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Platinum Priority – Editorial

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"Lincing" the Y Chromosome to Prostate Cancer: *TTTY15* Takes Center Stage

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The role of the Y chromosome in cancer biology has been the subject of numerous musings over the decades. Since only half of the population harbors a Y chromosome, and that half only has a single chromosomal copy, modulation of the Y chromosome in genetic males with cancer should be comparatively easy, as fewer genomic events would result in alteration of function compared to other chromosomes. Prostate cancer, with its androgen-driven biology in a male-specific organ, would seem to be a logical disease for Y chromosome modulation.

However, the precise relationship of the Y chromosome to prostate cancer has been complex. Do individuals with mosaic loss of the Y chromosome (XY/XO) have higher prostate cancer risk? Not really [1]. Do certain haplotypes in the Y chromosome identify high-risk populations for prostate cancer? Again, probably not [2].

Nevertheless, cytogenetic studies of prostate cancer patients have demonstrated frequent cancer-specific loss of the Y chromosome [3,4], although there is some heterogeneity in which parts of the chromosome are lost or retained [4]. Loss of one gene, *KDM5D*, is associated with inferior outcomes for patients with metastatic disease through activation of the androgen receptor and consequent docetaxel resistance [5]. At the same time, many Y chromosome genes are expressed in prostate cancer cells [6], suggesting that the chromosome is not simply subjected to loss-of-function events.

In this issue of *European Urology*, Xiao and colleagues [7] add an additional layer of complexity to the Y chromosome: long noncoding RNAs. With only approximately 78 known protein-coding genes, most of which have a homolog on the X chromosome [8], the Y chromosome has been considered "gene-poor". However, Xiao and colleagues identified a wealth of noncoding RNA expression on this chromosome. Using a set of 65 matched prostate cancer and adjacent normal tissues, the authors observed frequent upregulation of multiple noncoding RNAs, most prominently *TTTY15*.

TTTY15 is a known noncoding RNA of unclear function, although a role as a biomarker has been suggested [9]. Xiao and colleagues delved deeply into the biology of this transcript. Using CRISPR/Cas9 technologies, they demonstrated that genomic loss of *TTTY15* prevented prostate cell growth both in vitro and in murine xenograft models, as well as cell migration in vitro. Ectopic overexpression of *TTTY15* with lentiviral vectors increased cancer cell phenotypes and was able to rescue the phenotype of *TTTY15* genomic knockout.

Next, the authors probed *TTTY15* function. The authors hypothesized that as a cytoplasmic RNA, *TTTY15* may interfere with microRNA function through hybridization to microRNAs with homologous sequences, a phenomenon termed "sponging". Indeed, they identified the let-7 family of microRNAs, which are well established as a family of tumor suppressor microRNAs that directly bind and downregulate the mRNAs for RAS genes, *HMGA2*, and several cell-cycle genes including *CDK6*. They found that *TTTY15* antagonizes let-7 function, and that genomic knockout of *TTTY15* facilitates let-7-mediated gene regulation, specifically confirming regulatory effects on *CDK6* and *FN1*.

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Lastly, the authors searched the *TTTY15* locus for regulatory elements and discovered that the androgen receptor transactivator *FOXA1* has a binding motif in the *TTTY15* promoter. Xiao and colleagues showed that *FOXA1* binds the *TTTY15* promoter in cell culture models, and in human tissue samples expression of *FOXA1* and *TTTY15* are tightly correlated. The authors propose a model in which *FOXA1* transcriptionally activates *TTTY15* through direct promoter binding, and *TTTY15* facilitates prostate cancer biology via sponging of let-7 and de-repression of let-7 target genes such as *CDK6*.

These findings offer an interesting and meaningful advance in our knowledge about the Y chromosome in prostate cancer. Xiao and colleagues used numerous experimental methods to show a convincing and consistent effect of *TTTY15* on prostate cancer cell phenotypes. However, many unresolved questions remain, including the mechanisms of recruitment of *FOXA1* to *TTTY15* and whether differences exist between castrate-resistant states and naïve prostate cancers, among many others.

Perhaps most intriguingly, the findings reported by Xiao and colleagues harken to an aspect of fundamental human genetics. *TTTY15* is located in the *AZFa* region of the Y chromosome [10]. This region is well defined in male fertility, and its deletion causes azoospermia [8]. There are just two protein-coding genes in this region, *USP9Y* and *DDX3Y*. *TTTY15* is located just adjacent to *USP9Y* and both are located on the same genomic strand, which leads to the obvious question of whether *TTTY15* and *USP9Y* have a functional relationship, and whether *TTTY15* might also have a role in male fertility. These should be questions for future work, as the findings by Xiao and colleagues suggest that *TTTY15* may have a far broader role in physiology in the cancer context and perhaps outside that context as well.

Conflicts of interest: John R. Prensner is co-inventor on a patent for the detection of noncoding RNA biomarkers in prostate cancer and receives royalties from GenomeDx Biosciences for the licensing of that patent. Felix Y. Feng has nothing to disclose.

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