Emerging molecular pathways and targets in neuroendocrine prostate cancer

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Abstract: Small cell prostate cancer remains a poorly understood, aggressive form of prostate cancer that develops either de novo or in the setting of castrate resistant adenocarcinoma of the prostate. Frequently these tumors are advanced and are challenging to treat using current modalities. Research into molecular abnormalities that drive the development and propagation of small cell prostate cancer is ongoing and has the potential to revolutionize the management of these patients. Current research into the role of N-myc (NMYC) is altering our understanding of this aggressive disease. A recent study demonstrated that NMYC over expression can lead to development of invasive and androgen castrate resistant small cell prostate cancer. Furthermore, this research went on to show that NMYC over expression can lead to transformation of prostate adenocarcinoma into small cell prostate cancer. Finally, recent research has explored the role of aurora kinase A (AURKA) inhibitors in disrupting the NMYC pathway and providing a potential therapeutic target for treatment of small cell prostate cancer. As research continues to advance our understanding of the molecular underpinnings of small cell prostate cancer, we will be able to develop novel therapeutic targets and agents in order to better treat this aggressive form of prostate cancer.

Keywords: Prostate; neuroendocrine prostate cancer; molecular genetics; N-myc (NMYC); small cell prostate cancer; molecular pathway/targets; precision medicine

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Introduction

Small cell prostate cancer remains a poorly understood, aggressive form of prostate cancer that comprises less than 2% of prostate cancer diagnoses (1-6). Small cell prostate cancer remains a histological diagnosis and develops either de novo in patients with no prior history of prostate adenocarcinoma or, more commonly, in the setting of a patient with castrate resistant prostate cancer (Figure 1). The molecular underpinnings that determine which patients develop small cell prostate cancer in the de novo or castrate-resistant setting are not well defined although significant research is ongoing.

Mutations

Among the genetic mutations most commonly described in small cell prostate cancer, p53 and TMPRSS2-ERG are most common (1-6). TMPRSS2-ERG rearrangements are present in approximately half of small cell prostate cancer cases and are of particular value as they are not seen in other forms of small cell carcinomas (1-6). Interestingly, recent research has reported that TMPRSS2-ERG rearrangements can be associated with androgen receptor upregulation which may be associated with disease progression (7-10). Aurora kinase A (AURKA) and N-myc (NMYC) mutations are more commonly reported.
in small cell prostate cancer than in traditional prostatic adenocarcinoma, with a recent study reporting that 40% of small cell prostate cancer cases compared with 5% of prostatic adenocarcinoma had associated AURKA and NMYC overexpression (11). Further studies have suggested that up to 65% of small cell prostate cancer specimens and 86% of metastatic small cell prostate cancer specimens have AURKA amplification (12).

A recent article by Lee et al. provided the first preclinical study demonstrating the role that overexpression of NMYC maintains in the development of small cell prostate cancer (13). In this study the researchers examined human epithelial prostate cancer cells—a first as prior studies have almost exclusively studied xenografts. The researchers isolated benign prostate tissue from prostatectomy specimens and enforced expression of NMYC with eventual development of both adenocarcinoma and small cell prostate cancer in the previously benign prostate tissue. They further demonstrated that the tumors generated by NMYC over expression were both invasive and lacking androgen receptor expression, rendering the tumor castrate resistant (13).

**Development**

Multiple theories for the development of small cell prostate cancer exist. Many argue in favor of a divergent clonal evolution in which small cell prostate cancer develops from castrate resistant prostatic adenocarcinoma through epigenetic changes associated with cell plasticity and androgen receptor signaling (14). Alternatively, researchers have suggested that small cell prostate cancer represents dedifferentiation of adenocarcinoma, which is supported by the common finding of concomitant small cell prostate cancer with prostatic adenocarcinoma (15-17). Finally, research has suggested that the basal progenitor cells of the prostate may give rise to both traditional prostatic adenocarcinoma and the neuroendocrine cells observed in small cell prostate cancer (17-20).

In their recent study, Lee et al. report that the progenitor cells for adenocarcinoma in the prostate were able to transform into small cell prostate cancer when there was overexpression of NMYC, which supports the theory of a common basal progenitor cell (13). Furthermore, they report that increased expression of the malignant cells in the setting of castrate resistance results in further propagation of the small cell prostate cancer as opposed to adenocarcinoma (13). They propose that NMYC overexpression may enable stem cell progenitors to repopulate prostatic based tumors after treatment. Significant research is still required to fully understand the mechanisms underlying the development of small cell prostate cancer.

**Therapeutics**

While understanding the pathogenesis of small cell prostate cancer remains a critical area of research, the true benefit in determining its molecular underpinnings lies in the ability to identify molecular targets upon which medications can intervene and therapeutics can be designed. The recent study by Lee et al. is therefore a significant step forward as it demonstrated that NMYC is essential in maintaining the tumor through the AURKA pathway. With this in mind, the rationale behind AURKA inhibitors as therapeutic targets is strengthened. Using CD532, a novel therapeutic that interferes with the AURKA-NMYC complex (21), Lee et al. were able to demonstrate a significant decrease in NMYC activity in human prostate epithelial cells (13). This provides evidence that the AURKA and NMYC pathways...
may be excellent targets in the treatment of patients with NMYC overexpression small cell prostate cancer.

Prior therapeutic interventions for small cell prostate cancer have been directed by treatments for small cell cancer of the lung. Traditionally this includes cisplatin and etoposide. A study evaluating the role of docetaxel failed to demonstrate a benefit beyond that provided by cisplatin and etoposide alone (22). Beltran et al. evaluated the role of danusertib, an AURKA inhibitor, in both prostate adenocarcinoma and small cell prostate cancer. They reported that there was increased efficacy in patients who had NMYC and AURKA overexpression (11). Additional research is being performed using MLN8237/alisertib, a different AURKA inhibitor that is undergoing investigation in the setting of small cell prostate cancer and small cell cancer of the lung, although preliminary results have not yet demonstrated significant benefit (23). The research by Lee et al. demonstrating a benefit when using CD532 lends further credence to continued evaluation of NMYC and AURKA as therapeutic targets in small cell prostate cancer (13).

Continued research into the pathogenesis of small cell prostate cancer remains essential in determining therapeutic options. Recognizing the role that TMPRSS2-ERG fusion rearrangements play in small cell prostate cancer, recent studies have examined whether poly (ADP ribose) polymerase 2 (PARP1) inhibitors, which interact with ERG in prostate cancer cells, may offer an additional drug target. A recent phase 2 clinical trial of olaparib reported that 33% (n=16/49) of metastatic prostate cancer patients responded to treatment in the setting of failed treatment with docetaxel, abiraterone, enzalutamide, or cabazitaxel (24). Although this was not limited to patients with small cell prostate cancer, it is reasonable to conclude that small cell prostate cancer patients would similarly benefit based on our current understanding of the pathogenesis of small cell prostate cancer.

Conclusions

Based on the work of Lee et al., it is increasingly evident that NMYC plays a crucial role in both the initiation and propagation of small cell prostate cancer. These findings support what has been previously suspected and proposed but never demonstrated in human epithelial prostate cancer cells. Recognizing the essential role of NMYC provides an opportunity for targeted therapeutics that may revolutionize the treatments we use in the setting of small cell prostate cancer.

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Footnote

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