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Emerging role of ZBTB7A as an oncogenic driver and transcriptional repressor

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Abstract

ZBTB7A is a member of the POK family of transcription factors that possesses a POZ-domain at the N-terminus and Krüppel-like zinc-finger at the c-terminus. ZBTB7A was initially isolated as a protein that binds to the inducer of the short transcript of HIV-1 virus TAT gene promoter. The protein forms a homodimer through protein-protein interaction via the N-terminus POZ-domains. ZBTB7A typically binds to the DNA elements through its zinc-finger domains and represses transcription both by modification of the chromatin organization and through the direct recruitment of transcription factors to gene regulatory regions. ZBTB7A is involved in several fundamental biological processes including cell proliferation, differentiation, and development. It also participates in hematopoiesis, adipogenesis, chondrogenesis, cellular metabolism and alternative splicing of BCLXL, DNA repair, development of oligodendrocytes, osteoclast and unfolded protein response. Aberrant ZBTB7A expression promotes oncogenic transformation and tumor progression, but also maintains a tumor suppressive role depending on the type and genetic context of cancer. In this comprehensive review we provide information about the structure, function, targets, and regulators of ZBTB7A and its role as an oncogenic driver and transcriptional repressor in various human diseases.

Keywords ZBTB7A, Cancer, Disease, Zinc finger, BTB domain

1. Introduction

In humans, at least 49 genes encode for BTB (Broad-Complex, Tramtrack and Bric a brac)/ZF (Zinc finger) domain containing protein. These proteins are known as zinc finger and BTB (ZBTB) domain containing protein family and are sequence-specific silencers of gene expression. Siggs and Beutler (2012) identified three different types of ZBTB (ZBTB7A, ZBTB7B, and ZBTB7C) proteins which include ZBTB1-ZBTB6, ZBTB7A-ZBTB7C, ZBTB8A-8B, ZBTB9-ZBTB12, ZBTB16-17, ZBTB20-22, ZBTB24-26, ZBTB32-34, and ZBTB37-49 [1]. These proteins contain one BTB and four Zn-finger domains. ZBTB7A (584 amino acids) and ZBTB7C (619 amino acids) possess BTB domain at the same amino acid (34-101aa) position. ZBTB7C has highest amino acid sequence homology with ZBTB7A among all the BTB/Zn domain family protein. The four Zn-finger domains in ZBTB7A (382-404aa, 410-432aa, 438-460aa, and 466-490aa) and ZBTB7C (364-386aa, 392-414aa, 420-442aa, and 448-478aa) occur at different position in the amino acids sequence [2]. ZBTB7A, also known as Pokemon (POK), LRF (lymphoma related factor), or FBI-1 (factor binding IST protein 1), is a member of the POK family of transcriptional factors that contains an NH_2-terminal POZ/BTB domain and four COOH-terminal Krüppel-type zinc fingers. Proteins of POK family are known to function as transcriptional repressor through the recruitment of co-repressors such as NCoRs (nuclear co-repressor), SMRT (silencing mediator of retinoic acid and thyroid hormone receptor), mSin3A, BCOR (BCL6 interacting corepressor), CtBP (for C-terminal binding protein), or HDACs (histone deacetylases) to the promoter regions of various target genes. ZBTB7A regulates a large number of genes involved in cell proliferation, differentiation, and various developmental processes [3-11]. It binds DNA through its zinc-finger domains and regulates transcription both by regulating the organization of chromatin and recruitment of other transcription factors to the regulatory regions of the target genes [8, 12]. After binding to the DNA, ZBTB7A recruits various chromatin remodeling factors such as HDACs to facilitate target gene silencing **(Figure 1)** [13].

Studies reported that ZBTB7A/C play both proto oncogenic and tumor suppressive roles in cancer. It's oncogenic/tumor suppressive role is dependent on cancer type and stage-specific situation. ZBTB7A exerts proto oncogenic role generally by recruiting co-repressors at the promoter of tumor suppressive gene such as p21, to repress their transcriptional activity. In some cancers, such as colon, inhibition of key glycolytic enzymes positively correlate with ZBTB7A expression demonstrating its tumor suppressive role. ZBTB7A interaction with other proteins such as SOX9 and NF-κB results in the modification of cellular proliferation, invasion, apoptosis and drug-induced resistance in cancer cells. Literature revealed that miRNA-mediated regulation of ZBTB7A in human malignancy often depends on cancer type and is

stage-specific. Detailed mechanism of the role of ZBTB7A in cancer pathophysiology and its multifaceted functioning in other diseases has been presented in some recent reviews [14-15].

Accumulating evidences demonstrate that ZBTB7A regulates several key signaling pathways including EGFR, TGF-β, SMAD4, P^{14ARF}-MDM2-p53, androgen receptor (AR), and NF-κB [3, 16-19]. ZBTB7A interacts with transcription factors such as p65 (REL A) to regulate the accessibility of transcriptional regulatory regions for secondary transcription factors and specificity protein 1 (Sp1) to prevent their binding to the DNA [8, 20]. ZBTB7A functions as a transcriptional co-repressor for AR through the recruitment of NCoR1 and NCoR2 to the androgen response element (ARE) of target genes to negatively regulate AR signaling and AR-induced cell proliferation [19]. ZBTB7A is also reported to regulate the hemoglobin switching between fetal hemoglobin to adult hemoglobin during the maturation process of erythroid cells [21-23]. It plays a key role in the differentiation of B and T cell lineage by promoting the differentiation of B cells through inhibition of Notch signaling [9, 24]. ZBTB7A plays a significant role in the repair of double stranded breaks in DNA *via* non-homologous end joining pathway (NHEJ) and interacting with other proteins such as Ku70/80 [25]. It is reported that ZBTB7A regulates adipogenesis by indirectly controlling the expression of Cyclin E [26]. ZBTB7A also plays a significant role in the regulation of alternative splicing of BCLXL by interacting with the Src-Associated substrate in Mitosis of 68 kDa (SAM68) which results in reduced binding of SAM68 to BCLXL mRNA and selection of proximal 5′ splice site to produce BCLXL variants which supports cell proliferation and survival [27].

ZBTB7A has significant role in various developmental processes such as osteoclast growth, expansion of oligodendrocytes and uteri transplantation. It negatively regulates osteoclast development by downregulating nuclear factor of activated T cells c1 (NFATc1) [11, 28]. In the process of oligodendrocyte development, ZBTB7A regulates transcription of myelin-related genes and the Notch target Hes5, which is involved in the control of myelin formation and repair [29]. ZBTB7A mediates uterine receptivity in the process of uterine transplantation [30]. Involvement of ZBTB7A is also reported in the process of unfolded protein response (UPR) where it downregulates the process of UPR by binding to the lumen protein [31]. These observations highlight ZBTB7A as a key factor in the transcriptional regulation of fundamental pathways involved in cell proliferation, differentiation, and development.

