Abstract. The T-box (TBX) genes are part of an evolutionarily conserved family of transcription factors involved in organ development. They serve key roles in a number of molecular mechanisms, including proliferation, cell fate and organ identity. In addition, previous studies suggest that TBX genes have essential functions in the tumorigenesis and progression of various types of cancer. For example, TBX proteins served significant roles in carcinogenesis, proliferation and differentiation, senescence and apoptosis, invasion and migration, mesenchymal-epithelial and epithelial-mesenchymal transition, oncogenic signaling pathways and drug sensitivity. However, the exact mechanisms by which TBX genes carry out these functions have not yet been fully elucidated. The present review focuses on the role of TBX genes in cancer, with the aim of further clarifying their function. As altered levels of TBX proteins have detrimental consequences in numerous types of cancer, there is a need for further research into TBX genes, which this review may aid through providing a comprehensive insight into the topic.

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1. Introduction

The T-box (TBX) gene family is an evolutionarily ancient gene family, as indicated by phylogenetic analysis (1), and has been widely studied in the field of developmental biology (2). TBX genes serve key roles during organogenesis and pattern formation in vertebrate and invertebrate embryos (3). Previous studies have shown that TBX genes encode a group of transcription factors that are characterized by a highly conserved DNA-binding domain and an unusual mode of DNA recognition (4-7). Certain TBX genes are purely activators or repressors, while others contain activation and repression domains (8). Since the first TBX family member was discovered in 1927, the TBX family has been increasingly implicated in the development of various organs and the pathogenesis of a number of syndromes (9,10).

Over 20 TBX genes have been identified in various species, ranging from invertebrates, including Drosophila and Caenorhabditis elegans, to vertebrates, including zebrafish, Xenopus, mice, chickens and humans (11-13). Current phylogenetic analysis divides the TBX gene family into five subfamilies, T, Tbx1, Tbx2, Tbx6 and Tbr1 (2). TBX genes serve key roles during organogenesis and pattern formation in vertebrate and invertebrate embryos (3). Previous studies have shown that TBX genes encode a group of transcription factors that are characterized by a highly conserved DNA-binding domain and an unusual mode of DNA recognition (4-7). Certain TBX genes are purely activators or repressors, while others contain activation and repression domains (8). Since the first TBX family member was discovered in 1927, the TBX family has been increasingly implicated in the development of various organs and the pathogenesis of a number of syndromes (9,10).

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liver (TBX3), lung (TBX2, TBX4 and TBX5) and limb (TBX4 and TBX5) development, in addition to pigmentation (TBX15) and the immune system (TBX21) (8,14). Furthermore, TBX proteins function in proliferation, differentiation, tissue integrity and epithelial-mesenchymal transition (EMT) (8,14).

Recent studies have shown that defects in, or overexpression of, certain TBX genes may be involved in the genesis and progression of a variety of types of cancer (2,15). For example, unlike the majority of members of the TBX family, which function as transcriptional activators, TBX2 and TBX3 are the only mammalian TBX factors that function as transcriptional repressors (16,17). The role of TBX2 and TBX3 in the oncogenic process is thought to be associated with an increase in their level of expression, as they have been found to be overexpressed in 8 different types of cancer, including breast, cervical, ovarian, pancreatic, liver and bladder cancer (18,19).

However, there is no comprehensive summary of the molecular and mechanistic changes to TBX genes during the genesis and progression of cancer. Therefore, in the present review, the roles of TBX genes in cancer are discussed. Through increased understanding of TBX factors at a genetic and molecular level, targeted therapy of these factors may become a promising therapy for the treatment of cancer.

2. TBX genes are involved in tumor cell invasion and migration

Preliminary evidence suggests that overexpression of the TBX3 gene is associated with several types of cancer, and that increased levels of TBX3 are associated with the promotion of tumor migration and invasion (20). Peres et al (21) reported that TBX3 knockdown in MCF-7 breast cancer cells and in metastatic melanoma cells resulted in increased proliferation and reduced migration. Boyd et al (22) applied a genome-wide expression profiling approach in an attempt to identify an association between the expression of B-Raf proto-oncogene (B-RAF), the transcriptional repressor TBX3 and E-cadherin. The results of this study demonstrated that B-Raf induced the expression of TBX3, which potently repressed E-cadherin expression (Fig. 1). Therefore, TBX3 may act as a critical regulator of the oncogenic B-Raf signaling pathway and as a promoter of metastasis in B-RAF-mutant melanomas (22).

