Zones and Stripes: Development of Cerebellar Topography

3

Lauren N. Miterko, Roy V. Sillitoe, and Richard Hawkes

Contents

The Architecture of the Adult Cerebellar Cortex 46
From Allocation to Rhombomere 1 to Two Germinal Epithelia 48
Purkinje Cell Birth Date, Phenotype, and Location 49
From Ventricular Zone to Clusters 49
Purkinje Cell Subtype Specification 50
From Embryonic Clusters to Adult Stripes 50
Afferent Topography 52
Climbing Fibers 52
Mossy Fibers 53
Interneurons 54

L. N. Miterko
Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA

Program in Developmental Biology, Baylor College of Medicine, Houston, TX, USA

Jan and Dan Duncan Neurological Research Institute of Texas Children's Hospital, Houston, TX, USA

R. V. Sillitoe
Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA

Department of Neuroscience, Baylor College of Medicine, Houston, TX, USA

Program in Developmental Biology, Baylor College of Medicine, Houston, TX, USA

Jan and Dan Duncan Neurological Research Institute of Texas Children's Hospital, Houston, TX, USA
e-mail: sillitoe@bcm.edu

R. Hawkes (✉)
Department of Cell Biology and Anatomy Genes and Development Research Group, Hotchkiss Brain Institute, The University of Calgary, Calgary, AB, Canada
e-mail: rhawkes@ucalgary.ca

© Springer Nature Switzerland AG 2022

M. U. Manto et al. (eds.), *Handbook of the Cerebellum and Cerebellar Disorders*,
https://doi.org/10.1007/978-3-030-23810-0_3

Cerebellar Topography and Circuit Function ... 55
From Zones-And-Stripes to Complex Motor Behaviors ... 56
Conclusions ... 57
References ... 58

Abstract

Cerebellar architecture is organized around the Purkinje cell. Purkinje cells in the mouse cerebellum come in many different subtypes, organized first into four transverse zones and then further grouped into hundreds of reproducible topographical units – stripes. Stripes are identified by their functional properties, connectivity, and expression profiles. The molecular pattern of stripes is highly reproducible between individuals and is conserved through evolution. Pattern formation in the cerebellar cortex is a multistage process that begins with the generation of the Purkinje cells in the ventricular zone (VZ) of the fourth ventricle. During this stage, or shortly after, Purkinje cell subtypes are specified toward specific positions. Purkinje cells migrate from the VZ to form an array of clusters that form the framework for cerebellar topography. At around birth, these clusters begin to disperse, triggered by Reelin signaling pathway proteins, to form the adult stripe array.

The chapter will begin with a brief overview of adult cerebellar topography, primarily focusing on the mouse cerebellum, and then discuss the cellular and molecular mechanisms that establish these remarkable patterns. Considering how functionally diverse the cerebellum is despite its conserved organization of patterns, this chapter will end exploring how stripes might contribute to neuronal activity and the execution of cerebellar-dependent behaviors.

Keywords

Cerebellum · Purkinje cell · Patterning · Stripes · Zones · Topography

The Architecture of the Adult Cerebellar Cortex

The adult mouse cerebellum is shown in Fig. 1, immunoperoxidase stained for the antigen zebrin II (Brochu et al. 1990: zebrin II. aldolase C (AldoC) – Ahn et al. 1994). There are two subsets of Purkinje cells: zebrin II-immunopositive (zebrin II+) and zebrin II-immunonegative (zebrin II-). Purkinje cells in each subset are aligned to form an alternating array of parasagittal stripes (Brochu et al. 1990; Sillitoe and Hawkes 2002). Stripes are reproducible between individuals and symmetrically distributed about the midline (Hawkes et al. 1985; Hawkes and Leclerc 1987; Brochu et al. 1990). Zebrin II+ stripes are numbered as P1+ to P7+ starting from the midline and going laterally, and the intervening zebrin II- stripes are numbered with reference to the medial zebrin II+ stripe (i.e., P1- lies immediately lateral to P1 +, etc.). In the vermis, four transverse domains in the anterior–posterior axis are identified by zebrin II expression: the striped anterior zone (AZ: ~lobules I–V), the

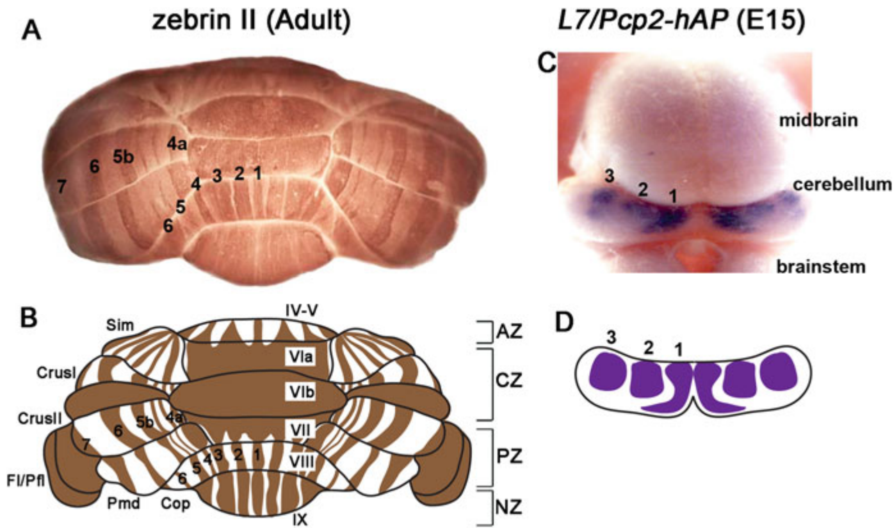

Fig. 1 The mouse cerebellum is organized into an array of transverse zones and parasagittal stripes. (**a**) Adult mouse cerebellum immunoperoxidase stained in whole mount with anti-zebrin II/aldolase C. (**b**) Schematic illustrating the pattern of zebrin II in the mouse cerebellum. (**c**) Embryonic day (E) 15 mouse cerebellum stained in whole mount for alkaline phosphatase (hAP) to detect the expression of an *L7/Pcp2-hAP* transgene (see Sillitoe et al. 2009 for details). (**d**) Schematic illustrating the pattern of embryonic Purkinje cell clusters as revealed by hAP staining in *L7/Pcp2-hAP* transgenic mice. Abbreviations: *AZ* anterior zone, *CZ* central zone, *PZ* posterior zone, *NZ* nodular zone, *Sim* simplex, *Fl/Pfl* flocculus/paraflocculus, *Pmd* paramedian, *Cop* copula pyramidis. Lobule numbers are indicated by Roman numerals, and stripes are labeled with Arabic numerals (panels C and D were adapted from Sillitoe et al. 2009)

uniformly zebrin II+ central zone (CZ: ~lobules VI–VII), the striped posterior zone (PZ: ~lobules VIII–dorsal IX), and the uniformly zebrin II+ nodular zone (NZ: ~lobules IX ventral and X: Ozol et al. 1999). A similar alternation of zones is seen in the hemispheres (Sarna et al. 2006).

Numerous molecular markers are co-localized with either the zebrin II+ or zebrin II- Purkinje cells. For example, the GABA-B receptor is expressed in the zebrin II+ population (Chung et al. 2008a) and phospholipase C(PLC) ß4 in the zebrin II- population (Sarna et al. 2006). However, detailed comparisons between zebrin II expression and other antigenic markers reveal that the parasagittal stripes are much more elaborate than the expression of any one antigen indicates. For example, comparisons between zebrin II and the glycoprotein epitope HNK1 reveal that although these two antigens are largely co-localized (Eisenman and Hawkes 1993),discrete Purkinje cell populations in several lobules can express these antigens separately (Marzban et al. 2004). Similarly, expression of the 25 kDa small heat shock protein (HSP) 25 reveals parasagittal Purkinje cell heterogeneity in both the CZ and NZ – areas in which zebrin II is homogeneously expressed in all Purkinje cells (Armstrong et al. 2000). As a result, the adult cerebellar cortex of the mouse can

reliably and reproducibly be subdivided into several hundred distinct regions, each typically comprising no more than a few hundred Purkinje cells (e.g., reviewed in Hawkes 1997; Sarna and Hawkes 2003; Apps and Hawkes 2009). Stripe and zone compartments influence all aspects of cerebellar biology. They are highly reproducible between individuals, conserved through evolution (AZ – Sillitoe et al. 2005; PZ – Marzban and Hawkes 2011), and insensitive to experimental manipulation (reviewed in Larouche et al. 2006). Afferent topography is also striped. Zone and stripe boundaries restrict afferent terminal fields (e.g., climbing fibers, spinocerebellar mossy fibers, and trigeminocerebellar mossy fibers that relay somatosensory signals terminate mainly in zebrin II- stripes throughout the AZ and into rostral lobule VI, where the AZ interdigitates with the CZ, e.g., reviewed in Voogd and Ruigrok 2004) into compartments that are reflected by functional cerebellar maps (e.g., Chockkan and Hawkes 1994; Hallem et al. 1999; Ebner et al. 2012).

Many cerebellar mutant phenotypes are restricted by zone and stripe boundaries. For example, *swaying* (Thomas et al. 1991), *rostral cerebellar malformation/Unc5h3* (Napieralski and Eisenman 1996), *cerebellar deficient folia* (Cook et al. 1997; Beierbach et al. 2001; Park et al. 2002), and *meander tail* (Ross et al. 1990) all exhibit deficits restricted primarily to the AZ; the gain of function δ2 glutamate receptor mutant *lurcher* (*Lc*/+) has a zebrin II expression domain during development that is restricted at the CZ/PZ boundary (Tano et al. 1992); and the *weaver* mouse exhibits a Purkinje cell ectopia that is primarily restricted to the CZ (Eisenman et al. 1998; Armstrong and Hawkes 2001). Finally, most examples of Purkinje cell death due to mutation or insult show restriction to parasagittal stripes (reviewed in Sarna and Hawkes 2003; Duffin et al. 2010; Armstrong et al. 2011; Williams et al. 2007; Ragagnin et al. 2017).

