ZBED1/DREF: A transcription factor that regulates cell proliferation (Review)

YARONG JIN[1,2], RUILEI LI[2], ZHIWEI ZHANG[2,3], JINJIN REN[1], XIN SONG[2] and GONG ZHANG[1]

[1]Department of Radiotherapy, People's Hospital of Shanxi Province, Taiyuan, Shanxi 030012; [2]Department of Cancer Biotherapy Center, The Third Affiliated Hospital of Kunming Medical University (Tumor Hospital of Yunnan Province), Kunming, Yunnan 650118; [3]Department of Oncology, Affiliated Hospital of Hebei University of Engineering, Handan, Hebei 056002, P.R. China

Abstract. Maintenance of genomic diversity is critically dependent on gene regulation at the transcriptional level. This occurs via the interaction of regulatory DNA sequence motifs with DNA-binding transcription factors. The zinc finger, BED-type (ZBED) gene family contains major DNA-binding motifs present in human transcriptional factors. It encodes proteins that present markedly diverse regulatory functions. ZBED1 has similar structural and functional properties to its *Drosophila* homolog DNA replication-related element-binding factor (DREF) and plays a critical role in the regulation of transcription. ZBED1 regulates the expression of several genes associated with cell proliferation, including cell cycle regulation, chromatin remodeling and protein metabolism, and some genes associated with apoptosis and differentiation. In the present review, the origin, structure and functional role of ZBED1 were comprehensively assessed. In addition, the similarities and differences between ZBED1 and its *Drosophila* homolog DREF were highlighted, and future research directions, particularly in the area of clinical cancer, were discussed.

Contents

1. Introduction

Multicellular organisms develop complex genomes through transcriptional regulation, which is crucial for spatial and temporal cellular specialization to promote phenotypic complexity. The interaction of regulatory DNA sequence motifs with DNA-binding transcription factors induces transcriptional regulation. These transcriptional factors serve a critical role in the activation or repression of target genes. Zinc-finger proteins are among the most commonly occurring DNA-binding motifs and constitute 2-3% of the transcription factors in the human genome (1). These proteins are associated with several biological functions, including differentiation, chromatin remodeling and development (2). The zinc finger, BED-type (ZBED) gene family is widely expressed in vertebrate tissues. It comprises a closely related group of genes that contribute to the regulation of various functions by encoding regulatory proteins. For example, the ZBED6 gene is involved in the regulation of diverse phenotypic effects. ZBED6 binds to the conserved target motif of insulin-like growth factor 2 and inhibits its expression, thereby promoting cell proliferation, growth and development in placental mammals (3). Furthermore, conflicting phenotypic changes were induced by the inactivation of ZBED6 in HCT116 and RKO human colorectal cancer cell lines, with consequences of reduced and increased growth, respectively, indicating that ZBED6 exhibits transcriptional modulating properties, and that the effect of ZBED6 on tumor development is dependent on the transcriptional state and genetic background of its target genes (4). The ZBED3 protein interacts with axin, which is vital for Wnt/β-catenin signal modulation in mammalian carcinogenesis and embryogenesis (5). Notably, Fan *et al* (6) reported higher expression levels of ZBED3 in cancer tissues compared with normal lung tissues and demonstrated that ZBED3 expression levels have clinicopathological significance. Downregulation

Correspondence to: Dr Gong Zhang, Department of Radiotherapy, People's Hospital of Shanxi Province, 29 Shuangta, Taiyuan, Shanxi 030012, P.R. China
E-mail: zhanggong7446@163.com

Dr Xin Song, Department of Cancer Biotherapy Center, The Third Affiliated Hospital of Kunming Medical University (Tumor Hospital of Yunnan Province), 519 Kunzhou Road, Xishan, Kunming, Yunnan 650118, P.R. China
E-mail: songxin_68@163.com

of ZBED3 by small interfering RNA significantly inhibits expression of p120ctn-1 and β-catenin in lung cancer cells; these results indicate that lung cancer cell invasion may be induced by ZBED3, which functions by regulating p120ctn-1 and β-catenin (6). Therefore, ZBED3 has potential application in the management of cancer, particularly non-small cell lung cancer. Furthermore, ZBED4 is restricted in glial Müller cells and the cone photoreceptors of the human retina (7). It binds to DNA and RNA sequences and effectively affects the transcription process of genes expressed in the retina via G-rich promoters (8).

