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# The role of the ZEB1–neuroinflammation axis in CNS disorders

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## Abstract

Zinc finger E-box binding homeobox 1 (ZEB1) is a master modulator of the epithelial–mesenchymal transition (EMT), a process whereby epithelial cells undergo a series of molecular changes and express certain characteristics of mesenchymal cells. ZEB1, in association with other EMT transcription factors, promotes neuroinflammation through changes in the production of inflammatory mediators, the morphology and function of immune cells, and multiple signaling pathways that mediate the inflammatory response. The ZEB1–neuroinflammation axis plays a pivotal role in the pathogenesis of different CNS disorders, such as brain tumors, multiple sclerosis, cerebrovascular diseases, and neuropathic pain, by promoting tumor cell proliferation and invasiveness, formation of the hostile inflammatory microenvironment surrounding neuronal tissues, dysfunction of microglia and astrocytes, impairment of angiogenesis, and dysfunction of the blood–brain barrier. Future studies are needed to elucidate whether the ZEB1–neuroinflammation axis could serve as a diagnostic, prognostic, and/or therapeutic target for CNS disorders.

**Keywords:** Glioblastoma, Microglia, Metastasis, Neural stem cells, MicroRNA

## Introduction

Central nervous system (CNS) disorders, such as multiple sclerosis (MS), Alzheimer's disease (AD), neuropathic pain, and glioblastoma (GBM), are of high scientific interest worldwide due to their increasing prevalence and a lack of effective therapies [1, 2]. Focusing on metabolic pathways to identify relevant biomarkers involved in the pathogenesis of neuroinflammation in disease may contribute to the advent of novel diagnostic and therapeutic strategies [3–5]. Epithelial–mesenchymal transition (EMT) is a crucial biological process in which a cell loses epithelial characteristics, like cell–cell adhesion, and converts into motile non-polarized mesenchymal cells with invasive properties [6]. The conversion from epithelial to mesenchymal cells facilitates cell proliferation, migration, and invasion [7, 8]. EMT contributes to

the pathophysiological mechanisms of wound healing, tissue fibrosis, and tumorigenesis [6]. Three different types of EMT have been distinguished: type I, which is observed during embryogenesis; type II, which occurs during wound healing and tissue fibrosis; and type III, which is activated during the spread of cancer cells [9]. The regulatory role of EMT on proliferating cells may be affected by various factors, such as inflammation, which contributes to the pathological processes of numerous neurological disorders [10, 11]. For example, alteration of transforming growth factor  $\beta$  (TGF- $\beta$ ) expression, the most potent activator of EMT, as well as genes involved in EMT may be of importance in the induction of chronic neuroinflammation in AD [12]. Moreover, EMT has been suggested to play a role in inflammation-related carcinogenesis [13, 14]. EMT is induced mainly through a series of EMT-promoting transcription factors (EMT-TFs), such as Twist-related protein 1 (TWIST1), Snail family proteins, and zinc finger E-box binding homeobox-1 (ZEB1) and -2 (ZEB2) [15]. The activation of EMT-TFs, such as ZEB1, is associated with loss of cellular connectivity and changes in epithelial apical–basal polarity,

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leading to changes in cell properties and alterations to their metabolic patterns [16].

The expression of ZEB1 differs markedly among various adult human tissues, showing low expression in the prostate, pancreas, and liver, moderate expression in the heart, mammary gland, and ovary, and high expression in the thymus, aorta, uterus, and bladder [5, 17]. ZEB1 and ZEB2 are involved in the regulation of uterine quiescence and contractility during pregnancy and labor [18]. Furthermore, ZEB1 modulates T-cell development in the thymus [19], controls self-renewal and generation of functional glandular structures in the prostate [20], governs cutaneous wound healing [21], regulates the activation of hepatic stellate cells [22], and maintains mammary basal cell fate and stem cell quiescence [23]. ZEB1 also plays a critical role in the development of embryos [17]. ZEB1 expression is essential for the maintenance of embryonic cells in undifferentiated states, as well as in the appropriate maturation and migration during development [24, 25]. Excessive expression of ZEB1, as a  $\delta$ 1-crystallin enhancer, has been observed in several organs of chicken embryos, including the nerve system, heart, thymus, lung, and lens [17]. ZEB1 regulates EMT late in gestation and is crucial for the capacity of embryos to develop into fetuses [26]. ZEB1 overexpression in a mouse model indicated lack of ZEB1 is associated with greater mortality during the perinatal period due to severe T-cell insufficiency, respiratory disorder, and skeletal deficiency [19]. Mutation of the *Zeb1* gene could have also resulted in a cleft palate as well as other craniofacial and skeletal anomalies [19]. A link between proliferative impairment in a subset of bone marrow-derived progenitors with *Zeb1* gene mutation has been suggested [20]. Moreover, evidence suggests the modulatory effects of Zeb1 on the differentiation of embryonic stem cells via the regulation of various cytoplasmic and nuclear proteins [24].

Alterations of ZEB1 expression regulate neural stem cell renewal and cell fate in the brain [27]. The expression of ZEB1 is pivotal for the balance between epithelial and mesenchymal gene expression as well as the proliferation of progenitor cells [28]. Loss of epithelial properties following ZEB1 activation is involved in several pathological conditions. ZEB1 alone or together with other EMT-TFs plays a key role in the metastasis of brain cancers [29–31]. Suppression of EMT by knocking down ZEB1 has been achieved in several studies [32–34], and inhibition of ZEB1 expression may prevent aggressive tumor progression [35]. Activation of ZEB1 can lead to chemoresistance in different types of cancers via the downregulation of E-cadherin [36, 37]. ZEB1 has an impact on pediatric solid tumors, such as neuroblastoma, via long intergenic noncoding RNAs (lncRNAs) and microRNAs

(miRNAs) [38]. Moreover, ZEB1 contributes to the regulation of immune system development and function [39, 40]. Here, we summarize the current understanding of the regulatory mechanisms of ZEB1 in the CNS. Furthermore, we provide a comprehensive review of the current knowledge regarding the potential roles of ZEB1 in neurological disorders.

