BTG2: A rising star of tumor suppressors (Review)

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Abstract. B-cell translocation gene 2 (BTG2), the first gene identified in the BTG/TOB gene family, is involved in many biological activities in cancer cells acting as a tumor suppressor. The BTG2 expression is downregulated in many human cancers. It is an instantaneous early response gene and plays important roles in cell differentiation, proliferation, DNA damage repair, and apoptosis in cancer cells. Moreover, BTG2 is regulated by many factors involving different signal pathways. However, the regulatory mechanism of BTG2 is largely unknown. Recently, the relationship between microRNAs and BTG2 has attracted much attention. MicroRNA-21 (miR-21) has been found to regulate BTG2 gene during carcinogenesis. In this review, we summarize the latest findings in the investigations of biological functions of BTG2 and regulation of its expression, with an emphasis on miR-21 in regulation of BTG2 gene in various cancers. B-cell translocation gene 2 (BTG2), also known as PC3 or TIS21, belongs to the antiproliferative (APRO) gene family. Several studies have demonstrated that BTG2 is involved in a large number of physiological and pathological processes, such as cell differentiation, proliferation, apoptosis, and other cellular functions, acting as a tumor suppressor. In this review, we summarize the latest findings in BTG2 studies, highlighting the mechanisms for the regulatory effects of microRNAs (miRNAs) on BTG2 gene expression in the most common human cancers.

Contents

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1. Discovery of BTG2 in TOB/BTG gene family

The TOB/BTG genes belong to the anti-proliferative gene family that includes six different genes in vertebrates: TOB1, TOB2, BTG1 BTG2/TIS21/PC3, BTG3 and BTG4 (Fig. 1). The conserved domain of BTG N-terminal contains two regions, named box A and box B, which show a high level of homology to the other domains (1-5). Box A has a major effect on cell proliferation, while box B plays a role in combination with many target molecules. Compared with other family members, BTG1 and BTG2 have an additional region named box C (Fig. 1) (6). Both box A and box B have a relationship with CCR4-associated factor 1 (Caf1), which attributes to the ribonuclease D (RNase D) family of deadenylases and belongs to the CCR4-Not deadenylase complex (7).

The BTG domain has an effect on a protein-protein interactions, and the interaction exists between BTG1/2 and a homeobox transcription factor Hoxb9 (5). In myoblasts, BTG1 has an effect on the activity of several transcription factors (8). BTG3 can affect E2F1, an important transcription factor in cell cycle progression especially for the S-phase. Moreover, the binding between DNA and the E2F1-DP1 transcription factor complex can be inhibited by BTG3, which has a negative effect on the inhibition of S-phase progression (9).

To our best knowledge, BTG2 is the first identified gene in the BTG/TOB family (10), which is located on band 2, region 3 of the long arm of chromosome 1 and encodes 158 amino acids (11). In 1991, the PC3 gene was discovered as an immediate early gene induced by nerve growth factor (NGF) in rat PC12 cell line during neuronal differentiation (12), which has the characteristics of anti-proliferation molecules. Fletcher *et al* (13) reported that tetradecanoyl phorbol acetate (TPA), a tumor-promoting agent, induced mouse NIH3T3 cell line to produce TIS21 that has the same gene sequence as PC3. In 1996, Rouault *et al* (14) cloned and localized the human BTG2 gene, and reported that its expression is regulated by a p53-dependent mechanism and its function is related to cell cycle regulation and cellular reaction to DNA damage. TIS21, PC3, and BGT2 are the homologous genes in mice, rats, and humans, respectively.

2. Biological functions of BTG2

BTG2 is expressed in various organs and tissues, such as the spleen, thymus, lungs, stomach and large intestine, with

high expression levels being reported in the lung, intestines, pancreas and prostate (15). It has been demonstrated that BTG2 can arrest cells at G1/S and G2/M transition, increase apoptosis (14), promote retinoic acid-induced differentiation in hematopoietic cells (16) and inhibit expansion of thymocytes (17). Moreover, BTG2 also plays important roles in cell differentiation, proliferation, DNA damage repair and apoptosis.

Differentiation. It has been demonstrated that BTG2 gene is involved in the development and differentiation of nerve cells and hematopoietic cells (18). It is overexpressed in the G0/G1 phase of the cell cycle in neuroepithelial cells (18), suggesting that it plays a role in the induction of nerve growth and differentiation. Overexpression of BTG2 is involved in the differentiation process of HL-60 cells after treatment with 12-O-tetra-decanoylphorbol-13-acetate (TPA) or retinoic acid (RA) (19). Most notably, BTG2 gene expression occurs earlier than p21 expression, indicating BTG2 plays an important role in the differentiation processes of hematopoietic cells (19).