ZBED1 was identified as a human homolog of *Drosophila* DNA replication-related element-binding factor (DREF) via BLAST search. Also known as human DREF, Activator (Ac)-like transposable element, TRAMP and KIAA0785, ZBED1 has been found to play a critical role in cell proliferation via the regulation of gene expression (9). As ZBED1 has similar structural and functional properties to DREF, the present review comprehensively describes recent progress on the origin, structure and functions on ZBED1, specifically highlights the similarities and differences between ZBED1 and DREF, and discusses future research directions.

2. Origin of ZBED1

A large proportion of vertebrate genomes consist of eukaryotic genome components and transposable elements (TEs), such as DNA transposons and retrotransposons (10-12). Several genes, particularly those that possess rapidly evolving coding sequence properties, have been shown to contain functionally important TEs that are involved in gene expression and regulatory changes (11,13,14). Notably, a quarter of analyzed human promoter regions have been found to have TE-derived sequences that potentially function as alternative promoters in several genes (13). TEs contribute entire functional genes to the host genome through molecular domestication (11,15,16). Domesticated TEs, which are immobile, often exist as single-copy orthologs within the genomes of associated organisms (15). Since DNA transposons encode multi-domain proteins with diverse functions, such as protein- and DNA-binding affinity, they may be suitable for domestication to perform host functions.

The hAT transposons and their associated domesticated sequences form a large superfamily that is divided into Buster and Ac families. These two families exhibit distinct target-site selections and were named according to the first identified transposon or transposon-like sequence in each family (17). Through phylogenetic methodology, Hayward *et al* (18) demonstrated that ZBED5, ZBED7, ZBED8 and ZBED9 are associated with the Buster family and are distinct from other ZBEDs. The remaining ZBEDs form two monophyletic clades within the Ac transposon family. Notably, ZBED2, ZBED3, ZBED4, ZBED6 and ZBEDX form a monophyletic group with C7ORF29 and differ from ZBED1 (Fig. 1). The ZBEDs exhibit structural similarity via the zinc finger domain that functions in DNA binding. Closely related ZBED molecules regulate a variety of different host functions, indicating that ZBED protein domains are particularly suitable for controlling host functions.

3. Similar zinc-finger structure of DREF and ZBED1

A palindromic 8 base-pair (bp) sequence 5'-TATCGATA was identified as being common to the promoter regions of the proliferating cell nuclear antigen (PCNA) and DNA polymerase α genes in *Drosophila* (19). This sequence is known as the DNA replication-related element (DRE) and is vital for transcriptional activation. Subsequently, several methods, including band mobility shift assays, were used to identify specific DREF (20), and the cDNA of DREF was then cloned (21). Notably, DREF was found to comprise a polypeptide with 709 amino acid (aa) residues. The DREF gene of *Drosophila virilis* (*D. virilis*) has been shown to share 71% of its aa sequence identity with its *D. melanogaster* homolog, with three highly conserved regions (CRs) at the aa positions 14-182 (CR1; identity, 86.4%), 432-568 (CR2; identity, 86.1%) and 636-730 (CR3; identity, 83.3%) of the *D. virilis* DREF (22).

DREF is proposed to have originated from a combination of the amino-terminal boundary element-associated factor (BEAF) and DREF (BED) zinc finger domain protein and the carboxy-terminal hATC domain (23). Aravind (24) conducted sequence analyses that led to the prediction of protein signature $C_{X2}C_{XN}H_{X3-5}$(H/C) for the BED finger, a name derived from DREF protein and domesticated *Drosophila* BEAF. The BED domain forms the zinc finger common to fungal, animal and plant proteins. This domain has been postulated to originate from transposons in cellular genes or to have been acquired for the cellular functions of transposases at independent occasions. A domain of BED zinc finger containing 50-60 aa residues has been found to contain a characteristic motif with two highly conserved aromatic residues. It has a shared pattern of histidines and cysteines that is considered to create a DNA-binding zinc finger domain. Furthermore, the BED domains of BEAF and DREF have been reported to exhibit DNA-binding properties (21,25).