How does this remarkable zone-and-stripe pattern develop?

From Allocation to Rhombomere 1 to Two Germinal Epithelia

In mice, the cerebellar primordium arises between E8.5 and E9.5 entirely from within the metencephalon (Wassef and Joyner 1997; Zervas et al. 2004). The boundary between Otx2 and Gbx2 expression domains initially demarcates the border between mes- and metencephalon and the location of the isthmic organizer, a tissue patterning structure that promotes interactions between cerebellar patterning genes (reviewed in Zervas et al. 2005). Several studies have examined putative allocation events during this period, which generate the Purkinje cell population: the general conclusion is that the entire Purkinje cell population in the adult arises from ~100 to 150 precursors, likely specified at around E7–E8 (Baader et al. 1996; Mathis et al. 1997; Hawkes et al. 1998; Watson et al. 2005), although there is no evidence that these are restricted to a particular Purkinje cell subset. The early stages of cerebellar development are reviewed in detail in ► Chap. 6, "Specification of Granule Cells and Purkinje Cells." This chapter will only consider mechanisms pertinent to the origin of stripe patterning (for other reviews, see Hawkes and Gravel 1991; Hawkes and Eisenman 1997; Herrup and Kuemerle 1997; Oberdick et al.

1998; Armstrong and Hawkes 2000; Larouche and Hawkes 2006; Sillitoe and Joyner 2007; White and Sillitoe 2013).

The cerebellum houses two distinct germinal matrices: the dorsally located rhombic lip and the ventrally located ventricular zone (VZ) of the fourth ventricle. Genetic fate mapping studies show that the rhombic lip gives rise to glutamatergic projection neurons of the cerebellar nuclei, cerebellar granule cells, and unipolar brush cells (Wingate 2001; Machold and Fishell 2005; Wang et al. 2005; Englund et al. 2006). The VZ gives rise to GABAergic components of the cerebellum including all GABAergic interneurons and all Purkinje cells: all cerebellar GABAergic neurons derive from progenitors expressing *Ptf1a*, which is required for their specification (Hoshino et al. 2005; Pascual et al. 2007). However, the VZ is not homogenous but divided by gene expression into numerous overlapping molecular domains (e.g., Chizhikov et al. 2006; Zordan et al. 2008). This issue is discussed in ► Chap. 15, "Genes and Cell Type Specification in Cerebellar Development."

Purkinje Cell Birth Date, Phenotype, and Location

Purkinje cells undergo terminal mitosis in the VZ between E10 and E13 in the mouse (Miale and Sidman 1961; Hashimoto and Mikoshiba 2002). Birthdating studies, using incorporation of either adenovirus (Hashimoto and Mikoshiba 2002), bromodeoxyuridine (e.g., Feirabend et al. 1985; Karam et al. 2000; Larouche and Hawkes 2006), or genetic fate mapping (Sudarov et al. 2011), reveal a direct correlation between the birthdate of a Purkinje cell and its final mediolateral location, suggesting that Purkinje cells acquire positional information at or shortly after their terminal differentiation in the VZ. It is not known whether positional information and phenotype are specified at the same time. Postmitotic Purkinje cells migrate dorsally out of the VZ, presumably along radial glia processes (Morales and Hatten 2006), and stack in the cerebellar anlage with the earliest-born Purkinje cells located most dorsally.

From Ventricular Zone to Clusters

After migration from the VZ, the Purkinje cells undergo a complex and poorly understood reorganization (E14–E18), possibly involving cell-signaling molecules including cadherin (Redies et al. 2010) and Eph-ephrin (Karam et al. 2000), to yield a stereotyped array of early clusters with a range of molecular phenotypes. The Purkinje cell migration pathways are carefully described in Miyata et al. (2010) (see also ► Chap. 9, "Purkinje Cell Migration and Differentiation"). During this same period, Purkinje cell clusters begin to express a variety of early markers that reveal both rostrocaudal and mediolateral compartments (e.g., calbindin, Wassef et al. 1985; cyclic GMP-dependent protein kinase, Wassef and Sotelo 1984; HSP25, Armstrong et al. 2001; neurogranin, Larouche et al. 2006; cadherins, reviewed in Redies et al. 2010; homeobox genes, including *En1*, *En2*, *Pax2*, and *Wnt17b*,

Bally-Cuif et al. 1992; Millen et al. 1995; *L7/pcp2-LacZ*, Smeyne et al. 1991; Oberdick et al. 1993; Ozol et al. 1999; *OMP-LacZ*, Nunzi et al. 1999; *inositol 1,4,5-trisphosphate (IP3) receptor (IP3R)nls-LacZ*, Furutama et al. 2010; etc.). Detailed comparisons of various other early markers are not comprehensive but such data as are available suggest that they all fit into a common schema.

Purkinje Cell Subtype Specification

When is Purkinje cell stripe phenotype specified? In order to answer this, many attempts have been made to alter Purkinje cell phenotype, which have almost always been ineffective. First, surgical interventions in the neonate have no effect on the expression of compartmentation markers (e.g., zebrin I, Leclerc et al. 1988; *L7/pcp2-LacZ*, Oberdick et al. 1993; HSP25, Armstrong et al. 2001). Secondly, in cerebellar explants taken as early as E13 and placed either in slice culture (Oberdick et al. 1993; Seil et al. 1995; Rivkin and Herrup 2003; Furutama et al. 2010) or transplanted (Wassef et al. 1990), Purkinje cell subtypes apparently develop normally. Finally, ectopic Purkinje cells in various mouse mutants develop their normal adult phenotypes (e.g., *reeler*, Edwards et al. 1994; *disabled*, Gallagher et al. 1998; *weaver*, Armstrong and Hawkes 2001). These data suggest that cell autonomous mechanisms early in cerebellar development direct the specification of Purkinje cell phenotypes toward distinct subtypes.

The only experimental manipulation that is known to alter Purkinje cell subtype is deletion of *Early B-cell Factor 2* (*Ebf2*, Croci et al. 2006; Chung et al. 2008b). In the adult cerebellum, *Ebf2* expression is restricted to the zebrin II- Purkinje cell subset. When *Ebf2* is deleted, a complex cerebellar phenotype results, but in particular a prominent subset of zebrin II- Purkinje cells express zebrin II+ markers in addition to the normal zebrin II- ones (Croci et al. 2006; Chung et al. 2008b). This suggests that EBF2 is a repressor of the zebrin II+ phenotype. The role of *Ebf2* is discussed in detail in ▶ Chap. 2, "Proneural Genes and Cerebellar Neurogenesis in the Ventricular Zone and Upper Rhombic Lip."

From Embryonic Clusters to Adult Stripes

Starting at around E18, the embryonic clusters begin to disperse. This occurs at the same time as cerebellar lobules begin to exhibit extensive morphogenetic changes (Sudarov and Joyner 2007). The two processes are coupled – if Purkinje cell dispersal is blocked, then lobulation is prevented, and the cerebellum is lissiform – but the mechanistic relationship is unknown. In contrast to the relationship between cluster dispersal and lobules, a recent genetic study demonstrated that Purkinje cell stripe patterning and foliation can be uncoupled and *En1/2* controls each process independently (Sillitoe et al. 2008b). Whether cluster dispersal is the passive concomitant of granular layer maturation and lobule formation or requires active Purkinje cell migration is not known. Whatever the case, because cluster dispersal

occurs primarily in the rostrocaudal plane – the rostrocaudal length of the mouse vermis increases ~25-fold from E17 to P30, while the width of the vermis increases only ~1.5× during the same time period (Gallagher et al. 1998) – the clusters elongate into long parasagittal stripes. About 50 embryonic clusters are thought to produce the adult pattern of stripes (Fujita et al. 2012). The transformation of embryonic Purkinje cell clusters into mature stripes is mediated by Reelin signaling (Tissir and Goffinet 2003). The external granular layer (EGL) secretes Reelin starting around E17 (D'Arcangelo et al. 1997; Jensen et al. 2002). Reelin binds two receptors on Purkinje cells – the apolipoprotein E receptor 2 (Apoer2) and the very low-density lipoprotein receptor (VLDLR, Trommsdorff et al. 1999). Binding induces receptor clustering (Strasser et al. 2004) and activates an intracellular protein kinase cascade leading to tyrosine phosphorylation of the docking protein Disabled-1 (mdab-1, Howell et al. 1997; Goldowitz et al. 1997; Sheldon et al. 1997).

Downstream of Disabled-1 are interactions with Src and Fyn cytoplasmic tyrosine kinases and with phosphatidylinositol 3-kinase (Bock and Herz 2003; Kuo et al. 2005). The cyclin-dependent kinase (cdk)5 signaling pathway has also been implicated in Reelin signaling as Purkinje cells in cdk5 pathway mutants phenocopy the *reeler* mouse (e.g., Ohshima and Mikoshiba 2002). The end result is thought to be a drop in Purkinje cell-cell adhesion, thereby allowing the early clusters to disperse.

Accordingly, mutations in the Reelin pathway affect all Purkinje cells and result in the complete failure of cluster dispersal and global Purkinje cell ectopia. However, deletion of either of the Reelin receptors, Apoer2 and Vldlr, results in selective, specific Purkinje cell ectopias (Larouche et al. 2008): in *Apoer2*$^{-/-}$ mice, ectopic Purkinje cells are largely restricted to the zebrin II- population of the anterior vermis; in contrast, *Vldlr*$^{-/-}$ mice have a much larger population of ectopic Purkinje cells that includes members from both zebrin II+/− phenotypes, and HSP25 immunoreactivity reveals that a large portion of ectopic zebrin II+ cells is destined to become stripes in lobules VI–VII. Finally, a small, very specific population of ectopic zebrin II- Purkinje cells is observed in animals heterozygous for both receptors (*Apoer2*$^{+/-}$: *Vldlr*$^{+/-}$: no ectopia is present in mice heterozygous for either receptor alone). Despite the known importance of the Reelin pathway in regulating Purkinje cell dispersal, other genetic cues are also likely required. For example, the HSP25+/zebrin II+ Purkinje cell subset in the CZ is selectively ectopic in *weaver* mutants (Armstrong and Hawkes 2001).

