Drivers of neuroendocrine prostate cancer

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Prostate cancer (PCa) is the most common malignancy in men and remains a leading cause of cancer death in males worldwide (1). The mainstay for patients with advanced and metastatic PCa, including castration-resistant disease, is hormonal therapy that targets the androgen receptor (AR) (androgen deprivation therapy) (2). Recently potent AR-targeted therapies were approved for the treatment of men with castration-resistant prostate cancer (CRPC), as de case of enzalutamide and abiraterone (3,4). While the use of these agents improves the survival of individuals with CRPC, most of them eventually develop resistance to therapy with a lethal outcome (5). This phenomenon may reflect an epithelial plasticity that enables tumor adaptation in response to AR-target therapies, which is not fully understood.

It has been highlighted that androgen-deprivation therapy frequently induces the emergence of highly aggressive prostate phenotypes with neuroendocrine features, also called neuroendocrine transdifferentiation (NEtD) (6). With the introduction of this new era of potent androgen receptor-targeted agents into the clinic, there is an evolving change in the clinical landscape of advanced PCa and treatment-related neuroendocrine prostate cancer (NEPC) is becoming an even more important condition to recognize.

NEPC is a high-risk, lethal subset of disease and is distinguished from prostate adenocarcinoma by the expression of neuroendocrine markers (as synaptophysin and chromogranin) and the loss of expression of the AR and PSA (6,7). Other neuroendocrine markers have been reported, although they are not typically used in the clinical practice (8). These markers include synaptic vesicle protein 2 (9), granin-A (10) and more recently the T-Box Brachyury (11) (*Figure 1*). Although some of these markers are promising, more studies are necessary before they can be used in clinical practice for detecting NEPC. NEPC is often referred to as representing only 2% of all diagnosed PCa (12). However, it is believed that probably occurs far more often, since the disease is not undistinguished of metastatic CRPC, and therefore, NEPC is underdiagnosed.

In 2010, Witte's group reported the first functional study addressing the origin of PCa. The authors showed that basal cells from primary benign human prostate tissue can initiate PCa in mice through cooperative effects of AKT1 and ERG overexpression (13). Further studies from the group identified that prostate adenocarcinoma and squamous cell carcinoma can arise from a common basal cell precursor with deregulation of c-Myc expression and AKT1 (14). The proto-oncogene c-Myc is highly expressed in prostate adenocarcinomas, at variance of N-Myc that is only expressed in 5% of prostate adenocarcinomas, but is overexpressed and amplified in about 40% of NEPC (15), indicating a potential role of N-Myc as a critical oncoprotein in NEPC.

