TELOMERASE AS AN IMPORTANT TARGET OF ANDROGEN-SIGNALING BLOCKADE FOR PROSTATE CANCER TREATMENT

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As the mainstay treatment for advanced prostate cancer, androgen-deprivation therapy (ADT) targets the action of androgen receptor (AR) by reducing androgen level and/or by the administration of anti-androgen that competes with androgens for binding to AR. Albeit effective in extending survival, ADT is associated with dose-limiting toxicity and the development of castration-resistant prostate cancer (CRPC) after prolonged use. Since CRPC is generally lethal and incurable, developing effective strategies to enhance the efficacy of ADT and circumvent resistance becomes an urgent task. Continuous AR signaling constitutes one major mechanism underlying the development of CRPC. The present study showed that methylseleninic acid (MSA), an agent that effectively reduces AR abundance, could enhance the cancer-killing efficacy of the anti-androgen bicalutamide in both androgen-dependent and castration-resistant prostate cancer cells. We found that combination of MSA and bicalutamide produced a robust downregulation of prostate-specific antigen and a recently identified AR target, telomerase and its catalytic subunit, telomere reverse transcriptase (hTERT). The downregulation of hTERT occurs mainly at the transcriptional level, through reducing AR occupancy of the hTERT promoter. Furthermore, apoptosis induction by the two agents is significantly mitigated by restoration of hTERT. Our findings thus indicate that MSA in combination with anti-androgen could represent a viable approach to improve the therapeutic outcome of ADT. Given the critical role of hTERT/telomerase downregulation in mediating the combination effect and the fact that hTERT/telomerase could be measured in blood and urine, hTERT/telomerase could serve as an ideal tumor-specific biomarker to monitor the efficacy of the combination therapy non-invasively. (Supported by the Department of Defense Prostate Cancer Training grant No. W81XWH-08-1-0291 (SL); the National Cancer Institute grant No. K01 CA114252 (YD); the American Cancer Society grant No. RSG-07-218-01-TBE (YD))