Cerebellar Developmental Disorders and Cerebellar Nuclei

Hong-Ting Prekop, Alessio Delogu, and Richard J.T. Wingate

Abstract While significant progress has been made in the last 10 years in understanding the development of cerebellar nuclei, they remain a relatively less well-studied cell group in the brain. In this chapter, we review the anatomical organisation of the cerebellar nuclei and their connections to highlight outstanding developmental questions. We then describe recent progress in dissecting the lineages of cerebellar neurons that may point to new understanding of their involvement in congenital clinical disorders.

Keywords Dentate nucleus • Interposed nucleus • Fastigial nucleus • Inferior olive • Purkinje cell • Rhombic lip • Ventricular zone • Ptf1a • Atoh1 • Pax2 • Nuclear transitory zone

What Are Cerebellar Nuclei?

The cerebellar nuclei (CN) are the final output units for cerebellar processing. For the most part, the CN output is a high-frequency tonic excitation, which is directed towards the midbrain and thalamus. However, a distinct, long-range inhibitory axon tract allows the CN to influence the activity of the inferior olive (IO), which in turn drives Purkinje cell (PC) activity via climbing fibres. CN output is modulated by the patterned firing of inhibitory PCs. They thus form the final common pathway for the integrated activity of a series of nested re-entrant loops via the inferior olive but also via the thalamus, cortex and pons (Fig. 1).

Despite the central position of CN within these major long-range networks, relatively little is known about their component cell types, the synaptic arrangement of their component interneurons or their processing role. Their development has only

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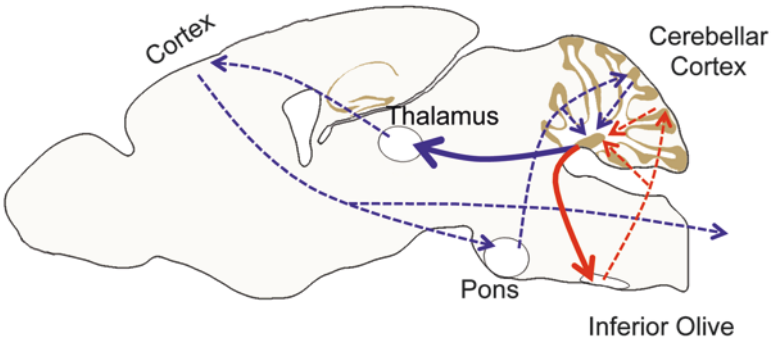

Fig. 1 The cerebellar nuclei are central to cerebellar circuitry. They lie at the centre of two cerebellar loops: the cerebello-thalamo-cerebro-cortical circuit (*blue*) which link the cerebellum back to the cerebral cortex and the olivo-cortico-nucleo-olivary loop (*red*)

recently been described, and, even then, the picture is partial. Major questions remain as to how nuclei achieve their spatial arrangement, integrate cell types of different origins and make connections. For a population of such significance for a wide variety of brain functions, this is a major omission. Similarly, while some nuclear disorders in humans have been described, the lack of anatomical and molecular description has hampered a systematic analysis of clinical disorders.

Cellular Anatomy and Diversity

The earliest descriptions of CN neurons distinguished cells with long axons from those with short axons [1] and identified large and small soma size [2]. The most detailed morphological studies of the rat and primate dentate (lateral) cerebellar nucleus were carried out by Victoria Chan-Palay in the 1970s. Using Golgi, Nissl and Weigert preparations combined with electron microscopy, she mapped out the complex, non-uniform cellular organisation of the nucleus [3–5] and demonstrated the presence of two types of projection neurons with at least three different types of cells with short axons and small soma. These latter neurons were designated as local interneurons on the basis of dendrite and axon morphology and could be distinguished by their multipolarity or bipolarity and fusiform soma.

