Development of Physiological Activity in the Cerebellum

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Sriram Jayabal and Alanna J. Watt

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Abstract

One remarkable aspect of cerebellar development is that intrinsic physiological activity of several neuronal cell types, including Purkinje cells, can be observed throughout a large portion of the developmental window. Although ion channels primarily drive this intrinsic activity, it can also be influenced by other cellular properties and inputs, including synaptic and neuromodulatory inputs, calcium buffers, and others. Many of the factors that drive or influence intrinsic activity are expressed in a tightly regulated manner during the development of the cerebellum. Here, we review how the ion channels, calcium buffers, synapses, and neuromodulators that are differentially expressed during development give

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rise to activity patterns with unique regulatory properties, which may serve important roles in sculpting the developing cerebellum. We also review recent lines of evidence that suggest changes in synaptic and intrinsic activity may be common developmental changes contributing to the pathophysiology of not only cerebellar ataxias but also neurodevelopmental diseases such as autism spectrum disorders. Finally, we posit that these findings support a hypothesis for an important role for early physiological activity in the formation of the cerebellum and that alterations in this activity can lead to pathology.

Keywords

Cerebellum · Purkinje cell · Ion channels · Autism · Ataxia · Development

Introduction

Neuronal Development

If you were to build a machine that specializes in planning and executing well-timed events – a mechanical cerebellum – you would likely approach the task systematically: assembling it piece by piece, connecting and checking each new addition before you move on to the next, and, at the end, once everything was assembled, you would hook up the electricity to start it, or "turn on the juice." This is a far cry from the way that biology has evolved for the task of building a cerebellum. The self-assembly of the cerebellum, and, indeed, the entire nervous system, is a complex, tumultuous process – neurons are born at different times in different places, far from their eventual home, and then migrate along neuronal highways like cars in rush hour, eventually making both pre- and postsynaptic connections with an excess of neuronal partners, before pruning away a subset of those connections. Surprisingly, many neurons will not survive this juvenile stage, but die before the circuit is mature. While scientists tend to study individual developmental processes in isolation, there are in fact multiple parallel processes occurring during development, which makes the process of brain development difficult to understand in its entirety.

Not only is brain development a complex process, but it is also noisy. The nervous system does not become active only when mature, but is active already throughout much of the assembly process. Activity of neurons arises from fluctuations in the membrane potential due to activation of ligand-gated and voltage-gated channels, causing synaptic signals and action potentials. A large number of ion channels, transporters, and other molecules that influence the activity are expressed in distinct patterns during development. This produces unique activity motifs during the developmental period in the healthy brain. In this review, we focus on the physiological activity of the developing cerebellum in health and cerebellar disease. Much of our review will focus on Purkinje cells, the principal cell and sole projection neuron of the cerebellar cortex and arguably the most studied cell type of the cerebellum. In the interest of space, we unfortunately cannot describe the

physiological development of all neurons in the cerebellum, although we will touch on the development of their activity when possible.

Cerebellar Physiology

One prominent feature of the cerebellum is that several cell types exhibit spontaneous rhythmic activity. This is best studied in Purkinje cells, which exhibit high-frequency rhythmic firing in adults, even in the absence of synaptic input (Arancillo et al. 2015; McKay and Turner 2005; Woodward et al. 1969; Llinas and Sugimori 1980; Nam and Hockberger 1997; Häusser and Clark 1997). However, several other cell types also exhibit spontaneous activity in the cerebellum, including cells of the deep cerebellar nuclei (DCN) (Jahnsen 1986; Llinas and Muhlethaler 1988) (Reviewed in Elsen et al. 2018), molecular layer interneurons (Häusser and Clark 1997), and Golgi cells (Forti et al. 2006; Edgley and Lidierth 1987). In general, a neuron's capacity for intrinsic activity is due to the constellation of ion channels that are expressed in the membrane of these cells, which for Purkinje cells we will discuss in greater detail below.

During postnatal development in mice, the cerebellum undergoes profound developmental changes. Purkinje cells increase their somatic size and dramatically expand their dendritic arbors during postnatal development (Altman 1972). Purkinje cell intrinsic firing emerges during the first few days of postnatal development in rodents at lower firing rates than in adults. Firing frequency then slowly increases during postnatal development until stabilizing at adult levels near the end of the postnatal developmental window (~4 weeks old) (McKay and Turner 2005; Watt et al. 2009; Woodward et al. 1969; Arancillo et al. 2015).

Early Influences of Adult Firing Patterns

While we will review the nuts and bolts of how Purkinje cell activity is regulated developmentally below, it is interesting to mention some new studies first that suggest that the ultimate state of Purkinje cell activity is influenced by very early embryonic events. Purkinje cells are born early in the developing embryo (Miale and Sidman 1961; Altman and Bayer 1985 reviewed in Butts et al. 2018). After birth, they migrate to the cerebellar cortex where they populate the early Purkinje cell layer (Altman and Bayer 1985 reviewed in Sotelo and Rossi 2018); in the cerebellar vermis, this occurs along a posterior–anterior axis, where posterior cells are born earlier than anterior cells (Altman and Bayer 1985). Recently, Kim and colleagues have elegantly shown that posterior lobule Purkinje cells in the vermis are less excitable than anterior, later-born Purkinje cells (Kim et al. 2012). How might the birthdate of a Purkinje cell influence its adult excitability? In the mature cerebellum, Purkinje cells can be classified by their zebrin expression profile, which is thought to be determined not long after a Purkinje cell is born (reviewed in Sillitoe and Hawkes 2018). Two groups have recently shown that difference in excitability correlates not

simply with anterior–posterior axis but with the zebrin expression profile of the Purkinje cells, where zebrin$^-$ cells fire at higher frequencies than zebrin$^+$ cells, irrespective of their location within the anterior–posterior axis (Zhou et al. 2014; Xiao et al. 2014). Thus, a fundamental property of a Purkinje cell in the adult brain – the rate of their stereotypical high-frequency firing – appears to be influenced by factors established at or shortly after the Purkinje cell is born. How is this firing established during development?

What Influences Physiological State of Developing Purkinje Cells?