This model suggests a direct genealogical relationship between embryonic clusters and adult stripes. This is not straightforward to establish because the parasagittal pattern of early antigens tends to disappear perinatally, either because they are downregulated (e.g., neurogranin, Larouche et al. 2006) or because they become expressed uniformly by all Purkinje cells (e.g., calbindin, Wassef et al. 1985), while most adult stripe antigens are not expressed in the mature pattern of stripes until ~P15 (e.g., zebrin II, Lannoo et al. 1991; HSP25, Armstrong et al. 2001). While the basic cerebellar architecture seems to be laid down in the embryo, the maturation of stripe phenotypes is not complete until P15 or so. For example, zebrin II is first expressed at around P6, but by P10–P12 all Purkinje cells express zebrin II. From P12 to P15 zebrin II is downregulated in the zebrin II- population to reveal the

mature stripe array (Brochu et al. 1990; Lannoo et al. 1991; Rivkin and Herrup 2003). The molecular mechanism that mediates zebrin II downregulation is not known. However, recent studies have identified markers that bridge between clusters to stripes (e.g., Larouche et al. 2006; Marzban et al. 2007; Sillitoe et al. 2009; White and Sillitoe, 2013). The current hypothesis is that embryonic clusters are the precursors of the adult stripes. While the hypothesis implies a direct relationship, experimental evidence indicates that it is not at all simple. On the one hand, current maps suggest about 20 different clusters but 10 times as many stripes in the adult. Where does the additional complexity come from? While the apparent lack of complexity could merely be a reflection of an underdeveloped toolkit, the internal consistency of the different cluster antigens does not support this view: all known embryonic markers conform to a common schema with ~10 clusters on each side of the cerebellum. Therefore, there may be secondary patterning stages, perhaps associated with the transformation of clusters into stripes, which takes the embryonic broad-stroke pattern and elaborates it into a more complex adult form. Perhaps the 20 clusters are partitioned into 50 during postnatal development before these go on to form the adult stripes (Fujita et al. 2012). On the other hand, there is evidence that some stripes in the adult result from the coalescence of multiple clusters (e.g., the P1-stripe in the AZ is the fusion of three distinct clusters in the embryo, Ji and Hawkes 1994; Marzban et al. 2007). Finally, genetic fate mapping using an *L7/pcp2-CreER* allele supports the hypothesis that at least some embryonic clusters contribute Purkinje cells to multiple stripes in the adult cerebellum (Sillitoe et al. 2009).

Afferent Topography

It is generally believed that the Purkinje cell map serves as a scaffold around which other cerebellar structures are organized – both afferent projections (climbing fibers and mossy fibers, reviewed in Sotelo 2004) and interneurons including granule cells, Golgi cells, and unipolar brush cells (e.g., Chung et al. 2009; reviewed in Apps and Hawkes 2009).

Climbing Fibers

In the adult, climbing fibers project from neurons in the contralateral inferior olivary complex and terminate on Purkinje cell dendrites, with each Purkinje cell receiving input from a single climbing fiber. Each subnucleus in the inferior olive projects to a limited number of Purkinje cell stripes (e.g., Voogd and Ruigrok 2004; Sugihara and Quy 2007; Apps and Hawkes 2009). The cerebellar projection neurons of the inferior olive are born in the caudal rhombic lip and migrate ventrally in the submarginal stream (Sotelo and Chédotal 2005). Similar to their target Purkinje cells, the fate, survival, differentiation, and migration of inferior olivary neurons are dependent on the function of *Ptf1a* (Yamada et al. 2007). Climbing fibers enter the cerebellar anlage at ~E15 and immediately terminate within specific Purkinje cell clusters (e.g., Chédotal and Sotelo

1992; Paradies et al. 1996). During Purkinje cell cluster dispersal into stripes, the climbing fibers are presumably carried along with them, thereby creating parasagittal terminal fields that align with the Purkinje cell stripes (Gravel et al. 1987; Apps and Hawkes 2009). In the neonatal cerebellum, each Purkinje cell receives input from several climbing fibers. This is converted to the adult mono-innervation pattern by the elimination of all but one (reviewed in Cesa and Strata 2009; Carrillo et al. 2013). However, it appears that the sculpting of climbing fiber innervation does not contribute significantly to the refinement of cerebellar stripe topography (Crépel 1982; Sotelo et al. 1984).

Sotelo and colleagues have argued that matching gene expression domains between the cerebellum and inferior olive contain cues that guide the formation of a precise topographical projection map (Wassef et al. 1992; Chédotal et al. 1997; Sotelo and Chédotal 2005). In support of this model, Nishida et al. (2002) demonstrated that overexpression of Ephrin-A2 by using retroviral vectors disrupts the general topography of the olivocerebellar projection. Moreover, inferior olivary axons expressing high Eph receptor activity are prevented from entering into domains with ectopic Ephrin-A2 ligand expression (Nishida et al. 2002). Although the parasagittal band topography of climbing fibers was never examined, these experiments identify the Eph/Ephrin signaling pathway as likely to provide positional information during afferent/target matching.

Mossy Fibers

The other major afferents of the cerebellum are mossy fibers, which arise from multiple sources and terminate in synaptic glomeruli on the dendrites of granule cells. Mossy fibers are also restricted by transverse zone and parasagittal stripe boundaries (e.g., Gravel and Hawkes 1990; Ji and Hawkes 1994; Armstrong et al. 2009; Sillitoe et al. 2010; Ruigrok 2011; Gebre et al. 2012). In some cases, mossy fiber terminal fields align with specific subsets of stripes (e.g., Armstrong et al. 2009), and in others they split Purkinje cell stripes into smaller units (e.g., cuneocerebellar/spinocerebellar terminal fields in the P1- stripes of the AZ, Ji and Hawkes 1994). The major features of the development of mossy fiber topography are similar to that for climbing fibers. The earliest mossy fibers enter the cerebellar anlage by around E12 (rat, Ashwell and Zhang 1992, 1998). Mossy fiber topography is established before most granule cells are formed (Arsenio-Nunes and Sotelo 1985) and is accompanied by direct contacts between mossy fiber growth cones and Purkinje cells in embryonic and early postnatal clusters (Mason and Gregory 1984; Takeda and Maekawa 1989; Grishkat and Eisenman 1995; Kalinovsky et al. 2011; Sillitoe 2016). This model is consistent with observations from mutant animals with agranular cerebella, in which the spinocerebellar mossy fiber topography is organized into bands despite the absence of a normal mossy fiber-granule cell-Purkinje cell pathway (e.g., Arsenio-Nunes and Sotelo 1985; Arsenio-Nunes et al. 1988; Eisenman and Arlinghaus 1991), and with the data from neonatal lesion studies demonstrating that there does not seem to be a significant role for

competition between mossy fiber sources in sculpting terminal fields (Ji and Hawkes 1995). The molecular basis of mossy fiber terminal field restriction is not well understood, but deletion of either the retinoic acid receptor-related orphan receptor alpha (RORalpha: Arsenio-Nunes et al. 1988) or *En1/2* (Sillitoe et al. 2010) or overexpression of *En2* in Purkinje cells (Baader et al. 1999) results in mossy fiber targeting defects.

As for climbing fibers, mossy fiber terminals are presumed to disperse along with the Purkinje cells as embryonic clusters transform into stripes. Then postnatally, as granule cells are born in the external granular layer and descend past the Purkinje cells to the granular layer, the mossy fiber terminals displace from the Purkinje cells and synapse with differentiated granule cells. As a result, the mossy fiber terminal fields become aligned with the overlying Purkinje cell stripes. Although there is evidence that the process of establishing afferent compartmentation is genetically controlled (Sillitoe et al. 2010), the refinement of the map may be in part dependent on neuronal activity (Tolbert et al. 1994; White et al. 2014).

Interneurons

Several cerebellar inhibitory interneurons show evidence of restriction by the Purkinje cell scaffold. First, Golgi cell dendrites are restricted by Purkinje cell stripe boundaries (Sillitoe et al. 2008a). Second, subsets of unipolar brush cells are associated with particular adult stripes (Chung et al. 2009; Lee et al. 2015). Models have been proposed by which both patterns of restriction involve mechanisms similar to those that organize mossy fiber afferent growth cones. Both Golgi cells and unipolar brush cells are thought to intermingle with Purkinje cells at the embryonic cluster stage. Hence, as the Purkinje cell clusters disperse, the interneurons become restricted to a particular stripe. Next, and as the granule cells form, the Golgi cells displace from the Purkinje cells to the neighboring granule cell axons, and the unipolar brush cells displace to the underlying granular layer, where mossy fibers contact them and they in turn synapse with granule cells and other unipolar brush cells (Mugnaini et al. 2010).

Granule cells are born in the external granular layer (EGL), a germinal epithelium that forms from the rhombic lip and spreads to cover the cerebellar surface. Postmitotic granule cells migrate into the cerebellar anlage, following Bergmann glial guides, for 20–30 days, to create the adult granular layer (reviewed in Sillitoe and Joyner 2007).

