Journal of Andrology, Vol. 24, No. 2, March/April 2003

Molecular Analysis of the Androgen Receptor in Ten Prostate Cancer Specimens Obtained Before and After Androgen Ablation

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Hormonal or androgen-ablation (AA) therapy is the predominant form of systemic treatment for metastatic prostate cancer. Although an initial response to AA is observed in 70%–80% of patients with advanced disease, most tumors eventually progress to androgen-independent growth, and only a minority of affected individuals are alive 5 years following initiation of treatment. Because AA induces a dramatic change in the hormonal milieu of the patient and because these tumors maintain the ability to proliferate, it is possible that this treatment selects a population of cells with mutated androgen receptors (ARs) that sustain growth despite the absence of circulating androgen. To test this hypothesis we investigated the molecular structure of the AR in 10 prostate cancer specimens obtained before and after AA. Tumors (coded A through L) were microdissected to uniquely enrich genomic DNA from cancer cells. Exons 1–8 of the AR were screened by polymerase chain reaction, single-stranded conformational polymorphism, and sequence analysis. A mutation consisting of an expansion of the polyglutamine (poly-Q) repeat from 20 (found in 100% of the sequences of specimens obtained before AA) to 26 (found in 70% of the sequences of specimens obtained after AA) was detected in patient F. The 26 glutamine (Q26) AR readily translocated to the nucleus upon addition of androgen, and did not show significant differences in its ability to bind ^{3}[H]-dihydrotestosterone compared to its wild-type counterpart. Nevertheless, analysis of transcriptional activity showed that the Q66 AR was transcriptionally 30%–50% less active than the wild-type molecule. Because clones of AR with an expanded poly-Q tract were detected only in the specimen from patient F obtained after AA, we conclude that in specific circumstances, AA treatments can select variant forms of the AR in the prostate of patients affected by prostate cancer. Further experiments are needed to conclusively determine whether the Q26 clone was responsible for sustaining survival of prostate cancer cells in the androgen-depleted milieu of this patient.

Key words: Androgen ablation, androgen receptor, CAG repeat, mutations, prostate cancer.

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