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ZEB1: New advances in fibrosis and cancer

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Abstract
Zinc finger E-box binding homeobox 1 (ZEB1) is an important transcription factor in epithelial mesenchymal transition (EMT) which participates in the numerous life processes, such as embryonic development, fibrosis and tumor progression. ZEB1 has multiple functions in human body and plays a crucial part in some life processes. ZEB1 is vital for the formation and development of the organs in the embryonic period. The abnormal expression of ZEB1 is a predictor for the poor prognosis or the poor survival in several cancers. ZEB1 contributes to the occurrence of fibrosis, cancer and even chemoresistance. Some research is indicated that fibrosis is finally developed into the cancers. Therefore, ZEB1 is probably taken as a biomarker in fibrosis or cancer. In this review, it is predicted of the structure of ZEB1 and the protein binding sites of ZEB1 with some protein, and it is discussed about the roles of ZEB1 in fibrosis and cancer progression to elaborate the potential applications of ZEB1 in clinic.

Keywords ZEB1 · EMT · Cancer · Chemoresistance · Fibrosis · Protein structure

Introduction

ZEB1 is known as the key factor in EMT, which is associated with many life processes [1]. ZEB1 is characterized by the occurrence of two zinc finger clusters, and it particularly binds to DNA motifs termed as E-boxes through these two zinc finger clusters [2]. Many proteins perform their functions effectively through binding to zinc finger cluster and other domain on ZEB1, such as small mother against decapentaplegic (SMAD), brahma-related gene 1 (BRG1) and yes-associated protein (YAP) [1–3]. ZEB1 plays the enormous roles in cancer progression, inflammation and aging. Therefore, ZEB1 is a pivotal protein among these life processes, especially in fibrosis and cancer.

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The structure of ZEB1

Zinc finger E-box-binding homeobox (ZEB) family comprises two proteins ZEB1 and ZEB2 in higher vertebrates. ZEB1 was also named as EF1, AREB6, BZP, MEB1, Nil-2-a, TCF8, ZEB, ZEB-1, Zfhep1 and Zfhx1a (reviewed by Ester et al. 2012) [2]. ZEB1 contains two zinc finger clusters which bind to the particular sequences of DNA, and these zinc finger clusters are located at the N-terminal end and the C-terminal end of ZEB1 [4]. ZEB1 locates on human chromosome 10p11.22 as a pivotal transcription factor with zinc finger in EMT [5]. As shown in Fig. 1, ZEB1 contains several independent segments which mediate the binding of ZEB1 with DNA to complete the physiological function of ZEB1. As shown as Fig. 1, ZEB1 regulates various biochemical processes such as tumor progression and metastasis by binding with particular proteins. The binding sites are mostly located in N-terminal zinc finger or C-terminal zinc finger and their vicinity. For instance, BRG1 binds to the N-terminal zinc finger region of ZEB1 to inhibit the expression of E-cadherin in colorectal cancer [3]. The downstream region of ZEB1 N-terminal zinc finger binds to the phosphorylated receptor activated SMADs (R-SMAD), so ZEB1 could regulate the transforming growth factor (TGF)-β signaling pathway [2]. In aggressive tumor, the binding site of YAP on ZEB1 is located on C-terminal zinc finger and

