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.

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