2. Gene structure, mutation and post-transcriptional modifications

In humans, ZBTB7A gene is located within the syntenic chromosomal region on chromosome 19 (19p13.3) from 4043303- 4066899bp [4]. The gene contains three exons namely exon 1 (0 to +130), exon 2 (+11586 to +12847) and exon 3 (+18574 to 19066) [32-33]. According to NCBI database, ZBTB7A gene is transcribed into two transcript variants of 6437bp and 6319bp encoding the same protein.

ZBTB7A protein is composed of 584 amino acids having a molecular weight of 86 kDa. BTB domain of ZBTB7A is located at amino terminal and consists of 120 conserved amino acids responsible for protein-protein interactions. BTB/POZ domains mediate homo-dimerization and/or hetero-dimerization while interacting with other proteins via its N-terminus BTB domain. The zinc-finger domain is found in a majority of human proteins characterized by two conserved cysteine and histidine residue pairs, coordinating a zinc ion. The zinc-finger domain of ZBTB7A is located at the carboxyl terminal and is responsible for its DNA binding activity. ZBTB7A zinc-finger domain binds at promoter regions of the target genes having the consensus sequence G (A/G) GGG (T/C) (C/T) (T/C) (C/T) [12]. At the carboxyl–terminal, a nuclear localization signal (NLS) is located starting from amino acid 498 to 502 to ensure the constitutive nuclear localization of ZBTB7A [34-35]. BTB domain containing transcriptional regulators utilize their amino-terminal BTB domain (or POZ domain) for multimerization and recruitment of co-repressors.

Recent studies demonstrate that loss of ZBTB7A function is associated with several human cancers. Liu *et al*. (2016) analyzed the mutational landscape of ZBTB7A zinc finger domain and demonstrated that loss of a gene within chromosome 19p13.3 significantly decreases the copy number variant as a key mechanism reducing ZBTB7A mRNA level in colon cancer cells. ZBTB7A downregulation consequently increases the expression of key glycolytic enzymes which correlated with tumor progression and poor patient survival [36]. Hartmann *et al*. (2016) identified recurring ZBTB7A mutations in acute myeloid leukemia (AML) patients. These missense and truncating mutations results in alteration/loss of the DNA binding domain of ZBTB7A. These mutations in DNA binding (Zn-finger) domain disrupts the transcriptional repressor potential of ZBTB7A which ultimately results in reduced anti-proliferative potential in AML cells [37]. ZBTB7A mutation frequency in various human cancers is shown in OncoMX database [38].

At the post-transcriptional level, ZBTB7A inhibition upregulates E3 ligase TRIM25 thereby enhancing the ER-α ubiquitination and its proteasomal degradation. ZBTB7A also transcriptionally increase the expression of ER-α via indirectly binding to the region +146 to +461 bp downstream of the transcription start site of estrogen receptor 1 (ESR1) in breast cancer cells [39]. Roh *et al*. (2007) demonstrated that sumoylation mediated posttranslational modification of ZBTB7A regulates its transcriptional repression activity. The group identified ten potential sumoylation sites in the primary sequence of ZBTB7A which are located at lysines 61, 354, 371, 379, 383, 396, 486, 487, 536 and 539. Out of these sites, number K61 is the most putative site for sumoylation as mutation on this site weakens the co-repressor activity of ZBTB7A [40].

3. Interaction with other proteins

ZBTB7A is important transcriptional regulator involved in various processes such as cell cycle progression, cell differentiation, and other developmental processes. ZBTB7A recruit various co-repressors such as BCoR, NCoR1, NCoR2, CBX-5, CHD-3, HDACs, SIN3A and MBD3 on different promoter sites altering the activity of target gene transcription. This protein-protein-DNA interaction results in the regulation of adipogenesis, hematopoiesis, chromatin remodeling, and other key cellular functions [13, 19-20, 41-42]. Studies have reported that ZBTB7A has potential to modulate fatty-acid synthase (FASN) transcription. FASN is an important enzyme regulating fatty acid synthesis pathway which produces palmitate by the condensation of malonyl-CoA and acetyl-CoA. FASN is positively associated with cancer progression and aggressiveness and the major regulators of FASN gene include specificity proteins 1 (Sp1), and sterol regulatory element-binding protein-1 (SREBP-1). Choi *et al*. (2008) investigated the role of ZBTB7A and its interaction with SREBP-1 and Sp1. ZBTB7A and SREBP-1 synergistically activate the transcription of FASN gene resulting in the regulation of lipid biosynthesis during adipocyte proliferation and oncogenesis [43]. Eukaryotic translation elongation factor 1A (eEF1A) transfer the aminoacyl-tRNA to the A-site of the ribosome during translation and also regulate different cellular processes including cancer pathophysiology [20]. CCS-3 or eEF1A1 is an isoform of eEF1A that interacts directly with POZ/BTB domain of ZBTB7A resulting in the co-localization of ZBTB7A-eEF1A1 in the nuclear periplasm. In the nucleus ZBTB7A−eEF1A1 binds with p21/waf1 gene promoter and recruit BCoR and SMRT corepressor which ultimately lead to the transcriptional repression of p21, a downstream regulator of tumor suppressor p53 [20]. MBD proteins (methyl-CpG-binding domain protein) are mediators of epigenetic silencing. Choi *et al*. (2013) reported that ZBTB7A interacts with MBD3 which further recruit other co-repressors such as NCOR/SMRT and BCoR on the p21 promoter resulting into its transcriptional suppression [13]. Published literature and databases searches demonstrate a large collection of proteins interacting with ZBTB7A affecting various cellular pathways which are summarized in **Table 1**.

4. Role of ZBTB7A in various biological processes

4.1 Adipogenesis. Laudes et *al.* (2008) reported that overexpression of ZBTB7A inhibits adipocyte proliferation and promotes preadipocytes differentiation [4]. ZBTB7A downregulates the expression of Cyclin A *via* an indirect mechanism which involves repression of promoter activity by inhibiting the binding of transcriptional activator Sp1 to a GC box at −452 to −443. ZBTB7A promotes terminal preadipocyte differentiation *via* a mechanism involving low expression of E2F-4. E2F-4 inhibits the expression of peroxisome proliferator-activated receptor ϒ (PPARϒ) thereby promoting the preadipocyte

differentiation. ZBTB7A induces repression of E2F-4 which is mediated by the direct binding of ZBTB7A at the regulatory element at −11 to −5, thus reducing its promoter activity, a mechanism different from cyclin A repression **(Figure 2)** [26].

4.2 Alternate splicing of BCLx. BCLx is an apoptotic protein whose function is tightly regulated by alternative splicing. There are two alternative splice sites in exon 2 of the BCLx gene that yields splice variants having antagonistic effects on cell survival. Selection of proximal 5′ splice site leads to the formation of BCLXL with anti-apoptotic functions whereas selection of distal 5′ splice site results in formation of a short variant BCL_{XS} that promote apoptosis. SAM68 a member of the evolutionary conserved signal transduction and activator of RNA (STAR) family of RNA binding proteins (RBPs) is identified as the regulator of alternative splicing of BCL. Constitutive expression of SAM68 promote cell survival by preferring the formation of BCLXL variant however its overexpression favors the formation of BCL_{XS} variant [50]. ZBTB7A exerts its influence on alternative splicing of BCL_X by interacting with SAM68 [27]. This interaction results in the reduced binding of SAM68 to BCL_X mRNA and selection of proximal 5′ splice site to produce BCLXL variants **(Figure 3)**.

