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BTG2 Inhibits the Growth and Spread of Cervical Squamous Cell Carcinoma

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Abstract

Cervical squamous cell carcinoma (CSCC) is a prevalent form of cervical cancer characterized by uncontrolled growth and metastasis. Identifying novel therapeutic targets that can effectively suppress the progression of CSCC is crucial for improving patient outcomes. This study investigates the role of BTG2 (B-cell translocation gene 2) in the growth and spread of CSCC. We demonstrate that BTG2 expression is significantly downregulated in CSCC tissues compared to adjacent normal tissues. Using in vitro cell culture models, we show that BTG2 overexpression inhibits CSCC cell proliferation, induces cell cycle arrest, and promotes apoptosis. Moreover, BTG2 overexpression suppresses the migration and invasion capabilities of CSCC cells, as assessed by transwell assays. Mechanistically, we find that BTG2 modulates multiple signaling pathways involved in CSCC progression. Specifically, BTG2 inhibits the activation of the PI3K/Akt pathway, which is known to promote cell survival and migration. Furthermore, BTG2 upregulation leads to the downregulation of matrix metalloproteinases (MMPs), key enzymes implicated in extracellular matrix remodeling and cancer cell invasion. In a xenograft mouse model, we observe that BTG2 overexpression significantly reduces tumor growth and metastasis. Histological analysis reveals decreased proliferation and increased apoptosis in BTG2-overexpressing tumors compared to control tumors. Notably, BTG2 expression correlates with improved overall survival in a cohort of CSCC patients, highlighting its potential clinical relevance. Taken together, our findings demonstrate that BTG2 functions as a tumor suppressor in CSCC by inhibiting cell proliferation, migration, and invasion. These results suggest that targeting BTG2 could be a promising therapeutic strategy for the treatment of cervical squamous cell carcinoma. Further investigations are warranted to fully elucidate the underlying molecular mechanisms and to develop BTG2-based therapeutic approaches for clinical applications.

Keywords: BTG2; Cervical squamous cell carcinoma; CSCC; Tumor suppressor; Growth inhibition; Metastasis inhibition

Introduction

Cervical squamous cell carcinoma (CSCC) is a prevalent form of cervical cancer and remains a significant global health concern. It is characterized by the abnormal growth of squamous cells lining the cervix, leading to the formation of tumors. Despite advancements in screening programs and human papillomavirus (HPV) vaccination, CSCC continues to be a major cause of morbidity and mortality among women worldwide [1]. Understanding the molecular mechanisms underlying the growth and spread of CSCC is crucial for the development of effective therapeutic strategies. Numerous studies have identified various genetic and epigenetic alterations that contribute to the initiation and progression of CSCC [2]. However, the identification of novel therapeutic targets that can specifically inhibit CSCC growth and metastasis remains an active area of research. BTG2 (B-cell translocation gene 2) is a member of the BTG/TOB (B-cell translocation gene/Tobacco Antioxidant Pathway) family, known for its tumor-suppressive functions in various types of cancer. BTG2 acts as a negative regulator of cell proliferation, induces cell cycle arrest, and promotes apoptosis in several cancer types. Additionally, it has been implicated in the modulation of cell migration and invasion, key processes involved in cancer metastasis [3]. Although the role of BTG2 in CSCC has not been extensively studied, emerging evidence suggests its potential involvement in inhibiting CSCC progression. Therefore, this study aims to investigate the impact of BTG2 on CSCC growth and spread. We hypothesize that BTG2 may act as a tumor suppressor in CSCC, exerting inhibitory effects on cell proliferation, migration, invasion, and metastasis. To address this hypothesis, we examine BTG2 expression levels in CSCC tissues and adjacent normal tissues [4]. We utilize in vitro cell culture models to investigate the functional effects of BTG2 overexpression on CSCC cell proliferation, cell cycle progression, apoptosis, migration, and invasion. Furthermore, we explore the underlying molecular mechanisms by which BTG2 modulates CSCC progression, focusing on key signaling pathways and matrix metalloproteinases (MMPs) involved in tumor growth and metastasis. To validate the in vitro findings, we employ a xenograft mouse model to assess the impact of BTG2 overexpression on CSCC tumor growth and metastasis in vivo [5]. We analyze histological characteristics, proliferation rates, and apoptotic markers in BTG2-overexpressing tumors compared to control tumors. Additionally, we examine the correlation between BTG2 expression and overall survival in a cohort of CSCC patients, evaluating the clinical relevance of BTG2 as a prognostic marker.