Immunohistological and molecular techniques have subsequently shown large projection neurons to be glutamatergic (projecting to the red nucleus, thalamus or brainstem), while projection neurons with very small soma that project to the inferior olive are GABAergic [6–8] (Fig. 2). In addition to these latter nucleo-olivary inhibitory projections, glycinergic neurons can project to both the brainstem [9] or to the granule cell layer of the cerebellar cortex [3, 10–12]. Unlike the other CN cell types, these latter nucleo-cortical neurons are not spontaneously active but instead are mostly silent. They most likely target Golgi interneurons, which express glycine receptors, unlike most cells of the granule cell layer [13].

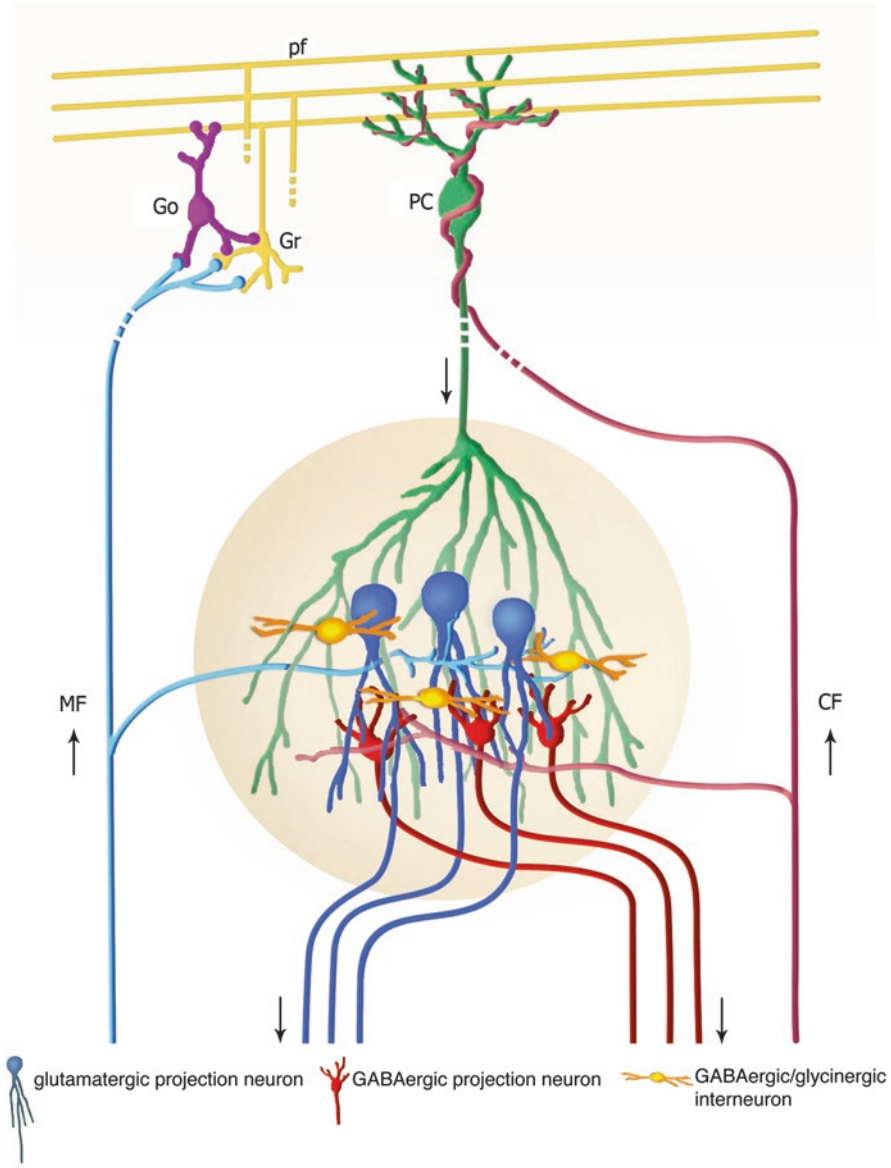

Fig. 2 The cellular composition of the cerebellar nuclei. Nuclei receive inputs from the Purkinje cells in the cerebellar cortex (*green*), as well as collaterals from the mossy fibres (*light blue*) and climbing fibres (*pink*) as they travel to the cortex. Within the nuclei, there are two types of projection neuron: large glutamatergic cells (*blue*), which are efferent cells in the cerebello-thalamo-cerebro-cortical circuits, and the nucleo-olivary neurons (*red*), which project to the inferior olive, forming the olivo-cerebellar loop. Interneurons (*orange*) participate in as yet uncharacterised local circuits