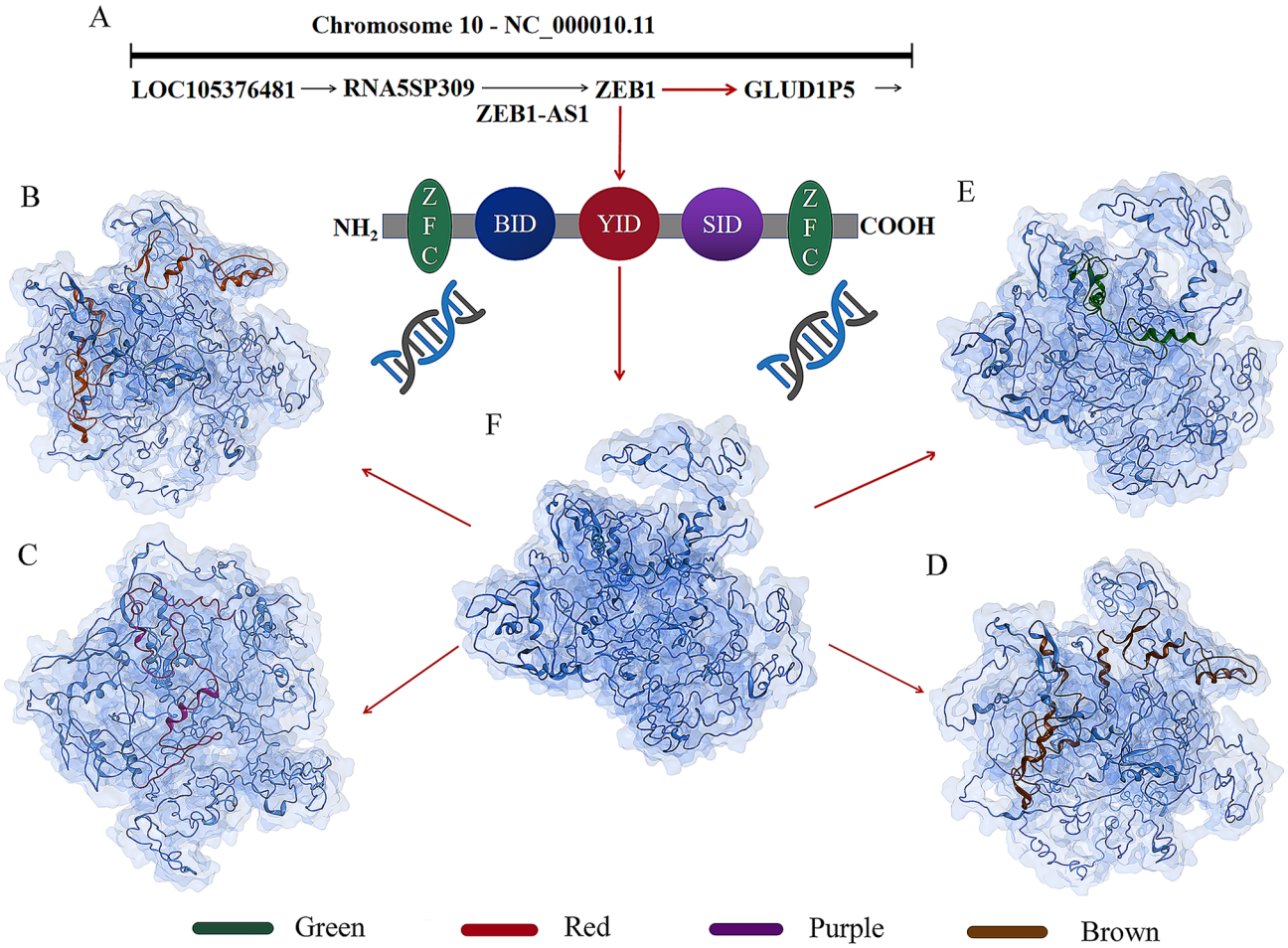

Fig. 1 The location of ZEB1 on chromosome and the protein binding sites on ZEB1. (**a**) The location of ZEB1 on chromosome and the structure of ZEB1. (**b**) SMAD binds to ZEB1 on red ribbon. (**c**) YAP binds to ZEB1 on purple ribbon. (**d**) DNA binds to ZEB1 on brown ribbon. (**e**) BRG1 binds to ZEB1 on green ribbon. (**f**) The structure of ZEB1 [*Homo sapiens* (human)], predicted by I-TASSER. *ZEB1* Zinc finger E-box binding homeobox 1, *SMAD* small mother against decapentaplegic, *YAP* yes-associated protein, *DNA* Deoxyribonucleic acid, *BRG1* brahma-related gene 1. (Color figure online)

