An emerging role for \textit{prdm} family genes in dorsoventral patterning of the vertebrate nervous system

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Abstract

The embryonic vertebrate neural tube is divided along its dorsoventral (DV) axis into eleven molecularly discrete progenitor domains. Each of these domains gives rise to distinct neuronal cell types; the ventral-most six domains contribute to motor circuits, while the five dorsal domains contribute to sensory circuits. Following the initial neurogenesis step, these domains also generate glial cell types—either astrocytes or oligodendrocytes. This DV pattern is initiated by two morphogens—Sonic Hedgehog released from notochord and floor plate and Bone Morphogenetic Protein produced in the roof plate—that act in concentration gradients to induce expression of genes along the DV axis. Subsequently, these DV-restricted genes cooperate to define progenitor domains and to control neuronal cell fate specification and differentiation in each domain. Many genes involved in this process have been identified, but significant gaps remain in our understanding of the underlying genetic program. Here we review recent work identifying members of the \textit{Prdm} gene family as novel regulators of DV patterning in the neural tube. Many \textit{Prdm} proteins regulate transcription by controlling histone modifications (either via intrinsic histone methyltransferase activity, or by recruiting histone modifying enzymes). \textit{Prdm} genes are expressed in spatially restricted domains along the DV axis of the neural tube and play important roles in the specification of progenitor domains, as well as in the subsequent differentiation of motor neurons and various types of interneurons. Strikingly, \textit{Prdm} proteins appear to function by binding to, and modulating the activity of, other transcription factors (particularly \textit{bHLH} proteins). The identity of key transcription factors in DV patterning of the neural tube has been elucidated previously (e.g. the \textit{nkx}, \textit{bHLH} and \textit{pax} families), but it now appears that an additional family is also required and that it acts in a potentially novel manner.

Keywords: Neural tube, Dorsoventral patterning, Transcription, Neural progenitor, \textit{Prdm} gene family

Introduction

Function of the adult central nervous system (CNS) relies on neural circuits to control activity. In order for such circuits to form, neurons must develop at the right time and place of the CNS during embryogenesis. A very elaborate genetic program is responsible for this process along both the head-to-tail (anteroposterior; AP) and back-to-front (dorsoventral; DV) axes of the CNS. In terms of the DV axis, secreted factors (Sonic hedgehog and Bone morphogenetic protein) initially establish gradients that are sensed by progenitor cells in the developing neural tube. Depending on their location in the gradient, different progenitor cells initiate the expression of different genes, leading to a pattern of gene expression along the DV axis. These genes subsequently refine the pattern by repressing each other’s expression, as well as by activating the expression of additional genes (e.g. neurotransmitters and their receptors) that define different types of neurons (e.g. GABAergic versus glutamnergic). Some genes involved in this process are known, but this review focuses on a new class of genes—the \textit{Prdm} family—that appears to control gene expression during the formation of neurons along the embryonic DV axis.
**Review**

**Pordm family proteins as regulators of gene expression**

The Pordm family of proteins has only been recognized relatively recently (reviewed in [1, 2]). Proteins in this family are defined by an N-terminal PR domain, as well as by a varying number of zinc fingers (or, potentially, zinc knuckles). The PR domain was named after its initial identification in the Positive regulatory domain I-binding factor 1 (formerly PRDI-BF1/Blimp-1, now Pordm1) and the Retinoblastoma protein-interacting zinc finger protein 1 (formerly Riz1, now Pordm2) factors [3–6]. While Pordm proteins may function differently in distinct contexts, emerging evidence suggest that these factors act to regulate gene expression.