Other larger glycinergic projection neurons are found in the medial nuclei [14] and project ipsilaterally to the vestibular nuclei, the ventral brainstem and the ipsilateral ventromedial medullary reticular formation. These are hence the ipsilaterally projecting counterparts to the large glutamatergic neurons of the same region, which project contralaterally to the same regions. This has raised suggestions that posture and balance rely on a system of cross-midline control, similar system to that of the vestibular control of horizontal eye movements [15].

Relatively little is known about the local interneurons. Chan-Palay [4] noted small GABAergic neurons with fusiform or multipolar somas, limited dendritic trees and short axons, but it is possible that some of the cells observed could be the small nucleo-olivary neurons. A population of glycinergic neurons with small somata have also been found in the interposed and lateral nuclei. Because glycinergic terminals are found mainly on adjacent, presumptive glutamatergic projection neurons, it has been suggested that these are interneurons [14, 15], which colocalise with GABA [16]. GABAergic terminals that did not derive from PCs are also indicative of GABAergic interneurons or possibly local collaterals from the nucleo-olivary neurons. Though it is not possible to differentiate nucleo-olivary neurons from other GABAergic cell types in the CN based on size, there are some electrophysiological differences that aid identification [9].

Despite the fact that cells differ along both rostral-caudal and lateral-medial axes in terms of prevalence and dendritic/axonal trees, models of cerebellar function assume a homogeneous spread of each CN cell type, paralleling the long-assumed homogenous and stereotyped circuitry of the cerebellar cortex, which itself is undergoing re-examination [17]. For example, there is a higher density of nucleo-olivary neurons in the ventral lateral and interposed CN [18]. Accordingly, the PC axon terminals spread in a different manner in these parts when compared to more dorsal and medial regions of the CN [19]. On the whole, the diversity, connectivity and processing function of local interneurons have remained elusive and thus disregarded in circuitry models.

The origins of CN, how their distribution is specified and how local circuits are set up and refined are all important questions that remain to be addressed. PCs can inhibit GABAergic CN neurons, so disinhibiting glutamatergic projection neurons through local networks.

Outputs of the Cerebellar Nuclei

The CN translate cerebellar output to the cerebral cortex via the thalamus, brainstem and spinal cord through two main long-range projection systems: glutamatergic projection neurons send signals to the red nucleus, thalamus, or brainstem, while the GABAergic nucleo-olivary neurons connect the cerebellum to the inferior olive [7]. Meanwhile, other forms of efferent connections have also been found linking the CN to the vestibular nuclei and the cerebellar cortex [10, 15].

Glutamatergic projection neurons form a vital link in the assorted cerebello-thalamo-cerebro-cortical circuits which link the cerebellum back to different parts of the cerebral cortex [20]. The nucleo-olivary neuronal projections are thought to form the olivo-cortico-nucleo-olivary (OCNO) loop, a closed feedback loop between the inferior olive, cerebellar cortex and CN, made up at a fine scale of individual closed loops, or cerebellar modules, of local connections via the CN [21]. While this closed loop model is challenged by the existence of bilaterally extending nucleo-olivary neurons [22, 23], it remains a compelling architecture to describe the functional properties of the cerebellar circuit.

The origins of the diversity and the mechanisms underlying the targeting of their axons are largely unexplored. Each of these characteristics is core to an understanding of how the cerebellum influences other parts of the brain.

