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Dualistic role of ZEB1 and ZEB2 in tumor progression

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Abstract

It is generally accepted that ZEB1 and ZEB2 act as master regulators of the epithelial-mesenchymal transition, which arguably is the key mechanism of metastasis. Accordingly, they are deemed as negative predictors of the survival of cancer patients by promoting the emergence of secondary foci of the disease. Paradoxically, in some types of cancer types the opposite effect is observed, i.e. ZEB1 and ZEB2 are associated with better prognosis for cancer patients. In this review, we discuss the hypothesis that the tumorigenic effects of ZEB1/ZEB2 can be different in various tissues depending on the initial status of these proteins in the corresponding healthy tissues. Emerging evidence suggests that ZEB1 and ZEB2 are constitutively expressed in several healthy tissues, performing vital functions. Consequently, reducing the expression of ZEB1 and ZEB2 could negatively affect these tissues causing various diseases, including cancer. Finally, the dualistic role of ZEB1 and ZEB2 as immune modulators and their effect on tumor microenvironment is also discussed.

Keywords Cancer, Carcinogenesis, Epithelial-mesenchymal transition, ZEB1, ZEB2

Introduction

Epithelial-mesenchymal transition (EMT) is a reversible biological process in which epithelial cells lose their cell polarity and intercellular adhesion and acquire a mesenchymal phenotype. As a result of this transition, cells gain the ability to migrate and invade, participating in developmental processes such as gastrulation, neural crest formation, cardiac morphogenesis, and formation of the musculoskeletal system and craniofacial structures. Noteworthy, EMT can also take place in adult tissues during wound healing or fibrosis and plays an important role in tissue homeostasis. However, in tumors of epithelial origin, EMT may play a negative role, giving rise to a population of highly invasive and drug-resistant cells, thereby accelerating metastasis [1–3].

The EMT program is largely governed by changes in gene expression of epithelial cells via so-called EMT-transcription factors including Snail, Slug, Twist, and ZEB1/ZEB2. It is believed that ZEB1 and ZEB2 serve mainly to induce EMT by participating in embryogenesis and promoting metastasis in various cancer types [4]. However, an ever-growing list of new roles of ZEB1 and ZEB2 in adult organisms, both in normal and cancerous tissues, continues to accumulate each year. These emerging findings challenge the existing paradigm of

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ZEB1 and ZEB2 as key proteins responsible for the promotion of metastatic phenotypes in oncogenic processes. For instance, although extensive evidence supports the notion that increased expression of ZEB1 correlates with oncogenic potential across various cancer types, an increasing number of reports contradicts this dogma, indicating that ZEB1/2-mediated effects are much more complex than previously understood [5].

Structure-functional organization of ZEB1 and ZEB2

The ZEB (zinc finger E-box binding homeobox) family of proteins includes two representatives: ZEB1 and ZEB2. The genes encoding these proteins are located on the short arms of chromosomes 10 and 2, respectively.

Proteins of the ZEB family consist of several domains that perform various functions. They have 2 clusters of zinc finger domains located at the N- and C-termini, as well as a homeodomain located in the center of their amino acid sequence (Fig. 1) [6]. ZEB1 and ZEB2 bind to their target genes by recognizing specific sequences, known as E-boxes (CACGTG sequences), within the promoter regions. This binding is mediated by their zinc finger domains. The N-terminal cluster of ZEB1 and ZEB2 (NZF) contains one CCHC motif and three C2H2 motifs, while the C-terminal cluster (CZF) comprises three CCHC motifs [6]. ZEB2 and ZEB1 exhibit a high degree of similarity in the amino acid sequences of the NZF (88%) and CZF (93%) clusters [7].

ZEB2 (also referred to as SIP1) interacts with SMAD proteins and binds to 5′-CACCT sequences in candidate target genes). The high homology of these two clusters (~90%) suggests that ZEB2 and ZEB1 are able to bind to similar DNA regions and, with a few exceptions, regulate the same targets [8].

ZEB2 contains a NuRD complex interacting motif (NIM) that interacts with nucleosome remodeling and histone deacetylation complex (NuRD) [9] which plays a central role in embryonic stem cell (ES) differentiation [10].

The homeodomain (HD), structurally consisting of a helix-loop-helix motif, does not bind to DNA, but facilitates protein-protein interactions [11]. ZEB factors also contain several independent domains that interact with other transcriptional regulators, acting through chromatin remodeling [12]. Thus, proteins of the ZEB family have a binding site for the CtBP protein (C-terminal binding protein) - the CtBP-interacting domain (CID) which determines the ability of ZEB proteins to act as a transcriptional suppressor [13]. CtBP downregulates the expression of target genes by interacting with histone deacetylase HDAC1 [14]. Near their N-termini, ZEB factors have SMAD binding domains (SBD), which play a key role in regulating SMAD protein activity. ZEB1 activates SMAD-mediated transcription, whereas ZEB2 acts as a repressor [15]. Interestingly, the direct binding of any activated phospho-SMAD protein to ZEB2 depends on a 51 amino acid segment that is absent in ZEB1. Within this segment, a critical tandem repeat (QXVX)2

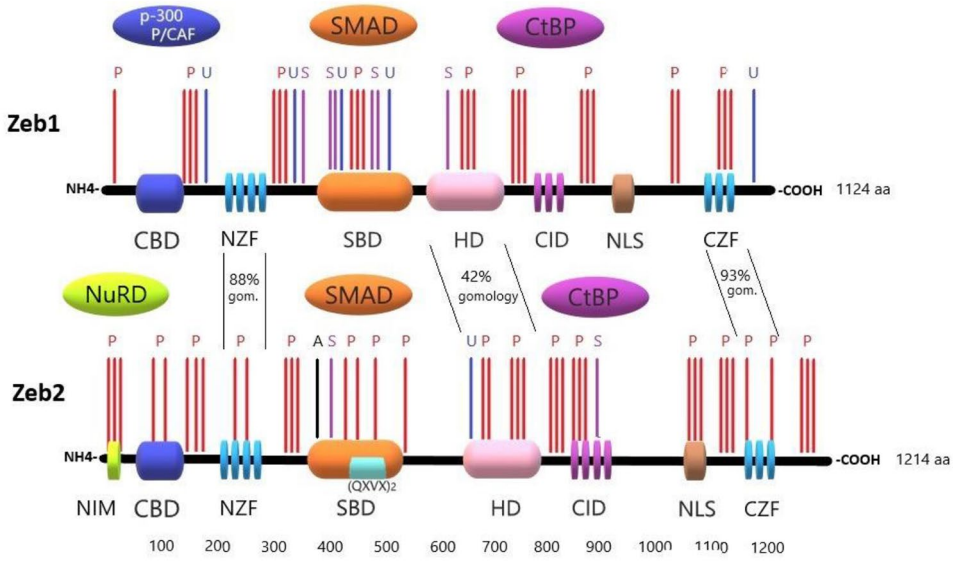

Fig. 1 Comparison of the structure of ZEB1 and ZEB2 proteins. Major domains of ZEB1 and ZEB2: NuRD complex interacting motif (NIM), P300-P/CAF interaction domain (CBD), N-terminal cluster of ZEB1 and ZEB2 (NZF), SMAD binding domain (SBD), homeodomain (HD), CtBP-interacting domain (CID), nuclear localization signals (NLS), C-terminal cluster (CZF). Amino acid modifications shown above the schematic diagram of the protein structure: phosphorylation (p), acetylation (a), ubiquitination (u), and sumoylation (s). Several ZEB-associated interactors – NuRD, p300 and P/CAF, SMAD, CtBP are depicted as colorized ovals

is essential for binding to all activated SMADs. In contrast, full-length ZEB1 does not directly bind to SMAD (segment 437–487) [16]. This difference accounts for the opposite regulatory effects of ZEB1 and ZEB2 on SMAD protein activity. This antagonism between ZEB1 and ZEB2 arises from their interaction with different sets of co-factors, including p300, P/CAF, and CtBP. While ZEB2 can only interact with CtBP and acts as a repressor for Smad proteins, ZEB1 recruits p300 and P/CAF via the P300-P/CAF interaction domain (CBD) to Smad proteins to form a complex that not only enhances Smad, but also displaces CtBP from ZEB1 [15]. Apparently, the switch in ZEB1 function from a repressor to an activator is modulated by the YAP1 protein, a member of the Hippo family: YAP binds to the (N)- and (C)-terminal domains of ZEB1, capturing both zinc finger clusters, NZF and CZF [17]. Additionally, it has been demonstrated that, unlike ZEB2, ZEB1 recruits the BRG1 protein, the catalytic core of the mammalian SWI/SNF chromatin remodeling complex. This recruitment allows ZEB1 to suppress target genes independently of CtBP, highlighting a key functional difference between the ZEB family proteins [18]. It is noteworthy that in Xenopus, XSIP1 (the ortholog of ZEB2) can interact with the coactivators pCAF and p300, as well as the corepressor CtBP [19]. This suggests that ZEB2 may have lost this ability during evolution, implying that ZEB2 might have originally functioned not only as a transcriptional suppressor but also as an activator.