The EGL of the developing cerebellum and the granular layer of the adult cerebellum are subdivided by transverse boundaries revealed by lineage tracing, gene expression patterns, or through the consequences of genetic mutations. Several patterns of granular layer and/or EGL gene expression reveal transverse expression boundaries (e.g., reviewed in Hawkes et al. 1999), one aligned with the AZ/CZ boundary (~lobule V–VI) and another at the PZ/NZ boundary (in lobule IX: reviewed in Ozol and Hawkes 1997). In addition, mRNA analysis reveals a complex map of *Fgf* receptor and ligand expression in the EGL and granular layer (Yaguchi

et al. 2009). These zonal relationships may reflect either epigenetic interactions with Purkinje cells or distinct cell autonomous effects. It is likely that both occur. From the spatial distribution of genotypes in embryonic stem cell chimeras, it was concluded that the cerebellar granular layer derives from two distinct precursor pools on either side of a lineage boundary within the rhombic lip (Hawkes et al. 1999). This is consistent with previous chimera studies, which also suggested that granule cells across the AZ/CZ and PZ/NZ boundaries have separate developmental origins (e.g., Goldowitz 1989). Additional evidence for a multiple origin of the EGL comes from studies of *scrambler* (Goldowitz et al. 1997) and *disabled* (Gallagher et al. 1998) mutants in which there is an incomplete fusion of the anterior and posterior granular layers in lobule VI leaving distinct, overlapping anterior and posterior leaflets. Finally, by using a *Math1*^{CreER} allele, Machold and Fishell (2005) demonstrated by genetic fate mapping that granule cell progenitors are destined to populate specific anterior–posterior zones. For example, lineages marked at E12.5 selectively populate the AZ, whereas those marked at E15.5 populate all but the NZ. Together, these data suggest that the allocation of cells to specific EGL compartments may be dependent on spatial and temporal regulation of cellular movements and gene expression.

It is difficult to imagine that the striped expression patterns in the granular layer are generated by the differential migration of EGL lineages. For example, neuronal nitric oxide synthase (nNOS – or its surrogate nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase) is expressed in the adult granular layer in stripes that align with Purkinje cell stripes (Hawkes and Turner 1994). NADPHd/nNOS activity is first detected at P3. During the first postnatal week of development, the granular layer expresses nNOS uniformly (Schilling et al. 1994). Subsequently, clusters of granule cells begin to suppress their expression of nNOS, and from this, a new heterogeneous pattern of nNOS expression emerges that persists into adulthood (Yan et al. 1993; Schilling et al. 1994; Hawkes and Turner 1994). In such cases, it seems more plausible that differential gene expression is induced by the local Purkinje cell environment or by the input from mossy fiber stripes (Schilling et al. 1994). However, the migration of differentiated granule cells within parasagittal “raphes” could provide a physical mechanism that supports the segregation of granule cells into different topographic domains as they proceed toward the internal granular layer (Lin and Cepko 1998; Karam et al. 2001).

Cerebellar Topography and Circuit Function

It is evident that Purkinje cells are central to cerebellar topography. Purkinje cells contact or communicate with climbing fibers, mossy fibers, and granule cells throughout development to organize the cerebellar cortex into distinct domains. Given the structural role Purkinje cells have, it is not surprising that they are also vital for cerebellar function. Purkinje cells serve as the sole output of the cerebellar cortex and project directly to cerebellar nuclei neurons to control the rate and pattern of cerebellar output (Chaumont et al. 2013; Witter et al. 2013; White et al. 2014).

This cortico-nuclear projection is also compartmentalized (Hawkes and Leclerc 1986; Sugihara et al. 2009) raising the possibility that cerebellar function depends on an interplay between extrinsic and intrinsic Purkinje cell factors.

From Zones-And-Stripes to Complex Motor Behaviors

At first glance, the cerebellar circuit is organized rather simplistically: structurally identical circuits comprised of Purkinje cells, cerebellar nuclei neurons, afferent inputs, and interneurons are reiterated throughout its entirety. However, the presence of evolutionarily conserved zones-and-stripes raises the possibility that patterning is important for functional compartmentalization, information processing, and the execution of behaviors (Attwell et al. 1999; Horn et al. 2010; Mostofi et al. 2010; Graham and Wylie 2012). This hypothesis is especially intriguing since stripe and zone representations can vary with ecological niche (Corfield et al. 2016), which is perhaps a reflection of species-related functional specializations (tenrec, Sillitoe et al. 2003; star-nosed mole, Marzban et al. 2015). Moreover, severe motor deficits develop in disease models where zone formation is delayed or stripe boundaries are left unrefined (Sarna and Hawkes 2003; Strømme et al. 2011; White et al. 2014, 2016).

One reason for why stripes may drive cerebellar function is because Purkinje cells in different stripes have intrinsically different molecular profiles and synaptic properties, which in turn influence learning and behavior (Furuta et al. 1997; Nagao et al. 1997; Dehnes et al. 1998; Mateos et al. 2001; Wadiche and Jahr 2005; Kano et al. 2008; Paukert et al. 2010; Wang et al. 2011). For example, zebrin II+ Purkinje cells are enriched for mGluR1 at parallel fiber synapses and neuronal glutamate transporter (EAAT4) in their cell bodies, dendrites, and spines. Due to increased expression of mGluR1, upon parallel fiber and climbing fiber stimulation, "long latency patches," or regions of increased Ca^{2+} release, form at zebrin II+ parallel fiber–Purkinje cell and zebrin II+ climbing fiber–Purkinje cell synapses. These molecular differences are thought to support the compartmental regulation of synaptic plasticity (Wadiche and Jahr 2005; Paukert et al. 2010; Wang et al. 2011). It is interesting that several proteins that are expressed in stripes are required for the expression of long-term depression at parallel fiber – Purkinje cells synapses (Hawkes 2014).

Despite these advances in understanding the heterogeneous expression of plasticity, it is only recently that we have begun to appreciate how cellular function might support these differences. Single unit extracellular recordings were used to show that zebrin II+ Purkinje cell cells fire at a relatively low rate and with a regular firing pattern and that zebrin II- Purkinje cells fire at a much higher rate with a more irregular pattern (mouse, Zhou et al. 2014; rat, Xiao et al. 2014). Although the mechanism by which zebrin II+ Purkinje cells maintain lower baseline firing frequencies or more regular spike trains is unknown, an enrichment in VGLUT2 is thought to manifest in longer complex spikes, higher phase amplitudes, and more

spikelets per complex spike (Paukert et al. 2010; Xiao et al. 2014; Tang et al. 2017). This is because increased VGLUT2 expression has been shown to correlate with a larger ready-release vesicle pool, enhanced multivesicular release, and larger glutamate transients (Paukert et al. 2010). In contrast, zebrin II- Purkinje cells express more active transient receptor cation channels (TRPC3) downstream of mGluR1 than do zebrin II+ Purkinje cells (Hartmann et al. 2008; Zhou et al. 2014; Tang et al. 2017). Blocking TRPC3 results in decreased simple spike frequencies only in zebrin II- Purkinje cells, which supports its role in influencing basal activity (Zhou et al. 2014).

Perhaps the biggest unknown is how stripes contribute to motor behavior (Horn et al. 2010; Cerminara and Apps 2011). Among the questions are whether each stripe controls a specific behavior, or if not, how do stripes communicate and cooperate during a particular task? Synchronous activity might play a critical role in either scenario. Synchrony within zones is dependent on olivocerebellar connectivity (Welsh et al. 2002; Schultz et al. 2009). The presence of parallel fibers that disregard stripe boundaries and Purkinje cell collaterals that link neighboring cells and stripes are two possible anatomical substrates for how Purkinje cell activity might synchronize across zones-and-stripes (Tsutsumi et al. 2015; Witter et al. 2016). Parallel fibers span multiple zones and likely connect distant, molecularly heterogeneous Purkinje cells (Valera et al. 2016; Levy et al. 2017). Purkinje cell collaterals, on the other hand, directly connect Purkinje cells to other Purkinje cells, granule cells, interneurons, and Lugaro cells in select lobules. Such local connectivity could provide additional means to regulate cerebellar circuit activity and enhance processing capabilities (Watt et al. 2009; Witter et al. 2016; Guo et al. 2016). Whatever the mechanism, synchronizing Purkinje cells within and across stripes might dynamically control the cerebellar nuclei during motor behavior (Welsh et al. 1995; Gauck and Jaeger 2000; Yamamoto et al. 2001; De Zeeuw et al. 2011; Person and Raman 2012).

Conclusions

Every facet of cerebellar structure and function is built around the zone-and-stripe architecture. While the pattern formation process is complex, so is the operation of circuits that are located in the functional maps that ultimately form. Despite these challenges, a simple theme emerges – Purkinje cells are both the scaffold around which other structures organize and the control center from which different outputs are produced; disrupting them can lead to widespread abnormalities in cerebellar topography, function, and behavior.

Acknowledgments This work was supported by funds from Baylor College of Medicine (BCM) and Texas Children's Hospital, BCM IDDRC Grant U54HD083092 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (The IDDRC Neuropathology Sub-Core contributed to the tissue staining experiments), and by the National Institutes of Neurological Disorders and Stroke (NINDS) R01NS089664 and R01NS100874 to RVS.

Conflicts of Interest The authors declare no conflicts of interest.

