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Review

Role of Zeb2/Sip1 in neuronal development

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HIGHLIGHTS

- Mutations in Sip1 cause the Mowat-Wilson syndrome in humans.
- Sip1 controls the formation of the hippocampus.
- Sip1 is important for cell fate switch in the neocortex development.
- Sip1 controls migration of interneurons and is required for the onset of gliogenesis.
- Sip1 is needed for axonal growth and branching.

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ABSTRACT

Zeb2 (Sip1, Zfhx1b) is a transcription factor that plays essential role in neuronal development. Sip1 mutation in humans was shown to cause Mowat-Wilson syndrome, a syndromic form of Hirschprung's disease. Affected individuals exhibit multiple severe neurodevelopmental defects. Zeb2 can act as both transcriptional repressor and activator. It controls expression of a wide number of genes that regulate various aspects of neuronal development. This review addresses the molecular pathways acting downstream of Zeb2 that cause brain development disorders.

1. Zeb2 structure, expression and interactions

Zeb2 is a member of the small Zeb family of two transcription factors Zeb2 (also known as Sip1 and Zfhx1b) and δ EF1 (Zeb1). A common structural feature of these proteins is the presence of a homeodomain separated by two clusters of "zinc-finger" domains with DNA-binding activity. The alternate name of Zeb1, 'Sip1', was given for the protein's ability to interact with activated SMAD transcriptional co-factors (Sip stands for Smad interacting protein). The SMAD interacting domain was not detected in the other family member, Zeb1. It is not completely clear what part of Zeb2-mediated downstream targets depend on Zeb2-SMAD interactions. Zeb2 is expressed in many tissues during development. In early embryonic development it is expressed in the neural tube and neural crest cells. Later in development its expression is found in all parts of the developing forebrain including the hippocampus, the cerebral cortex, ganglionic eminences as well as the thalamus. Zeb2 is highly expressed in various neuronal subtypes, including but not limited to pyramidal neurons of the hippocampus and neocortex, migrating cortical interneurons, and dopaminergic neurons in the brainstem. It is also found in tissues that are not derived from the neuroectoderm, including the wall of the digestive tract, kidney and skeletal muscles. (Miquelajauregui et al., 2007; Nishizaki et al., 2014; Parthasarathy et al., 2014; Srivatsa et al., 2015).

Zeb2 is a 140-kDa protein with two N- and C-terminal zinc fingers clusters which enable high-affinity DNA binding (Nelles et al., 2003; Verschueren et al., 1999). The full-length Zeb2 protein is 1215 amino acids (aa) in the mouse and 1214 aa in human. Zeb2 acts mostly as a transcriptional repressor, but can also activate the transcription of target genes together with its co-factors (Conidi et al., 2011; Weng et al., 2012). Zeb2 regulates target gene transcription through the interaction between two zinc fingers in each of its two zinc finger clusters and CACCT(G) or CACANNT(G) sites in regulatory regions of genes (Remacle et al., 1999). Zinc finger domains are among the most common DNA eukaryotic binding motifs. Zeb2 binds DNA as a monomer and the integrity of both zinc finger clusters is important for the binding of Zeb2 to DNA (Remacle et al., 1999). The N-terminal zinc finger cluster (NZF) contains three CCHH-type zinc fingers and one CCCH-type finger, and the C-terminal zinc finger cluster (CZF) contains three zinc fingers. Between these two clusters an isolated zinc finger and a POU-like homeodomain (HD) are present (Higashi et al., 2002;

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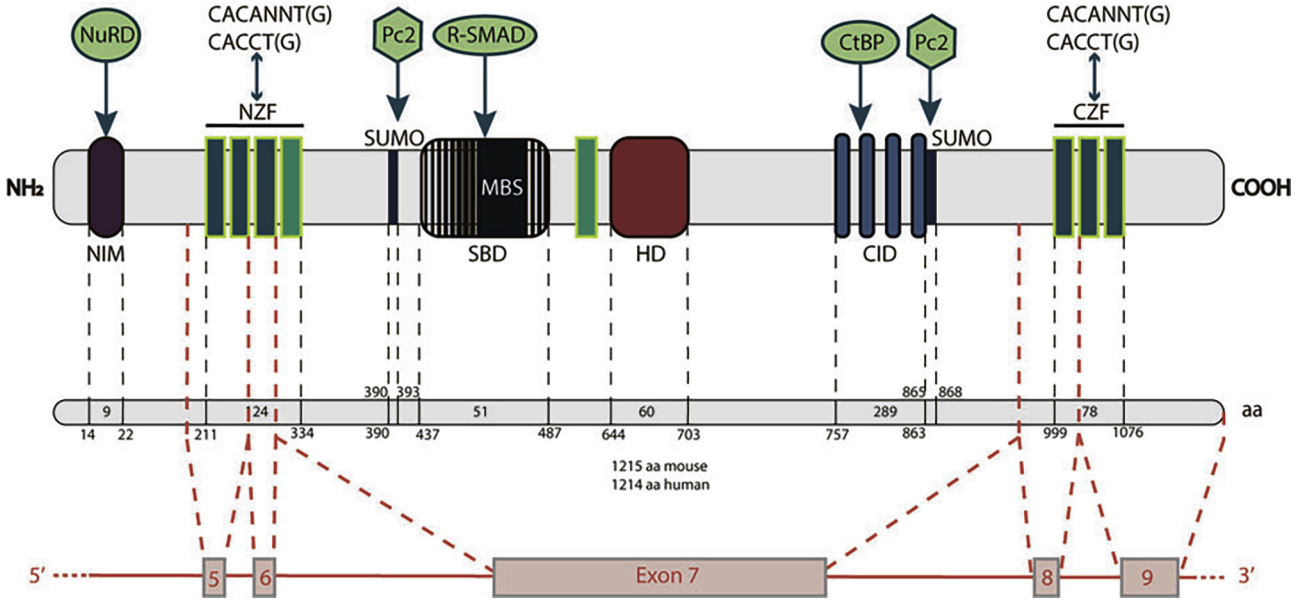

