Compound clamps down on prostate cancer

Most individuals with metastatic prostate cancer develop resistance to standard treatments, which antagonize the action of growth-promoting androgens. The origins of such 'castration-resistant' tumors have been traced in part to increases in expression of the androgen receptor and to shortcomings in receptor-blocking drugs, which can even act as agonists. Research by Chris Tran *et al.*[1] could provide a new option. They identified two orally available compounds that bind with high affinity to the androgen receptor and block its activity more effectively than current drugs. When the researchers treated mouse models of castration-resistant prostate cancer with the compounds, the tumors shrank. The investigators also treated 30 subjects with castration-resistant tumors with one of the compounds, MDV3100. In 13 subjects they observed sustained declines in a biomarker of prostate cancer, prostate-specific antigen (PSA).

> "Randomizing patients to receive a probably active drug against placebo presents an ethical quandary."—Ian Tannock

Massimo Loda:

The treatment of prostate cancer resistant to antiandrogen therapy is the single most important therapeutic challenge in this disease. Drugs currently used for this purpose may not adequately suppress circulating or even intraprostatic androgen levels, and progression to castration-resistant prostate cancer may thus occur because of lack of androgen receptor pathway inhibition. This report shows that diarylthiohydantoins have a greater affinity for the androgen receptor when compared to traditional antiandrogens, and, importantly, reduce nuclear import of the androgen receptor. This is a very important step toward complete androgen blockade. If castration-resistant prostate cancers are indeed dependent on androgen receptor signaling, regardless of upstream activators, these drugs are likely to have profound clinical effects in all such cancers. It will be essential, however, to ascertain that molecular inhibition of the androgen receptor pathway has occurred. Alternatively, assuming that blockade of androgen receptor signaling is complete, androgen receptor–independent progression of prostate cancer may be revealed by tumors that escape this therapeutic approach.

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Arul Chinnaiyan:

Many cases of prostate cancer may originate with a curious type of initiating mutation: a gene fusion juxtaposing a regulatory sequence that responds to androgens with a gene encoding an ETS transcription factor that promotes tumor growth. The new drugs decreased expression of a common 5′ fusion partner in prostate cancer, TMPRSS2, and attenuated growth of a TMPRSS2-ETS–positive prostate cancer cell line. So, it seems likely that the drugs will quash the expression of androgen-regulated gene fusions.

Over 50% of men with prostate cancer harbor TMPRSS2-ETS fusions, and 43% of subjects treated with MDV3100 showed a sustained decline in PSA levels, begging the question as to whether these individuals harbor androgen-regulated gene fusions.

Future studies will reveal whether these tantalizing findings represent durable clinical responses leading to decreased tumor burden and increased survival. Given the numerous mechanisms for restoring androgen receptor signaling in castration-resistant prostate cancer, combined treatment with multiple androgen receptor–targeting agents will probably be more successful than single-agent approaches.

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COMPETING INTERESTS STATEMENT
The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

Ian Tannock:

Improved understanding of the causes of initial resistance to androgen-deprivation therapy is now leading to development and clinical evaluation of new agents. These agents are either more potent and more selective inhibitors of androgen synthesis, such as abiraterone acetate, or more potent inhibitors of the androgen receptor, such as RD162 and MDV3100. The initial clinical experience with these agents is encouraging: abiraterone acetate and MDV3100 have both led to substantial reductions in serum levels of PSA in heavily pretreated patients with metastatic prostate cancer, and phase 3 trials to evaluate their effect on survival are underway. These agents are being evaluated clinically after failure of standard initial androgen-deprivation therapy before or after men receive chemotherapy with docetaxel. Clinical evaluation is not simple, as there is no obvious comparator, and randomizing patients to receive a probably active drug against placebo presents an ethical quandary. However, the large, more than 1,000-patient trial of abiraterone acetate after docetaxel-based chemotherapy used a 2:1 randomization against placebo (although men in both arms received low-dose prednisone), and completed enrollment very rapidly. A planned trial of MDV3100 will use a similar format. These new agents seem well tolerated and offer men with advanced prostate cancer the possibility of additional treatments that might improve quality of life and prolong survival.

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1. Tran, C. *et al.* Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* published online, doi: 10.1126/science.1168175 (9 April 2009).