Furthermore, a previous study has shown that overexpression of TBX2 and TBX3 in melanoma cells downregulated endogenous E-cadherin expression, whereas depletion of TBX3, but not TBX2, increased E-cadherin mRNA and protein levels, and decreased melanoma invasion in vitro (23). Consistent with these observations, TBX3 and E-cadherin expression are inversely correlated in melanoma tissue.

A previous study has shown that the phorbolester phorbol-12-myristate-13-acetate (PMA) increases TBX3 protein and mRNA levels in a protein kinase C-dependent manner, via activator protein 1 (AP-1) (24). Furthermore, AP-1 mediated activation of the TBX3 gene by binding to a non-consensus PMA-response element in the TBX3 promoter in vitro and in vivo (24). This demonstrates that TBX3 contributes to PMA-induced cell migration, which has previously been observed in the MCF-7 breast epithelium cancer cell line (25). These results provide evidence that increased levels of TBX3 contribute to tumor cell migration (Fig. 1).

3. TBX genes are involved in tumor cell immortality and proliferation

TBX genes, p14<sup>ARF</sup> and p21<sup>CIP1</sup>. During mouse oncosis, TBX2 and TBX3 have been associated with the repression of tumor suppressor genes p19<sup>ARF</sup> (p14<sup>ARF</sup> in humans) and the cyclin-dependent kinase (CDK) inhibitor p21<sup>CIP1</sup> (18). p14<sup>ARF</sup> increases the level of p53 by elevating the level of MDM2 proto-oncogene (MDM2). Increased p53 levels lead to increased levels of p21<sup>CIP1</sup>, and subsequent cell cycle arrest in G1 and G2/M (29,30). A further study demonstrated that p14<sup>ARF</sup> expression could be induced by overexpression of various oncogenes or by mitogenic signals (31). p14<sup>ARF</sup> can bind to MDM2, causing stabilization of p53, which initiates a program of gene expression leading to cell cycle arrest or apoptosis (31). Activated p53, which can initiate growth arrest in senescent cells, causes activation of p21<sup>CIP1</sup>, which is necessary for p53-mediated growth arrest (31). TBX2 and TBX3 suppressed senescence efficiently in a mouse model through the inhibition of p19<sup>ARF</sup> expression (31). Therefore, inhibition of p19<sup>ARF</sup> expression reduced the level of MDM2, blocking stabilization of p53 and thus inhibiting p53-mediated upregulation of p21<sup>CIP1</sup>, which has been implicated in the control of proliferation, differentiation and senescence (31). Therefore, it may be necessary for the p14<sup>ARF</sup>/p19<sup>ARF</sup>/MDM2-p53-p21 signaling pathway (Fig. 1), a well-characterized mechanism of cellular senescence, to be targeted at multiple points for the treatment of cancer.

TBX genes and early growth response (EGR) 1. The EGR protein family includes zinc-finger transcription factors involved in cell proliferation and apoptosis. EGR1 is best characterized as a direct regulator of a number of signaling pathways, it has significant tumor-suppressing properties, including the promotion of apoptosis in response to stress and DNA damage in a number of types of cancer (32,33). Redmond et al (34) described a novel
mechanism of TBX2 interaction with EGR1, which drove cell proliferation and survival in breast cancer cell lines. Depletion of TBX2 or EGR1 resulted in growth inhibition, and the expression of cell senescence and apoptotic markers, including deleted in esophageal cancer 1 (Dec1), p21<sup>CIP1</sup> and p53 (34). The putative breast cancer suppressor, N-myc downregulated gene 1 (NDRG1), is implicated in cell differentiation, apoptosis and senescence (34). TBX2 was found to repress NDRG1 not through direct promoter interaction, but as a corepressor through recruitment of EGR1. In this way, TBX2 drove the proliferation of breast cancer cells (34). NDRG1 was demonstrated to be a significant effector of growth control downstream of EGR1, and its expression recapitulated growth inhibition and induced expression of the cell senescence marker Dec1 (34). These results demonstrate the significance of the EGR1 signaling pathway in cancer (Fig. 1) and reveal it to be a potential novel therapeutic target.