Ion Channels

Sodium Channels

During the postnatal period, profound morphological and physiological developmental changes take place, including the molecular identity of the cells. These changes, such as the differential expression of ion channels, can influence firing properties. As firing properties of cells mature (McKay and Turner 2005; Watt et al. 2009; Woodward et al. 1969; Arancillo et al. 2015), an increase in peak sodium conductances has been observed in mouse and rat Purkinje cells (McKay and Turner 2005; Fry 2006). The sodium conductances are produced by voltage-gated sodium channels: adult Purkinje cells richly express voltage-gated sodium channel $Na_v1.1$ (Felts et al. 1997; Black et al. 1994; Gong et al. 1999) and $Na_v1.6$ (Schaller and Caldwell 2000; Schaller et al. 1995; Vega-Saenz de Miera et al. 1997) in both the soma and dendrites. These are thought to be the fast voltage-dependent sodium channels that underlie action potential generation. Purkinje cells also expresses Naβ1 and β2 auxiliary subunits (Shah et al. 2001; Levy-Mozziconacci et al. 1998; Sashihara et al. 1995) that regulate sodium channel function (Oh et al. 1994).

Not surprisingly, expression of several sodium channels is regulated during development. Two-day old rodent Purkinje cells do not express sodium channel $Na_v1.1$; however, by the beginning of the 3rd week of postnatal development (~postnatal day (P)15), Purkinje cells express them (Felts et al. 1997; Gong et al. 1999; Westenbroek et al. 1995). In granule cells, expression of $Na_v1.1$ is present in adult granule cells, but the onset of expression is even later than in Purkinje cells (Felts et al. 1997; Gong et al. 1999; Westenbroek et al. 1995). The developmental expression pattern of sodium channel $Na_v1.2$ has been somewhat controversial. Early reports suggested that it was not expressed in the cerebellum (Brysch et al. 1991); however, since then, $Na_v1.2$ sodium channels have been reported in Purkinje cells in a developmental pattern that is almost the inverse of that of $Na_v1.1$, with $Na_v1.2$ expression detected during early postnatal development, but not in adulthood (Felts et al. 1997; Gong et al. 1999; Westenbroek et al. 1995). Similarly, the expression of the sodium channel $Na_v1.3$ is widely observed throughout the cerebellum starting as early as embryonic day 17. Expression declines during development, and by P15 and thereafter, $Na_v1.3$ channels are no longer expressed in rodent cerebellum (Felts et al. 1997).

Not all sodium channels are regulated during development. For example, sodium channel $Na_v1.6$ has been reported to be expressed at all stages of the development and in adulthood in the Purkinje cell soma and dendrites (Felts et al. 1997; Schaller and Caldwell 2000). This is interesting as these channels are known to be responsible for the resurgent sodium currents which are important in Purkinje cells' pacemaker firing ability (Raman and Bean 1997, 1999).

Potassium Channels

Purkinje cells also undergo an increase in the rate of repolarization during development, which suggests changes in the potassium channel conductance (McKay and Turner 2005). The slow-activating and large-amplitude afterhyperpolarization (AHP) observed during early postnatal development matures into a fast-activating and deactivating smaller-amplitude AHP, suggesting a change in the density of potassium channels as Purkinje cells grow (McKay and Turner 2005). Purkinje cells express a wide variety of potassium channels during the development including voltage-gated channels such as K_v1, K_v2, K_v3, and K_v4 (Drewe et al. 1992; Weiser et al. 1994; Martina et al. 2003). These channels undergo developmental regulation, where the expression of the potassium channel from the K_v3 family first emerges at P8 in rodents, and is then rapidly upregulated during development so that all Purkinje cells express these channels by P12 (Goldman-Wohl et al. 1994).

In addition to voltage-gated potassium channels, Purkinje cells also express a rich array of calcium-activated potassium channels, whose expression is markedly regulated during development (Raman and Bean 1999; Womack and Khodakhah 2002, 2003; Womack et al. 2004; Swensen and Bean 2003). The AHP of the Purkinje cell action potential is also influenced by big conductance (BK) and small conductance (SK) potassium channels (Womack and Khodakhah 2002, 2003; Womack et al. 2004; Swensen and Bean 2003). Electrophysiology studies from cultured cells and acute slices suggest BK channels are expressed at low levels in the 1st week of postnatal development, which then are upregulated so that BK channels are highly expressed in the adult Purkinje cells (Muller and Yool 1998; Edgerton and Reinhart 2003; Womack et al. 2009). In contrast, SK channel expression is high during postnatal development and undergoes downregulation during development so that lower SK channel levels are detected in the adult cerebellum (Stocker and Pedarzani 2000; Cingolani et al. 2002). Both SK and BK channels contribute to the pacemaker properties of Purkinje cells (Womack and Khodakhah 2002, 2003; Haghdoost-Yazdi et al. 2008). This suggests that the differences in Purkinje cell action potential properties during development, especially of the AHP, may arise from the differential regulation of both the voltage-gated and calcium-activated potassium channels.

Calcium Channels

Purkinje cell spontaneous firing is influenced by other ion conductances including calcium. It is well established that rodent Purkinje cells express both high-threshold (L-, P-, R-, and N-type) and low-threshold (T-type) voltage-gated calcium channels at all stages of development and in adulthood (Nam and Hockberger 1997; Kaneda et al. 1990; Meacham et al. 2003), leading one to ask: Is the expression of these

channels dynamically regulated across development? In the 1st week of postnatal development in mice, more than half of the calcium influx into the Purkinje cell is conducted by the L-type calcium channels that are expressed in the soma (Liljelund et al. 2000). Other calcium channels such as P/Q-, R-, and N-type channels are expressed by the Purkinje cells but were found to contribute less to intrinsic activity (Liljelund et al. 2000; Raman and Bean 1999). However, starting from the 2nd week of postnatal development in mice, P/Q- and R-type channel expression is upregulated, while the expression of the L-type channel decreases (Meacham et al. 2003). In adult Purkinje cells, the majority of the calcium influx in the soma and dendrites comes from the P/Q-type channels, with only a small fraction arising from L- and N-type channels (Mintz et al. 1992; Watanabe et al. 1998), suggesting that L-type calcium channels are downregulated dramatically during development.

