ZEB Family Members in Cancer Progression

Subjects: Cell Biology

Contributor: Mi Kyung Park, Ho Lee, Chang Hoon Lee

Post-translational modification (PTM), the essential regulatory mechanisms of proteins, play essential roles in physiological and pathological processes. In addition, PTM functions in tumour development and progression. Zinc finger E-box binding homeobox (ZEB) family homeodomain transcription factors, such as ZEB1 and ZEB2, play a pivotal role in tumour progression and metastasis by induction epithelial-mesenchymal transition (EMT), with activation of stem cell traits, immune evasion and epigenetic reprogramming.

Keywords: zinc finger E-box binding homeobox (ZEB) ; post-translational modifications (PTM) ; cancer progression

1. Introduction

Cancer-associated mortality represents the second leading cause of death worldwide after cardiovascular disease [1]. Cancer metastasis is the primary cause of cancer mortality, accounting for approximately 90% of tumour-related deaths. The epithelial-mesenchymal transition (EMT) is the tissue repair and developmental process, along with neural crest formation, heart morphogenesis, and mesoderm formation, facilitating gastrulation and secondary palate formation [2][3][4][5]. Moreover, EMT is a vital clue to tumour invasion and metastasis. Zinc finger E-box binding homeobox transcription factors (ZEBs) play a crucial role in the progression and metastasis of various cancers, as EMT-related transcription factors [6][7][8][9][10][11][12][13], in the regulation of DNA damage repair [14] and neuronal differentiation [15].

Furthermore, ZEBs are associated with the degree of malignancy in various types of cancer and the activation of EMT signalling, which are widely believed to contribute to invasion, metastasis, recurrence and therapeutic resistance. ZEBs are also associated with cancer transformation and EMT. Post-translational modification (PTM) is the enzymatic modification of proteins after synthesis [16] and induces proliferation in cancer progression by regulating the cell cycle, cell survival and cellular signalling [17].

2. ZEB1 and ZEB2 Proteins and Their Physiological Functions

The zinc finger E-box-binding homeobox 1 (ZEB1) is also known as δEF1, ZFHX1A, MEB1, Nil-2-a, TCF8, AREB6, ZFHEP1 or BZP [18]. The human *ZEB1* gene is located on chromosome 10p11.22 and encodes the 1117 amino acid ZEB1 protein [19]. Zinc finger E-box-binding homeobox 2 (ZEB2) is identified as KIAA0569, SIP1, ZFHX1B and ZFX1B; the human *ZEB2* gene is located on chromosome 2q22.3 and encodes a 1214 amino acid protein [20]. The ZEB proteins consist of a homeodomain (HD) in the middle of the structure and other protein binding domains, including the SMAD interaction domain (SID), which regulates the transforming growth factor beta (TGFβ)-mediated transcription with bone morphogenetic proteins (BMP) signalling, zinc finger domain (ZFD), coactivator binding domain (CBD), CtBP interaction domain (CID) and the p300-CBP-associated factor (P/CAF) binding domain, which control EMT as a trigger of for tumour progression and metastasis (**Figure 1**) [21][22][23][24][25].