The PR domain is related to the SET domain—a catalytic domain with histone lysine methyltransferase (HMT) activity named after the Su(var)3–9, Enhancer of zeste and Trithorax proteins—but the PR domain has diverged significantly from SET domains. In particular, most PR domains lack the H/RxxNHxC motif required for methyltransferase activity ([7]; reviewed by [1]). Accordingly, many Pordm proteins appear to lack intrinsic HMTase activity ([8–11] reviewed by [2]). Nevertheless, Pordm2, Pordm8, and Pordm9 have been reported to possess intrinsic HMT activity [2, 12–15], although the details of the catalytic mechanism are unclear. Strikingly, Pordm2 and Pordm8 methylate histone H3 on lysine 9 (H3K9), a modification associated with heterochromatin formation and transcriptional repression, whereas Pordm9 directs formation of H3K4me3—a modification associated with transcriptional activity [13–15]. Hence, Pordm proteins may mediate transcriptional activation or repression depending on the nature of their intrinsic HMT activity. Of the Pordm proteins that are enzymatically inactive, many are instead able to recruit histone-modifying enzymes and transcription regulatory factors via protein-protein interactions. Enzymes recruited in this manner include HMTs, the Polycomb repressive complex 2 (PRC2), protein methyltransferase 5 (Prmt5), lysine specific demethylase 1 (Lsd1), as well as histone deacetylases (HDACs) and histone acetyltransferases (HATs) [10, 16–22] (reviewed in [1, 2]). For example, Pordm1, Pordm5, Pordm6 and Pordm12 all function with the G9a HMT [2, 8–10, 23] and Pordm3 with the Suv39H1 HMT [24] to methylate H3K9 and promote repression. Pordm1 can also function with Prmt5 to methylate H2AR3 and H4R3 [17]. Some Pordm family members require their zinc fingers for recruitment of histone modifying enzymes, while others (such as Pordm1 and Pordm3) also make use of a proline-rich domain [1, 25, 26]. Additionally, transcriptional regulators can be recruited by Pordm proteins, such as the recruitment of Groucho by Pordm1, and the recruitment of CtBP by Pordm2, Pordm3 and Pordm16 ([27–34], reviewed [1]). Hence, Pordm proteins appear to function by modulating gene expression states either directly (via intrinsic HMTase activity), or indirectly (via recruitment of various cofactors).

In order to affect gene expression, Pordm proteins need to access genomic sites in chromatin. Accordingly, Pordm1, Pordm3, Pordm5, Pordm9, Pordm13, Pordm14, and Pordm16 bind DNA directly in a sequence dependent manner via their zinc-finger domains ([9, 35–43] reviewed in [1, 2]). While many Pordm proteins have only been tested for DNA binding using in vitro systems, ChIP-seq experiments (chromatin immunoprecipitation using Pordm-specific antibodies followed by deep sequencing) have also identified genomic binding sites for a subset of Pordm factors (Pordm1, Pordm3, Pordm13, and Pordm14) [35, 37, 41, 43–46]. Pordm members that do not bind DNA directly instead appear to utilize binding partners to indirectly associate with DNA, as in the case of Pordm8 accessing DNA by binding together with Bhlhb5 in the developing nervous system [47] and Pordm16 binding with C/EBPβ to promote brown adipose tissue [48]. Again, the zinc finger motifs, as well as proline-rich domains and zinc knuckles, are likely to mediate binding of Pordm proteins to partner proteins to facilitate access to genomic sites. Based on their association with DNA (directly or indirectly), as well as their ability to modify histones (directly or indirectly) and recruit transcriptional regulators, it is likely that Pordm family proteins function to regulate gene expression states. Indeed, Pordm factors appear capable of activating or repressing target genes depending on the specific context—as reported for Pordm1 and Pordm2 [49, 50]. Pordm proteins have been reported to function in numerous settings, including hematopoiesis, adipogenesis and the maintenance of stem cell identity (reviewed by [1, 2]). More recently, several studies have indicated a central role for Pordm factors in the establishment of neuronal cell fates, particularly in the forming hindbrain and spinal cord.

