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The Role of BTBD7 in Normal Development and Tumor Progression

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Abstract

BTB/POZ domain-containing protein 7 (BTBD7) has a relative molecular weight of 126KD and contains two conserved BTB/POZ protein sequences. BTBD7 has been shown to play an essential role in normal human development, precancerous lesions, heat-stress response, and tumor progression. BTBD7 promotes branching morphogenesis during development and participates in the salivary gland, lung, and tooth formation. Furthermore, many studies have shown that aberrant expression of BTBD7 promotes heat stress response and the progression of precancerous lesions. BTBD7 has also been found to play an important role in cancer. High expression of BTBD7 affects tumor progression by regulating multiple pathways. Therefore, a complete understanding of BTBD7 is crucial for exploring human development and tumor progression. This paper reviews the research progress of BTBD7, which lays a foundation for the application of BTBD7 in regenerative medicine and as a biomarker for tumor prediction or potential therapeutic target.

Keywords

BTBD7, e-cadherin, development, tumor, EMT, invasion, metastasis

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Introduction

Human development is a continuous process with stages and procedures during which various organs gradually shape specific patterns and play certain physiological functions through repeated morphogenesis and tissue differentiation.[1] It has been found that most organs are composed of thousands of branches that maximize the exchange surface between epithelial cells and the lumen, such as the liver, lung, kidney, prostate, and breast.[2] However, when the cell undergoes mutation, it no longer follows the typical trajectory and may lead to various diseases, like tumors. Tumors, characterized by proliferation, transformation, and uncomplicated metastasis, are complex tissues composed of many different[3] interacting tumor cells. In recent years, studies have demonstrated that low survival rate of tumor patients[4] because of the presence of various factors in the tumor stroma that promote tumor recurrence[5] and resist treatment.

BTB/POZ proteins, belonging to the kuppel zinc finger protein family, play an important role in drosophila, mammals, and other eukaryotes.[6,7] BTB domain exists in the N-terminal, an evolutionarily highly conserved domain[8] containing approximately 115 amino acids.[9,10] The mRNAs of many BTB/POZ family members have alternative splicing, such as BTBD7. Researchers[11] found that it contains two conserved BTB/POZ protein sequences. BTBD7 is involved in human developmental processes, such as promoting meristem morphogenesis[12] and the differentiation of tooth roots and dentin.[13] During human development, cancer is a significant contributor to human mortality.[14,15] In tumor progression, various genes promote tumor progression, such as BTBD7, which is thought to contribute to the poor prognosis of tumors.[16,17] An in-depth study of the effects of BTBD7 in this review will help us better understand the process of normal development, regeneration, and disease progression.

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Effects of BTBD7 in Normal Tissues

BTBD7 Promotes Branching Morphogenesis

Embryonic organs are formed mainly by the repeated branching of epithelial cells,[18] such as the lungs and salivary glands. The study found that epithelial-mesenchymal transition (EMT), a process in which epithelial cells are transformed into cells with an interstitial phenotype by a specific procedure, plays an important role in embryonic development,[19] chronic inflammation,[20] tissue reconstitution,[21] and cancer metastasis.[22] EMT is characterized by decreased expression of cell adhesion molecules such as E-cadherin.[23] E-cadherin, a member of the cell adhesion factor family, plays an essential role in maintaining normal epithelial cell morphology and structural integrity.[24] Researchers discovered[12] that loss of E-cadherin in stably transfected cells led to unstable interepithelial cell adhesion and spreading. Therefore, loss of E-cadherin expression will accelerate EMT[22,25] and promote tumor metastasis.[26]

Fibronectin (FN), the main glycoprotein in the basement membrane, plays a catalytic role in EMT.[27] At the same time, the research found that[12,28] FN activated BTBD7, promoting cell proliferation by inducing Snail-2 and cell nuclear aggregation. Thus, when BTBD7 is knocked out, Snail2 expression and cleft formation are inhibited, resulting in reduced bud formation and branching inhibition (Figure 1). William P. Daley et al performed in vitro MDCK cell mock ectoblast experiments in which they found[29] that activated BTBD7 provided a mechanical link between the extracellular matrix and fissure growth. BTBD7 locally promotes epithelial branch morphogenesis by promoting Snail2(Slug) and inhibiting E-cadherin. Similarly, the knockdown of BTBD7 also inhibits the morphogenesis of pulmonary branches[30] (Figure 1). So BTBD7 aggregates locally in the process of branch morphogenesis to enable the regulation of the dynamics of epithelial cells.