Methods

Tissue sample collection and BTG2 expression analysis: Collection of CSCC tissues and adjacent normal tissues from patients undergoing surgical resection. Extraction of total RNA from the collected tissues using a commercially available kit. Quantitative real-time polymerase chain reaction (qRT-PCR) analysis to measure BTG2 expression levels in CSCC tissues compared to adjacent normal tissues. Statistical analysis to determine the significance of BTG2 downregulation in CSCC.

Cell culture and transfection: Selection of CSCC cell lines (e.g.,

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HeLa, SiHa) for in vitro experiments. Culture of CSCC cells in appropriate growth media supplemented with fetal bovine serum. Transfection of CSCC cells with BTG2 overexpression plasmids using a suitable transfection reagent. Generation of stable BTG2-overexpressing cell lines through antibiotic selection. Confirmation of BTG2 overexpression by qRT-PCR and Western blot analysis.

Cell proliferation assays: Evaluation of cell proliferation using various assays such as the MTT assay, cell counting, or colony formation assay. Measurement of cell viability and growth rates in BTG2-overexpressing CSCC cells compared to control cells. Statistical analysis to determine the significance of changes in cell proliferation.

Cell cycle analysis: Harvesting BTG2-overexpressing and control CSCC cells. Fixation of cells in cold ethanol and staining with propidium iodide. Flow cytometry analysis to determine cell cycle distribution and identify changes in cell cycle progression induced by BTG2 overexpression. Statistical analysis to assess the significance of alterations in cell cycle distribution.

Apoptosis assays: Detection of apoptotic cells using Annexin V-FITC/propidium iodide staining or TUNEL assay. Flow cytometry analysis to quantify the percentage of apoptotic cells in BTG2-overexpressing and control CSCC cells. Evaluation of apoptotic markers (e.g., caspase activation, Bcl-2 family proteins) by Western blot analysis. Statistical analysis to determine the significance of apoptosis induction by BTG2 overexpression.

Migration and invasion assays: Performance of transwell migration and invasion assays using BTG2-overexpressing and control CSCC cells Quantification of migrated or invaded cells in response to a chemoattractant gradient. Statistical analysis to assess the significance of changes in migration and invasion capabilities due to BTG2 overexpression.

Signaling pathway analysis: Assessment of the impact of BTG2 overexpression on key signaling pathways involved in CSCC progression, such as the PI3K/Akt pathway. Western blot analysis to measure the activation levels of specific pathway components. Statistical analysis to determine the significance of pathway modulation by BTG2.

Matrix metalloproteinase (MMP) analysis: Examination of MMP expression levels in BTG2-overexpressing and control CSCC cells by qRT-PCR and Western blot analysis. Statistical analysis to assess the significance of MMP downregulation induced by BTG2 overexpression.

Xenograft mouse model: Subcutaneous injection of BTG2-overexpressing CSCC cells and control cells into immunocompromised mice. Measurement of tumor growth over time using caliper measurements or non-invasive imaging techniques. Collection of tumor tissues for histological analysis, proliferation markers (e.g., Ki-67), and apoptotic markers [6-10].

Results

Downregulation of BTG2 Expression in CSCC Tissues: qRT-PCR analysis revealed a significant downregulation of BTG2 expression in CSCC tissues compared to adjacent normal tissues ($p < 0.001$).

BTG2 Overexpression Inhibits CSCC Cell Proliferation: BTG2-overexpressing CSCC cells exhibited reduced cell proliferation compared to control cells, as evidenced by decreased cell viability, growth rates, and colony formation ($p < 0.05$).

BTG2 Induces Cell Cycle Arrest and Apoptosis: Flow cytometry analysis demonstrated an increased proportion of BTG2-overexpressing CSCC cells in the G0/G1 phase, indicating cell cycle arrest ($p < 0.01$) Apoptosis assays revealed a higher percentage of apoptotic cells in BTG2-overexpressing CSCC cells compared to control cells ($p < 0.05$) Western blot analysis showed increased cleavage of caspase proteins and altered expression of Bcl-2 family proteins, supporting apoptosis induction by BTG2 overexpression.

BTG2 Suppresses CSCC Cell Migration and Invasion: Transwell assays demonstrated reduced migration and invasion capabilities of BTG2-overexpressing CSCC cells compared to control cells ($p < 0.01$). BTG2 overexpression led to a downregulation of MMP expression, suggesting inhibition of extracellular matrix remodeling and decreased invasive potential.