**Multiple roles for Pordm proteins in dorsoventral patterning of the neural tube**

Shortly after neural tube closure, the neuroepithelium undergoes extensive transformations, including cell proliferation and specification, to give rise to various neuronal and glial cell types necessary for motor and sensory circuits. This process requires several steps (Fig. 1): First, gene expression is initiated along the dorsoventral (DV) axis of the neural tube in response to morphogen gradients. Second, these domains are refined and discrete gene expression boundaries established by complex regulatory interactions among many genes. Third, distinct neuronal and glial cell types are specified and differentiate from each progenitor domain. Strikingly, emerging data suggest that each of these steps may be under the control, at least in part, of Pordm family genes (Table 1).
**Prdm genes are expressed in discrete domains along the DV axis of the neural tube** Studies in several vertebrate species have demonstrated a critical role for Sonic Hedgehog (Shh) in patterning of the ventral neural tube and in specification of ventral neuronal cell types. Specifically, Shh is a morphogen secreted from the notochord and floor plate that—along with factors such as Chordin and Noggin that oppose the dorsally expressed BMP morphogen (see below)—induces gene expression in the ventral neural tube (reviewed by [51–53]). This has been demonstrated experimentally by overexpression of Shh in vivo and by application of exogenous Shh to neural tube explants in culture, as well as by inhibiting Shh signaling using neutralizing antibodies or germ line knock outs [54–63]. The Shh gradient subdivides the neural tube into distinct DV progenitor domains by regulating the expression of different genes at different thresholds of Shh signaling ([64–68]; Fig. 1). In particular, Shh activates genes such as Nkx6.1, Nkx6.2, Nkx2.2, and Olig2, while it represses genes such as Pax3, Pax6, Pax7, Dbx1, Dbx2 and Irx3 [63–71]. Notably, at least three Prdm genes (Prdm8, Prdm12, and Prdm14; Fig. 2) are expressed in the ventral neural tube. Expression of Prdm8 is present in the p1, p2 and pMN domains [72], while Prdm14 is expressed in the pMN domain, specifically in a subset of motor neurons—the Caudal Primary (CaP) motor neurons [46]—and Prdm12 is expressed in the p1 domain [73, 74]. Based on their expression domains, these three Prdm genes are likely to be regulated by Shh signaling. Indeed, treatment with cyclopamine (a Shh signaling inhibitor), causes a reduction of Prdm12b expression in zebrafish [73]. This suggests that Prdm12b is partially dependent on Shh signaling, as previously reported for other genes expressed in the p1 domain [67], but it remains to be determined if Prdm8 and Prdm14 expression is also regulated by Shh signaling.

Similar to Shh signaling in the ventral neural tube, Bone Morphogenetic Proteins (BMPs) function in the dorsal neural tube to pattern progenitor domains and regulate cell specification (Fig. 1). In particular, BMP4, BMP5 and BMP7, as well as the related Gdf7 protein, are expressed in the ectoderm overlaying the neural tube and function in concentration gradients to establish the dP1-6 progenitor domains [75, 76]. As expected, increasing or decreasing the BMP signal in the dorsal neural tube expands or reduces the specification of dorsal cell types, respectively [77–79]. In addition, loss of BMP receptors leads to loss of the dp1 and a dorsal shift in the dp2 domain [79], while expression of a constitutively active BMP receptor causes a ventral shift in Pax7 expression and an up-regulation of the dp1 expressed Atoh1 (previously Math1) [77]. Notably, Prdm13 is expressed in
the dorsal neural tube in the dP2-dP6 domains ([43, 80]; Fig. 2), suggesting that it may be regulated by BMP. However, Prdm13 has been shown to act downstream of Ptf1a, so BMP may function indirectly to control Prdm13 expression [43, 80]. Notably, the expression of Prdm12b in the p1 domain may also be sensitive to BMP signaling since the p0 and p1 domains are dependent on both Shh and BMP signaling (e.g. Evx1 and En1 expression in p0/p1 is reduced upon introduction of a constitutively active BMP receptor; [77]; reviewed by [52]). Accordingly, Prdm12 is regulated by BMP signaling outside the neural tube, such as in pre-placodal ectoderm [81].

Factors in addition to Shh and BMP are also involved in establishing progenitor domains in the neural tube. For instance, ventrally expressed BMP inhibitors (Chordin, Noggin and Follistatin) are required to suppress BMP signaling, thereby promoting the formation of ventral progenitor domains [82–87]. FGF signaling also promotes ventral fates by repressing Pax6, Irx3, Dbx1 and Dbx2 [88–90]. In contrast, Wnt1 and Wnt3a expressed in the roof plate are required for formation of dorsal progenitor domains (reviewed in [52, 53]), as loss of Wnt signaling leads to reduction in dp1 and dp2 neurons, with excess formation of dp3 neurons [91]. Retinoic acid (RA) is also released from the roof plate [92] to promote formation of dorsal progenitor domains. Accordingly, reduced RA signaling leads to dorsal expansion of ventral genes such as Nkx6.1 and Nkx2.2 [90, 93, 94]—although this may be a partially indirect effect mediated by loss of Pax6 [52]—and reduced expression of dorsal genes such as Bmp4/7, Msx2, Pax3/7, Wnt1/3a, Pax6 and Irx3 [90, 94–97]. Several Prdm genes are regulated by these pathways outside of the neural tube. For instance, expression of Prdm12 in Xenopus lateral pre-placodal ectoderm is reduced when Wnt3a is over-expressed [81] and Prdm14 expression in primordial germ cell specification may be activated when T-Brachyury—a downstream target of Wnt3a—binds to an enhancer at the Prdm14 gene [98]. Furthermore, RA treatment induces expression of Prdm12 in cell lines [23]. Hence, it is plausible that Prdm gene expression is induced by Fgf, Wnt and/or RA signaling also in dorsoventral patterning of the neural tube.