BTBD7 Is Involved in Root Divergence, Dentin Differentiation, and Multitooth Formation

The tooth is divided into three parts: the crown, the neck, and the root. The root plays the role of chewing and fixing the tooth position.[31] The tooth is also divided into enamel, dentin, and pulp. The dental pulp, located in the dental pulp cavity surrounded by dentin, is the only soft tissue in the dental tissue. It is a highly vascularized nerve tissue, which can not only deal with the damage caused by bacterial invasion but also provide neurons with the sensitivity required for repair and regeneration.[32] Human dental pulp cells (hDPCs) play a pivotal role in the formation and regeneration of dentin,[33,34] and many genes are involved in dentin formation. For example, dentine salivary phosphoprotein (Dspp) is a major noncollagen protein. Dspp plays an essential role in dentin differentiation and mineralization,[35,36] while mutations in that can lead to dentin hypoplasia[37] and dentin mineralization defects.[38]

It has been confirmed[13] that BTBD7 was found in the cytoplasm and nucleus of hDPCs. Bao et al[13] showed that the knockdown of BTBD7 could temporarily promote the

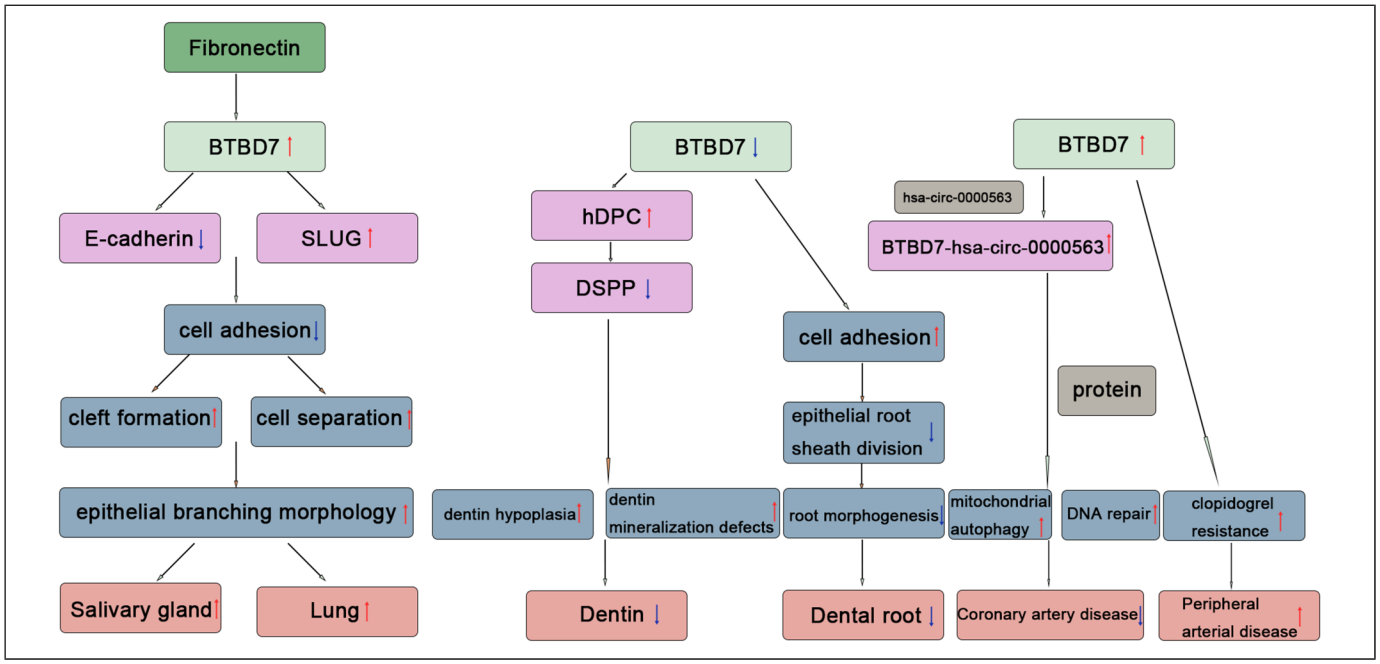

Figure 1. Fibronectin activates BTBD7, promoting cell separation and cleft formation by inducing SLUG and E-cadherin. As a result, BTBD7 affects the development of salivary glands and lungs. Knockdown of BTBD7 inhibits dentin differentiation by temporarily promoting hDPCs proliferation and inhibiting Dspp expression in hDPCs. BTBD7 affects root development by inhibiting epithelial root sheath formation. BTBD7-hsa-circ-0000563 is a circRNA, which binds proteins to participate in mitochondrial autophagy and DNA repair, promoting the repair of coronary artery disease. BTBD7 is involved in clopidogrel resistance, which affects the repair of peripheral artery disease. "↑" Promote, "↓" Inhibit.