Anti-proliferation. BTG2 plays an important role in regulation of cell proliferation, through regulating the cell cycle in some solid tumors. Zhang *et al* (20) reported that BTG2 inhibited the proliferation and invasion of gastric cancer cells. Ma and Ni (21) demonstrated that BTG2 overexpression can suppress the cell growth and promote apoptosis in pancreatic cancer cells. Moreover, BTG2 overexpression inhibits the expression of cyclin D1, MMP-1, and MMP-2, and suppresses the proliferation of lung cancer cells (22). These findings support that BTG2 acts as an anti-proliferative gene in carcinogenesis. However, Wagener *et al* (23) showed that BTG2 promoted the migration of bladder cancer cells and BTG2 overexpression is associated with poor survival in patients with bladder cancer. Thus, the roles of BTG2 in oncogenesis may be cancer type-dependent.

DNA damage repair. Our previous studies demonstrated that p53, the most investigated tumor suppressor gene, can upregulate BTG2 expression, and downregulate cyclins D1 and E during hepatocarcinogenesis (1,24). When DNA is damaged, p53 is upregulated, which will induce DNA repair and cause the cell cycle arrest at G1/S-phase. If damage cannot be repaired, p53 will induce programmed cell death or apoptosis. It has been demonstrated that BTG2 exerts its antitumor effect through p53-dependent Ras signal transduction pathway (3). Thus, the BTG2 gene expression is significantly increased when DNA is damaged. Various DNA-damaging agents, such as, ionizing radiation, some chemical substances and ultraviolet may induce the BTG2 expression via p53 and cause the cell cycle arrest at G1 phase through inhibiting cyclin D1, which may promote DNA damage repair (25,26). Recently, Choi *et al* (27) reported that TIS21/BTG2/PC3 plays a role in the DNA damage response. In their study, TIS21/BTG2/PC3 accelerates the repair of DNA double strand breaks (DSBs) according to the increased activity of the methylation of Mre 11 and protein arginine methyltransferase 1 (PRMT1) (27). However, the detailed mechanisms for the involvement of BTG2/TIS21/PC3 in DNA damage repair are not fully understood and need further investigation.

Apoptosis. Several studies demonstrated that BTG2 can promote or induce cell apoptosis (21,28). Zhang *et al* (20) reported that BTG2 not only restrains the biological activities of gastric cancer cells, such as cell growth and proliferation, cell migration and invasion, but also promotes tumor cell apoptosis. Zhang *et al* (28) found that BTG2 induces cell apoptosis and suppresses cell invasion of human triple-negative breast cancer MDA-MB-231 cells. Hong *et al* (29) report that the treatment of U937 cells with BTG2 inhibits the expression of cell division cycle 2 kinase (cyclin B1-CDC2) and causes cell apoptosis. However, it is reported that high level of PC3 gene in PC12 cells can inhibit cell apoptosis (30). Thus, the effects of BTG2 on cell apoptosis may be cell type-dependent and the precise mechanisms need further investigation.

3. Regulation of BTG2 gene

BTG2 is considered an early growth response gene. In our previous study, we established an improved diethylnitrosamine (DEN)-induced primary hepatocellular carcinoma (HCC) rat model and evaluated the expression of BTG2, p53, cyclins D1 and E in HCC (1). We found that expression of the BTG2 and p53 was detected at the early stage of DEN treatment, and peaked at 5 weeks and then declined gradually. The expression of cyclins D1 and E was increased significantly during hepatocarcinogenesis (1). Actually, the expression of BTG2 appears to be time-dependent in the cell cycle, but the regulatory mechanism of BTG2 is complicated. BTG2 regulates cell growth, death, migration, apoptosis, and radiosensitization through several important signaling pathways (Fig. 2).

The classical pathway of BTG2 on senescence phenotype. As aforementioned, following DNA damage, BTG2 expression is stimulated by p53 and the expression of cyclin D1 is downregulated, inhibiting G1/S transition via the pRB pathway. This pathway is a classical pathway and the activation of BTG2 is p53-dependent. BTG2 expression is also upregulated by oxidative stress via reactive oxygen species-protein kinase C-NFκB pathway, which is independent of p53 status (31). Additionally, BTG2 suppresses the expression of cyclin E and inhibits G1/S transition in 293 cells in the absence of p53, Rb and cyclin D1 (32).