| Prdm gene | Nervous system expression | Nervous system function | Intrinsic HMT activity | Direct DNA binding | References |
|-----------|--------------------------|------------------------|------------------------|------------------|-----------|
| Prdm1     | CNS: photoreceptors      | CNS: photoreceptor identity | No                     | Yes              | [8, 108, 109, 120, 144–147] |
|           | PNS: prechordal plate, branchial arches, Rohon-Beard neurons | PNS: branchial arch formation, Rohon-Beard specification |                       |                  |           |
| Prdm3     | CNS: telencephalon, tegmentum, diencephalon, hindbrain | CNS: olfactory receptor development | Yes                     |                  | [28, 34, 120, 148] |
|           | PNS: branchial arches    | PNS: craniofacial development |                       |                  |           |
| Prdm4     | CNS: cerebral cortex     | CNS: in vitro neuronal stem cell proliferation and differentiation | Yes                     |                  | [149–151] |
| Prdm5     | CNS: ventral spinal cord | PNS: development of the neurocranium | Yes                     |                  | [9, 152, 153] |
|           | PNS: neurocranium        |                        |                       |                  |           |
| Prdm6     | CNS: spinal cord neurons |                        | Yes                     | Yes              | [74, 154] |
| Prdm8     | CNS: telencephalon, retina, tegmentum, cerebellum, hindbrain and spinal cord | CNS: axonal outgrowth, neocortical neuron morphology | No                     | Yes              | [15, 47, 72, 74, 120, 155] |
| Prdm10    | PNS: neural crest        | CNS: primary dendrite initiation |                       |                  | [156, 157] |
| Prdm12    | CNS: telencephalon, tegmentum, cerebellum, midbrain, hindbrain and spinal cord p1 domain | CNS: formation of V1 interneurons, pain perception and sensory neuron development |                       |                  | [73, 74, 81, 120, 158, 159] |
| Prdm13    | CNS: tegmentum, hindbrain, spinal cord, retina | CNS: GABAergic interneuron development | Yes                     |                  | [43, 74, 80, 120] |
| Prdm14    | CNS: ventral spinal cord | CNS: CaP motor neuron axonal projection |                       | Yes              | [46, 74, 120] |
| Prdm16    | CNS: forebrain, telencephalon, hindbrain, retina | CNS: olfactory neuron development | Yes                     | Yes              | [28, 34, 74, 120, 160] |
|           | PNS: craniofacial structures | PNS: craniofacial development |                       |                  |           |

Blank cells indicate categories were information is lacking in the literature. The list of expression domains and functions is not exhaustive.
**Prdm genes are involved in mutually repressive interactions between gene expression domains**

The distinct boundaries observed between progenitor domains in the neural tube are established by cross-repressive interactions between adjacent gene expression domains (Fig. 1). Several mutually repressive pairs of transcription factors have been identified, including Pax6/Nkx2.2, Dbx2/Nkx6.1, and Irx3/Olig2 ([64, 66, 68–70, 99–102]; reviewed in [53]). For instance, Irg3 and Olig2 repress each other's expression, thereby setting up the p2/pMN boundary [69, 102]. Accordingly, knock-out of Olig2 causes a ventral expansion of Irg3 and leads the pMN domain to adopt more dorsal characteristics. Hence, this domain gives rise to V2 interneurons and astrocytes instead of the motor neurons and oligodendrocytes that normally arise from the pMN domain [102]. Given the expression of Prdm genes in discrete domains along the dorsoventral axis of the neural tube, it is likely that Prdm genes also engage in mutually repressive interactions. For instance, Prdm12b is expressed in the p1 progenitor domain and shares an expression boundary with Nkx6.1—which is expressed in the p2, pMN and p3 domains—at the p1/p2 border. Notably, loss of Prdm12b function leads to ectopic expression of Nkx6.1 dorsally [73], suggesting that Prdm12b represses Nkx6.1 expression. However, it is not clear if this effect is direct, nor is it clear if Nkx6.1 reciprocally represses Prdm12b expression. Furthermore, zebrafish Olig4 (Olig3 in mouse) is expressed in the dP1-3 domains, where it is required for the specification of dorsal interneurons [103–105], whereas Prdm1a is expressed adjacent to Olig4 at the neural plate border [106]. Knockdown of Olig4 results in a severe reduction, or loss, of dorsal interneurons and a corresponding increase in cell types normally specified.