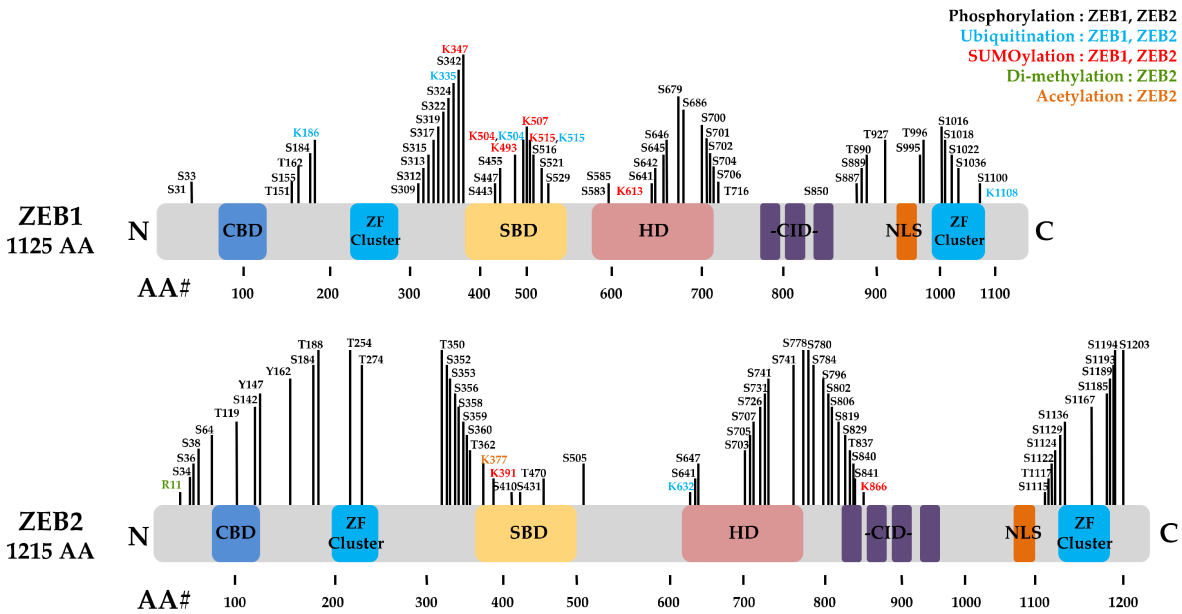

Figure 1. Overviews of ZEB1 and ZEB2 PTMs. It is characterized by the presence of two zinc finger clusters, one at each end (NZF and CZF) and located homeodomain (HD). Other domains are P300-P/CAF interaction domain (CBD), the Smad binding domain (SBD) and the CtBP interaction domain (CID). ZF, zinc finger; NLS, nuclear localization signal. PTM site. Black, Phosphorylation (ZEB1, ZEB2); Sky blue, Ubiquitination (ZEB1, ZEB2); Red, SUMOylation (ZEB1, ZEB2); Green, Di-methylation (ZEB1, ZEB2); Orange, Acetylation (ZEB2).

ZEB1 can recruit cosuppressors or coactivators by high-affinity binding of the ZFD to specific DNA binding sites (CACCTG), upregulating or downregulating its target genes [26]. ZEB proteins bind to SMADs. However, while ZEB-1/dEF1 synergises with SMAD proteins to activate transcription, promote osteoblastic differentiation and induce cell growth arrest, ZEB1 is expressed during development in the central nervous system, heart, skeletal muscle and haematopoietic cells; this plays pivotal roles in regulating development, differentiation and maintenance [23][27].

Additionally, ZEB1 is a transcriptional activator, or, has repressor functions in normal regulatory processes and dysregulated progress, such as cancer progression and metastasis. ZEB2 is expressed during the development in the neural tube and crest cells and all parts of the developing forebrain. In addition, it plays a role as a regulator of the TGFβ/BMP signal pathway. When the TGFβ/BMP factor binds to the receptor, the SMAD proteins are translocated to the nucleus, activating the target genes' transcription. ZEB2 interacts with R-SMADs to induce embryo neutralisation and disrupts the expression of the activin-dependent *Brachyury* gene in *Xenopus* [28][29]. ZEB2 also endures post-transcriptional regulation by several micro-RNAs (miRNAs), such as postnatal brain miRNA (miR9) [30].

3. ZEB1 and ZEB2 in Cancer Progression

ZEB protein is involved in tumour invasion and metastasis in the invasive front of carcinomas by EMT induction. ZEB1 is highly expressed in several tumours, including breast [6][7], pancreatic [9][24][31], colorectal [32], gastric [33][34], lung [35][36][37], uterine [38], hepatocellular carcinoma [39], prostate [40][41] and lymphoma [42] cancers. In these tumours, ZEB1 expression correlates with the loss of E-cadherin and is associated with advanced disease or metastasis, indicating the relevance of ZEB1 induction of EMT and tumour progression [13]. Mechanistically, TGF-β enhances pSMAD2/3 and ZEB1 [43] and ZEB2 [44] expression to increase tumour invasion. The β-catenin translocates into the nucleus to activate ZEB1 [45] transcription. WNT signaling induces ZEB2 expression in tumour metastasis [46]. Activation of MEK1/2 and ERK1/2 promotes tumour progression by ZEB1 [47] and ZEB2 [48]. TNF-α induces the mesenchymal phenotype via NF-κB, ZEB1 and ZEB2 signaling [49]. Fos-related antigen 1 (Fra-1) is a member of the Fos family that dimerizes with Jun proteins to form AP-1. Fra-1 induces EMT by modulating ZEB1, ZEB2 and TGFβ expression [50]. E2F1, a transcription factor, regulates EMT and metastasis by increasing ZEB2 expression in small-cell lung cancer [51]. ZEB2 is coexpressed with the POU family and upregulates EMT induction [52]. PRC2-mediated ZEB2 expression represses PTM by SUMOlation [53]. FOXO1, a member of the FOXO family of transcription factors (FoxOs), binds the ZEB2 promoter and destabilizes the ZEB2 mRNA. As a result, it inhibits ZEB2-induced EMT [54] (**Figure 2**). Loss of E-cadherin is a casual prerequisite for progressing from adenocarcinoma to invasive carcinomas by genetic and epigenetic mechanisms during malignant transformation [8]. In analogy with their function, ZEB1 lose the epithelial phenotype and gain the mesenchymal phenotype with motile and migratory abilities in cancer [5]. Moreover, ZEB1/miR-200 plays an essential role in embryonic

development and malignant tumour progression [55]. ZEB1 is an essential factor in the regulation of the initiation and development of tumours through EMT (**Figure 3**).