References

Ahn AH, Dziennis S, Hawkes R, Herrup K (1994) The cloning of zebrin II reveals its identity with aldolase C. Development 120:2081–2090

Apps R, Hawkes R (2009) Cerebellar cortical organization: a one-map hypothesis. Nat Rev Neurosci 10:670–681

Armstrong C, Hawkes R (2000) Pattern formation in the cerebellar cortex. Biochem Cell Biol 78:551–562

Armstrong CL, Hawkes R (2001) Selective failure of Purkinje cell dispersion in the cerebellum of the *weaver* mouse. J Comp Neurol 439:151–161

Armstrong CL, Krueger AM, Currie RW, Hawkes R (2000) Constitutive expression of the 25 kDa heat shock protein Hsp25 reveals novel parasagittal bands of Purkinje cells in the adult mouse cerebellar cortex. J Comp Neurol 416:383–397

Armstrong CL, Krueger-Naug AMR, Currie RW, Hawkes R (2001) Expression of heat-shock protein Hsp25 in mouse Purkinje cells during development reveals novel features of cerebellar compartmentation. J Comp Neurol 429:7–21

Armstrong C, Chung SH, Armstrong J, Hochgeschwender U, Jeong YG, Hawkes R (2009) A novel somatostatin-immunoreactive mossy fiber pathway associated with HSP25-immunoreactive Purkinje cell stripes in the mouse cerebellum. J Comp Neurol 517:524–538

Armstrong CL, Duffin CA, McFarland R, Vogel MW (2011) Mechanisms of compartmental Purkinje cell death and survival in the Lurcher mutant mouse. Cerebellum 10(3):504–514

Arsenio-Nunes ML, Sotelo C (1985) Development of the spinocerebellar system in the postnatal rat. J Comp Neurol 237:291–306

Arsenio-Nunes ML, Sotelo C, Wehrle R (1988) Organization of spinocerebellar projection map in three types of agranular cerebellum: Purkinje cells vs granule cells as organizer elements. J Comp Neurol 272:120–136

Ashwell KW, Zhang L (1992) Ontogeny of afferents to the fetal rat cerebellum. Acta Anat 145(1):17–23

Ashwell KW, Zhang LI (1998) Prenatal development of the vestibular ganglion and vestibulocerebellar fibres in the rat. Anat Embryol (Berl) 198(2):149–61.

Attwell PJ, Rahman S, Ivarsson M, Yeo CH (1999) Cerebellar cortical AMPA-Kainate receptor blockade prevents performance of classically conditioned nictitating membrane responses. J Neurosci 19(24):RC45

Baader SL, Schilling ML, Rosengarten B, Pretsch W, Teutsch HF, Oberdick J, Schilling K (1996) Purkinje cell lineage and the topographic organization of the cerebellar cortex: a view from X inactivation mosaics. Dev Biol 174:393–406

Baader SL, Vogel MW, Sanlioglu S, Zhang X, Oberdick J (1999) Selective disruption of “late onset” sagittal banding patterns by ectopic expression of engrailed-2 in cerebellar Purkinje cells. J Neurosci 19:5370–5379

Bally-Cuif L, Alvarado-Mallart RM, Darnell DK, Wassef M (1992) Relationship between Wnt-1 and En-2 expression domains during early development of normal and ectopic met-mesencephalon. Development 115:999–1009

Beierbach E, Park C, Ackerman SL, Goldowitz D, Hawkes R (2001) Abnormal dispersion of Purkinje cell subset in the mouse mutant cerebellar deficient folia (cdf). J Comp Neurol 436(1):42–51

Bock HH, Herz J (2003) Reelin activates SRC family tyrosine kinases in neurons. Curr Biol 13:18–26

Brochu G, Maler L, Hawkes R (1990) Zebrin II: a polypeptide antigen expressed selectively by Purkinje cells reveals compartments in rat and fish cerebellum. J Comp Neurol 291:538–552

Carrillo J, Nishiyama N, Nishiyama H (2013) Dendritic translocation establishes the winner in cerebellar climbing fiber synapse elimination. J Neurosci 33(18):7641–7653

Cerminara NL, Apps R (2011) Behavioural significance of cerebellar modules. Cerebellum 10(3):484–494

Cesa R, Strata P (2009) Axonal competition in the synaptic wiring of the cerebellar cortex during development and in the mature cerebellum. Neuroscience 162:624–632

Chaumont J, Guyon N, Valera AM, Dugue GP, Popa D, Marcaggi P, Gautheron V, Reibel-Foisset S, Dieudonne S, Stephan A, Barrot M, Cassel JC, Dupont JL, Doussau F, Poulain B, Selimi F, Lena C, Isope P (2013) Clusters of cerebellar Purkinje cells control their afferent climbing fiber discharge. Proc Natl Acad Sci U S A 110(40):16223–16228

Chédotal A, Sotelo C (1992) Early development of olivocerebellar projections in the fetal rat using CGRP immunocytochemistry. Eur J Neurosci 4:1159–1179

Chédotal A, Bloch-Gallego E, Sotelo C (1997) The embryonic cerebellum contains topographic cues that guide developing inferior olivary axons. Development 124:861–870

Chizhikov VV, Lindgren AG, Currle DS, Rose MF, Monuki ES, Millen KJ (2006) The roof plate regulates cerebellar cell-type specification and proliferation. Development 133:2793–2804

Chockkan V, Hawkes R (1994) Functional and antigenic maps in the rat cerebellum: Zebrin compartmentation and vibrissal receptive fields in lobule IXa. J Comp Neurol 345:33–45

Chung S, Kim C-T, Hawkes R (2008a) Compartmentation of GABA B receptor 2 expression in the mouse cerebellar cortex. Cerebellum 7:295–303

Chung SH, Marzban H, Croci L, Consalez CC, Hawkes R (2008b) Purkinje cell subtype specification in the cerebellar cortex: EBF2 acts to repress the zebrin II-negative Purkinje cell phenotype. Neuroscience 153:721–732

Chung SH, Sillitoe R, Croci L, Baldoni A, Consalez G, Hawkes R (2009) Unipolar brush cells use Purkinje cells to restrict their topography. Neuroscience 164:1496–1508

Cook SA, Bronson RT, Donahue LR, Ben-Arie N, Davisson MT (1997) Cerebellar deficient folia (cdf): a new mutation on mouse chromosome 6. Mamm Genome 8:108–112

Corfield JR, Kolominsky J, Craciun I, Mulvany-Robbins BE, Wylie DR (2016) Is cerebellar architecture shaped by sensory ecology in the New Zealand Kiwi (Apteryx mantelli)? Brain Behav Evol 87(20):88–104

Crépel F (1982) Regression of functional synapses in the immature mammalian cerebellum. Trends Neurosci 5:266–269

Croci L, Chung SH, Masserdotti G, Gianola S, Motti E, Tonini R, Braida D, Bizzoca A, Gennarini G, Corradi A, Sala M, Rossi F, Hawkes R, Consalez GG (2006) A key role for the HLH transcription factor EBF2 (COE2, O/E-3) in Purkinje neuron migration and cerebellar cortical topography. Development 133:2719–2729

D'Arcangelo G, Nakajima K, Miyata T, Ogawa M, Mikoshiba K, Curran T (1997) Reelin is a secreted glycoprotein recognized by the CR-50 monoclonal antibody. J Neurosci 17(1):23–31

De Zeeuw CI, Hoebeek FE, Bosman LWJ, Schonewille M, Witter L, Koekkoek SK (2011) Spatiotemporal firing patterns in the cerebellum. Nat Rev Neurosci 12:327–344

Dehnes Y, Chaudhry FA, Ullensvang K, Lehre KP, Storm-Mathisen J, Danbolt NC (1998) The glutamate transporter EAAT4 in rat cerebellar Purkinje cells: a glutamate-gated chloride channel concentrated near the synapse in parts of the dendritic membrane facing astroglia. J Neurosci 18(10):3606–3619

Duffin CA, McFarland R, Sarna JR, Vogel MW, Armstrong CL (2010) Heat shock protein 25 expression and preferential Purkinje cell survival in the lurcher mutant mouse cerebellum. J Comp Neurol 518(11):1892–1907

Ebner TJ, Wang X, Gao W, Cramer SW, Chen G (2012) Parasagittal zones in the cerebellar cortex differ in excitability, information processing, and synaptic plasticity. Cerebellum 11 (2):418–419

Edwards MA, Leclerc N, Crandall JE, Yamamoto M (1994) Purkinje cell compartments in the *reeler* mutant mouse as revealed by zebrin II and 90-acetylated glycolipid antigen expression. Anat Embryol (Berlin) 190:417–428

Eisenman LM, Arlinghaus LE (1991) Spinocerebellar projection in the meander tail mutant mouse: organization in the granular posterior lobe and the agranular anterior lobe. Brain Res 558:149–152

Eisenman LM, Hawkes R (1993) Antigenic compartmentation in the mouse cerebellar cortex: zebrin and HNK-1 reveal a complex, overlapping molecular topography. J Comp Neurol 335:586–605

Eisenman LM, Gallagher E, Hawkes R (1998) Regionalization defects in the *weaver* mouse cerebellum. J Comp Neurol 18:431–444

Englund C, Kowalczyk T, Daza RA, Dagan A, Lau C, Rose MF, Hevner RF (2006) Unipolar brush cells of the cerebellum are produced in the rhombic lip and migrate through developing white matter. J Neurosci 26:9184–9195

Feirabend HK, van Luxemburg EA, van Denderen-van Dorp H, Voogd J (1985) A 3H-thymidine autoradiographic study of the development of the cerebellum of the White Leghorn (Gallus domesticus): “evidence for longitudinal neuroblast generation patterns”. Acta Morphol Neerl Scand 23(2):115–126

Fujita H, Morita N, Furuich T, Sugihara I (2012) Clustered fine compartmentalization of the mouse embryonic cerebellar cortex and its rearrangement into the postnatal striped configuration. J Neurosci 32(45):15688–15703

Furuta A, Martin LJ, Lin CL, Dykes-Hoberg M, Rothstein JD (1997) Cellular and synaptic localization of the neuronal glutamate transporters excitatory amino acid transporter 3 and 4. Neuroscience 81(4):1031–1042

Furutama D, Morita N, Takano R, Sekine Y, SAdakata T, Shinoda Y, Hyashi K, Mishima Y, Mikoshiba K, Hawkes R, Furuishu T (2010) Expression of the IP3R1 promoter-driven *nls-LacZ* transgene in Purkinje cell parasagittal arrays of developing mouse cerebellum. J Neurosci Res 88:2810–2825

