

Low-PSA Expressing High Risk Prostate cancer: Clinical Significance and Molecular Characterization

Nabila Zaman^{1,2,4}, Adriana M. Pedraza¹, Sarah Ann King^{1,2,4}, Prathiksha Prabhakaraalva^{1,2,4}, Neeraja Tillu¹, Natasha Kyprianou^{1,2,4}, Edgar Ernesto Gonzalez Kozlova^{3,4}, Ashutosh K. Tewari^{1,4}, **Goutam Chakraborty**^{1,2,4}.

1. Department Of Urology, Icahn School of Medicine at Mount Sinai, New York, NY
2. Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY
3. Department of Immunology and Immunotherapy, Icahn School of Medicine at Mount Sinai, New York, NY
4. Mount Sinai Tisch Cancer Center, Icahn School of Medicine at Mount Sinai, New York, NY

Background: A significant subset of patients diagnosed with localized Androgen Pathway Modulation Naïve (APMN) prostate cancer (PCa) presents with clinically high-risk tumors yet paradoxically exhibits remarkably low levels of prostate-specific antigen (PSA) at diagnosis. Emerging clinical observations suggest that these tumors are linked to poor therapeutic outcomes and often demonstrate limited responsiveness to hormone therapy. This contradiction—aggressive disease coexisting with extremely low-PSA levels—points to the existence of a biologically distinct and underexplored subtype of lethal PCa. However, the molecular determinants that define this phenotype remain inadequately characterized, and no specialized therapeutic strategies have been developed for this patient population. Consequently, there is an urgent need for a systematic investigation into the biological mechanisms and therapeutic vulnerabilities of low-PSA PCa.

Methodology: To address this knowledge gap, we conducted a comprehensive pathological evaluation of over 3,600 radical prostatectomy specimens from the Mount Sinai cohort, along with transcriptomic analyses of more than 350 high-grade tumors from TCGA. To characterize the intra-tumoral heterogeneity of PSA/KLK3 expression and its association with distinct signaling networks, we performed single-cell RNA sequencing on fresh needle biopsies from two localized and two metastatic hormone-naïve PCa patients using publicly available datasets. Additionally, we established naturally occurring low-PSA LNCaP cell clones to experimentally model these clinical observations.

Results: We identified a consistent pattern: tumors exhibiting extremely low PSA expression, characterized by either low serum PSA levels or reduced KLK3 mRNA expression—including single-cell clones with low KLK3 expression—harbor multiple high-risk molecular features. These features include enhanced invasive capacity, accelerated disease progression, increased lineage plasticity, elevated genomic instability, and extensive immune remodeling, all characteristics typically associated with metastatic and lethal PCa. Functional characterization of LNCaP low-PSA clones demonstrated de novo cellular plasticity, impaired DNA damage repair capacity, and markedly increased invasive potential, thereby validating our clinical observations in an experimental context. Importantly, integrative proteomic and transcriptional analyses revealed extensive reconfiguration of the androgen receptor (AR) cistrome in low-PSA cells. This remodeling may facilitate a mesenchymal-basal lineage state that is distinct from neuroendocrine differentiation, underscoring a unique and previously unrecognized biological identity for this aggressive subtype of PCa.

Conclusion: Clinically aggressive localized PCa with extremely low PSA expression is recognized in urologic practice; however, its biology and therapeutic vulnerabilities remain largely undefined. We establish a strong link between low PSA expression, lineage plasticity, genomic instability, and immune remodeling—hallmarks of aggressive and metastatic PCa. Considering various clinical evidence alongside our observations, we propose that the aggressiveness pattern of high-risk APMN PCa follows a U-shaped progression. In this model, both low-PSA and high-PSA tumors drive aggressive disease through distinct biological mechanisms that are not acknowledged by current clinical PCa guidelines, resulting in a lack of appropriate therapeutic and management strategies.

Conflicts of Interest Disclosure Statement: No Conflict

Funding: This research is supported in part by National institute of Health, R01CA274967 to G. Chakraborty. G. Chakraborty also awarded by Prostate Cancer Foundation Young Investigator Award (Class of 2019).