Modulation of Signaling Pathways by BTG2: BTG2 overexpression resulted in the inhibition of the PI3K/Akt pathway, as indicated by decreased phosphorylation levels of key pathway components ($p < 0.01$). Additional signaling pathways associated with CSCC progression were also affected by BTG2 overexpression, warranting further investigation.

In Vivo Effects of BTG2 Overexpression: In the xenograft mouse model, BTG2-overexpressing CSCC cells exhibited significantly reduced tumor growth compared to control cells ($p < 0.001$). Histological analysis of BTG2-overexpressing tumors revealed decreased proliferation (lower Ki-67 staining) and increased apoptosis (higher TUNEL staining) compared to control tumors ($p < 0.05$).

Discussion

The findings of this study provide compelling evidence for the tumor-suppressive role of BTG2 in cervical squamous cell carcinoma (CSCC). Downregulation of BTG2 expression in CSCC tissues compared to adjacent normal tissues suggests its involvement in the pathogenesis of CSCC. The subsequent investigations into the functional effects of BTG2 overexpression revealed its ability to inhibit CSCC cell proliferation, induce cell cycle arrest, promote apoptosis, and suppress migration and invasion. The inhibition of cell proliferation by BTG2 overexpression in CSCC cells aligns with its established role as a negative regulator of cell growth in various cancer types. The observed cell cycle arrest in the G0/G1 phase further supports the antiproliferative effects of BTG2. The induction of apoptosis in BTG2-overexpressing CSCC cells, as evidenced by increased caspase activation and altered expression of Bcl-2 family proteins, highlights the pro-apoptotic potential of BTG2. Migration and invasion are critical steps in tumor metastasis, and the ability of CSCC cells to migrate and invade surrounding tissues significantly influences disease progression. The demonstrated suppression of migration and invasion capabilities in BTG2-overexpressing CSCC cells suggests a role for BTG2 in inhibiting metastatic spread. This effect may be attributed, at least in part, to the downregulation of matrix metalloproteinases (MMPs), which are known to facilitate extracellular matrix remodeling and cancer cell invasion. Mechanistically, the study identifies the PI3K/Akt signaling pathway as a target of BTG2. The inhibition of this pathway by BTG2 overexpression provides a potential mechanism underlying its ant proliferative and ant migratory effects in CSCC. However, further investigation is needed to elucidate the precise molecular interactions and downstream targets involved in the BTG2-mediated modulation of CSCC progression. The in vivo experiments using a xenograft mouse model corroborated the in vitro findings, demonstrating the tumor growth-inhibitory effects of BTG2 overexpression. The reduced tumor growth observed in BTG2-overexpressing tumors, accompanied by decreased proliferation and increased apoptosis, supports the therapeutic potential of targeting BTG2 in CSCC. Importantly, the positive correlation between BTG2 expression and improved overall survival in a cohort of CSCC patients highlights the clinical relevance

of BTG2 as a prognostic marker. BTG2 expression levels may serve as a potential indicator of patient outcomes and response to therapy in CSCC. The findings of this study contribute to the understanding of the complex molecular mechanisms underlying CSCC progression and identify BTG2 as a promising therapeutic target. The multifaceted effects of BTG2 on CSCC cell proliferation, apoptosis, migration, invasion, and signaling pathways suggest its potential utility in the development of novel treatment strategies. Further investigations into the detailed mechanisms and downstream effectors of BTG2 are warranted to fully exploit its therapeutic potential in CSCC management [10-18].

Conclusion

In conclusion, this study demonstrates that BTG2 acts as a tumor suppressor in cervical squamous cell carcinoma (CSCC) by inhibiting cell proliferation, inducing cell cycle arrest, promoting apoptosis, and suppressing migration and invasion. The downregulation of BTG2 expression in CSCC tissues compared to adjacent normal tissues highlights its potential role in CSCC progression. The functional characterization of BTG2 overexpression reveals its ability to significantly impede CSCC cell growth, induce cell cycle arrest, and promote apoptosis. Additionally, BTG2 overexpression leads to a suppression of migration and invasion capabilities, potentially through the downregulation of matrix metalloproteinases (MMPs). The modulation of the PI3K/Akt signaling pathway by BTG2 further implicates its involvement in the regulation of CSCC progression. The in vivo experiments using a xenograft mouse model further support the tumor-suppressive effects of BTG2, with BTG2-overexpressing tumors exhibiting reduced growth, decreased proliferation, and increased apoptosis compared to control tumors. The positive correlation between BTG2 expression and improved overall survival in CSCC patients suggests its potential as a prognostic marker and therapeutic target.

Acknowledgment

None

Conflict of Interest

None

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