Gallagher E, Howell BW, Soriano P, Cooper JA, Hawkes R (1998) Cerebellar abnormalities in the *disabled* (mdab1-1) mouse. J Comp Neurol 402:238–251

Gauck V, Jaeger D (2000) The control of rate and timing of spikes in the deep cerebellar nuclei by inhibition. J Neurosci 20(8):3006–3016

Gebre SA, Reeber SL, Sillitoe RV (2012) Parasagittal compartmentation of cerebellar mossy fibers as revealed by the patterned expression of vesicular glutamate transporters VGLUT1 and VGLUT2. Brain Struct Funct 217(2):165–180

Goldowitz D (1989) Cell allocation in mammalian CNS formation: evidence from murine inter-species aggregation chimeras. Neuron 3:705–713

Goldowitz D, Cushing RC, Laywell E, D’Arcangelo G, Sheldon M, Sweet HO, Davisson M, Steindler D, Curran T (1997) Cerebellar disorganization characteristic of *reeler* in *scrambler* mutant mice despite presence of Reelin. J Neurosci 17:8767–8777

Graham DJ, Wylie DR (2012) Zebrin-immunopositive and –immunonegative stripe pairs represent functional units in the pigeon vestibulocerebellum. J Neurosci 32(37):12769–12779

Gravel C, Hawkes R (1990) Parasagittal organization of the rat cerebellar cortex: direct comparison of Purkinje cell compartments and the organization of the spinocerebellar projection. J Comp Neurol 291:79–102

Gravel C, Eisenman LE, Sasseville R, Hawkes R (1987) Parasagittal organization of the rat cerebellar cortex: a direct correlation between antigenic Purkinje cell bands revealed by mabQ113 and the organization of the olivocerebellar projection. J Comp Neurol 263:294–310

Grishkat HL, Eisenman LM (1995) Development of the spinocerebellar projection in the prenatal mouse. J Comp Neurol 363:93–108

Guo C, Witter L, Rudolph S, Elliott HL, Ennis KA, Regehr WG (2016) Purkinje cells directly inhibit granule cells in specialized regions of the cerebellar cortex. Neuron 91:1–12

Hallem JS, Thompson J, Gundappa-Sulur S, Hawkes R, Bjallie JG, Bower JM (1999) Spatial correspondence between tactile projection patterns and the distribution of the antigenic Purkinje cell markers *anti-zebrin I* and *anti-zebrin II* in the cerebellar folium crus IIa of the rat. Neuroscience 93:1083–1094

Hartmann J, Dragicevic E, Adelsberger H, Henning HA, Sumser M, Abramowitz J, Blum R, Dietrich A, Freichel M, Flockerzi V, Birnbaumer L, Konnerth A (2008) TRPC3 channels are required for synaptic transmission and motor coordination. Neuron 59(3):392–398

Hashimoto M, Mikoshiba K (2002) Mediolateral compartmentalization of the cerebellum is determined on the “birth date” of Purkinje cells. J Neurosci 23:11342–11351

Hawkes R (1997) An anatomical model of cerebellar modules. Prog Brain Res 114:39–52

Hawkes R (2014) Purkinje cell stripes and long-term depression at the parallel fiber-Purkinje cell synapse. Front Syst Neurosci 8(41):1–11

Hawkes R, Eisenman LM (1997) Stripes and zones: the origins of regionalization of the adult cerebellum. Persp Dev Neurobiol 5:95–105

Hawkes R, Gravel C (1991) The modular cerebellum. Prog Neurobiol 36:309–327

Hawkes R, Leclerc N (1986) Immunocytochemical demonstration of topographic ordering of Purkinje cell axon terminals in the fastigial nuclei of the rat. J Comp Neurol 244(4):481–491

Hawkes R, Leclerc N (1987) Antigenic map of the rat cerebellar cortex: the distribution of parasagittal bands as revealed by a monoclonal anti-Purkinje cell antibody mabQ113. J Comp Neurol 256:29–41

Hawkes R, Turner RW (1994) Compartmentation of NADPH-diaphorase activity in the mouse cerebellar cortex. J Comp Neurol 346:499–516

Hawkes R, Colonnier M, Leclerc N (1985) Monoclonal antibodies reveal sagittal banding in the rodent cerebellar cortex. Brain Res 333:359–365

Hawkes R, Faulkner-Jones B, Tam P, Tan SS (1998) Pattern formation in the cerebellum of murine embryonic stem cell chimeras. Eur J Neurosci 10:790–793

Hawkes R, Beirebach E, Tan SS (1999) Granule cell dispersion is restricted across transverse boundaries in mouse chimeras. Eur J Neurosci 11:3800–3808

Herrup K, Kuemerle B (1997) The compartmentalization of the cerebellum. Ann Rev Neurosci 20:61–90

Horn KM, Pong M, Gibson AR (2010) Functional relations of cerebellar modules of the cat. J Neurosci 30(28):9411–9423

Hoshino M, Nakamura S, Mori K, Kawauchi T, Terao M, Nishimura YV, Fukuda A, Fuse T, Matsuo N, Sone M, Watanabe M, Bito H, Terashima T, Wright CV, Kawaguchi Y, Nakao K, Nabeshima Y (2005) Ptf1a, a bHLH transcriptional gene, defines GABAergic neuronal fates in cerebellum. Neuron 47:201–213

Howell BW, Hawkes R, Soriano P, Cooper JA (1997) Neuronal position in the developing brain is regulated by mouse *disabled*-1. Nature 389:733–737

Jensen P, Zoghbi HY, Goldowitz D (2002) Dissection of the cellular and molecular events that position cerebellar Purkinje cells: a study of the math1 null-mutant mouse. J Neurosci 22:8110–8116

Ji Z, Hawkes R (1994) Topography of Purkinje cell compartments and mossy fiber terminal fields in lobules II and III of the rat cerebellar cortex: spinocerebellar and cuneocerebellar projections. Neuroscience 61:935–954

Ji Z, Hawkes R (1995) Developing mossy fiber terminal fields in the rat cerebellar cortex may segregate because of Purkinje cell compartmentation and not competition. J Comp Neurol 359:197–212

Kalinovsky A, Boukhtouche F, Blazesk R, Bornmann C, Suzuki N, Mason CA, Scheiffele P (2011) Development of axon-target specificity of ponto-cerebellar afferents. PLoS Biol 9(2): e1001013

Kano M, Hashimoto K, Tabata T (2008) Type-1 metabotropic glutamate receptor in cerebellar Purkinje cells: a key molecule responsible for long-term depression, endocannabinoid signaling and synapse elimination. Philos Trans R Soc B 363:2173–2186

Karam SD, Burrows RC, Logan C, Koblar S, Pasquale EB, Bothwell M (2000) Eph receptors and ephrins in the developing chick cerebellum: relationship to sagittal patterning and granule cell migration. J Neurosci 20:6488–6500

Karam SD, Kim YS, Bothwell M (2001) Granule cells migrate within raphes in the developing cerebellum: an evolutionarily conserved morphogenic event. J Comp Neurol 440(2):127–135

Kuo G, Arnaud L, Kronstad-O'Brien P, Cooper JA (2005) Absence of Fyn and Src causes a reeler-like phenotype. J Neurosci 25:8578–8586

Lannoo MJ, Brochu G, Maler L, Hawkes R (1991) Zebrin II immunoreactivity in the rat and in the weakly electric teleost *Eigenmannia* (Gymnotiformes) reveals three modes of Purkinje cell development. J Comp Neurol 310:215–233

Larouche M, Hawkes R (2006) From clusters to stripes: the developmental origins of adult cerebellar compartmentation. Cerebellum 5:77–88

Larouche M, Che P, Hawkes R (2006) Neurogranin expression identifies a novel array of Purkinje cell parasagittal stripes during mouse cerebellar development. J Comp Neurol 494:215–227

Larouche M, Beffert U, Herz J, Hawkes R (2008) The reelin receptors Apoer2 and Vldlr coordinate the patterning of Purkinje cell topography in the developing mouse cerebellum. PLoS One 3(2): e1653

Leclerc N, Gravel C, Hawkes R (1988) Development of parasagittal zonation in the rat cerebellar cortex: mabQ113 antigenic bands are created postnatally by the suppression of antigen expression in a subset of Purkinje cells. J Comp Neurol 273:399–420

Lee SK, Sillitoe RV, Silva C, Martina M, Sekerkova G (2015) α-Synuclein expression in the mouse cerebellum is restricted to VGluT1 excitatory terminals and is enriched in unipolar brush cells. Cerebellum 14(5):516–527

Levy SL, White JJ, Lackey EP, Schwartz L, Sillitoe RV (2017) WGA-Alexa conjugates for axonal tracing. Curr Protoc Neurosci 79:1.28.1–1.28.24

Lin JC, Cepko CL (1998) Granule cell raphes and parasagittal domains of Purkinje cells: complementary patterns in the developing chick cerebellum. J Neurosci 18(22):9342–9353

Machold R, Fishell G (2005) Math1 is expressed in temporally discrete pools of cerebellar rhombic-lip neural progenitors. Neuron 48:17–24

Marzban H, Hawkes R (2011) On the architecture of the posterior zone of the cerebellum. Cerebellum 10(3):422–434

Marzban H, Sillitoe RV, Hoy M, Chung S, Rafuse VF, Hawkes R (2004) Abnormal HNK-1 expression in the cerebellum of an N- CAM null mouse. J Neurocytol 33:117–130

Marzban H, Chung SH, Watanabe M, Hawkes R (2007) Phospholipase Cß4 expression reveals the continuity of cerebellar topography through development. J Comp Neurol 502:857–871

Marzban H, Hoy N, Buchok M, Catania KC, Hawkes R (2015) Compartmentation of the cerebellar cortex: adaptation to lifestyle in the star-nosed mole *Condylura cristata*. Cerebellum 14(2):106–118

