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Research Article

Research Progress of BTG2 as a Tumor Prognostic Factor

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Abstract

Cancer is a major public health issue and the main cause of death worldwide. Despite improvements in diagnostic techniques and treatment methods, cancer still seriously affects the quality of life of patients, which cause serious social and economic burdens. Therefore, there is an urgent need to identify potential biomarkers to improve diagnosis, treatment, and prognosis of cancer. BTG2 is a cell proliferation suppressor gene that serves as a tumor suppressor gene in the occurrence and development of various tumors. Many studies have shown that BTG2 can serve as a prognostic marker in various tumors. So, fully tap the potentials of BTG2 as a tumor prognostic marker will bring more possibilities to provide a new method or new diagnostic and therapeutic tool for treating cancer.

Introduction

BTG2 (B cell translocation gene 2) is a member of the BTG/Tob antiproliferative protein family of the BTG gene. It has a conserved domain at the N-terminus, known as the BTG domain, which characterizes the BTG/Tob factor [1-3]. It is a cell proliferation suppressor gene that can inhibit the proliferation of various tumor cells. BTG2 was initially identified as a p53 inducible gene. The expression of BTG2 significantly increases in response to DNA damage, which is a result of p53 induction, as in this case, the expression of functionally lost p53 mutants does not lead to BTG2 accumulation (Figure 1). BTG2 has also been proven to be effective against nuclear factors- κB (NF-κB) Activation sensitivity. BTG2 expression is induced by a variety of genotoxicity reagents (ionizing radiation, ultraviolet ray, doxorubicin), growth factors, estrogen, serum, tetradecanoyl acetate phorbol ester, interleukin-6 and cyclic adenosine monophosphate (cAMP) [4].

BTG2 is expressed in various tissues and organs such as lung tissue, thymus, spleen, and gastrointestinal tissue, and participates in various biological processes such as cell proliferation, differentiation, DNA damage repair, and apoptosis [5]. Previous studies have reported low expression

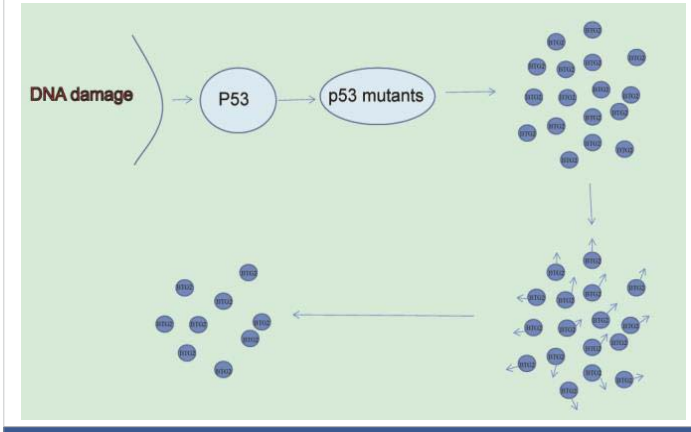

Figure 1: The mechanism of BTG2 that was regulated by P53 during DNA damage.

of BTG2 in many malignant tumors, such as lung cancer, hepatocellular carcinoma, and gastric cancer [6-8] and serve as potential targets for cancer prevention and treatment.

The role of BTG2 in cancer

BTG2 in lung adenocarcinoma: Lung cancer is one of the most common malignant tumors, ranking first in terms of cancer-related mortality worldwide. Research has found

that BTG2 can inhibit the occurrence and development of lung adenocarcinoma through multiple pathways. CircCRIM1 functioned as a sponge of miR-125b-5p to improve BTG2 expression, thereby suppressing lung adenocarcinoma development. Circular RNA circCRIM1 suppresses lung adenocarcinoma cell migration, invasion, EMT, and glycolysis by regulating the miR-125b-5p/ BTG2 axis [9]. Zhang, et al. found that when BTG2 is downregulated, the prognosis of patients is poor, which may be due to its close correlation with immune infiltration in lung adenocarcinoma [10].

BTG2 in hepatocellular carcinoma: Hepatocellular carcinoma is the third leading cause of cancer-related deaths worldwide, causing approximately 6 million deaths annually. In China, HCC is the third leading cause of cancer death and the fourth most commonly diagnosed cancer. We found that the mechanism of PRMT5-induced proliferation was partly mediated by the down-regulation of BTG, which led to the cell cycle arrest of hepatocellular carcinoma cells in the G1 phase. Downregulation of BTG2 can mediate PRMT5-induced proliferation, leading to cell cycle arrest of hepatocellular carcinoma cells in the G1 phase. Overexpression of BTG2 leads to cell cycle arrest in the G1 phase and down-regulates the expression of cyclin D1 and cyclin E1, thus slowing down the growth rate of hepatocellular carcinoma [11]. Moreover, Lv, et al. found that the ROS/ P65/ BTG2 signaling center regulates epithelial-mesenchymal transition (EMT) and is closely related to the metastasis of hepatocellular carcinoma, which can mediate the pro-metastatic effect of SRXN1 in hepatocellular carcinoma cells [12]. The BTG2 gene can regulate the cells (CSCs)-like traits of side population (SP) cells in HCC cell lines and serve as a molecular prognostic marker for hepatocellular carcinoma [13].