proliferation of hDPCs and inhibit the expression of Dspp in hDPCs. BTBD7 participated in the diffusion of hDPCs and regulated the presentation of the critical pluripotent gene Dspp. Therefore, BTBD7 might be involved in dentin differentiation by regulating the formation of Dspp. It was demonstrated that BTBD7 was expressed in a specific spatiotemporal pattern in the epithelial root sheath of the tooth root of a baby rat. This distribution suggested that the BTBD7 might be involved in molar root development. Therefore, BTBD7 may play a significant role in dentin formation and tooth roots' growth (Figure 1). In summary, BTBD7 may be involved in root development and dentin differentiation of molars, and the specific mechanism needs further study.

Regulation of BTBD7 in Human Coronary Artery

Coronary artery disease (CAD) is a significant cause of human mortality.[39] Mitochondrial autophagy[40,41] and DNA repair[42,43] have been found to reduce atherosclerosis[41] and thus inhibit CAD. CircRNA is an endogenous RNA[44] whose high stability and conserved phenotype are thought to be important for human cancer, diabetes,[45–47] and CAD.[48,49]

BTBD7_hsa_circ_0000563 is a circRNA[50] first identified in animals[51] and later found in both normal human tissues[50,52,53] and cancer cells.[54] It contains a conserved binding site for RNA-binding proteins. Researchers[55,56] found seven proteins bound to it by GO and KEGG enrichment analysis. They are involved in mitochondrial autophagy and DNA repair pathways, accelerating the healing process of CAD. However, when the BTBD7 gene acts alone, it is engaged in clopidogrel resistance, leading to treatment failure in peripheral arterial disease[57] (Figure 1). Thus, BTBD7 may be an independent predictor of CAD.

BTBD7 Is Involved in the Heat-Stress Response and Progress of Precancerous Lesions

Global warming[58] can pose a significant challenge to animal husbandry.[59] Heat stress can cause heat stroke, heat cramps in humans,[60] and reduced immunity in animals,[61,62] which leads to disease[63]and reduces productivity.[63] Thus, researchers[64,65] have conducted a series of studies in which they found that the BTBD7 gene is involved in heat stress/heat shock and cellular adaptation functions in the presence of stressors. BTBD7 promotes angiogenesis,[16] which causes vasodilation in animals with heat stress,[66] leading to heat shock. Therefore, it is crucial to understand the heat stress response better and to develop effective methods to mitigate it.

Precancerous lesions, such as leukoplakia and chronic atrophic gastritis, are equally life-threatening in humans. They are lesions that have the potential to develop into malignant tumors. Various genes, such as BTBD7,[67] are involved in the precancerous process and promote carcinogenesis. BTBD7 gene is controlled by abnormally expressed microRNAs[67] and is involved in the precancerous process of gastric cancer,[68,69] thus enabling the transformation of gastric cancer.[70,71] Nilva K Cervigne et al found[72] that BTBD7 acts as a promoter and is involved in progressive leukoplakia, and promotes the formation of oral squamous carcinoma. In summary, BTBD7 encourages the progression of oral and gastric cancers. Therefore, enhanced functional studies of the BTBD7 gene could help to understand better the transformation process of leukoplakia to oral squamous cell carcinoma and gastric cancer.

BTBD7: A Tumor Promoter

BTBD7: Invasion and Metastasis Promoter of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a common malignant tumor that occurs in normal liver tissue cells and has the characteristics of high incidence and mortality. It is reported that liver cancer has a high mortality rate as one of the fastest factors of cancer-related death in the United States.[73] HCC with EMT features exhibits higher metastasis, invasion, and poorer prognosis.[74]