Although ZEB1 and ZEB2 are true homologs with significant structural similarity, they exhibit important differences in their interactomes. In some instances, ZEB1 and ZEB2 can substitute for or complement each other's functions, while in other cases, they carry out opposing actions. For example, ZEB2 may serve as an alternative to ZEB1 to interact with SMAD proteins without involving ZEB1-associated factors [20]. This is indirectly supported by the fact that in cell lines or in tumors, activation of ZEB2 expression often precedes ZEB1 expression [20].

Generally, ZEB proteins are described as transcriptional repressors, but in the regulation of the TGFβ/BMP pathway [15] they act antagonistically, which is the result of differential recruitment of coactivators (p300 and P/CAF) and corepressors (CtBP). While ZEB2 binds only CtBP and acts as a repressor of SMAD, ZEB1 attracts also p300 and P/CAF to SMAD to form a complex that displaces CtBP from ZEB1 and thus activates the transcription of TGFβ-dependent genes more efficiently [15]. Typically, transcription factor acetylation is associated with transcriptional stimulation, and P/CAF transforms ZEB1 to an activator; whereas a deletion of the p300-P/CAF N-terminal binding site makes ZEB1 similar to ZEB2 in terms SMAD interactions [15].

Notably, besides the aforementioned interactions, ZEB1 can interact with many tumor suppressor proteins [21], including p53 [22]. In addition, Postigo's group has shown that in cancer cells with mutant *TP53*, ZEB1 triggers a new regulatory cascade that involves DKK1, mutant p53, Mdm2 and CtBP sequentially activated of to ultimately affect macroH2A1 (H2AFY), thus escaping tumor-associated senescence [15]. Another report suggests that ZEB1 can physically associate with mutant p53 in AML, underpinning the proliferative phenotype of such cells [23]. Taken together, these results not only underscore the importance of mutual negative feedback loops that exist between ZEB1 and p53 [24], but also highlight the fact that ZEB1 (and potentially ZEB2) can alter the interactome of p53 [21, 25] resulting in global dysregulation of p53-dependent gene expression [26]. Accordingly, a pharmacologically-induced effect on ZEB1 using p53-activating drugs [27–29] should attenuate the tumorigenicity and metastatic potential of cancer cells.

Modifications of ZEB1 and ZEB2

Post-translational modifications (PTM) can affect the intracellular localization of ZEB family proteins, their ability to bind to DNA and protein regions, contributing to the process of metastasis and cancer development [30]. Like other proteins, ZEB family factors can be modified by phosphorylation, acetylation, ubiquitination, and sumoylation at various sites. These modifications can affect the stability, nuclear localization, expression level of the protein, and its activity and including its ability to bind DNA [31]. ZEB1 and ZEB2 differ in their PTM patterns, and this likely influences their regulation pathways.

Phosphorylation increases half-life and promotes nuclear import of ZEB family proteins [30]. Serine-threonine ATM kinase (Ataxia Telangiectasia Mutated) phosphorylates and stabilizes ZEB1, which promotes DNA damage response (DDR) and stabilization-induced tumor radioresistance (CHK1) [32]. GSK3β was found to phosphorylate ZEB2 at Ser705 and Tyr802 in colorectal cancer, leading to EMT triggering and metastasis [33]. Interestingly, GSK3β also phosphorylates unused β-catenin, facilitating its ubiquitination and degradation in proteasomes. At the same time, mutations in β-catenin at phosphorylation sites, or its interaction with YAP1, lead to the stabilization of β-catenin and its translocation into the nucleus, where it acts as a co-transcription factor for various factors [34]. ZEB1-mediated attenuation of E-cadherin expression results in the release of β-catenin, which is associated with cell-adhesion complexes and its translocation to the nucleus [35] and activation of EMT. Thus, the ZEB1-YAP1- β-catenin axis seems to be instrumental in the onset of EMT. Lysine acetylation by PCAF impairs CtBP binding to ZEB1 [31] thus affecting its repressor potential.

Role of ZEB1/ZEB2 in non-malignant diseases

In recent years, the understanding of the significance of ZEB1 and ZEB2 factors has expanded significantly, and it has become clear that they perform different functions in various nervous, immune, mesenchymal, and endothelial cells of the adult organism [36]. In these cells, ZEB family proteins are involved in the regulation of differentiation, stemness, survival, and proliferation [37]. Normally, ZEB1 and ZEB2 are expressed in various types of tissues (Fig. 2).

Fibrosis occurs in many chronic degenerative diseases, accompanied by a decrease in the functionality of organs [38] and a reduced life expectancy for patients. In cases of progressive chronic kidney damage, renal fibrosis often becomes irreversible due to tubular EMT, a process triggered by ZEB1 and ZEB2, which are activated during kidney damage [39]. Increased levels of ZEB1 and ZEB2 promote fibrogenesis in kidney tissue and are associated with diabetic nephropathy [40], which is the main cause of chronic kidney disease in patients.

For example, liver fibrosis underlies the progression of hepatitis to liver cirrhosis and liver cancer. ZEB1 can promote cellular collagen formation, cell proliferation and migration via EMT, as well as promote fibrosis [41], since ZEB1 expression is associated with the expression of liver fibrosis-associated pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) [42].

It has been shown that ZEB1 contributes to the development of interstitial pulmonary fibrosis through the regulation of paracrine signaling that causes the development of a profibrogenic microenvironment [38]. In idiopathic pulmonary fibrosis (IPF), ZEB1 is overexpressed in alveolar epithelial cells located in an area of perturbed extracellular matrix [42].

Importantly, ZEB2 also contributes to tissue fibrosis. The level of ZEB2 is inversely proportional to collagen expression and the formation of a pathological hypertrophic skin scar that occurs after injury [43]. Additionally, ZEB2 downregulation is associated with renal fibrosis [44]. Interestingly, in a mouse study, endothelial ZEB2 was shown to protect the liver from fibrosis in mice [45], but in the heart, ZEB2 promotes fibrosis by affecting fibroblasts [46].

In pulmonary fibrosis, the role of ZEB1 and ZEB2 in the scar formation has also been shown [47]. As noted by other authors, increased levels of ZEB1 are associated with idiopathic pulmonary fibrosis [48]. ZEB1 also plays a key role in the progression of liver fibrosis by participating in the activation of hepatic stellate cells (HSCs) [49], which acquire the myofibroblast-like phenotype that occurs during fibrosis [50]. In addition, ZEB1 contributes to liver inflammation in alcohol-induced fatty liver disease in humans [51], and ZEB2 is also invloved in liver fibrosis [52].

ZEB1 and ZEB2, as a key drivers of Endothelial Mesenchymal Transition (EndMT), are implicated in a number of diseases that involve cardiac fibrosis resulting, for example, from multiple episodes of rheumatic fever [53]. On the other hand, the lack of ZEB1 and ZEB2 factors in the adult organism can also play a negative role in some cases. A recent study showed that delivery of ZEB1 via extracellular vesicles promotes angiogenesis-dependent bone formation and may promote bone regeneration in patients with diabetes mellitus [54]. This study also shows the positive role of ZEB1 in suppressing osteoclasts [54]. ZEB2 has also been shown to be involved in the differentiation of bone marrow mesenchymal stem cells (BMSCs) and its downregulation causes diabetic osteoporosis in mice [55].