**TBX genes, histone deacetylase (HDAC) 1 and p21.** Rhabdomyosarcomas (RMSs) are the most prevalent soft tissue sarcomas in children and share many features with developing skeletal muscle tissue. A recent study by Zhu et al (35) identified that TBX2 was highly upregulated in tumor cells of the major RMS subtypes. The results of this study demonstrated that elevated expression of TBX2 contributes to the pathology of RMS cells. TBX2 inhibited the regulatory factors myogenic differentiation 1 and myogenin, leading to the promotion of proliferation (35). Furthermore, TBX2 recruited the histone deacetylase HDAC1 and inhibited p21, which led to increased proliferation and decreased differentiation-specific gene expression (35). Depletion or inhibition of TBX2 completely inhibited tumor cell growth in RMS cells (35). These results indicate that deregulated TBX2 serves as an oncogene in RMS, and may be a novel diagnostic marker and/or therapeutic target in patients with RMS.

The CDK inhibitor 2A (CDKN2A) locus, which encodes p16<sup>INK4A</sup> and p14<sup>ARF</sup>, promotes senescence (36). A previous study found that CDKN2A-null B16 cells exhibited a specific deletion at the CDKN2A locus, leading to loss of function of p16<sup>INK4A</sup> and...
p14\(^{ARF}\) (37). In addition, the activation of a dominant-negative TBX2 (dnTBX2) gene induced senescence in the CDKN2A-null B16 melanoma cells (37). Furthermore, senescence was accompanied by increased expression of the TBX2 target gene p21 and displacement of HDAC1 from the p21 promoter, which markedly reduced proliferation (37). This TBX2-mediated molecular mechanism of transcriptional repression suggests that continued TBX2 activity is required to prevent CDKN2A-independent senescence in transformed cells.

Holt-Oram syndrome is characterized by upper limb malformations and cardiac septation defects (38). Mutations in the TBX5 gene were found to cause Holt-Oram syndrome in humans (38). In addition, a previous study reported that ectopic expression of TBX5 induced apoptosis and decreased the growth rate of U2OS cells, indicating that TBX5 is a novel regulator of apoptosis and cell growth (39). These results suggest that the TBX5 gene and protein serve important roles in the development of certain tissues.

4. TBX genes are involved in tumorigenesis

Liu et al (40) investigated the expression and association of prostate stem cell antigen (PSCA), piwi-like RNA-mediated gene silencing 1 (PIWIL1) and TBX2 in endometrial adenocarcinoma (EAC). Elevated expression of PSCA, PIWIL1 and TBX2 was observed significantly more frequently in EACs compared with normal endometrium (40). TBX2 expression was positively correlated with PSCA and PIWIL1 expression (40), indicating that TBX2 may upregulate PSCA and PIWIL1 (Fig. 1). The association between clinicopathological features and the three genes (40) revealed that they may have roles in the development and progression of EAC, and that PIWIL1 and TBX2 may be candidate markers for early pathological diagnosis and detection. PSCA, PIWIL1 and TBX2 were not associated with cancer stage (40), suggesting an involvement in the initiation of EAC rather than invasion. However, PSCA and TBX2 were associated with lymph node metastasis, and may be candidate targets for EAC prognosis and therapy (40). This study provides a basis for further investigations into the carcinogenesis of EAC.

HDACs serve an essential role in transcriptional regulation (41-44) and have been found to be overexpressed in a number of malignancies, including breast cancer (45,46). The results of a study by Harosh et al (47) indicated that overexpression of TBX3 increases the degradation of p53 via downregulating p14\(^{ARF}\) expression, leading to the promotion of breast cancer tumorigenesis. TBX3 was found to interact with HDAC1, 2, 3 and 5 to repress their downstream effects on gene expression (47). In the MCF-7 breast cancer cell line, HDACs were tested for their ability to reverse TBX3 regulation of p14\(^{ARF}\) in a dose-dependent manner (47). TBX3-mediated gene repression may function by recruiting HDACs to the T-box binding site in the promoter region of genes and was dependent on HDAC activity (47). The results of this study suggest that TBX3-HDAC interaction is important in breast cancer development (47). Therefore, HDACs may have an anticancer effect through TBX3-HDAC interaction (Fig. 1).