The FUP1 could be a nuclear protein that may be an essential gene associated with HCC.[75] According to the GenBank database, FUP1 was also named BTBD7, which was first reported in 2001.[75] BTBD7 is a branching morphogenesis-related gene that regulates FN, E-cadherin, and Snail2, mediating EMT in HCC.[12,30] Yi-Ming Tao[16] et al selected HCCLM3[76] cells with high BTBD7 expression and metastasis rate as the study subjects and found that BTBD7 could activate the hoC-Rock2-FAK signaling pathway to promote MMP-9 and MMP-2 to produce microvessels. Moreover, this pathway promotes BTBD7 expression through a positive feedback process, resulting in decreased E-cadherin expression and increased expression of FN and Tvsit1, which promotes the EMT process (Figure 2 and Table 1). High MVD in HCC patients, a marker of angiogenesis in tumor tissue, is usually associated with poor prognosis.[77] In contrast, BTBD7 is associated with venous invasion, MVD, and HCC staging.[16] Therefore, BTBD7 is expected to be a critical factor in the treatment of hepatocellular carcinoma.

BTBD7 Promotes the Progress of Lung Cancer

Lung cancer, the malignancy with leading morbidity and mortality, is divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[78,79] SCLC, the most common type of lung cancer, is closely related to smoking. Lung cancer is a malignant tumor with a late diagnosis and no progress in treatment.[80] Standardized surgical treatment, radiotherapy, and chemotherapy can delay tumor growth and metastasis, prolong patient survival, and improve quality of life. However, there are still more challenges to completely curing lung cancer. The main reasons for treatment failure are recurrence, distant metastasis, and drug resistance. Therefore, to improve the cure rate and survival rates of lung cancer, we should

continuously strengthen the exploration of lung cancer-related genes and the progress of lung cancer treatment.

BTBD7 not only plays an essential role in the development of salivary glands and lungs,[12,30] but is also highly expressed in cancer development, progression, and metastasis.[17] In tumor progression, multiple factors can downregulate E-cadherin expression,[81,82] which in turn promotes EMT and tumor progression,[24,83] for example, transforming growth factor β (TGF-β).[84] In non-small cell lung cancer[85] and TGF-β1-induced lung cancer A549 cells,[17,86] BTBD7 downregulates E-cadherin expression and upregulates N-cadherin, vimentin, and FN expression, which in turn induces EMT and promotes lymphatic metastasis and lung cancer progression. The CD133 molecule is the most widely used surface marker in lung cancer stem cells, so researchers[87] selected these cells for follow-up experiments. It was found[87] that high expression of BTBD7 inhibits E-cadherin expression, thereby inhibiting EMT in CD133 cells. This process promotes the expression of the core embryonic stem cell transcription factors SOX2, OCT4, and Nanog, which promotes tumor stem cell properties and chemoresistance (Figure 2 and Table 1). In summary, BTBD7 promotes EMT and tumor progression, and patients with high BTBD7 expression have higher metastasis rates and lower survival rates than those with low expression. Therefore, inhibition of BTBD7, such as artesunate,[88] maybe a potential therapeutic target for lung cancer.

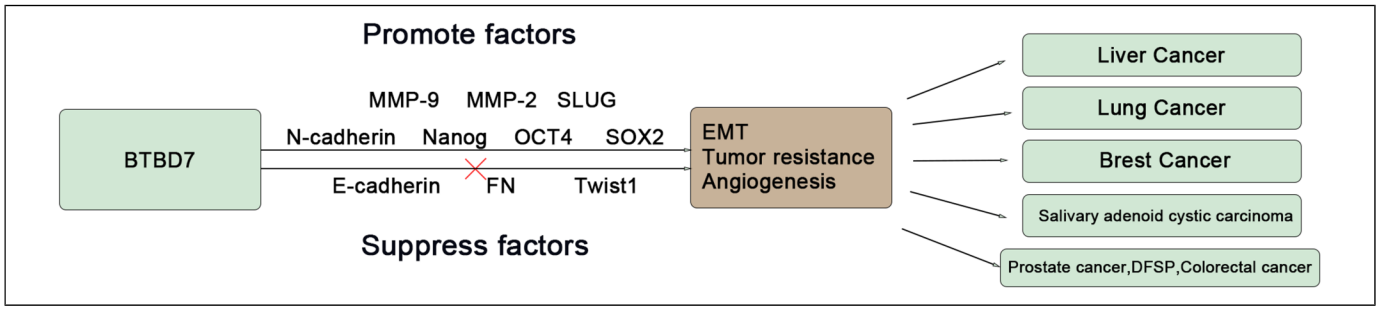

Figure 2. BTBD7 can activate N-cadherin, Nanog, OCT4, SOX2, MMP-9, MMP-2, and SLUG factors, and inhibit E-cadherin, FN, and Twist1 factors. Its processes promote EMT, tumor resistance, and angiogenesis, ultimately accelerating the progression of many cancers.