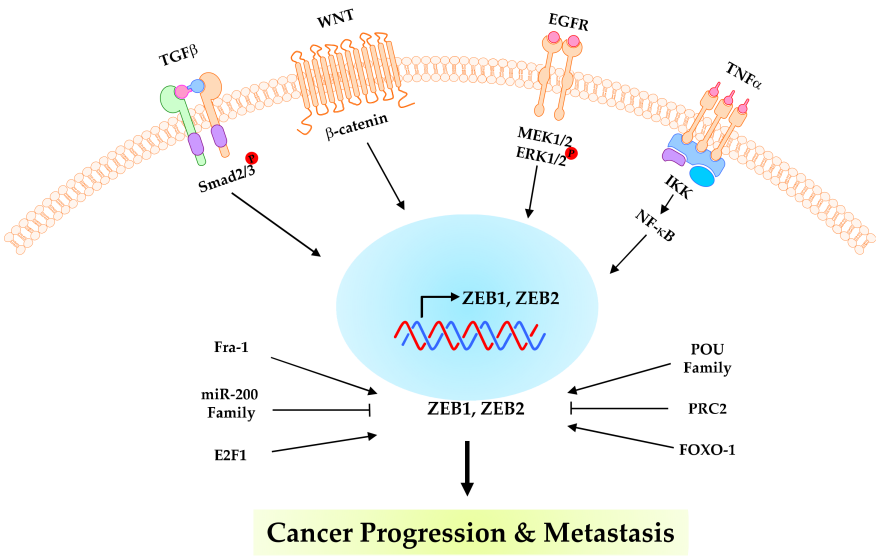

Figure 2. Mechanisms of ZEB family in cancer progression and metastasis. EGFR, WNT, tumor necrosis factor-a (TNFa), transforming growth factor beta (TGF-b), Fos-related antigen 1 (Fra-1), miR-200 family, POU family, PRC2 and FOXO-1 trigger expression of ZEB1 proteins. As a result, the ZEB family controls cancer progression and metastasis.

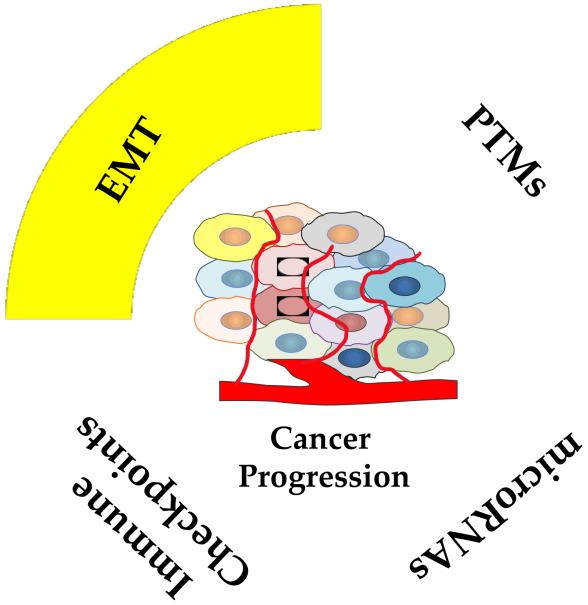

Figure 3. Regulation of ZEB family in cancer progression. PTMs, EMT, miRNA and immune checkpoints of ZEBs functionally are linked to cancer progression.

In the genetically engineered mouse model (GEMM), *ZEB1* knockout mice die perinatally, exhibiting respiratory failure; severe T cell deficiency of the thymus; and various skeletal defects, including craniofacial abnormalities, limb and sternum defects, and malformed ribs [56]. These developmental defects are associated with mesenchymal-epithelial transition, as evidenced by the re-expression of E-cadherin and loss of vimentin in several tissues and embryonic fibroblasts [57]. In addition, ZEB1 is a crucial factor for local invasion, colonisation capacities and distant metastasis in the Pdx1-Cre-mediated mutant KRAS and the p53 pancreatic cancer mouse (KPC) model [9]. ZEB1 was also shown to affect p53 and RB-dependent oncosuppressive pathways and to prevent senescence and apoptosis, two critical barriers against tumour development. In line with this notion, mouse embryonic fibroblasts (MEF) from *ZEB1* knockout mice undergo early replicative senescence.

4. Post-Translational Modifications of ZEBs in Cancer Progression

PTMs are covalent modifications that occur after the transcript has been translated into proteins, such as the ZEB1, ZEB2, SNAIL (*SNAI1*), SLUG (*SNAI2*) and twist-related (Twist 1) proteins. The human *SNAI1* is located on chromosome 20q13.13 and encodes the 264-amino acid Snail protein. It is a member of the Snail superfamily, and acts as a

transcriptional regulator of EMT [58]. The human *SNAI2* is located on chromosome 8q11.21 and encodes the 268-amino acid Slug protein. Slug binds the nuclear receptor corepressor (NCoR) and C-terminal binding protein 1 (CtBP1) to stabilize Slug and inhibit the expression of E-cadherin [59]. The human *Twist1* genes are located on chromosome 7p21.2 and encodes the 202-amino acid Twist1 protein. The Twist1 plays a critical role in the progression of cancer by modulating EMT [60][61]. These covalent modifications include adding a modifying chemical group or another small protein to one or more residues of the target protein [62]. PTM can occur within the protein on single or multiple residues, undergoing the same or different modifications [63]. **Table 1** provides an overview of the molecular mechanisms and biological functions of PTMs of ZEBs in cancer progression.