Are all voltage-dependent calcium channels developmentally regulated? T-type calcium channels are expressed at all ages across development and contribute to a lesser degree to Purkinje cell intrinsic activity, with little evidence of age-dependent regulation (Nam and Hockberger 1997; Raman and Bean 1999; Swensen and Bean 2003; Kaneda et al. 1990). Interestingly, N-type calcium channels have also been reported to be relatively uniformly expressed across development in rodent Purkinje cells where they influence intrinsic activity (Alvina et al. 2016). This is, however, in stark contrast to the developmental expression profile of N-type calcium channels in other cerebellar neurons. In the DCN, N-type calcium channel expression is high in early postnatal development when it is the primary calcium channel type contributing to intrinsic activity (Alvina and Khodakhah 2008; Alvina et al. 2016). By adulthood, however, N-type calcium channels appear to no longer contribute significantly to pacemaker activity in DCN neurons (Alvina et al. 2016).

An interesting study by Fletcher and colleagues suggests that the regulation of individual calcium channels may depend on the expression level of other channels. They studied how the cell-specific disruption of one calcium channel (P/Q-type knockout in cerebellar granule cells) influenced expression of other calcium channels and observed that some (L- and N-type), but not all (R-type was not regulated), calcium channels were upregulated (Fletcher et al. 2001). These results suggest that active adaptive mechanisms exist in neurons that help titrate the relative expression levels of similar channels in order to preserve cellular physiological function.

Ion Channels Summary

Purkinje cells start firing action potentials spontaneously at low rates early during the 1st week of postnatal development (Arancillo et al. 2015). They then gradually increase their firing rate due to changes in the type and density of ion channels they express (Fig. 1). The age-dependent regulation of multiple ion channels described above suggests that during development, each neuronal cell type regulates its channels in unique patterns which differ across cell types, conferring different properties to the intrinsic activity of the different pacemaker neurons.

In addition to changes in the overall ratios of different channel types, it is likely that within a given channel type, subunit composition may change during development, leading to even more molecular diversity. Auxiliary subunits are known to

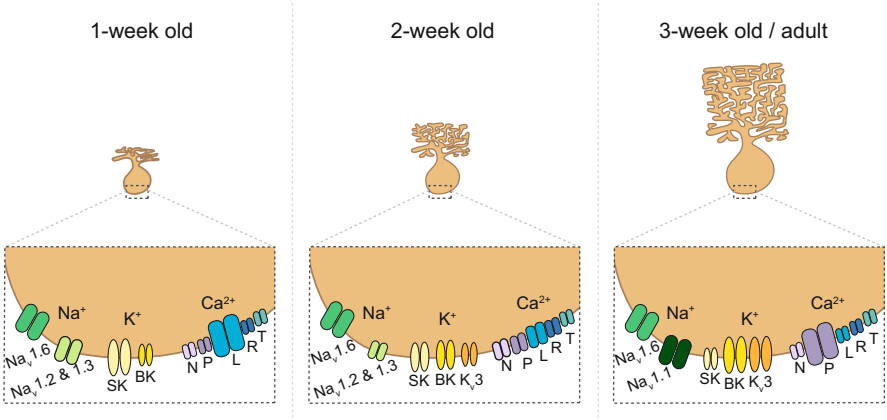

Fig. 1 Developmental regulation of ion channels underlies modulation of Purkinje cell firing properties. Schematic shows rodent Purkinje cells during postnatal development at 1 week (left), 2 weeks (middle), and 3 weeks or adult (right) of postnatal development. Purkinje cells grow and their dendritic trees enlarge across development. Multiple types of sodium channels (green), potassium channels (yellow), and calcium channels (blue) are regulated by development, while others (e.g., $Na_v1.6$ sodium channels, T-type calcium channels) are not regulated. Relative size of cartoon channel represents relative expression levels in Purkinje cells

influence channel properties for all three types of voltage-gated ion channels described above (Moreno et al. 1997; Gonzalez-Perez et al. 2014; Ransdell et al. 2017). Furthermore, changes in auxiliary subunits can favor distinct signaling pathways that ion channels interact with (Campiglio and Flucher 2015), as well as other cellular functions (Davis et al. 2004). In adult Purkinje cells, for example, loss of the Navβ4 accessory subunit for voltage-dependent sodium channels alters channel function and cellular firing properties, leading to dramatic deficits in cerebellar-related behavior (Ransdell et al. 2017). Although developmental regulation of channel subunit composition occurs in other brain regions (e.g., in the hippocampus (Schlick et al. 2010)), this has been largely unexplored in the cerebellum to date. Yet the putative regulation of auxiliary subunit composition across development would likely have important functional consequences and thus merits further exploration.

Other Regulators of Physiological Activity During Development

Calcium Buffers

Purkinje cells possess a large soma and one of the largest and most complex dendritic structures of all neuronal cell types. Given their large dendrites and the corresponding massive excitatory synaptic input they receive, it could be hypothesized that Purkinje cells are particularly susceptible to calcium-mediated excitotoxicity. Yet Purkinje cells stay healthy in part due to an enormous calcium buffering capacity that enables them to handle large calcium influxes (Schwaller

et al. 2002). Purkinje cells highly express the calcium buffer proteins calbindin and parvalbumin (Celio 1990; Scotti and Nitsch 1992), and their expression is tightly regulated during very early development (Milosevic and Zecevic 1998). In humans, calbindin expression is detected very early during embryonic development in Purkinje cells as early as it has been looked for (~embryonic weeks 4–5) (Milosevic and Zecevic 1998), while parvalbumin expression is found in Purkinje cells only several months later in the human fetus (Fig. 2) (Milosevic and Zecevic 1998). The developmental pattern of expression of calbindin and parvalbumin in rodents is similar to that seen in humans, with calbindin expressed first and parvalbumin expressed later during embryonic development (Altman 1969; Arnold and Heintz 1997; Solbach and Celio 1991). These buffers play a role in several physiological processes. The absence of calbindin in knockout mice leads to altered calcium dynamics in Purkinje cells (Airaksinen et al. 1997), while the absence of parvalbumin causes changes in synaptic release at cerebellar synapses (Caillard et al. 2000), and both are associated with changes in cerebellar-related motor function (Farre-Castany et al. 2007). Evidence suggests that Purkinje cells possess multiple mechanisms to regulate intracellular calcium in order to preserve intrinsic activity: Kreiner and colleagues found that there were alterations in P/Q channel auxiliary subunits from knockout mice lacking calbindin and parvalbumin in a manner that increased voltage-dependent channel inactivation while preserving action potential properties of Purkinje cells (Kreiner et al. 2010). Adaptations like these that are observed in transgenic mice give us a tool with which we can probe the mechanisms underlying the developmental homeostatic plasticity that cerebellar neurons possess and use to stabilize firing output, reminiscent of homeostatic mechanisms described in other brain regions (Turrigiano 1999).