Fig. 1. Zeb2 gene and protein structure. Zeb2 contains two clusters of zinc fingers (NZF and CZF) that flank a centrally located homeodomain-like domain (HD). Between the HD and the CZF cluster, there is a segment containing 4 CtBP co-repressor interacting sequences (forming the CtBP-interacting domain, CID). Zeb2 also binds the chromatin remodeling co-repressor NuRD. Zeb2 is post-translationally modified by sumoylation (SUMO; exerted by Pc2). Zeb2 contains a R-Smad-binding domain (SBD).

Nelles et al., 2003). In contrast to most HD domain in other transcription factors, HD in Zeb2 protein does not seem to recognize specific DNA sequences. Also there are some other domains such as Smad binding domain (SBD), the CtBP interaction domain (CID) and NuRD complex interaction motif (NIM). A 51 aa-long SBD domain is necessary for interaction with phosphorylated Smad MH2 domain and it has a 14 aa minimal binding segment (MBS) which is needed for binding of both TGFβ and BMP Smads (Conidi et al., 2013b; Verschueren et al., 1999). Zeb2 binds C-terminal binding protein (CtBP) co-repressors (Postigo and Dean, 1999; van Grunsven et al., 2007) and the chromatin-remodeling/co-repressor complex NuRD (Verstappen et al., 2008). Hence, Zeb2 can act as a transcriptional activator by binding to P300/PCAF (van Grunsven et al., 2006). Zeb2 can be post-translationally modified at two sumoylation sites (K391 (SUMO 390-393) and K866 (SUMO 865-868)) by the Polycomb protein Pc2, which acts as a small ubiquitin-like modifier E3 ligase, and this can affect the repressor activity of Zeb2 (Long et al., 2005) (Fig. 1).

Zeb2 takes part in different developmental pathways and it is essential for normal embryonic development (Vandewalle et al., 2009) and has been shown to associate with a number of different Smads (Smad1, Smad2, Smad3, Smad4 and Smad5) (Verschueren et al., 1999). Smads are key mediators of TGFβ signaling. They transduce signals from cell membrane to the nucleus acting as transcriptional co-factors (Kretzschmar and Massague, 1998). There are two types of Smads: receptor-regulated Smads or R-Smad (which include Smad1, Smad2, Smad3 and Smad8) and inhibitory Smads or I-Smad (Smad6 and Smad7).

R-Smads are activated by association with TGFβ and BMP superfamilies ligand-receptor complexes, which bind common-mediator Smad (Co-Smad) or Smad4 and together they translocate to the nucleus and regulate expression of target genes (Attisano and Wrana, 2000; Heldin et al., 1997; Kretzschmar and Massague, 1998; Massague, 2012; Moustakas et al., 2001). Conversely, I-Smads prevent the activation and nuclear translocation of R-Smads and thus inhibit signal transduction. A complex of R-Smads and Co-Smads activates the transcription of target genes but Zeb2 in the presence of Zeb2 this same complex becomes a transcriptional repressor complex (Weng et al., 2012). Interestingly, in the absence of interaction with Smads, the Zeb2-p300 complex acts as a transcriptional activator (Conidi et al., 2011). Moreover, Zeb2 can activate transcription on association with Smad8 (van Grunsven et al., 2006). Also Zeb2 can indirectly negatively regulate BMP signaling through the transcriptional activation of I-Smad Smad7 (Weng et al., 2012). At the same time Smad2 can repress Zeb2 expression by binding to *Zeb2* promoter (Chng et al., 2010).

2. Zeb2 haploinsufficiency in humans is associated with Mowat–Wilson syndrome

In humans, large scale deletions on chromosome 2 (chr2q22) were found in patients with syndromic forms of Hirschprung disease. This pathology was later attributed to be due to loss of function of the *ZEB2* gene (Wakamatsu et al., 2001). Later, as more human patients with heterozygous ZEB2 deficiency were identified and characterized, this condition was named Mowat–Wilson syndrome (MWS). MWS is characterized by various malformations. The major defects appear in the CNS and PNS. They include intellectual disability, absence of corpus callosum, microcephaly, epilepsy, delayed motor development, Hirschsprung's disease. Defects outside CNS include ventricle septum defects, characteristic facial appearance and congenital heart disease (Conidi et al., 2013a; Garavelli and Mainardi, 2007; Wilson et al., 2003). These multiple effects do not appear in all MWS patients displaying a wide range of forms from severe to milder ones. In characterizing the human mutation, Zweier et al., 2003 observed that, pre- or postnatal microcephaly was identified in 97% of cases, seizures (82%), Hirschsprung's disease (67.6%), congenital heart defects (47%), agenesis of the corpus callosum (35%) and intellectual retardation and facial gestalt were found in all observed human patients. Recently, a study by Ivanovski et al. (2018) investigated the largest group of MWS patients reported to date (87). Ivanovski and colleagues observed that the characteristic facial abnormalities were found almost in all MWS cases except several patients with missense mutations. All patients suffered from varying degrees of intellectual disabilities. As well as distinctive facial appearance and mental retardation the various and frequent musculoskeletal anomalies were demonstrated. Likewise microcephaly sometimes occurred at birth and postnatally was observed only in 35.7% of patients in the range of age from 0 to 5 years. 79.6% of cases were characterized by anomalies of corpus callosum, 77.8% – hippocampal abnormalities, 68.5% – enlargement of cerebral

ventricles, 40.7% – white matter abnormalities. Epilepsy was demostrated to be one of the most frequently detected features of MWS (Ivanovski et al., 2018; Cordelli et al., 2013). The observations of Ivanovski et al are largely concordant with those of the Zweier study. Importantly, Ivanovski could distinguish more precisely how specific MWS features contributes to MWS phenotype.