Table 1. Functions of ZEBs-PTMs.

PTMs Type	PTM Sites	Kinase/Enzyme	Biological Function	Cancer Type	Ref.
			ZEB1		
	Thr867	ERK	Inhibition of the nuclear localisation of ZEB1	-	[64]
Phosphorylation	Thr851, Ser852, Ser853	PKC	Inhibition of the nuclear localisation of ZEB1	-	[64]
	Ser585	ATM	Promotes DDR and tumour radioresistance	BC	[14]
SUMOylation	-	Senp1	Promotes migration and EMT.	HCC	[65]
Ubiquitination	-	Siah	Promotes cell proliferation and invasion	BC	[66]
	N-terminal	USP51	Promotes cell proliferation and invasion	BC	[67]
Deubiquitination		CSN5	Promotes metastasis and EMT	RCC	[68]
		USP18	Promotes EMT	ESCC	[69]
Acetylation	Lys741, Lys774, Lys775	P/CAF	Promotes the formation of a p300-SMAD transcriptional complex		[22]
	N-terminal	TIP60	Corepressor of the ZEB	T lymphoma	[70]
Deacetylation		HDAC1/2	Promotes EMT	PAAD	[71] [72]
			ZEB2		
Phosphorylation	Ser705, Tyr802	GSK-3β	Promotes metastasis and chemoresistance	CRC	[73]
SUMOylation	Lys391, Lys866	Pc2	Promotes EMT		[53]

PTMs Type	PTM Sites	Kinase/Enzyme	Biological Function	Cancer Type	Ref.
Ubiquitination	Lys48	FBXO45	Promotes EMT initiation and cancer progression		[74]
		FBXL14	Promotes EMT	COAD	[75]
		FBXW7	Promotes metastasis and chemoresistance	CRC	[73]

BC, breast cancer; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma; ESCC, oesophageal squamous cell carcinomas; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; PAAD, pancreatic adenocarcinoma; CRC, colorectal cancer; COAD, colon adenocarcinoma; ERK, extracellular signal-regulated kinase; PKC, protein kinase C; ATM, ataxia–telangiectasia mutated kinase; USP51, ubiquitin-specific peptidase 51; CSN5, COP9 signalosome subunit 5; USP18, ubiquitin-specific peptidase 18; PCAF, p300/CBP-associated factor; TIP60, tat-interacting protein of 60 kDa; HDAC1/2, histone deacetylase 1/2; GSK3β, glycogen synthase kinase 3 beta; FBXO45, F-box only protein 45; FBXL14, F-Box and leucine-rich repeat protein 14; FBXW7, F-box/WD repeat-containing protein 7.

References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics, 2022. CA Cancer J. Clin. 2022, 72, 7–33.
2. Hay, E. An Overview of Epithelio-Mesenchymal Transformation. Acta Anat. 1995, 154, 8–20.
3. Thiery, J.P.; Sleeman, J.P. Complex networks orchestrate epithelial–mesenchymal transitions. Nat. Rev. Mol. Cell Biol. 2006, 7, 131–142.
4. Thiery, J.P.; Acloque, H.; Huang, R.Y.J.; Nieto, M.A. Epithelial-Mesenchymal Transitions in Development and Disease. Cell 2009, 139, 871–890.
5. Kalluri, R.; Weinberg, R.A. The basics of epithelial-mesenchymal transition. J. Clin. Investig. 2009, 119, 1420–1428.
6. Yu, J.-M.; Sun, W.; Hua, F.; Xie, J.; Lin, H.; Zhou, D.-D.; Hu, Z.-W. BCL6 induces EMT by promoting the ZEB1-mediate d transcription repression of E-cadherin in breast cancer cells. Cancer Lett. 2015, 365, 190–200.
7. Eger, A.; Aigner, K.; Sonderegger, S.; Dampier, B.; Oehler, S.; Schreiber, M.; Berx, G.; Cano, A.; Beug, H.; Foisner, R. DeltaEF1 is a transcriptional repressor of E-cadherin and regulates epithelial plasticity in breast cancer cells. Oncogene 2005, 24, 2375–2385.
8. Schmalhofer, O.; Brabletz, S.; Brabletz, T. E-cadherin, β-catenin, and ZEB1 in malignant progression of cancer. Cancer Metastasis Rev. 2009, 28, 151–166.
9. Krebs, A.M.; Mitschke, J.; Lasierra Losada, M.; Schmalhofer, O.; Boerries, M.; Busch, H.; Boettcher, M.; Mougiakakos, D.; Reichardt, W.; Bronsert, P.; et al. The EMT-activator Zeb1 is a key factor for cell plasticity and promotes metastasis i n pancreatic cancer. Nat. Cell Biol. 2017, 19, 518–529.
10. Wu, C.-Y.; Tsai, Y.-P.; Wu, M.-Z.; Teng, S.-C.; Wu, K.-J. Epigenetic reprogramming and post-transcriptional regulation d uring the epithelial–mesenchymal transition. Trends Genet. 2012, 28, 454–463.
11. Gheldof, A.; Hulpiau, P.; van Roy, F.; De Craene, B.; Berx, G. Evolutionary functional analysis and molecular regulation of the ZEB transcription factors. Cell. Mol. Life Sci. 2012, 69, 2527–2541.
12. Wu, L.; Zhou, Z.; Han, S.; Chen, J.; Liu, Z.; Zhang, X.; Yuan, W.; Ji, J.; Shu, X. PLAGL2 promotes epithelial–mesenchy mal transition and mediates colorectal cancer metastasis via β-catenin-dependent regulation of ZEB1. Br. J. Cancer 20 20, 122, 578–589.
13. Zhang, P.; Sun, Y.; Ma, L. ZEB1: At the crossroads of epithelial-mesenchymal transition, metastasis and therapy resista nce. Cell Cycle 2015, 14, 481–487.
14. Zhang, P.; Wei, Y.; Wang, L.; Debeb, B.G.; Yuan, Y.; Zhang, J.; Yuan, J.; Wang, M.; Chen, D.; Sun, Y.; et al. ATM-media ted stabilization of ZEB1 promotes DNA damage response and radioresistance through CHK1. Nat. Cell Biol. 2014, 16, 864–875.