Interestingly there is another type of calcium buffer that is extensively expressed in the granule cells and unipolar brush cells but is typically absent from adult Purkinje cells, calretinin (Dino et al. 1999). However, a recent study shows that calretinin expression is transiently observed in Purkinje cells and molecular layer interneurons during human embryonic development (Pibiri et al. 2017). This suggests that the calretinin plays a brief but potentially important role during

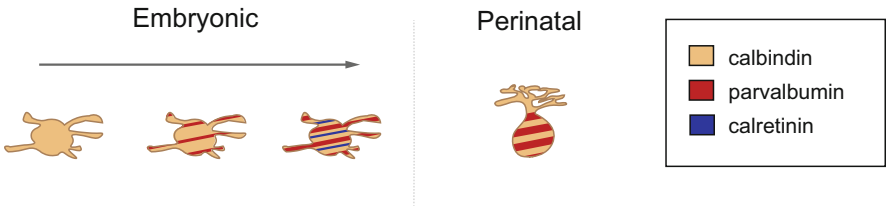

Fig. 2 Developmental regulation of calcium buffers in Purkinje cells. Schematic shows human Purkinje cells during embryonic (left) and perinatal (right) development. Calbindin is expressed earliest during embryonic development, followed by parvalbumin. There is transient expression of calretinin in human Purkinje cells during late embryonic development. Both calbindin and parvalbumin are expressed at higher levels postnatally (not shown)

development in Purkinje cells (Fig. 2), although a similar developmental transition has not been identified to date in rodent models to our knowledge.

Synapses

Synaptic development in the cerebellum is a complex process that has been reviewed in other chapters (Kano and Watanabe 2018). Both excitatory (Shim et al. 2016) and inhibitory (Häusser and Clark 1997) synapses can influence Purkinje cell firing output. Protocols that alter the long-term strength of synapses such as long-term depression (LTD) and long-term potentiation (LTP) have been shown to alter intrinsic excitability as well (Belmeguenai et al. 2010; Shim et al. 2017), suggesting that there are strong links between Purkinje cell synapses and intrinsic activity. This is important since changes in Purkinje cell activity have also been shown to causally underlie motor learning behavior (Nguyen-Vu et al. 2013). Interestingly, links between synaptic plasticity and intrinsic excitability have also been observed in other cerebellar neurons in the DCN (Aizenman et al. 1998), suggesting that the relationship between synaptic alterations and intrinsic excitability may be a general feature of cerebellar neurons.

How might early synaptic activity influence the development of the cerebellar circuit? Below we will touch upon a few examples of ways in which cerebellar development appears to be shaped by the synaptic input and the resulting physiological activity neurons experience.

Molecular layer interneurons are born in the ventricular zone over a relatively long developmental period which in mice spans several weeks perinatal and then migrate to their final location in the molecular layer (Leto et al. 2009; Sudarov et al. 2011). This means that migrating molecular layer interneurons migrate through a network of cells and projections that are already in their final location. A recent study by Wefers and colleagues show that molecular layer interneurons receive both excitatory and inhibitory synaptic input that influences their migration: without it, migration is slow and lacks directional cues (Wefers et al. 2017). This suggests that local synaptic-mediated activity plays an instructive role in neuronal migration in molecular layer interneurons. It is unknown whether earlier-born migrating cerebellar neurons like Purkinje cells receive synaptic input during migration. There are comparatively few neurons in the cerebellar cortex at early embryonic ages when Purkinje cells are migrating (reviewed in (Sotelo and Rossi 2018)). However, there are axons that transiently innervate the cerebellum from the trigeminal ganglia even before Purkinje cells are born (Marzban et al. 2018), which suggests that such a mechanism is theoretically possible.

Another way that synapses can play a role in development is through the modulation of network activity, which is widespread across the developing nervous system (Ackman et al. 2012; Blankenship and Feller 2010). In the developing cerebellum, Purkinje–Purkinje synapses, which are mediated by asymmetrically projecting axonal collaterals and are enriched in early postnatal development, produce wavelike activity in the early developing cerebellum (Watt et al. 2009). Similar activity in other brain regions plays a role in sculpting developing circuits (Burbridge et al. 2014; Pratt et al. 2016), and modelling suggests that such wavelike

activity can play a role in refinement and pattern formation in developing circuits (Bennett and Bair 2015). In support of this, a more recent study observed highly synchronized activity of both climbing fibers and Purkinje cells in vivo during the 1st week of postnatal development in rodents that desynchronized during the second postnatal week. Desynchronization of Purkinje cell activity was abolished when climbing fiber synapse elimination was perturbed (Good et al. 2017), suggesting that proper synapse elimination of climbing fibers influenced circuit activity.

Many excitatory synapses in the brain express NMDA receptors throughout development but experience an activity-dependent subunit shift during postnatal development, leading to changes in a synapse's capacity for plasticity (Yashiro and Philpot 2008). Cerebellar Purkinje cells have a rather more complicated developmental profile. In rodents, functional NMDA receptors are observed in Purkinje cells until the end of the first postnatal week (Rosenmund et al. 1992), after which their expression is decreased to low levels. Initially, it was believed that low expression persisted throughout the rest of the life span (Dupont et al. 1987). Surprisingly, however, this is only a transient feature of excitatory synapses in Purkinje cells, which again express NMDA receptors starting after the 3rd week of postnatal development (Piochon et al. 2007; Renzi et al. 2007), where they play a role in synaptic plasticity (Piochon et al. 2010). Why Purkinje cells experience a transient decrease in the expression of functional NMDA receptors during postnatal development is poorly understood, but given the role of NMDA receptors in excitotoxicity and cell death (Vyklicky et al. 2014), it may be a neuroprotective measure to ensure cerebellar health during this critical period when the parallel fiber input a Purkinje cell receives increases in number dramatically or perhaps is related to some other property of the developing cerebellum.

