Chapter 13
Cerebellar Neurogenesis

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Abstract The mechanisms of cerebellar neurogenesis have been redefined in the last few years, showing the precise spatio-temporal sequence of neuronal generation from neurochemically heterogeneous pools of progenitors. Here we describe these processes, highlighting the principal strategies used within this system to generate appropriate cell numbers and phenotypes.

Keywords GABAergic neurogenesis • Glutamatergic neurogenesis • Purkinje cell type specification • Ptf1a • AtoH1 • Ebf2 • GABAergic interneurons • Deep cerebellar nuclei (DCN) neurons • Unipolar brush cells (UBCs) • Granule cells • Purkinje cells (PCs)

13.1 Introduction

The murine cerebellum represents an ideal model to study mechanisms of neural development and specification, as it is composed by a limited number of phenotypes, arranged in a finely patterned network and unambiguously identified by morphological features and by the expression of distinctive neurochemical markers (Ramon y Cajal 1911; Palay and Chan-Palay 1974; Miale and Sidman 1961; Ito 1984; Altman and Bayer 1997; Sotelo 2004). In addition, the principal dynamics

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regulating the whole period of cerebellar ontogenesis have been elucidated (Ramón y Cajal 1911; Hatten and Heintz 1995; Altman and Bayer 1997; Sotelo 2004; Carletti and Rossi 2008; Hoshino 2012).

Here we discuss the major features of cerebellar neurogenesis, highlighting both cell intrinsic programs and environmental influences governing neuronal generation and specification within developing cerebellar circuitries.

13.2 Cerebellar Territory and Germinal Zones

A series of studies that took advantage of the chick/quail chimeric approach have shown that the cerebellum arises from a specialized region at the midbrain/hindbrain boundary (Hallonet et al. 1990; Hallonet and Le Douarin 1993; Hallonet and Alvarado-Mallart 1997). Here, at embryonic day 8.5 (E8.5), the interaction between homeobox genes Otx2 and Gbx2 defines the Isthmic Organizer region (Broccoli et al. 1999; Li et al. 2005), which orchestrates the development of cerebellar structures via the morphogenic activity of two secreted factors, Fgf8 and Wnt1 (Martinez et al. 1991, 1999; Sotelo 2004). After territorial specification, cerebellar histogenesis starts at E9 in the mouse. At this age the cerebellar anlage is comprised of two separate and symmetric bulges that, during the following days, grow and fuse together, giving rise to the unitary cerebellar plate comprising the vermis and two hemispheres (Altman and Bayer 1997). This developmental process is also characterized by the formation of two germinative compartments just above the opening of the fourth ventricle: the rhombic lip (RL), located at the outer aspect of the cerebellar plate, adjacent to the roof plate and the ventricular zone (VZ), facing the lumen of the fourth ventricle. These germinative districts are defined by the region-specific expression of two basic helix-loop-helix transcription factors: the pancreas transcription factor 1-a (PTF1A), expressed in the VZ (Hoshino et al. 2005), and the mouse homolog of Drosophila atonal (ATOH1), present in the RL (Akazawa et al. 1995). This spatially-restricted expression pattern defines the neurochemical compartmentalization of cerebellar precursors, as all GABAergic neurons (Purkinje cells, PCs, nucleo-olivary projection neurons of deep cerebellar nuclei, DCN, and all inhibitory interneurons - basket, stellate, Golgi and Lugaro cells-) originate from *Ptf1a*+ precursors (Hoshino et al. 2005; Seto et al. 2014; Yamada et al. 2014), while glutamatergic lineages (large projection neurons of DCN, unipolar brush cells, UBCs, and granule cells) derive from *Atoh1*+ progenitors (Alder et al. 1996; Wingate 2001; Machold and Fishell 2005; Wang et al. 2005; Fink et al. 2006; Englund et al. 2006; Yamada et al. 2014). The two primary germinative epithelia disappear at birth. Dividing VZ precursors migrate into the cerebellar prospective white matter (PWM), whereas those of the RL move tangentially along the pial cerebellar surface, where they form the external granular layer (EGL). Postnatal neurogenesis is active in the secondary PWM and EGL epithelia up to the third postnatal week, in order to generate appropriate numbers of GABAergic and glutamatergic interneurons, respectively (Altman and Bayer 1997; Carletti and Rossi 2008).

The temporal schedule of generation of cerebellar phenotypes is also finely organized. Birthdating studies have shown that projection neurons are produced first, at the onset of cerebellar neurogenesis, while both inhibitory and excitatory interneurons are generated later, during late embryonic and early postnatal life (Miale and Sidman 1961; Altman and Bayer 1997; Sekerkova et al. 2004b).