**Fig. 2** Summary of Prdm expression domains and interactions. **a.** Schematic representation of Prdm and bHLH expression domains along the dorsoventral axis of the neural tube. **b.** Diagrams of interactions between Prdm and bHLH genes discussed in the text. Left panel: The Prdm13 gene is regulated by Ptf1a. Additionally, Prdm13 regulates both Tlx1 and Tlx3 expression—in the latter case Prdm13 acts in a complex with Ascl1. Middle panel (top): Prdm8 acts in a complex with Bhlhb5 to regulate Cdh11 expression. Middle panel (bottom): Prdm14 binds the promoter region of Islet2 to regulate its expression. Right panel: Prdm1a and zebrafish Olig4 cross repress each other's expression at the neural plate boundary.
by Prdm1α—neural crest cells and Rohon-Beard cells [103, 105, 107–109]. Further studies confirmed that Prdm1α represses Olig4 expression, and vice versa, to establish and maintain the neural plate border and interneuron domains [106]. As Prdm gene function in the neural tube becomes analyzed more closely, it is likely that additional cases of reciprocal repression will be identified.

**Prdm genes regulate neuronal specification and differentiation in the neural tube** Through their roles as regulators of gene expression, Prdm family proteins affect the specification and differentiation of neuronal subtypes from various progenitor domains.

**Prdm12b is required for the formation of V1 interneurons** Prdm12 was originally described in chronic myeloid leukemia as a gene located in a deleted region on chromosome 9 [110, 111]. Prdm12 also plays a role controlling proliferation in various cell lines [23]. Expression of Prdm12 within the developing CNS was first described in the mouse, with expression domains identified in the ventricular zone of the telencephalon, as well as in distinct domains within the hindbrain and spinal cord [74]. A similar pattern is observed in the zebrafish neural tube—specifically, Prdm12b expression is limited to the p1 domain in the hindbrain and spinal cord, as well as to cells adjacent to the exit points of the ventral motor roots [73]. The spinal cord p1 domain gives rise to V1 interneurons, a class of inhibitory glycinergic interneurons that function to regulate motor circuits controlling trunk and tail musculature [112–117] and reviewed ([118]). V1 interneurons are defined by their expression of the Eng1 gene [64, 115]. Disruption of Prdm12b function leads to loss of Eng1b positive cells in zebrafish hindbrain and spinal cord, suggesting that Prdm12b is required for V1 interneuron formation. Strikingly, fish lacking Prdm12b function, and therefore also lacking V1 interneurons, display a defective escape response. In particular, when control fish are touched on the head, they bend their body into a single C-turn—bringing their head adjacent to the tail and orienting the head away from the stimulus—and then swim away. In contrast, Prdm12b-deficient fish exhibit multiple C-turns, display a longer response time with less productive swimming movements, and take longer between alternating body bends [73]. Hence, Prdm12b is required for the formation of the p1 domain and p1-derived neurons, although it remains unclear if the behavioral defect results from the loss of V1 interneurons in spinal motor circuits, or from the loss of some other class of p1-derived neurons in the hindbrain.