These studies show that synapses are highly developmentally regulated and are important in shaping neuronal activity, directing migrating neurons along their migratory paths, thereby serving important roles in the development of the cerebellum.

Other Influences of Normal Developmental Physiology

There are many different regulators of the physiological state of the cerebellum that we are only able to touch upon here. Some, such as the role that hormones play in cerebellar development, are reviewed in other chapters (Koibuchi and Ikeda 2018). Hormones have been shown to modulate several facets of adult Purkinje cell physiology: for example, estradiol modulates Purkinje cell excitability (Smith et al. 1988), while the hormone leptin influences Purkinje cell firing and inhibitory synaptic input (Forero-Vivas and Hernandez-Cruz 2014); however, little is known about how these processes are regulated developmentally.

Neuromodulators are another example of molecules that regulate cerebellar physiology that are tightly regulated throughout development. To take just one example, serotonin has been implicated in regulating the physiological properties of several cerebellar neuronal types. Purkinje cell excitability (Wang et al. 1992; Li et al. 1993) and synaptic inputs (Strahlendorf et al. 1984, 1986) are modulated by serotonin in adults. Interestingly, Purkinje cells exhibit changes in their morphology and excitability that are reminiscent of an older stage of development in a knockout

mouse of the developmentally transiently expressed serotonin type 3 ($5HT_3$) receptors, suggesting that serotonin acts as a brake during normal development (Oostland et al. 2011, 2013). Indeed, several serotonin receptors display tight developmental regulation (Li et al. 2004; Oostland et al. 2011, 2014). Recently, Saitow and colleagues show that in the DCN, effects of serotonin are also developmentally regulated: serotonin modulates inhibitory inputs more strongly during early postnatal development than in the young adult (Saitow et al. 2018). Other neurotransmitters, like acetylcholine, also display developmentally regulated responses in Purkinje cells (Kawa 2002). We may only be in the infancy of understanding the developmental implications of neuromodulator actions in the cerebellum, yet this regulation will likely have profound effects on Purkinje cell physiology, activity, and function.

We have a reasonable understanding of the developmental regulation of the channels that directly contribute to intrinsic activity in the cerebellum (see above, Fig. 1). Yet physiological activity is also regulated by many other factors, some of which we have summarized above. Beyond hormones and neuromodulators, there is a vast array of growth factors (Tian et al. 2014; Shakkottai et al. 2009), transporters (Forrest et al. 2012), and other signaling molecules (Smith and Otis 2003), which are also capable of regulating Purkinje cell intrinsic activity. It is also likely that many other as-yet-unidentified factors exist that also modulate the intrinsic or synaptic activity of cerebellar neurons. For example, transient morphological changes in axonal morphology have been observed during cerebellar development whose functional impact remain unexplored (Ljungberg et al. 2016). In most cases, little is known about if and how these changes are regulated during development. Thus, there is much that remains to be discovered for a complete understanding of the mechanistic control of physiological activity in the healthy developing cerebellum.

Development Gone Awry: Disease States

Proper function of the cerebellum is crucial for fine motor coordination, motor learning, and memory. More recently it has become clear that cerebellar function extends beyond the motor system to cognitive functions as well (Schmahmann 2004; Stoodley et al. 2012; Koziol et al. 2014). What diseases arise when cerebellar development goes awry?

Cerebellar abnormalities have been implicated in autism spectrum disorders (ASD) (Wang et al. 2014), as well as in several rodent models of ASD (Tsai et al. 2012; Peter et al. 2016; Piochon et al. 2014). The developmental onset of autism suggests that abnormal cerebellar development may be implicated in its etiology. We will discuss recent findings about the role that abnormal cerebellar physiological synaptic and intrinsic activity plays in ASD below.

Classically, cerebellar dysfunction has been associated with cerebellar ataxias and dystonia (Manto and Marmolino 2009b; Rossi et al. 2014; Anheim et al. 2012). There are several causes of ataxia, including drugs, environmental toxins, and fever (Incecik et al. 2013; Manto 2012). However, the best studied ataxias to date are the rare genetic diseases including autosomal dominant and recessive ataxias.

The mechanistic underpinnings of ataxias and dystonias have been well studied in rodent models of these genetic diseases (e.g., Manto and Marmolino 2009a; Walter et al. 2006; Watase et al. 2008; Jayabal et al. 2016; Inoue et al. 2001; Hourez et al. 2011; Shakkottai et al. 2009, 2011; Fremont et al. 2015, 2014). Ataxias encompass a diverse group of disorders with variable symptoms that manifest at different ages, from early- or childhood-onset to late-onset (Rossi et al. 2014; Anheim et al. 2012). Recent work that we will review suggests that abnormal cerebellar development may occur in late-onset ataxias and thus may contribute to disease pathophysiology even in these late-onset disorders. Below we will review disorders where abnormal cerebellar development is thought to contribute to disease.

Autism Spectrum Disorders

ASD refers to a group of developmental disorders that can be diagnosed as early as 2 years of age. ASD presents with a wide range of symptoms that include cognitive and social impairment, communication problems, and repetitive stereotypic motor movements. Research into ASD have garnered astounding interest in the last decade, and the involvement of cerebellum in ASD has become well established (Wang et al. 2014). Several genes have also been identified that confer susceptibility to ASD (Abrahams and Geschwind 2008).