As it was mentioned above, one of the most frequent MWS features is epilepsy. It is known that seizures are often associated with disturbance of interneurons development and loss of the inhibition/excitation balance in the cerebral cortex, hippocampus, striatum and amygdala (Powell, 2013). It was shown that Zeb2 is important for GABAergic interneurons migration and maturation and Zeb2 absence in interneurons leads to increase in the level of the repulsive receptor Unc5b. Abnormal numbers of interneurons can cause seizures in MWS patients (van den Berghe et al., 2013).

Various mutations in MWS patients cause either complete ablation of ZEB2 protein or they can cause the production of nonfunctional ZEB2 protein. Some symptoms can be explained by the irregular development of the structures derived from the neural crest such as peripheral and enteric neurons and glia, craniofacial cartilage, bones and connective tissue, smooth muscle cells of the cardiovascular system At the same time Hirschsprung's disease also has many symptoms that can be explained by lack of ZEB2 during development of the digestive tract neurons. This disease causes severe constipation and enlargement of the colon (Cacheux et al., 2001; Conidi et al., 2013a; Garavelli and Mainardi, 2007; Mowat et al., 1998; Mowat et al., 2003). Point mutations in *ZEB2* have been identified in 81% of MWS patients, 15% of patients had full or partial deletions of *ZEB2* gene, 2% – chromosomal rearrangements which lead to *ZEB2* disruption and 2% have intermediate-sized deletions (Adam et al., 2007). Garavelli et al. (2009) showed that frameshift and nonsense mutations in *ZEB2* were the major reason of MWS in investigated patients. This was confirmed by Ivanovski et al. (2018) who showed that full or partial *ZEB2* deletions were involved in 11.5% cases, the nonsense mutations – in 37.9%, small insertions/deletions (indels) – in 46%. Large deletions in patients range from 300 kb to 16.7 Mb, yet no correlation between phenotype and deletions up to 5 Mb has been observed suggesting minor intergenic loss in this loci is tolerable. However, larger deletions, such as the one found in a patient with 11 Mb deletion had severe phenotype characterized by early seizures with a lethal course (Ivanovski et al., 2018; Zweier et al., 2003). Mutations disrupting a splice site in ZEB2 leading to loss of the NuRD interaction motif result in a mild form of MWS (Verstappen et al., 2008). Furthermore, Wu et al. (2016) identified the atypical missense Zeb2 mutation (single residue R22G mutation) which leads to a patient phenotype with a facial gestalt reminiscent of mild MWS. It affects Zeb2 interaction with NuRD complex without affecting CtBP binding.

3. Zeb2 deficient mice as models of MWS

The model for studying the molecular mechanism of MWS is Zeb2 knock-out mouse. The excision of exon 7 of *Zeb2* generates a null allele in the mouse by premature termination of the protein caused by a frame shift in exon 8 (Higashi et al., 2002; Van de Putte et al., 2003). The first published Zeb2 knock-out model was generated by flanking exon 7 with loxP sites. The conditional exon 7 deletion was performed via crossing the Zeb2flox mouse to Cre expressing mouse (Ella-Cre) (Higashi et al., 2002). Full Zeb2 constitutive "knock-out" embryos exhibited defects starting from embryonic stage E8.5 and died at E9.5. In this model the neural tube fails to close, the sharp boundary between the neural plate and the rest of the ectoderm is absent, and the first brachial arch is missing. Homozygous mutant embryos exhibit severe growth retardation and eventually die (Van de Putte et al., 2003).

Zeb2 is widely expressed in various tissues and the conditional inactivation of Zeb2 at different time points and in different tissues using Cre recombinase under specific promoter gave an opportunity to investigate the Zeb2 role during diverse developmental events. To circumvent early embryonic lethality, different Cre lines were used to delete the gene from different tissues and cell types. To study the function of Zeb2 in the dorsal telencephalon, Emx1-Cre, Nex-Cre and Nestin-Cre lines were used. *Zeb2* expression in the dorsal telencephalon is detected from E12.5 in young postmitotic cells, but not in the progenitors. Conditional deletion of Zeb2 in the dorsal telencephalon strongly affects the development of the hippocampus as well as corpus callosum. This phenotype is also reported for MWS patients (Miquelajauregui et al., 2007; Nityanandam et al., 2012). The neural crest-specific knockout of the *Zeb2* gene (driven by Wnt-cre) results in craniofacial and gastrointestinal malformations that show resemblance to human patients with Mowat–Wilson syndrome, and it results in developmental defects in the heart, melanoblasts and sympathetic and parasympathetic anlagen (Van de Putte et al., 2003). Heterozygous deletion of exon7 of *Zeb2* gene with Protamine-Cre (Prm-Cre Tg), that specifically expresses Cre recombinase in the male germ cells, leads to multiple defects relevant to MWS, including craniofacial abnormalities, defective corpus callosum formation and the decreased number of parvalbumin interneurons in the cortex. In behavioral tests, these mice demonstrated reduced motor activity, increased anxiety and impaired sociability (Takagi et al., 2015). Interestingly, MWS patients have one functional copy of Zeb2, while in most conditional knock-out mouse models of Zeb2, the phenotype is present in homozygous null mice, very few defects are reported for heterozygous mice. Takagi et al., 2015 reported that the MWS features in described above mouse models depend on the genetic background of the mouse line. There is, for example, backcrossings of Zeb2 Δex7/+ mice with a mixed genetic background as the inbred C57BL/6 was problematic due to the gradual appearance of growth retardation. Zeb2 mouse with CD1 background show decreased thermal pain responses and do not show defects related to MWS symptoms. De novo Zeb2 Δex7/+ mice with the ICR background did not show the abnormal skull phenotype and the reduced motor activities observed in the de novo Zeb2 Δex7/+ mice with the C57BL/6 background. Results of Takagi et al. (2015) suggest that an inbred C57BL/6 strain is better suitable for generating Zeb2 Δex7/+ mice as the MWS animal model (Takagi et al., 2015). Bluntly, a universal model of MWS encompassing all MWS features and defects doesn't exist. Taking into account that MWS is characterized by different defects which are not present in all MWS patients it makes it difficult to create a universal model. That fact accounts for a variety existing Zeb2 mouse models (see Table 1).