### ZEB1 structure

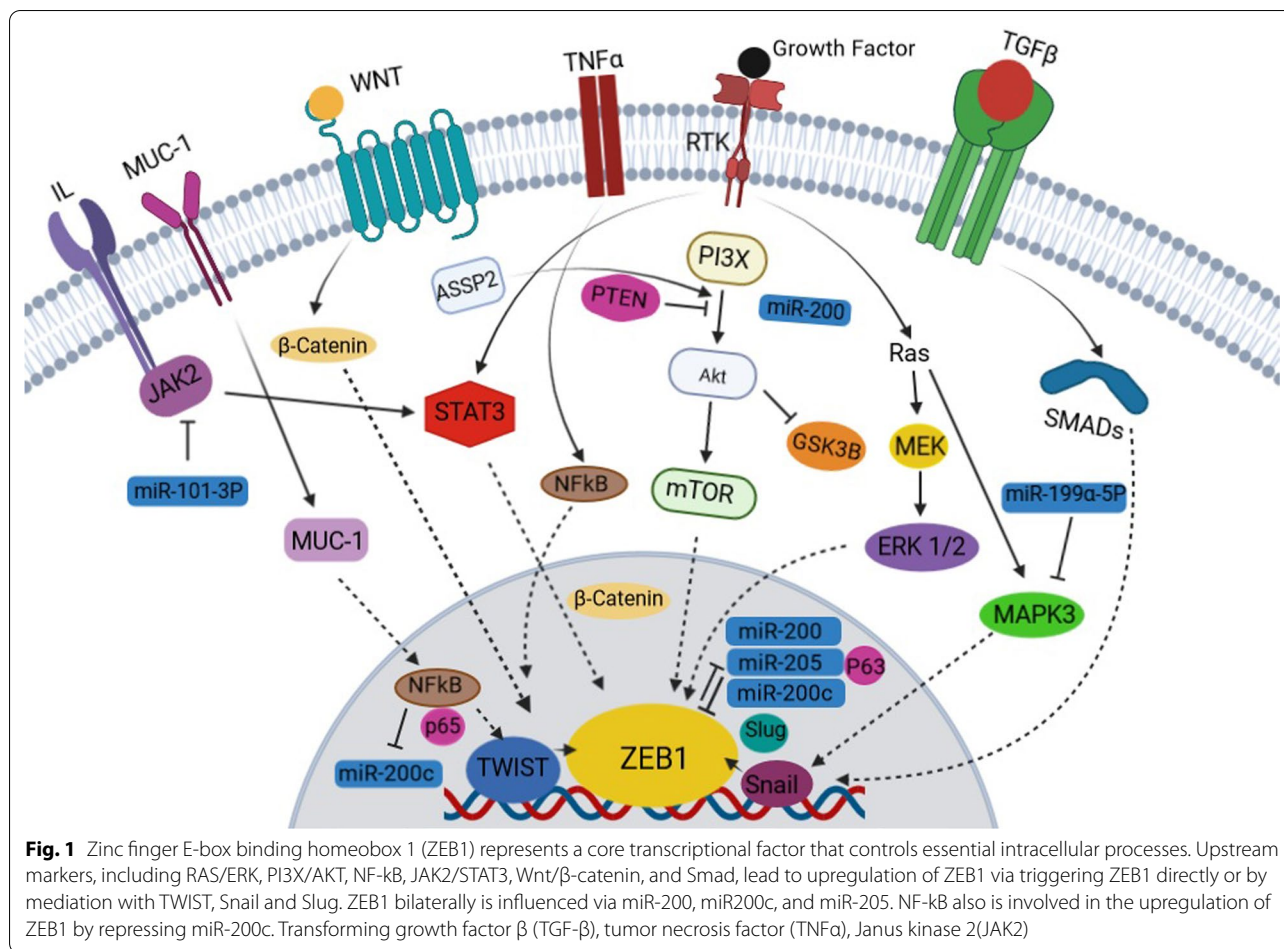
ZEB1, also known as TCF8 and  $\delta$ EF-1, belongs to the ZEB family encoded by the *ZEB1* gene on chromosome 10p11.2 [41, 42]. ZEB1 is a DNA-binding protein, which contains a homeodomain and two C2H2-type zinc finger clusters and binds to two high-affinity binding sites (E-boxes) [43]. Its DNA-binding activity is related to two zinc finger clusters present in the structure, which is essential for the recognition of the 5'-CANNTG 3' sequence [36, 44, 45]. The ZEB1 protein is composed of 1117 amino acids with a homeodomain structure (HD) in the middle and a carboxy-terminal cluster [46]. The HD as the middle region is able to interact with the C-terminal binding protein (CtBP) and a Smad interaction domain [37]. ZEB1 proteins have Smad-interacting domains that modulate the TGF- $\beta$  signal at the cell surface to affect gene regulation within the nucleus. The regulatory effect of ZEB1 is mediated via multiple motifs within the central area of this protein [47].

### Mechanism of ZEB1 and its effect on EMT

ZEB1 induces EMT by binding to the promoter region of the *E-cadherin* gene (*CDH1*) and preventing its expression. It is downstream of many cascades linked to EMT, such as TGF- $\beta$ , nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B), Ras-Raf-MEK-ERK (RAS/ERK), Wnt/ $\beta$ -catenin, and tyrosine kinase receptors. Recent studies have focused on ZEB1 and its influence on EMT function causing both malignancy and chemotherapy resistance in tumors. In addition, this important transcription factor has influenced many CNS diseases through various pathways (Fig. 1).

### Effects of ZEB1 on the different signaling pathways

ZEB1 has been shown to be a major participant in various signaling pathways (Table 1). Expression of ZEB1 is modulated by multiple signaling pathways, like TGF- $\beta$ , Wnt, NF- $\kappa$ B, hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), cyclooxygenase-2 (COX-2), phosphatidylinositol 3-kinase (PI3K)/Akt strain transforming AKT (AKT) and AKT/mTOR as well as miRNAs [5, 47]. ZEB1 regulates the BMP/TGF- $\beta$  pathway through its antagonist effect on TGF- $\beta$  signaling. The TGF- $\beta$ -mediated EMT effect on this pathway is induced via a stimulatory complex that binds the Smad domain along with binding to a co-activator consisting



of P/CAF and P300 [48, 49]. TGF-β is a trigger of EMT together with signaling pathways such as Wnt, RAS, and Notch, similar to ZEB1 [50]. TGF-β acts as a potent marker for the activation of ZEB1 and Smad2, which promote EMT, tumorigenesis, and cancer recurrence [51]. However, increased levels of Smad2 and ZEB1 were also observed in cells that did not respond to TGF-β suppression, suggesting an alternative unknown mechanism [52, 53]. Finally, the significant interdependence between TGF-β and ZEB-1 and vice versa with miR200 has been shown to regulate EMT [54]. It has also been shown that the expression of ZEB1 can be affected by B-cell CLL/lymphoma 6 (BCL6), which stimulates transcriptional suppressors causing E-cadherin abrogation and EMT enhancement [55, 56].

