BTG2 suppresses the invasion and metastasis of triple-negative breast cancer by inhibiting the ubiquitination-mediated degradation of BECN1.

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Abstract

Background: Triple-negative breast cancer (TNBC) is aggressive, heterogeneous, and lacks effective targeted therapies. BTG2 is implicated as a tumor suppressor, but its specific role and mechanism in TNBC metastasis remain elusive.

Objective: This study aims to elucidate whether and how BTG2 inhibits TNBC invasion and metastasis by regulating the degradation of the key autophagy protein, BECN1.

Key Finding: BTG2 is Downregulated in TNBC and Correlates with Poor Prognosis

Functional Validation: BTG2 Inhibits Malignant Phenotypes of TNBC

Mechanism: BTG2 Stabilizes BECN1 Protein and Activates Autophagy; BTG2 Competitively Binds RNF123 to Prevent BECN1 Ubiquitination

Conclusion: BTG2 suppresses TNBC invasion and metastasis by stabilizing BECN1 and activating autophagy, through antagonizing its E3 ligase RNF123. Our findings establish BTG2 as a promising prognostic biomarker and therapeutic target for TNBC.

Introduction

Triple-negative breast cancer (TNBC) is an aggressive subtype associated with high rates of relapse, metastasis, and poor overall survival[1, 2]. The absence of established therapeutic targets limits treatment options, and the clinical benefits of newer therapies like immune checkpoint inhibitors remain heterogeneous[3, 4]. Therefore, elucidating new molecular mechanisms driving TNBC progression is critical for developing effective treatments.

The ubiquitin-proteasome system (UPS) is a key regulator of protein stability, and its dysregulation is implicated in tumorigenesis[5]. E3 ubiquitin ligases, such as RING-finger protein RNF123 (KPC1), provide specificity to the UPS by recognizing target substrates, making them attractive therapeutic targets[6].

BTG2 is an antiproliferation protein whose expression is frequently reduced in cancers, suggesting a tumor-suppressive role[7]. However, its precise functions and underlying mechanisms in TNBC are not fully understood. BECN1, a core autophagy regulator, is a well-established tumor suppressor, and its degradation is a critical control point in oncogenesis[8, 9].

While both BTG2 and BECN1 are implicated in cancer suppression, the regulatory link between them is unknown. This study aims to investigate a novel mechanism: whether BTG2 inhibits TNBC progression by interacting with the E3 ligase RNF123 to prevent the ubiquitin-mediated degradation of BECN1, thereby stabilizing this key tumor suppressor.

Methods and Materials

Using the TCGA database, we analyzed BTG2 expression levels and their prognostic significance in TNBC, which we further validated through IHC staining of clinical TNBC samples. Functional assays, including cell viability, colony formation, transwell migration, and invasion assays, as well as mouse xenograft experiments, were performed to assess the impact of BTG2 on TNBC cell proliferation, migration, and invasion. To elucidate the underlying mechanism, we employed mass spectrometry (MS), co-immunoprecipitation (Co-IP), and immunofluorescence confocal microscopy to examine the interaction between BTG2 and BECN1. Additionally, Western blotting, qPCR, cycloheximide chase, and ubiquitination assays were conducted to determine how BTG2 regulates BECN1 protein stability and ubiquitination.

Results

BTG2 was significantly downregulated in TNBC tissues, and this downregulation correlated with poor prognosis (Figure 1). Functional studies demonstrated that BTG2 suppressed TNBC cell proliferation, colony formation, migration, and invasion, findings further corroborated by xenograft tumor models (Figure 2). Mechanistically, BTG2 increased BECN1 levels by inhibiting its proteasomal degradation. Specifically, BTG2 expression reduced BECN1 ubiquitination, prolonged its half-life, and activated autophagy (Figure 3). Furthermore, we discovered that BTG2 stabilizes BECN1 by binding to RNF123, thereby blocking RNF123-mediated ubiquitination of BECN1 (Figure 3).