Mason CA, Gregory E (1984) Postnatal maturation of cerebellar mossy and climbing fibers: transient expression of dual features on single axons. J Neurosci 4:1715–1735

Mateos JM, Osorio A, Azkue JJ, Benitez R, Elezgarai I, Bilbao A, Diez J, Puente N, Kuhn R, Knopfel T, Hawkes R, Donate-Oliver F, Grandes P (2001) Parasagittal compartmentalization of the metabotropic glutamate receptor mGluR1b in the cerebellar cortex. Eur J Anat 5:15–21

Mathis L, Bonnerot C, Puelles L, Nicolas JF (1997) Retrospective clonal analysis of the cerebellum using genetic laacZ/lacZ mouse mosaics. Development 124:4089–4104

Miale IL, Sidman RL (1961) An autoradiographic analysis of histogenesis in the mouse cerebellum. Exp Neurol 4:277–296

Millen KJ, Hui CC, Joyner AL (1995) A role for En-2 and other murine homologues of *Drosophila* segment polarity genes in regulating positional information in the developing cerebellum. Development 121:3935–3945

Miyata T, Ono Y, Okamoto M, Masaoka M, Sakakibara A, Kawaguchi A, Mitsuhiro M, Ogawa M (2010) Migration, early axonogenesis, and Reelin-dependent layer-forming behavior of early/posterior-born Purkinje cells in the developing mouse lateral cerebellum. Neural Dev 5:23

Morales D, Hatten ME (2006) Molecular markers of neuronal progenitors in the embryonic cerebellar anlage. J Neurosci 26:12226–12236

Mostofi A, Holtzman T, Grout AS, Yeo CH, Edgley SA (2010) Electrophysiological localization of eyeblink-related microzones in rabbit cerebellar cortex. J Neurosci 30(26):8920–8934

Mugnaini E, Sekerkova G, Martina M (2010) The unipolar brush cell: a remarkable neuron finally receiving the deserved attention. Brain Res Rev 66(1–2):220–245

Nagao S, Kwak S, Kanazawa I (1997) EAAT4, a glutamate transporter with properties of a chloride channel, is predominantly localized in Purkinje cell dendrites, and forms parasagittal compartments in rat cerebellum. Neuroscience 78(4):929–933

Napieralski JA, Eisenman LM (1996) Further evidence for a unique developmental compartment in the cerebellum of the *meander tail* mutant mouse as revealed by the quantitative analysis of Purkinje cells. J Comp Neurol 364:718–728

Nishida K, Flanagan JG, Nakamoto M (2002) Domain-specific olivocerebellar projection regulated by the EphA-ephrin-A interaction. Development 129:5647–5658
Nunzi MG, Grillo M, Margolis FL, Mugnaini E (1999) Compartmental organization of Purkinje cells in the mature and developing mouse cerebellum as revealed by an olfactory marker protein-lacZ transgene. J Comp Neurol 404:97–113
Oberdick J, Schilling K, Smeyne RJ, Corbin JG, Bocchiaro C, Morgan JI (1993) Control of segment-like patterns of gene expression in the mouse cerebellum. Neuron 10:1007–1018
Oberdick J, Baader SL, Schilling K (1998) From zebra stripes to postal zones: deciphering patterns of gene expression in the cerebellum. Trends Neurosci 9:383–390
Ohshima T, Mikoshiba K (2002) Reelin signaling and Cdk5 in the control of neuronal positioning. Mol Neurobiol 26:153–166
Ozol K, Hawkes R (1997) Compartmentation of the granular layer of the cerebellum. Histol Histopathol 12:171–184
Ozol K, Hayden JM, Oberdick J, Hawkes R (1999) Transverse zones in the vermis of the mouse cerebellum. J Comp Neurol 412:95–111
Paradies MA, Grishkat H, Smeyne RJ, Oberdick J, Morgan JI, Eisenman LM (1996) Correspondence between L7-lacZ-expressing Purkinje cells and labeled olivocerebellar fibers during late embryogenesis in the mouse. J Comp Neurol 374:451–466
Park C, Falls W, Finger JH, Longo-Guess CM, Ackerman SL (2002) Deletion in *Catna2*, encoding aN-catenin, causes cerebellar and hippocampal lamination defects and impaired startle modulation. Nat Genet 31:279–284
Pascual M, Abasolo I, Mingorance-Le Meur A, Martinez A, Del Rio JA, Wright CV, Real FX, Soriano E (2007) Cerebellar GABAergic progenitors adopt an external granule cell-like phenotype in the absence of Ptf1a transcription factor expression. Proc Natl Acad Sci U S A 104:5193–5198
Paukert M, Huang YH, Tanaka K, Rothstein JD, Bergles DE (2010) Zones of enhanced glutamate release from climbing fibers in the mammalian cerebellum. J Neurosci 20(21):7290–7299
Person AL, Raman IM (2012) Purkinje neuron synchrony elicits time-locked spiking in the cerebellar nuclei. Nature 481:502–505
Ragagnin A, Ezpeleta J, Guillemain A, Boudet-Devaud F, Haeberlé A, Demais V, Vidal C, Demuth S, Beringué V, Kellerman O, Schneider B, Grant NJ, Bailly Y (2017) Cerebellar compartmentation of prion pathogenesis. Brain Pathol. In press
Redies C, Neudert F, Lin J (2010) Cadherins in cerebellar development: translation of embryonic patterning into mature functional compartmentalization. Cerebellum 10(3):393–408
Rivkin A, Herrup K (2003) Development of cerebellar modules: extrinsic control of late-phase zebrin II pattern and the exploration of rat/mouse species differences. Mol Cell Neurosci 24:887–901
Ross ME, Fletcher C, Mason CA, Hatten ME, Heintz N (1990) *Meander tail* reveals a discrete developmental unit in the mouse cerebellum. Proc Natl Acad Sci U S A 87:4189–4192
Ruigrok TJ (2011) Ins and outs of cerebellar modules. Cerebellum 10(3):464–474
Sarna JR, Hawkes R (2003) Patterned Purkinje cell death in the cerebellum. Prog Neurobiol 70:473–507
Sarna JR, Marzban H, Watanabe M, Hawkes R (2006) Complementary stripes of phospholipase Cß3 and Cß4 expression by Purkinje cell subsets in the mouse cerebellum. J Comp Neurol 496:303–313
Schilling K, Schmidt HH, Baader SL (1994) Nitric oxide synthase expression reveals compartments of cerebellar granule cells and suggests a role for mossy fibers in their development. Neuroscience 59:893–903
Schultz SR, Kitamura K, Post-Uiterweer A, Krupic J, Hausser M (2009) Spatial pattern coding of sensory information by climbing fiber-evoked calcium signals in networks of neighboring cerebellar Purkinje cells. J Neurosci 29(25):8005–8015
Seil FJ, Johnson ML, Hawkes R (1995) Molecular compartmentation expressed in cerebellar cultures in the absence of neuronal activity and neuron-glia interactions. J Comp Neurol 356:398–407

Sheldon M, Rice DS, D'Arcangelo G, Yoneshima H, Nakajima K, Mikoshiba K, Howell BW, Cooper JA, Goldowitzk D, Curran T (1997) Scrambler and yotari disrupt the disabled gene and produce a reeler-like phenotype in mice. Nature 389(6652):730–733
Sillitoe RV (2016) Mossy fibers terminate directly within Purkinje cell zones during mouse development. Cerebellum 15(1):14–17
Sillitoe RV, Hawkes R (2002) Whole-mount immunohistochemistry: a high-throughput screen for patterning defects in the mouse cerebellum. J Histochem Cytochem 50:235–244
Sillitoe RV, Joyner AL (2007) Morphology, molecular codes, and circuitry produce the three-dimensional complexity of the cerebellum. Annu Rev Cell Dev Biol 23:549–577
Sillitoe RV, Künzle H, Hawkes R (2003) Zebrin II compartmentation of the cerebellum in a basal insectivore, the Madagascan hedgehog tenrec *Echinops telfairi*. J Anat 203(3):283–296
Sillitoe RV, Marzban H, Larouche M, Zahedi S, Affanni J, Hawkes R (2005) Conservation of the architecture of the anterior lobe vermis of the cerebellum across mammalian species. Prog Brain Res 148:283–297
Sillitoe RV, Chung SH, Fritschy JM, Hoy M, Hawkes R (2008a) Golgi cell dendrites are restricted by Purkinje cell stripe boundaries in the adult mouse cerebellar cortex. J Neurosci 28:2820–2826
Sillitoe RV, Stephen D, Lao Z, Joyner AL (2008b) Engrailed homeobox genes determine the organization of Purkinje cell sagittal stripe gene expression in the adult cerebellum. J Neurosci 28:12150–12162
Sillitoe RV, Gopal N, Joyner AL (2009) Embryonic origins of ZebrinII parasagittal stripes and establishment of topographic Purkinje cell projections. Neuroscience 162:574–588
Sillitoe RV, Vogel MW, Joyner AL (2010) Engrailed homeobox genes regulate establishment of the cerebellar afferent circuit map. J Neurosci 30:10015–10024
Smeyne RJ, Oberdick J, Schilling K, Berrebi AS, Mugnaini E, Morgan JI (1991) Dynamic organization of developing Purkinje cells revealed by transgene expression. Science 254:719–721
Sotelo C (2004) Cellular and genetic regulation of the development of the cerebellar system. Prog Neurobiol 72:295–339
Sotelo C, Chédotal A (2005) Development of the olivocerebellar system: migration and formation of cerebellar maps. Prog Brain Res 148:1–20
Sotelo C, Bourrat F, Triller A (1984) Postnatal development of the inferior olivary complex in the rat. II. Topographic organization of the immature olivocerebellar projection. J Comp Neurol 222:177–199
Strasser V, Fasching D, Hauser C, Mayer H, Bock HH, Hiesberger T, Herz J, Weeber EJ, Sweatt JD, Pramatarova A, Howell B, Schneider WJ, Nimpf J (2004) Receptor clustering is involved in Reelin signaling. Mol Cell Biol 24:1378–1386
Strømme P, Dobrenis K, Sillitoe RV, Gulinello M, Ali NF, Davidson C, Micsenyi MC, Stephney G, Ellevog L, Klungland A, Walkley SU (2011) X-linked Angelman-like syndrome caused by Slc9a6 knockout in mice exhibits evidence of endosomal-lysosomal dysfunction. Brain 134:3369–3383
Sudarov A, Joyner AL (2007) Cerebellum morphogenesis: the foliation pattern is orchestrated by multi-cellular anchoring centers. Neural Dev 2:26
Sudarov A, Turnbull RK, Kim EJ, Lebel-Potter M, Guillemot F, Joyner AL (2011) Ascl1 genetics reveals insights into cerebellum local circuit assembly. J Neurosci 31(3):11055–11069
Sugihara I, Quy PN (2007) Identification of aldolase C compartments in the mouse cerebellar cortex by olivocerebellar labeling. J Comp Neurol 500:1076–1092
Sugihara I, Fujita H, Na J, Quy PN, Li BY, Ikeda D (2009) Projection of reconstructed single Purkinje cell axons in relation to the cortical and nuclear aldolase C compartments of the rat cerebellum. J Comp Neurol 512(2):282–304
Takeda T, Maekawa K (1989) Transient direct connection of vestibular mossy fibers to the vestibulocerebellar Purkinje cells in early postnatal development of kittens. Neuroscience 32:99–111