13.3 Glutamatergic Neurogenesis

From the rostral portion of the RL (rRL), named the germinal trigone, distinct cerebellar glutamatergic cell populations are generated during subsequent embryonic phases, as demonstrated by genetic fate mapping experiments (Wingate and Hatten 1999; Wingate 2001; Lin et al. 2001; Machold and Fishell 2005; Machold et al. 2007). Atoh1 expression in the RL begins at E9.5 in mice (Akazawa et al. 1995) and it is regulated by the antagonistic interaction between Notch1 in the cerebellar primordium and bone morphogenetic proteins secreted by the roof plate. Such interaction produces subsequent streams of migratory cells directed to the cerebellum: large glutamatergic DCN projection neurons, unipolar brush cells (UBCs) and granule cells (Machold and Fishell 2005; Machold et al. 2007). First, from E10.5 to E12.5, progenitors leaving the rRL give rise to large DCN projection neurons, which migrate to the surface of the cerebellar anlage and aggregate in the nuclear transitory zone (NTZ). From here, DCN neurons move inward below the developing Purkinje cell plate to form the three pairs of cerebellar nuclei (Wang et al. 2005; Fink et al. 2006; Morales and Hatten 2006; Machold and Fishell 2005; Machold et al. 2007). *Atoh1* expression is switched off as soon as these neurons leave the RL (Ben-Arie et al. 1997). Secondly, progenitors migrating from the rRL between E14 and E21 give rise to two different subsets of UBCs, distinguished on the basis of their birthdating and neurochemical profiles (Sekerkova et al. 2004; Nunzi et al. 2001; 2002). UBCs become regionally restricted during development through a non–cell-autonomous mechanism involving embryonic interactions with different Purkinje cell subtypes (Chung et al. 2009). Thirdly, the following wave exiting the rRL is represented by granule cell progenitors (GCPs) that migrate tangentially along the cerebellar surface, maintaining the expression of *Atoh1* and other transcription factor genes as *Zic1*, *Zic3* and *Zscan21*, encoding RU49 (Wingate 2001).

GCPs move tangentially towards their secondary germinal zone, the EGL, which by E16 covers the entire surface of the cerebellar anlage (Rakic 1990). It is initially composed of a single row of proliferating cells, but after birth it expands to a layer of about eight cells in thickness and its outer portion is occupied by actively proliferating GCPs (Miale and Sidman 1961; Fujita et al. 1966; Komuro et al. 2001). The proliferation window of murine GCPs closes at the end of the second postnatal week, when the last postmitotic granule cells from the deepest portion of the EGL migrate inward into the nascent IGL, marking the end of the EGL and extinguishing *Atoh1* expression (Acazawa et al. 1995; Helms and Johnson 1998; Ben-Arie et al. 2000). Evidence from transplantation (Gao and Hatten 1994), retroviral labelling

(Zhang and Goldman 1996a, b) and in vitro studies (Gao et al. 1991; Alder et al. 1996) demonstrates that the EGL gives rise to granule cells only. Interestingly, it has been shown that GCPs are also generated by some proliferative GFAP$^+$ astroglial cells present in the neonatal EGL (Silbereis et al. 2010).

Another salient feature of granule cell neurogenesis is the active control exerted by PC-derived mitogenic factors. In fact, the relative number of granule cells is abnormally reduced in animal models characterized by a primary PC degeneration (Sonmez and Herrup 1984; Vogel et al. 1989; Smeyne et al. 1995), whereas if the loss of PCs occurs later, in the postnatal period, the granule cell layer appears near-normal (Mullen et al. 1976; Smeyne et al. 1995). Sonic hedgehog (SHH), produced by PCs, is the most potent mitogen acting on granule cell development. Treatment of GCPs with SHH prevents their differentiation and induces a long-lasting proliferative response, while an inhibition of SHH signal dramatically reduces the mitotic activity of these precursors (Dahmane and Ruiz-i-Altaba 1999; Wallace 1999; Wechsler-Reya and Scott 1999; Lewis et al. 2004).

13.4 GABAergic Neurogenesis

GABAergic neurons are produced by *Ptf1a*$^+$ VZ progenitors according to a two-step process (Carletti and Rossi 2008). First, projection neurons (nucleo-olivary DCN neurons and PCs) are generated locally, from fate-committed precursor populations. Second, some progenitors become restricted to interneuron identities and migrate from the VZ to the nascent deep nuclei or cortical layers, where they acquire final phenotypic identities under the influence of instructive environmental cues.

Nucleo-olivary DCN neurons are generated between E10.5 and E12.5 in the mouse and join their glutamatergic counterparts (Palay and Chan-Palay 1974). PC progenitors undergo their terminal mitosis between E11 and E13 and populate different cortical regions according to their birthdate (Altman and Bayer 1997). Postmitotic PCs migrate radially towards the prospective cortex, where they form the multi-cell thick Purkinje cell plate (Morales and Hatten 2006). As early as E14–15, they aggregate in clusters and finally align into a monolayer through a process that is completed around P4 (Altman and Bayer 1997). The double-step migration allows the anteroposteriorly migrating PCs to constitute the adult parasagittal stripes, characterized by the expression of specific markers, which achieve a stable pattern in the third postnatal week (Larouche and Hawkes 2006; Consalez and Hawkes 2013).

