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Understanding the role of TM9SF1 in bladder cancer pathogenesis

TM9SF1 in bladder cancer

Venkata Krishna Vamsi Gade, Budhi Singh Yadav

Abstract

In this editorial we comment on the article by Wei L et. al., published in the recent issue of the World Journal of Clinical oncology. Primary central nervous system lymphoma (PCNSL) is the disease of elderly and immunocompromised patients. The authors investigated the role of Transmembrane 9 superfamily member 1 (TM9SF1) protein in Bladder cancer (BC) carcinogenesis. Lentiviral vectors were used to achieve silencing or overexpression of TM9SF1 gene in three BC cell lines. These cell lines were then subject to CCK8, wound-healing assay, transwell assay, and flow cytometry. Proliferation, migration, and invasion of BC cells were increased in cell lines subjected to TM9SF1 overexpression. TM9SF1 silencing inhibited proliferation, migration and invasion of BC cells. The authors conclude that TM9SF1 may be an oncogene in bladder cancer pathogenesis.

Key Words: Urinary bladder cancer; TMSF1 protien; cell line

Gade VKV, Yadav BS. Understanding the role of TM9SF1 in bladder cancer pathogenesis. *World J Clin Oncol* 2024; In press

Core Tip: Core Tip: TM9SF1 silencing inhibited proliferation, migration and invasion of BC cells.

INTRODUCTION

In a novel basic study, Wei L *et al* investigate the role of Transmembrane 9 superfamily member 1 (TM9SF1) protein in Bladder cancer (BC) carcinogenesis (1). Lentiviral vectors were used to achieve silencing or overexpression of TM9SF1 gene in three BC cell lines. These cell lines were then subject to CCK8, wound-healing assay, transwell assay, and flow cytometry. Proliferation, migration, and invasion of BC cells were increased in cell lines subjected to TM9SF1 overexpression. Whereas TM9SF1 silencing inhibited proliferation, migration and invasion of BC cells. The authors conclude that TM9SF1 may be an oncogene in bladder cancer pathogenesis.

Bladder cancer is the most common cancer of the urinary tract with more than 500,000 cases diagnosed in 2020 worldwide (2). Non muscle invasive bladder cancer (NMIBC) comprise around 60 % of all cases. Although NMIBC has an estimated 5 year overall survival rate of 71-90%, they have a 15-30 % recurrence rate and up to a 10% rate of progression to muscle invasive bladder cancer (MIBC) (3). MIBC has a 5 year survival rate of 60-70% with patients having an aggressive clinical course as compared to NMIBC (4). Patients of MIBC develop distant metastasis in up to 29% of cases (5). However systemic therapy protocols in BC have remained largely unchanged in the last 2 decades (6,7). The development of immune checkpoint inhibitors has led to their use in advanced BC. Randomised trials however have only demonstrated a modest survival advantage with the use of immune check point inhibitors in advanced BC (8,9). There is hence a pressing need to identify new molecular targets in BC through basic research.

Increasing age, tobacco smoke, Schistosoma infection, exposure to aromatic amines and polycyclic hydrocarbons, ionizing radiation and phenacetin-containing analgesics are all proven risk factors for bladder cancer development (10). A review of the genomic landscape of urinary BC shows that polymorphisms of N-acetyltransferase 2 (NAT2) and glutathione S-transferase-μ1 (GSTM1) genes confer an increased risk of BC (11,12).

Other genes suspected to play a role in the pathogenesis include MYC, TP63, TERT, FGFR3, PSCA, UGT1A1, TACC3 and APOBEC3A (13). TM9SF1, first identified in 1997 is a transmembrane protein localised to the autophagosomal and lysosomal membranes in the cytoplasm. TM9SF1 was identified to be one of the 17 common differentially expressed genes in BC samples but its precise role in BC pathogenesis was unclear.

