Extracellular Domain Shedding of TROP2 Activates EGFR Signaling to Drive Prostate Cancer Metastasis

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Background, Methods, Results, Conclusion: Metastasis is the main cause of prostate cancer-associated deaths, highlighting the urgent need to determine the mechanisms underlying prostate cancer progression. TROP2 (TACSTD2, Trop-2, Trop2) is an oncogenic transmembrane surface protein that is highly expressed in metastatic prostate cancer. Naturally occurring cleavage of TROP2 leads to a release of the TROP2 extracellular domain (TECD) into the extracellular environment. In this study, we report that TECD is detected in media from prostate cancer cells and serum from patients with clinically significant prostate cancer. Furthermore, our study reveals an important functional role of TECD in prostate cancer metastasis. We found that while shed TECD does not affect prostate cancer cell and tumor growth, it increases cell migration, invasion, metastatic colonization, and spontaneous metastasis both *in vitro* and *in vivo*. TECD interactome and proteomic studies reveal that TECD binds to epidermal growth factor receptor (EGFR) and shed TECD modulates a set of proteins associated with invasion, migration, mTOR signaling, and epithelial-to-mesenchymal transition. Furthermore, elevated shed TECD increases EGFR phosphorylation, resulting in the activation of the EGFR-PI3K-AKT-mTOR pathway in prostate cancer. EGFR inhibitors suppress the invasive ability of prostate cancer cells driven by TECD overexpression, further supporting the key role of EGFR in TECD-mediated prostate cancer progression. Our study reveals a new function of TECD in driving prostate cancer progression and uncovers new mechanisms of TECD function through EGFR.

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