Furthermore, ZEB1 causes EMT induction through the suppression of E-cadherin via the ctBP-independent pathway by linking to the SWI/SNF BRG1, a chromatin restructuring protein. E-cadherin expression increases by preventing linkage between ZEB1 and BRG1 [57]. CtBP has been identified as a critical co-repressor for the regulation of BCL6 [58, 59]. The mucin 1 (MUC1) forms a

complex with ZEB1, which mediates NF-κB and p65, suppresses miR-200c, and contributes to EMT activation [60]. Anoikis (detachment-induced apoptosis) can be suppressed by receptor tyrosine kinase (TrkB) at the cell surface. The crucial role of ZEB1 in TrkB-induced EMT leads to the suppression of anoikis has also been demonstrated [61, 62]. Moreover, ZEB1 stimulates TrkB and promotes EMT by the modulation of a Twist–Snail axis [63]. Conversely, tyrosine kinase B1 (TKB1) increases glycogen synthase kinase-3β (GSK-3β), which prevents the induction of EMT, by suppressing ZEB1 [64]. Indeed, GSK-3β is the major factor of the Wnt/β-catenin cascade, and together with the phosphatidylinositol 3-kinase PI3K/AKT pathway, may control ZEB1 expression [65]. Serine/threonine kinase B also known as protein kinase B (PKB) or AKT is responsible for stimulating ZEB1 through the modulation of some signaling pathways, such as PI3K/AKT and/or AKT/mTOR [66, 67]. It has been shown that miR-708 and miR-199a-5p with a similar function are able to downregulate ZEB1 and reduce EMT through the PI3K/AKT/mTOR cascade [68, 69]. Aside from this, the apoptosis-stimulating protein of

**Table 1** Various modulators of ZEB1 expression

Markers	ZEB1 suppressor	ZEB1 inducer	Mechanisms	Refs.
TGF- $\beta$		*	Making complex with SMADs and co-activators and involved in pathways (WNT, RAS, and Notch) to induce EMT	[22, 33, 80–85]
miR200c	*		Through ROS/miR-200c/ZEB1 axis suppresses ZEB1 and increase E-Cadherin	[60, 86–88]
ERK1/2		*	Directly activated ZEB1 via ERK/ZEB1 signaling pathway	[78, 79]
NF-kB		*	Activation of NF-kB signaling due to different markers such as IL-7 and MUC1 leads to ZEB1 induction	[22, 89]
AKT		*	It has an induction effect on ZEB1 through PI3K/AKT/mTOR	[66, 67, 69, 90, 91]
ASSP2		*	Correlated with the PI3K/AKT pathway	[71]
TKB1	*		Augmenting GSK-3B which is deterrence on radiation-induced EMT by repressing ZEB1	[64]
MiR-200	*		Works as a suppressor of ZEB1 and tumor invasion	[29, 54, 72, 92]
MUC1		*	Creating a complex with ZEB1 intermediating NF-kB p65 leads to miR-200c repression and contributes to EMT activation	[60]
Snail		*	Corporation with ZEB1 and TGF $\beta$ to increase tumor invasiveness	[63]
miR-33b	*		Inactivation of the Wnt/ $\beta$ -catenin/ZEB1 pathway concludes to EMT silencing	[76, 77]
PI3K		*	Involves in different pathways in the induction of EMT	[65–68, 70, 72, 90]
ESE1	*		Downregulating through the MEK–ERK pathway, resulted in overexpression of ZEB and EMT upregulation	[78]
miR-708	*		Suppressing ZEB1 resulted in EMT reduction	[68]
miR-199a-5p	*		Suppressing ZEB1 resulted in EMT reduction	[69]

AKT: Ak strain transforming, ASPP2: Apoptosis-stimulating protein of P53, EMT: Epithelial-mesenchymal transition, ESE1: Epithelial-specific ETS transcription factor 1, GSK-3B: Glycogen synthase kinase-3B, MUC1: Mucin 1, NF- $\kappa$   $\beta$ : Nuclear factor kappa $\beta$ , TGF- $\beta$ : Transforming growth factor  $\beta$ , TKB1: Tyrosine kinase B1

P53 (ASPP2), which correlates with the PI3K/AKT pathway, forms an intermediate complex with  $\beta$ -catenin and promotes EMT through ZEB1-mediated suppression of E-cadherin [70, 71]. ZEB1 enhances cell migration via the regulation of miR-200 and PI3K signaling [72]. ZEB1 modulates the polarization of M2-polarized tumor-associated macrophages (TAMs) via EMT regulation [73]. Furthermore, Zeb1 regulates T-cell migration [74]. FLF3, an antagonist of the oncogenic pathway and a negative regulator of EMT, inhibits ZEB1 transcription and regulates the Wnt and RAS oncogenic pathways [75]. MiR-33b suppresses ZEB1 which can lead to EMT silencing via inactivating the Wnt/ $\beta$ -catenin/ZEB1 signaling pathway [76, 77]. Epithelial-specific ETS transcription factor 1 (ESE1) is induced in the epithelial confined state and luminal subtype of breast cancer. ESE1 is downregulated by the MEK–ERK pathway, leading to overexpression of ZEB1 and upregulation of EMT [78]. The ERK1/2-mediated signaling cascades ERK/ZEB1 axis stimulates EMT and regulates cell apoptosis and migration [79].

### Effects of ZEB1 on various cell types of the CNS

ZEB1 plays a crucial role in cell differentiation and migration as well as cell fate in the CNS. The function of ZEB1 has a complex transcriptional regulatory effect on neural progenitor cells. It can act as a

repressive marker in embryonic NSC proliferation and migration via interaction with CTBP2 and the regulation of Neurod1 and Pard6b [93]. Conversely, it plays a key role in the differentiation of human embryonic stem cells into neurons [94]. The HIF-1 $\alpha$  pathway regulates neuronal polarization, maturation, and differentiation through the modulation of ZEB1 values [95]. Furthermore, Zeb1 affects the trans-differentiation of mouse embryonic fibroblasts into functional neurons [96]. In the absence of ZEB1, immature differentiation and mal-migration of neurons and radial glial cells occur due to the activity of Pak3, a p21-activated serine/threonine-protein kinase [97]. Moreover, ZEB1 is necessary for the differentiation of radial glial-like stem cells, which are required in the adult hippocampus for the formation of neurons and astrocytes [27]. ZEB1 also controls the onset of astrocyte precursor emigration from the ventricular zone and regulates the timing of their differentiation via the modulation of the adhesion protein Cadherin-1 [98]. Moreover, ZEB1 expression in neurons may act as a regulator of their differentiation by repressing polarity genes in neural stem cells [99]. ZEB1 is also a prerequisite factor for NSC migration [100]. It has been suggested that ZEB1 is implicated in the regulation of retinal organoid development [101].