15. Wang, H.; Xiao, Z.; Zheng, J.; Wu, J.; Hu, X.-L.; Yang, X.; Shen, Q. ZEB1 Represses Neural Differentiation and Cooperates with CTBP2 to Dynamically Regulate Cell Migration during Neocortex Development. Cell Rep. 2019, 27, 2335–2353.e2336.
16. Chang, R.; Zhang, P.; You, J. Post-translational modifications of EMT transcriptional factors in cancer metastasis. Open Life Sci. 2016, 11, 237–243.
17. Chen, L.; Liu, S.; Tao, Y. Regulating tumor suppressor genes: Post-translational modifications. Signal Transduct. Target. Ther. 2020, 5, 90.
18. Hill, L.; Browne, G.; Tulchinsky, E. ZEB/miR-200 feedback loop: At the crossroads of signal transduction in cancer. Int. J. Cancer 2013, 132, 745–754.
19. Williams, T.M.; Montoya, G.; Wu, Y.; Eddy, R.L.; Byers, M.G.; Shows, T.B. The TCF8 gene encoding a zinc finger protein (Nil-2-a) resides on human chromosome 10p11.2. Genomics 1992, 14, 194–196.
20. Wakamatsu, N.; Yamada, Y.; Yamada, K.; Ono, T.; Nomura, N.; Taniguchi, H.; Kitoh, H.; Mutoh, N.; Yamanaka, T.; Mushiake, K.; et al. Mutations in SIP1, encoding Smad interacting protein-1, cause a form of Hirschsprung disease. Nat. Genet. 2001, 27, 369–370.
21. Postigo, A.A. Opposing functions of ZEB proteins in the regulation of the TGFbeta/BMP signaling pathway. EMBO J. 2003, 22, 2443–2452.
22. Postigo, A.; Depp, J.L.; Taylor, J.J.; Kroll, K.L. Regulation of Smad signaling through a differential recruitment of coactivators and corepressors by ZEB proteins. EMBO J. 2003, 22, 2453–2462.
23. Peinado, H.; Olmeda, D.; Cano, A. Snail, Zeb and bHLH factors in tumour progression: An alliance against the epithelial phenotype? Nat. Rev. Cancer 2007, 7, 415–428.
24. Wellner, U.; Brabletz, T.; Keck, T. ZEB1 in Pancreatic Cancer. Cancers 2010, 2, 1617–1628.
25. Chung, D.-W.D.; Frausto, R.F.; Ann, L.B.; Jang, M.S.; Aldave, A.J.; Rosales, M.A.B.; Silva, K.C.; Duarte, D.A.; Rossato, F.A.; de Faria, J.B.L.; et al. Functional Impact of ZEB1 Mutations Associated With Posterior Polymorphous and Fuchs' Endothelial Corneal Dystrophies. Investig. Opthalmol. Vis. Sci. 2014, 55, 6159–6166.
26. Vandewalle, C.; van Roy, F.; Berx, G. The role of the ZEB family of transcription factors in development and disease. Cell. Mol. Life Sci. 2009, 66, 773–787.
27. Scott, C.L.; Omilusik, K.D. ZEBs: Novel Players in Immune Cell Development and Function. Trends Immunol. 2019, 40, 431–446.
28. Verschueren, K.; Remacle, J.E.; Collart, C.; Kraft, H.; Baker, B.S.; Tylzanowski, P.; Nelles, L.; Wuytens, G.; Su, M.-T.; Bodmer, R.; et al. SIP1, a Novel Zinc Finger/Homeodomain Repressor, Interacts with Smad Proteins and Binds to 5′-CACCT Sequences in Candidate Target Genes. J. Biol. Chem. 1999, 274, 20489–20498.
29. Remacle, J.E.; Kraft, H.; Lerchner, W.; Wuytens, G.; Collart, C.; Verschueren, K.; Smith, J.; Huylebroeck, D. New mode of DNA binding of multi-zinc finger transcription factors: Delta EF1 family members bind with two hands to two target sites. EMBO J. 1999, 18, 5073–5084.
30. Kropivšek, K.; Pickford, J.; Carter, D.A. Postnatal Dynamics of Zeb2 Expression in Rat Brain: Analysis of Novel 3′ UTR Sequence Reveals a miR-9 Interacting Site. J. Mol. Neurosci. 2014, 52, 138–147.
31. Bronsert, P.; Kohler, I.; Timme, S.; Kiefer, S.; Werner, M.; Schilling, O.; Vashist, Y.; Makowiec, F.; Brabletz, T.; Hopt, U.T.; et al. Prognostic significance of Zinc finger E-box binding homeobox 1 (ZEB1) expression in cancer cells and cancer-associated fibroblasts in pancreatic head cancer. Surgery 2014, 156, 97–108.
32. Zhang, G.-J.; Zhou, T.; Tian, H.-P.; Liu, Z.-L.; Xia, S.-S. High expression of ZEB1 correlates with liver metastasis and poor prognosis in colorectal cancer. Oncol. Lett. 2013, 5, 564–568.
33. Okugawa, Y.; Toiyama, Y.; Tanaka, K.; Matsusita, K.; Fujikawa, H.; Saigusa, S.; Ohi, M.; Inoue, Y.; Mohri, Y.; Uchida, K.; et al. Clinical significance of zinc finger E-box binding homeobox 1 (ZEB1) in human gastric cancer. J. Surg. Oncol. 2012, 106, 280–285.
34. Jia, B.; Liu, H.; Kong, Q.; Li, B. Overexpression of ZEB1 associated with metastasis and invasion in patients with gastric carcinoma. Mol. Cell. Biochem. 2012, 366, 223–229.
35. Zhang, J.; Lu, C.; Zhang, J.; Kang, J.; Cao, C.; Li, M. Involvement of ZEB1 and E-cadherin in the invasion of lung squamous cell carcinoma. Mol. Biol. Rep. 2013, 40, 949–956.
36. Matsubara, D.; Kishaba, Y.; Yoshimoto, T.; Sakuma, Y.; Sakatani, T.; Tamura, T.; Endo, S.; Sugiyama, Y.; Murakami, Y.; Niki, T. Immunohistochemical analysis of the expression of E-cadherin and ZEB1 in non-small cell lung cancer. Pathol. Int. 2014, 64, 560–568.