4.3 B-cell development. B-cell development occurs in the bone marrow [51]. During this developmental process Notch signaling and other regulatory proteins acquires a central role through the Delta-like family member Dll-4 as a major ligand inside the thymus with subsequent development of T cells [52]. The hematopoietic progenitor cells (HPCs) residing inside the bone marrow develops into B-cells due the absence of Notch signaling. ZBTB7A represses Notch signaling in HPCs and shifts the niche towards B-cell development. ZBTB7A expression is reported in HPCs present in the thymus however high expression of Notch genes overcomes ZBTB7A-mediated blockade [53]. ZBTB7A is also involved in the regulation of mature B-cell lineage fate, humoral response, and germinal center response [54]. ZBTB7A assists B-cell proliferation and survival by repressing ARF-Mdm2-p53 pathway [9]. On the contrary, activation of EGF-mediated signaling promotes ZBTB7A expression in various cancer cells (**Figure 4**).

4.4 Chondrogenesis. Studies demonstrate that ZBTB7A inhibits cartilage oligomeric matrix protein (COMP) gene expression and thereby chondrogenesis by direct binding to its promoter. COMP is an essential factor in the formation and maintenance of cartilage. The yeast one-hybrid screening demonstrates that ZBTB7A binds to COMP promoter on a negative regulatory element (NRE) and this binding has been reported in both *in vivo* and *in vitro* systems. A sequence of nine nucleotides, GAGGGTCCC is essential for the binding of ZBTB7A at 30bp NRE. After binding to the promoter region of COMP gene, ZBTB7A recruits histone deacetylase 1 (HDAC1) which silences the COMP gene

expression. ZBTB7A is also reported to inhibit chondrogenesis induced by bone morphogenetic protein 2 (BMP2) [55-56].

4.5 Erythropoiesis. GATA binding protein 1 (GATA1) is an important transcription factor involved in the development and function of erythroid cells as an activator or repressor depending on gene context. ZBTB7A is a direct target of GATA1 and plays an important role in preventing apoptosis of erythroid progenitor cells during terminal erythroid development. Yu *et al.* (2009) reported that loss of ZBTB7A induces lethal anemia in embryos due to increased apoptosis during the late stage erythroblasts [57]. This late stage apoptosis in erythroblasts is independent of Arf and p53 pathway instead it is induced by pro-apoptotic factor Bim. ZBTB7A represses Bim-mediated apoptosis in late-stage erythroblasts and allows the terminal differentiation of erythroid cells [58].

4.6 Non-homologous end joining (NHEJ). ZBTB7A plays an important role in non-homologous end joining and connects with proteins involved in NHEJ such as DNA-PKcs and Ku70/Ku80 heterodimer. Association between ZBTB7A and Ku70/Ku80 heterodimer is dependent on the presence of DNA while association between ZBTB7A and DNA-PKcs is increased by presence of DNA but it is not obligatory. It has been observed that in absence of ZBTB7A the mobilization of DNA-PKcs to the chromatin fraction after DNA damage is significantly reduced [25].

4.7 Oligodendrocyte development. Oligodendrocytes function as the myelinating cells in the central nervous system. They are produced by a cell lineage which undergoes a complex regulated program of proliferation, migration, differentiation, and myelination to finally generate an insulating sheath of axons [59]. Expression of ZBTB7A in oligodendrocyte progenitors is very low, but its level rises in mature oligodendrocytes during remyelination. *In vitro* studies reveal that ZBTB7A regulates transcription of myelin-related genes and the Notch target Hes5, which are involved in control of myelin formation and repair [29]. ZBTB7A is expressed mainly in mature oligodendrocytes but it is not required for oligodendrocyte repopulation of demyelinated lesions, although it can modulate the extent of remyelination [60].

4.8 Osteoclast development. The osteoclasts belong to the family of monocytes/macrophages. Differentiation of cells belonging to this family is under the influence of two major cytokines, namely receptor activator of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF). RANKL is reported to induce the expression of ZBTB7A in osteoclasts [32]. ZBTB7A plays stage-specific distinct roles in osteoclast differentiation, it negatively regulates osteoclast differentiation

by repressing nuclear factor of activated T cells c1 (NFATc1) induction in the early phase of osteoclastogenesis while positively regulating the osteoclast-specific genes by functioning as a coactivator of NFATc1 in the bone resorption phase. [11, 56].

4.9 T-cell differentiation. Maeda et *al.* (2007) demonstrated that ZBTB7A genes are expressed during T-cell differentiation [53]. Carpenter et *al.* (2012) reported that ZBTB7A plays a key role in Th17 and Treg cell differentiation [24, 61-63]. Intracellular staining detected the presence of ZBTB7A protein in $CD4^+$ and $CD8^+$ single positive thymocytes and T-cells *in vitro* [64]. ZBTB7A and its homolog ThPOK (ZBTB7B), play a decisive role in differentiating T-cell into CD4 or CD8 lineage [65]. In the presence of ThPOK and ZBTB7A, developing thymocytes differentiate into CD4 lineage whereas in presence of RUNX3 these thymocytes develop into CD8 lineage [10]. Naïve CD4 T cells can differentiate into T helper (Th) cells including Th17 and Treg (T regulatory) cells.

4.10 Unfolded protein response. ZBTB7A plays an important role in preventing unfolded protein response. Luman/CREB3 (also called LZIP) is an endoplasmic reticulum (ER)-bound cellular transcription factor which is considered as the master regulator of unfolded protein response (UPR). During the UPR lumen dissociates from the ER and undergoes a regulated intramembrane proteolysis; and subsequently the N-terminal region of lumen translocates into the nucleus. Once inside the nucleus, lumen along with host cell factor-1 (HCF-1) activates homocysteine-responsive endoplasmic reticulum-resident ubiquitin-like domain member 1 (HERP) and ER degradation-enhancing alpha-mannosidase-like protein 1(EDEM) genes, which are essential during the unfolded protein response. ZBTB7A inhibits UPR by binding to lumen inside the nucleus and preventing the expression HERP and EDEM [31].

4.11 Uteri implantation. During pregnancy, the blastocyst hatches from the zona pellucida and implants into uterus initiating the next step of development. Yang *et al.* (2013) reported that ZBTB7A expression is upregulated in uteri and embryo of pregnant mice at all stages and this expression is localized specifically at the implantation sites [30]. These observations suggest that ZBTB7A mediates uterine receptivity in the process of implantation. Further analysis revealed that the expression of ZBTB7A at implantation sites is regulated by steroid hormones like progesterone and estradiol [30].