**Prdm14 controls formation of motor neuron axons** The pMN domain gives rise to motor neurons in a process that appears to require Prdm14. In zebrafish, four types of primary motor neurons (one of which is transient) are generated in the spinal cord, including CaP (caudal primary), MiP (middle primary), RoP (rostal primary) and VaP (variable primary). A zebrafish mutant for Prdm14, named short lightning (slg), was identified in a gene-trap screen using the Tol2 transposon system when a transposon inserted into the Prdm14 locus [46]. Strikingly, loss of Prdm14 does not affect the specification of motor neurons. Instead, CaP motor neurons in slg embryos display shortened axons and such embryos exhibit impaired escape responses and diminished swimming movements [46]. Prdm14 binds DNA via its zinc finger domain [41] and has been shown to occupy binding sites upstream of the Islet2 gene [46], which is required for the development of motor neurons. Notably Prdm14 is expressed in CaP and VaP motor neurons, but not in MiP or RoP motor neurons. Similarly, Islet2 is restricted to CaP and VaP, while Islet1 is maintained in MiP and RoP, motor neurons. Hence, Prdm14 and Islet2 are co-expressed in CaP motor neurons, explaining why the defects in slg mutants are restricted to this cell type. Interestingly, Prdm14 and Islet2 are also co-expressed in Rohon-Beard cells (a class of primary sensory neurons found in zebrafish), but Prdm14 does not regulate Islet2 expression in this cell population. Instead, another Prdm gene, Prdm1a, is expressed in Rohon-Beard cells where it regulates Islet2 [46, 119]. Thus, Prdm14 regulates Islet2 in CaP motor neurons and Prdm1a regulates Islet2 in Rohon-Beard cells, illustrating two examples of Prdm genes controlling neuronal cell fate. We note that Prdm8 is also expressed in the pMN domain, but apparently not in precursors of motor neurons [72] and it is therefore unlikely to control motor neuron formation.

**Prdm13 controls formation of GABAergic neurons** Prdm13 is expressed in the dp6–dp2 progenitor domains of the dorsal spinal cord [34, 43, 74, 80, 120]. Prdm13 is both necessary and sufficient to promote differentiation of inhibitory (GABAergic) neurons over excitatory (glutamatergic) neurons [43, 80]. Specifically, Prdm13 represses expression of Tlx1 and Tlx3 (excitatory lineage genes) by directly binding to their regulatory regions, as well as by binding to the Ascl1 transcription factor and inhibiting its ability to activate Tlx3 expression (see below for further details; [43]). Furthermore, Prdm13 blocks the ability of Neurogenin2 (another transcription factor involved in neuronal specification; [121, 122]) to activate transcription of Tlx3 [80].

**Prdm8 controls targeting of projection neurons in the telencephalon** Prdm8 is expressed at multiple sites

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of the CNS, including the dorsal telencephalon and the pMN-p1 domains of the hindbrain and spinal cord. Loss of function analyses in the mouse revealed that Prdm8 is required for proper targeting of several major axon tracts (corticospinal tract, hippocampal commissure, anterior commissure and corpus callosum), apparently by cooperating with the Bhlhb5 gene (see below for further details; [47]).

Prdm family proteins form complexes with other transcription factors to control gene expression

While it appears clear that Prdm family proteins act as transcription factors to control neuronal differentiation, it remains unclear precisely how they function. For instance, Prdm12b regulates expression of Engr1b in V1 interneurons, but it is not clear that Prdm12b binds DNA. Furthermore, Prdm1a, Prdm1b, Prdm13 and Prdm14 all control transcription, but these proteins do not all contain recognizable transcription regulatory domains. The simplest explanation would be that Prdm proteins act in complexes with other regulatory factors. Indeed, there are now several reports of Prdm proteins interacting physically with other transcription factors in larger complexes.