37. Larsen, J.; Nathan, V.; Osborne, J.K.; Farrow, R.K.; Deb, D.; Sullivan, J.P.; Dospoy, P.D.; Augustyn, A.; Hight, S.K.; Sato, M.; et al. ZEB1 drives epithelial-to-mesenchymal transition in lung cancer. J. Clin. Investig. 2016, 126, 3219–3235.

38. Spoelstra, N.S.; Manning, N.G.; Higashi, Y.; Darling, D.; Singh, M.; Shroyer, K.R.; Broaddus, R.R.; Horwitz, K.B.; Richer, J.K. The Transcription Factor ZEB1 Is Aberrantly Expressed in Aggressive Uterine Cancers. Cancer Res. 2006, 66, 3893–3902.

39. Zhou, Y.-M.; Cao, L.; Li, B.; Zhang, R.-X.; Sui, C.-J.; Yin, Z.-F.; Yang, J.-M. Clinicopathological Significance of ZEB1 Protein in Patients with Hepatocellular Carcinoma. Ann. Surg. Oncol. 2012, 19, 1700–1706.

40. Contreras, H.; Orellana-Serradell, O.; Herrera, D.; Castellón, E. The transcription factor ZEB1 promotes chemoresistance in prostate cancer cell lines. Asian J. Androl. 2019, 21, 460–467.

41. Wang, H.; Huang, B.; Li, B.M.; Cao, K.Y.; Mo, C.Q.; Jiang, S.J.; Pan, J.C.; Wang, Z.R.; Lin, H.Y.; Wang, D.H.; et al. ZEB1-mediated vasculogenic mimicry formation associates with epithelial–mesenchymal transition and cancer stem cell phenotypes in prostate cancer. J. Cell. Mol. Med. 2018, 22, 3768–3781.

42. Wu, C.; Li, J.; Tian, C.; Shi, W.; Jiang, H.; Zhang, Z.; Wang, H.; Zhang, Q.; Sun, W.; Sun, P.; et al. Epigenetic dysregulation of ZEB1 is involved in LMO2-promoted T-cell acute lymphoblastic leukaemia leukaemogenesis. Biochim. Biophys. Acta (BBA)—Mol. Basis Dis. 2018, 1864, 2511–2525.