A previous study reported that mRNA and protein levels of TBX3 were increased in head and neck squamous cell carcinoma (HNSCC) samples compared with their normal tissue counterparts (48), and another study found that phosphatase and tensin homolog (PTEN) mRNA levels were decreased in HNSCC tissues (49). Furthermore, overexpression of TBX3 in human HeLa and HEK cell lines was demonstrated to cause a reduction in endogenous PTEN mRNA and protein levels (48). In addition, transcription activity assays have shown that TBX3 is capable of repressing basal and induced activity of PTEN (48). These results suggest that TBX3 represses PTEN and is overexpressed in HNSCC (Fig. 1).

5. TBX genes are involved in EMT

EMT has been increasingly recognized as a key step in the progression of primary tumors into metastases (50). EMT interrupts cell-to-cell contact in a homocellular manner in tumors, allowing the dissemination of cells from the primary site (51). During tumor progression, the EMT process appears to be triggered by genes typically expressed in the early embryo, including TWIST, SNAIL, SLUG, GOOSECOID and SIP1 (52-55), and targeting them may prevent tumor invasion and metastasis.

Shimoda et al (51) reported that metastatic ACCS-M green fluorescent protein cells (ACCS-M GFP cell line), established from AdCC cells, demonstrated characteristics of EMT, exhibited sphere-forming ability, and had high expression levels of EMT-related genes and stem cell and differentiation markers. These observations suggest that ACCS-M\(^{GFP}\) cells show characteristics of cancer stem-like cells (CSCs), which may be involved in the EMT of adenoid cystic carcinoma (AdCC) cells. Surprisingly, short hairpin RNA silencing of the TBX transcription factor, T, resulted in downregulation of EMT and CSC markers in clinical samples of AdCC (51). Notably, sphere-forming ability, EMT characteristics and tumorigenicity were simultaneously lost (51). Therefore, T may be a regulator of CSC marker expression and EMT in AdCC cells. In addition, T may be a potential therapeutic target for future anti-CSC treatment for AdCC.

Wang et al (56) reported that ectopic expression of TBX2 in wild-type HC11 and MCF10A mammary epithelial cells induced morphological, molecular and behavioral changes characteristic of EMT. This included loss of expression of proteins involved in epithelial cell adhesion (E-cadherin, \(\beta\)-catenin and zonula occludens 1), abnormal gain of mesenchymal markers (N-cadherin, vimentin), and increased cell motility and invasiveness (56). Conversely, depletion of overexpressed endogenous TBX2 in the malignant human breast carcinoma cell lines MDA-MB-435 and MDA-MB-157 led to the restoration of epithelial characteristics and loss of mesenchymal markers (56). In addition, chromatin immunoprecipitation (ChIP) analysis and cell-based reporter assays revealed that TBX2 directly repressed transcription of E-cadherin, a tumor suppressor gene, the loss of which is essential for malignant tumor progression (56). The results of this study demonstrated an unanticipated link between TBX2 deregulation in cancer, and the acquisition of EMT and invasive features in epithelial tumor cells (Fig. 1).

6. TBX genes are involved in tumorigenic signaling pathways

ATM serine/threonine kinase (ATM)-checkpoint kinase 2 (CHK2)-p53 signaling pathway. Wansleben et al (57)
demonstrated that silencing of TBX2 reversed several features of transformation in breast cancer and melanoma cells. In addition, it was shown that ectopic expression of TBX2 resulted in genetically unstable polyploidy cells with resistance to cisplatin (57). In an attempt to identify whether the overexpression of endogenous TBX2 was associated with cisplatin resistance in TBX2-driven cancers, TBX2 was silenced in a cisplatin-resistant breast cancer cell line (57). This demonstrated that TBX2 knockdown sensitized the cells to cisplatin by disrupting the ATM-CHK2-p53 signaling pathway (Fig. 1). Cell cycle analyses demonstrated that TBX2 knockdown led to a decrease in S-phase arrest, but robust G2/M arrest, which correlated with a reduction in phosphorylated CHK2 and p53 protein levels. This knockdown prevented DNA repair, and resulted in TBX2-deficient cells entering mitosis with damaged DNA and consequently undergoing mitotic catastrophe (57). These results suggest that targeting TBX2 in combination with typical chemotherapeutic drugs, including cisplatin, may improve the efficacy of current anticancer treatments.

