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Poster Submissions**Poster Title**

Cohesin complex subunit (stromal antigen1): Potential molecular determinant of racial disparities in prostate cancer

Authors and their Affiliation**Authors in order**

Navneet Momi - Boston University Medical Center, MA

Charles B Brendler - Northshore University Health System, IL

Ramesh K Wali - Boston University Medical Center, MA

Christopher Weber- University of Chicago, IL

Hemant K Roy- Boston University Medical Center, MA

Please describe the extent of your work in this research

I am the post-doctoral fellow in Dr. Hemant K Roy's lab. This work aims to explore the concept of field carcinogenesis (specialty of Dr. Roy's lab) for the hunt of potential biomarkers that could risk stratify the high risk prostate cancer patients. The human prostate biopsy samples were received from Dr. Brendler and were scored by Dr. Weber and Dr. Wali.

I was involved in the project design, execution of all the experiments and data interpretation. My findings indicate plausible associations of genomic stability gene, cohesion subunit (Stromal antigen1 (SA1), with PCa field carcinogenesis predominantly in Blacks.

Abstract Submission

- [Abstract.docx](#)

Would you like your abstract to be considered for an oral presentation (students and post docs only)?

Yes

PURPOSE: The overarching goal is to determine the molecular cause of racial disparities in Prostate Cancer (PCa) and exploit its clinical implications. **BACKGROUND:** African Americans (AA) have two-thirds higher risk of being diagnosed with PCa with mortality rate twice as high compared to Whites. Evidence supports an earlier transformation to clinically significant PCa in AA. While PCa incidence has declined in the last decade, the racial disparity has not narrowed. Even the improved healthcare, socio-economic/lifestyle factors does not seem to benefit this disparity greatly. Thus, it is evocative that certain biological factors may hold crucial links, therefore necessitating emerging biomarkers for valuable risk stratification. We have recently provided a sensitive/specific optical biomarker as an indicator of field carcinogenesis, segregating patients with indolent vs aggressive PCa. A susceptible genetic background or a field effect is very vital for tumor initiation, allowing accumulation of mutations in neoplastic lesions leading to genomic instability. On these lines, recent studies have demonstrated novel role of cohesion complex genes driving aneuploidy and tumorigenesis. Intriguingly, our investigations in human bio-specimens revealed a consistent downregulation of a putative cohesion complex subunit, Stromal Antigen1 (SA1), in PCa progression. We **hypothesized** that “*SA1 aberrations may serve as an indicator of genomic field carcinogenesis, providing insights into the biological mechanisms for racial disparities in PCa*”. For this, we aimed to characterize SA1 expression in PCa initiation/progression in AA vs Whites, primarily focusing on its relevance with the widely recognized signaling axis in PCa, (pAKT/PI3K), and androgen responsiveness, since both are disproportionately prevalent among AA. **METHODS:** To characterize SA1 levels in PCa field carcinogenesis for AA vs Whites, immunohistochemistry (IHC) for SA1 and PI3K was performed on histologically normal biopsies collected from racially-distinct Gleason6-7 PCa patients undergoing prostatectomy. Further, we investigated by IHC the SA1 expression/sub-cellular localization in PTEN (tumor suppressor gene that negatively regulates AKT/PI3K) PCa transgenic mice model. The findings were corroborated in cell-line models using PCa cells (PC3 and DU145) and prostate epithelial cells (RWPE1) by inhibitor studies (for PI3K(LY-294002), nuclear exportin CRM1(LeptomycinB)) via immunofluorescence/immunoblotting. **RESULTS:** Interestingly, prostate biopsies from AA demonstrated amplified PI3K levels and attenuated SA1 expression with significantly higher cytoplasmic/nuclear ratio compared to Whites, indicating a localization-allied role of SA1. Additionally, SA1 demonstrated altered expression/localization wrt PTEN milieu: nuclear in benign prostatic tissues of PTEN^{+/+} mice, whereas relatively less and predominantly cytoplasmic in tumor tissues of PTEN^{-/-} mice. Further, PC3 and DU145 PCa cells demonstrated lesser overall SA1 expression with cytoplasmic co-localization with CRM1, whereas in RWPE1 cells SA1 was localized to the nucleus/nuclear membrane. The mechanistic substantiation by antagonist studies revealed significant blocking (~2fold) of CRM1-mediated nuclear-cytoplasmic SA1 shuttling in PC3 cells with LY+LeptomycinB treatment. Moreover, by transiently downregulating SA1, substantial induction of androgen receptor (AR) was noted in AR-negative PC3 cells. **CONCLUSIONS:** Overall, our studies provide a greater role of pAKT/PI3K/PTEN and CRM1 in SA1 mislocalization, facilitating PCa field carcinogenesis, with potential implications in PCa aggressiveness and therapeutic resistance, the two major aspects of poor clinical outcome in AA patients. Our findings may lead to the discovery of novel biomarkers to identify high-risk AA men potentially providing “druggable” targets.