## Malfunctions of ZEB1

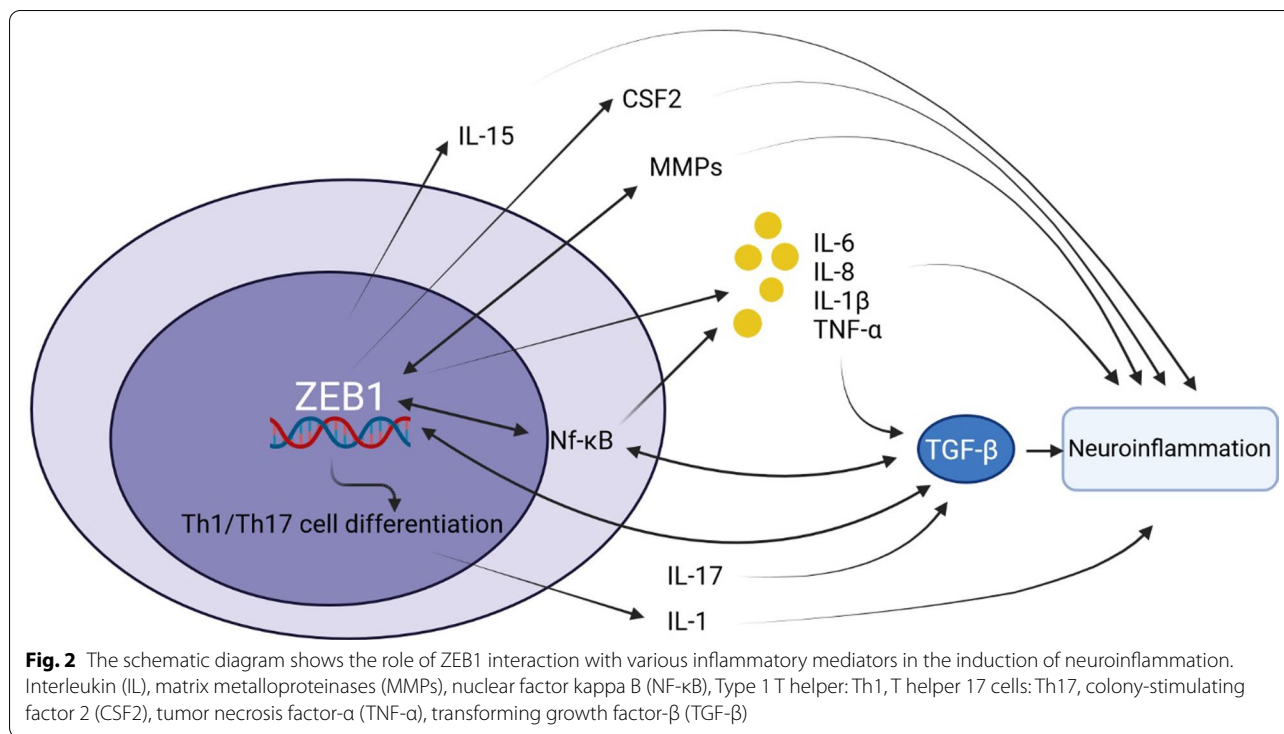
ZEB1 is implicated in the pathological mechanisms of various diseases. Mutations in *ZEB1* in humans have been linked to multiple developmental malformations, such as posterior polymorphous corneal dystrophy with corpus callosum maldevelopment, malformations of the inner ear, obesity, and cleft palate [102, 103]. In addition to the initiation of corneal cell apoptosis, stromal fibrosis, and squamous metaplasia, the loss of function of ZEB1 inhibits corneal vascularization and activates immune-mediated processes of the ocular surface [104]. Furthermore, it has been suggested that tumor cells that have undergone EMT obtain stem cell properties including, self-renewal, invasiveness, radioresistance, and chemoresistance [5]. ZEB1 plays a critical role in the regulation of DNA damage by controlling EMT in multiple tissues [44] and modulates cancer cell differentiation and invasiveness, vascular functionality, tumor angiogenesis, and immune responses [105]. It has been elucidated that increased ZEB1 activity influenced by hyaluronic acid through the ZEB1/epithelial splicing regulatory protein 1/CD44 axis promotes EMT and tumor invasion in breast cancer [106]. BCL6 also has a positive effect on the induction of EMT associated with the increase of ZEB1, leading to the suppression of E-cadherin and consequently tumor progression [56]. Silencing ZEB1 also decreases PD-L1 as an immune checkpoint ligand along with the downregulation of miR200 and consequently EMT activations in cancer cells [92]. Ultrasound-targeted microbubble destruction, a novel therapeutic approach, has been suggested as a means of inhibiting cell migration via the suppression of ZEB1 and deactivation of EMT by targeting the ROS/miR-200c/ZEB1 axis [107]. Moreover, miR-200c suppressed ZEB1 via the modulation of the PI3K/Akt pathway and the function of TGF $\beta$  in non-small cell lung cancer [33, 90]. The activation of miR200a is linked to the suppression of the Wnt/ $\beta$ -catenin pathway that leads to overexpression of E-cadherin [108]. Downregulation of ZEB1 also affects the enhancement of apoptosis of cancer cells, followed by a reduction in tumor invasiveness and migration through the expression of Wnt5a and vimentin [109]. The key role of HIF-1 $\alpha$  in promoting EMT through the activation of ZEB1 is substantial tumorigenicity [110, 111]. Furthermore, the negative effect of the circadian gene timeless, an essential protein that modulates circadian rhythm, on ZEB1 overexpression and EMT values has been described [112]. CSN5 is an oncogenic marker that directly interacts with ZEB1 and enhances its stability while promoting EMT in renal cell carcinoma cells [113]. Assessment of the function of X-inactive specific transcript (XIST) revealed that it mainly represses miR-429, a tumor suppressor, and then results in a higher expression

of ZEB1 and EMT via the critical axis of XIST/miR-429/ZEB1 and enhances tumor cell invasiveness [114]. MiR-127 also has an attenuating effect on cell proliferation by targeting ZEB1 on smooth muscle cells [115]. The inhibitory function of miR-200c on ZEB1 is also elucidated in trastuzumab-resistant gastric cancer, leading to suppression of EMT and enhancement of drug sensitivity [116]. The activity of NF- $\kappa$ B has been demonstrated to stimulate the induction of ZEB1 and EMT through the action of interleukin-17 (IL-17) and phosphorylation of ezrin Tyr353, respectively, in different cancers [91, 117]. ZEB1 serves an important role in controlling the size of the neural progenitor pool, neuronal migration, and cleavage plane orientation of dividing progenitor cells. Upon the knockout of *Zeb1*, an extra number of premature neurons are produced and the cleavage plane of mitotic progenitor cells fails to orientate appropriately, resulting in random orientation and premature neuronal differentiation, particularly in the upper layer of neocortical tissues. It has been suggested that a malfunction of ZEB1 together with its effector Pak3 could contribute to neocortical developmental disorders [97].