4. Role of Zeb2 in nervous system formation and development

4.1. Zeb2 is essential for neural tube and neural crest formation

Zeb2 plays an important role in neural tube patterning where it regulates a number of key genes. Knockout of Zeb2 leads to failure of neural tube closure, and the absence of a sharp boundary between the neural plate and the rest of the ectoderm (Van de Putte et al., 2003). In the development of the neural crest Zeb2 seems to act by limiting BMP-Smad signaling at the border between epidermal ectoderm and neuroectoderm (Hegarty et al., 2013). One of the important Zeb2 downstream targets is adhesion molecule Cdh1 (Also known as E-cadherin). An important step in the neural crest development is epithelial-to-mesenchymal transition (EMT). Zeb2 seems to be one of the main regulators of EMT. Epithelial cells of the neural crest undergo two distinct phases of EMT, detachment and mesenchymalization. This step seems to require Zeb2 mediated repression of Cdh1. Zeb2 is it is expressed in pre-migratory/migrating crest cells and seems to be a key regulator that promotes the neural crest cell transition to a mesenchymal state. After Zeb2 loss, the neural crest specifier gene *FoxD3* becomes abnormally retained in the dorsal neuroepithelium, whereas *Sox10,* which is normally required for migration, becomes diminished (Rogers et al., 2013). Cdh1 is required for cell-cell adhesion between the neural crest cells while Zeb2 is necessary for neural crest dissociation (Simoes-Costa and

Table 1
Described Zeb2 knockout mouse models.

Knockout model		Description	Background
Sip1$^{-/-}$	Constitutive deletion of Zeb2 exon 7	Created by Higashi et al. (2002). Knockout mice showed cranial neural crest cells delamination and migration arrest, failure of neural tube closure, lack of postotic vagal neural crest cells development (Van de Putte et al., 2003).	CD1/C57/BL6
Sip1$^{flox(ex7)}$	Conditional inactivated Zeb2 mutant	Created by Higashi et al. (2002).	CD1/C57/BL6
	Wnt1–Cre	Zeb2$^{flox(ex7)}$ were crossed with Wnt1–Cre transgenic mice in order to enable recombination in neural crest precursor cells. This mutant showed malformations in gastrointestinal, craniofacial, cardiovascular, sympathetic and parasympathetic systems and melanoblasts formation (Van de Putte et al., 2007).	CD1/C57/BL6
	Emx1-Cre	Emx1-Cre mouse line was used to inactivate Zeb2 function specifically in the dorsal telencephalic precursors. These mice demonstrated lack of corpus callosum and hippocampal formation, abnormal astrocytogenesis and cortical layering (Miquelajauregui et al., 2007; Seuntjens et al., 2009; Nityanandam et al., 2012).	CD1/C57/BL6
	Nex-Cre	Nex-Cre approach was used to delete Zeb2 in dorsal telencephalic postmitotic cells. Mice exhibited the disturbed cortical neuronal layering, neocortical axonal growth and astrocytogenesis (Seuntjens et al., 2009; Nityanandam et al., 2012; Srivatsa et al., 2015).	CD1/C57/BL6
	Nestin-Cre	Nestin-Cre was used to delete Zeb2 in the entire mouse CNS. Sip1/Nestin mice died at birth and they demonstrated abnormal cortical neuronal layerin and interneurons migration failure (Seuntjens et al., 2009; van den Berghe et al., 2013).	CD1/C57/BL6
	Brn4-Cre	Brn4-Cre was used to restrict Zeb2 expression to presence in neural progenitors and absence in differentiating neurons. Loss of Zeb2 led to reduction of the number of preganglionic column motoneurons (Roy, 2012)	CD1/C57/BL6
	Nkx2.1-Cre	To remove Zeb2 in the early progenitors of the medial ganglionic eminence the Nkx2.1-Cre was used. These mice demonstrated switch between cortical interneurons and a subtype of GABAeric striatal interneuron and Zeb2 knockout interneurons migration failure (McKinsey et al., 2013; van den Berghe et al. (2013).	CD1/C57/BL6
	DlxI1/2b-Cre	DlxI1/2b-Cre drives Cre expression in the subventricular and mantle zones of the entire subpallium. In these mice cells which were supposed to become cortical interneurons transform towards a subtype of GABAeric striatal interneuron (McKinsey et al., 2013).	CD1/C57/BL6
	Dlx5/6-Cre	Dlx5/6-Cre produces Cre in the entire ventral telencephalon, except the ventricular zone, and it led to abnormal cortical GABAergic interneurons migration (van den Berghe et al., 2013).	CD1/C57/BL6
	Gsh2-Cre	Gsh2-Cre targets partially medial and completely lateral and caudal ganglionic eminences. Mice showed abnormal cortical GABAergic interneurons migration and seizures (van den Berghe et al., 2013).	CD1/C57/BL6
	Olig1-Cre	*Olig1-Cre* line produces Cre in the oligodendrocyte lineage. Zeb2 loss leads to absence of mature oligodendrocytes, disruption of myelin formation in the central nervous system, seizures (Weng et al., 2013; He et al., 2018).	CD1/C57/BL6
	hGFAP-Cre	GFAP-Cre promotes Cre expressed in cerebellar radial glia or neural stem/progenitors. Mice lacking *Zeb2* exhibit severe deficits in Bergmann glia specification (He et al., 2018).	CD1/C57/BL6
Sip1 −/−; δEF1 −/−	Zeb2/Zeb1 constitutive double knockout	Sip1 −/− was created by Higashi et al. (2002). δEF1 −/− (Takagi et al., 1998). The double-heterozygous mice were smaller than wild-type mice and suffered from closure of the vaginal orifice. Also Sip1flox(ex7)/+; δEF1 −/+;Zp3(zona pellucida 3)-Cre mice were used to improve the efficiency of generating double homozygous. Double homozygous mice developed similar phenotype to Sip1 −/− embryos but exhibited more severe defects in dorsal neural tube morphogenesis (Miyoshi et al., 2006).	ICR
Zeb2 +/−; Sox10 +/−		Double mutants exhibit abnormal enteric nervous system development (Stanchina et al., 2010).	CD1/C57/BL6 or C3HeB/FeJ
Zeb2$^{\Delta ex7/+}$	De-novo inbred heterozygous mutant	De novo Zeb2 Δex7/+ mice were produced by Takagi et al. (2015) by applying an inducible de novo mutation system to the germline cells. These mice with the C57BL/6 background exhibited multiple defects that are typical MWS, such as craniofacial defects, reduced number of parvalbumin interneurons in the cortex, agenesis of corpus callosum (Takagi et al., 2015).	C57/BL6
		De novo Zeb2 Δex7/+ mice with the ICR background did not show the abnormal skull phenotype and the reduced motor activities observed in the de novo Zeb2 Δex7/+ mice with the C57BL/6 background (Takagi et al., 2015).	ICR