5. Role of ZBTB7A in cancer

Metabolic reprogramming is one of the hallmarks of cancers and increased rate of glycolysis is observed in nearly all cancer cell types [66]. Cancer cells metabolize most of the glucose into lactate and generate a plethora of glycolytic intermediates to meet their anabolic demands. Oncogenic pathways are described to

contribute to these metabolic adaptations of cancer cells [36, 67]. ZBTB7A has been reported as a key transcriptional repressor of important genes involved in the operation and regulation of glycolysis [36]. ZBTB7A is reported to repress the transcription of glucose transporter 3 (GLUT-3), platelet specific isoform of phosphofructokinase (PFKP), and pyruvate kinase (PKM). GLUT-3 is involved in the transport of glucose inside the cell and other two enzymes control the key steps in the glycolysis. ZBTB7A represses the transcription of these glycolytic enzymes by directly binding to their promoter (**Figure 5**). Multiple putative ZBTB7A binding sites are present in the promoter region of GLUT-3, PFKP and PKM. ZBTB7A deficient tumors progress rapidly and these tumors exhibit high sensitivity to the therapies targeting glycolysis. Liu *et al.* (2014) have shown that 2-deoxy-D-glucose (2-DG), a glycolytic inhibitor significantly reduced the proliferation of cells lacking ZBTB7A while having mild effect on the ZBTB7A containing control cells [67]. Due to the fact that cancer cells depend on aerobic glycolysis to sustain their proliferation, ZBTB7A deficient tumors show increased sensitivity to glycolysis inhibitors [67].

Dysregulated expression of various genes involved in cell survival, proliferation, chemo-resistance is observed in cancer [68]. ZBTB7A is overexpressed in many types of human malignancies and triggers abnormal expression of effector genes and signaling pathways. ZBTB7A normally function as a transactive or suppressive transcription factor that inhibits transcription of tumor suppressor genes such as p53 and Rb and promote NF-κB transcription thereby contributing to the tumorigenesis process [69]. Mao et *al.* (2019) analyzed ZBTB7A expression in breast cancer specimens and in several breast cancer cell lines. Significantly high expression of ZBTB7A and NF-κB were noted in breast cancer samples and cell lines. The study indicates that ZBTB7A regulates NF-κB and exerts epithelial-to-mesenchymal transition (EMT)-resulting in increased cell migration, invasion and metastasis in breast cancer [70]. Choi et *al.* (2019) reported that under hypoxic condition NF-κB is activated and its nuclear translocation increases in cancer cells. NF-κB represses ZBTB7A by binding to the NF-κB-response elements at 5'-upstream regulatory region of ZBTB7A resulting into lactate efflux in colon cancer cells. In hypoxic condition expelling of glycolysis derived lactate plays a critical role in the growth and survival of colon cancer cells [71]. In another study, Wang et *al.* (2018) reported a role for ZBTB7A in 5-fluorouracil (5-FU) resistant colorectal cancer cells. They found that ZBTB7A induces NF-κB mediated 5-FU resistance in colorectal cells. The study indicated that targeting ZBTB7A and NF-κB will be an effective strategy to reverse 5-FU resistance in these cells [72]. Zhao et *al.* (2011) reported that ZBTB7A reduces Bcl2 protein expression through NF-κB and thereby induce cell proliferation and reduced apoptosis in liver cancer cells [73]. It has been reported that ZBTB7A facilitate metastasis and EMT by downregulating the expression of E-cadherin, β-catenin and promoting the expression of matrix metalloproteinases in a number of solid

tumors including bladder, brain, breast, colon, head & neck, liver, ovarian, prostate, uterus and some hematological and soft tissue malignancies [74-76]. Details on the role of ZBTB7A in various human cancer is shown in **Table 2**.

Contrary to the proto-oncogenic role of ZBTB7A, it is also reported to act as a tumor suppressor in few cancer types including nasopharyngeal carcinoma [102], gastric adenocarcinoma [100] and lung adenocarcinoma [109]. The tumor suppressor role of ZBTB7A is evident from the fact that it is a *bona fide* repressor of key glycolytic genes and its downregulation in cancer contributes to retard tumor metabolism [36, 67]. Wang et *al.* (2013) demonstrated context-dependent role of ZBTB7A in prostate cancer as it shows both the oncogenic and onco-suppressive activity. ZBTB7A inactivation in the prostate leads to *PTEN* loss driven tumor initiation. Interaction of ZBTB7A with SOX9 and subsequent regulation of the MIA and H19 genes involved in tumor cell progression and invasion exert tumor suppressive function [48]. Bezzi et *al.* (2018) showed that loss of *PTEN* gene along with ZBTB7A induces CXCL5 expression, a granulocyte attractant, in prostate cancer which play a crucial role in tumorigenesis [117]. Guarnerio et *al.* (2015) reported tumor suppressive role of ZBTB7A in sarcoma. They demonstrated that ZBTB7A exerts onco-suppressive role in sarcoma by negatively regulating the DLK1 and SOX9 oncogenes [118].

Zhang et *al.* (2019) reported that ZBTB7A has pro-survival role in drug induced endoplasmic reticulum (ER) stress in osteosarcoma cells. The study revealed that ER stress induces miR-663a which directly downregulates ZBTB7A binding to its 3'-UTR. Downregulation of ZBTB7A induces apoptosis in osteosarcoma cells [85]. Hojo et *al.* (2015) reported that miR-125a potentially targets ZBTB7A by direct binding with Zbtb7a-3'-UTR. The study showed that miR-125a-mediated downregulation of ZBTB7A led to cell cycle arrest and induction of apoptosis in lung cancer cells [119]. Liang et *al.* (2018) reported that miR-106b is significantly increased in hepatocellular carcinoma. The study indicates that miR-106b has potential to regulate ZBTB7A inversely. Overexpression of ZBTB7A and inhibition of miR-106b showed increased apoptosis in *in vivo* tumor model [120]. Zhijun and Jingkang (2017) reported that miR-520e has potential to regulate ZBTB7A at protein level by targeting its 3'-UTR region in non-small-cell lung cancer (NSCLCs). Downregulation of ZBTB7A resulted in NSCLCs cell growth, invasion and migration [110]. Jiao et *al.* (2017) reported that miR-106b was significantly downregulated in 5-FU resistant cholangiocarcinoma cells. The study showed that miR-106b overexpression significantly re-sensitizes the cells to 5-FU treatment by downregulating ZBTB7A expression [121-122]. In another study, Shi et *al.* (2015) reported that overexpression of miR-100 suppresses gastric cancer by inhibiting ZBTB7A [101]. These findings demonstrate that ZBTB7A interacts with miRNAs in various contexts. A list of predicted

miRNAs that regulate ZBTB7A signaling pathway genes including ZBTB7A, TP53, P14ARF, Retinoblastoma, Survivin, and MDM2 were identified using miRDB online database (**Supplementary table 1**) [123].