Inputs to Cerebellar Nuclei

The inputs to the CN comprise a complex matrix that modulates cerebellar output by influencing the spontaneous baseline firing rate of CN neurons [24, 25]. The most significant of these inputs are PCs from cortical layers directly above the corresponding part of the CN: the medial receiving input from the vermis, interposed from paravermis and the lateral receiving the bulk of its input the hemispheric PCs [26]. Sugihara et al. mapped PC projections to the various CN and found correspondence between aldolase C expression in subsets of PCs and the terminations in specific subdivisions of CN, demonstrating some conservation of topographic organisation [27].

While both PCs and CN neurons are spontaneously active [28, 29], evidence of synaptic plasticity at the CN neurons shows that the CN are involved in modulating cerebellar cortical output and not merely relaying information from the PC population [30–32]. When PC and CN neurons are monitored simultaneously, they do not give the expected reciprocal firing rates that would result from PC inhibition [33–36]. Instead CN neurons are extremely sensitive to the synchronous activity of PC inputs [37] suggesting that the development of a mapping of PC populations into the CN is a critical factor in cerebellum function.

In addition to afferents from the PCs, the CN also receive collaterals from mossy fibres (MFs) and climbing fibres (CFs). These send signals directly to the CN, bypassing cerebellar cortical processing [26]. In the overlying cerebellar cortex, MFs and CFs are topographically mapped onto GCs and PCs, and their collateral projections to CN follow approximately the same topography. MFs from the pontine nuclei, nucleus reticularis tegmenti pontis and lateral reticular nucleus send their cortical terminations such that they divide the cerebellar cortex into zones to process information from particular parts of the body or sensory modes [23, 38, 39]. In contrast, the MF collaterals to the CN are bilateral and show a looser zonal organisation [26, 40]. Likewise, anterograde tracing from the inferior olive has revealed a strict topographic alignment of CFs to the zebrin II-positive PC parasagittal zones in the contralateral cerebellar cortex [19]. The collaterals of these same CFs target the contralateral CN and terminate in specific areas of the CN [27, 41, 42].

Relatively little is known of how inputs to the CN are organised at a cellular level and the intrinsic networks that are built up by interneurons and local collaterals. A natural entry point to these questions is trying to understand the degree of convergence of a relatively orderly PC layer on to the three-dimensional assembly of CN neurons. In terms of numbers, there are around 20 PC to every CN neuron [43, 44] with inputs targeting both glutamatergic [45, 46] and GABAergic projection neurons [8]. However, since the PC axonal target field is wide and conical [47], it is estimated that each PC can encompass tens of CN neurons complicating a simple explanation of convergence. Similarly the proximity of axon terminations to the soma of CN neurons is likely to be of considerable significance in determining synaptic strength [14]. Chan-Palay noted that around 14% of larger neurons in the lateral CN were not innervated directly on their somata by PCs, setting apart a subset of projections neurons [48], which may comprise the glycinergic, nucleo-cortical neurons [11].

How the PC axon numbers are developmentally matched to CN targets and the mechanisms that regulate mapping are unknown. Similarly, how the topography of collateral projections from different afferent populations is coordinated within the nucleus is an important question that remains to be addressed. For example, it has been suggested that collaterals of inputs to the cerebellar cortex form a template for topographic refinement of outputs of Purkinje cells to the CN.

Development of Cerebellar Nuclei

The origins of the cerebellum, which sits at the boundary of the midbrain and hindbrain, were an intensely investigated problem at the end of the last century. The advent of molecular techniques revised the concept that the cerebellum received contributions from both the midbrain and hindbrain and identified the cerebellar anlage within the dorsal part of rhombomere (r)1 of the hindbrain [49–51]. Within the anlage, two distinct progenitor zones, which are defined by the mutually exclusive expression of basic helix-loop-helix (bHLH) transcription factors Ptf1a and Atoh1, produce all the cell types of the cerebellum [52]. Ptf1a is expressed in the dorsal ventricular zone of r1 and characterises progenitors of GABAergic cells [53]. The boundary between the ventricular zone and the dorsal roof plate is known as the rhombic lip [54] and expresses Atoh1 [55]. This highly proliferative zone of Atoh1 induction gives rise to glutamatergic cerebellar neurons [56, 57].