Roles of ZEB1 and ZEB2 in cancers

Cancer is currently the second leading cause of death worldwide [56]. ZEB1 and ZEB2 play an important role in the formation of metastases, the main cause of cancer-related mortality. In different human cancers, aberrant expression of ZEB1 has been noted, it is believed to promote cell migration, and invasion, important metastatic processes, affected by secreted extracellular

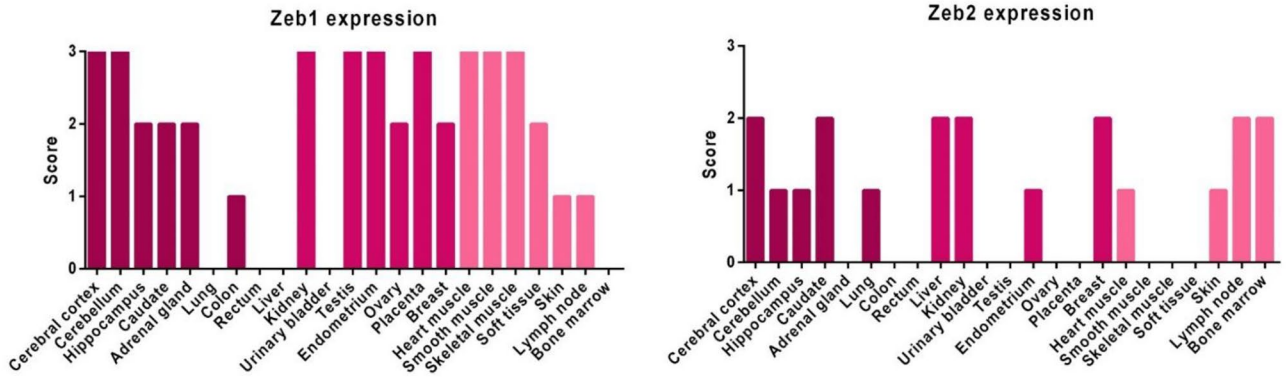

Fig. 2 Expression levels of ZEB1 and ZEB2 in different normal adult tissues. Data from the Human Protein Atlas

molecules in the tumor microenvironment (TGFβ, FGF, EGF, HGF, Wnt, Notch, Hedgehog, etc.), and activation of signaling pathways (MAPK, PI3K, NF-κB, Wnt/β-catenin, Notch, etc.) by activating EMT [57]. For instance, in lung cancer bone metastases, ZEB1 is directly activated by β-catenin, resulting in decreased E-cadherin levels and triggering EMT [58]. One of the key events of EMT is the loss of E-cadherin, which us responsible for adhesive junctions between cells due to direct repression of its *CDH1* gene by transcription factors, among which ZEB1 and ZEB2 are important [57]. ZEB2 is associated with various cancers, its expression being under the control of signals from the TGFβ, TNFα, IL1, AKT and other pathways [59], and serves as one of the regulators of EMT, increasing the migratory and invasive potential of cancer cells [60].

EMT is a key step in metastasis, in which cells lose epithelial features and acquire a mesenchymal characteristics [61, 62]. The aggressiveness of the sarcoma relies on the mesenchymal state maintained by ZEB1, and ZEB2 and other EMT factors. Particularly, ZEB1 protein levels in human sarcoma tissues are associated with lung metastasis [63].

Metastasis is the leading cause of death in breast cancer patients [12]. The ZEB2-dependent transcription program EMT activates the nucleotide excision repair (NER) pathway, mainly by activating the key components of its pathway - the ERCC1 and ERCC4 genes and this leads to an increase in the viability of CRC (secondary colorectal cancers) cells during treatment with oxaliplatin [64]. It should be noted that resistance to adjuvant chemotherapy is a serious clinical problem in cancer treatment.

Both ZEB1, and ZEB2 bind to the regulatory E-box sequences of their target genes, affecting their transcription [12]. For example, both ZEB factors repress E-cadherin, P-cadherin, gap junction components connexin 26 (GJB2) and connexin 31 (GJB3) [65–67]. Cell polarity genes Crumbs3, PATJ (Pals1-associated tight junction protein), and HUGL2 (human lethal giant larvae homologue 2), tight junction components (occludin, JAM1, claudin 7, tricellulin and shroom), desmosome components (desmoplakin, plakophilin 3, desmocollin 2 and desmoglein 2) are also potential targets for ZEB1 [67]. Moreover, ZEB1 suppresses cell polarity factors, basement membrane synthesis and activates the expression of matrix metalloproteases (MMP-1, MMP-9 and MMP-14), thereby promoting basement membrane remodeling and invasion into surrounding tissues [68]. Similarly, ZEB2 represses the tight junction protein claudin 4 (tight junction protein) 3 (ZO-3), plakophilin 2, desmoplakin [69]. In addition, ZEB2 enhances the expression of matrix metalloproteinases MMP-1 and MMP-2 [70].

Some authors note a synergic effect of increased expression levels of ZEB1 and ZEB2 in cancer. For example, Chu and colleagues noted that co-expression of ZEB1 and ZEB2 is a poor prognostic marker for tumor formation in head and neck cancer [71]. Other researchers declare that ZEB1 and ZEB2 complement each other's effect on enhancing invasion and migration of tumor cells in glioma [72].

We analyzed the expression of ZEB1 and ZEB2 in normal and malignant conditions using the database from the Artyomov Lab (wustl.edu) (Fig. 3). For all cancer types a significant difference in the expression of ZEB1 and ZEB2 between normal and pathological tissues was observed (except for liver hepatocarcinoma in the case of ZEB1). Surprisingly, in pathology, the expression levels of ZEB1 and ZEB2 in cancers are reduced in comparison to control. Our data also correspond very well to those posted on the TNMplot resource (except for AML, and cancers from pancreas, kidney, skin and stomach). Importantly, most changes in the expression of either ZEB1 or ZEB2 are similar within the same cancer types, and usually excellent correlations in their expression can be observed (Fig. 4), the primary data were retrieved from the Artyomov Lab Home page (wustl.edu).

Numerous studies have identified ZEB1 and ZEB2 as negative prognostic markers for most types of cancer. However, in certain cancers, an intriguing paradox has been observed: increased levels of ZEB1 or ZEB2 are associated with improved patient survival.

Survival curves were obtained using the Kaplan-Meier plotter (kmplot.com), which combines data from studies involving several thousand patients (Fig. 5). It is important to note that in our bioinformatics analyses we used the expression level of lncRNA ZEB1-AS1 instead of ZEB1, because the former showed a very strong correlation with ZEB1 activity in several studies [73, 74]. For the same reason, in some cases lncRNA ZEB2-AS1 was used [75].

ZEB1 and ZEB2 in liver cancer

A study conducted on patients with HCC (Hepatocellular Carcinoma) showed that overexpression of cytoplasmic ZEB2 in both tumor and peritumoral liver tissues is closely associated with improved survival outcomes [76]. The authors expressed surprise to find that patients with hepatocellular carcinoma (HCC) with higher levels of ZEB2 expression exhibited better survival compared to those with lower levels. Furthermore, the researchers observed no correlation between ZEB2 expression and the levels of E-cadherin or vimentin [76]. However, they also reported that an analysis of 110 patients revealed that high ZEB1 expression may be a favorable factor for both overall and relapse-free survival. This latter finding is supported by Kaplan-Meier plots [77]. It is important to note that in this study, ZEB1 protein levels were higher

