Project title: Comprehensive Cancer Center of Taipei Medical University Program title: Prostate Cancer Research

Loss of SPDEF and Gain of TGFBI Activity After Androgen Deprivation Therapy Promote EMT and Bone Metastasis of Prostate Cancer

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Androgen deprivation therapy (ADT) targeting the androgen receptor (AR) is a standard therapeutic regimen for treating prostate cancer. However, most tumors progress to metastatic castration-resistant prostate cancer (CRPC) after ADT. In this study, we identified the type I/II/IV collagen-binding protein transforming growth factor–β (TGF-β)–induced (TGFBI) as an important factor in the epithelial-to-mesenchymal transition (EMT) and malignant progression of prostate cancer. In prostate cancer cell lines, AR signaling stimulated the activity of the transcription factor SPDEF, which repressed the expression of TGFBI. ADT, AR antagonism, or overexpression of TGFBI inhibited the activity of SPDEF and enhanced the proliferation rates of prostate cancer cells. Knockdown of TGFBI suppressed migration and proliferation in cultured cells and reduced prostate tumor growth and brain and bone metastasis in xenograft models, extending the survival of tumor-bearing mice. Analysis of prostate tissue samples showed that CRPC reduced the nuclear abundance of SPDEF and increased the production of TGFBI. Our findings suggest that induction of TGFBI promotes prostate cancer growth and metastasis and can be caused by dysregulation or therapeutic inhibition of AR signaling.