N-terminal zinc finger [1]. Furthermore, C-terminal zinc finger and N-terminal zinc finger are the functional domains which can mediate the interaction between ZEB1 and DNA [2]. We utilized I-TASSER server for the prediction of the structure and the binding sites of ZEB1, which are labeled out in different color and are presented as Fig. 1. In addition, Fig. 2 showed a gene network associated with ZEB1, which is generated by the STRING database using ZEB1 as input. This network also includes the protein-protein interactions associated with ZEB1.

ZEB1-mediated signaling

ZEB1 can interact with some microRNAs (miRNAs) such as miR-200c and miR-205 to mediate multiple signaling pathways, such as wingless/integrated (Wnt), hippopathway, TGF-β to regulate the biological processes of inflammation, fibrosis, tumor metastasis and proliferation [1, 6–9]. The signal pathways related to ZEB1 are concluded in Fig. 3 and the physiological functions are showed in Table 1.

The role of ZEB1 in fibrosis

The damages in organs and tissues are fibrosis and inflammation [10]. Fibrosis is considered as a continuous repairment response to persistent or recurrent harm, alternatively, a disordered or inadequate repairment response to previous injury irritation [11]. EMT plays an important role in fibrosis. ZEB1 is the key transcription factor of EMT. Therefore, ZEB1 can promote the cell proliferation, migration and collagen formation and induce the fibrosis through EMT [12, 13].