Birthdating has shown that some neurons within the CN are among the first-born cell types of the cerebellum [58]. Experiments using either BrdU or a replication-defective adenovirus [59] have shown that PCs are born around the same time as the CN. The time window for the production of glutamatergic and the GABAergic projection neurons in mice lies between E10.75 and E12.5 [60] and appears to be regulated by a common temporal signal [61]. However, the allocation of GABAergic versus glutamatergic fate is strictly a property of progenitor position within either a Ptf1a- or Atoh1-positive pool [53, 56, 57, 61, 62].

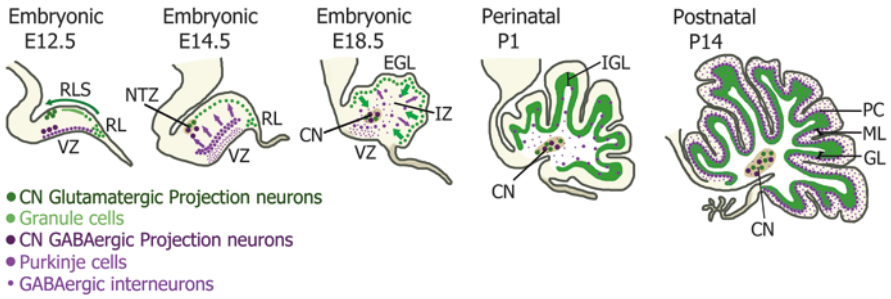

Fig. 3 The developmental timeline of the cerebellum, depicted in sagittal view. GABAergic neurons are derived from the ventricular zone (*VZ*), while glutamatergic neurons arise at the rhombic lip (*RL*). The cerebellar nucleus projection neurons are the first born from both progenitor zones, preceding first Purkinje cells (*VZ*-derived) and then granule cells (*RL*-derived). Cerebellar nucleus interneurons are believed to be born alongside other cerebellar cortical interneurons, which are generated from E13 from the *VZ* and later a stem cell population within the future white matter

Origin of Glutamatergic Neurons

One key motif of CN development is the assembly of neurons within an embryonic nuclear transitory zone (NTZ), which appears as almost a "staging post" in the formation of distinct CN (Fig. 3). The derivation of glutamatergic CN neurons initially appeared to be via a radial migration from the ventricular zone [63]. A detailed analysis of postmitotic precursors of CN neurons identified the expression of the transcription factors Lhx2/Lhx9, Meis 1, Meis 2 and Irx3, as well as genes that are not frequently used as markers in development: Gja9, Mbd2, Htr3a and Girk4 [64]. Subsequent analysis showed that Meis 2 co-expresses with Lhx2/Lhx9 in glutamatergic projection neurons of the lateral CN derived from the rhombic lip [57], while Irx3 may instead represent a separate population of neurons, likely the GABAergic nucleo-olivary neurons [65].

Glutamatergic projection neurons represent the first cohort in a sequence of neurogenesis from the rhombic lip that ends with the generation of granule cells [49, 56, 57]. A separate domain of Atoh1 expression at the midbrain-hindbrain boundary gives rise to earlier-born extracerebellar neurons [66]. At the rhombic lip, lateral and then medial CN are produced in discrete temporal waves [67, 68]. CN neurons actively migrate from the rhombic lip in a subpial layer guided by diffusible netrin and slit proteins [69, 70] and sequentially express Pax6, Tbr2, Tbr1 and Lmx1a [65, 71]. As the postmitotic neurons enter the NTZ, Tbr1 and Tbr2 are upregulated and Pax6 is downregulated [71]. In the absence of Pax6, rhombic lip-derived CN neurons are absent from the cerebellum [65]. The differential retention of transcription factors defines different CN populations in mouse. Tbr1 expression is retained until E14.5 for lateral and interposed CN and into adulthood for the medial CN. In contrast, the lateral and interposed CN projection neurons express Brn2 at early postnatal stages.

