cornell Medicine, New York, New York, USA

Abstract

Background
Early-onset somatic point mutations in the E3 ubiquitin ligase SPOP (SPOPmut) drive prostate tumorigenesis through modulating stability of oncogenic proteins including androgen receptor (AR) and its cofactors, thereby resulting in reactivation of AR signaling. Accumulating evidence shows that SPOPmut prostate cancer (PCa) respond favorably to AR targeting therapies. Interestingly, SPOPmut is rarely present in neuroendocrine prostate cancer (NEPC), an AR-indifferent, clinically aggressive subtype of castration-resistant prostate cancer (CRPC) with poor survival rate, while prevalent across other PCa subclasses. A mechanistic understanding accounting for the resistance of SPOPmut PCa cells to progress to NEPC would provide novel insight into this progression and potentially benefit patient care.

Methods
We analyzed the frequency of SPOPmut in two large cohorts of well-characterized tumors from metastatic CRPC and NEPC patients. To assess the impact of SPOPmut on NEPC progression and maintenance, we introduced the $SPOP^{F133V}$ mutation into models of NEPC, including genetically engineered mouse (GEM) models with prostate-specific *Pten/Rb1* loss and human *MYCN* expression (PRN) and patient-derived NEPC organoids. We performed large-scale phenotypic and molecular analyses which included single-cell RNA sequencing (scRNA-seq).

Results
Based on analyses from the clinical cohorts, we found that *SPOP* point mutations were exclusively observed in CRPCAdenocarcinoma, but rare in NEPC patients (SU2C 2019 and Beltran et al 2016). In model systems, our results show that $SPOP^{F133V}$ significantly impaired N-Myc overexpression/Rb1-loss driven growth of GEM-derived prostate organoids. Similarly, subcutaneously injection with $SPOP^{F133V}$-PRN organoids significantly impaired allograft tumor development in nude mice. Intriguingly, scRNA-seq identified that prostates from 6-week-old PRN mice had both luminal (*Ar, Cd24a, Krt8*) and NE (*Ascl1, Chga, Syp, Insm1*) cell populations, while the NE cell population was not present in age-matched $SPOP^{F133V}$-PRN mice. Furthermore, ectopic expression of $SPOP^{F133V}$ reduced mRNA and protein levels of NEPC markers (NKX2-1 and ASCL1) and restored adenocarcinoma markers (NKX3-1 and TMPRSS2) in patient-derived NEPC PM154 cells and organoids.

Conclusion
Our current findings demonstrate that SPOPmut hampers N-Myc overexpression/RB1 loss-driven allograft tumorigenesis, impairs NEPC maintenance, and restores an adenocarcinoma phenotype. Our findings will also lead to the development of critical predictive biomarkers, guiding which CRPC patients should receive additional AR targeting therapy, and which should transition to other forms of treatment and/or develop lethal metastatic PCa.

2021 Travel Awardees – Podium Presentation Abstracts

77 – Shed Trop2 Extracellular Domain is a Regulator of Prostate Cancer Metastasis

Postdoc Shiqin Liu MD, PhD[1], Postdoc En-chi Hsu PhD[1], PhD candidate Merve Aslan MS[2], Postdoc Fernando Garcia Marques PhD[1], Research Scientist Rosalie Nolley N/A[1], Research Scientist Abel Bermudez N/A[1], Professor James Brooks MD[1], Professor Sharon Pitteri PhD[1], Assistant Professor Tanya Stoyanova PhD[1]

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Abstract

Background
Metastasis is the main cause of cancer associated deaths in prostate cancer, highlighting the urgent clinical need to determine the mechanisms underlying cancer progression. Trop2, an oncogenic transmembrane cell surface protein, is highly expressed in metastatic prostate cancer and is a prognostic biomarker for early detection of clinically significant localized prostate cancer. Trop2 is cleaved via A disintegrin and metalloproteinase 17 (ADAM17) resulting in the release of shed Trop2 extracellular domain (TECD) into the extracellular environment. Here, we define the functional role of shed TECD in prostate cancer tumor growth and metastasis, and further identify shed TECD as a potential prognostic liquid biomarker for prostate cancer.