Bronner, 2015). At E8.5 Zeb2 is expressed in two major populations of cells in the neural plate. One is the neuroepithelium, where expression levels closely follow the maturation of the neural plate. Another one is the neural crest. High levels of Zeb2 transcripts are detected in pre-migratory and migrating neural crest cells of cranial and postotic vagal origin and in the branchial arch mesenchyme. Zeb2 knockout mice do not form vagal neural crest cells, which are the precursors of the enteric nervous system that is affected in Hirschsprung's disease patients. Mice demonstrate a delamination arrest of cranial neural crest cells, which form the skeletomuscular elements of the vertebrate head. This suggests that Zeb2 is key regulator for the development of vagal neural crest precursors and the migratory behavior of cranial neural crest in the mouse (Van de Putte et al., 2003). The neural crest-specific knockout of the *Zeb2* gene (driven by Wnt-cre) also leads to defective derivatives of cranial and vagal neuronal crest precursors (Van de Putte et al., 2007). It has been shown that fibroblast growth factor (Fgf) induces the formation of definitive neural stem cells in the mouse neuroectoderm through the upregulation of Zeb2 and Sox2 (Dang and Tropepe, 2010). All published data indicate that Zeb2 is one of the key molecules that control formation of the neural tube and neural crest.

4.2. *Zeb2 in the differentiation of the hippocampal neurons*

In the developing neocortex and hippocampus Zeb2 is highly

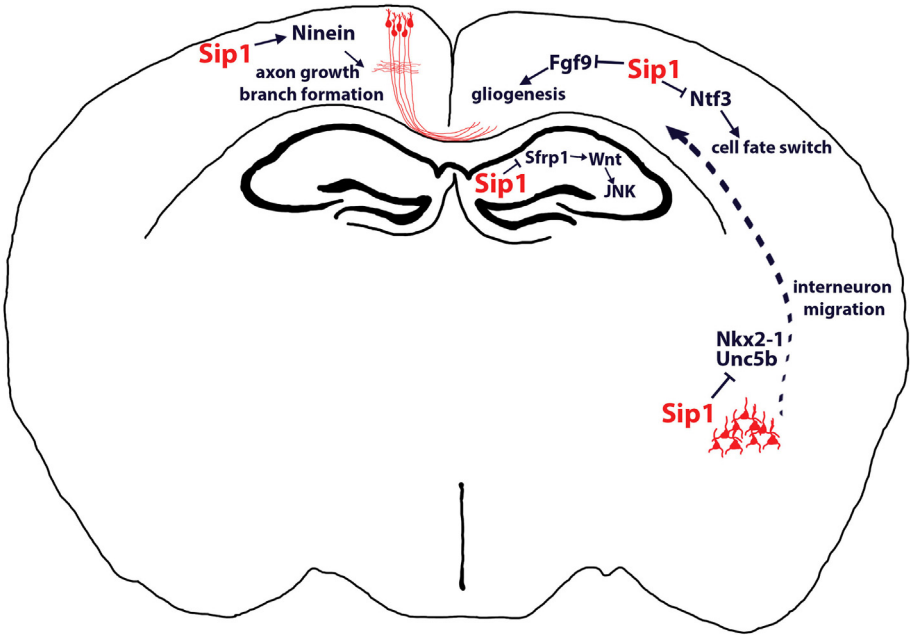

Fig. 2. Zeb2 targets in the developing forebrain. Zeb2 has different downstream targets which activation or downregulation lead to different molecular events in the brain. Thus, ninein activation by Zeb2 cause the corpus callosum formation, axonal branching and cortico-spinal tract formation. On the other hand, Zeb2 acts as a repressor in the neocortex in case of Fgf9 and Ntf3, which regulate gliogenesis and cell fate switch respectively. At the same time Zeb2 downregulates the Sfrp1 expression in hippocampus. Moreover, Zeb2 blocks two downstream targets Nkx2-1 and Unc5b in order to control the cortical interneurons migration.

