Targeting the Androgen Receptor in Prostate Cancer — A Resilient Foe

Peter S. Nelson, M.D.

Personalizing the use of cancer therapeutics is a major focus of current biomedical research. The pioneering work of Huggins and colleagues more than 70 years ago foreshadowed the modern era of precision medicine by treating advanced prostate cancers with approaches designed specifically to impair androgen-receptor signaling. The androgen receptor regulates critical cellular growth and survival programs in neoplastic prostate cells (Fig. 1) and consequently represents a unique treatment-defining feature of prostate cancer. Reports of dramatic remissions in clinical symptoms resulting from this targeted therapy transformed medical practice conceptually and practically, and today strategies that impair androgen-receptor activity by lowering levels of circulating testosterone or antagonizing androgen-receptor ligand binding remain the standard initial treatments for men with metastatic disease.

Though most prostate cancers respond to androgen suppression initially, progression to a disease state termed castration-resistant prostate cancer is almost inevitable. Importantly, progression is accompanied by the resumption of androgen-receptor activity. Research defining mechanisms that contribute to androgen-receptor reactivation supported the development of abiraterone, a cytochrome P450 17A1 (CYP17A1) inhibitor capable of further suppressing intratumoral androgens, and enzalutamide, a potent antagonist of androgen-receptor ligand binding.

Even though both drugs extend survival, resistance develops in essentially all patients, and this resistance is again accompanied by persistent androgen-receptor signaling. Emerging clinical data indicate that response rates to each drug are diminished after previous exposure to the other drug, suggesting a degree of cross-resistance through undefined mechanisms.

Understanding precisely how the androgen receptor is activated has major clinical implications for determining which patients will most benefit from existing drugs and provides a foundation for developing new therapeutics. Variant forms of the androgen receptor have been identified with the use of laboratory models of prostate cancer. These variants are generated through somatic mutation or aberrant RNA splicing, and they encode receptors lacking the C-terminal domain, to which androgens bind. (The activity of abiraterone and enzalutamide is dependent on the presence of the C-terminal domain of the androgen receptor.) Remarkably, instead of losing function, several androgen-receptor variants — including the most predominant variant, splice variant 7 — encode protein isoforms that activate the androgen-receptor pathway in the absence of androgens (Fig. 1).

Antonarakis et al. now report in the Journal compelling clinical data endorsing the importance of androgen-receptor variants in mediating treatment resistance. They assayed levels of full-length androgen receptor messenger RNA (mRNA) and androgen-receptor splice variant 7 mRNA (AR-V7) in circulating tumor cells from prospectively enrolled men with metastatic castration-resistant prostate cancer, in the context of response and resistance to abiraterone and enzalutamide. Although the number of patients was small (31 men initiating a course of abiraterone and 31 men initiating a course of enzalutamide), the results were striking: no patient with detectable AR-V7 in circulating tumor cells had a response to either enzalutamide or abiraterone, as determined by a reduction in serum prostate-specific antigen levels of 50% or more. The presence of AR-V7 was also associated with shorter progression-free survival and overall survival. The prevalence of detectable
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**A**

- **Prostate cancer cell**
- Androgen
- **DNA-binding domain**
- **Ar**
- **N**
- **C**
- Ligand binding
- **Androgen dimerization**
- **Nuclear translocation**
- **Cell response**
  - ↑ Proliferation
  - ↑ Survival
  - ↑ Secretion of PSA

**B**

- **Abiraterone**
- **Enzalutamide**
- **Ar**
- **N**
- **C**
- **DNA-binding domain**
- Cryptic exon
- **Cell response**
  - ↓ Proliferation
  - ↑ Apoptosis
  - ↓ Secretion of PSA

**C**

- **Abiraterone**
- **Enzalutamide**
- **Ar**
- **N**
- **C**
- **DNA-binding domain**
- **AR-V**
- **N**
- **C**
- **AR-V program**
- **Canonical AR program**
- **Cell response**
  - ↑ Survival
  - ↑ Metabolism
  - ↑ PSA
  - ↑↑ Proliferation
  - Other phenotypes
Figure 1 (facing page). Androgen-Receptor Splice Variant–Mediated Resistance to Therapeutics Directed at the Androgen Receptor.

As shown in Panel A, the androgen receptor (AR) is activated by the binding of androgen ligands, which prompts AR dimerization, translocation to the nucleus, and activation of a canonical transcriptional program that promotes cell survival, proliferation, and the secretion of prostate-specific antigen (PSA). As shown in Panel B, abiraterone reduces the availability of androgens, and enzalutamide inhibits androgen binding; both processes lead to the suppression of the canonical AR program and result in cell-growth arrest, apoptosis, and diminished secretion of PSA. As shown in Panel C, AR splice variants (AR-Vs) resist the inhibitory effects of abiraterone and enzalutamide because they lack the C-terminal ligand-binding domain of full-length AR. AR-Vs, functioning independently or together with full-length AR, exhibit constitutive activation of a transcriptional program that overlaps and extends the canonical AR program, with enhanced tumour-cell proliferation.

AR-V7 was low before treatment with enzalutamide or abiraterone (9 to 15%) but increased substantially after progression during treatment with either drug (approximately 50%), supporting a common resistance mechanism.

There are several intriguing results of this study that serve to populate a to-do list of next steps. Androgen-receptor variants were not expressed in every tumor. Consequently, establishment of the mechanisms leading to the generation of androgen-receptor variants may provide additional predictive and therapeutic insights. In virtually every study participant, the presence of AR-V7 was accompanied by high (on a logarithmic scale) levels of full-length androgen receptor mRNA, suggesting a requirement for the normal androgen receptor in the genesis of androgen-receptor variants, a need for cooperative interactions, or both. Although the AR-V7 isoform is capable of activating the canonical androgen-receptor program, its repertoire is more expansive than that of full-length androgen receptor and includes genes known to promote adverse tumor behavior. Preclinical studies show that induction of androgen-receptor variants can be rapid and reversible, and so strategies to limit the production of androgen-receptor variants may be viable.

What are the immediate clinical implications? A biomarker with 100% specificity in predicting lack of treatment response would be a major step forward and would probably achieve rapid adoption. However, the small number of patients in the study by Antonarakis and colleagues mandates validation. The proprietary combination of antibodies used to capture circulating tumor cells is a potential limitation. Whether other methods of isolating prostate-cancer cells would yield similar results should be determined. Fundamentally, the androgen receptor in its many permutations still represents the key target in prostate cancer. Continued efforts directed toward ablating androgen-receptor activity, particularly by interfering with the functions of the N-terminal domain of the androgen receptor, are likely to be fruitful. In the broader context, the study by Antonarakis and colleagues serves as a reminder that the ability to interrogate molecular features of a solid tumor in a longitudinal, iterative, and relatively noninvasive manner opens up new opportunities for precision oncology.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Fred Hutchinson Cancer Research Center, Seattle.

This article was published on September 3, 2014, at NEJM.org.


DOI: 10.1056/NEJMee1409306
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