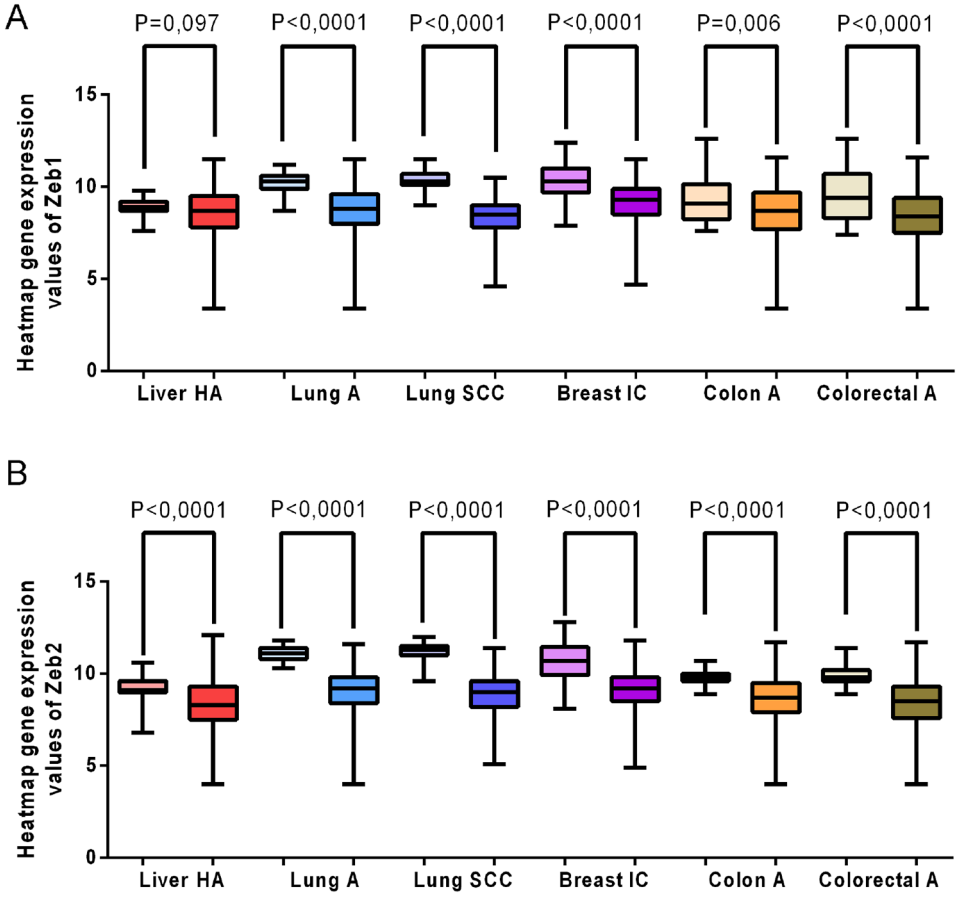

Fig. 3 Comparison of the level of expression of ZEB1 and ZEB2 in normal tissues (left) and in cancers (right), for patients with liver hepatocellular adenocarcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, colon adenocarcinoma and colorectal adenocarcinoma. The data were from the Artyomov Lab Home page resource (wustl.edu). Median, 25% + 75% quartiles and min + max data is shown. The number of normal samples varied from 41 to 112, the number of oncological patients was from 500 to 1170. Comparisons of data groups were carried out using Mann-Whitney U test at a significance level of 0.05

in cancer tissues than in the healthy ones, conflicting with the data from the TNMplot resource, according to which the amount of ZEB1 mRNA is downregulated. We can explain this phenomenon, which is also inherent in other tissues, by the compensatory effects of ZEB1 gene expression. Therefore, ZEBs RNA levels should be correlated with protein levels obtained by immunohistochemistry or western analysis, not only based on RNA-sec or chip-sec.

The difference in effects of ZEB1 and ZEB2 on the survival of patients with liver cancer support the idea of Mu-Yan Cai and colleagues that, in general, ZEB2 mediates EMT and reduces survival, however, in some cancers, increased ZEB2 expression can actually correlate with better survival outcomes [76].

Immunohistochemistry analysis of 108 samples from HCC patients found that high ZEB1 levels may be associated with poor prognosis [78]. Another study showed a similar effect in 110 HCC patients, with ZEB1 protein levels correlated with TNM stage, larger tumor size, local metastases, vascular invasion, and early recurrence rates [77]. When analyzing the Artyomov Lab Home database (wustl.edu), it was found that in patients with HCC with an elevated level of ZEB1, there is a decrease in survival, but an increase in the level of ZEB2 does not affect the survival of patients. In addition, the correlation of ZEB1 and ZEB2 expression in patients with Liver hepatocellular adenocarcinoma was only 0.56 (results based on the data from Artyomov Lab Home), which may indicate a different effect of ZEB1 and ZEB2 on the given type of disease.

ZEB1 and ZEB2 in gastric cancer

Gastric cancer remains the leading cause of cancer death despite a decline in incidence worldwide. Patient survival remains unsatisfactory due to metastasis, a hallmark of gastric cancer progression [79].

In a study of 116 gastric cancer patients in the high ZEB1 expression group, survival was significantly lower than in the low expression group [80]. In another

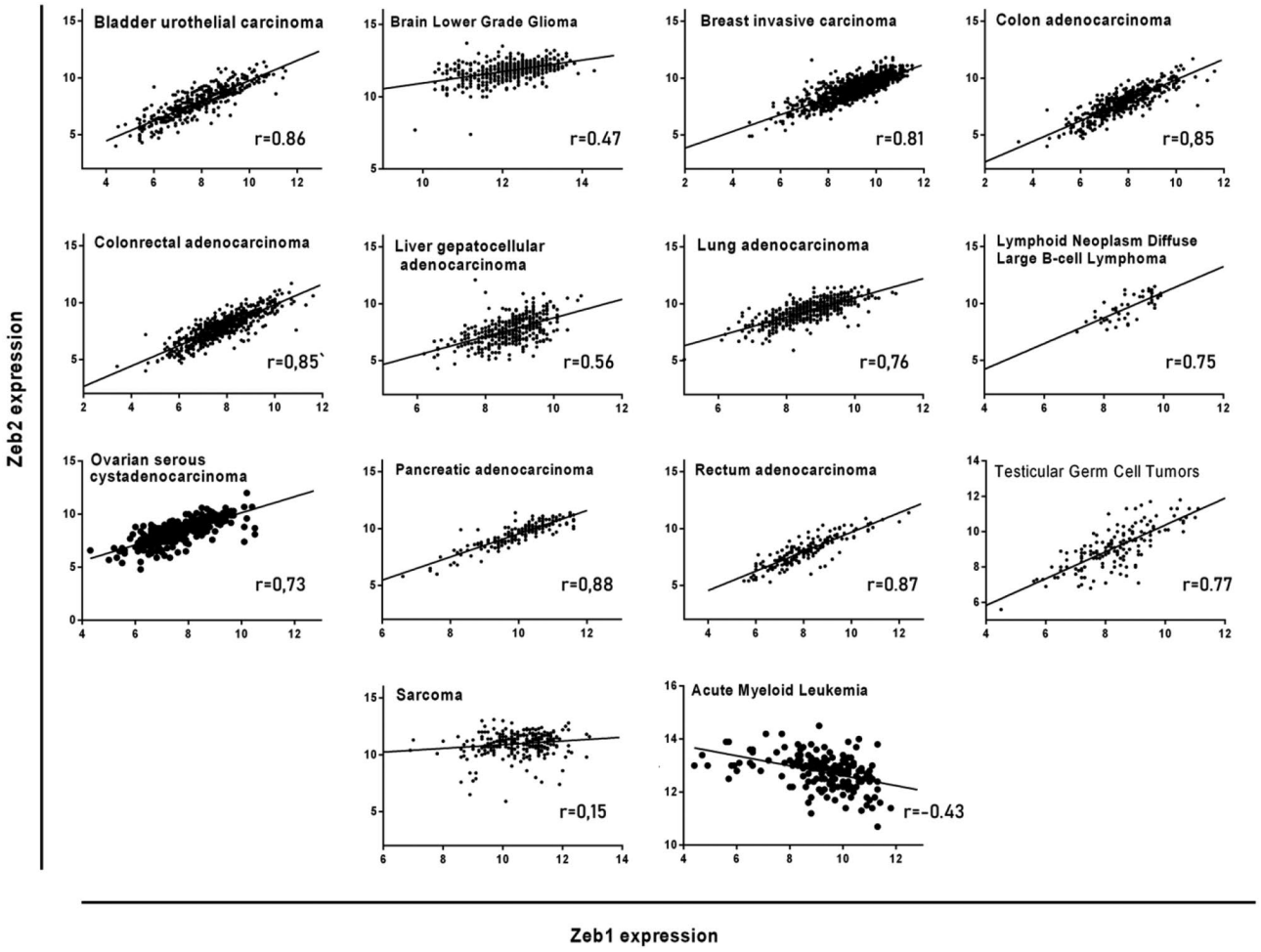

Fig. 4 Correlation of ZEB1 and ZEB2 expression in different cancer types. The data for the calculation were from the Artyomov Lab Home resource (wustl.edu), r - correlation coefficient.

study of 134 patients with gastric cancer, a similar situation was observed: for patients with high ZEB1 expression, the prognosis was significantly worse than for patients with low ZEB1 expression [81]. In clinical samples obtained from 135 patients with gastric cancer, it was shown that the average level of ZEB1 mRNA in cancer tissues was significantly higher than in the corresponding adjacent normal mucosa [81]. With an increased level of ZEB1, the survival of patients significantly worsened, while there was an increase in peritoneal dissemination. In another study on 76 patients with gastric cancer, it was shown that a high level of ZEB2 significantly reduced the survival of patients [79], this was confirmed by an analogous study on a group of 371 patients [82].