Methods
Shed TECD was determined in prostate cancer cell culture media, serum, and urine of normal vs prostate cancer patients by Western Blot and ELISA. Prostate cancer cell lines (22Rv1, DU145, and PC3) treated with vehicle or TECD were tested in migration, invasion, proliferation, and tumorsphere assays *in vitro*. To determine the effect of TECD on tumor growth *in vivo* , DU145 xenografts bearing mice have been treated with vehicle or TECD and the tumors were measured every five days. To identify the functional role of TECD in metastasis, DU145 and 22Rv1 cell lines were utilized to generate intracardiac injection metastatic model and spontaneous metastasis model. Label-free proteomic profiling was performed on DU145 cells treated with TECD to identify TECD function. The top targets were validated by Western Blot.

Results
Our results demonstrate that shed TECD can be detected in cell culture media, serum, or urine samples from prostate cancer patients compared to cancer free patients. Moreover, treatment with TECD significantly increases cell migration and invasion *in vitro* and *in vivo*, while did not affect prostate cancer cell growth, and tumor growth. Proteomics profiling reveals that TECD modulates a set of proteins associated with invasion and migration.

Conclusion
Our study reveals a new function of TECD in prostate cancer migration and metastasis that is independent from the full-length Trop2. Furthermore, our study suggests that TECD could be potentially used as a liquid biomarker for clinically significant localized and metastatic prostate cancer.

2021 Travel Awardees – Podium Presentation Abstracts

116 – FOXA1 regulates hypoxia and macrophage infiltration in prostate cancer

Graduate Student Lourdes Brea BS, Visiting Scholar Xiaohai Wang MD, PhD, Postdoctoral Fellow Xiaodong Lu PhD, Associate Professor Jonathan Zhao MD, MS, Principal Investigator Jindan Yu MD, PhD
Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Abstract

Background
Androgen-deprivation therapies are the mainstay treatment for metastatic prostate cancer (PCa). Yet, many patients relapse with castration-resistant PCa (CRPC). We have recently shown that FOXA1, an epithelial transcription factor, is downregulated in CRPC. Its loss contributes to aberrant signaling by the androgen receptor (AR) and induces epithelial-mesenchymal transition and cell motility by regulating cytokines such as TGF-β and IL-8. In addition to such tumor-intrinsic factors, hypoxia in the tumor microenvironment has been associated with CRPC. Hypoxia Inducible Factor 1 (HIF-1) is a heterodimeric transcription factor composed of HIF-1 alpha (HIF1A) and HIF-1 beta (HIF1B). Notably, HIF-1 signaling has been shown to promote tumor infiltration by immunosuppressive cells, such as tumor-promoting M2-like macrophages. However, how hypoxia may be regulated by tumor-intrinsic factors is incompletely understood.

Methods
We performed RNA-seq, ChIP-seq, qPCR, western blot, and ELISA analyses to evaluate gene regulation and HIF1A cistrome. We utilized an *in vitro* macrophage infiltration transwell assay, in which M2-like macrophages were added to the upper chamber, and PCa cells were plated in the lower chamber to examine how perturbations to PCa cells affect macrophage migration. Finally, we performed bioinformatic analysis of PCa patient datasets to confirm the clinical relevance of our findings.

Results
By integrating RNA-seq and ChIP-seq data, we showed that FOXA1 proteins bound an intragenic enhancer of the HIF1A gene to repress its expression directly, such that FOXA1 depletion induced HIF1A expression and increased HIF1A occupancy at hypoxia gene loci. We further showed that Monocyte Chemoattractant Protein-1 (MCP-1/CCL2) became upregulated upon FOXA1 depletion in a HIF1A-dependent manner. Moreover, loss of FOXA1 or gain of CCL2 promoted macrophage migration toward PCa cells and increased PCa cell motility, which was abolished by genetic or pharmacological inhibition of the HIF1A-CCL2 axis. In accordance, bioinformatics analysis of human PCa patient datasets demonstrated that FOXA1 level is negatively correlated with CCL2 and macrophage infiltration. Future studies are needed to further elucidate the effects of FOXA1 on tumor hypoxia and metastasis *in vivo* and evaluate its therapeutic targeting in preclinical models.

Conclusion
This study proposes a novel role for FOXA1 loss in promoting hypoxia and macrophage infiltration in PCa and suggests HIF-1 targeting as a promising approach for CRPC treatment.

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