In addition to hereditary mutations, environmental factors that affect the developing brain have been implicated in ASD (Mandy and Lai 2016; Modabbernia et al. 2017). Cerebellar injury or dysfunction during early development has been correlated with ASD (Hashimoto et al. 1995), with cerebellar injury predicted to be the second most common risk factor in developing ASD (Wang et al. 2014). How is cerebellar physiology altered in ASD? Studies from several transgenic mouse models that perturb genes implicated in human ASD have argued that Purkinje cell spontaneous firing and synaptic deficits are implicated in ASD. In a TSC1 genetic mouse model of ASD, Purkinje cell firing rate is reduced in a gene dosage-dependent manner that is correlated with the autistic behavioral deficits (Tsai et al. 2012), and more recently, the restoration of Purkinje cell activity chemically was found to rescue ASD-like symptoms (Stoodley et al. 2017). In a separate Shank2 ASD mouse model, deficits in the regularity of Purkinje cell firing are correlated with autistic-like behavior (Peter et al. 2016). Finally, in another ASD model based on deletion mutations on chromosome 10 (*PTEN*), Purkinje cell firing rate deficits are observed to be associated with autistic behavior (Cupolillo et al. 2016). These findings suggest that Purkinje cell intrinsic activity is important during cerebellar development and that abnormal firing deficits can contribute to ASD. Furthermore, rescue of firing properties can reduce autism-like behavior in these mouse models.

In addition to the firing properties of Purkinje cells, altered Purkinje cell synaptic properties have been observed in several different autism models. For instance, Piochon and colleagues showed that altered plasticity of parallel fiber input and altered development of climbing fiber inputs were associated with motor

abnormalities in a mouse model that replicates a human duplication that gives rise to ASD (Piochon et al. 2014). Likewise, both excitatory (Ha et al. 2016) and inhibitory (Lim et al. 2017) synaptic deficits have been observed in a Shank2 ASD mouse model. Interestingly, reversing inhibitory synaptic deficits can rescue spatial memory deficits in Shank2 ASD mice (Lim et al. 2017). Additionally, in several of the mouse ASD models described above in which Purkinje cell firing deficits are observed, synaptic deficits in climbing fiber and parallel fiber deficits have also been observed (Peter et al. 2016; Cupolillo et al. 2016) although not in all models (Tsai et al. 2012). Purkinje cell degeneration is observed at later ages in several mouse models of ASD, suggesting that these synaptic and intrinsic alterations in Purkinje cell function may contribute to later cell death (Peter et al. 2016; Cupolillo et al. 2016; Tsai et al. 2012). It is important to understand the full spectrum of cellular alterations of connectivity and intrinsic activity across models of ASD, both genetic and environmental, to understand how they contribute to disease. This may reveal common pathophysiology that might generalize the therapeutic targets for several different types of ASD.

Ataxia

Genetic ataxias can be classified in several different ways. We often group ataxias according to the type of root genetic mutation: for example, there are over 40 autosomal dominantly inherited ataxias (Rossi et al. 2014; Mundwiler and Shakkottai 2018) and more than 10 recessive ataxias (Anheim et al. 2012). One of the most studied groups of autosomal dominant ataxias are the spinocerebellar ataxias (SCAs), many of which share a triplet-repeat expansion in their mutated gene, including SCA1, SCA2, SCA3, SCA6, and others (Paulson et al. 2017). Symptoms of SCAs vary greatly, probably owing to the different genes that harbor the mutation (Paulson et al. 2017). For instance, while the most common SCAs are late-onset progressive ataxias that onset after 20 years old – such as SCA1, SCA2, and SCA6 – other SCAs are early-onset disorders that arise during childhood (Paulson et al. 2017). Even for a given disorder with the same genetic mutation, the age of disease onset can vary widely. There are several examples of typically late-onset disorders manifesting earlier during childhood (Globas et al. 2008; Wang et al. 2010; Figueroa et al. 2017), suggesting that no strict division exists between diseases which onset during development and those that onset later, after development.

One common feature of many ataxias is that as the disease progresses, cerebellar Purkinje cells undergo severe degeneration (Paulson et al. 2017), although as we have seen in the case of ASDs, Purkinje cell degeneration is by no means limited to ataxia. While certain ataxias such as SCA1 and SCA3 (Machado-Joseph disease) (Durr et al. 1996) involve alterations in other brain regions like brainstem and striatum in addition to the cerebellum, other ataxias, such as SCA6, are considered pure cerebellar disorders, with minimal extra-cerebellar neuronal degeneration (Zhuchenko et al. 1997).

Regardless of their onset and symptoms, many studies of mouse models of genetic ataxias show alterations in Purkinje cell firing and/or excitatory synaptic

inputs at or near the age when motor abnormalities are first observed, including autosomal-recessive spastic ataxia of the Charlevoix-Saguenay (ARSACS) (Ady et al. 2018), episodic ataxia type 2 (EA2) (Walter et al. 2006; Alviña and Khodakhah 2010a, b), SCA1 (Hourez et al. 2011; Inoue et al. 2001; Dell'Orco et al. 2015; Power et al. 2016; Shuvaev et al. 2017), SCA2 (Kasumu et al. 2012; Scoles et al. 2017; Meera et al. 2017), SCA3 (Shakkottai et al. 2011), SCA5 (Perkins et al. 2010), SCA6 (Mark et al. 2015; Jayabal et al. 2016; Du et al. 2013), SCA13 (Irie et al. 2014), and SCA27 (Shakkottai et al. 2009). The fact that similar changes are observed across so many different ataxias suggests that a group of common mechanisms involving aberrant synaptic and intrinsic physiology may underlie motor deficits in many or even all ataxias (Meera et al. 2016). Similar changes have been observed in animal models of dystonia (Isaksen et al. 2017; Fremont et al. 2014, 2015). Furthermore, as we described in the section above, several animal models of ASDs exhibit altered Purkinje cell physiology reminiscent of that seen in ataxias (Fig. 3; Tsai et al. 2012; Peter et al. 2016). Finally, there are mouse models of several other disorders in which similar Purkinje cell changes are reported, including Alzheimer's disease (Hoxha et al. 2012) and multiple sclerosis (Shields et al. 2012; Mandolesi et al. 2013). How can similar cellular physiological changes manifest across such diverse diseases? This raises the questions of whether Purkinje cell physiological changes give rise to specific disease abnormalities – that is they act causally – or are they observed whenever the cerebellum functions poorly? This is an important question that is yet to be fully answered. In some diseases, Purkinje cell vulnerabilities are restricted to certain populations, such as anterior vermis in ARSACS (Ady et al. 2018;