ZBED1 comprises a polypeptide of 694 aa residues that has 21% similarity and 22% identity when compared with DREF (9). Three CRs between *D. virilis* and *D. melanogaster* as aforementioned have aa sequences highly similar to those of the ZBED1 polypeptide, particularly the CR1 region, which is essential for DRE-binding and dimerization. The ZBED1 binding sequence [hDRE; 5'-TGTCG(C/T)GA(C/T)A] was identified using the CASTing method and found to overlap with the DREF (5'-TATCGATA) sequence (9). Furthermore, the 6-bp sequence 5'-TCG(C/T)GA at the center of ZBED1 was indicated to serve an important role in ZBED1 binding (9). Two regions of ZBED1, CR1 and CR3, correspond with two domains that are conserved within the family, namely the amino-terminal BED zinc finger (aa 23-72) and the carboxyl-terminal hATC domain (26). The BED zinc finger is regarded as a DNA-binding domain of chromatin boundary element-binding transposase (24), whereas the hATC domain of hAT transposase family members is considered as the dimerization domain, as assessed through *in vitro* cross-linking experiments and yeast two-hybrid assays using Ac and housefly Hermes family members (27,28).

The DNA-binding protein ZBED1 has granular structures and is predominantly distributed in the nucleus (9). A study by Yamashita *et al* (26) explored the mechanism of action of ZBED1 using detailed mutagenesis analyses to investigate
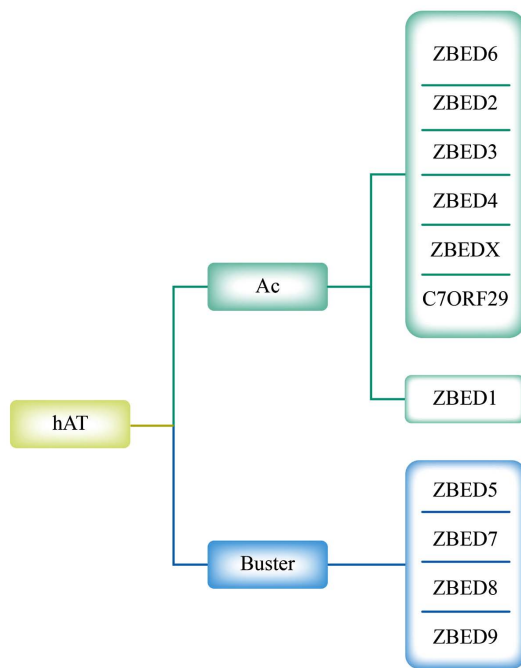
Figure 1. Phylogenetic relationships of ZBED genes with related sequences. The hAT transposons comprise Buster and Ac families. ZBED6, ZBED2, ZBED3, ZBED4, ZBEDX, C7ORF29, and ZBED1 belong to the Ac family. ZBED5, ZBED7, ZBED8, and ZBED9 belong to the Buster family. ZBED, zinc finger, BED-type; Ac, Activator.

the functions of the hATC domain. Trp-590, Trp-591 and Leu-601, which are highly conserved hydrophobic aa residues in hATC domains, were found to be crucial for the *in vivo* self-association of ZBED1. Furthermore, through substitution and truncated mutant evaluation, it was found that the hATC domain (aa 571-651) has two regions with distinct functions. The first region, namely the amino-terminal region aa 571-624, is required for various processes, including ZBED1 DNA-binding, nuclear accumulation and self-association. The second region, namely the carboxyl-terminal region aa 625-651, is vital for granular pattern formation and self-association. These findings indicate that ZBED1 self-association via the hATC domain is required for nuclear accumulation prior to nuclear importation. Furthermore, the aa 652-694 region has been identified to contain highly ordered complexes of ZBED1 binding sequences, whereas the aa 520-551 region is a classical nuclear localization signal (Fig. 2).