Tang T, Xiao J, Suh CY, Burroughs A, Cerminara NL, Jia L, Lang EJ (2017) Heterogeneity of Purkinje cell simple spike-complex spike interactions: zebrin- and non-zebrin-related variations. J Physiol 595(15):5341–5357

Tano D, Napieralski JA, Eisenman LM, Messer A, Plummer J, Hawkes R (1992) Novel developmental boundary in the cerebellum revealed by zebrin expression in the lurcher (Lc/+) mutant mouse. J Comp Neurol 323:128–136

Thomas KR, Musci TS, Neumann PE, Capecchi M (1991) *Swaying* is a mutant allele of the proto-oncogene Wnt-1. Cell 67:969–976

Tissir F, Goffinet AM (2003) Reelin and brain development. Nat Rev Neurosci 4:496–505

Tolbert DL, Pittman T, Alisky JM, Clark BR (1994) Chronic NMDA receptor blockade or muscimol inhibition of cerebellar cortical neuronal activity alters the development of spinocerebellar afferent topography. Dev Brain Res 80(1–2):268–274

Trommsdorff M, Gotthardt M, Hiesberger T, Shelton J, Stockinger W, Nimpf J, Hammer RE, Richardson JA, Herz J (1999) Reeler/disabled-like disruption of neuronal migration in knockout mice lacking the VLDL receptor and ApoE receptor 2. Cell 97:689–701

Tsutsumi S, Yamazaki M, Miyazaki T, Watanabe M, Sakimura K, Kano M, Kitamura K (2015) Struture-function relationships between aldolase c/zebrin II expression and complex spike synchrony in the cerebellum. J Neurosci 35(2):843–852

Valera AM, Pawlowski SA, Dupont J, Casella J, Rothsten JD, Poulain B, Isope P (2016) Stereotyped spatial patterns of functional synaptic connectivity in the cerebellar cortex. eLife 5:e09862

Voogd J, Ruigrok TJH (2004) The organization of the corticonuclear and olivocerebellar climbing fiber projections to the rat cerebellar vermis: the congruence of projection zones and the zebrin pattern. J Neurocytol 33:5–21

Wadiche JI, Jahr CE (2005) Patterned expression of Purkinje cell glutamate transporters controls synaptic plasticity. Nat Neurosci 8(10):1329–1334

Wang VY, Rose MF, Zoghbi HY (2005) Math1 expression redefines the rhombic lip derivatives and reveals novel lineages within the brainstem and cerebellum. Neuron 48:31–43

Wang X, Chen G, Gao W, Ebner TJ (2011) Parasagittally aligned, mGluR1-dependent patches are evoked at long latencies by parallel fiber stimulation in the mouse cerebellar cortex. J Neurophysiol 105:1732–1746

Wassef M, Joyner AL (1997) Early mesencephalon/metencephalon patterning and development of the cerebellum. Perspect Dev Neurobiol 5:3–16

Wassef M, Cholley B, Heizmann CW, Sotelo C (1992) Development of the olivocerebellar projection in the rat: II. Matching of the developmental compartmentations of the cerebellum and inferior olive through the projection map. J Comp Neurol 323(4):537–550

Wassef M, Sotelo C (1984) Asynchrony in the expression of guanosine 3′:5′-phosphate-dependent protein kinase by clusters of Purkinje cells during the perinatal development of rat cerebellum. Neuroscience 13(4):1217–1241

Wassef M, Zanetta JP, Brehier A, Sotelo C (1985) Transient biochemical compartmentalization of Purkinje cells during early cerebellar development. Dev Biol 111:129–137

Wassef M, Sotelo C, Thomasset M, Granholm A-C, Leclerc N, Rafrafi J, Hawkes R (1990) Expression of compartmentation antigen zebrin I in cerebellar transplants. J Comp Neurol 294:223–234

Watson CM, Pelka GJ, Radziewic T, Shahbazian MD, Christodoulou J, Williamson SL, Tam PPL (2005) Reduced proportion of Purkinje cells expressing paternally derived mutant *Mecp2308* allele in female mouse cerebellum is not due to a skewed primary pattern of X-chromosome inactivation. Hum Mol Genet 14:1851–1861

Watt AJ, Cuntz H, Mori M, Nusser Z, Sjöström PJ, Häusser M (2009) Traveling waves in developing cerebellar cortex mediated by asymmetrical Purkinje cell connectivity. Nat Neurosci 12:463–473

Welsh JP, Lang EJ, Sugihara I, Llinás R (1995) Dynamic organization of motor control within the olivocerebellar system. Nature 374:453–457

Welsh JP, Yuen G, Placantonakis DG, Vu TQ, Haiss F, O'Hearn E, Molliver ME, Aicher SA (2002) Why do Purkinje cells die so easily after global brain ischemia? Aldolase C, EAAT4, and the cerebellar contribution to posthypoxic myoclonus. Adv Neurol 89:331–359

White JJ, Sillitoe RV (2013) Development of the cerebellum: from gene expression patterns to circuit maps. Wiley Interdiscip Rev Dev Biol 2(1):149–164

White JJ, Arancillo M, Stay TL, George-Jones NA, Levy SL, Heck DH, Sillitoe RV (2014) Cerebellar zonal patterning relies on Purkinje cell neurotransmission. J Neurosci 34(24):8231–8245

White JJ, Arancillo M, King A, Lin T, Miterko LN, Gebre SA, Sillitoe RV (2016) Pathogenesis of severe ataxia and tremor without the typical signs of neurodegeneration. Neurobiol Dis 86:86–98

Williams BL, Yaddanapudi K, Hornig M, Lipkin WI (2007) Spatiotemporal analysis of Purkinje cell degeneration relative to parasagittal expression domains in a model of neonatal viral infection. J Virol 81(6):2675–2687

Wingate RJ (2001) The rhombic lip and early cerebellar development. Curr Opin Neurobiol 11:82–88

Witter L, Canto CB, Hoogland TM, de Gruijl JR, De Zeeuw CI (2013) Strength and timing of motor responses mediated by rebound firing in the cerebellar nuclei after Purkinje cell activation. Front Neural Circuits 7:133

Witter L, Rudolph S, Pressler RT, Lahlaf SI, Regehr WG (2016) Purkinje cell collaterals enable output signals from cerebellar cortex to feed back to Purkinje cells and interneurons. Neuron 91:1–8

Xiao J, Cerminara NL, Kotsurovskyy Y, Aoki H, Burroughs A, Wise AK, Luo Y, Marshall SP, Sugihara I, Apps R, Lang EJ (2014) Systematic regional variations in Purkinje cell spiking patterns. PLoS One 9(8):e105633

Yaguchi Y, Yu T, Ahmed MU, Berry M, Mason I, Basson MA (2009) Fibroblast growth factor (FGF) gene expression in the developing cerebellum suggests multiple roles for FGF signaling during cerebellar morphogenesis and development. Dev Dyn 238:2058–2072

Yamada M, Terao M, Terashima T, Fujiyama T, Kawaguchi Y, Nabeshima Y, Hoshino M (2007) Origin of climbing fiber neurons and their developmental dependence on Ptf1a. J Neurosci 27:10924–10934

Yamamoto T, Fukuda M, Llinás R (2001) Bilaterally synchronous complex spike Purkinje cell activity in the mammalian cerebellum. Eur J Neurosci 13(2):327–339

Yan XX, Yen LS, Garey LJ (1993) Parasagittal patches in the granular layer of the developing and adult rat cerebellum as demonstrated by NADPH-diaphorase histochemistry. Neuroreport 4:1227–1230

Zervas M, Millet S, Ahn S, Joyner AL (2004) Cell behaviors and genetic lineages of the mesencephalon and rhombomere 1. Neuron 43:345–357

Zervas M, Blaess S, Joyner AL (2005) Classical embryological studies and modern genetic analysis of midbrain and cerebellum development. Curr Top Dev Biol 69:101–138

Zhou H, Lin Z, Voges K, Ju C, Gao Z, Bosman LWJ, Ruigrok TJH, Hoebeek FE, De Zeeuw CI, Schonewille M (2014) Cerebellar modules operate at different frequencies. elife 3:e02536

Zordan P, Croci L, Hawkes R, Consalez GG (2008) A comparative analysis of proneural gene expression in the embryonic cerebellum. Dev Dyn 237:1726–1735