Downregulation of transmembrane 4 superfamily 1 gene expression inhibits esophageal squamous cell carcinoma cell viability and Cisplatin resistance and regulates microRNA expression

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ABSTRACT

Introduction: Esophageal squamous cell carcinoma (ESCC) is the most aggressive subtype of esophageal cancer (EC) having a 5-year survival rate below 25% due to chemoresistance and poor treatment outcome, thus necessitating strategies to counteract. Transmembrane 4 Superfamily 1 (TM4SF1) is a cell surface protein that regulates cancer phenotypes and chemoresistance but remains elusive in ESCC. MicroRNAs (miRNAs) play key roles as tumor suppressors or oncogenes and are potential EC diagnostic and prognostic biomarkers. This study investigates the effects of TM4SF1 silencing on ESCC cell viability and cisplatin resistance, and explores differential miRNA expression as potential mechanisms. **Materials and Methods:** TM4SF1 gene expression in ESCC KYSE150 cells and normal esophageal epithelial HET-1A cells was measured using qRT-PCR. It was then silenced by transfecting with short-hairpin RNA (shTM4SF1). After TMS4F1 silencing, its effect on ESCC cell viability and half-maximal inhibitory concentration (IC50) of cisplatin after 24 h was determined using MTT assay. Differential miRNA expressions were sequenced using whole transcriptomic analysis pairing with KEGG pathway enrichment analysis and target gene prediction. **Results:** TM4SF1 gene was highly expressed in KYSE-150 cells compared to HET-1A cells. Silencing TM4SF1 significantly reduced ESCC cell viability by ~70% compared to transfection controls. The IC50 of cisplatin was lower in TM4SF1-silenced cells (34.59±0.27µM) than in non-silenced cells (40.62±1.13 µM). Sequencing results revealed 36 upregulated and 54 downregulated miRNAs, with hsa-miR-7-5p and hsa-miR-210-3p being the highest upregulated and hsa-miR-30a-3p the lowest downregulated. KEGG identified cell cycle and proteoglycans in cancer as potential pathways, while highly dysregulated targeted genes were involved in cell cycle, apoptosis, and cell survival signaling, including BCL2, CASP9, BAX, FADD, AKT3, MSH3, PIK3CB, PIK3CD, TOP2A, BCL2L12, PIK3R3, XPA, CASP3, MDM2, REV3L, and ERCC1. **Conclusion:** TM4SF1 regulates ESCC cell viability, chemosensitivity, and miRNAs associated with cell cycle, apoptosis, and survival, necessitating further studies to confirm the underlying molecular mechanisms.