## ZEB1 contributes to inflammatory responses

Several studies have demonstrated the critical role of ZEB1 in promoting inflammatory responses. ZEB1 is crucial for the development of both T-cell and B-cell development [39]. Mutations of ZEB1 have been implicated in T-cell immunodeficiency [89]. ZEB1 is a pivotal element to maintain immune cell viability, mobility, and cytokine expression, and regulates the expression of various cytokines, such as IL-1b, IL-6, IL-8, and TNF- $\alpha$ , by the modulation of the TGF- $\beta$ -related Stat3 signaling pathways and Nf- $\kappa$ b [22, 80–82, 118–120]. Conversely, several pro-inflammatory cytokines, like TGF- $\beta$ , increase the expression of ZEB1 via the activation of Smad, TK receptors, NF- $\kappa$ B, and the JAK1–STAT3 signaling pathways [121].

IL-1 $\beta$  upregulates ZEB1 expression and promotes inflammation [86]. ZEB1 modulates the expression of several inflammatory response genes. Direct enhancement of the production of inflammatory cytokines, such as IL-6 and IL-8, initiates inflammatory processes and facilitates tumor growth [122]. ZEB1-mediated immune responses also contribute to inflammation in the tumor microenvironment via its direct regulatory effect on the expression of IL-6 [123]. ZEB1 induction of programmed death-ligand 1 and CD47 contributes to the formation of the hostile inflammatory microenvironment surrounding tumors [74]. ZEB1 promotes inflammatory responses through the suppression of *N*-methyl purine glycosylase, a DNA glycosylase, in epithelial cells via the induction of inflammatory mediators, such as IL-1 $\beta$ , and the



generation of reactive oxygen species [124]. Furthermore, IL-17 influences the upregulation of the ZEB1-mediated NF-κB pathway as well as tumor cell migration through stimulation of EMT [117]. Sodium tanshinone IIA sulfonate, an antioxidant and anti-inflammatory substance, can prevent EMT by targeting ZEB1, Snail1, and the Smad signaling pathway [125]. Using lipopolysaccharide application to induce local inflammation in the lungs enhances tumor cell migration through a Zeb1-dependent mechanism [126]. The enhancement of TNF-α values increases ZEB1 as a target of miR-200c and miR-141 in cells, suppresses E-cadherin, and regulates EMT progression [87]. MiR-9 directly targets NF-κB that leads to inflammatory responses in lymphatic endothelial cells via the promotion of EMT-associated genes, such as ZEB1 (Fig. 2) [87].

Microglia act as the first line of the innate immune defence [127], and astrocytes are pivotal regulators of both innate and adaptive immune responses in the CNS [128]. The expression of ZEB1 in both microglia and astrocyte critically contribute to neuroinflammation in the CNS [129]. The expression of ZEB1 regulates microglia immune responses to CNS insults and reduces the production of astrocytic CXCL1 via the TGFβ-dependent signaling pathway [11]. ZEB1 enhances the neuronal output of neural stem cells of the hippocampus at the expense of glial cells [27]. The *ZEB1* gene has been reported to be involved in cognitive impairment in

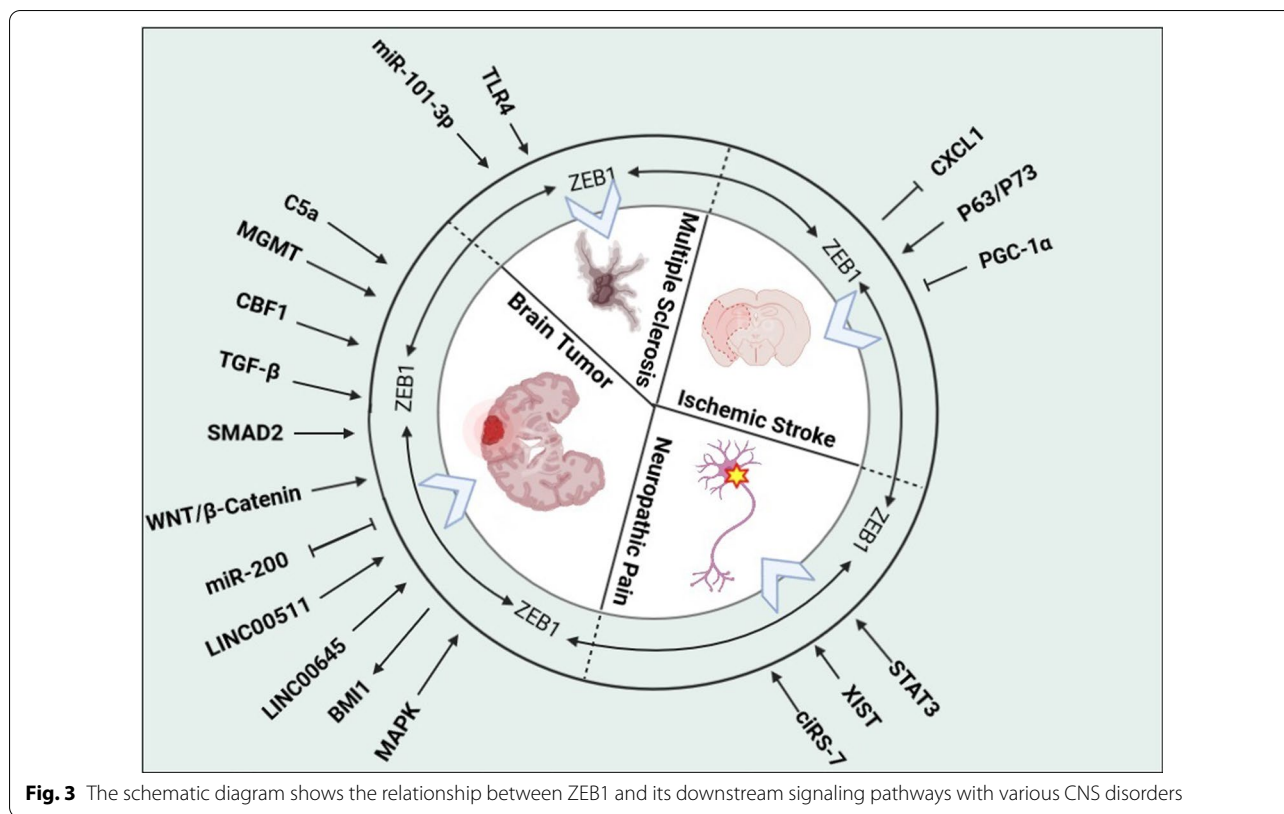
humans [83]. The reduction in Zeb1/2 and lncRNA-1604 in the neocortex and striatum can lead to a neurodegenerative process in a mouse model of Huntington's disease [130]. The dysregulation of the lncRNA-1604/miR-200c/ZEB axis during neural differentiation could also lead to neurodegenerative diseases [131]. Fused in sarcoma, an RNA-binding protein linked to neurodegenerative diseases acts through miR-200c and its target transcript ZEB1 [132]. Loss of ubiquitin 1, a protein critical for combating neurological disorders linked to protein aggregation, significantly increases the expression of ZEB1 [133].