Origin of GABAergic Projection Neurons

The developmental origins of the GABAergic nucleo-olivary neurons are enigmatic. It is assumed that they are born from the ventricular zone like the other GABAergic cell types of the cerebellum, although direct evidence for this is lacking. Like the glutamatergic populations of the CN, GABAergic neurons are likely to arise as part of a discrete temporal window of cell production. It is thought that the GABAergic projection nucleo-olivary neurons are first in a ventricular zone temporal lineage (Kim et al. 2011) that subsequently gives rise to PCs (e10.5–e12.5 in mouse) followed by other GABAergic interneurons [72]. In contrast to these later-born cell types, both PCs and GABAergic CN neurons express Neurog2 [73]. Postmitotic cells expressing Neurog1 appear to be candidate CN nucleo-olivary projection neurons [74]. Irx3 immunopositive cells are evident in the VZ from E10.25 to E12.5, the NTZ at E13.5 and by E15.5 the cells have migrated into an intermediate zone outside the NTZ [64, 65]. Irx3 expression persists in the sey/sey ("small eye" pax6 null) cerebellum confirming that the specification of GABAergic and glutamatergic neurons is independent of each other.

Other GABAergic Neurons

VZ progenitors require the expression of Ptf1a for GABAergic specification [53, 62]. Within the Ptf1a ventricular zone, combinatorial gene expression demarcates discrete germ zones that are thought to give rise to the different types of interneurons [64, 72, 74–79]. Thus, for example, Neurog1 and Neurog2 expression defines subsets of the Ptf1a+ VZ population.

However, this topographic explanation of diversity is complicated by evidence that proliferation continues within a single population of Pax2+ precursors from the VZ [80] that persists in the prospective white matter well into postnatal development in mouse. Heterotopic and heterochronic grafting experiments have found that Pax2 progenitors generate all the remaining inhibitory interneurons [80, 81], including Neurog1 (Ngn1)-positive interneurons of the CN, which are born at E17.5 in mouse [82]. Mutation of PC progenitor transcription factors Olig2 and Gsx1 disrupts the production of Pax2 lineages suggesting that the latter is derived from the former in development [83]. The origin and development of the various types of glycinergic neurons in the CN have yet to be characterised.

Nucleogenesis and Cell Migration

The different developmental origins of different types of CN neurons require that cells recognise each other and assemble nuclei distant to their origins. How nucleogenesis – the migration, organisation and synaptogenesis of CN neurons – is organised is

unknown. Clearly, either intrinsic programming or cues in the surrounding environment or a combination of both will be key factors in this developmental process.

For rhombic lip derivatives, unipolar neuroblasts move within a subpial stream towards the NTZ guided by both diffusible netrin and slit [69, 70] (NTZ); however the cues that determine the position of the NTZ itself are unclear. One possible determinant is the underlying axon scaffold of the fasciculus uncinatus, to which first-born CN cells then contribute [67, 69]. Changing the fate of CN neuroblasts blurs the boundaries between distinct populations in the NTZ but does not compress or expand the map of presumptive CN. Thus when either Lhx9 (lateral CN in mouse) is overexpressed in chick [67] or Tbr1 knocked down in mouse [71], CN neuron number remains similar but boundaries are less discrete. From the NTZ, cells are then incorporated into the white matter through what might constitute an active radial migration or a passive translocation as a consequence of the overall pattern of cerebellar morphogenesis [60, 63].

Evidence in favour of radial migration being a component of nucleogenesis comes from the analysis of the reeler mouse. Pax6/reelin-positive neuroblasts migrate from the rhombic lip, and at least some go on to become Tbr2-positive CN neurons. The reeler mouse has disrupted CN architecture; however, the initial tangential migration of rhombic lip derivatives to the NTZ is normal [71].