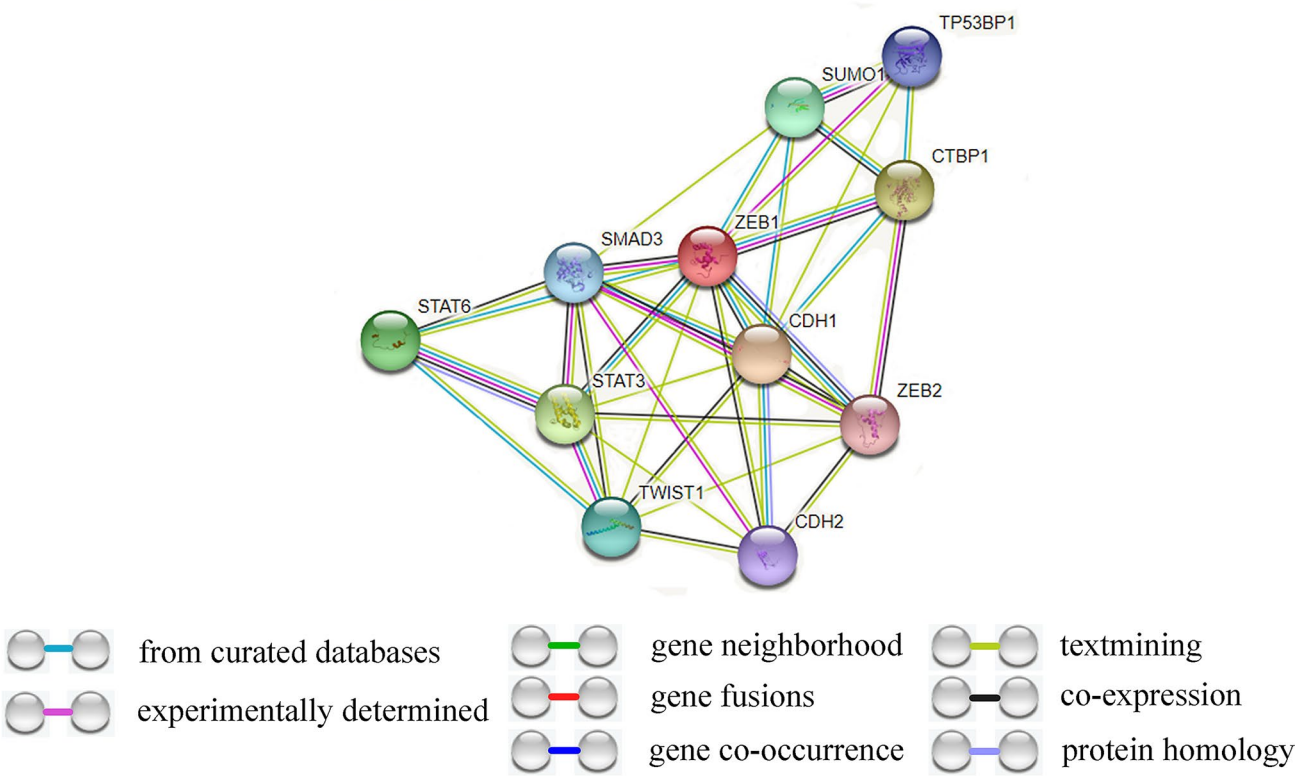

Fig. 2 ZEB1-related gene network generated by the STRING database. This network uses different color nodes to represent different proteins (TP53BP1, SUMO1, CTBP1, ZEB1, ZEB2, CDH1, CDH2, SMAD3, TWIST1, STAT3, STAT6). Different color lines represent different interactions among the gene levels (gene neighborhood, gene fusions, gene co-occurrence) or the protein levels (co-expression, protein homology). These interactions in the STRING database are from curated databases, experimental determination, text mining and so on. *TP53BP1* The p53-binding protein 1, *SUMO1* small ubiquitin-like modifier, *CTBP1* C-terminal binding protein 1, *ZEB1* Zinc finger E-box binding homeobox 1, *ZEB2* Zinc finger E-box binding homeobox 2, *CDH1* E-cadherin, *CDH2* N-cadherin, *SMAD3* small mother against decapentaplegic 3, *TWIST1* twist-related protein 1, *STAT3* signal transducer and activator of transcription 3, *STAT6* signal transducer and activator of transcription 6. (Color figure online)

Lung fibrosis

Lung fibrosis is a degenerative disease related to lung dysfunction and lung failures. As a pivotal transcription factor in EMT, ZEB1 is strongly expressed in the epithelial cells of hypertrophic alveolar septum to mediate EMT in human alveolar epithelial type II cells to induce lung fibrosis through the paracrine epidermal growth factor receptor/rat sarcoma/extracellular signal-regulated kinase (EGFR/RAS/ERK) signaling pathway. The downstream of EGFR/RAS signaling pathway includes phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), signal transducer and activator of transcription (STAT) and mammalian target of rapamycin (mTOR) pathways, which are participated into the migration and invasion of cancer cells [14, 15].

The high expression of ZEB1 was observed in alveolar epithelial cells near the excessive extracellular matrix in idiopathic pulmonary fibrosis (IPF), which indicates that EMT is dependent on ZEB1 in lung fibrosis. Hence, ZEB1 could therapeutically prevent IPF [14]. In addition, some environmental contamination can lead to lung fibrosis and chronic lung injury. Repeated exposure to the heavy metals such as nickel (Ni) can cause ZEB1-dependent EMT, and this process is irreversible after the termination of Ni exposure [16]. ZEB1 is regulated by miR-200, along with β-tubulin-III (Tubβ3) and β-catenin. ZEB1 is also directly regulated by miR-141a-3p, promotes EMT through TGF-β1 and activates the fibrogenesis of RLE-6TN cells [17]. ZEB1 is conspicuously related to pulmonary dysfunction and fibrosis, which affirms that ZEB1 is possibly associated with the prognosis of these patients [18]. The increasing expression of ZEB1 in bronchiolar fibro-proliferative lesions suggests that ZEB1 may serve as a particular early biomarker to predict lung fibrosis and lung failure [19, 20]. This test method reduces the harm resulted from lung biopsies to patients.

