The Transcriptional and Functional Landscape of N^6-Methyladenosine in Localized Primary Prostate Cancer

Xin Xu[1], Helen Zhu[1,2], Rupert Hugh-White[3], Julie Livingstone[3], Stefan Eng[3], Paul C. Boutros[2,3], Hansen He[1,2]
[1]Princess Margaret Cancer Center; [2]University of Toronto; [3]University of California

Background: Cancer progression involves intricate genomic dysregulation, with emerging evidence pointing towards the role of epitranscriptomic modifications such as N^6-methyladenosine (m^6A) in driving tumor initiation and progression. Understanding the landscape of m6A modifications in specific cancer types, such as prostate adenocarcinoma, offers insights into underlying molecular mechanisms and potential therapeutic targets.

Methods:
We profiled 162 localized prostate tumors by using m^6A antibody based methylated RNA Immunoprecipitation Sequencing (MeRIP-Seq). Comprehensive analysis was done to characterize the m^6A landscape of prostate cancer with matched multi-modal DNA, RNA and protein profiling.

Results:
Our study reveals diverse m^6A abundances across tumors and intricate germline-somatic interactions regulating m^6A patterns. These patterns were closely associated with prognostic clinical features, establishing the biomarker potential of m^6A modifications. Furthermore, we observed widespread dysregulation of m^6A profiles under tumor hypoxia conditions, bridging genomic and proteomic observations. Importantly, specific m^6A sites within key genes like *VCAN* were linked to disease aggressiveness, highlighting their functional significance in prostate cancer progression.

Conclusions:
Our findings underscore the multifaceted role of m^6A dysregulation in prostate cancer, implicating germline risk, microenvironmental factors, somatic mutations, and metastasis. The identification of specific m^6A modifications driving disease aggression suggests potential targets for therapeutic intervention. Overall, elucidating the role of m^6A modifications enhances our understanding of prostate cancer biology and may pave the way for personalized treatment strategies.

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Conflicts of Interest:
For a portion of the time during the preparation of this manuscript, H.Z. was an employee at Deep Genomics Inc.. All contributions to the design, analysis and interpretation of results of this project were completed outside of the term of employment. P.C.B. sits on the Scientific Advisory Boards of Sage Bionetworks, Intersect Diagnostics Inc. and BioSymetrics Inc.