In a recent publication in *Cancer Cell* (16), Lee and colleagues (from Witte's group) elegantly show the major role of N-Myc and AKT1 in NEPC phenotype and as potential targets for therapeutic intervention (*Figure 1*). The authors establish a novel *in vivo* model that reflect the histology and molecular features of human end-stage PCa with mixed NEPC and prostate adenocarcinoma, by deregulating the expression of N-Myc and AKT1 in primary human prostate epithelial cells. This outstanding model of NEPC (M-Myc/AKT1 tumors) showed to be androgen-independent, as demonstrated by the low or absent of AR expression, a similar feature of human CRPC and NEPCs (17). The importance of N-Myc in NEPC
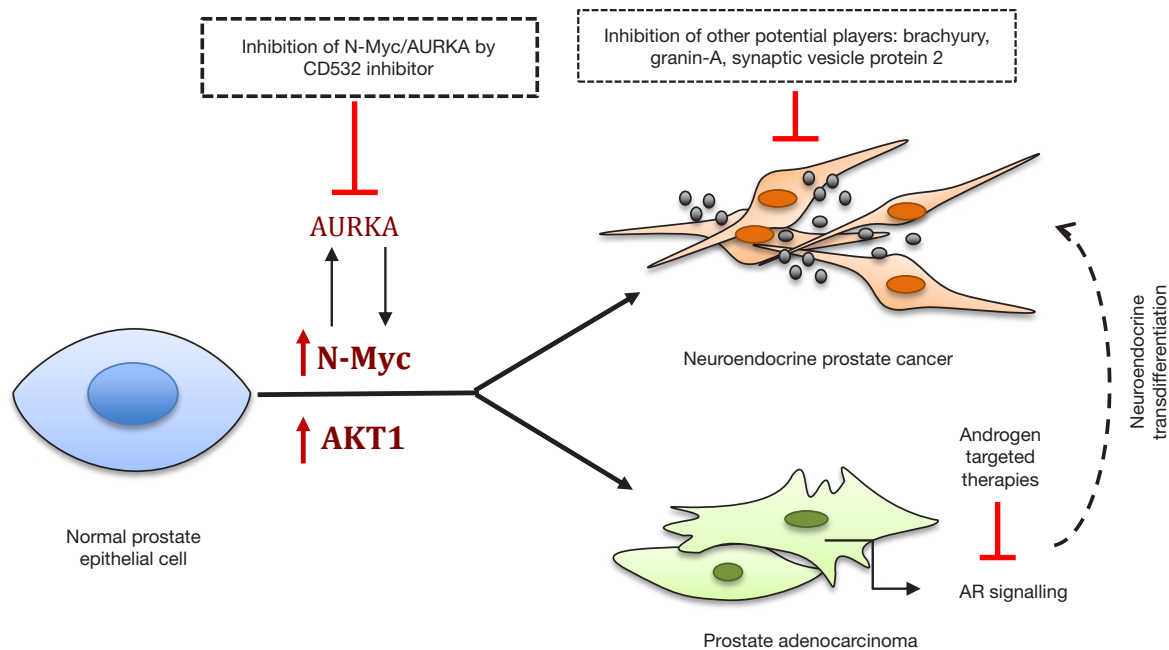
Figure 1 Overexpression of N-Myc and AKT1 in human prostate epithelial cells give rise to prostate adenocarcinoma and neuroendocrine prostate cancer. Prostate adenocarcinoma under selective pressure, as androgen deprivation, undergoes neuroendocrine transdifferentiation and present increased levels of N-Myc/AKT1. Destabilization of N-Myc/AKT1 through AURKA inhibition (CD532 inhibitor) and/or other key players in neuroendocrine prostate cancer development could be a novel therapeutic strategy in this deadly disease. AURKA, aurora A kinase; AR, androgen receptor.

was highlighted by the contrasting results obtained by the combination of c-Myc and AKT1, which generates prostate adenosquamous carcinomas in the same system (16). These results also demonstrate the importance of different MYC members in the susceptibility to different kinds of cancer. Importantly, this work has brought a new *in vivo* tool for proper studies of NEPC, that lack of suitable models with good defined genetic drivers.

NEPC usually harbor genetic abnormalities also present in prostate adenocarcinoma as *ETS* rearrangements and *PTEN* mutations (17-19). The recently identified independent prognostic biomarker in prostate adenocarcinomas, Brachyury (20), showed also to be highly associated with tumors with neuroendocrine markers, which also present *ETS* overexpression and loss of *PTEN* (11). These studies indicate that NEPC type may arise from common clonal origin. Lee and colleagues (16) successful demonstrated that the NEPC and prostate adenocarcinoma can arise from a common prostate epithelial cell with N-Myc/myrAKT1 alteration, but not from luminal epithelial cells (where the benign neuroendocrine cells are present). Future studies will be necessary to clarify the influence of N-Myc/myrAKT1 in this subpopulation of cells.

Interestingly, the authors also showed that the incidence

of NEPC tumors increases compared with adenocarcinoma when the N-Myc/myrAKT1 clones are propagated in castrate conditions (16), indicating that prostate adenocarcinomas undergo NEtD under selective pressure of androgen deprivation (*Figure 1*). Moreover, tumors with N-Myc overexpression presented stem cell-like properties that could act as repopulation clones of NEPC and consequently therapy resistance (16). These novel evidences are in agreement with a previous study where it was shown a correlation between acquisition of stem cell properties in PCa, NEtD and resistance to conventional chemotherapy (11) (*Figure 1*). It was been reported that patients with prostate adenocarcinoma that develop NEPC present amplification of both N-Myc and aurora A kinase (AURKA) (18). Based in these findings, Lee and colleagues (16), have shown that inhibition of AURKA and N-Myc (by positive feedback) by using the CD532 inhibitor, reduce tumor growth *in vivo* (*Figure 1*).

Concluding, the work published by Lee *et al*. in *Cancer Cell* (16) have provided novel and important data about the etiology and molecular basis of this aggressive subset of PCa, that could be further explored to increase our ability to diagnose NEPC at an earlier stage and may guide future pre-clinical studies for the treatment of patients with NEPC.

Footnote

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