In general, it can be noted that the effect of ZEB1 and ZEB2 on outcome in gastric cancer is consistent with traditional views that they are a negative prognostic markers in this type of cancer.

ZEB1 and ZEB2 in pancreatic cancer

Pancreatic cancer is considered to be a disease with a poor prognosis, which is characterized by the formation of very dense solids and early metastasis [83]. In pancreatic head cancer patients, ZEB1 is very rare in the nuclei of epithelial cancer cells (ECC), but the surrounding stroma have increased ZEB1 expression, mainly due to ZEB1-expressing stromal fibroblasts [84]. Survival appears to be reduced in patients with high levels of ZEB1 protein in ECC, as well as in stromal fibroblasts [84]. Another study found similar results in 72 patients with pancreatic head cancer. In patients with high expression of either ZEB1 or ZEB2, the prognosis was significantly worse than in patients with low expression, and with increased expression of both ZEB1 and ZEB2, the difference in survival was even more prononounced [85].

According to the data posted on The Human Protein Atlas, ZEB1, and ZEB2 are not significantly expressed in the normal pancreas (Fig. 1), and their upregulation in

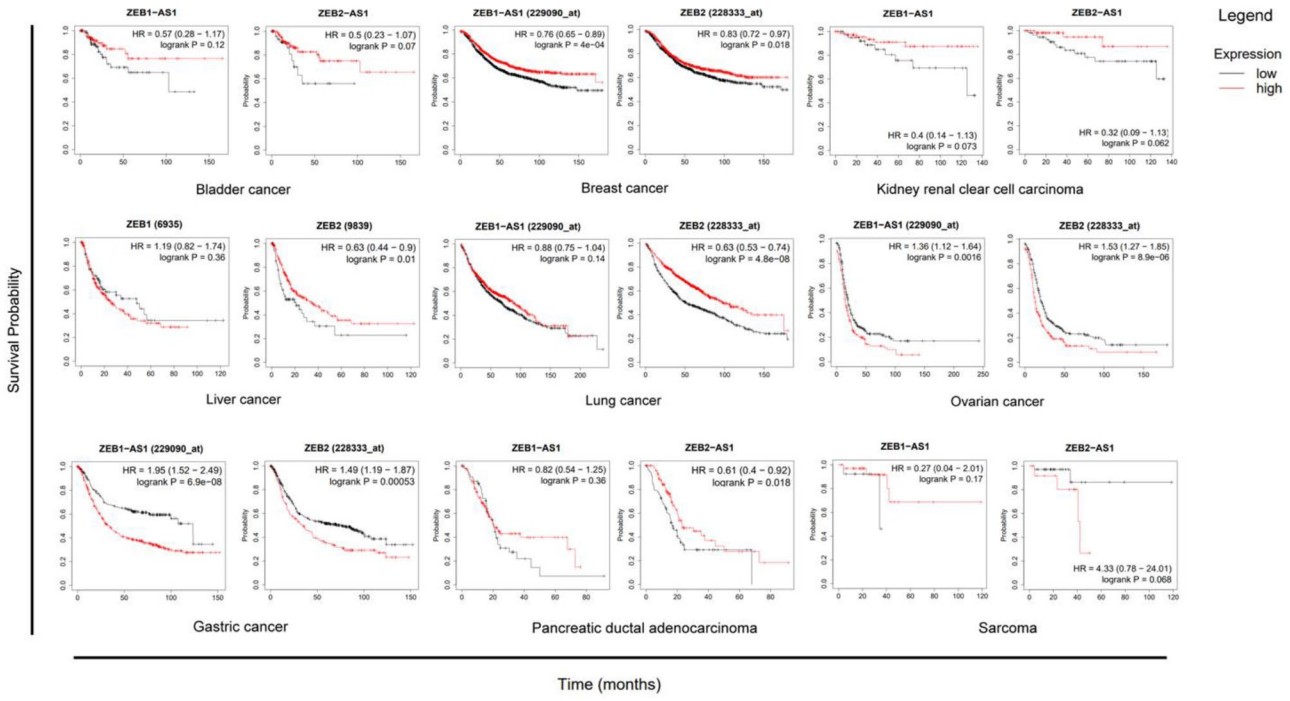

Fig. 5 Overall survival of patients with different cancer types, stratified by ZEB1 or ZEB2 expression level. Kaplan-Meier plotter resource data (kmplot.com)

pancreatic cancer tends to decrease patient survival also according to kmplot.com.

ZEB1 and ZEB2 in colorectal cancer

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in Europe and a key public health problem [86]. It has been shown that patients with increased expression of the genes, which are responsible for triggering EMT, respond poorly to adjuvant chemotherapy, these patients usually have earlier relapses and reduced survival [87]. In an analysis of 250 patients with CRC, a better patient survival correlated with lower ZEB1 expression [88]. Similary, survival of 175 CRC patients was negatively correlated with high expression of ZEB2 [89]. Virtually similar results were obtained in another study on 99 patients with CRC [64]. Overall, elevated levels of ZEB1 and ZEB2 in CRC are associated with a worsening of the patients' condition and can be regarded as negative prognostic markers for the disease.

ZEB1 and ZEB2 in renal cell carcinoma

Renal cell carcinoma (RCC) is the most common fatal urological cancer, accounting for 2–3% of all cancers in adults [56]. However, more than 40% of patients with RCC develop metastases after surgical resection of the primary tumor [90]. A study by Fang and colleagues showed that ZEB2 contributes to worse survival in patients with RCC [91]. In another study by Sugimoto et al., neoplasms with rhabdoid features (resembling a mesenchymal phenotype) were identified among RCC, accounting for 1.4–7.4%, characterized by a highly aggressive behavior and poor prognosis. These rhabdoid neoplasms showed no differences in ZEB1 and ZEB2 in comparison with the normal tissues [92] using either immunohistochemistry or RT-PCR in rhabdoid cells. However, in non-rhabdoid RCC there was an increase in ZEB1 and ZEB2 compared to controls. This study suggests a controversial role for the factors ZEB1 and ZEB2 in RCC: an increase in ZEB1 and ZEB2 is associated with the epithelial phenotype of RCC, and not with the mesenchymal one.

ZEB1 and ZEB2 in ovarian cancer

According to the data from The Human Protein Atlas, ZEB1 is normally expressed in the ovaries, while ZEB2 is not detected. Increased expression of the ZEB1 in patients with ovarian cancer correlates with a decrease in survival, whereas ZEB2 just tends to a correlation with worse survival. This is consistent with the data published by Elloul and colleagues, where stage IV ovarian carcinoma was found to have a higher ZEB2/E-cadherin expression ratio compared to stage III ovarian carcinoma [93].

Immunohistochemistry showed that ZEB2 expression in epithelial ovarian cancer (EOC) samples was increased compared to benign ovarian tumor samples or normal ovarian samples, whereas no significant difference was found in ZEB2 expression between benign ovarian

tumor samples and normal ovarian samples [94]. Among 64 EOC patients, higher ZEB2 expression was linked to lower overall survival [94].