GABAergic interneurons comprise multiple subsets of morphologically and neurochemically distinct phenotypes integrated at different levels of the cerebellar cortex and DCN. These cells are produced from the late embryonic life to the second postnatal week; the peak is reached around P5 and 75 % of all inhibitory interneurons are born prior to P7 (Weisheit et al. 2006). The origin of these cells has been controversial for a long time. Until a few years ago, molecular layer (ML) interneurons were thought to derive from the EGL, the only germinal layer known to be

active during postnatal development (Ramón y Cajal 1911; Altman 1972). More recently, the analysis of chick-quail chimeras, transplantation experiments and retroviral injections have demonstrated that the EGL only generates granule cells, suggesting that ML interneurons derive from the VZ (Hallonet et al. 1990; Napieralski and Eisenman 1993; Alvarez et al. 1993; Gao and Hatten 1994; Zhang and Goldman 1996a, b). Marichich and Herrup (1999) identified the progenitors of inhibitory interneurons as a population of PAX2$^+$ cells, which appear in the VZ around E12 and, later, migrate deep into the cerebellar cortex. Inhibitory interneuron precursors continue to proliferate during their migration in the PWM (Zhang and Goldman 1996a, b; Leto et al. 2006, 2009; Weisheit et al. 2006), and generate interneuron phenotypes according to an inside-out progression. DCN interneurons are the first to be born during embryonic and early postnatal life, followed by granular layer (GL) interneurons (Golgi and Lugaro cells) and, finally, by ML ones (basket and stellate cells; Maricich and Herrup 1999; Leto et al. 2006; Weisheit et al. 2006; Sudarov et al. 2011). Transplantation experiments have demonstrated that all types of cerebellar inhibitory interneurons derive from a single population of multipotent progenitors that acquire mature phenotypic traits under the influence of local instructive cues provided by the PWM microenvironment (Leto et al. 2006, 2009). It has been shown that proliferative progenitors of GABAergic interneurons in the PWM are *Ptf1a*$^+$ cells that start expressing *Pax2* during their last S phase (Maricich and Herrup 1999; Leto et al. 2009; Fleming et al. 2013). Importantly, it has been recently demonstrated that SHH delivered by PCs maintains the PWM niche and sustains the proliferation of neural stem cell-like primary progenitors able to generate both CD15$^+$ astroglial precursors and *Ptf1a*$^+$ GABAergic interneuron progenitors (Fleming et al. 2013). The same morphogen secreted by the choroid plexi in the embryonic cerebrospinal fluid is critically involved in the amplification of early VZ-derived GABAergic progenitors (Huang et al. 2010), suggesting that similar influences could sustain neurogenesis in the embryonic and postnatal cerebellum.

13.5 Neurogenesis and Purkinje Cell Type Specification

A regulatory network involving *Ptf1a*, Neurogenin 1/2 (*Neurog1/2*) and Early B-cell factor 2 (*Ebf2*) is implicated in PC differentiation and subtype specification (Zordan et al. 2008; Florio et al. 2012). By this model, the early-born PC cohort expresses neither *Neurog1/2* nor *Ebf2*, and expresses the ZII+ phenotype in the adult. Soon after E11, *Neurog1/2* transcription is upregulated by PTF1A in the later-born PC progenitors (e.g. Henke et al. 2009). In this context, *Neurog2* regulates cell cycle progression, neuronal output and early dendritogenesis in PC progenitors (Florio et al. 2012), but neither *Neurog1* nor *2* deletions affect the specification of PC subtypes (R. Hawkes, unpublished observation). In turn, *Neurog1/2*+ precursors express Ebf2, which represses the ZII+ phenotype (Croci et al. 2006; Chung et al. 2008): *Ebf2* deletion results in transdifferentiated PCs that express markers characteristic of both the ZII+ and ZII- subtypes - the only manipulation known to alter a PC

subtype phenotype. In addition, *Ebf2* plays a subtype-specific anti-apoptotic role in ZII- PCs by locally regulating *Igf1* gene expression (Croci et al. 2011). As a result of these events, early-born PCs become ZII+ in the adult, while late-born PCs adopt the ZII- phenotype.

13.6 Concluding Remarks

Different strategies active within cerebellar neurogenic niches determine the precise sequence of phenotype generation: projection neurons are produced by defined pools of fate-restricted progenitors, whose specification programs mainly develop early in embryogenesis, while interneuron precursors proliferate until the second postnatal week, acquiring mature phenotypes under the influence of local instructive cues. The cellular/molecular mechanisms underlying these processes remain to be fully clarified. It is possible that these different mechanisms might support the correct establishment of topographically patterned long–distance connections on one hand, and of local experience-dependent networks on the other. Further analyses will be required to better clarify these issues.

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