4. Multiple functions of DREF and ZBED1

Matsukage *et al* (29) used bioinformatics analysis to determine the type and number of genes regulated by the DRE/DREF system. They established that 456 DRE sequences and 156 genes with DRE sequences are <1 kb upstream of their transcription initiation sites. Most of these genes are associated with processes required for cell proliferation (30), including chromatin remodeling, cell cycle regulation and protein metabolism, while others are associated with apoptosis and differentiation. This indicates that the DRE/DREF system functions as a regulator of several cell proliferation-associated genes (Fig. 3). Ohshima *et al* (9) searched the GenBank® and EMBL databases to identify genes controlled

by ZBED1 protein. Through BLAST analysis, they found >500 TGTCG(C/T)GA(T/C)A-like sequences in the human genome. Notably, ZBED1 binding sequences exist in a series of genes involved in DNA synthesis (DNA replication) and repair, protein synthesis, regulation of chromatin structure and cell cycle regulation, which seems to be consistent with DREF (31), as some of these genes have been shown to be controlled by the DRE/DREF system (20,32-35). These findings indicate that ZBED1 is a potential functional homolog of *Drosophila* DREF and can regulate the expression of genes involved in cell proliferation via a similar mechanism.

A notable study indicates that DREF preferentially binds to and activates housekeeping enhancers that are located closely to ubiquitously expressed genes with specificity to its core promoter, and suggests that the DRE motif is required and sufficient for housekeeping enhancer function (36). The CGCG sequence is central to the ZBED1 binding sequence TGTCGCGACA that occurs mostly in promoter regions of housekeeping genes within the mammalian genome, suggesting that ZBED1 could regulate numerous housekeeping genes with CpG islands (37).

Chromatin remodeling. Chromatin-remodeling protein contains many conserved motifs and is encoded by human alpha-thalassemia and mental retardation X-linked syndrome (hATRX) gene. The ATRX protein contains a helicase/ATPase domain at its carboxyl terminus, which has catalytic subunits of chromatin remodeling complexes (38). Valadez-Graham *et al* (39) found that dATRX, a *Drosophila* homolog of hATRX, interacts with transcription factor DREF *in vivo* and *in vitro*. This results in transcriptional regulation of the pannier (pnr) gene, which belongs to the GATA family of transcription factors. Therefore, the transcriptional factor DREF is proposed to associate with the chromatin remodeling factor dATRX in the regulation of the pnr gene. These studies on *Drosophila* may provide insights for further research exploring the functional interaction of hATRX with ZBED1 in humans.

Studies conducted by Hart *et al* (25,40) suggested that DREF functions as a BEAF antagonist that is necessary for boundary activity of the special chromatin structure region of the *Drosophila* 87A7 hsp70 gene (25,40,41). The boundary element sequence 5'-CGATA-3', which is also present in DRE (5'-TATCGATA-3'), binds to BEAF-32. This induces the blockade of upstream regulatory elements such as enhancers (25), as demonstrated by chromatin immunoprecipitation. Thus, it is suggested that BEAF may bind to the same sequences as DREF and binding sequence competition between BEAF and DREF may be crucial in the regulation of chromatin boundary activities.