Liver fibrosis

Liver fibrosis is the basis for the progression of some liver diseases such as liver cancer, liver cirrhosis and hepatitis,

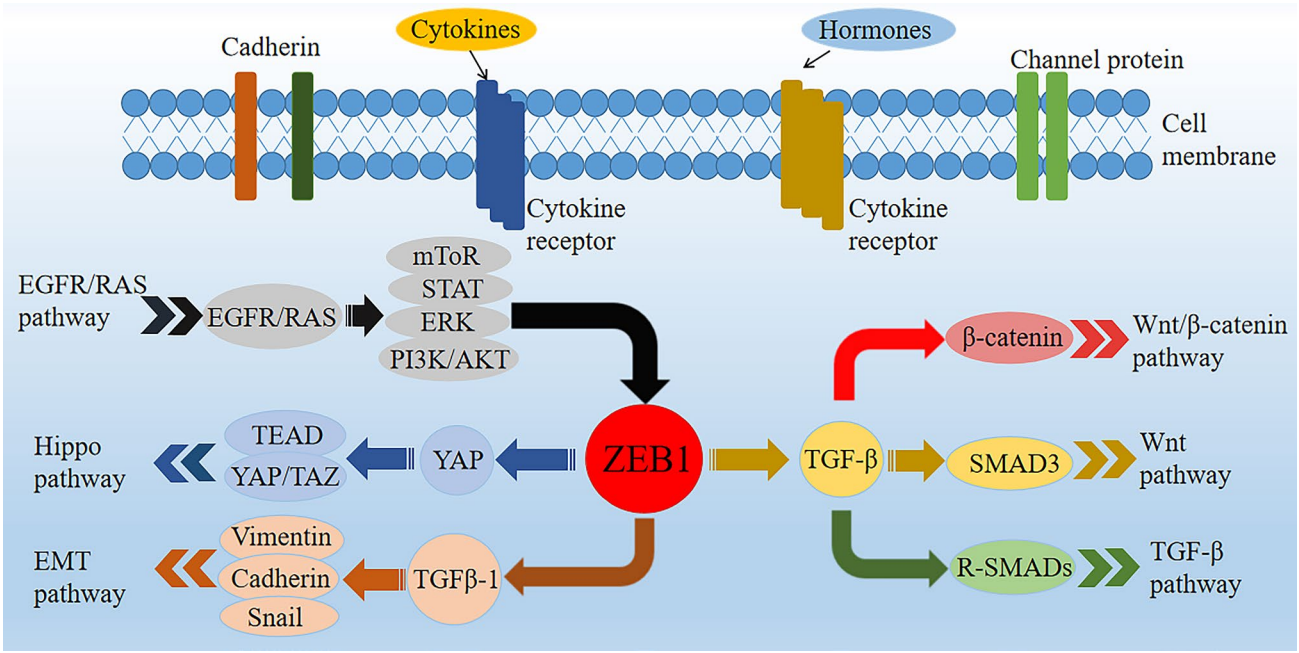

Fig. 3 Signal transduction pathways related to ZEB1. The different color balls represent different proteins, different color arrows represent different pathways which mentioned in the manuscript. The black arrows represent EGFR/RAS pathway, the blue arrows represent hippo pathway, the brown arrows represent EMT pathway, the yellow arrows represent Wnt pathway, the red arrows represent Wnt/β-catenin pathway, and the green arrow represents TGF-β pathway. *ZEB1* Zinc finger E-box binding homeobox 1, *EGFR/RAS* epidermal growth factor receptor/rat sarcoma, *EMT* epithelial mesenchymal transition, *Wnt* wingless/integrated, *TGF-β* transforming growth factor β. (Color figure online)