43. Joseph, J.V.; Conroy, S.; Tomar, T.; Eggens-Meijer, E.; Bhat, K.; Copray, S.; Walenkamp, A.M.E.; Boddeke, E.; Balasubramanyian, V.; Wagemakers, M.; et al. TGF-β is an inducer of ZEB1-dependent mesenchymal transdifferentiation in glioblastoma that is associated with tumor invasion. Cell Death Dis. 2014, 5, e1443.

44. Massagué, J. TGFbeta in Cancer. Cell 2008, 134, 215–230.

45. Kalra, R.S.; Chaudhary, A.; Yoon, A.-R.; Bhargava, P.; Omar, A.; Garg, S.; Yun, C.-O.; Kaul, S.C.; Wadhwa, R. CARF enrichment promotes epithelial–mesenchymal transition via Wnt/β-catenin signaling: Its clinical relevance and potential as a therapeutic target. Oncogenesis 2018, 7, 39.

46. Xu, J.; Lamouille, S.; Derynck, R. TGF-beta-induced epithelial to mesenchymal transition. Cell Res. 2009, 19, 156–172.

47. Han, Y.; Luo, Y.; Wang, Y.; Chen, Y.; Li, M.; Jiang, Y. Hepatocyte growth factor increases the invasive potential of PC-3 human prostate cancer cells via an ERK/MAPK and Zeb-1 signaling pathway. Oncol. Lett. 2016, 11, 753–759.

48. Sinh, N.D.; Endo, K.; Miyazawa, K.; Saitoh, M. Ets1 and ESE1 reciprocally regulate expression of ZEB1/ZEB2, dependent on ERK1/2 activity, in breast cancer cells. Cancer Sci. 2017, 108, 952–960.

49. Chua, H.L.; Bhat-Nakshatri, P.; Clare, S.E.; Morimiya, A.; Badve, S.; Nakshatri, H. NF-κB represses E-cadherin expression and enhances epithelial to mesenchymal transition of mammary epithelial cells: Potential involvement of ZEB-1 and ZEB-2. Oncogene 2007, 26, 711–724.

50. Bakiri, L.; Macho-Maschler, S.; Custic, I.; Niemiec, J.; Guío-Carrión, A.; Hasenfuss, S.C.; Eger, A.; Müller, M.; Beug, H.; Wagner, E.F. Fra-1/AP-1 induces EMT in mammary epithelial cells by modulating Zeb1/2 and TGFβ expression. Cell Death Differ. 2015, 22, 336–350.

51. Wang, T.; Chen, X.; Qiao, W.; Kong, L.; Sun, D.; Li, Z. Transcription factor E2F1 promotes EMT by regulating ZEB2 in small cell lung cancer. BMC Cancer 2017, 17, 719.

52. Katoh, M. Integrative genomic analyses of ZEB2: Transcriptional regulation of ZEB2 based on SMADs, ETS1, HIF1α, POU/OCT, and NF-κB. Int. J. Oncol. 2009, 34, 1737–1742.

53. Long, J.; Zuo, D.; Park, M. Pc2-mediated Sumoylation of Smad-interacting Protein 1 Attenuates Transcriptional Repression of E-cadherin. J. Biol. Chem. 2005, 280, 35477–35489.

54. Dong, T.; Zhang, Y.; Chen, Y.; Liu, P.; An, T.; Zhang, J.; Yang, H.; Zhu, W.; Yang, X. FOXO1 inhibits the invasion and metastasis of hepatocellular carcinoma by reversing ZEB2-induced epithelial-mesenchymal transition. Oncotarget 2017, 8, 1703–1713.

55. Brabletz, S.; Brabletz, T. The ZEB/miR-200 feedback loop—A motor of cellular plasticity in development and cancer? EMBO Rep. 2010, 11, 670–677.

56. Takagi, T.; Moribe, H.; Kondoh, H.; Higashi, Y. DeltaEF1, a zinc finger and homeodomain transcription factor, is required for skeleton patterning in multiple lineages. Development 1998, 125, 21–31.

57. Liu, Y.; El-Naggar, S.; Darling, D.S.; Higashi, Y.; Dean, D.C. Zeb1 links epithelial-mesenchymal transition and cellular senescence. Development 2008, 135, 579–588.

58. Cano, A.; Pérez-Moreno, M.A.; Rodrigo, I.; Locascio, A.; Blanco, M.J.; Del Barrio, M.G.; Portillo, F.; Nieto, M.A. The transcription factor Snail controls epithelial–mesenchymal transitions by repressing E-cadherin expression. Nat. Cell Biol. 2000, 2, 76–83.