BTG2 in breast cancer: Metastases are responsible for the majority of deaths due to breast cancer. BTG2 has been proven to be significantly reduced in breast cancer, and its overexpression inhibits the proliferation and invasion of the MDA-MB-231 cell line and promotes apoptosis [14]. Another study suggests that BTG2 inhibits breast cancer progression by differentially regulating the mTORc2-AKT1-NFAT1-PHLPP2 and mTORc1 signaling axes [15]. Although there is a lot of evidence that BTG2 plays an important role in the development of breast cancer, few researchers have studied BTG2 as a prognostic factor of breast cancer.

BTG2 in non-small cell lung cancer: Lung cancer, predominantly non-small cell lung cancer, which constitutes more than 85% of all lung cancers, is the most commonly diagnosed malignant disease and is a leading cause of cancer-related deaths worldwide. BTG2 promotes cell apoptosis and inhibits cell growth during the occurrence and development of non-small cell lung cancer [16]. Upregulated LINC01234 promotes metastasis of non-small cell lung cancer cells by activating VAV3 and inhibiting BTG2 expression [17]. The methylation and integrated prognostic signatures based on BTG2 are stable and reliable biomarkers for early-stage non-small cell lung cancer. They may have new applications for appropriate clinical adjuvant trials and personalized treatments in the future [18].

BTG2 in leukemia and lymphoma: There have been no studies that have reported that BTG2 can serve as a prognostic factor for leukemia tumors, but some studies have shown that BTG1, in the same family with BTG2, may have a downregulation of gene expression during diagnosis, which may accompany the occurrence of leukemia [19]. Our data demonstrated that the mutation profiles of Primary testicular diffuse large B-cell lymphoma (PT-DLBCL) were distinguished from classic DLBCL and the mutation of the BTG2 gene may serve as a valuable biomarker in the prognosis of PT-DLBCL [20].

BTG2 in esophageal squamous cell carcinoma: Esophageal cancer is one of the most common malignant tumors in the digestive system. In addition, esophageal cancer is the fourth deadliest cancer in China, with 3.07 million cases and 2.83 million deaths annually, with esophageal squamous cell carcinoma (ESCC) accounting for approximately 90% of the total. A result showed that through the Cox regression model univariate and multivariate analysis, tumor differentiation, N stage, M stage, clinical stage, and BTG2 level were closely related to patient prognosis, and the gene expression of BTG2 would be an independent prognostic factor for ESCC [21].

BTG2 in colorectal cancer: Colorectal cancer is the third most common cancer and has become a major concern worldwide. BTG2 can inhibit the proliferation and metastasis of colon cancer cells, thereby regulating the occurrence of colorectal cancer, and there is a negative correlation between BTG2 expression and promoter methylation level, indicating that epigenetic modification may be the mechanism for regulating the expression of these genes in colon cancer cells. Therefore, these genes may be the targets of Nor-methods, thus becoming the targets of colon cancer treatment [22].

BTG2 in ovarian cancer: Ovarian cancer is the main and most common female reproductive malignancy among female patients, with 25000 deaths per year in China alone. BTG2 inhibits the proliferation and migration of ovarian cancer cells in vitro, induces cell cycle arrest, and enhances cisplatin sensitivity. BTG2 is downregulated in ovarian cancer tissue and is associated with patient survival [23].

BTG2 in other cancer: BTG2 expression was downregulated in skin cancer cell lines [24]. The expression level of BTG2 is downregulated in prostate cancer, but no research has shown that BTG2 can serve as a prognostic factor for prostate cancer [25]. Some studies have found that BTG2 may be a key target for pancreatic cancer, but no researchers have found that BTG2 can be a tumor prognostic factor for

pancreatic cancer. BTG2 can serve as a key gene in regulating the proliferation, apoptosis, and cell cycle arrest of thyroid cancer cells [26]. The BTG2 can reduce some malignant phenotypes of these tumor cells. But it could not impact the ability of invasion of gastric cancer cells, so could not restrain the metastasis of gastric cancer [27].

Conclusion and perspective

Cancer is a major public health issue and the main cause of death worldwide. Despite the diagnostic techniques and treatment methods has been improved, malignancy still affects the quality of life of patients, causing serious social and economic burdens. Therefore, it is an urgent need to explore the potential mechanisms to identify potential biomarkers to improve the diagnosis, treatment, and prognosis of cancer. Numerous studies have shown that BTG2 plays an important role in the occurrence and development of tumors. And research has found that the gene expression levels of BTG2 were downregulated in various tumors, including lung adenocarcinoma, hepatic cancer, ESCC, colorectal cancer, and ovarian cancer, skin cancer, prostate cancer, pancreatic cancer. But BTG2 could be a prognostic marker only in lung adenocarcinoma, hepatic cancer, ESCC, colorectal cancer, and ovarian cancer. However, we have only summarized whether BTG2 could serve as a prognostic factor in a few types of tumors, and there is insufficient research on the prognostic role of BTG2 in all tumors. These two shortcomings will make our article's argument insufficient. BTG2 is a tumor prognostic factor with the potential for tumor diagnosis. I think the potential of BTG2 as a tumor prognostic marker still needs further development. And I believe that an in-depth study through research on BTG2 will bring more possibilities for the diagnosis and treatment of tumors.

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