Evolution and the Diversification of Cerebellar Nuclei

While some aspects of the cerebellar circuit are among the most evolutionarily conserved across vertebrates, cerebellar nuclei are relatively variable in composition [84]. There is some debate over whether an organism is considered to have cerebelloid structures if they lack CN, since it is these cells that form the dominant output [85]. For example, teleost fish have no white matter or CN. Instead, their PCs project to eurydendroid cells, which then project to other parts of the brain. However, eurydendroid cells also receive inputs from granule cells via parallel fibres and are found within the granule cell layer and so are not homologous to CN projection neurons in terms of inputs [86, 87].

The replacement of CN by eurydendroid cells appears to be a ray-finned fish adaptation as there is evidence for a single cerebellar nucleus in the shark [88]. CN are absent in lampreys, where the cerebellum is reduced or absent. Across fish species the medial and dorsal octavolateral nuclei receive inputs from lateral line systems and are involved in spatial calculations that are analogous to those carried out in the cerebellum. It seems conceivable, though yet to be proved, that these may be considered as ontological homologues of CN [89].

Like sharks, amphibians have a single CN; however the number and diversity of CN increases in amniotes. There are two CN in birds [90] and three sets of CN in rodents: the medial, interpositus and lateral [91, 92]. In cats, rabbits and primates, there are four major CN: the medial, or fastigial, nucleus; the anterior and posterior interposed and the lateral, or dentate, nucleus. Each of these nuclei can be functionally

further subdivided such that complexity of CN organisation is a marked feature of mammalian brains [14]. This systematic variation in organisation suggests that comparative studies may offer an important insight into the significant genetic factors in the development of CN diversity.

Cerebellar Nuclei and Disease

The relatively recent discoveries of the developmental lineages of CN neurons highlight previously unexplored relationships in cerebellar disorders and disease. Glutamatergic projection neurons are formed from Atoh1 progenitors that not only generate granule cells but also neurons in the pons, vestibular and auditory systems of the hindbrain [57, 93]. GABAergic neurons share a progenitor transcriptional profile with auditory nuclei and, perhaps most prominently, the inferior olive [53].

This is particularly significant in that developmental disorders where cerebellar nucleus exclusively malformed have not been reported. Congenital dysplasia of the dentate and olivary nuclei (DOD), though rarely recorded [94], can sometimes be detected as a minor pathology of more extensive developmental defects (Table 1). Though pathogenesis may differ across different forms of DOD, it is interesting to note that many of the below conditions have pathologies of the inferior olive too. While the correlation in pathologies could be linked by lineage, the possibility of retrograde degeneration of the cerebellar nucleus as a result of inferior olive dysplasia cannot be discounted. Similarly, the possibility that the modularity of the cerebellar-inferior olive closed loop extends to a single cell level [95] means that heavily interconnected microzones might suffer a conductive degeneration when any element of the system is disrupted.

While DOD might represent a failure of Ptf1a lineage development, pontocerebellar dysplasia might conversely reflect a dysgenesis of Atoh1 lineage neurons, affecting both precerebellar and granule cell populations in addition to portions of the dentate CN. In both cases, the spectrum of associated phenotypes raises the possibility of a developmental origin within the specification or maturation of specific populations of derivatives.

Future Perspectives on Cerebellar Nucleus Development

In recent years, significant progress has been made with regard to understanding the development of the glutamatergic CN neurons, while physiologically, models of cerebellar function increasingly recognise how plasticity and modulation within the CN by mossy fibre and climbing fibre collaterals place these cells at the heart of cerebellar networks [43, 115]. However, less is known of other, equally significant, CN neuronal types and key questions about their specification and lineage remain