ZEB1 and ZEB2 in lung cancer

Lung cancer remains the leading cause of cancer-related deaths worldwide, despite a decrease in incidence over the last decade. Several studies have shown that ZEB1 acts as an oncogene in invasive and metastatic lung cancer cells [95–97]. ZEB1 acts as an oncogene in KRAS-mutated lung cancer models, but in EGFR-mutated lung cancer cells ZEB1 plays the opposite role, acting as a cell growth suppressor. ZEB1, through repression of miR-200 transcription, increases mRNA expression levels of miR-200 targets [98]. In turn, the protein products of these mRNAs inhibit the ERBB3 receptor tyrosine kinase required for the growth of EGFR-mutated lung cancer cells. Thus, ERBB3 is repressed in lung adenocarcinoma tissues, if ZEB1 is overexpressed [98]. Notably, EGFR mutations correlate with the loss of ZEB1 in lung adenocarcinomas [98].

Lung tumors in non-smokers tend to have more EGFR mutations but fewer KRAS mutations compared to tumors in smokers [99], so we would expect that an augmentation of ZEB1 in smokers will not increase their survival. However, when analyzing data from kmplot.com, the picture is different – in smokers, ZEB1 and ZEB2 had an even more positive effect on their survival (Fig. 6). Probably, there are other mechanisms for improving the condition of patients by factors of the ZEB family. One explanation for this paradox may stem from the fact that ZEB proteins can have both cytoplasmic and/or nuclear localization. Recently cellular localization of ZEB1 in lung cancer was found to be heterogenous: nuclear in the cells at the invasive edge but cytoplasmic in the middle part of the tumor [100]. This phenomenon may be associated with the ability of ZEB1 to suppress the formation of actin microfilaments, which is associated with stimulation of tumor invasion. Irrespectively of the exact molecular mechanism, if cytoplasmic ZEB attenuates the cancer invasion capacity, then its higher expression should be positively associated with anti-cancer effects.

If our hypothesis proves correct, it would suggest that the cytoplasmic pool of ZEB proteins is associated with improved survival, while nuclear ZEB proteins would indicate a poorer prognosis and shorter survival. This hypothesis underscores the need for future investigations into the cellular localization of ZEB proteins, in addition to their expression levels.

No significant difference in survival was found among 267 patients with non-small cell lung cancer (NSCLC) among the cohort with increased and decreased expression of ZEB1 and ZEB2 [101]. This is confirmed by data from kmplot.com. ZEB1 protein was found

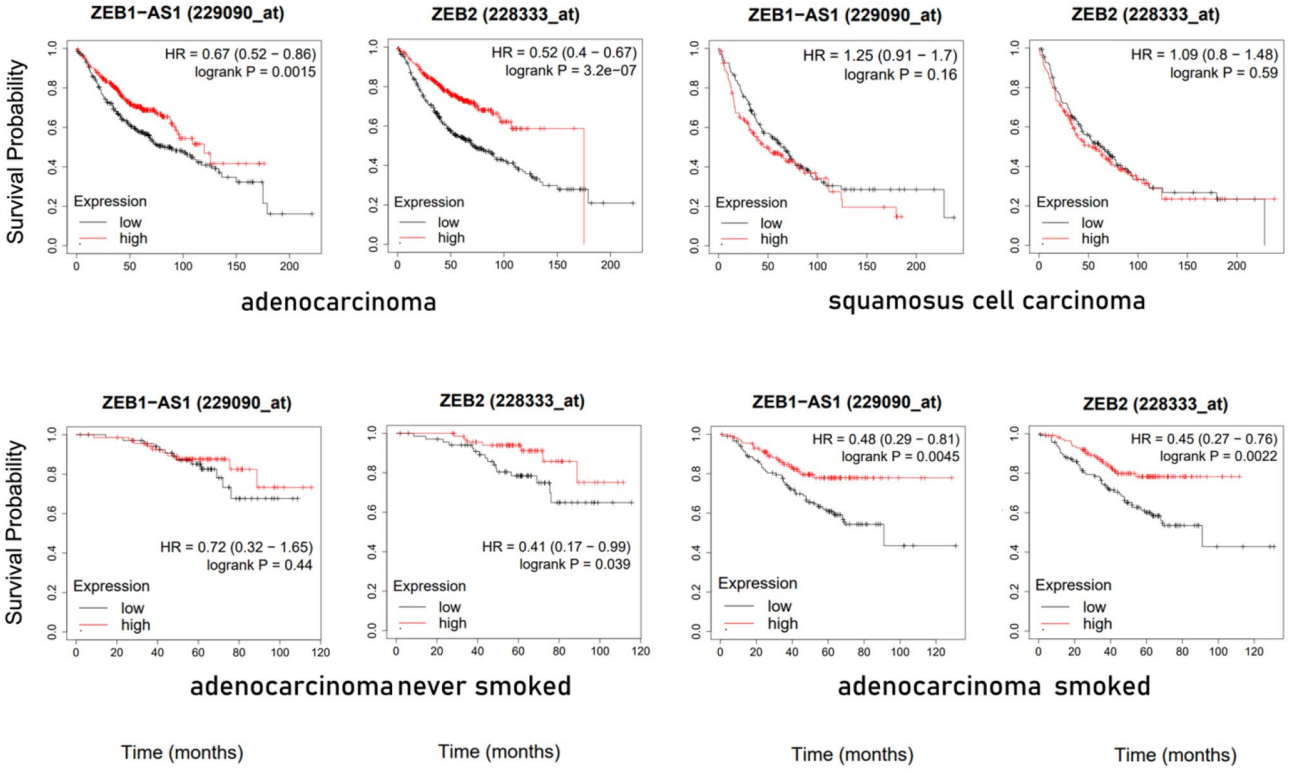

Fig. 6 Overall survival of patients with adenocarcinoma and squamous cell carcinoma between smokers and non-smokers stratified by ZEB1 or ZEB2 expression level. Kaplan-Meier plotter resource data (kmplot.com)

overexpressed in lung squamous cell carcinoma (LSCC) compared to the normal lung, in addition, its expression was also significantly higher in patients with lymph node metastases and distant metastases compared to patients without metastases [102].

The above arguments suggest that ZEB1 and ZEB2 have a complex and multifarious impact on cancer patient health, depending on the type of cancer and their oncogene mutations profiles.

ZEB1 and ZEB2 in breast cancer

Breast cancer is the leading cause of cancer death among women and is the second leading cause of cancer death after lung cancer in the Western world [103]. In breast cancer, elevated levels of ZEB1 and ZEB2 are associated with improved patient survival, particularly in the luminal subtype. In contrast, the opposite effect is observed in the basal subtype, including triple-negative breast cancer (TNBC). One explanation is that ZEB1 can interact with DNA through AP-1 and YAP/TEAD to form the ZEB1/YAP/AP-1 activator complex, which preferentially localizes to distal regulatory regions. While ZEB1 typically acts as a repressor in the promoter regions of target genes, in TNBC, it can simultaneously function in both capacities. This dual role of ZEB1 contributes to the aggressiveness of the cancer in this subtype [104].

Other authors have found that activation of EMT occurs in the MaSC subpopulation of normal breast stem cells, as well as in TNBC with a low level of CNA (copy-number alterations), one of the types of CIN genome instability [105]. The authors proposed that ZEB1 attenuates oxidative stress in MaSC, activates DDR, preventing the formation of DNA damage mediated by oncogenes. Perhaps, in normal human mammary epithelial cells ZEB1 plays a protective role against oncogenic DNA damage [105].

In another study, authors compared ZEB1 expression with outcome in patients with ERα + and ERα- breast cancer subtypes. They found that high levels of ZEB1 improved overall survival and distant metastasis-free survival (DMFS) in ERα + patients, and in ERα- patients, higher ZEB1 expression did not affect overall survival but negatively affected DMFS [106].

A similar pattern can be traced in the analysis of the data from https://kmplot.com of ERα + and ERα- patients with different expression levels of ZEB1 and ZEB2. The influence of PR status on the survival of patients with different levels of expression of ZEB1 was not statistically significant, but showed a trend similar to those in ERα studies (Fig. 7). High ZEB2 expression in PR + tumors was also found to increase survival, unlike PR- breast cancer. Collectively, this suggests that a somewhat better survival of breast cancer patients with increased expression of ZEB1 and ZEB2 may be the affected by ERα and PR receptors.

