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The role of TERE1/UBIAD1 in urologic oncology: History and current investigations

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The discovery and characterization of TERE1/UBIAD1 gene and protein occurred duringefforts to characterize the phenotype of urothelial carcinoma. AcDNA fragment from normal bladder mucosa similar to an EST from a T cell line led to a unique gene denoted **T**ransitional **E**pithilial **RE**sponse gene 1 encoding a protein (36.8 KD /338 AA) on 1p36.3. Its ubiquitous expression in normal tissues and diminished expression in urothelial carcinoma was demonstrated as well as its capacity to profoundly inhibit tumor cell growth (80%) and colony formation. Similar findings were demonstrated in prostate cancer and more recently in clear cell renal cell carcinoma (ccRCC).

Interrogation of interaction and function was assessed through bacterial two hybrid assays and biochemical confirmation of an interaction with Apolipoprotein E and other interesting protein-protein interactions. The lipid connection was confirmed by the association of SCCD and TERE1/UBIAD1 mutations. TERE1/UBIAD1 modulates cholesterol levels in genitourinary tumors by 20-40 percent.When its central role in vitamin K metabolism was elucidated, a defect in menaquinone-mediated cholesterol homeostasis was suggested as a component of tumor progression. This has obvious impact in the phenotype of castrate resistant prostate cancer where autocrine production of androgens is key through alterations in cholesterol synthesis and decreased efflux.

A general metabolic role for TERE1/UBIAD1 is noted through its interaction with TBL2, a protein found predominantly in the mitochondria. This complex may function in lipid metabolism and oxidative/nitrosative stress. Altered general metabolism in ccRCC is a key area of investigation and the contribution of TERE1/UBIAD1 to these changes in neoplastic cells is intriguing. Also of interest is the clarification of the Vitamin K related and TERE1/UBIAD1- independent contributions to the neoplastic phenotype of GU tumors and the potential for elucidating unique therapeutic targets for these disease states

Biography

S. Bruce Malkowicz is Professor of urology and the Thomas Stichter Memorial Professor of Urologic Research at the University of Pennsylvania. He also serves as co-director of the urologic cancer program at that institution. He is a graduate of the University Of Pennsylvania School Of Medicine and performed his general and urological training at the Hospital of the University of Pennsylvania. Malkowicz completed his urological oncology training at the University of Southern California and the Wistar Institute. He also serves as Chief of Urology at the Philadelphia VA Medical Center. His major research interests include basic mechanisms of tumor progression and the molecular epidemiology of prostate cancer. He is author of nearly 300 original articles and reviews. Malkowicz has served on several editorial boards including Urologic Oncology and the BJU International. He is a member of multiple professional societies including the American Association of Genitourinary Surgeons, The Society of Pelvic Surgeons (past president), The Urologic Research Society, The Society of Surgical Oncology, and is past president of the Philadelphia Urological Society and the Southeastern Pennslyvania chapter of the American Cancer Society. He has been listed multiple times on Best Doctors in Philadelphia and Best Doctors in the USA directories including Top Doctors for Cancer in the country.

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