Drosophila Mi-2 (dMi-2), a nucleosome-stimulated ATPase, employs energy from ATP hydrolysis to deacetylate nucleosomal histones and mobilize histone octamers in certain cases (42). A study revealed that dMi-2 negatively regulates DREF by inhibiting DNA binding activity when the C-terminal region of dMi-2 binds to DREF (43). The chromatin remodeling factor Mi-2 has also been reported to be a ZBED1-interacting protein (43). The above findings indicate that the activity of DREF is regulated via protein complexes that determine the chromatin structure.
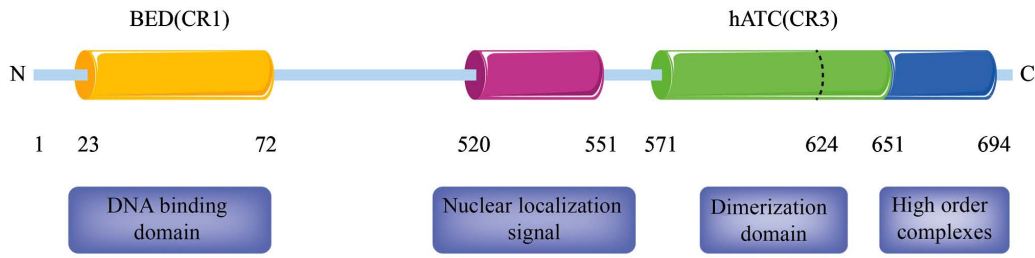
Figure 2. Structural representation of ZBED1 protein. Different colors represent different protein domains. Numbers correspond to the amino acid positions of estimated domain boundaries. ZBED1, zinc finger, BED-type 1; CR, conserved region.
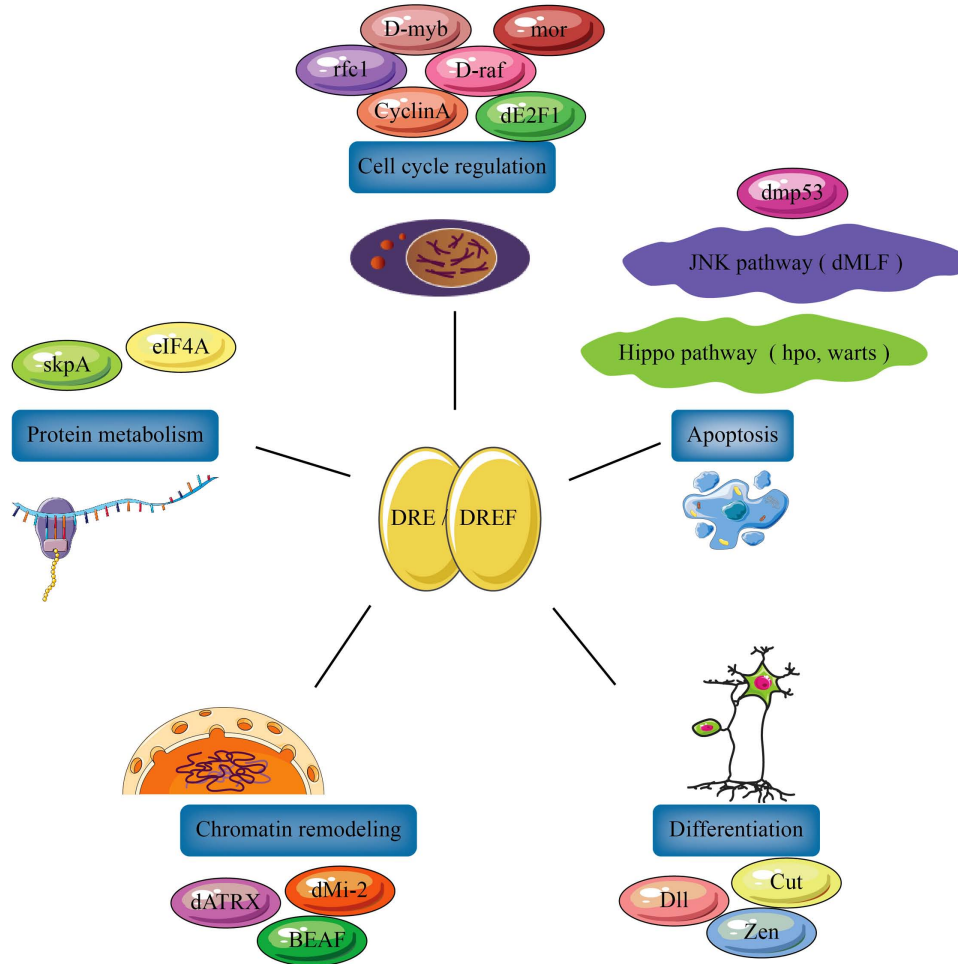

Figure 3. Regulatory network of transcription factor DREF. The genes regulated by DRE/DREF are associated with chromatin remodeling, cell cycle regulation, protein metabolism, apoptosis and differentiation. DRE, DNA replication-related element; DREF, DNA replication-related element-binding factor.