ZBTB7A is an important transcription factor in tumorigenesis and other chronic diseases, therefore, is an attractive therapeutic target. RNA interference (RNAi) is a powerful technique for specific gene silencing and has emerged as an effective therapeutic approach to treat cancer and other chronic diseases. Tian *et al.* (2010) documented mimoretrovirus containing a recombinant retrovirus plasmid expressing a siRNA targeting ZBTB7A gene, encapsulated by Arg-Gly-Asp (RGD) peptide ligand and polylysine (K18) fusion peptide. This RNAi/RGD-based mimoretrovirus demonstrated stability, homogeneity and provided complete protection from DnaseI exhibiting excellent anti-tumor activity [124]. Ding *et al.* (2012) have shown results of ZBTB7A silencing by RNA interference through preparation of a biomimetic nano-vector, reconstituted high density lipoprotein (rHDL), mediating targeted cholesterol-conjugated siRNA (Chol-siRNA) delivery system. The rHDL/Chol-siRNA-ZBTB7A complex showed promising tumor growth inhibition and significant decrease in ZBTB7A and Bcl2 protein expression [125]. These observations reveal that targeting ZBTB7A *via* RNA interference could be an effective therapeutic strategy.

Other than RNA interference approaches, immunotherapy has been utilized to target ZBTB7A in cancer treatment. The grp170 is a stress protein which functions as molecular chaperone, binding to large protein substrates and acting as a potent vaccine against specific tumors when purified from the same tumor. Yuan *et al.* (2012) demonstrated that mice bearing lung carcinoma treated with grp170-ZBTB7A chaperone complex significantly inhibited tumor growth and prolonged the life span of tumor bearing mice. This study shows that grp170-ZBTB7A chaperone complex could be a powerful strategy for cancer immunotherapy [126]. In another study, Yuan *et al.* (2012) tested HLA-A*0201-restricted cytotoxic T lymphocyte (CTL) epitopes derived from ZBTB7A with computer-based epitope prediction against various cancer cell lines. The results suggest that ZBTB7A32, ZBTB7A61, ZBTB7A87, and ZBTB7A319 peptides were novel HLA-A*0201-restricted restricted CTL epitopes, that could be utilized against a broad spectrum of tumors targeting ZBTB7A [127].

6. Role of ZBTB7A in other chronic diseases

Studies demonstrate that ZBTB7A along with BCL11A plays an important role in hemoglobin switching between fetal to adult stage [128]. These two transcription factors bind to the promoter region of fetal hemoglobin gene and prevent its expression through a chromatin remodeling pathway [129]. In a rare

benign condition called hereditary persistence of fetal hemoglobin (HPFH), individuals express the γ-globin gene throughout adulthood as a result of point mutations in the γ –globin gene promoter upstream of the transcription start site. It has been reported that major fetal globin gene repressors BCL11A and ZBTB7A directly bind to the sites at –115 and –200bp, respectively [130]. Both these genes are activated by the Krüppel-like factor 1 (KLF1), a transcription factor required for the maturation of erythroid cells [131]. Once activated by KLF1, ZBTB7A binds to the promoter region of fetal hemoglobin and maintains the nucleosome density necessary for γ-globin gene silencing in adults. This silencing of fetal hemoglobin by ZBTB7A is independent of BCL11A and involves the action of Nucleosome Remodeling Deacetylase (NuRD), a chromatin remodeling complex which regulates gene transcription, genome integrity and cell cycle progression [21]. Through computational identification, Dhaouadi *et al*. (2014) predicted ZBTB7A is overexpressed in atherosclerosis along with other transcription factors including PATZ1, ZNF263, SLC2A4RG and MAZ [132]. Some evidences suggest that ZBTB7A might be involved in regulation of TGF-β expression thereby playing a critical role in astherosclerosis. In another study, Giacopelli *et al.* (2013) identified that Fibrodysplasia ossificans progressive patients harbor point mutations in *ACVR1* gene, a type I receptor for bone morphogenetic protein (BMP) [133]. ZBTB7A has been reported to control the promoter activity of *ACVR1* gene along with several other transcription factors such as Egr1, Egr2 and Hey1. ZBTB7A and these additional transcription factors lead to the overexpression of *ACVR1* gene by binding to the -762/-308 promoter region, which is essential to confer maximal transcription activity [134].

7. Conclusion and future perspective

ZBTB7A plays significant role in controlling key biological processes and remains an essential player in the development and progression of a majority of cancer types regulating metabolism, differentiation, cell cycle progression, angiogenesis, apoptosis, and metastasis. The role of ZBTB7A depends on the context and type of cancers. In majority of the reported cases ZBTB7A functions as a proto-oncogene whereas in other contexts it is described to act as a tumor suppressor. The reason of this unorthodox behavior of ZBTB7A could be due to the differential transcriptional machinery functioning in a complex signaling network. Any mutation or dysregulation both at the gene and/or protein level affects the whole machinery and its components. ZBTB7A is regulated by several transcription factors; any dysregulation in these transcription factors affects its expression. In cancer, there is a large rearrangement of transcriptional machinery which in turn affects the activity of ZBTB7A. Depending on the context of these rearrangements and alteration in ZBTB7A is decisive in its function to act as tumor suppressor or an oncogene.

Several attempts have been made towards application of ZBTB7A as a therapeutic target employing gene silencing and immunological approaches in various cancer types. These observations indicate utilization of ZBTB7A as a novel target which can provide significantly improved results in cancer treatment. Although simultaneous targeting of multiple individual components of ZBTB is therapeutically challenging, targeting of their common upstream regulator(s) or downstream effector(s) can coordinately modulate the pathway output. Information of ZBTB7A expression level can be used in prognosis of cancer and to define cancer type. Thus, ZBTB7A can be utilized as a promising therapeutic target as it remains a key player in ensuring the survival of cancer cells. However, to achieve such feat, extensive investigation is required to define the role of ZBTB7A according to the type of cancer due to its unorthodox behavior.

In conclusion, advancement in the field of biochemistry, genetics and cell biology will improve the understanding of ZBTB7A processes of regulation. Uncovering the definite role of ZBTB7A in cancer progression and development will assist in attaining an effective and assuring therapeutic strategy. Owing to the fact that role of ZBTB7A in cancer is context dependent and affected by different mechanisms, we anticipate that based on its expression profile could be utilized in designing personalized treatment for cancer patients.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Figure Legends

Figure 1. ZBTB7A regulate gene expression by the recruitment of co-repressors and epigenetic modifiers. (A) At the time of target gene expression, ZBTB7A remains dissociated in the nucleus from other regulatory factors such as HDAC, NcoR, and co-repressors. This results in constitutive expression of target genes. **(B)** To achieve repression, ZBTB7A binds to its target gene promoter region with consensus sequence G (A/G) GGG (T/C) (C/T) (T/C) (C/T). Binding of ZBTB7A to DNA is conducted by the zinc finger domains followed by recruitment of additional regulatory factors such as co-repressors and epigenetic modifiers NcoR and HDAC to suppress the target gene expression. NcoR=Nuclear receptor corepressor; HDAC=Histone deacetylase.