The pathway of BTG2 on cell migration. The low expression of BTG2 is found in many human cancer tissues and its loss is related to cell migration and invasion. Lim *et al* (33) reported that BTG2 has a negative effect on cancer cell metastasis by inhibiting Src-FAK (focal adhesion kinase) signaling through downregulation of reactive oxygen species (ROS) generation. Wagener *et al* (23) also reported that endogenous BTG2 expression contributes to the migratory potential of bladder cancer cells and the high levels of BTG2 in bladder cancers are correlated with poor clinical prognosis in patients with bladder cancer.

The pathway of BTG2 on cell growth. A recent study demonstrated that cisplatin attenuates prostate cancer cell proliferation in part by upregulation of BTG2 through the p53-dependent pathway or p53-independent NF-κB pathway (34). BTG2 negatively regulates JAK2/STAT3 signaling

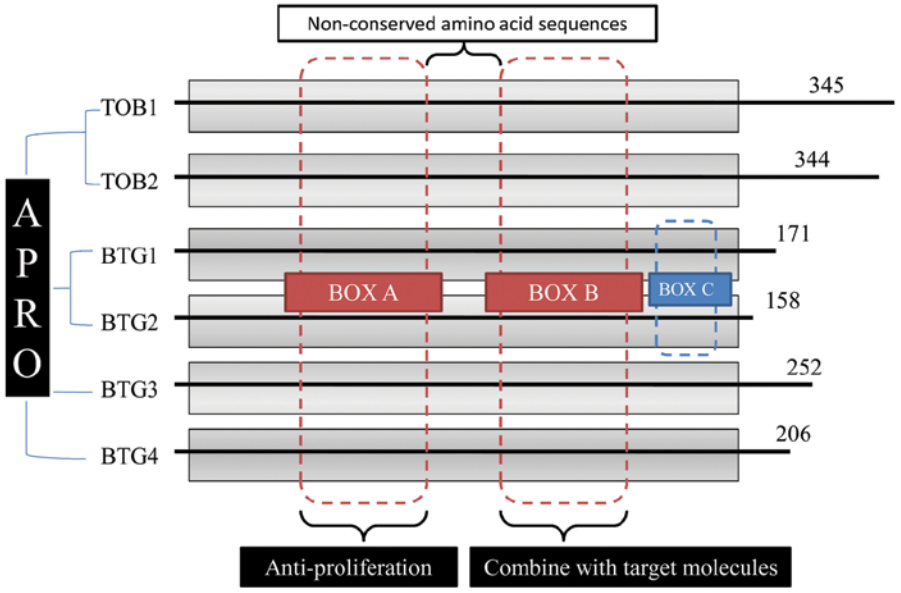

Figure 1. Structures of six members of the APRO gene family.

