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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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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.

Biography

Yow-Ling Shiue has her expertise in Translational Oncology. She focuses on data-mining, correlating gene/protein expression levels to clinicopathological features and preclinical experiments such as cellular and xenograft animal models. Though there are drugs available for targeting therapies, she also studies the drug mechanisms involving in the signaling pathways.

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