Figure 2. Transcriptional repression of Cyclin A and E2F4 by ZBTB7A and subsequent de-repression of PPARϒ in the regulation of adipogenesis. (A) Absence of ZBTB7A promotes Sp1 binding to cyclin A promoter region and facilitates transcription of cyclin A gene. **(B)** In the presence of ZBTB7A, it binds with transcriptional activator Sp1 forming an inactive complex. This event downregulates the expression of cyclin A gene *via* repressing the cyclin A promoter activity. **(C)** In the absence of ZBTB7A, PPARγ, a master regulator of terminal differentiation is downregulated by E2F4. **(D)** Presence of ZBTB7A recruits epigenetic silencers Sin3A and HDAC1 which downregulates E2F4 expression and promotes terminal differentiation. SP1=*Specificity protein 1;* PPARγ=Peroxisome proliferator-activated receptor gamma; E2F4=E2F transcription factor 4; SIN3A=SIN3 transcription regulator family member A; HDAC1=Histone deacetylase 1.

Figure 3. Regulation of alternate splicing of BCLx by ZBTB7A. BCLx mRNA (pre-spliced) contains two alternative splice sites in exon 2. Presence of ZBTB7A promotes formation of anti-apoptotic variant BCLxL by interacting with SAM68 which results in the selection of proximal 5′ splice site. In the absence of ZBTB7A, distal 5′ splice site is selected by Sam68 resulting in the formation of BCLxS variant that promotes apoptosis. SAM68=SRC associated in mitosis of 68 kDa; BCLxL=B-cell lymphoma-extra-large; BCLxS=Bcl-2- like protein 1.

Figure 4. Activation of EGF-mediated signaling promotes ZBTB7A expression in cancer cells. EGF binds to its receptor (EGFR) and activates signaling cascade which transcribes ZBTB7A. ZBTB7A mRNA translocates into the cytosol and gets translated. ZBTB7A protein moves back into the nucleus

and inhibit activity of p14ARF which is a critical regulator of p53 activity. p14ARF suppresses the activity of MDM-2 which is a direct inhibitor of p53. Binding of MDM-2 to p53 results in the immediate translocation of MDM-2/p53 complex into the cytosol and proteasomal degradation of p53. By inhibiting the activity of p14ARF, ZBTB7A promotes p53 inhibition. Inhibition of p53 by ZBTB7A ultimately results in cell proliferation and inhibition of apoptosis in cancer cells. EGF=Epidermal growth factor; EGFR= Epidermal growth factor recptor; PyC=Phospholipase C-ϒ; MEKK1=Mitogen-activated protein kinase kinase kinase 1; JNKK1=Dual specificity mitogen-activated protein kinase kinase 4; JNK1=Mitogen-activated protein kinase 8.

Figure 5. Glycolysis regulation by ZBTB7A in cancer cells. ZBTB7A is a *bona fide* repressor of key glycolytic genes. ZBTB7A inhibits transcription of GLUT-3, PFKM and PFM by directly binding to their promoter. GLUT-3 facilitates the glucose entry in cancer cells and PFKM regulates the third reaction (conversion of fructose-6-phosphate to fructose-1, 6-bis-phosphate) of glycolysis and PKM regulates the conversion of phosphoenolpyuvte to pyruvate in the final step of glycolysis.

Table 1. ZBTB7A interaction with other proteins and its consequence.

S. No.	Protein	Function	Interaction with ZBTB7A and its consequence	Techniques	References
1	B-cell lymphoma 6 (**BCL6**)	Facilitates naive helper T cells differentiation into follicular helper T cells.	Forms heterodimer with ZBTB7A and activates downstream genes.	ACW, THS	[6]
2	BCL6 Corepressor (**BCoR**)	Inhibits BCL6 and MLLT3 gene expression.	ZBTB7A recruits BCoR Mi-2/NuRD-HDAC with the help of MBD3 which results in silencing of target genes.	ACW, THS	[13, 41]
3	Chromobox protein 5 (**CBX-5**)	Epigenetic repression.	ZBTB7A recruit CBX-5 to target gene promoter and thereby inhibit the associated gene expression.	ACW	[13]
4	CCAAT/enhancer-binding protein beta (**CEBPB**)	Adipogenesis, liver regeneration, and hematopoiesis.	ZBTB7A recruits CEBPB to target promoter mediated gene expression.	GPDA, ACW	[42]
5	Chromo domain helicase binding protein-3 (**CHD-3**)	Chromatin remodeling	ZBTB7A recruits CHD-3 to target promoter mediated gene expression.	ACW	[13]
6	Cereblon (**CRBN**)	Facilitates ubiquitination of ion channels.	ZBTB7A-CRBN interaction promotes degradation of ZBTB7A.	TRFET, RC	[44]
7	DNA (cytosine-5) methyltransferase (**DNMT**)	DNMT1 reduces transcription at the sites of oxidative damage.	ZBTB7A interacts with MBD3/BCoR and promotes silencing of target genes.	ACW, ChIP	[13]
8	Eukaryotic translational elongation factor1 alpha1 (**EEF1A1**)	Recruits aminoacyl-tRNA to the A-site of the 80S ribosome.	ZBTB7A-eEF1A interaction suppresses *p21CIP1* gene transcription.	ACW, GPDA	[45]
9	Eukaryotic translation initiation factor 4 gamma 2 (**EIF4G2**)	Switches cap-dependent translation towards internal ribosome entry site-mediated translation during mitosis, apoptosis and viral infection.	ZBTB7A-EIF4G2 interaction suppresses P53 gene transcription.	ACW, ChIP	[46]
10	Histone deacetylases (**HDACs**)	Deacetylation of lysine residues on the	ZBTB7A-HDAC interaction deacetylate	ACW, ChIP	[20]

		N-terminal part of the core histones.	histones and represses the associated gene transcription.		
11	KH-domain containing, RNA binding, signal transduction associated 1 (**KHDRBS1**)	An adapter protein binds to SH2 and SH3 domain-containing proteins.	KHDRBS1-ZBTB7A interaction prevents alternative splicing of BCLx mRNA.	THS, RC	[27]
12	Methyl-CpG binding domain protein 3 (**MBD3**)	Act as transcriptional repressor.	MBD3-ZBTB7A interaction recruit Mi-2/NuRD-HDAC-BCoR to silence p21WAF/CDKN1A gene.	THS, ACW, RC	[13]
13	Nuclear receptor corepressor 1 (**NCoR 1**)	Promote histone deacetylation.	NCoR1-ZBTB7A promotes chromatin condensation.	GPDA, ChIP, ACW	[13, 19, 20]
14	Nuclear receptor corepressor 2 (**NCoR 2**)	Promote chromatin condensation.	ZBTB7A recruits NCoR 2 to silence androgen response element gene.	EMSA, ChIP, THS	[13, 19-20]
15	NF-kappa-B inhibitor alpha (**NF-κBIα**)	Inhibits the activity of dimeric NF-kappa-B/REL complexes.	ZBTB7A promotes NF-κB mediated gene transcription by inhibiting NF-κBIα.	ChIP, ACW	[15]
15	NF-κB inhibitor beta (**NF-κBIβ**)	Keeps NF-κB in inactive form.	ZBTB7A promotes NF-κB mediated gene transcription by inhibiting NF-κBIβ.	ChIP, ACW	[15]
16	v-rel avian reticuloendotheliosis viral oncogene homolog A (**RELA**)	A transcriptional repressor required for germinal center formation.	ZBTB7A-RELA interaction enhances E-selectin gene expression which facilitates germinal center formation.	ChIP, ACW	[15, 47]
17	Transcriptional regulator family member A (**SIN3A**)	Involve in protein-protein interactions.	ZBTB7A-SIN3A interaction facilitates deacetylation of H3 and H4 histones at promoter region.	ChIP, ACW	[20]
18	SMAD family member 4 (**SMAD4**)	A key factor of TGF-β signaling pathway.	ZBTB7A-SMAD4 interaction represses TGF-β mediated gene response.	THS, GPDA, ChIP	[16]
19	SRY (sex determining region of the Y chromosome) box 9 (**SOX9**)	Skeleton and sex determination.	ZBTB7A antagonizes SOX9 function on its associated genes.	ChIP, ACW	[48]
20	Transcription factor	Regulates gene	ZBTB7A-Sp1	EMSA,	[8, 26]