ZEB1 and ZEB2 in acute myeloid leukemia

Acute myeloid leukemia (AML) is a malignant bone marrow stem cell cancer that is mainly found in older people [107]. The role of ZEB1 and ZEB2 in this disease is

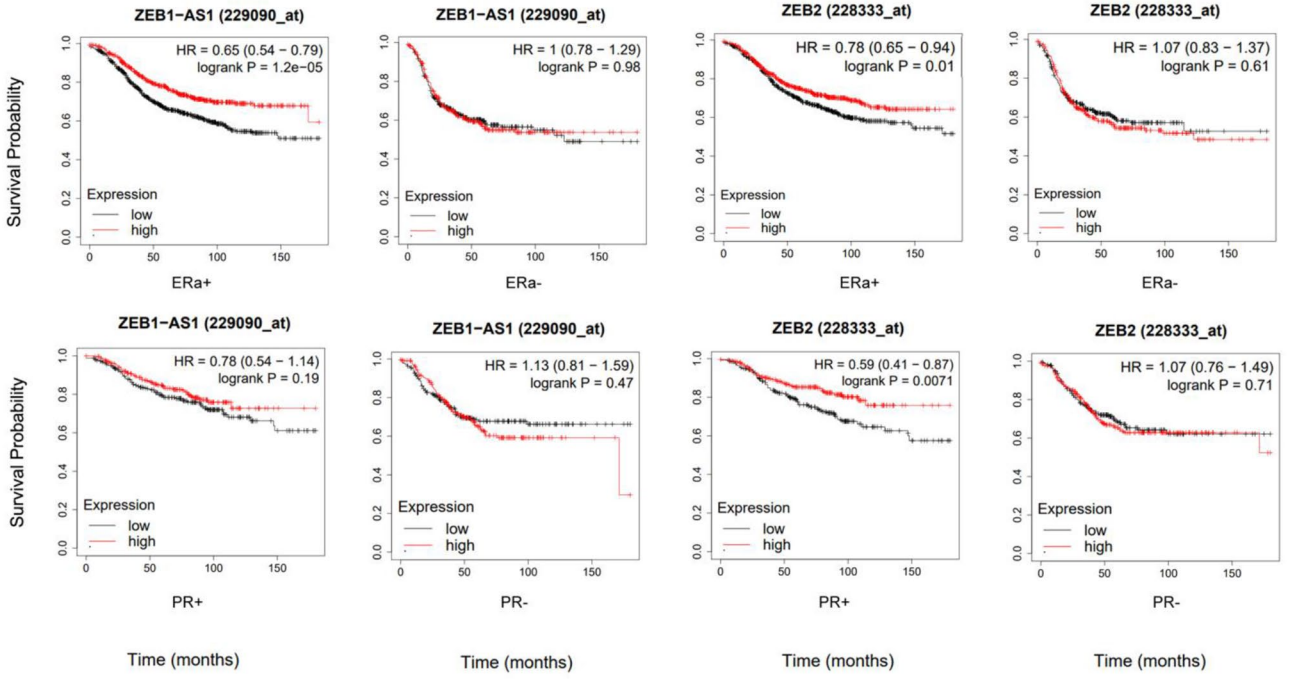

Fig. 7 Overall survival of ERa+and ERa- patients with different expression of ZEB1 and ZEB2 levels. Kaplan-Meier plotter resource data (kmplot.com)

unusual. In acute myeloid leukemia, ZEB1 may act as a tumor suppressor [108].

Inducible deletion of ZEB1 in HSCs affects clonal fate and cell survival of T cells, leading to rapid loss of thymocytes and CD8 + T cell subpopulations [108]. In CD8 + T cells, ZEB2 does not compensate for the absence of ZEB1. Moreover, ZEB1 and ZEB2 exhibit inverse expression patterns and have distinct functional roles: ZEB2 promotes the terminal differentiation of CD8 + T cells, whereas ZEB1 is essential for the survival and function of memory T cells. Additionally, in CD8 + T cells, the miR-200 family represses ZEB2 but does not affect ZEB1 [109].

Thus, while immune cells involved in immune surveillance within the tumor microenvironment require ZEB1, ZEB1 itself may promote cancer cell metastasis. Consequently, the impact of ZEB1 presence and ZEB1-targeted therapies in cancer remains uncertain [108]. In hematological malignancies, ZEB1 has been described as a tumor suppressor in adult T-cell leukemia and lymphoma [110, 111] or as an oncogene in mantle cell lymphoma [112].

ZEB2 also plays an important role in the development of cells of the immune system. A dysfunction of ZEB2 may lead to negative consequences in cancer patients. This may be confirmed by the fact that somatic amd germline mutations in the human ZEB2 gene were found in patients with myeloid disease [113].

ZEB1 and ZEB2 in gliomas

Glioma is a type of brain tumor that originates from glial progenitor cells. Gliomas are classified into grades 1 through 4 based on their aggressiveness, with grades 1 and 2 being referred to as "low-grade gliomas". These tumors are the most common primary intra-axial brain tumors in adults [72]. ZEB expression level is higher in gliomas than in the normal brain, and this level increases even more in high grade gliomas [114]. An increase in ZEB1 expression in lower-grade gliomas was also noted in another study, stating that a high level of ZEB1 is correlated with an increase in overall survival, unlike the level of ZEB2 [115].

Roles of ZEB1 an ZEB2 in tumor microenvironment

In solid cancer, the tumor microenvironment is formed by the extracellular matrix, fibroblasts, endothelial and immune cells [116]. The tumor microenvironment includes immunosuppressive cells, T cells (Treg), myeloid-derived suppressor cells (MDSC), and tumor-associated macrophages (TAM), which suppress T cell activity and promote tumor growth [117].

Cytotoxic CD8 + T cells (CTL) play a major role in the antitumor response, and tumor cells attempt to evade the action of CTLs by producing the immunosuppressive factors CTLA4 (a negative costimulatory molecule that inhibits T cell activation) and the receptor PD-1 (which helps to reduce the number of T cells and inhibit T cell activation and proliferation) [117]. In addition, tumor cells secrete cytokines CCL2, CCL5, and CSF1 that attract monocytes and monocytic MDSCs that differentiate into TAMs, which, through cytokines TGFβ and IL10, inhibit T cell activity, and can also express PD-L1 on the surface, leading to T cell depletion via PD-1 [117]. TAMs also promote angiogenesis by producing VEGFA and MMP9 [116, 118], acquisition of stemness by cancer cells, and resistance to chemotherapy [119, 120].

ZEB1 plays an essential role in the formation of the immunosuppressive tumor microenvironment by activating immunosuppressive cells and releasing chemokines into the tumor microenvironment (TME) [121]. In a mouse model of ovarian cancer, ZEB1 has been shown to be a key factor in the tumor microenvironment [122]. ZEB1 expression in TAM causes direct activation of CCR2 (CCL2 receptor) and induces a stem-like phenotype in tumor cancer cells [122]. In hypoxic cancer cells in vitro, ZEB1 promotes TAM migration by altering the expression of several chemokines, including CCL8 which attracts macrophages by engaging the CCR2-NF-κB pathway [123]. ZEB1 expression in melanoma cells impairs CD8 + T cell recruitment in mice by suppressing the secretion of chemokines that attract T cells, including CXCL10 [124]. In melanoma cells, ZEB1 promotes T-cell exclusion, leading to the immune escape [124].

ZEB2 is also involved in the formation of the tumor microenvironment. In PDAC patients, stromal cells surrounding tumor cells were found to have elevated levels of ZEB1 and ZEB2, and the tumor immune microenvironment was represented by Foxp3 + cells and M1-macrophages; M2-macrophages and CD8 + T cells were extremely scarce [125].

It is widely believed that neutrophils suppress tumor growth; however, recent data suggest that tumor cells can instead prompt neutrophils to promote oncogenesis, metastasis, angiogenesis, and immunosuppression [126]. Neutrophils may carry out these functions through mechanisms such as chemotaxis, phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs) rich in proinflammatory molecules that provide entrapment of circulating tumor cells and impair recognition of primary tumors by CTL and NK cells [127, 128]. A close association of NET with ZEB2 was found, perhaps due to ZEB2 interactions with NET-related proteins such as MPO, LTF, ACTN1, ENO1, ACTB, LYZ [126].

