Identification and characterization of PLUTO-201, a novel lncRNA associated with prostate cancer metastasis

Haolong Li,[1*] Noah Younger,[1,2*] Jin Shin,[1] Bhavna Malik,[3] Chao Zhang,[4] Yashar Niknafs,[4] Shuang Zhao,[3] Kari Wilder-Romans,[3] Sethuramasundaraman Pitchiaya,[4] Sumin Han,[3] Travis Barnard,[1] Paul Lloyd,[1] Meng Zhang,[1] Lisa Chesner,[1] Emily Egusa,[1] Jonathan Chou,[1,2] Rajdeep Das,[1] Vishal Kothari,[1] Rohit Malik,[4] Alma Burlingame,[5] Arul Chinnaiyan,[4,6,7] Hui Li,[1] Felix Feng.[1,8]

[1]Dept of Radiation Oncology, UCSF. [2]Dept of Hematology/Oncology, UCSF. [3]Dept of Radiation Oncology, University of Michigan. [4]Center for Translational Pathology, University of Michigan. [5]Dept of Pharmaceutical Chemistry, UCSF. [6]Howard Hughes Medical Institute. [7]Dept of Cellular and Molecular Biology, University of Michigan. [8]Dept of Urology, UCSF.

Background

Prostate cancer is the most common non-cutaneous malignancy in men, accounting for approximately 268,000 cases and 35,000 deaths in the United States each year. This disease is a heterogeneous entity with a wide spectrum of clinical behaviors and outcomes - while a majority of men will be cured of early-stage prostate cancer, approximately 20% will develop metastatic disease, which is incurable and ultimately fatal. Despite extensive investigation, the factors promoting aggressive prostate cancer are incompletely understood.

Long non-coding RNAs (lncRNAs) are RNA transcripts of over 200 nucleotides that are not transcribed into proteins, but by virtue of base pair interactions and unique tertiary structure can form specific RNA-RNA, RNA-DNA, and RNA-protein interactions that are important for biology and disease. The vast majority of the estimated 58,648 lncRNAs have only been annotated in the past decade, and remain poorly understood.

Methods

We sought to identify lncRNAs associated with poor prognosis using high-density microarray data from a cohort of 1564 patients with a history of localized PCa treated with prostatectomy who then underwent long-term follow-up. Further investigation characterized the function of our top hit both *in vitro* and *in* vivo.

Results

This analysis identified the novel lncRNA PLUTO-201 as more strongly associated with metastatic progression than any other protein-coding or non-coding gene. We find that manipulation of PLUTO-201 expression levels in prostate cancer cell lines modulates proliferation rates and markers of aggressive phenotype both *in vitro* and *in vivo*. We also find that PLUTO-201 localizes to the nucleus and regulates transcription of multiple genes including those responsible for steroid biosynthesis and the MHC class 1 complex, driving increased growth in androgen-depleted conditions and decreased susceptibility to T cell-mediated cytotoxicity. Finally, we demonstrate direct binding between PLUTO-201 and hnRNPK, and show that hnRNPK is a critical mediator of PLUTO-201 activity.

Conclusions

Overall, our findings nominate PLUTO-201 as a driver of aggressive prostate cancer phenotypes and poor clinical outcomes and suggest possible mechanisms accounting for this activity. We anticipate that these findings will lead to development of a prognostic biomarker based on PLUTO-201 expression, as well as new therapeutic approaches.

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