In this study by Wei L *et al*, stable transfectants overexpressing TM9SF1 were successfully constructed in all three BC cell lines which was detected by qRT-PCR. The CCK8 (Cell counting kit 8) assay showed that compared with the control group the proliferation rate of BC cells in the TM9SF1 overexpression group was significantly higher. The scratch wound healing assay and transwell assay showed significantly improved cellular migration in the TM9SF1 overexpression group. Matrix gel testing and flowcytometry showed TM9SF1 cells were more likely to demonstrate cell invasion and transition to G2/M phase. In performing these tests in transfectants with silenced TM9SF1, authors noted reduced cellular proliferation, invasion, migration and G1 cell block. With these findings TM9SF1 has been proposed to be a novel oncogene in BC pathogenesis.

In addition to bladder cancer, TM9SF1 has been found to be overexpressed in esophageal and cervical cancer with a speculated link to poorer survival and recurrence rates in some preclinical studies (14,15). Its role as an oncogene might be due to its effects on the G1 phase The precise molecular interaction of TM9SF1 with cell cycle proteins needs further investigation. The synergistic interaction of TM9SF1 with proteins regulating the epithelial mesenchymal transition such as EBAG9 might explain the increased invasion and migration in TM9SF1 overexpressed cells (16).

The inhibition of cellular proliferation, migration and invasion caused by TM9SF1 silencing hints at its pro-oncogenic role. Future directions might involve correlation of stage, grade and histology of BC patients with TM9SF1 overexpression. The prognostic and predictive value of TM9SF1 overexpression in BC would first need to be established in a retrospective study. For instance, while point mutation of the FGFR3 gene is observed in 60-70% of NMIBC cases, it is only detected in 5-10% of MIBC cases (17) .

The upregulation of EGFR is observed in 20% of NMIBC cases, but it can be seen in up to 50% of MIBC cases. (18). Response of TM9SF1 overexpressing BC to standard chemotherapy regimens and radiation needs investigation.

The study also highlights the possible utility of TM9SF1 as a therapeutic molecular target. Since transfectants with silenced TM9SF1 had reduced cellular proliferation, invasion, migration and G1 arrest, therapeutic molecules inhibiting TM9SF1 might improve bladder cancer outcomes. The use of targeted therapy and immunotherapy is quickly gaining acceptance in BC treatment. Bacillus Calmette Guerin (BCG) is one of the oldest forms of immunotherapy used in BC treatment. Its intravesical use is recommended in intermediate and high risk NMIBC after TURBT (Transurethral resection of bladder tumour). BCG acts on BC cells *via* direct and indirect effects. Direct cytotoxicity of BC cells occurs due to apoptosis mediated by TLR7 and cellular necrosis mediated by HMGB7. Indirect effects occur due to the internalization of BCG followed by signal transduction leading to cytokine release that ultimately result in modulation of innate and acquired immune response (19).

This study by Wei L *et al* was based on *in vitro* cell line experiments. In a large meta-analysis of genomic hybridisation studies, it was seen that there was a high degree of correlation between mutation patterns in tissue and cell line groups of similar histology. However, quantitatively it was seen that cell lines showed a higher locus specific and cell line specific aberrations when compared with tissue samples (20). Microarray studies in other tumour sites such as in cervical cancer have shown that though major pathogenic mutations are reflected in cell lines, there were also several notable discordant genes forming major clusters. The reason for such discordance has not been definitively established and has been speculated to be due to changes in the tumour microenvironment (21). Hence TM9SF1 expression patterns and behaviour in BC tissue samples warrants further investigation.

The importance of TM9SF1 as an oncogene and its use as a therapeutic target would ultimately depend on the prevalence of the mutation in BC tissues and replication of invitro activity in tumour tissue.

CONCLUSION

The importance of TM9SF1 as an oncogene and its use as a therapeutic target would ultimately depend on the prevalence of the mutation in BC tissues and replication of invitro activity in tumour tissue.

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PRIMARY SOURCES

1	Long Wei, Shi-Shuo Wang, Zhi-Guang Huang, Rong-Quan He et al. "TM9SF1 promotes bladder cancer cell growth and infiltration", World Journal of Clinical Oncology, 2024 Crossref	34 words — 3%
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