Case Report

Down regulation of trans-membrane and coiled-coil domain 1 in urinary bladder urothelial carcinoma: A characterization of tumor suppressor function impairs AKT signaling pathway

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ABSTRACT:

Statement of the Problem: Urinary bladder urothelial carcinoma (UBUC) is a common malignant disease with preference for developed countries. Cell cycle dysregulation resulting in uncontrolled cell proliferation has been associated with UBUC development. This study aimed to explore the roles of TMCO1 in UBUCs. Methodology & Theoretical Orientation: Data mining, branched DNA assay, immunohistochemistry, xenograft, cell culture, quantitative RT-PCR, immunoblotting, stable and transient transfection, lentivirus production and stable knockdown, cell cycle, cell viability and proliferation, soft agar, wound healing, transwell migration and invasion, co-immunoprecipitation, immunocytochemistry, AKT serine/threonine kinase (AKT) activity assays and site-directed mutagenesis were used to study in vivo and in vitro. Findings: Data mining identified that the TMCO1 transcript was downregulated in the progression of UBUCs. Stable overexpression of the TMCO1 gene suppressed tumor growth in xenograft mice. In distinct UBUC-derived cell lines, changes of the TMCO1 level altered cell-cycle distribution, cell viability, cell proliferation, colony formation and modulated the AKT pathway; TMCO1 recruited the PH domain and leucine rich repeat protein phosphatase 2 (PHLPP2) to dephosphorylate pAKT1(serine 473) (S473). Mutagenesis on S60 of the TMCO1 protein released TMCO1-induced cell cycle arrest and revised the AKT pathway; upregulated nuclear cyclin dependent kinase inhibitor 1A (CDKN1A) and CDKN1B protein levels in UBUC-derived cells. Conclusion & Significance: Clinical associations, xenograft mice and in vitro indications provide solid evidences that the TMCO1 gene is a novel tumor suppressor in UBUCs. TMCO1 dysregulates cell cycle progression via suppression of the AKT pathway and S60 of the TMCO1 protein is crucial for its tumor suppressor roles.

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