expressed in postmitotic cells, although a low level of expression was also found in the proliferative compartment of the ventricular zone (Fig. 2). Development of the hippocampus is severely affected in mutant mice where Zeb2 is deleted throughout the entire telencephalon (Miquelajauregui et al., 2007). In these mice the initial patterning and development of the hippocampus was not affected. However, at later stages of hippocampal development, CA1 and CA3 fields (the major pyramidal cell fields in the hippocampus) were reduced in size. In three week old animals the entire hippocampus was no longer present. It was shown that this progressive degeneration of the hippocampus was caused by increased apoptotic cell death of young hippocampal neurons. Interestingly, while proliferation rates of hippocampal progenitors do not seem to be affected by Zeb2 deletion, the proliferation of cells in the Secondary Proliferative Population (SPP), the region responsible for proliferation of the dentate gyrus cells, was decreased. Deficiencies in the development of the hippocampal formation in Zeb2 mutant mice were similar to those reported in mice deficient in components of the Wnt signaling pathway (Lee et al., 2000). Miquelajauregij et al. had performed transcriptomics analysis to identify a direct cause of hippocampal degeneration. Among other targets they identified a negative extracellular regulator of Wnt signaling, Sfrp1 (Secreted Frizzled-Related Protein-1) to be upregulated in hippocampal formation of Zeb2 mutants (Miquelajauregui et al., 2007). Normally, Sfrp1 is expressed in both proliferating and postmitotic cells in the neocortex, but not in the hippocampus. In the Zeb2 mutants the border of Zeb2 expression is shifted more medially. The up-regulation of Zeb2 in the hippocampus coincided with decreased activity of one of the effectors of non-canonical Wnt, of JNK (c-Jun N-terminal kinase) (Davies and Tournier, 2012). As JNK deficiency in the forebrain causes apoptotic cell death, the authors concluded that Zeb2 prevents cell death in the hippocampus by negative regulation of inhibitor of non-canonical Wnt, the Sfrp1. Zeb2 juvenile mutant mice also show a lateral ventricle enlargement, the hydrocephalus, but the molecular mechanism of this phenotype was not investigated. Although the morphology of choroid plexus, the structure that often causes overproduction of ventricular fluid seemed to be normal, the function of choroid plexus might be affected by Zeb2 mutation (Miquelajauregui et al., 2007).

4.3. Role of Zeb2 in gliogenesis

Zeb2 also plays important role in generation of glial precursors and postnatal astrocytogenesis in the cerebral cortex. Gliogenesis in the mouse neocortex starts at embryonic stage E17.5 and it coincides with end of neurogenesis. *Zeb2* deletion in neocortical postmitotic cells causes the premature end of neurogenesis which causes enhanced proliferation of Olig2 positive glial precursors and that in turn leads to the production of higher numbers of astrocytes at early postnatal stages (Seuntjens et al., 2009). This coincides with depletion of Tbr2 positive progenitors in the SVZ (Seuntjens et al., 2009). It is known that Tbr2 is an indicator of neuronal commitment (Arnold et al., 2008).

The premature gliogenesis in Zeb2 deficient brains coincides with upregulation of fibroblast growth factor 9 (Fgf9) at E15.5. Normally, Fgf9 is expressed in the developing CP, but at relatively low level at E15.5. Its expression is higher at later stages, E17.5 that coincides with the onset of gliogenesis as well as with decrease of Zeb2 expression. The addition of Fgf9 to cortical slices enhances gliogenesis and can mimic this aspect of Zeb2 mutant phenotype in the neocortex. Interestingly, even localized addition of Fgf9 loaded beads can cause excessive gliogenesis in the VZ. This is another indication that RG cells can sense the changes in the CP environment, possibly by their long processes and can switch from neurogenic to gliogenic divisions. Therefore, Zeb2 seems to control two phases of CP to VZ feedback, DL to UL switch on one hand and switch from neurogenesis to gliogenesis. (Seuntjens et al., 2009).

Zeb2 mutation also seems to affect postnatal development of stem cells in the dorsal telencephalon. It was shown that during early postnatal stages, the dorsal neocortical SVZ in Zeb2 mutants harbors an excessive pool of progenitors that differentiate into GFAP positive Type-B-like astrocytes. These cells populate the the glial tube-the part of the rostral migratory stream. Rostral migratory stream is a structure that contains stem cells migrating towards olfactory bulb. It is surrounded by the glial cells whose number and specification is regulated non-cell autonomously by the expression of Zeb2 in postmitotic cortical neurons during development (Nityanandam et al., 2012)

Zeb2 also participates in differentiation of oligodendrocytes. It was shown that Zeb2 loss disturbs oligodendrocyte differentiation and this can be partially rescued by Zeb2 target overexpression – *Smad7*. Normally Smad 7 induces myelination by blocking the b-catenin and BMP negative regulatory pathways. Moreover Zeb2 is essential for oligodendrocyte precursor cells maturation and Zeb2 loss prevents oligodendrocyte precursor cells from further differentiation (Weng et al., 2012). It was shown by He et al. (2018) that Zeb2 is highly

expressed in Bergmann glia cells. In contrast, Zeb2 is hardly detectable in cerebellum astrocytes. Zeb2 ablation in the cerebellum leads to disturbance of granule neuron progenitors migration, reduction of glial precursors proliferation and failure of radial glia differentiation into Bergmann glia in the Purkinje cell layer (He et al., 2018).