Table 1 Signaling pathways related to ZEB1 and its physiological functions

Signal pathways related to ZEB1	Related physiological functions
Hippo pathway [2]	Regulate cell differentiation;
	Regulate tumor progression, metastasis and treatment resistance.
Wnt [6, 28, 54]	Regulate adult intestinal stem cells homeostasis, and aberrant activation induces the development of the stem cells of colorectal cancer (CRC);
	Promote fibrosis in hepatic cells;
	Play a decisive role in endometrial gland formation and mesenchymal development.
Wnt/β-catenin [6, 23]	Promote EMT;
	Induce the release of pro-inflammatory cytokines;
	Promote fibrosis in hepatic cells;
	Promote cell proliferation
EGFR/RAS [14]	Promote EMT;
	Enhance paracrine signaling.
EMT [11, 14]	Promote tumor progression;
	Drive wound healing response;
	Promote embryogenesis and development.
TGF-β [35, 40]	Induce EMT;
	Suppress the development of early tumor;
	Promote the development of advanced tumor;
	Regulate cell growth and proliferation.

and ends up with destructive consequences such as liver failure. ZEB1 has been widely investigated and found of its abnormal expression in numerous hepatic diseases. It is reported that ZEB1 could be a pivotal factor in chronic virus hepatitis and liver cancer [21, 22].

ZEB1 can activate hepatic stellate cells (HSCs) through Wnt/β-catenin signaling pathway to regulate the progression of pro-fibrosis [23]. The expression of ZEB1 is in positive correlation with the expression of pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) in hepatic cells to lead to liver fibrosis. Furthermore, ZEB1 can be targeted by H19RNA to promote cholestatic liver fibrosis in mice [24].

ZEB1 and tumor progression

As a key transcription factor in EMT, ZEB1 plays a crucial role in tumor dissemination, metastasis and therapy resistance. More importantly, the expression of ZEB1 is associated with many aggressive tumors [1, 25].

The role of ZEB1 as an oncogene

The tumor derived from C918 cells with high expression of ZEB1 destroyed the structure of the eye in 13 days after transplantation on eyes, while the tumor derived from OCM1 cells with low expression of ZEB1 did not destroy the structure of the eyes on the 13th days after transplantation, which suggests that ZEB1 may be an oncogene that endows cancer cells with the ability of rapid proliferation and metastasis [26]. ZEB1 is strongly expressed in the hypoxic cervical carcinoma cell lines [27]. The mechanism how hypoxia induces ZEB1 expression is that hypoxia inducible factor 1α (HIF-1α) directly binds to the proximal promoter of ZEB1 via hypoxia response element sites to increase the transcription activity and expression of ZEB1 [28].

It is confirmed that hypoxic tumor microenvironment (TME) facilitates malignant tumor development and resistance to immunotherapies by accelerating transformation of tumor and triggering tumor resistance to immune system [29]. ZEB1 is proved to be a crucial transcription factor in tumor growth, and is sensitive to hypoxia. Tumor associated macrophage (TAM) is invariably adjacent to ZEB1-positive cells in cell matrix, which suggests that ZEB1 may gather TAMs [30]. Overexpression of ZEB1 in tumor cells could lead to TAM infiltration, and the interaction between cancer cells and TAMs also simultaneously influences the expression of ZEB1. Moreover, the expression of ZEB1 in TAM can increase chemoresistance of cancer cells [31].

The role of ZEB1 in breast cancer

ZEB1 may repair the DNA damage and clear the double-stranded breaks (DSBs), and its overexpression also is related to chemoresistance in breast cancer. It is confirmed that patients with high levels of ZEB1 has weaker response to the chemotherapy. ZEB1 confers chemoresistance on breast cancer cells by decreasing drug-induced DSBs in an ataxia telangiectasia mutated (ATM)-dependent manner and by accelerating DNA damage response (DDR) [32]. Furtherly, ZEB1 was regulated by miR340 in primary breast cancer. miR-340 inhibits breast cancer progression by down-regulating ZEB1 levels through TGF-β signaling pathway [33]. Survival analysis of breast cancer revealed that the patients with high expression of ZEB1 display shorter relapse-free survival and overall survival, especially for hormone receptor-negative cancers (ER-/PR-) and other aggressive subtypes [1].