Protein metabolism. DREF has been indicated to directly regulate the expression of the eukaryotic initiation factor 4A (eIF4A) gene (44). The eIF4A gene belongs to the DEAD-box family of ATP-dependent RNA helicases (45) and is proposed to function by unwinding the secondary structure of 5'-untranslated regions of mRNA in the cap(m^7GpppN)-dependent initiation of protein synthesis (46,47). Furthermore, eIF4A plays a significant regulatory role in the initiation of translation (48). A study by Ida *et al* (44) showed that eIF4A gene promoter activity and eIF4A mRNA levels decreased following the knockdown of DREF in *Drosophila* S2 cells. Also, through a band mobility shift assay, DRE sequences in the eIF4A gene promoter were found to bind with DREF *in vitro*. These findings together indicate that the eIF4A gene is regulated via the DREF pathway and that, therefore, DREF regulates protein synthesis, particularly by initiating translation.

DREF has been found to bind to the skpA gene locus via DRE sequences. DRE1 and DRE2 sites present in the 5'-flanking region of the skpA gene have been reported to serve vital roles in skpA promoter activity in living flies and cultured cells (49). SKP1 protein is a key constituent of the SKP1, cullin/CDC53, F-box protein (SCF) complex and functions in protein degradation, linking the substrate recognition subunit F-box protein to a cullin that then binds the

ubiquitin-conjugating enzyme. Notably, the SKP1 constituent among *Drosophila* SCF ubiquitin ligases is referred to as skpA (50). Further study has shown that the knockdown of DREF in tissues with highly distributed skpA abrogates the skpA gene expression whereas the overexpression of DREF activates endogenous skpA expression, indicating that skpA may be effectively regulated via the DRE/DREF pathway at the transcriptional level (49). The available data, therefore, indicate that DREF enhances protein degradation and protein synthesis by activating genes involved in various processes, presumably through active protein metabolism in proliferating cells.

Cell cycle regulation. A study revealed via luciferase transient expression assays that DREs localized in the replication factor C (rfc)1 gene promoter participate in transcriptional regulation. Subsequent *in vitro* and *in vivo* assays in the study showed that DRE sequences of the rfc1 gene are bound to DREF (51). RFC is a five-subunit protein complex involved in DNA replication, of which RFC140 is the largest subunit. The study conducted by Tsuchiya *et al* (51) also identified via phenotype observation that the rfc1 gene encoding *Drosophila* RFC140 protein is vital for G_1/S cell-cycle progression. Furthermore, through immune-cytochemical experiments, the study found that the cell cycle is closely associated with rfc1 gene expression. These findings indicate that DREF effectively regulates the rfc1 promoter involved in G_1/S cell-cycle regulation. Additionally, the DRE/DREF system has been found to regulate several *Drosophila* genes associated with cell cycle progression, including dE2F1, cyclin A and D-myb for progression through the S phase (32,33,52), and D-raf for progression through the G_1 and M phases (35).

It has been reported that DRE/DREF regulates the transcription of the *Drosophila* osa and moira (mor) genes (53). These two genes encode subunits of the brahma (BRM) complex, which is an ATP-dependent chromatin remodeling complex conserved from yeast to humans (54,55). The BRM complex is thought to negatively regulate entry into the S phase whereas, by contrast, DREF promotes G_1/S and S phase progression. Thus, DREF functions simultaneously as a negative and positive regulator of G_1/S progression. This type of regulation may inhibit excess induction of the S phase when cell cycle progression is finely tuned.

Ohshima *et al* (9) used the western blot technique to examine the fluctuation of ZBED1 protein levels during the cell cycle. In this analysis, they used primary cultures from human embryonic lung fibroblasts (HEL cells) that could easily be transformed to a quiescent state when subjected to serum deprivation and then returned to cell cycling after the addition of 10% fetal calf serum. Progression in the cell cycle was assessed after the cells were released from serum starvation using propidium iodine staining followed by flow cytometric analysis. The results indicated that ZBED1 expression is induced at the G_1/S transition stage, and so potentially plays an important role in G_1/S progression. Therefore, it is hypothesized that DREF/ZBED1 highly regulates G_1/S progression as a transcription factor, thereby promoting cell proliferation.