Table 1. BTBD7 Promotes Tumor Progression.

BTBD7	Access	Genes	Mechanisms	Cell	Types of cancer	Reference
↑	**Hoc-Rock2-FAK↑**	**MMP-9↑, MMP-2↑, E-cadherin↓, FN↓, Twist1↓**	**Angiogenesis↑, EMT↑**	**HCC-LM3↑**	**Liver Cancer↑**	15
↑		**E-cadherin↓, SOX2↑, OCT4↑, Nanog↑**	**EMT↑, Tumor resistance↑**	**CD133↑**	**Lung Cancer↑**	61
↓	**Wnt/β-catenin↓, Notch↓**		**EMT↓, Tumor resistance↓, Angiogenesis↓**	**MCF-10A, SKBR-3↓, MDA-MB-231↓. MCF-7↓, MCF-7/DOX↓. BT474↓, BT474/CIS↓**	**Breast Cancer↓**	67,108,73,79
↑		**SLUG↑, MMP-9↑, E-cadherin↓, FN↑**	**EMT↑**	**SACC-LM↑, SACC-83**	**Salivary adenoid cystic carcinoma↑**	87,88,89,90
↑		**E-cadherin↓, N-cadherin↑**	**EMT↑**		**Prostate cancer↑, dermatofibrosarcoma protuberans↑, Colorectal cancer↑**	123,102,101,

BTBD7: A Double-Edged Sword in Breast Cancer

Breast cancer is one of the most common malignant tumors in women,[89] accounting for 7% to 10% of all malignant tumors in the body. Moreover, we found breast cancer is a malignant tumor with a high degree of intertumor and intertumor heterogeneity.[90] Most patients with early breast cancer can have a reasonable cure rate through surgery combined with radiotherapy and chemotherapy, while some may not be cured. It has been found that poor treatment outcomes for breast cancer are often related to its drug resistance.[91] Therefore, we must continuously explore the genes related to the disease progression process to detect and treat cancer in time.

BTBD7 plays a crucial role in epithelial branching morphogenesis and tumor cell invasion. So, what role does BTBD7 play in the occurrence and development of breast cancer? Can it also promote the progress of breast cancer? SLUG acts as an essential transcription factor regulating EMT.[92] Zi-Xiong Li et al found[93] that silencing BTBD7 suppressed SLUG expression, suppressing EMT and inhibiting the tumor progression process. In addition, by studying common tumor signaling pathways, researchers found that only the Wnt signaling pathway was significantly repressed after the knockdown of BTBD7[94] and the Wnt signaling pathway is usually closely associated with the invasive metastatic effects of tumors.[95,96] β-catenin is a critical protein in the classical Wnt signaling pathway (ie, Wnt /β-catenin signaling pathway).[97] Therefore, Li Jun et al found that knockdown of the BTBD7 gene inhibited the activation of the Wnt/β-catenin signaling pathway, inhibiting the metastatic and proliferative capacity of human breast cancer MCF-7 cells. Similarly, it was found[98,99] that Notch signaling plays a crucial role in breast cancer progression. Researchers[100] analyzed the Cignal Finder Cancer 10-Pathway Reporter Array. They found that BTBD7 affects the Notch signaling pathway, and later experiments revealed that BTBD7 could inhibit cell proliferation, invasion, and migration by suppressing Notch1 signaling in breast cancer (Figure 2 and Table 1).

In breast cancer resistance studies, researchers have found that extracellular vesicles can regulate EMT[101] and promote tumor angiogenesis [102] and chemotherapy resistance.[103] MiR-887-3p is a microRNA[104] and is widely considered to be a promising biomarker of drug resistance in breast cancer.[105] Later, researchers[106] searched the Coexpedia database and found that BTBD7 was the target gene of miR-887-3p. In addition, it was found in related experiments that MDA-MB-231-derived extracellular vesicles carried miR-887-3p into breast cancer cells and inhibited the expression of BTBD7. This process activates the Notch1/Hes1 signaling pathway, which enhances drug resistance in breast cancer cells (Figure 2 and Table 1). The role of BTBD7 in human breast cancer needs to be better understood to accurately identify breast cancer and each therapeutic approach to breast cancer. Therefore, the application of BTBD7 may provide a promising avenue for treating breast cancer.