	Sp1	expression.	interaction represses its DNA binding activity.	ChIP, ACW	
21	Sterol regulatory element-binding protein 1 (**SREBP1**)	Regulate transcription of LDL receptor, fatty acid and cholesterol synthesis related genes.	ZBTB7A interaction with SREBP-1 facilitates fatty acid synthase gene transcription.	ChIP, ACW	[43]
22	Trans-activating regulatory protein (**TAT**)	Nuclear transcriptional activator of viral genes.	ZBTB7A-TAT stimulates TAT activity.	ChIP, ACW	[7]
23	Transcription factor AP4 (**TFAP4**)	Transcription of viral and cellular genes.	ZBTB7A-TFAP4 interaction regulates MDM2 gene expression.	ACMS	[47]
24	Tumor protein 53 (**TP53**)	Tumor suppressor gene.	ZBTB7A-TP53 interaction diminishes tumor suppressive activity of p53.	EMSA, ACW, RC	[20, 49]

ACW=Affinity capture western; THS=Two hybrid screening; GPDA= Glutathione-S-transferase pull-down assay; TRFET=Time resolved fluorescence energy transfer; RC= Reconstituted complex; ChIP=Chromatin immunoprecipitation; EMSA= Electrophoretic mobility shift assay; ACMS=Affinity capture mass spectrometry.

Table 2. Expression of ZBTB7A in various cancer types and its outcome.

Cancer Type	Cancer Subtype	Study type	Experimental model	NZE	Mode of modulation	Mechanism of action	References
Bladder cancer	TCC	*In vitro*	T24 cell line	↑	ZBTB7A inhibited by siRNA	Inhibition of E-cadherin expression	[74]
		In vitro	T24 and EJ cell line	↑	Downregulation by TGF-β1	Downregulation of E-cadherin, β-catenin	[77]
Blood cancer	AML	Clinical	CBF-AML patients	-	-	t (8; 21) translocation	[78-82]
	NLPHL	Clinical	HL patients	↑	-	Strong nuclear activity of ZBTB7A	[83]
	CLL	Clinical	CLL patients	ND	-	-	[84]
Bone cancer	Osteosarcoma	*In vitro*	U2OS, 143B, MG63, and Saos-2 cell lines	↑	Downregulated by miRNA-663a	ZBTB7A downregulated the expression of Lnc-GAS5	[85]
		In vitro	U2OS and MG63 cell lines	↑	RNA interference	ZBTB7A downregulated the expression of LINC-00473- C/EBPβ-IL24 pathway	[86]
	Chondrosarcoma	*In vitro*	FS090, and SW1353 cell lines	↑	ZBTB7A targeting siRNA	Downregulation of p53 and p21	[87]
Brain cancer	Glioblastoma	*In vitro*	U343, U251, A172, U118, and T98G cell lines	↑	RNA interference	14-3-3β-FBI1/Akirin-2 complex represses transcription of BCAM	[88]
	Glioma	*In vitro*	U87MG, T98G, and U251 cell lines	↑	Resveratrol induced downregulation	Decreased SP1 transcription factor and increased HDAC1 binding to promoter	[89]
Breast cancer	Breast carcinoma	*In vitro*	MCF-7, and MDA-MB-231 cell lines	↑	-	ZBTB7A promotes breast cancer by upregulating survivin expression	[90]
		In vitro	MCF-7, and MDA-MB-231 cell lines	↑	-	P-glycoprotein regulates the expression of ZBTB7A through the presence of p53	[91]
		Clinical	Breast carcinoma patients	↑	ZBTB7A gene amplification	Comparatively higher expression of ZBTB7A promotes oncogenesis of breast cancer	[92-93]
		In vitro	MCF-7 cell	↑	shRNA	ZBTB7A silencing	[94]

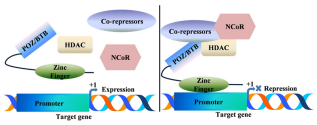
			line		expression vector controlled by CMV enhancer-tRNALys	results in cell cycle arrest and apoptosis	
	Sporadic breast cancer	Clinical	Sporadic breast cancer patients	-	-	ZBTB7A showed no association with sporadic breast cancer development	[95]
Colon cancer	CRC	*In vitro*, Clinical	HT-29, HCT 116, SW480, SW620, DLD-1, and WiDr cell lines, CRC patients	↑	-	ZBTB7A expression is higher in metastatic CRC cell in comparison to primary CRC cells	[96]
		In vitro, Clinical	LIM1215, and HCT116 cell lines, CRC patients	↑	RNA interference	ZBTB7A is upregulated by PAR-2 activation and forms a complex with DAP-5 to suppress the expression of p53	[46]
		In vitro	HCT116	↑	Nutrient restriction	Nutrient restriction results in downregulation of ZBTB7A expression	[97]
		In vitro	Lovo, HR8348, and HT29 cell lines	↑	RNA interference	ZBTB7A enhances ETS-1 activity by downregulating the p53 mediated inhibition on ETS-1	[49]
		In vitro, Clinical	SW480 SW620 cell lines, CRC patients	↑	-	RNA interference Silencing of ZBTB7A inhibited cell proliferation	[98]
	CRA CRC	Clinical	CRA and CRC patients	↑	shRNA-ZBTB7A vectors	ZBTB7A promotes carcinogenesis of CRC independent of p14-ARF pathway	[99]
Gastric cancer	Gastric adenocarcinoma	*In vitro*	SGC-7901 cell line	↑	RNA interference	ZBTB7A overexpression promoted cell cycle arrest in S phase and induced apoptosis	[100]
	Primary gastric cancer	*In vitro*, Clinical	Primary gastric cancer patients, MKN-45, MKN-28, SGC-7901, and BGC-823 cell lines	↑	RNA interference	Downregulation of ZBTB7A by mir-100	[101]
Head	NPC	*In vitro*	CNE2, and 5-	↓	RNA	Stable knockdown of	[102]