59. Molina-Ortiz, P.; Villarejo, A.; MacPherson, M.; Santos, V.; Montes, A.; Souchelnytskyi, S.; Portillo, F.; Cano, A. Characterization of the SNAG and SLUG Domains of Snail2 in the Repression of E-Cadherin and EMT Induction: Modulation by Serine 4 Phosphorylation. PLoS ONE 2012, 7, e36132.
60. Yang, J.; Mani, S.A.; Donaher, J.L.; Ramaswamy, S.; Itzykson, R.A.; Come, C.; Savagner, P.; Gitelman, I.; Richardson, A.; Weinberg, R.A. Twist, a Master Regulator of Morphogenesis, Plays an Essential Role in Tumor Metastasis. Cell 2004, 117, 927–939.
61. Chang, A.T.; Liu, Y.; Ayyanathan, K.; Benner, C.; Jiang, Y.; Prokop, J.W.; Paz, H.; Wang, D.; Li, H.-R.; Fu, X.-D.; et al. An evolutionarily conserved DNA architecture determines target specificity of the TWIST family bHLH transcription factors. Genes Dev. 2015, 29, 603–616.
62. Deribe, Y.L.; Pawson, T.; Dikic, I. Post-translational modifications in signal integration. Nat. Struct. Mol. Biol. 2010, 17, 666–672.
63. Pejaver, V.; Hsu, W.-L.; Xin, F.; Dunker, A.K.; Uversky, V.N.; Radivojac, P. The structural and functional signatures of proteins that undergo multiple events of post-translational modification. Protein Sci. 2014, 23, 1077–1093.
64. Llorens, M.C.; Lorenzatti, G.; Cavallo, N.L.; Vaglienti, M.V.; Perrone, A.P.; Carenbauer, A.L.; Darling, D.S.; Cabanillas, A.M. Phosphorylation Regulates Functions of ZEB1 Transcription Factor. J. Cell. Physiol. 2016, 231, 2205–2217.
65. Zhang, W.; Sun, H.; Shi, X.; Wang, H.; Cui, C.; Xiao, F.; Wu, C.; Guo, X.; Wang, L. SENP1 regulates hepatocyte growth factor-induced migration and epithelial-mesenchymal transition of hepatocellular carcinoma. Tumor Biol. 2016, 37, 7741–7748.
66. Chen, A.; Wong, C.S.; Liu, M.C.; House, C.M.; Sceneay, J.; Bowtell, D.D.; Thompson, E.W.; Möller, A. The ubiquitin ligase Siah is a novel regulator of Zeb1 in breast cancer. Oncotarget 2015, 6, 862–873.
67. Zhou, Z.; Zhang, P.; Hu, X.; Kim, J.; Yao, F.; Xiao, Z.; Zeng, L.; Chang, L.; Sun, Y.; Ma, L. USP51 promotes deubiquitination and stabilization of ZEB1. Am. J. Cancer Res. 2017, 7, 2020–2031.
68. Zhang, S.; Hong, Z.; Chai, Y.; Liu, Z.; Du, Y.; Li, Q.; Liu, Q. CSN5 promotes renal cell carcinoma metastasis and EMT by inhibiting ZEB1 degradation. Biochem. Biophys. Res. Commun. 2017, 488, 101–108.
69. Song, C.; Peng, J.; Wei, Y.; Shao, J.; Chen, X.; Zhang, X.; Xu, J. USP18 promotes tumor metastasis in esophageal squamous cell carcinomas via deubiquitinating ZEB1. Exp. Cell Res. 2021, 409, 112884.
70. Hlubek, F.; Löhberg, C.; Meiler, J.; Jung, A.; Kirchner, T.; Brabletz, T. Tip60 Is a Cell-Type-Specific Transcriptional Regulator. J. Biochem. 2001, 129, 635–641.
71. Aghdassi, A.; Sendler, M.; Guenther, A.; Mayerle, J.; Behn, C.-O.; Heidecke, C.-D.; Friess, H.; Büchler, M.; Evert, M.; Lerch, M.M.; et al. Recruitment of histone deacetylases HDAC1 and HDAC2 by the transcriptional repressor ZEB1 down regulates E-cadherin expression in pancreatic cancer. Gut 2012, 61, 439–448.
72. Schneider, G.; Krämer, O.H.; Saur, D. A ZEB1-HDAC pathway enters the epithelial to mesenchymal transition world in pancreatic cancer. Gut 2012, 61, 329–330.
73. Li, N.; Babaei-Jadidi, R.; Lorenzi, F.; Spencer-Dene, B.; Clarke, P.; Domingo, E.; Tulchinsky, E.; Vries, R.G.J.; Kerr, D.; Pan, Y.; et al. An FBXW7-ZEB2 axis links EMT and tumour microenvironment to promote colorectal cancer stem cells and chemoresistance. Oncogenesis 2019, 8, 13.
74. Xu, M.; Zhu, C.; Zhao, X.; Chen, C.; Zhang, H.; Yuan, H.; Deng, R.; Dou, J.; Wang, Y.; Huang, J.; et al. Atypical ubiquitin E3 ligase complex Skp1-Pam-Fbxo45 controls the core epithelial-to-mesenchymal transition-inducing transcription factors. Oncotarget 2015, 6, 979–994.
75. Lander, R.; Nordin, K.; LaBonne, C. The F-box protein Ppa is a common regulator of core EMT factors Twist, Snail, Slug, and Sip1. J. Cell Biol. 2011, 194, 17–25.