### ZEB1 in CNS disorders

Several studies have shown that ZEB1, along with other factors such as TWIST, Snail, and Slug, is an important transcription factor involved in EMT promotion in the CNS and plays an important role in the pathophysiology of different neurological disorders, including brain tumors, neuropathic pain, acute ischemic stroke, and MS (Fig. 3; Table 2).

### ZEB1 effects in CNS tumors

ZEB1 as a key element of EMT promotion has been extensively studied in different brain tumors, particularly GBM. GBM is the most aggressive malignant primary brain tumor in which a variety of therapeutic strategies have failed to demonstrate efficacy [155]. Several investigations have reported that the ZEB1 pathway contributes



to GBM initiation and progression, invasion, radioresistance, and chemoresistance. ZEB1 is expressed in the tumor invasive zone of human GBM tissues, which is associated with hypoxic regions of the tumor [156]. The clinical studies demonstrate that GBM patients with a high level of *ZEB1/YAP1* gene signature have a shorter median overall survival [144]. The expression of Smad interacting protein 1 (SIP1, also known as ZEB2), a member of the ZEB group of transcription factors, plays a role in the impairment of colony formation and invasion of tumorigenic glioma cells through the regulation of E-cadherin and mesenchymal proteins, such as fibronectin and vimentin [157]. SIP1 and N-cadherin are also implicated in the migration of IL-1β/TGF-β-induced neurosphere cells from the human LN-229 glioma cell line [158, 159]. TGF-β showed a regulatory effect on ZEB1 expression along with Smad2 and EMT signaling leading to GBM cell aggression [52]. Moreover, the Wnt/β-catenin pathway promotes GBM aggregation and tumor malignancy via activation of EMT inducers such as ZEB1, Twist, and Snail [143]. Lef1, an effector of the Wnt signaling pathway, activates ZEB1 and enhances GBM cell migration and chemoresistance [160]. It has been revealed that GBM invasiveness is mediated by an alteration in N-cadherin dynamics, through the regulatory effect of ZEB1 on roundabout guidance protein 1 [139]. *BMI-1* is an

important gene for controlling the proliferation and self-renewal of GBM cancer stem cells. Suppression of BMI1 has been shown to downregulate GBM stem cell proliferation [161]. It has also been shown that increasing ZEB1 in parallel with BMI1 can synergistically induce EMT and stem cell proliferation [162]. The EMT-activator ZEB1 is a promoter of metastasis, and SOX2 and BMI1 are targets of EMT activators, especially ZEB1 [29]. Mesenchymal stem-like cells expressed C5a contribute to ZEB1 expression and brain tumor invasiveness through the stimulation of p38 mitogen-activated protein kinase [146]. The interaction between ZEB1 and O-6-methylguanine-DNA methyltransferase, the most reliable prognostic marker for GBM therapy resistance, has been demonstrated in poor response to temozolomide (TMZ) through the upregulation of c-MYB by the ZEB1–miR-200 feedback loop [139]. Furthermore, ZEB1 was a crucial role in TMZ resistance in GBM cells through the upregulation of c-MYB by the ZEB1–miR-200 pathway [139]. The antagonistic effect of IL-24 on ZEB1 leads to a suppression of GBM cell migration and invasion as well as an enhancement of the chemosensitivity of tumor cells to TMZ [163]. Alfa-6-integrin, a regulator of GBM proliferation and stemness, regulates the expression of GBM stem cells via the modulation of the ZEB1/YAP1 transcription complex that leads to enhancement of cell proliferation

**Table 2** A summary of markers and signaling pathways and their related mechanisms implicated in ZEB1-related CNS disorders

CNS diseases	Markers and pathways	Mechanisms	Refs.
Cerebrovascular diseases	TGF-b1	Inhibition of astrocytic CXCL1 via TGF-b1 pathways	[83, 129]
	PGC-1 $\alpha$	Its expression happens after ischemic stroke to reduce brain damage via the downregulation of inflammatory cytokines and interaction with ZEB1	[134]
	p63, p73	ZEB1 creates a linkage between p63 and p73 for promoting the cell survival pathway	[135]
	CXCL1, TGF- $\beta$ 1 pathway	Brain protection by ZEB1 via CXCL1 inhibition in the TGF- $\beta$ 1 pathway	[129]
Neuropathic pain	XIST	Sponging miR-150 leads to overexpression of ZEB1 and neuropathic pain	[136]
	ciRS-7, STAT3	Sponging of miR-641 or activation of miR-135a-5p contributes to expressing pro-inflammatory cytokines, such as IL-6, IL-12, and TNF $\alpha$ leading to EMT induction	[137, 138]
GBM	MGMT	Lower effect of temozolomide therapy by the interference of ZEB1 with MGMT	[139]
	CBF1	Activating EMT inducers such as <i>ZEB1</i> , <i>SNAIL1</i> , and <i>CD44</i> genes	[140, 141]
	miR-205-3p, LINC00645, TGF- $\beta$	LINC00645 in collaboration with miR-205-3p and ZEB1 promotes EMT stimulated by TGF- $\beta$	[84]
	LINC00511, miR-524-5p, YB1	By influencing on ZEB1 promoted GBM aggression	[142]
	miRNA-200	GBM invasiveness increases followed by inhibition of miRNA-200 by ZEB1	[29]
	TGF- $\beta$ , SMAD2	Along with ZEB1 lead to GBM cell aggression	[52]
	WNT/ $\beta$ -catenin, twist, snail	Wnt/ $\beta$ -catenin pathway via activation of EMT inducers such as ZEB1, twist, and Snail promotes GBM aggregation and tumor malignancy	[143]
	$\alpha$ 6-integrin, FGFR1, YAP1, FOXM1	$\alpha$ 6-integrin is involved in radioresistance as well as GBM stemness and proliferation by administering FGFR1 under the coordination of ZEB1 and YAP1 leading to FOXM1 stimulation	[144, 145]
	ma, MAPK	These markers with influence on ZEB1 expression lead to tumor invasion	[146]
	Multiple sclerosis	JAK2, miR-101-3p	JAK2 is suppressed followed by the inhibition of miR-101-3p through ZEB1 activities and increasing cytokines relevant to pathogenicity
<i>Zfhfp1</i> , <i>Zfhfp2</i> , <i>IL2</i>		IL2 was associated with T-cell formation and can be suppressed via ZEB1 (related to upregulation of <i>Zfhfp1</i> and not <i>Zfhfp2</i> )	[148, 149]
TLR4, miR-200a-3p			[150, 151]
CNS traumatic injuries	ErbB2, TGF- $\beta$		[72, 152]
	XIST, miR-27a, Smurf1	Suppressing XIST caused to inhibit of miR-494 in the PTEN/AKT/mTOR signaling pathway leading to alleviating neuroinflammation via the deactivation of ZEB1 after SCI	[136, 153, 154]