Moreover, Zeb2 regulates oligodendrocyte differentiation, as mutant cells fail to fully differentiate and produce myelin (Weng et al., 2012). Schwann cells are the major glia of peripheral nervous system which are important for survival and function of neurons. They participate in axons myelination, neuronal guidance and cellular waste removal. There are two types of Schwann cells – myelinating and non-myelinating. Differentiation of Schwann cells is controlled by various transcription factors such as Sox10, Gap43, p75, S100, Krox20, Oct6 (Bhatheja and Field, 2006). Recently it was shown that Zeb2 also plays an important role in controlling Schwann cells maturation. It recruites histone deacetylase 1/2 (HDAC1/2)–nucleosome remodeling deacetylase (NuRD) co-repressor complex and inhibites a Notch–Hey2 signaling axis (Weng et al., 2012). Zeb2 acts as a canonical transcriptional repressor via inhibiting the negative regulators of Schwann cells maturation Sox2 and Ednrb (Quintes et al., 2016). Moreover Zeb2 expression is necessary for myelination and it participates in myelin repair (Weng et al., 2012). Zeb2 is expressed in neural crest cells-precursors of Schwann cells, as well as in peripheral nerves. The onset of expression takes place before myelination in development and during remyelination after nerve injury. Downregulation of Zeb2 in mice leads to severe peripheral neuropathy, caused by failure of axonal sorting and virtual absence of myelin membranes. Also it was reported that lack of Zeb2 causes a complete arrest of Schwann cell maturation and leads to a myelin-deficient phenotype. However, Zeb2-deficient Schwann cells survive in vivo, provide axonal integrity but fail to efficiently support nerve regeneration myelinate peripheral nerve axons (Quintes et al., 2016).

4.4. Role of Zeb2 in the development of interneurons

Zeb2 participates in development of not only pallial (cortical and hippocampal) neurons but striatal interneurons too. In mice, cortical interneurons arise from the medial and caudal ganglionic eminences and preoptic area (Fogarty et al., 2007; Miyoshi et al., 2007). *Zeb2* subpallial expression is directly positively regulated by Dlx1 and Dlx2 transcription factors, and is required in the medial ganglionic eminences to generate cortical interneurons that express Cxcr7, MafB and cMaf. Zeb2 is required for switching differentiation program in the medial ganglionic eminences. If *Zeb2* is deleted, expression of Nkx2.1 transcription factor is not down-regulated, and cells that would become cortical interneurons upon Nkx2.1 inactivation, appear to transform towards a subtype of GABAergic striatal interneurons. (McKinsey et al., 2013).

On the other hand, Zeb2 is also expressed in migrating cortical interneurons and it is required for their correct migration. Zeb2 deficient interneurons fail to migrate to the neocortex and stall in the ventral telencephalon. This coincides with upregulation of Unc5b receptor and the effect can be rescued by reducing the levels of Unc5b (van den Berghe et al., 2013).

4.5. Zeb2 as a regulator of midbrain dopaminergic neurons

Midbrain dopaminergic neurons are one of the major catecholaminergic neuronal populations in the brainstem. Midbrain dopaminergic neurons project axons to the striatum and play an essential role in controlling of voluntary movement, reward and working memory (Hegarty et al., 2017; Roeper, 2013). Zeb2 mRNA expression occurs during the period of striatal innervation. It was shown that Zeb2 downregulation leads to dopaminergic hyperinnervation of the striatum that correlates with BMP signaling repression during nervous system development by Zeb2. At the same time it didn't affect the numbers of midbrain dopaminergic neurons. Zeb2 negatively regulates axon growth and target innervation of dopaminergic neurons. Thus, Smad signaling is repressed by Zeb2 in order to limit midbrain dopaminergic neurons growth and target innervation (Hegarty et al., 2017).

4.6. Cell intrinsic role of Zeb2 in the differentiation of neocortical pyramidal neurons

Zeb2 also controls another critical developmental process, the formation of neocortical projections. MWS patients with have agenesis of corpus callosum, the major axonal tract connecting two cerebral hemispheres. In the mouse model, Nex-Cre driven Zeb2 "knock-out" multiple cortical axonal tracts are affected. Zeb2-deficient mice do not form corpus callosum, anterior commissure, and corticospinal tract, while the corticothalamic tract does not seem to be affected. Loss of Zeb2 affects the rate of growth of axons but does not seem to affect the axonal navigation (Srivatsa et al., 2015). Branching of neocortical axons is also affected by *Zeb2* mutation. Normally, neocortical axons branch at specific locations in order to form synapses with multiple targets and establish correct neocortical circuitry (O'Leary and Terashima, 1988). Interhemispheric callosal axons of UL neurons after they cross over to the contralateral hemisphere by P0, start intracortical branch formation at P4 in the mouse. Zeb2 controls the timing of the ipsilateral axon collateral formation aiding in the establishment of intracortical connections as well (Srivatsa et al., 2015). The average length of the axon of Zeb2-deficient neurons was significantly shorter when compared to wild-type neurons. This effect seems to be dependent on Zeb2 cell in a cell-autonomous manner (Srivatsa et al., 2015). Microtubule (MT) dynamic and stability is decreased in Zeb2 mutant neurons and this effect is cell autonomous.