BTBD7: A New Marker of Salivary Adenoid Cystic Carcinoma

Salivary adenoid cystic carcinoma (SACC) is a relatively common malignancy of salivary gland origin. It is prone to metastasize along the nerves and blood circulation with a high recurrence rate.[107] SACC is mainly treated by surgery. However, the therapeutic effect still needs improving due to the lack of practical therapeutic markers, especially in patients with distant metastasis.[108]

EMMPRIN is a transmembrane glycoprotein that enhances EMT in hepatocellular carcinoma.[109] Slug enables cancer cells to maintain their stem cell properties[110,111] and promotes EMMPRIN, inhibits E-cadherin,[112] and promotes perineural infiltration of SACC.[113] It was found[114,115] that SLUG correlated significantly with BTBD7 expression and that BTBD7 promoted SLUG to promote MMP9 and inhibit E-cadherin, which in turn promoted the EMT process. In SACC tissues, researchers have also found that BTBD7 may stimulate feedback signals that impede the secretion of FN from the cell layer into the culture fluid in SACC tissues.[116,117] The mechanism of the role of BTBD7 and FN in cancer development needs to be further investigated (Figure 2 and Table 1). Therefore, BTBD7 may be a new therapeutic target for predicting SACC metastasis.

BTBD7 Plays a Facilitating Role in Other Tumors

Prostate cancer is a malignant tumor that occurs in the epithelial cells of the prostate[118] and is most common in elderly men. It is usually considered a relatively slow-progressing cancer that can be cured by surgery in the early stages and treated conservatively in the late stages. A related study of prostate cancer in Sardinia found that 13% of patients had a new BTBD7-SLC2A5 fusion,[119] demonstrating the importance of BTBD7 in the prostate cancer population. Similarly, Chen Bin[120] et al found that in patients with prostate cancer, higher levels of BTBD7 promoted EMT by down-regulating E-cadherin and up-regulating N-cadherin, thus promoting the progression of prostate cancer. In dermatofibrosarcoma protuberans (DFSP), a soft tissue sarcoma of the skin, the second exon of platelet-derived growth factor β (PDGFβ) was found to be genetically fused to collagen one alpha1 (COL1A1)[111,121] promoting tumor progression. Researchers have also found[122] that SLC2A5-BTBD7 fusions also occur at high frequencies in DFSP (Figure 2 and Table 1). Therefore, exploring gene fusions is a novel potential diagnostic and therapeutic target for this disease.

The role of BTBD7 was also found in colorectal cancer. Colorectal cancer is a multifocal tumor, accounting for 10% of oncology-related diagnoses yearly.[123] In industrialized countries, colorectal cancer is a common malignancy. Nearly 50% of colorectal cancer patients develop metastases and have a low survival rate. Furthermore, patients with metastatic or recurrent colorectal cancer require long-term intermittent treatment. To reveal the regulatory factors of colorectal cancer metastasis,

Grisard et al performed a forced single-cell suspension assay (FSCS).[124] They found that FSCS specifically selected CRC cells with EMT traits and pro-metastatic potential. Screening of microRNA libraries identified miR-23b[125,126] as a negative regulator of CRC metastasis. It was found[124,127] that transposon BTBD7-3′UTR insertion disrupted miR-23b and promoted BTBD7 expression, thereby conferring a metastatic advantage to CRC cells by conferring resistance to FSCS. Therefore, research on mir-23b and BTBD7 should be intensified to provide diagnostic and prognostic possibilities for colorectal cancer (Figure 2 and Table 1). Patients with these biological features should receive more aggressive treatment and closer follow-up.

Conclusion

Further exploration of the mechanism of BTBD7, its role in the human body's normal development, and how it affects the growth of tumors have also been reported. In human malignancies, high expression of BTBD7 may be a potential biomarker for tumor diagnosis, prognosis, or treatment. It is of great significance to guide the proliferation, differentiation, pathological typing, clinical symptoms, and prognosis of tumor cells. However, questions such as how BTBD7 plays a role in human development and how BTBD7 affects the progression, metastasis, and invasion of cancer require further research and exploration. In conclusion, further studies of BTBD7 markers will contribute to the exploration of human development and provide new methods for diagnosing, treating, and prognosis of tumor diseases. This review article will attract more relevant researchers to work together to reveal and validate the ideas presented in this paper.

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Declaration of Conflicting Interests

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An Ethics Statement

None. Because this article is a review and does not cover animal and human experimentation.

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