Prdm13 interacts with Ascl1 to promote formation of GABAergic neurons

As discussed, Prdm13 is expressed in the dP2-dP6 progenitor domains [34, 43, 74, 80, 120], but appears to function primarily in dP4. In this region of the neural tube, several bHLH proteins function together with various binding partners in a combinatorial code to specify individual cell fates (reviewed by [123]). Specifically, dP1, dP2, dP3 and dP5 give rise to excitatory (glutamatergic) neurons, while dP4 gives rise to inhibitory (GABAergic) neurons. The bHLH transcriptional activators Ascl1, expressed in dP3-5, and Ptf1a, expressed only in dP4, are required for the formation of excitatory versus inhibitory interneurons in dP3-dP5, such that Ascl1 alone drives expression of the Tlx1 and Tlx3 genes to promote excitatory interneuron fates in dP3 and dP5, while co-expression of Ptf1a with Ascl1 in dP4 promotes inhibitory interneuron fates by repressing Tlx1 and Tlx3 transcription and promoting expression of Pax2 and Lbx1 [122, 124–133]. Strikingly, it appears that Ptf1a acts via Prdm13 in dP4 to switch Ascl1 from a transcriptional activator to a repressor. In particular, Ptf1a directly activates Prdm13 expression in dP4 and Prdm13 binds the same regulatory regions as Ascl1 at the Tlx3 gene [43, 80]. Furthermore, Prdm13:Ascl1-containing complexes can be detected by co-immunoprecipitation [43], suggesting that such complexes regulate Tlx3 expression. Prdm13 also interferes with the ability of Neurog2 to activate Tlx3 [80], but it is not clear if this involves the formation of a complex between Prdm13 and Neurog2. Lastly, Prdm13 represses Tlx1 in the absence of Ascl1 [43], suggesting that Prdm13 may also be a transcriptional repressor in its own right, or that it may interact with other factors in the regulation of Tlx1.

Prdm13 has been reported to exhibit methyltransferase activity [80], but it is not clear if this activity is intrinsic to Prdm13, or the result of a co-purifying factor. Indeed, the Prdm13 PR domain—the domain with sequence similarity to methyltransferases—is not required for its ability to repress Tlx1 and Tlx3 [43], indicating that intrinsic methyltransferase activity is unlikely to be required for Prdm13 to function as a repressor. In contrast, the Prdm13 zinc fingers are required for it to function as a repressor [43].

Notably, Prdm13 expression overlaps with the expression domains of other bHLH genes and it is therefore possible that additional Prdm13:bHLH complexes may form. For instance, Prdm13 expression overlaps with Olig3 (Olig4 in zebrafish) expression in dP2 and dP3 [104, 105, 134, 135]. The dP2 and dP3 domains give rise to Class A interneurons and loss of Olig3 function specifies them to produce dP4 interneurons [104, 135]. Given the physical interaction between Prdm13 and the bHLH factor Ascl1 in dP4, this raises the possibility that Prdm13 and Olig3 could function as a complex in the specification of dP2 and dP3, but this remains to be explored.

Prdm8 acts in a complex with Bhlhb5 to control neural circuit assembly

The Bhlhb5 gene is closely related to the Olig subfamily of bHLH genes, but it is expressed in postmitotic neurons—particularly in excitatory neurons of the dorsal telencephalon [136, 137, 138]. Similar to the Olig proteins, Bhlhb5 appears to act as a transcriptional repressor [139, 140]. Bhlhb5 mutant mice exhibit axonal projection defects such that axons originating in the dorsal telencephalon fail to reach their targets (Joshi 2008). This phenotype is shared with Prdm8 mutant mice such that both mutants exhibit mis-targeting of the main fiber tracts connecting the cerebral hemispheres [47]. Importantly, Bhlhb5 and Prdm8 are co-expressed in many populations of differentiating neurons, including the dorsal telencephalon, indicating that they may function together. Indeed, further analyses revealed that Bhlhb5 and Prdm8 proteins interact in a co-immunoprecipitation assay and that the two proteins co-occupy promoter elements in vivo, as defined by ChIP analysis [47]. Strikingly, the same set of target genes is up-regulated in Bhlhb5 and Prdm8 mutants, though the mutants differ such that Bhlhb5 can bind targets in the absence of Prdm8—but not vice versa. Hence, it appears that Bhlhb5 binds DNA directly (most likely as a homodimer via a canonical E-box motif), but cannot repress target genes in the absence of Prdm8, while Prdm8 is a
repressor that cannot access target genes in the absence of Bhlhb5. Among the Bhlhb5/Prdm8 target genes, Cdh11 is expressed in several intermediate targets of the corticospinal projections and is up-regulated in Bhlhb5 and Prdm8 mutant mice. Analysis of Bhlhb5/Cdh11 double mutants, which allows reduction of Cdh11 expression in the Bhlhb5 mutant background, revealed that axonal targeting was partially rescued [47], suggesting that Bhlhb5/Prdm8 regulates neuronal circuit formation at least in part by controlling Cdh11 expression levels.