**Wnt/β-catenin signaling pathway.** The Wnt signaling pathway, a critical regulator of stem cell function, is involved in numerous aspects of embryonic development and controls homeostatic self-renewal in a number of adult tissues (58). Germline mutations in the Wnt signaling pathway cause several hereditary diseases, and somatic mutations in this signaling pathway are associated with cancer of the intestine, liver and a variety of other tissues (59). Therefore, the tightly regulated self-renewal mediated by the Wnt signaling pathway in stem and progenitor cells may be disrupted in cancer cells, allowing for malignant proliferation.

Using ChIP and reporter assays, a previous study identified TBX3 as a direct downstream regulatory target gene of the Wnt/β-catenin signaling pathway that has been implicated in hepatocarcinogenesis (60). Furthermore, TBX3 transcription was activated by ectopic expression of β-catenin in mouse and human tumor cell lines (60) (Fig. 1). In addition, it has been shown that inhibition of TBX3 by small interfering RNAs (siRNAs) blocks β-catenin-mediated cell survival and renders cells sensitive to doxorubicin-induced apoptosis (60). Conversely, ectopic expression of TBX3 has been identified to inhibit apoptosis induced by β-catenin depletion (60). The results of this study reveal a role for TBX3 as a mediator of β-catenin-induced cell proliferation and regulator of hepatocarcinogenesis. Fong et al (61) demonstrated that TBX2 functions within the context of the Wnt signaling pathway to mediate cell migration in early embryonic development, indicating that TBX2 may be a target of the Wnt signaling pathway. However, whether TBX2 is a direct target of the Wnt signaling pathway in cancer cells remains unclear.

**Akt serine/threonine kinase 3 (AKT)/TBX3/E-cadherin axis.** The AKT family includes AKT1, AKT2 and AKT3, among which AKT3 is the predominant isoform (62,63). There is growing evidence that AKT3 serves a key role in the proliferation, invasion and migration of melanomas (64). A previous study demonstrated that there is a synergistic co-operation between B-RAF-V600E and AKT3 in promoting melanoma development (65). In addition, TBX3 may be regulated by AKT3 (65). Notably, Peres et al (66) tested three TBX3 overexpressing melanoma cell lines, MM200, ME1402 and 501-mel, and observed a direct correlation between TBX3 mRNA and protein levels, suggesting that TBX3 may be upregulated at the transcriptional and post-transcriptional level in cancer. In addition, a direct positive correlation between phosphorylated AKT levels and TBX3 expression was identified through western blotting (66). Following AKT3 silencing by siRNA in ME1402 and MM200 melanoma cells in vertical growth phase (VGP), TBX3 protein levels were reduced (66). Subsequently, site-directed mutagenesis and *in vitro* kinase assays demonstrated that TBX3 was phosphorylated at Ser-720 by AKT3 *in vitro* (66). Furthermore, it was observed that the phosphorylation of S720 enhanced the ability of TBX3 to repress its target gene, E-cadherin (23). TBX3 and E-cadherin protein levels were found to be inversely correlated in ME1402 VGP melanoma cells (66), indicating that the AKT/TBX3/E-cadherin axis is involved in melanoma invasion and migration, and that TBX3 may function downstream of the AKT3 pathway (Fig. 1). Therefore, TBX3 may become a target gene for the treatment of advanced melanomas.

7. **TBX genes as targets for cancer therapy**

There is a lack of effective long-term cancer treatments. Therefore, there is a need for novel therapeutic targets for the treatment of cancer. The studies examined in the present review indicate that further studies on TBX genes and their protein products are important, and that any effective anticancer treatments must inhibit these genes. No other proteins have small repression domains (RD), so it may be possible to design a drug targeting the RD, and thus TBX genes, with a high specificity (67). This may block the function of TBX proteins in cancer cells. Furthermore, highly specific treatments have the advantage of possessing low toxicity and a minimal side-effect profile (68-70). Through increased understanding of the interaction between TBX proteins and their signaling partners in various types of cancer, it may be possible to develop successful TBX RD-specific inhibitors in the future.

8. **Conclusion**

In conclusion, the present review provides an overview of the roles of TBX genes in the development of various types of cancer, including tumor cell invasion and migration, anti-senescence and proliferation, tumorigenesis, EMT and tumorigenic signaling. In addition, the current review illustrates the potential to use TBX genes as targets for cancer therapy, which is currently being examined (1.71). The theoretical rationale behind this is based on the fact that TBX genes are overexpressed in various types of cancer and function as potential oncogenes. An increased understanding of TBX genes and their protein products will accelerate the development of new cancer therapies targeting these genes.

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