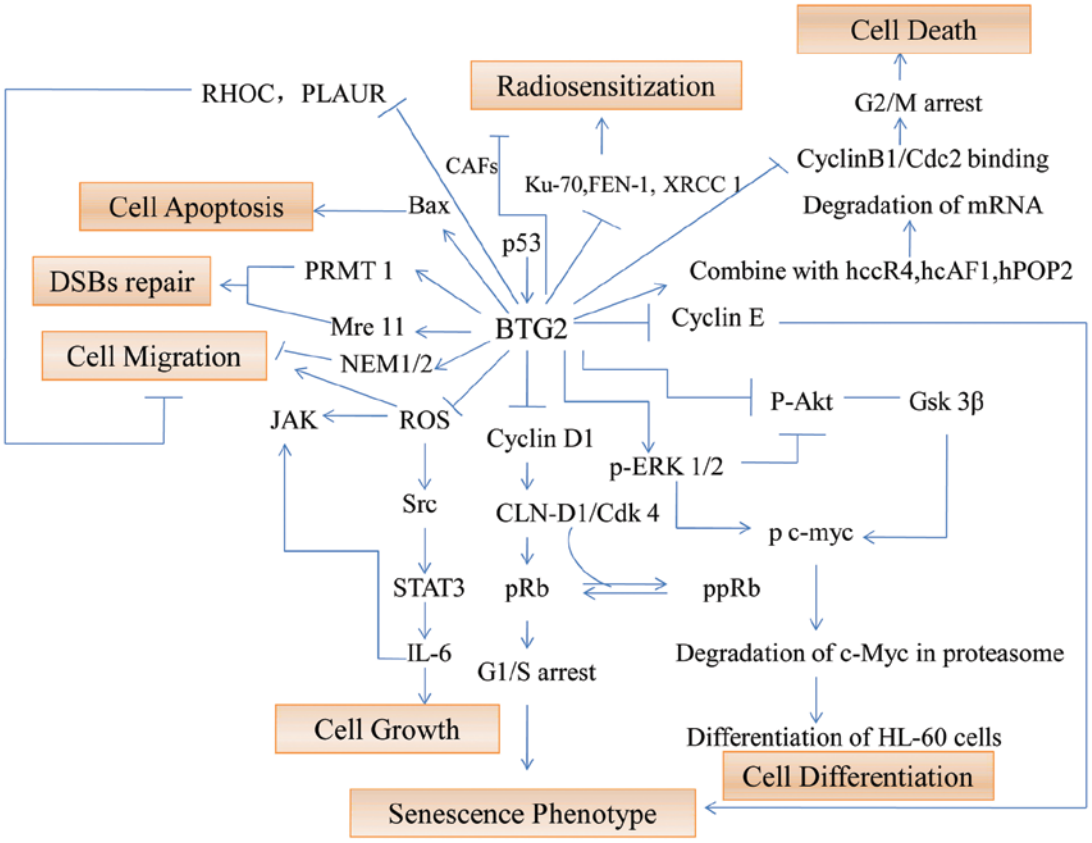

Figure 2. The signaling pathways involving the BTG2 gene.

through the regulation of ROS generation indirectly (35). Therefore, it is likely that BTG2 exerts its antitumor activity via the downregulation of cytokine secretion.

The pathway of BTG2 on cell differentiation. PC3/Tis21 knockout mice display impaired terminal differentiation of hippocampal granule neurons and defective contextual memory (36). Moreover, BTG2 regulates the differentiation of HL-60 cells mainly through activation of Erk1/2 and inhibition of Akt, resulting in the downregulation of c-Myc (37).

The pathway of BTG2 on cell death. BTG2 negatively regulates cyclin D1 and decreases the expression of FoxM1 cell cycle regulatory factor through inhibiting the binding of cyclin B1/

Table I. The roles of BTG2 in different cancers.

Cancer type	Major findings
Laryngeal carcinoma	BTG2 is a pan-cell cycle regulator and tumor suppressor (51)
Lung cancer	BTG2 inhibits cell proliferation and invasion (22,44,47,54)
Prostate cancer	BTG2 loss leads to acquisition of epithelial-mesenchymal transition (EMT) (49)
Gastric cancer	BTG2 inhibits cell invasion and proliferation (20)
Renal cell carcinoma	Impaired BTG2 expression is found in clear cell renal carcinoma (61)
Breast cancer	Downregulation of BTG2 is associated with poor survival in patients with breast carcinoma; upregulation of BTG2 increases the radiosensitivity of breast cancer cells (42,50)
Pancreatic cancer	BTG2 inhibits cell growth and induces apoptosis (21)
Bladder cancer	BTG2 promotes cell migration and BTG2 overexpression is associated with poor survival in patients with bladder cancer (23)

Cdks (38). Ryu *et al* (39) found that BTG2 is upregulated by PKC-δ in U937 cells, and induces G2/M arrest and cell death through inhibiting cyclin B1-Cdc2 binding. BTG2 stimulates PRMT1 (protein arginine methyltransferase 1), promoting DNA repair of DSBs and Mre 11 methylation (27,40). In addition, BTG2 upregulates Bax gene to promote apoptosis (41).

The pathway of BTG2 on radiosensitization. It has been demonstrated that BTG2 is one of the important radiation response genes (25). A recent study showed that BTG2 improves the radiosensitivity of breast cancer cells by affecting cell cycle distribution, enhancing radiation-induced apoptosis, and inhibiting DNA repair-related protein expression (42). Moreover, Chu *et al* (26) reported that cancer-associated fibroblasts (CAFs) can reduce the levels of GADD45 and BTG2, both are major radiation-induced genes. These data suggest that BTG2 may be one of the most important response genes during radiotherapy.

In summary, BTG2 plays an important role in cancer development and progression (Fig. 2). However, like other genes, the regulatory mechanisms of BTG2 in cancer are complex and need further investigation.

4. Relationship between miRNAs and BTG2

It is well documented the miRNAs inhibit mRNA translation and reduce mRNA stability by binding to the 3'-untranslated region (3'UTR) of the target mRNAs (43-45). Nearly 30% of human genes are regulated by miRNAs (46). A miRNA has multiple target genes, while a target gene can be regulated by multiple miRNAs. It has been found that miRNAs are associated with tumor formation and progression through regulation of oncogenes or tumor suppressor genes (46).