The role of ZEB1 in lung cancer

As a transcription factor, ZEB1 leads to the changes of epithelial genes expression in lung cancer, such as SEMA3F [34]. ZEB1 is closely related to the mesenchymal phenotype of non-small cell lung cancer (NSCLC). Additionally, ZEB1 is crucial for the development of pulmonary mesenchymal cancer phenotype [9].

The increased expression of ZEB1 involved in EMT is associated with the grades and stages of lung cancer. ZEB1 was required for myelocytomatosis oncogene cellular homolog (MYC)- and TGF-β-induced EMT in $HBEC3^{p53, KRAS}$ (referred to as $HBEC3^{p53, KRAS, shZEB1}$) [35]. It has been reported that ZEB1 can be a therapeutic target for metastatic NSCLC [36].

The role of ZEB1 in colorectal cancer

ZEB1 is considered as a key factor in Wnt signaling pathway. Approximately 90% of colorectal cancer patients have aberrant Wnt signaling, such as ZEB1. Hence, ZEB1 plays a crucial role in the cancer metastasis and stemness [37]. Moreover, it has been reported that ZEB1 and ZEB1 downstream molecules are regulated positively by the adjacent Lnc-RNA ZEB1-AS1 which has been confirmed to be associated with various cancers. Survival of colon adenocarcinoma patients with high expression of ZEB1-AS1 is generally low [38, 39].

The role of ZEB1 in other cancers

ZEB1 is regulated by ETS transcription factor 3 (ELF3) through miRNA-141-3p, which can stimulate EMT in hepatocellular carcinoma (HCC) cells [40]. miR-126 can

suppress EMT in osteosarcoma by targeting ZEB1 via the janus-activated kinase (JAK)/STAT pathway [41]. In A431 cells, ZEB1 is down-regulated by ovo-like transcriptional repressor 1 (OVOL1) or ovo-like zinc finger 2 (OVOL2) which is a common conserved gene that encodes C2H2 zinc finger transcription factors in mammals. ZEB1 also plays an important part in the progression of actinic keratosis (AK) to cutaneous squamous cell carcinoma (cSCC). This progression is particularly rare, whereas advanced cSCC always ends up with devastating consequences [42]. Overexpression of ZEB1 induces metastasis and invasion of osteosarcoma cells [43]. ZEB1 may serve as an important regulator of the stem cells in glioma, and the deletion of ZEB1 will lead to the increasing in stem cells and tumorigenicity and even the reduced survival of the patients [44]. In addition, ZEB1 can be regulated by centrosomal protein 55 (CEP55) through PI3K/AKT/mTOR signaling pathway to inhibit the EMT in renal cell carcinoma [45].

Endometriosis is a common benignant gynecological disease among fertile women, which is characterized by extraordinary invasion. It also considered as a benignant tumor. ZEB1 is highly expressed in the epithelial cells of endometriosis, while it is rarely expressed in normal endometrial epithelial cells. ZEB1 promotes the transferring of endometrial epithelial cells to mesenchymal cells, which is suggested that ZEB1 would become an indicator of cell invasion and metastasis in endometriosis. ZEB1 can be regulated by miR-199a-5p via PI3K/AKT/mTOR pathway to inhibit the EMT in endometriosis. Based on the strong correlation between ZEB1 and endometriosis, ZEB1 can be served as a predictor of endometriosis [46, 47].

ZEB1 and chemoresistance

Chemoresistance can be divided into drug resistance and radio resistance, which is a huge challenge to cure cancer [8, 48, 49]. Chemoresistance is enhanced by cancer stem cells with self-renewal ability to avoid DNA damage, clear reactive oxygen species (ROS), and activate cancer cell survival [7, 40, 48]. ZEB1 is prone to generate the cells with stem-like properties by the interaction with YAP. It has been investigated that ZEB1 participates in the clearance of chemotherapy-induced DSBs and promotes cancer resistance to drugs and radio. ATM is regarded as a major mediator in DNA repairment. ZEB1 can interact with ATM to involve in the DNA repairment to promote chemoresistance [1, 50].