Apoptosis. Although DREF serves a role in the regulation of cell proliferation, it also activates various apoptosis-inducing genes. Cell proliferation is restricted via the Hippo pathway through cell cycle arrest and the induction of apoptosis (56-58). Notably, it has been reported that the DRE/DREF pathway is required for the transcriptional activation of the hpo gene to positively regulate the Hippo pathway (59). Warts, a tumor suppressor gene that encodes a core kinase in the Hippo pathway, is also controlled through the DRE/DREF pathway (60). Using *in vivo* chromatin immunoprecipitation assays, DREF was demonstrated to selectively bind to the warts gene promoter region containing DREs, and endogenous warts mRNA expression was shown to be reduced in S2 cells following the knockdown of DREF (60). These findings confirm the association between DRE/DREF and the Hippo pathway. Furthermore, in addition to Hippo pathway-associated genes, DREF also associates with *Drosophila* myeloid leukemia factor in thorax development to positively regulate the basket gene and thereby activate the JNK signaling pathway (61,62), which induces apoptosis and protects the genome.

Studies indicate that the regulation of *Drosophila* p53 (dmp53) gene expression is highly attributable to the binding of the DRE-containing region of dmp53 to the DREF and that DREF affects apoptosis through the transcriptional activation of dmp53 (63). The dmp53 gene has limited sequence similarity to the human p53 gene (64); however, the function and structure of p53 are conserved in flies and mammals (65,66). P53 is a critical regulatory protein required for diverse cellular metabolic processes, including cell cycle arrest, DNA repair and apoptosis (67). Nearly all common human cancers possess mutations or loss of function of the p53 gene (68,69). The p53 gene, regarded as the 'guardian of the genome', acts as a tumor suppressor gene. Therefore, the finding that DREF positively regulates the expression of the dmp53 gene indicates the role of the former in the fine-tuning of cell proliferation.

Through the database searching of other tumor suppressor genes, including Rbf, APC, Brca2, NF1 and Vhl, DRE and DRE-like sequences have been identified to be regulated by DREF in upstream regions of *Drosophila* (63). The activation of oncogenes such as Ras or Myc through increased proliferation simultaneously induces apoptosis (70). Apoptosis then represses inappropriate cell proliferation, a function that acts as a mechanism to prevent the proliferation of damaged cells (71). Therefore, DREF is potentially critical in maintaining tissue kinetics and the balance between cell proliferation and apoptosis.

Differentiation. For cells to shift from a proliferating state to a resting state, it is necessary to coordinatively shut down several cell proliferation-associated genes. This process is controlled through differentiation signals. DREF as a major transcription factor of proliferation-related genes is thus a potential mediator of this repression (72). Some differentiation signals have been found to target DRE/DREF. The zerknullt (zen) gene is expressed in the dorsal region of the early embryo at the cellular blastoderm stage. It encodes a homeodomain-containing protein Zen that participates in differentiation of the optic lobe and the amnioserosa (73). Notably, when DREF activity is reduced, Zen expression in cultured cells represses DRE-containing genes (74). Therefore, the DRE/DREF system appears to be a point of intersection between growth and differentiation signaling pathways. Another homeodomain protein, Distal-less (Dll), has been

found to negatively regulate *Drosophila* DREF activity (75). The DNA-binding domain of DREF was revealed to selectively bind to Dll and thereby inhibit its transcriptional activity via electrophoretic mobility shift assays. Co-immunoprecipitation assays for Dll and DREF were also conducted; however, they did not yield positive results, indicating that interactions between Dll and DREF may be transient.