BTG2 and miR-21. miRNA-21 (miR-21) is one of the important miRNAs and is widely distributed in human tissues and cells. The overexpression of miRNA-21 has been observed in a variety of carcinomas, such as prostate, gastric, colon breast and lung cancers; miRNA-21 promotes cell growth and proliferation and inhibits cell apoptosis (47-53). Recent studies demonstrated that BTG2 is a new target gene of miR-21 in prostate cancer cells (49), laryngeal cancer cells (52) and melanoma cells (53). Liu *et al* (52) uncovered that miR-21 promotes the proliferation of laryngeal cancer cells through downregulation of BTG2. Sun *et al* (54) reported that miR-21 is overexpressed and negatively regulates BTG2 expression in lung cancer cells, promoting lung cancer cells growth, progression and invasion. Coppola *et al* (49) demonstrated that the loss of BTG2 and upregulation of miR-21 contribute to the epithelial-mesenchymal transition in prostate cancer cells. Thus, miR-21 plays an important role in regulating BTG2 gene during carcinogenesis.

BTG2 and other miRNAs. Several studies have shown that BTG2 is regulated by other miRNAs in different cancers. A recent study demonstrated that miR-21, miR-23A and miR-27A cooperatively regulate the expression of tumor suppressor genes, including PDCD4, BTG2 and NEDD4L (55). Jalava *et al* (56) reported that androgen-mediated miR-32 is overexpressed in castration-resistant prostate cancer (CRPC), resulting in a reduced expression of BTG2. Alvarez-Saavedra *et al* (57) report that BTG2 and Paip2a are direct targets of miR-132 in the mouse suprachiasmatic nucleus. Interestingly, our previous study also observed that overexpression of miR-18 in hepatocellular cancer cells negatively regulates the BTG2 expression (58).

5. Relationship between BTG2 and cancer

Several studies have suggested that BTG2 can be a potential biomarker for prognosis in cancer patients (23,28,59,60). BTG2 is closely associated with other tumor suppressor genes, such as RB, p53 and p73 (1-3,14); BTG2 expression is downregulated in laryngeal carcinoma (52). In patients with pancreatic cancer, the mRNA expression of BTG2 is obviously suppressed in tumor tissues compare with the surrounding non-cancerous tissues (21). Struckmann *et al* (61) reported that the BTG2 expression is reduced in clear cell renal cell

carcinomas. Zhang *et al* (20) demonstrated that BTG2 inhibits cell invasion and proliferation of the gastric adenocarcinoma cells SGC7901 and MKN45. Takahashi *et al* (59) revealed that low expression of BTG2 is related to tumor size, grade, metastasis, recurrence and poor survival in patients with breast carcinoma. Our study also found that BTG2 is involved in the differentiation of cancer cells and associated with the clinical pathology (24). The low level of BTG2 expression is associated with poor differentiation of cancer cells. Moreover, Hu *et al* (42) found that BTG2 overexpression in human breast cancer cell line MCF-7 increases cell sensitivity to ionizing radiation; increased apoptosis is observed alongside decreased expression of cyclins D1 and B1, Ku70, FEN-1, and XRCC1 protein as well as increased BAX protein expression. Furthermore, Quy *et al* (35) observed that BTG2 plays a role in cancer microenvironment by downregulating IL-6 expression in human dermal fibroblasts through inhibiting STAT3 activation. In summary, BTG2 acts as a tumor suppressor in most solid tumors. However, upregulation of BTG2 promotes cell migration and is related to poor survival in bladder cancer. Future studies should explore the underlying mechanisms (Table I).

6. Concluding remark

In this review, we summarized evidence supporting that the BTG2 gene has anti-proliferative properties in most human cancers. BTG2 mediates the expression of several genes that decide the fate of cells through activation of some downstream factors in different pathways. It is also a radiosensitizer in breast cancer cells, through inducing cell cycle arrest, promoting radiation-induced apoptosis, and modulating the expression of DNA repair-related proteins. However, the underlying mechanisms of the BTG2 tumor suppressing activities are not fully understood. There are many issues to be addressed in future investigations, including the regulation of BTG2-associated signal pathways, identification of BTG2 target molecules, interactions between miRNAs and BTG2 expression and function of the different roles of BTG2 in different cancers, and the potential of BTG2 as a diagnostic and prognostic marker in cancer patients.

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