Low expression of the androgen-induced tumor suppressor PLZF in lethal prostate cancer

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Background: Four to nine percent of prostate cancers harbor homozygous deletions of the androgen-induced tumor suppressor gene, PLZF (ZBTB16). PLZF loss induces an in vitro phenotype of castration- and enzalutamide-resistant prostate cancer. The association of low expression of PLZF with clinical outcomes is unknown.

Methods: We assessed PLZF mRNA expression in patients diagnosed with primary prostate cancer during prospective follow-up of the Health Professionals Follow-up Study (HPFS; n = 254) and the Physicians’ Health Study (PHS; n = 150), as well as in The Cancer Genome Atlas (TCGA; n = 333). We quantified PTEN status using copy number data or a genomically-validated immunohistochemistry and measured transcriptional activation of the mitogen-activated protein kinase (MAPK) pathway. Patients from HPFS and PHS were followed for a median of 15.3 years for metastases and prostate cancer-specific mortality (113 lethal events).

Results: PLZF mRNA expression was lower in tumors with PLZF deletions. There was a strong, positive association between intratumoral androgen receptor signaling and PLZF expression. PLZF expression was also lower in tumors with PTEN loss. Low PLZF expression was associated with higher MAPK signaling. Patients in the lowest quartile of PLZF expression compared to those in the highest quartile were more likely to develop lethal prostate cancer, independent of clinicopathologic features, Gleason score, and androgen receptor signaling (odds ratio, 3.17; 95% CI, 1.32 to 7.60).

Conclusions: Low expression of the tumor suppressor gene PLZF, an androgen-induced gene whose expression is suppressed by androgen deprivation therapy, confers a worse prognosis in primary prostate cancer, and should be tested as a predictive biomarker for response to androgen deprivation therapy.

Conflict of Interest: None.

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