The Path of Most Resistance: Transdifferentiation Underlies Exceptional Nonresponses to Androgen Receptor Pathway Inhibition in Prostate Cancer

Seema Sinha and Peter S. Nelson

Summary: In this issue of Cancer Discovery, Zou and colleagues describe a mechanism involving cellular transdifferentiation that promotes exceptional resistance to antiandrogen therapy in prostate cancer. A background of coinactivation of Trp53 and Pten increased the frequency of the transdifferentiated neuroendocrine phenotype. These findings have implications for developing approaches to repress cellular plasticity and overcome treatment resistance. Cancer Discov; 7(7); 673–4. ©2017 AACR.

See related article by Zou et al., p. 736 (3).

Metastatic prostate cancer is a lethal disease. Since the 1950s, the treatment of advanced prostate cancer has focused on inhibiting the activity of the androgen receptor (AR), which functions as a lineage oncogene to maintain the survival and growth of malignant prostate cells. Although initial responses to AR inhibition are nearly universal, so is the eventual development of resistance progressing to a clinical state broadly defined as castration-resistant prostate cancer (CRPC). The emergence of CRPC is usually accompanied by reactivation of AR signaling, which is then retargeted using agents such as abiraterone and enzalutamide that inhibit key mechanisms serving to maintain AR pathway activity (1). Unfortunately, resistance to these agents is essentially universal, but in this setting, the mechanisms appear to be more varied and can involve cellular programs that obviate the need for AR activity. One notable resistance pathway involves the acquisition of histopathologic features that distinguish small-cell and neuroendocrine carcinomas (NEPC). The mechanism(s) responsible for the transition from an AR-dependent tumor to one with neuroendocrine characteristics remains poorly understood, but appears to fit within the parameters that define the process of metaplasia and, more specifically, transdifferentiation: the conversion of one differentiated cell type into another differentiated cell type without undergoing a pluripotent cell transition (2). Understanding this process may lead to important insights that can be exploited to circumvent the development of this highly lethal cancer subtype.

In the current article, Zou and colleagues sought to ascertain mechanisms that contribute to the development of resistance to AR pathway targeting (3). Previous studies have identified genomic aberrations that are enriched in CRPCs, including copy loss or mutation in several well-studied tumor suppressors: RB1, TP53, and PTEN (4). These alterations are further enriched in NEPC compared with those CRPCs that maintain features of adenocarcinomas in which AR signaling is active (5). To evaluate these molecular aberrations in the context of therapy, Zou and colleagues first constructed genetically engineered mouse (GEM) models designed to inactivate the tumor suppressors Nkx3.1 and Pten (NP GEM) with or without the combined loss of Trp53 (NPp53 GEM) specifically in mouse prostate luminal epithelium. Both models developed adenocarcinomas, and, following androgen deprivation, both models progressed to CRPC with an adenocarcinoma phenotype. Notably, following further AR pathway repression with abiraterone, the models exhibited divergent responses: The growth of NP CRPCs was significantly inhibited, whereas NPp53 CRPCs were refractory to abiraterone, and, in a subset, tumor growth accelerated. These tumors were classified as “exceptional nonresponders.” Metastases were also identified in several abiraterone-treated NPp53 GEM mice, whereas metastases were not identified in those treated with a vehicle.

Histopathologic assessment of the CRPCs revealed that NPp53 tumors exhibited a range of histologies, including several with small-cell/NEPC characteristics, which were most commonly observed following abiraterone treatment. These latter tumors were highly proliferative, lacked AR expression, and exhibited gene expression profiles concordant with those observed in human NEPC. Although most prevalent in the NPp53 tumors treated with abiraterone, regions of neoplastic cells without adenocarcinoma features were identified in tumors that had not been exposed to abiraterone or androgen deprivation treatment, suggesting that preexisting tumor cells lacking Pten and Trp53 are primed to resist therapy. Extrapolating these findings across species leads to the testable hypothesis that patients with PTEN/TP53–deficient tumors may resist abiraterone and potentially other AR-directed therapeutics and consequently also exhibit “exceptional nonresponder” phenotypes.

Central to the question of how AR-positive prostate adenocarcinomas evolve to a therapy-resistant neuroendocrine
phenotype is defining their cell of origin. NEPC could arise from a benign neuroendocrine precursor cell that directly undergoes malignant transformation. Alternatively, NEPC may diverge from a common adenocarcinoma precursor or exhibit linear progression through phenotypic states potentially driven by sequential genomic alterations (5). To address this issue, Zou and colleagues devised an elegant lineage-tracing strategy to permanently mark, with a yellow fluorescent protein (YFP), prostate luminal epithelial cells in NPP53 GEM mice. Using synaptophysin as a marker for neuroendocrine differentiation, they found that synaptophysin-positive cells within NPP53 tumors were positive for YFP. These results provide direct in vivo evidence that NEPC is derived from luminal epithelium and supports transdifferentiation as a key process leading to the neuroendocrine phenotype, although the studies do not completely rule out a transition through a dedifferentiated intermediary stem cell-like state before acquiring neuroendocrine characteristics.

Recent studies have begun to shed light on key drivers of neuroendocrine differentiation that include the involvement of developmental transcription factors such as SOX2 that serve to influence self-renewal and pluripotency, and epigenetic modifiers such as EZH2 that influence embryonic development and cell proliferation (6, 7). In this context, Zou and colleagues found that Sox11, a member of the SOXC subclass of HMG-box transcriptional regulators, was upregulated in treatment-resistant NPP53 tumors. Sox11 is a pan-neuronal differentiation factor that regulates neural and mesenchymal progenitors during organogenesis. The repression of Sox11 diminished neuroendocrine markers, including synaptophysin, without changes in Sox2 expression. The known functions of SOX2 and Sox11 suggested a developmental pathway whereby initial Sox2 upregulation serves to promote cell plasticity, which then allows for Sox11-driven induction of a neuroendocrine program.

Overall, the findings reported by Zou and colleagues are timely and have clear clinical implications. As targeted therapies are increasingly successful in impairing key cellular survival pathways that also function to maintain lineage characteristics, tumor cells appear to be able to jettison their original forms and adopt new attributes. Consequently, the frequency of NEPC is likely to rise as AR pathway repression becomes more effective, an event that will necessitate the development of new treatment approaches. Although tumors deficient in RB1 and TP53 are known to have a predilection for acquiring neuroendocrine features, the current studies determined that tumors with the combination of PTEN and TP53 loss also have this ability. The status of these tumor suppressors may serve as predictive biomarkers of response, or lack of response, to targeted agents. It is notable that transdifferentiation to a neuroendocrine phenotype is not a treatment resistance mechanism unique to prostate cancer. Carcinoma of the lung and other tumor types have been shown to adopt neural and neuroendocrine characteristics under therapeutic pressure (8). The profound alterations that occur in these transdifferentiated cells strongly implicate widespread epigenetic changes that serve to reprogram entire genomes and support the investigation of agents that are capable of targeting epigenetic modifications that include inhibitors of EZH2, histone deacetylases, methylation, and BET proteins. The preclinical models developed in the context of the current study provide ideal systems to evaluate these agents.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

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