Furthermore, knockdown of ZEB1 in glioblastoma can reduce both its invasion and drug-resistance [51]. ZEB1 is investigated as indicator of the metastasis and chemoresistance of liver cancer [52].

Clinical applications of ZEB1

As chemo sensitizer

ZEB1 plays a great part in chemoresistance in cancer patients [51, 53, 54]. ZEB1 can interact with ATM or miRNA, which is of great importance in the DNA repairment and the clearance of DNA breaks [32, 54]. ZEB1 is inhibited by miR-203 to suppress stemness, which indicates that ZEB1 can be taken as the drug sensitizer [55].

Some research demonstrates that early-stage cancer patients with high expression of ZEB1 may be accompanied by higher drug resistance, which reveals the possibility of using ZEB1 as an indicator of drug resistance in cancer patients. This provides us with a new idea for chemo sensitizer. Drugs which can suppress ZEB1, as chemo sensitizers, are combined with chemotherapy drugs to improve the survival and cure rates of the cancer patients.

As diagnostic indicator

The abnormal expression and location of ZEB1 are discovered in the early stage of some diseases such as IPF, which suggests that ZEB1 could be a diagnostic indicator of these disease. ZEB1 is closely associated with the emergence of early lung fibrosis, especially the early IPF [14, 16, 20]. The high expression of ZEB1 was observed in IPF tissue. ZEB1 is also related with the prognosis of lung fibrosis [14, 18, 20]. These studies demonstrate that ZEB1 can be a specific indicator of IPF. It is hypothesized that ZEB1 could replace lung biopsy to reduce the harm in medical tests [20].

ZEB1 is highly expressed in the epithelial cells of endometriosis, while it is rarely expressed in normal endometrial epithelial cells. This also indicates that endometriosis can be diagnosed with high expression of ZEB1 [47, 56].

Conclusion

It is widely believed that EMT plays an important role in nerve system development, embryo development and organ formation [57–62]. In contrast, EMT participates in fibrosis and some cancers. ZEB1 is the most representative among the proteins associated with EMT. ZEB1 mediates the interaction with some signaling pathways, such as TGF-β, Wnt, hippopathway. These signaling pathways maintain positive or negative correlation with ZEB1, and eventually promote or weaken the EMT [1, 7, 8]. The overexpression of ZEB1 represents the severity of lung fibrosis and predicts the prognosis of patients [19]. ZEB1 is strongly related to lung fibrosis and endometriosis [14, 16, 47]. Furthermore, ZEB1

facilitates tumor progression and promotes tumor stemness and metastasis. High expression of ZEB1 represents the poor prognosis of the cancer patients [1, 26]. ZEB1 has the capacity of conferring the stemness on cancer cells to enhance the chemoresistance [1, 43, 55]. Based on these studies, it is found that ZEB1 is involved in the pathogenesis of fibrosis and cancer.

In summary, ZEB1 could be designed as a blood biochemical index to support the clinical diagnosis of pulmonary fibrosis or endometriosis. It is possible that ZEB1 is used as an indicator of chemoresistance in cancer patients. The inhibition of ZEB1 can be served as chemo sensitizer to improve the survival rate of cancer patients. A thorough understanding of ZEB1 in fibrosis and cancer tissues can provide the sufficient supports for the clinical development and application of ZEB1 in the future.

Author contributions All authors contributed to the study conception and design. All authors read and approved the final manuscript. Lin Cheng had the idea for the article, Lin Cheng, Ming-Yuan Zhou, Ying-Jian Gu, Lei Chen performed the literature search and data analysis, Lin Cheng drafted the work, and Yun Wang critically revised the work.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interest.

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