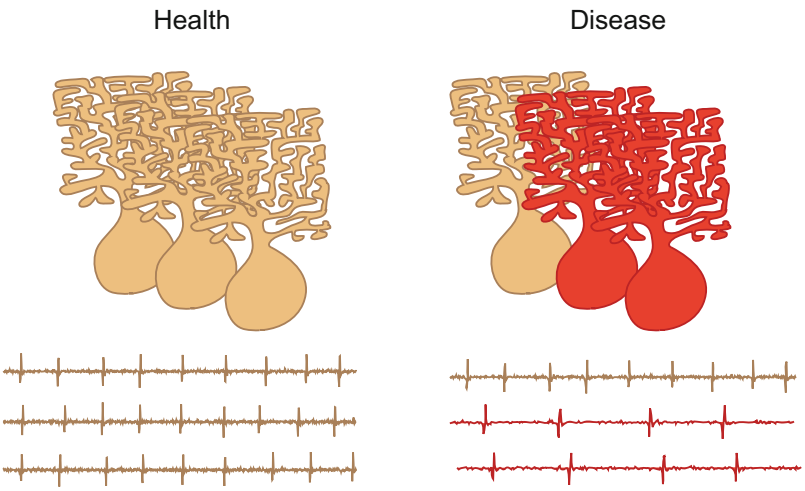

Fig. 3 Schematic showing Purkinje cell firing patterns in healthy rodent cerebellum (left) and diseased cerebellum (right), including rodent models of ataxias and ASD. Affected Purkinje cells (red) display lowered firing rates (right). Cells can be affected at specific developmental or adult ages, or in specific spatial patterns; these differences likely contribute to disease manifestation

Lariviere et al. 2015), posterior vermis in SCA5 (Perkins et al. 2016), and RCrusI in ASD (Stoodley et al. 2017), suggesting that different susceptible pools of cerebellar neurons when affected give rise to different symptoms (Fig. 3). Furthermore, although the presence of Purkinje cell deficits in other disorders may at first suggest that they contribute to other deficits aside from ataxia, ataxia is commonly observed in disorders like multiple sclerosis (Salci et al. 2017; Wilkins 2017), and gait deficits may predict some forms of dementia (Beauchet et al. 2016), arguing that motor control deficits in diverse diseases may nonetheless reflect cerebellar alterations.

Early-Onset Ataxias

While many ataxias onset in midlife, there are several that typically onset early, during brain development. The most common early-onset ataxia is Friedrich's ataxia, an autosomal-recessive slowly progressive ataxia that typically onsets in young school-aged children (Barbeau 1976). Friedrich's ataxia is typically characterized as involving multiple parts of the nervous system, including the spinal cord, with only minimal cerebellar alterations that are limited to the dentate nucleus of the DCN (Koeppen et al. 2011). However, a more recent study has demonstrated changes in excitatory parallel fiber synapses made onto Purkinje cells in a mouse model of Friedrich's ataxia (Lin et al. 2017), which is consistent with reports of structural changes in Purkinje cells in Friedrich's ataxia patients (Kemp et al. 2016; Stefanescu et al. 2015).

Another early-onset disorder, ARSACS, typically onsets during childhood (Bouchard et al. 1978) and is caused by inheriting two mutated copies of the *Sacs* gene (Thiffault et al. 2013; Engert et al. 2000; Synofzik et al. 2013). Like many ataxias, this is a progressive ataxia that gets worse over time. In a mouse model of the disorder, subcellular changes in protein localization have been detected early during postnatal development (Lariviere et al. 2015). Interestingly, we have also recently reported that both synaptic and intrinsic firing properties of Purkinje cells are altered and that at least some of these changes occur early in development (Ady et al. 2018). This suggests that the pathophysiology of ARSACS may be similar to several late-onset ataxias despite their earlier time of onset.

SCA41 is one of the most recently described human ataxias (Fogel et al. 2015), but a mouse model of this disease, called "Moonwalker," has been studied for years (Becker et al. 2009). This form of ataxia is well described in ▶ Chap. 77, "Moonwalker Mouse," but for our purposes, it is worth mentioning briefly that the ataxia is accompanied by changes in Purkinje cell dendritic structure and metabotropic glutamatergic synaptic signaling in Moonwalker mice (Becker et al. 2009).

One puzzling form of SCA is SCA13, which is classified by mutations to the KCNC3 gene (Waters et al. 2005). Since KCNC3 encodes the *Shaw*-type potassium channel which is important for action potential spiking in Purkinje cells (as well as other cell types), SCA13 would be predicted to decrease Purkinje cell intrinsic activity. Several different allelic mutations give rise to different forms of ataxia in SCA13: an adult-onset progressive ataxia, as well as a childhood-onset ataxia that is not progressive (Waters et al. 2006; Khare et al. 2017). All the mutations identified to date likely involve changes to channel expression or gating properties that will

impact firing in Purkinje cells (Waters et al. 2006; Khare et al. 2017). Yet the onset and prognosis of ataxia is different with different ataxia-causing mutations. Early-onset ataxia is typically caused by mutations that are predicted to have a more pronounced effect on a neuron's ability to sustain high-frequency firing than late-onset ataxia (Waters et al. 2006; Khare et al. 2017). But why is this early-onset ataxia not progressive like adult-onset ataxia, which worsens with time? In fact, the opposite is typically seen: early-onset SCA13 typically shows lifetime improvement of motor function, suggesting that compensatory mechanisms are employed by the brain to counteract the impact of early ataxia. This difference may arise because the developing brain is more adept at plasticity and thus better able to compensate for changes in Purkinje cell function than the adult brain. Further research into these two forms of SCA13, nonprogressive early-onset ataxia versus progressive late-onset ataxia, may be a powerful means to identify the compensatory plasticity mechanisms that the developing brain is able to employ. If we understand these mechanisms during development, perhaps we can find tools to redeploy them in the case of late-onset diseases to counteract disease progression.

Altered Cerebellar Development in Late-Onset Ataxias?