Figure 1

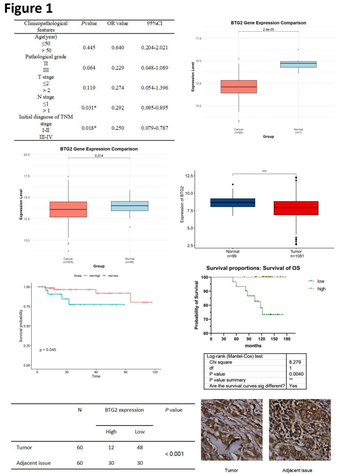


Figure 2

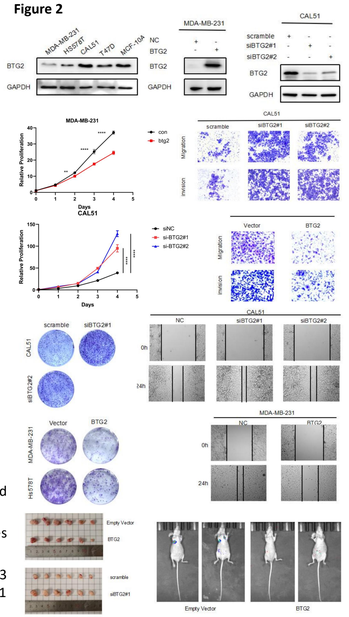


Figure 3

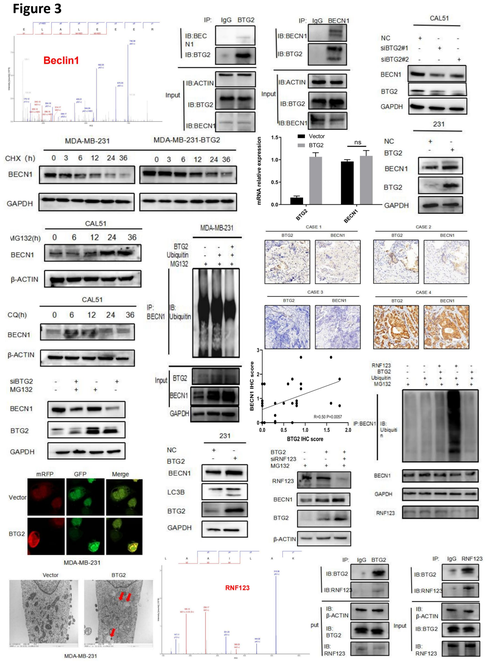


Figure 1. BTG2 is downregulated in TNBC tissues and associated with poor prognosis.

Figure 2.BTG2 suppresses TNBC malignant phenotypes (proliferation, migration, invasion) in vitro and in vivo.

Figure 3. BTG2 stabilizes BECN1 by binding to the E3 ligase RNF123, thereby blocking RNF123-mediated BECN1 ubiquitination and proteasomal degradation.

Discussion

In this study, we demonstrate that BTG2 suppresses invasion and metastasis in triple-negative breast cancer (TNBC) by inhibiting the ubiquitination-mediated degradation of BECN1. Consistent with previous reports describing BTG2 as a tumor suppressor in multiple malignancies[7], our analyses revealed that BTG2 expression is markedly reduced in TNBC tissues and correlates with poor prognosis. Functional experiments showed that BTG2 restoration significantly inhibited TNBC cell proliferation, colony formation, migration, and invasion, both in vitro and in xenograft models.

Mechanistically, our data identify a novel pathway through which BTG2 binds to the E3 ubiquitin ligase RNF123, thereby blocking RNF123-mediated ubiquitination and proteasomal degradation of BECN1. Since BECN1 plays a pivotal role in autophagy regulation and tumor suppression[8], the stabilization of BECN1 by BTG2 enhances autophagy and reduces metastatic potential in TNBC cells. These findings expand the known functions of BTG2 beyond cell cycle and apoptosis control, positioning it as a key regulator of the autophagy-metastasis axis in aggressive breast cancer.

Importantly, modulation of the ubiquitin–proteasome system has emerged as a promising therapeutic approach for restoring the stability of critical tumor suppressors in various cancers[10]. Thus, pharmacological activation of BTG2 or inhibition of the RNF123-BECN1 interaction may provide new therapeutic opportunities for TNBC, a subtype that currently lacks effective molecular targets.

In conclusion, our findings reveal that BTG2 suppresses TNBC progression by preventing RNF123-mediated BECN1 degradation, leading to enhanced autophagy and reduced metastatic capacity. This study highlights the BTG2-BECN1-RNF123 signaling axis as a potential diagnostic marker and therapeutic target for TNBC management.

Conclusions

Our findings demonstrate that BTG2 interacts with the E3 ligase RNF123 to suppress BECN1 ubiquitination and proteasomal degradation, leading to autophagy activation and inhibition of TNBC invasion and metastasis. These results highlight BTG2 as a potential diagnostic marker and therapeutic target for TNBC.

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