and stemness via the stimulation of the forkhead box M1 gene [144] and promotes radioresistance of GBM cells through the modulation of DNA damage response [145]. The E3 ubiquitin-protein ligase parkinsonian protein 2 acts as a ZEB1 antagonist, inhibits EMT, and prevents GBM cell invasion [164]. Hypoxia is a strong inducer of a mesenchymal shift in GBM cells, which is associated with increased migration and invasiveness of GBM cells. Knockdown of HIF1 $\alpha$  has been shown to not only suppress ZEB1, but also inhibit the mesenchymal trans-differentiation in GBM [100, 156]. Moreover, the direct effect of recombination signal binding protein for immunoglobulin kappa J on the activation of EMT inducers, such as *ZEB1*, *SNAIL1*, and *CD44* genes, could increase the invasiveness of GBM cells, which has been correlated with the hypoxic pseudopalisading regions [140, 141]. The function of lncRNAs has been studied in various cancers, including GBM [165, 166]. LINC00645,

a lncRNA, was identified as a collaborator with miR-205-3p and ZEB1 in a signaling pathway promoting EMT stimulated by TGF- $\beta$ . Indeed, miR-205-3p modulated TGF- $\beta$  under the function of LINC00645, leading to the invasiveness of gliomas [84]. Moreover, LINC00511 in conjunction with the LINC00511/miR-524-5p/YB1/ZEB1 axis contributes to EMT. While LINC00511 is influenced by ZEB1, it indirectly upregulates YB1 via sponging miR-524-5p and promotes GBM tumorigenesis [142]. Moreover, the lncRNA ZEB1 antisense 1 (ZEB1-AS1) showed excessive expression in cancer cells, such as gliomas, compared with primary normal cells [167]. ZEB1-AS1 enhanced tumorigenesis and proliferation of GBM cells by interacting with miR200c/141 [168]. The interaction between miR-200c and miR-141 decreased EMT as well as glioma cell growth and aggression by downregulating ZEB1 [88, 168]. A link between isocitrate dehydrogenase 1 (IDH1) and ZEB1 expression has been



reported in lower-grade glioma. The expression of ZEB1 was enhanced in IDH1/2-mutant gliomas, and IDH1/2-mutant gliomas exhibited significantly lower values of ZEB1 protein [169]. The role of ZEB1 as a potential prognosis biomarker and drug target in medulloblastoma has been reported [170].

Various miRNAs have shown therapeutic potential by acting on GBM cancer cell migration and invasion via the modulation of ZEB1. GBM invasion increases through the inhibition of the ZEB1–miRNA-200 axis effects on stem cell markers, such as OLIG2, SOX2, and CD133 [29]. miR-200c negatively modulates ZEB1 regulation and consequently reduces the migration of these cells [171]. Similarly, miR-574 independently targeted ZEB1 in GBM cells, which contributed to the inhibition of GBM proliferation [172]. miR-205 also inhibited the proliferation of GBM cells by affecting the Akt/mTOR cascade via interaction with ZEB1 [173]. Moreover, metformin suppresses the AKT/mTOR/ZEB1 signaling pathway via the inhibition of the TGF- $\beta$ 1-induced EMT-like process in GBM cancer stem cells [174]. Moreover, the activation of miR-590-3p, as well as miR-139-5p, prevented GBM tumor invasion by targeting ZEB1 and ZEB2 and inhibiting EMT [175, 176].

### ZEB1 and MS

Although the exact role of ZEB1 in MS needs to be clarified, some studies have clarified the different roles of ZEB1 in the pathology of MS. The dysfunction of brain endothelial cells plays a role in the initiation of neuroinflammation and cell injury in MS. A link between the damage of the blood–brain barrier (BBB) and the EMT process has been suggested [177]. Evidence suggests the implication of ZEB1 in the dysfunction of BBB under pathological conditions [178]. Furthermore, one of the hallmarks of MS is inappropriate activation of interferon-gamma (IFN- $\gamma$ )-producing Th1 and Th17 cells [179]. ZEB1 contributes to pathogenic Th1 and Th17 cell differentiation in MS. ZEB1 mutation inhibits the expression of miR-101-3p, which leads to the suppression of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway and excessive release of IL-17 and IFN- $\gamma$  [180]. Dysregulation of the JAK/STAT pathway plays an important role in the pathophysiology of several autoimmune diseases, including MS [181]. Moreover, ZEB1 regulates IL-2 expression and is implicated in T-cell development through the modulation of the balance between Zfh1 and not Zfh2, the splice variants of ZEB1, in an experimental model of MS [147–149]. Knockdown of ZEB1 in dendritic cells decreases IL-12 secretion and increases Th2 differentiation [182]. The highly upregulated liver cancer (HULC), an lncRNA determined to be upregulated in patients with MS, may

be involved in MS progression. HULC activates the miR-200a-3p/ZEB1 signaling pathway and regulates EMT [150].

### ZEB1 and neuropathic pain

ZEB1-related neuroinflammatory responses could contribute to neuropathic pain. The miR-28-5p/ZEB1 pathway has been suggested as a potential therapeutic target for neuropathic pain. Overexpression of miR-28-5p reduces neuropathic pain behaviors in a chronic sciatic nerve injury model in rats through the inhibition of neuroinflammation induced by the release of Cox-2, IL-6, and IL-1 $\beta$ . MiR-28-5p binds to the 3-untranslated area of Zeb1, downregulates Zeb1 expression, and inhibits cytokine expression [183]. Moreover, miR-128-3p and miR-96-5p are reported to suppress Zeb1 expression and regulate neuroinflammation and neuropathic pain [184, 185]. In addition, miR-200b/miR-429 serves as a key regulator of neuropathic pain via targeting ZEB1 [186]. lncRNA X-inactive specific transcript (XIST) increased significantly in the spinal cord tissues and microglia in a chronic constriction injury rat model. Silencing ZEB1 alleviated neuropathic pain and downregulated the expression of XIST through the regulatory effects of miR-150 [136]. Circular RNAs, such as ciRS-7, increased EMT by upregulating ZEB1 and STAT3. This was associated with either sponging of miR-641 or activation of miR-135a-5p, which contributed to the expression of pro-inflammatory cytokines, like IL-6, IL-12, and TNF $\alpha$ , and the induction of neuropathic pain [137, 138]. Furthermore, lncRNAs, such as LINC00657, contribute to the development of neuropathic pain in animal models of chronic pain through the regulation of the miR-136/ZEB1 axis. MiR-136 regulates neuroinflammatory responses as well as the expression of ZEB1. Inhibition of ZEB1 inhibits neuropathic pain behaviors in vivo [187]. Oxaliplatin-induced chronic pain enhanced the values of ZEB1 in the spinal dorsal horn neurons through the regulatory effects of NF- $\kappa$ B and/or Ras/Erk as well as by triggering the interaction between DNA (cytosine-5)-methyltransferase-3 $\beta$  and ZEB1 [188].