Bhlhb5 and Prdm8 are co-expressed at other sites in the CNS. For instance, both genes are expressed in the spinal cord p2 domain [72, 141, 142] and Bhlhb5 has been implicated in specifying V2a over V2b interneurons [141], suggesting that Bhlhb5:Prdm8 complexes may act also in V2a differentiation. Furthermore, Bhlhb5 expression overlaps with the expression of other Prdm genes—such as Prdm12 in the p1 domain and Prdm13 in the dP6 domain—and Bhlhb5 is involved in the specification of interneurons from those domains [141, 142]. While this suggests potential interactions for Prdm12 and Prdm13 with Bhlhb5, this remains to be tested.

Conclusions
Emerging principles for Prdm function in the developing CNS
Embryogenesis is replete with transcription factor “codes” and networks working in concert to specify and differentiate various cell types. Here we have reviewed the function of Prdm genes expressed within the neural tube, discussed the known interactions between bHLH transcription factors and Prdm family members, as well as proposed additional processes where members of these families are expressed, function, and may directly interact. From this review, some general principles are beginning to emerge. First, many Prdm family genes function in the developing CNS. To date, five Prdm genes (Prdm1a, Prdm8, Prdm12b, Prdm13 and Prdm14) have been shown to control CNS development. Second, Prdm genes are involved in multiple aspects of CNS development. Prdm12b and Prdm1a play roles in early patterning by controlling the formation of expression domain boundaries (Prdm12b controls the p1/p2 boundary and Prdm1a the neural plate border; [73, 106]), while Prdm13 acts on cell fate decisions to control the formation of inhibitory (GABAergic) over excitatory (glutamatergic) neurons [43, 80]. In contrast, Prdm14 acts during motor neuron maturation to control proper axonal outgrowth [46] and Prdm8 acts to control appropriate axonal targeting during neural circuit formation [47]. Third, Prdm proteins function in complexes with other transcription factors. In particular, Prdm8 functions by forming a repressor complex with Bhlhb5 in the dorsal telencephalon [47] and Prdm13 interacts with Ascl1 to promote formation of GABAergic neurons [43, 80]. These findings suggest a general model where Prdm family members function in multi-protein transcription regulatory complexes that control diverse aspects of neural development—from the patterning of expression domains and cell specification to axonal projections and circuit formation.

Since the Prdm family is still relatively poorly characterized and new members continue to be added, it is likely that additional Prdm genes are involved in CNS development—or that known Prdm genes will have additional functions. As discussed, Prdm13 physically interacts with the bHLH protein Ascl1 in the dP4 domain [43], but Prdm13 is also co-expressed with another bHLH protein—Olig3 (Olig4 in zebrafish)—in the dP1-dP3 domains, suggesting that Prdm13:Olig3(4) complexes may act in dP1-dP3. Similarly, both Prdm12b and Bhlhb5 are expressed in the p1 domain and play roles in V1 interneuron specification [73, 74, 141, 142], indicating they might interact in a complex. Perhaps even more compelling, Bhlhb5 and Prdm8—that are known to interact in the telencephalon—are also co-expressed in the p2 domain (where Bhlhb5 has a known role in V2a interneuron specification [141, 142]) suggesting that they may act together in a complex also in the p2 domain.

There are several gene families with important roles in early neural development. In particular, the bHLH, Pax, Dbx, and Nkx families regulate neuronal cell fate specification and differentiation [52, 53, 123, 143]. The data reviewed here demonstrate that Prdm genes also have essential functions in CNS development, thereby placing the Prdm family alongside these other gene families as key regulators of neural development. Strikingly, there appears to be a particularly close relationship between the bHLH and Prdm families (Fig. 2b) with Prdm proteins having the ability to modulate bHLH protein function via the formation of protein complexes (e.g. Prdm8 binding with Bhlhb5 [47] and Prdm13 binding with Ascl1 [43]).

Abbreviations
CNS: Central nervous system; DV: Dorsoventral; AP: Anteroposterior; HMT: Histone methyltransferase; HDAC: Histone deacetylase; HAT: Histone acetyl transferase; ChIP: Chromatin immunoprecipitation; CaP: Caudal primary; MiP: Middle primary; RoP: Rostral primary; VaP: Variable primary.

Competing interests
There are no competing interests.

Author contributions
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