Both axonal outgrowth and branch formation defects detected in Zeb2 deficient neurons seem to be dependent on Zeb2 target ninein. Ninein is a microtubule-associated (MT) protein that was initially identified as a centrosome-associated protein acting at MT minus end to help anchor the MTs to the centrosome (Bouckson-Castaing et al., 1996). However, Ninein function is not restricted to proliferative compartment in the brain. It is strongly expressed in both the VZ and in the CP with no laminar restriction. Expression of ninein protein was also detected within the WM. Zeb2 directly binds the ninein enhancer and activates the expression of ninein in the cortex (Srivatsa et al., 2015). In addition to localizing to the dendrites and the soma (Ohama and Hayashi, 2009), ninein also localizes to axons and axonal branches. Ninein in the axons seem to act as a stabilizer of MT. Restoration of the ninein expression in the Zeb2-deficient neurons can partially rescue both the stability and dinamics of MT and restore all defects of axonal outgrowth in Zeb2 mutants: corpus callosum agenesis, delayed branching and cortico-spinal tract formation. Zeb2-deficient UL neurons, on expression of ninein, are able to form ipsilateral axonal collaterals at the level of layer V neurons, similar to the controls (Srivatsa et al., 2015).

It was shown by (Turovskaya et al., 2017) that Zeb2 plays an important role in the maintaining the activity of NMDA-, AMPA- and KA-receptors. Zeb2 deletion in the mouse causes changes in the activity of both NMDA- and AMPA-receptors in the neocortical neurons in vitro. Neurons from Zeb2 mutant mice demonstrate higher resistance to receptor agonists. There are lower amplitudes of $Ca2+$-responses which takes a higher concentration of receptor activators. At the same time, it is interesting that Zeb2 hererozygous cells cortical neurons are more sensitive to both NMDA- and AMPA-receptors agonists (Turovskaya et al., 2017). The molecular basis of this phenotype is not described and requires further investigation.

4.7. Zeb2 regulates cell fate in the developing neocortex by a feedback signaling

Similar to developing hippocampus, in the developing neocortex

Zeb2 is produced at high levels in postmitotic neocortical neurons and at low levels in the neocortical progenitors. When the phenotype of Zeb2 mutants was analyzed in the neocortex, it was shown that lack of Zeb2 causes premature generation of upper layer pyramidal neurons at expense of deep layer neurons. Not only Zeb2 deletion affected the proportion of neocortical cells but also the normal onset of the cell fate switch (Seuntjens et al., 2009). The laminar fate of newly born neocortical neurons depends on their birth time in the VZ. Cell fate specification in the neocortex follows “inside-out” gradient of development, so that Deep Layer (DL) neurons of layers V-VI are born first, followed by Upper Layer (UL) cells of layer IV later by layer II-III neurons (Rubenstein, 2011). The peaks of production of layer V neurons as well as layer II-IV neurons in Zeb2 mutants took place one-two days earlier then normally expected. On the other hand, the onset of neurogenesis and the onset of production of layer VI neurons were not affected (Seuntjens et al., 2009). These experiments were performed with Emx1-Cre as a deleter. In this line Cre recombinase is active early on in all dorsal telencephalon progenitors. In order to discriminate between the roles of Zeb2 in the progenitors and postmitotic cells, the authors used another line, Nex-Cre. In this line the pattern of Cre activity is similar to that of Emx1-Cre, except that the Cre is not active in the progenitors. Unexpectedly, the phenotype of both Zeb2 conditional mutants was nearly identical as far as neocortical cell fate was concerned. This suggested that the role of Zeb2 in the neurogenesis was cell extrinsic rather than cell intrinsic. The authors hypothesized that there is a Zeb2 controlled “feedback” signaling between young neurons in the cortical plate (CP) and progenitors in the VZ (Seuntjens et al., 2009). The authors suggested that Zeb2 restrains the production of certain signaling factors in postmitotic neurons that feed back to progenitors to regulate the timing of cell fate switch and the number of neurons of different cell types throughout corticogenesis. The premature upper-layer generation in Zeb2 mutants coincided with overexpression of the neurotrophin-3 (*Ntf3*) gene. It was shown that Zeb2 directly binds to the *Ntf3* promoter region. and that *Ntf3* overexpression in young neocortical neurons has a strong effect on neocortical progenitors and caused an expansion of basal neocortical progenitors in the SVZ with simultaneous decrease in apical progenitors in the VZ (Parthasarathy et al., 2014). SVZ located basal progenitors seem to contribute to UL neuronal production (Haubensak et al., 2004). Since (Parthasarathy et al., 2014) restricted Ntf3 expression to postmitotic neurons, and the effect was detected in the progenitors, it served as a good indication that Zeb2 mediated feed-back signaling indeed acts via regulation of Ntf3 levels. The authors suggested that the high levels of Ntf3 can be detected by long basal processes of Radial Glia cells that are the main neocortical stem cells. Therefore the unique structure of RG cells with their long basal process could serve not only classical guidance function for radial migration, but also be a “detector” of cell numbers of certain types in the cortical plate.

5. Conclusion

To sum up, Zeb2/Sip1 is an important regulator of neuronal development. Mutations in Zeb2 cause the Mowat-Wilson syndrome in humans, which is characterized, in the first instance, by severe mental retardation, various intellectual disorders, craniofacial abnormalities and also by various defects such as absence of corpus callosum, microcephaly, epilepsy, delayed motor development, Hirschsprung’s disease. Mutation of Zeb2 in the mouse has pleiotropic effect. It is essential for normal differentiation of almost all neuronal cell types where it is expressed and that have been investigated so far. Zeb2 contributes to the formation of the hippocampus, neocortex, corpus callosum, rostral migratory stream. It also controls the generation of intracortical, intercortical, and cortico-subcortical connections in the forebrain. Moreover, Zeb2 regulates the gliogenesis, Schwann cell differentiation, myelination and nerve repair. The investigation of Zeb2 participation in nervous system development and formation is a key for understanding of MWS pathogenesis. By now there are still some unknown molecular pathways, interactions and biological processes controlled by Zeb2. Further studies can help understanding it and potentially identify treatment approaches of MWS patients and in the future.

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