Serican Journal of Medicine
2025, VOL. 2, NO. 2, 23724
https://doi.org/10.17161/sjm.v2i2.23724

Novel Roles of Mitochondrial Outer Membrane Protein TOMM20 in Prostate Cancer

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ARTICLE HISTORY
Received: March 14, 2025
Accepted: March 21, 2025

KEYWORDS
TOMM20, prostate cancer, mitochondria, Nrf2 pathway, androgen receptor

Commentary:

TOMM20 is a mitochondrial outer membrane protein composed of five conserved subdomains: the N-terminal membrane-anchor domain, a linker domain rich in charged amino acids, a tetratricopeptide repeat (TPR) motif, a glutamine-rich domain, and a C-terminal domain [1]. The transcription of the *TOMM20* gene is regulated by NRF2 [2], and its subcellular distribution is correlated with mitochondrial membrane potential [3]. As a key import receptor of the mitochondrial pre-protein translocation system, TOMM20 recognizes and transports precursor proteins with N-terminal cleavable pre-sequences synthesized in the cytoplasm. Together with TOMM22, TOMM70, TOMM5, TOMM6, TOMM7, and TOMM40, TOMM20 forms the outer membrane translocation enzyme complex (TOM complex), ensuring efficient and accurate protein import into mitochondria. This process is critical for maintaining mitochondrial function and cellular homeostasis. Additionally, TOMM20 plays a role in regulating mitophagy by binding to PINK1 [4], cell pyroptosis by interacting with BAX [5-7], and apoptosis by binding to BCL2 [8]. Due to its essential role in mitochondrial function, TOMM20 is widely used as a marker for mitophagy [9-12], mitochondrial mass [13, 14], cellular oxidative phosphorylation [15], and mitochondrial respiration [16].

Aberrant TOMM20 expression has been implicated in various diseases, including neurodegenerative disorders such as Parkinson's disease [17, 18] and multiple cancers [19-26]. TOMM20 overexpression has been reported in colon cancer [19], osteosarcoma [20], anaplastic thyroid cancer [23], liver cancer and stomach cancer [24], chordoma [25], and laryngeal cancer [26]. Upregulated TOMM20 promotes proliferation, invasion, and migration in colon cancer cells [19], and enhances proliferation, apoptosis resistance, and chemoresistance in osteosarcoma cells [20]. Moreover, TOMM20 expression is positively correlated with metastasis and recurrence in chordoma [25] and is associated with poor prognosis in gastric cancer [22] and laryngeal cancer [26]. Conversely, TOMM20 knockdown in melanoma cells reduces sensitivity to CCCP and iron [6].

Our recent study revealed that TOMM20 expression is elevated in prostate cancer (PCa) tissues compared to non-malignant prostate tissues and is positively correlated with androgen receptor (AR) expression. As a transmembrane protein, TOMM20 interacts with AR through its TPR domain in the cytoplasm, stabilizing AR protein levels and influencing its transcriptional activity. Since PCa progression is driven by androgen/AR signaling, androgen deprivation therapy (ADT) is the first-line treatment. However, the response to ADT is temporary, and most patients develop castration-resistant prostate cancer (CRPC) and metastasis within 2-3 years. Second-generation AR antagonists such as Enzalutamide and Abiraterone, have extended survival and improved the quality of life for patients with metastatic CRPC, but resistance remains a major challenge. The underlying mechanisms of drug resistance are not fully understood.

We discovered that TOMM20 plays a crucial role in maintaining AR protein stability and transcriptional activity. RNA-seq analysis revealed that TOMM20 knockdown significantly downregulates AR-regulated genes, including *KLK2, KLK3, FKBP5,* and *TMPRSS2*. Furthermore, TOMM20 depletion reduces both cytoplasmic and nuclear AR protein levels, promoting AR degradation through an SKP2-mediated ubiquitin-proteasome pathway, independent of heat shock proteins (HSPs) [27]. While previous

studies have reported that the cytoplasmic domain of TOMM20 exhibits chaperone-like activity [27], our findings demonstrate that AR stability depends not only on HSP70/HSP90 but also on TOMM20's chaperone-like function. These results suggest that TOMM20 may serve as a biomarker for PCa progression and a promising target for therapeutic development [28].

Approximately 10-17% of PCa patients develop neuroendocrine prostate cancer (NEPC), an aggressive subtype that often arises from conventional PCa following treatment with second-generation AR antagonists like Enzalutamide or Abiraterone [29]. NEPC is characterized by the expression of neuroendocrine markers such as synaptophysin (*SYP*) and chromogranin A (*CHGA*) and low or absent AR and PSA secretion [28-30]. Although significant progress has been made in characterizing the molecular characteristics of NEPC, the mechanisms underlying neuroendocrine trans-differentiation remain elusive, and the key driver genes of NEPC have yet to be fully elucidated.

Our study suggests that Enzalutamide induces TOMM20 degradation via the autophagy-lysosomal pathway, leading to increased intracellular reactive oxygen species (ROS) levels and activation of the PI3K/AKT signaling pathway. TOMM20 depletion promotes epithelial-mesenchymal transition (EMT), enhances cancer stem-like properties, and confers resistance to AR antagonists. Stable TOMM20 knockdown facilitates the trans-differentiation of PCa adenocarcinoma into NEPC [31]. Two potential mechanisms may contribute to treatment-induced NEPC trans-differentiation: (1) Enzalutamide-induced AR degradation and downregulation of AR-regulated genes allow the survival of PCa cells lacking AR expression, and (2) loss of TOMM20 triggers PI3K/AKT-driven EMT, promoting the acquisition of a stem-like and NEPC phenotype.

Beyond its established roles, TOMM20 may have additional functions due to its dynamic interactions within the TOM complex [32]. It regulates apoptosis and mitophagy through interactions with BCL2 and PINK1 [4, 8] and is localized at the mitochondria-associated endoplasmic reticulum membrane (MAM), a crucial hub for mitochondrial-ER signaling. Future studies should explore TOMM20's role in mitochondrial-ER communication and its impact on mitochondrial mass and quality control, further elucidating its significance in cancer biology.

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