DREF has been shown to bind to its DRE sequence thereby promoting the expression of dPCNA in cell proliferation, whereas Cut, which is a *Drosophila* homolog of the mammalian CCAAT-displacement protein (CDP)/Cux, functions as a transcriptional repressor of the dPCNA gene by binding to the promoter region during cell differentiation (76). The dPCNA promoter was shown to be activated by DREF and repressed by Cut via the measurement of dPCNA promoter activity in transient luciferase expression assays. Moreover, Cut and DREF were demonstrated to be localized in genomic regions containing the dPCNA promoter, which initiates Cut-induced differentiation, using chromatin immunoprecipitation assays. These findings indicate that the DRE sequence binds to DREF during cell proliferation, which causes the state of expression of the dPCNA gene to become 'on'. The dPCNA promoter recruits Cut to its region when the cell is in a differentiated state. Cut then associates with other factors to inhibit expression of dPCNA gene. Therefore, we suggest that during cell proliferation, the differentiation-coupled reduction could be linked to DREF, which is a key regulatory factor for proliferation-associated genes.

5. ZBED1 as a transcription factor for cell proliferation

To examine whether ZBED1 regulates human DNA replication-related genes, Ohshima *et al* (9) assessed the histone H1 gene, the expression of which is stringently coupled with DNA replication. This gene has a single 10-bp sequence in its promoter region that completely matches with the ZBED1 binding sequence (77,78). Co-transfection experiments indicate that the activity of the human histone H1 gene promoter is stimulated when it specifically binds to ZBED1, and RNA interference experiments targeting ZBED1 indicate that transcription of the histone H1 gene is likely under the control of ZBED1 in the G_1/S phase during the cell cycle (9).

Notably, a study established that 22 of the 79 human ribosomal protein (RP) genes have sequences similar to that of hDRE in their transcriptional start sites <200 bp upstream. The study also demonstrated that ZBED1 potentially binds to the hDRE-like sequences in the RP genes *in vivo* and *in vitro*, and the hDRE-like sequences function as positive elements for RP gene transcription (79). In a similar manner to ZBED1 expression, RP gene expression is enhanced in the late G_1 to S phases, whereas a reduction in the expression of the RP gene occurs when ZBED1 is depleted, thus impairing cell proliferation and the G_1/S transition in normal human fibroblasts. These findings indicate that ZBED1 significantly regulates cell proliferation at the transcriptional level via the histone H1 and several RP genes. Also, ZBED1 has a key role in the cell cycle-dependent regulation of these genes. Furthermore, a study by Yamashita *et al* (80) explored the underlying transcriptional regulation mechanism and demonstrated that ZBED1 has a slight ubiquitin-like modifier (SUMO) ligase

activity and may stimulate transcriptional activation by specifically SUMOylating Mi2α. This results in the dissociation of Mi2α from the gene loci, thus maintaining active states of housekeeping target genes for ZBED1.

6. Conclusions and future perspectives

The present review highlights that *Drosophila* DREF has different structural features than its human ortholog ZBED1. However, there are notable similarities between the two species based on protein functions associated with, for example, the regulation of DNA replication, chromatin structure, protein synthesis and the cell cycle. Furthermore, ZBED1 potentially participates in the regulation of the expression of housekeeping genes within the mammalian genome. Also, the potential regulatory sites of different genes for DREF binding are likely to be conserved between *Drosophila* and humans. Therefore, numerous other genes may be regulated similarly in humans via the ZBED1 pathway. However, further research is essential to identify substrates of ZBED1 other than Mi2α in order to clarify the underlying molecular mechanism and comprehensively analyze the effect of ZBED1 in humans. Additionally, ZBED3 and ZBED6 are associated with tumor development. A recent study has shown that ZBED1 is upregulated in gastric cancer cells, thereby promoting their proliferation and decreasing their chemosensitivity, although the molecular mechanism requires full elucidation (81). Therefore, it is concluded that ZBED1 may be a novel cancer biomarker and therapeutic target in the future. However, further investigation is required to verify this.

Availability of data and materials

Not applicable.

Authors' contributions

YJ, RL, XS and GZ conceived and designed the review. YJ, ZZ, JR, XS and GZ were involved in the collection and collation of references. YJ and ZZ drew the figures. YJ, RL and GZ wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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