Table 1 Cerebellar disorders exhibiting nuclear pathology

Disorder	Aetiology	Pathology	Clinical features	Reference
Zellweger (cerebro-hepato-renal) syndrome	Autosomal recessive disease caused by mutations in PEX genes. Migration failure from 14 weeks of gestation in humans	Dysplasia of the dentate and olivary nuclei (DOD), as well as cerebellar hypoplasia and migrational defects of PCs	Developmental delay, seizures and EEG abnormalities, as well as generalised hypotonia, renal cysts and joint calcifications	[96–98]
Dentato-olivary dysplasia with intractable seizures in infancy	Unknown, though suggested to be autosomal recessively inherited	DOD – The dentate nuclei are seen as a solid ovoid or tear-shaped structure rather than the characteristic thin, convoluted band	Hypotonia with frequent seizures from birth and gross developmental delays. Survival is no longer than 3 years	[99, 100]
Joubert syndrome	Autosomal recessive disease approximately 50% of cases are genetically linked to mutations in genes that encode parts of the primary cilia. These may be important in progenitor cells for sensing morphogens like Wnt and Shh during development	Fragmentation of the dentate CN as one of many hindbrain symptoms, along with hypoplasia of vermis (molar tooth sign), dysplasia of the inferior olive and non-decussation of the SCP	Congenital ataxia, hypotonia, episodic breathing dysregulation and mental retardation	[101–103]
Rhombencephalosynapsis	Defective dorsal patterning and proliferation in the rhombic lips during early foetal development	Absence or severe dysgenesis of the cerebellar vermis. This leads to fusing of the two cerebellar hemispheres, peduncles and in the CN so that morphologically, there seems only to be one dentate nucleus that spans the breadth of the white matter	Cerebellar dysfunction, hypotonia, nystagmus, ataxia and mild to severe mental and motor developmental delays	[60, 104–106]

(continued)

Table 1 (continued)

Disorder	Aetiology	Pathology	Clinical features	Reference
Thanatophoric dysplasia	Due to gain of function mutations of FGF receptor 3 (FGFR3), which is involved in various parts of brain development, so pathological features are widespread across many brain regions as well as bones	Primarily a skeletal dysplasia with macrocephaly. Within the cerebellum, there are abnormalities of the cerebellar cortex, and CN are enlarged and hyperconvoluted and dysplastic. There is also dysplasia of the inferior olive	Generally is a lethal condition where foetuses are usually stillborn or die as neonates due to respiratory failure. For the very few survivors, clinical symptoms include seizures, dependence on ventilator and mental and motor impairments	[107–109]
Pontocerebellar hypoplasias	A group of neurodegenerative autosomal recessive disorders. Some variants are caused by tRNA splicing endonuclease mutations	Common feature is cerebellar hypoplasia and cerebellar and pons atrophy. In the cerebellum, there is scattered loss of PCs and segmental loss of dentate CN neurons, while specific regions of CN are preserved	Severe mental and motor impairments as well as swallowing problems and seizures	[110, 111]
Autism spectrum disorder	Heterogeneous: it may be caused by genetic, epigenetic or environmental factors during neurodevelopment. There is some consensus in that brain connectivity is affected. In the cerebellum, lower levels of GABA synthesis have been found in CN and PCs	Cerebellar vermal hypoplasia, reduction of superior cerebellar peduncle, decreased connectivity between the DN and cerebral regions (dentatorubrothalamic tract)	Heterogeneous spectrum or clinical features affecting social interaction, communication and behaviour	[112–114]

unanswered. A defining feature of development is that cells transit through the NTZ, yet nothing is known of the factors that regulate nucleogenesis.

Similarly, there are relatively few reports that highlight differences in cell types across the different CN. For example, Bagnall et al. [15] identified projections that are restricted to the fastigial CN, while molecular and cellular analyses point to underlying temporal cues that may explain how different nuclei are formed [67, 71]. Given that different densities of CN cell types are found across the already diversely shaped CN, and that the various CN have been found to be involved with wide ranges of motor control, from eye blinks to posture, it may be that connectivity and plasticity differ across similar cells to bring about an assortment of functions.

Finally, the diversity of different CN cells types, their origins and how they develop a network of intranuclear connectivity are key developmental questions whose answers will be of huge significance for functional models of the cerebellar network. The answer to these questions may also point towards new landmarks for the identification of disease processes in the cerebellum. This somewhat neglected population of brain cells is poised at a threshold of new understanding that offers the promise of new perspectives on the both how the cerebellum works and its clinical vulnerabilities.

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