Despite the prevailing belief that ZEB1 and ZEB2 generally promote tumor development by affecting immune system cells, emerging data suggest that they may also exert immunostimulatory effects that suppress tumor progression. For instance, an

immunocytochemical analysis of breast cancer tumors revealed that CD8 + T-cell density was low in regions with cancer cells expressing ZEB1. Conversely, CD8 + T-cell density was higher in those areas that lacked ZEB1 expression in tumor cells but showed its high expression in stromal cells [129]. This paradox may be explained by the fact that stromal cells have special properties to attract CD8 + T cells when expressing ZEB1, unlike tumor cells, and ZEB1 as a putative biomarker of intratumoral immunosuppression needs further investigation [129].

The accumulated data present a complex and contradictory picture regarding the effect of ZEB2 on the tumor microenvironment. Database analyses revealed that ZEB2 expression is associated with the infiltration of various immune cells, including macrophages, B cells, Tregs, CD4 + T cells, CD8 + T cells, dendritic cells (DCs), and NK cells. Additionally, ZEB2 impacts the expression of cytokines, chemokines, and HLA histocompatibility antigens, contributing to a multifaceted regulation of the immune response and indicating an ambiguous effect of ZEB2 on the tumor microenvironment [126]).

Currently, the mechanisms by which ZEB1 and ZEB2 influence the tumor microenvironment are not fully understood, and this requires further exploration. Nevertheless, it is evident that the roles of ZEB1 and ZEB2 are highly complex and ambivalent. It is likely that various mechanisms, both stimulatory and inhibitory, interplay to modulate the immune response, ultimately affecting patient prognosis across different tumor types. Further studies are expected to clarify the diverse effects of ZEB1 and ZEB2 on cancer outcomes and enhance our understanding of their roles in various cancers.

ZEB1 and ZEB2 mRNAs are normally present in various tissues, but reduced in cancers. In The Human Protein Atlas database, ZEB1 and ZEB2 mRNAs are also found in all types of tissues, while the proteins are found only in certain types: nervous, muscle, connective, skin, lymphoid, renal, colon, testis, mammary gland, and female reproductive system. When patients were categorized by cancer stage using data from http://gepia.cancer-pku.cn, ZEB1 and ZEB2 expression levels were notably increased in stage 4 of pancreatic and rectal adenocarcinomas. However, in patients with diffuse large B-cell lymphoma, only ZEB2 expression was elevated. This observation is surprising given that both ZEB1 and ZEB2 are usually regarded as tumor markers. One possible explanation is the inherent functions of ZEB family proteins in normal adult tissues, where they perform highly tissue-specific roles. It appears that the expression of ZEB1 and ZEB2 genes is generally stable, and important regulatory events occur at the post-transcriptional level, involving various microRNAs and long non-coding RNAs. Consequently, microRNAs play a crucial role in regulating EMT and metastasis. As shown in our recent review on breast cancer [130], microRNAs and long non-coding RNAs repeatedly duplicate each other's functions and finely regulate all the main EMT master regulators ZEB1, ZEB2, Snail, Slug, Twist1, Twist2.

It is interesting that ZEB1 and ZEB2 have opposing effects on the survival of patients with different diagnoses: in patients with breast invasive carcinoma, lung adenocarcinoma, kidney cancer, testicular germ cell tumors the increased levels of ZEB1 and ZEB2 correlate with increased survival. On the contrary, patients with lung squamous cell carcinoma, pancreatic adenocarcinoma, ovarian, and bladder urothelial carcinoma tend to show a decrease. In rectal adenocarcinoma, expression of ZEB1 and ZEB2 do not affect survival. In sarcoma, ZEB1 and ZEB2 have opposing effects: ZEB2 promotes survival, whereas patients with elevated ZEB1 tend to have decreased survival. It should be noted, however, that in each individual case the mechanism for affecting the survival time of patients with increased expression of ZEB1 and ZEB2 may be unique: mutation in EGFR may turn ZEB1 from an oncogene into a tumor suppressor in lung adenocarcinoma, whereas in breast cancer of the luminal subtype the effect of ZEB1 and ZEB2 on patient survival depends also on estrogen and progesterone receptors.

The fact that ZEB1 and ZEB2 affect patient survival in similar ways is likely due to their similarity in structure and overlapping functions. The existing differences in the functions of ZEB1 and ZEB2 in some organs are most likely determined by differences in the structures of these proteins, affecting their interactomes: differences in the SMAD-binding domain and possible interaction of ZEB1 with p300 and P/CAF through CBD may lead to opposite regulation of the SMAD functions. Indeed, since ZEB1 and ZEB2 participate in different signaling pathways, their clinical relevance my also differ [94].

Conclusions

To summarize, the ZEB1 and ZEB2 genes are consistently expressed across various tissue types, as indicated by the presence of their mRNA. However, the proteins encoded by these genes may be absent in some tissues, while present in varying amounts—high, medium, or low—in others. In patients, elevated levels of ZEB1 or ZEB2 proteins often correlate with decreased survival, though in some cases, they are associated with improved survival. This dualism is particularly observed in tissues where ZEB1 and ZEB2 are normally expressed. Interestingly, while ZEB1 and ZEB2 mRNAs are usually present, the proteins may not be detected, suggesting that their regulation primarily occurs at the post-translational level. This regulation may be crucial for the rapid production of these proteins in response to urgent needs, such as wound healing. Consequently, the levels of ZEB1 and

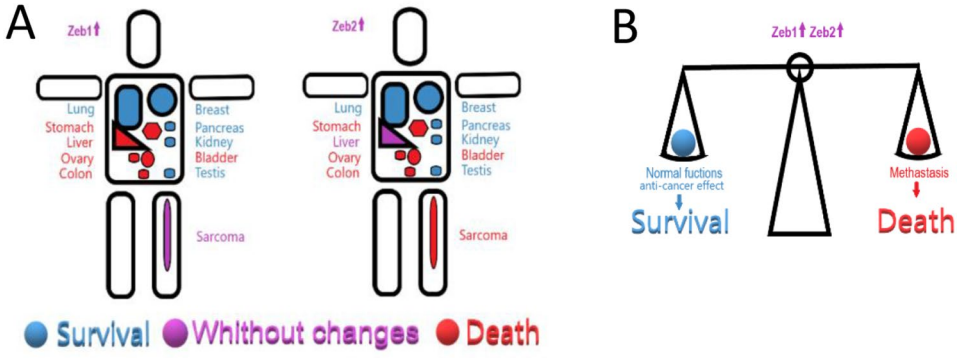

Fig. 8 Impact of ZEB1 and ZEB2 elevation on patient survival in different types of cancer (**A**); the balance diagram of the effect of Zeb1 and Zeb2 on patient survival rates (**B**)

ZEB2 have tissue-specific effects on patient survival: they may serve as negative prognostic markers in certain cancers, while in others, they could be positive markers or have no effect. These insights could be valuable for diagnosing and treating cancer (Fig. 8).

It is generally accepted that ZEB1 and ZEB2 act as master regulators of EMT and negatively affect survival of cancer patients [2, 128, 131, 132] by promoting metastasis. However, in some types of cancer the opposite effect is observed. Since ZEB1 and ZEB2 are constitutively expressed in several healthy tissues, a pharmacological reduction in their activity may have negative consequences for the whole organism. The role of ZEB1 in maintaining vital functions in the cell was highlighted by Brabletz and colleagues: ZEB1, by affecting tissue-specific stem cells, acts as an important regulator of adult tissue homeostasis [68]. Thus, the intracellular localization, as well as the structural differences between ZEB1 and ZEB2, may determine their interactions with different proteins, which in turn may influence the expression program of certain genes. According to our concept, the effect of ZEB1 and ZEB2 on survival may be the integral of both positive and negative effects due to changes in their levels (Fig. 8). For example, reducing the expression of ZEB1 and ZEB2 may decrease the ability of cells to metastasize, but it could also disrupt normal cell homeostasis.

Author contributions

Writing — S.E.P., A.A.D., O.Y.S., O.A.F., N.A.B.; Editing – N.B.P., T.V.K., N.A.B; Illustrations — S.E.P., N.A.B. All authors have read and agreed to the published version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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