Investigating the Role of The Long Noncoding RNA SChLAP1-AS in Prostate Cancer Progression

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Background: Our group has previously shown, in unbiased high-throughput analyses, that overexpression of certain long non-coding RNAs (lncRNAs) are more strongly associated with metastatic progression than the top prognostic protein-coding genes. Our research team previously applied in silico approaches to 7,256 RNA sequencing libraries from tumors, normal tissues, and cell lines from 25 independent studies, and identified 58,648 lncRNAs, of which 48,952 (79%) were novel and previously unreported. We subsequently assessed the prognostic significance of these lncRNAs using gene expression data generated from applying high-density microarrays on a cohort of 1564 PCa patients treated with prostatectomy with long-term follow-up. This analysis nominated a novel lncRNA SChLAP1-AS (Second Chromosome Locus Associated with Prostate-1 Antisense Strand) as being more strongly associated with metastatic progression, in this cohort, than any other assessed protein-coding or non-coding gene.
Methods: Rapid Amplification of cDNA Ends (RACE) was used to define SChLAP1-AS gene structure, and Fluorescence In-Situ Hybridization (FISH) was used to study the cellular localization of SChLAP1-AS transcripts. Knockdown and over-expression studies were performed to characterize the oncogenic functions of SChLAP1-AS. Gene set enrichment analysis (GSEA) was performed to identify classes of genes associated with this lncRNA. Protein pulldown experiments were performed to identify its binding partners. We also investigated the role of this lncRNA in prostate tumorigenesis by generating transgenic mouse models. Moreover, we designed and constructed locked nucleic acid antisense oligos to specifically target SChLAP1-AS.
Results: SChLAP1-AS was the top gene that associated with metastatic progression of PCa in our analysis. Knockdown of SChLAP1-AS significantly inhibited the proliferation and invasion of PCa cells. Conversely, SChLAP1-AS over-expression increases the invasion potential of prostate epithelial cell lines. The top two proteins binding to SChLAP1-AS are identified as Heterogeneous nuclear ribonucleoprotein K (hnRNPK) and Polypyrimidine tract-binding protein 1 (PTBP1). High hnRNPK expression is associated with poor metastasis free survival, suggesting hnRNPK may be further explored as a potential biomarker for prostate cancer survival. Based on PCR genotyping, we also have successfully confirmed the knock-in of SChLAP1-AS and PbCre in transgenic mice.
Conclusions: We have identified a novel, prostate-specific lncRNA (SChLAP1-AS) that promotes PCa proliferation and metastasis, and is associated with poor clinical prognosis. We have identified its protein binding partners and established a transgenic mouse model. We are on the way to elucidate the mechanisms of action of this lncRNA.

Conflict of Interest: FYF is a co-founder of and has ownership interests (including patents) at PFS Genomics, is a consultant/advisory board member for Bayer, Blue Earth Diagnostics, Celgene, Clovis, Janssen, EMD Serono, Sanofi, Dendreon, Ferring, Astellas, and Reflexion, and reports receiving commercial research grants from Zenith and Amgen.

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