### ZEB1 and ischemic/traumatic brain injuries

The induction of ZEB1 is part of a neuroprotective response by neurons after brain ischemic insults. High values of ZEB1 expression in neocortical tissues are observed in neocortical specimens of patients with stroke [135]. ZEB1 regulates microglial activities in acute ischemic stroke. After the induction of brain ischemia, ZEB1 expression significantly increases in the ischemic cerebral tissues, particularly in microglia. A greater ramified morphology of microglia in ischemic tissues is associated with a higher expression of ZEB1, which enables

microglia to react more precisely to stimuli and promotes inflammatory responses following ischemic events. Furthermore, in an experimental ischemic stroke model, upregulation of ZEB1 leads to the inhibition of astrocytic CXCL1 expression during the response to TGF- $\beta$ 1-dependent signaling and reduction in the entrance of neutrophils into the brain. It has been suggested that targeting ZEB1 expression may lead to moderate acute ischemic brain injuries [83, 129]. The expression of PPAR $\gamma$ -coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) enhances after ischemic stroke and reduces brain damage by downregulating neuroinflammatory cytokines and regulating neurotrophins. ZEB1 expression was indirectly related to PGC-1 $\alpha$  through the modulation of Sirt1 [134]. ZEB1 expression promotes cell survival in the neocortex after acute ischemic insults through the modulation of proapoptotic isoforms of p63 and p73 [135]. In addition, the application of ZEB1 antagonist improved neurological function and cerebral edema, and decreased the expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and GFAP in ischemic tissues in an intracerebral hemorrhage rat model [189].

The astrocytic response to CNS injury is implicated in EMT and upregulation in ZEB expression. CNS injury-related astrogliosis enhances EMT and its related gene expression. In experimental models of spinal cord injury or transient ischemic stroke, the knockdown of the *Zeb2f* in astrocytes lessened astrogliosis, induced greater lesions, and delayed functional motor recovery [190]. Following CNS injury, meningeal cells actively migrate into the injury site undergoing EMT and build the meningeal barrier between normal and injured tissues, which is regulated by the TGF- $\beta$ 1/non-Smad/SNAI1 pathway [191]. Expression values of the TGF- $\beta$  receptor and the Ephrins receptor (ErbB2) are greatly enhanced in the meningeal cells of the injury site to maintain the integrity and homeostasis of CNS cells within the lesion site [152]. Thus, ZEB1 could be a potential target to regulate tissue reconstruction after CNS injuries. The suppression of XIST after spinal cord injury (SCI) enhances the function of the XIST/miR-27a/Smurf1 pathway and causes the inhibition of miR-494. This process leads to the alleviation of neuroinflammation via the deactivation of ZEB1 and the reduction of neuroinflammatory mediators, such as COX-2, TNF- $\alpha$ , and IL-6 [136, 153, 154].

## Conclusion

Considering the critical role of neuroinflammation in various diseases, EMT is known to be an important process of pathogenicity in various neurological disorders. ZEB1 as a focal transcription factor of EMT has been considered a potential target for the prognosis and treatment of various neurological diseases. Although recognition of the exact role of ZEB1 in CNS

dysfunction requires additional analysis and evaluation, it was concluded that ZEB1, in partnership with other EMT transcription factors, has dominant functions in EMT and neuroinflammation. The complex interaction between ZEB1, immune cells, and various cytokines is tightly connected to neuroinflammation through the regulation of different signaling pathways. The ZEB1–inflammation axis plays a crucial role in the pathogenesis of various CNS disorders through promoting tumor cell proliferation and invasiveness, formation of the hostile inflammatory microenvironment surrounding neuronal tissues, dysfunction of BBB, dysfunction of microglia and astrocytes, and disturbances of angiogenesis. The molecular mechanisms and signaling pathways orchestrating the association between ZEB1 and inflammatory processes are linked with the initiation, progression, and outcomes of various CNS disorders. Future studies are required to demonstrate whether the modulation of ZEB1 could play a beneficial role as a diagnostic, prognostic, and/or therapeutic approach for CNS disorders.

## Abbreviations

AKT: Akt strain transforming; AD: Alzheimer's disease; ASP2: Apoptosis-stimulating protein of P53; BCL6: B-cell CLL/lymphoma 6; EMT: Epithelial–mesenchymal transition; CtBP: C-terminal binding protein; CNS: Central nervous system; COX-2: Cyclooxygenase-2; CSF2: Colony-stimulating factor 2; EMT-TFs: EMT-promoting transcription factors; ESE1: Epithelial-specific ETS transcription factor 1; GBM: Glioblastoma; GSK-3 $\beta$ : Glycogen synthase kinase-3 $\beta$ ; HD: Homeodomain structure; IFN- $\gamma$ : Interferon-gamma; lncRNAs: Long intergenic noncoding RNAs; HIF-1 $\alpha$ : Hypoxia-inducible factor 1 $\alpha$ ; IL: Interleukin; IDH1: Isocitrate dehydrogenase 1; JAK2: Janus kinase 2; TNF $\alpha$ : Tumor necrosis factor; MMPs: Matrix metalloproteinases; MS: Multiple sclerosis; NF- $\kappa$  B: Nuclear factor kappa $\beta$ ; MUC1: Mucin 1; PGC-1 $\alpha$ : PPAR $\gamma$ -coactivator-1 $\alpha$ ; PKB: Protein kinase B; PI3K: Phosphatidylinositol 3-kinase; Th1: T helper 1; Th17: T helper 17; TMZ: Temozolomide; TGF- $\beta$ : Transforming growth factor  $\beta$ ; TKB1: Tyrosine kinase B1; TWIST1: Twist-related protein 1; XIST: X-inactive specific transcript; ZEB1: Zinc finger E-box binding homeobox 1.

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## Author contributions

EP performed an extensive literature review and prepared the first draft of the manuscript, figures, and tables. UK and SGM critically revised and improved the design and quality of the manuscript. AG conceived, designed, and coordinated the study, and contributed to and finalized the draft. All authors read and approved the final manuscript.

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## Declarations

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**Consent for publication**

Not applicable as no patients/participants were involved in this review.

**Competing interests**

The authors declare no conflict of interest.

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