Long non coding RNAs: potential biomarker and therapeutic target in prostate cancer

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Background: Sequencing of the human genome has revealed a myriad of insights into the complexities of transcriptional program and has shed light on regulatory role of the non-coding transcriptome beyond the speculated “transcriptional noise” (1). Intriguingly these RNA entities have direct influence on the coding transcriptome and biologic homeostasis (2). In recent years our laboratory has explored the role of these in prostate cancer. Of the several upstream regulators of non-coding genome, nuclear receptors are receiving greater attention, primarily due to tissue specific expression and influence on transcriptional programs. A recent report from our laboratory demonstrated that Estrogen receptor alpha (ERα) contributes to development of prostate cancer although the molecular mechanism was elusive. We hypothesized an alternate-nuclear receptor signaling and transcriptional role for ERα in prostate cancer and evaluated functional consequence of ERα signaling in PCa.

Methods: By integrating ChIP and RNA-sequencing pipelines, we analyzed estrogen receptor binding and influence on the prostate cancer coding and non-coding trancriptome. In-silico targets were experimentally validated in a panel of cell lines, tumor microarray and pre-clinical animal models.

Results: We found that ERα specifically regulates a subset of non-coding transcriptome in prostate cancer and nominated NEAT1 long non-coding RNA (lncRNA) as a downstream

mediator of ERα signaling. ERα-NEAT1 axis was refractile to androgen receptor (AR) or AR antagonists. NEAT1 promoted prostate tumorigenesis by generating an epigenetic “on” state of downstream prostate cancer specific signature genes. NEAT1 expression positively correlated with PSMA in prostate adenocarcinoma and with B3GAT1 in neuroendocrine prostate cancer. Using NEAT1 long non-coding RNA as a prototype we have explored the possibility of using long-noncoding RNA as a marker for cancer progression. Analysis of a large clinical cohort suggested that NEAT1 is a novel prognostic biomarker of clinically aggressive disease. NEAT1 overexpression is also potentially a predictive biomarker of patients with advanced prostate cancer who might benefit from co-targeting ERα and AR.

Conclusion: Our studies revealed that cancer cells hijack specific groups of long non-coding RNA for cellular adaptations that favor growth, proliferation and therapy resistance. We observed that several of the long non-coding RNA responds to cellular cues and ligand signaling in a manner reminiscent of the coding transcriptome.

Cancer evolution: The preference of an ERα-NEAT1 axis represents an example of positive selection of alternate nuclear receptor signaling in prostate cancer cells to maintain cancer favourable transcriptome that was refractile to anti-androgens. We believe that NEAT1 is directly involved in modulation of the phenotype of advanced disease and combinatorial targeting of NEAT1 and AR represents a unique therapeutic regimen within a subset of patients with advanced prostate cancer. In summary our studies open up several new avenues to explore possibility to use long-noncoding RNA as markers for disease progression.

Funding: NCI U01 CA111275 (MAR), Prostate Cancer Foundation Young Investigator award (DC)

Resources:

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