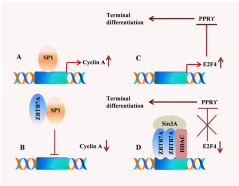
and neck cancer			8F cell lines		interference	ZBTB7A promotes cell proliferation and progression in nasopharyngeal carcinoma	
	OSCC	Clinical	OSCC patients	↓	-	-	[85]
	Undifferentiated non-keratinizing nasopharyngeal carcinoma	*In vitro*, Clinical	UNCT patients, CNE1, CNE2, CNE3, and C666-1 cell lines	↑	-	-	[103]
Liver cancer	Human Hepatoma	*In vitro*	QGY7703 cell lines	↑	RNA interference	ZBTB7A silencing leads to the Bim-mediated anoikis	[104]
		In vitro	HepG-2, and QGY7703 cell lines	↑	RNA interference	ZBTB7A downregulates expression of CDK-2 and E2F4	[105]
	HCC	*In vitro*, Clinical	HCC patients, HepG2 cell line	↑	RNA interference	ZBTB7A promotes carcinogenesis dependent of H-RAS	[106]
		In vitro	HepG2, and SMMC7721 cell lines	↑	RNA interference	ZBTB7A downregulates the expression of Bcl-2 via NF-κB-P65	[73]
		In vitro, Clinical	HCC patients, LO2, MHCC97-L, SMMC-7721, HCCLM3, MHCC97-H, and Huh-7 cell lines	↑	RNA interference	ZBTB7A promotes cell proliferation but not migration of HCC cells by Down-Regulating p27, p53, and p21. It also prevents 5-fluorouracil induced or doxorubicin induced cell death by suppressing the activation of p53	[107]
		In vitro	HepG2 cell line	↑	5'-3' deletion constructs of ZBTB7A	SP1 enhances the expression of ZBTB7A by direct binding to its promoter	[108]
Lung cancer	lung adenocarcinoma	*In vitro and In vivo*	LUAD cell lines, K-Ras-LSL-G12D mice	↓	RNA interference	ZBTB7A is downregulated by HP-1ϒ which results in carcinogenesis	[109]

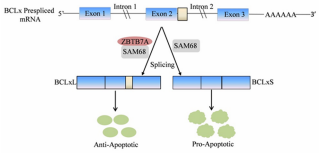
	NSCLC	*In vitro*, and clinical	NSCLC patients, A549, 95D, H1650, and SK-MES-1 cell line	↑	-	mir-520e inhibits growth of NSCLC by downregulating ZBTB7A mediated Wnt-pathway	[110]
		In vitro, and clinical	NSCLC patients, Pc-9, H358, and H1975 cell lines	↑	RNA interference	LncRNA CCAT2 promotes oncogenesis via over-expression of ZBTB7A	[111]
	Lung carcinoma	*In vitro*	A549 cell lines	↑	Curcumin induced downregulation	Decreases the binding of SP-1 to ZBTB7A promoter thereby downregulating its expression	[112]
Ovarian cancer	Ovarian cystenomas	*In vitro*, Clinical	Ovarian cancer patients, OVCA420, OVCAR-3, SKOV-3, 2780 S, 2780CP, 2008, 2008/C13, SW626, ES2, OC316, DOV13, and TOV21G cell lines	↑	pEGFP-C3 vector containing cloned ZBTB7A gene	ZBTB7A promotes expression of matrix metalloproteinases which results in the induction of metastasis	[76]
Prostate cancer	PTEN loss driven prostate cancers	*In vivo*	Ptenflox/flox, Lrfflox/flox and Pb-Cre4 mice	↓	RNA interference	ZBTB7A suppresses oncogenesis of prostate cancer by repressing SOX-9 transcription factor dependent pathway	[48]
	Prostate adenocarcinoma	*In vivo, in vitro*	NOD/SCID mice, PC3, and LNCAP cell lines	↑	RNA interference	ZBTB7A repression by siRNA significantly reduced cell proliferation and induced apoptosis	[113]
		In vitro	PC3, LNCAP cell lines	↑	EGF induced expression	EGF signaling pathway promotes expression of ZBTB7A thereby oncogenesis.	[114]
		In vitro	PC3, LNCAP cell lines	↑	RNA interference	ZBTB7A functions as a co-repressor of AR-signaling along with HDAC and SMRT	[19]
Uterine cancer	Type II endometr	Clinical	EC patients	↑	-	over expression of ZBTB7A upregulates	[115]

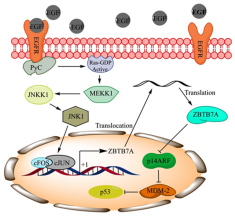
	ial carcinoma					the expression of mutant p53, which may be one of the carcinogenesis modes	
	Choriocarcinoma	*In vitro, in vivo,* clinical	CCA patients, BALB/c female nude mice, JAR, and JEG-3 cell lines	↑	RNA interference	ZBTB7A promotes cell migration and invasion via phosphoinositide 3-kinase/Akt signaling	[75]
Skin cancer	Melanoma	*In vitro, in vivo*	Nude mice, SK-MEL-28, and UACC62 cell lines	↓	RNA interference	ZBTB7A suppresses melanoma metastasis by downregulating MCAM expression	[116]

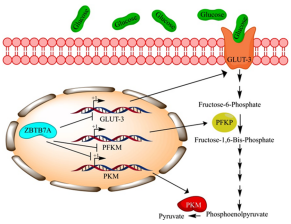
NZE=Native ZBTB7A expression; TCC=Transitional cell carcinoma; CBF=Core binding factor; AML=Acute myeloid leukemia; TGF=Transforming growth factor; NLPHL=Nodular lymphocyte predominant Hodgkin lymphoma; HL=Hodgkin lymphoma; CLL=Chronic lymphocytic leukemia; BCAM=Basal cell adhesion molecule; SP1=Specificity protein 1; HDAC1=Histone deacetylase 1; PAR-2=Protease-activated receptor 2; DAP-5=Death-associated protein 5; CRC=Colorectal carcinoma, CRA=Colorectal adenoma; NPC=Nasopharyngeal carcinoma; OSCC=Oral squamous cell carcinoma; CDK=Cyclin-dependent kinase; EGF=Epidermal growth factor; EC=Endometrial cancer; CAA=Cholangiocarcinoma; HCC=Hepatocellular Carcinoma; NSCLC=Non-small cell lung cancer; MCAM=Melanoma Cell Adhesion Molecule; ND=Not detected. ↑ refers upregulation and ↓ refers downregulation.











POKEMON (ZBTB7A): A master switch regulating cancer and other chronic diseases

Highlights

- ZBTB7A is a member of POZ domain containing transcription factors family.
- ZBTB7A repress transcription by recruiting co-repressor complexes at DNA.
- ZBTB7A overexpression is positively associated with various cancers.
- Oncogenic role of ZBTB7A is cancer type dependent.
- ZBTB7A plays an important role in various cellular and developmental processes.