Most SCAs have a late onset of disease symptoms and are classically thought of as neurodegenerative diseases, where pathophysiology slowly builds up over a time scale of years to decades. Yet the brain harbors the pathogenic mutation from conception, so one may wonder why development proceeds normally. Do developmental changes occur in late-onset diseases, and could they contribute to later behavioral deficits?

We recently reported that in a mouse model of SCA6, developing Purkinje cells display enhanced firing rate and firing precision (Jayabal et al. 2017), contrary to the firing properties observed at the age when motor symptoms emerged (Jayabal et al. 2016). Additionally, deficits in climbing fiber synapse elimination, similar to those observed in some models of ASD (Piochon et al. 2014), were also observed (Jayabal et al. 2017). Interestingly, these changes were transient in SCA6 mice as the firing properties and climbing fiber synapses appear normal in young adult SCA6 mice (Jayabal et al. 2017). This suggests that the developing SCA6 brain has the capacity to overcome certain developmental abnormalities and function normally for a time, before motor dysfunction emerges in midlife (Fig. 4) (Watase et al. 2008; Jayabal et al. 2015). Mechanistically, it is at present unknown how this developmental adaptation occurs. However, it has been reported that cerebellar granule cells can upregulate specific voltage-gated channels to compensate for the loss of P/Q calcium channels (Fletcher et al. 2001), suggesting that similar mechanisms may be employed in cerebellar Purkinje cells, since the underlying mutation in SCA6 is in a P/Q-type calcium channel subunit (Zhuchenko et al. 1997).

Do these early changes contribute to later disease onset? While we do not currently have an answer for this in SCA6, evidence from another late-onset ataxia, SCA1, suggests that they may. Using a conditional mutant mouse strain that allows researchers to turn on or off expression of the mutated SCA1 gene (Zu et al. 2004), researchers tested whether development was involved in the manifestation of ataxia

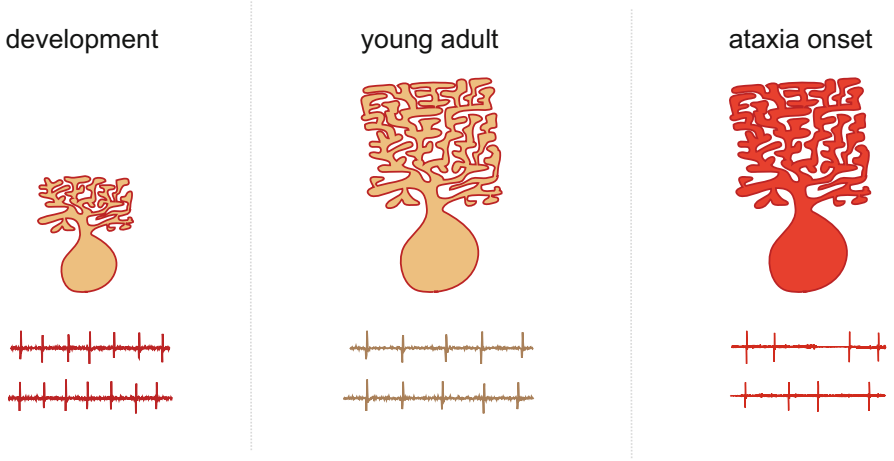

Fig. 4 Altered firing properties during development prior to disease onset in a mouse model of SCA6. Purkinje cells display elevated firing rates during the second postnatal week of development (left) that are restored to normal levels by the time mice are young adults (middle). Although Purkinje cells display normal morphology during both development and young adult time periods, the complement of ion channels they express may be different from wild-type mice (illustrated by red outline). Ataxia onset occurs at 7 months and is accompanied by reduced Purkinje cell firing rate and precision (red, right panel). Summary of findings from (Jayabal et al. 2017)

(Serra et al. 2006). In this study, researchers delayed expression of the pathogenic SCA1 mutation until the mice were young adults and development was complete. One would predict that if the disease were purely neurodegenerative and did not involve development, the absence of expression during development would have little impact on disease prognosis. On the contrary, however, the age of onset was delayed, and the severity of motor symptoms was reduced when the mutated gene was not expressed during development (Serra et al. 2006; Ibrahim et al. 2017), suggesting that development influences disease progression in SCA1. Conditional mutant animal models allow researchers to study disease onset while dissecting the relative contributions of different temporal periods and will be an important tool for elucidating the role that altered cerebellar development plays in ataxia onset. This will have important implications for screening, diagnosis, and treatment of these inherited diseases.

Conclusions and Future Directions

Physiological synaptic and intrinsic activities are present in the developing cerebellum over a wide period of development and may be influenced by factors determined not long after neurons are born. Since the factors that shape this activity are highly developmentally regulated (Figs. 1 and 2), it suggests that although superficially similar, the nuts and bolts of the activity observed at different time points during the

maturation of the cerebellum has unique properties. This may in part explain our hypothesis that activity likely serves several functions during development; for example, synaptically mediated activity can direct migrating neurons to their proper terminal location (Wefers et al. 2017).

When physiological activity is altered in development, there can be adverse consequences. Interestingly, developmental changes in synaptic and intrinsic activity in several mouse models of ASD mimic the alterations observed around the onset of motor symptoms in late-onset ataxias, suggesting that while alterations in these properties are typically pathological, it may be in part the timing of their onset that predicts which types of pathophysiological changes manifest in different disorders, although other factors such as the regional expression of these changes (Ady et al. 2018) contribute as well (Fig. 3). Understanding the role that pathophysiological activity plays in the developing cerebellum, and how this contributes to disease, is an important avenue that requires further study. While we do not fully understand how mature Purkinje cells encode information in the timing or rate of their action potentials (Eccles 1973; Person and Raman 2012; Hong et al. 2016; Abbasi et al. 2017), we have even less understanding of how this activity contributes to information transfer during development. However, understanding information transfer in the developing brain is an important question that demands further study. Given the differences in the underlying mechanisms contributing to this activity, it is possible that information is encoded differently in the developing and mature cerebellum. It remains important for scientists to continue to study how the cerebellum "turns on the juice" during development as well as why and how this goes wrong in several diseases and disorders.

Cross-References

► Moonwalker Mouse

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