Chapter 14
Zones and Stripes

Carol Armstrong and Richard Hawkes

Abstract The cerebellar cortex is built around different classes of Purkinje cell, which form an array of transverse zones, each of which is further divided into parasagittal stripes. There are >200 stripes, which are reproducible between individuals and the pattern is conserved across birds and mammals. Other features of cerebellar organization, including the topography of afferent projections and cerebellar interneurons, are built around the Purkinje cell framework. Zone and stripe architecture is established early in cerebellar development. Purkinje cells are born between E10 and E13 (in mouse) in the subventricular zone of the fourth ventricle. Purkinje cell subtype specification likely happens at this time. Postmitotic Purkinje cells migrate into the cerebellar anlage and form a stereotypes array of clusters (E14–E18). Clusters are the forebears of the stripes and are the targets of the ingrowing afferent projections. Reelin signaling at around birth triggers the rostrocaudal dispersal of the clusters into the adult stripes.

Keywords Zebrin • Zone • Stripe • Development

14.1 Zones and Stripes

The cerebellar cortex is traditionally described in terms of lobes and lobules separated by fissures. However lobulation does not reflect the functional organization of the cerebellum, its connectivity or its embryology. A more fundamental architecture is shown by intrinsic differences between subsets of Purkinje cells (PCs) through the expression of molecular markers such as zebrin II/aldolase C (Brochu et al. 1990), phospholipase C (PLC)β4 (Sarna et al. 2006: see Figure 1) and HSP25 (Armstrong et al. 2000). These reveal an elaborate and reproducible pattern of zones

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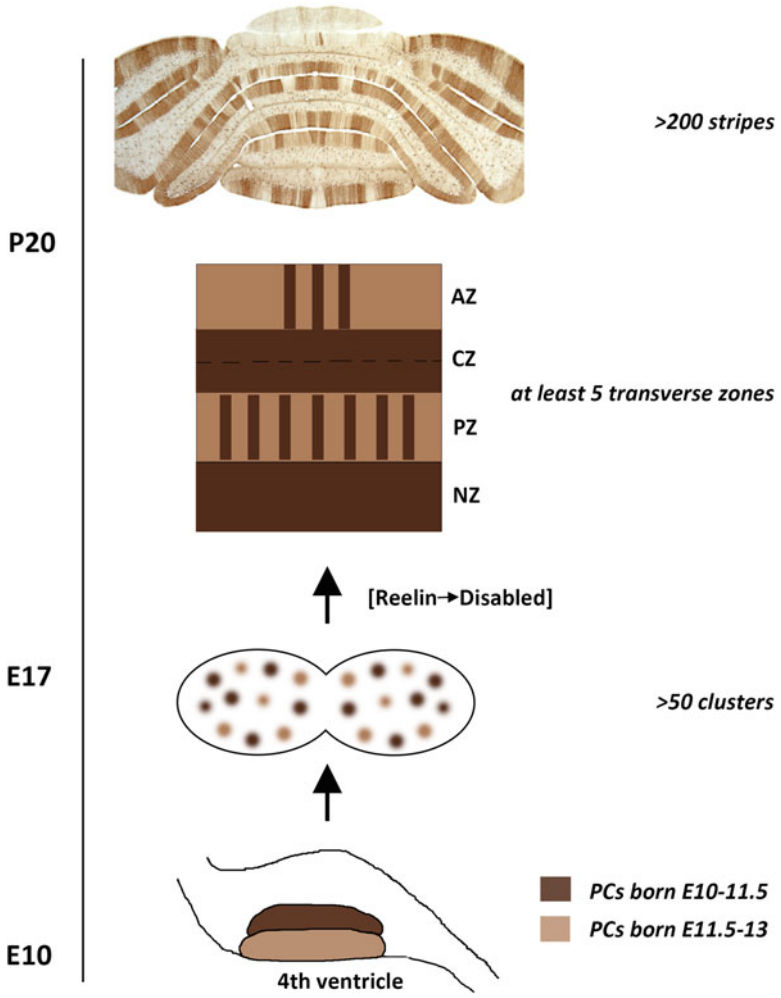

Fig. 14.1 Zones and stripes. Newborn PCs exit the subventricular zone of the fourth ventricle and stack by birthdate. Subsequently, they migrate to form a symmetrical array of clusters. Reelin-Disabled signaling triggers cluster dispersal into the adult transverse zones and parasagittal stripes (seen here in an adult mouse transverse section immunoperoxidase-stained for PLCβ4: Sarna et al. 2006)

and stripes that is conserved in birds and a diverse group of mammals (Sillitoe et al. 2005; Marzban and Hawkes 2011), and form the scaffold around which the rest of the cerebellar cortex is organized.

The mammalian cerebellum includes at least five zones (Fig. 14.1): regions of cerebellar cortex that extend anterior to posterior and can be distinguished as distinct expression domains separated by transverse boundaries that do not align with anatomical boundaries (Fig. 14.1). The anterior zone (AZ) is roughly equivalent to

lobules I–V ("roughly" because transverse zones interdigitate). The central zone (CZ) comprises lobules VI and VII and can be further divided into an anterior CZa (~lobule VI) and a posterior CZp (~lobule VII: Marzban et al. 2008). The posterior zone (PZ) occupies lobule VIII and the dorsal half of lobule IX. The nodular zone (NZ) includes the ventral half of lobule IX and lobule X. In birds, a sixth transverse zone – the lingular zone (LZ) – has been identified in lobule I (Pakan et al. 2007; Marzban et al. 2010).

Each transverse zone is further divided into parasagittal stripes (Armstrong and Hawkes 2013: Figure 1). For example, zebrin II+/– stripe arrays are found in the AZ and PZ (Hawkes and Leclerc 1987; Brochu et al. 1990) and HSP25+/– stripe arrays in the CZ and NZ (Armstrong et al. 2000). However, no single marker reveals the full complexity of the cerebellar architecture: distinct stripes illustrated by one marker are revealed as composite with another (e.g. zebrin II–/PLCβ4+ stripes subdivided by L7/pcp2-*lacZ* in the AZ – Ozol et al. 1999: zebrin II+ stripes subdivided by HSP25 in the PZ during development – Armstrong et al. 2001). The intrinsic zone-and-stripe organization of the cerebellar cortex also encompasses interneurons and glial cells (Consalez and Hawkes 2013), and PC death in cerebellar pathologies is typically restricted to particular PC subtypes (Sarna and Hawkes 2003).

Afferent tract tracing has shown that both climbing fiber and mossy fiber afferent terminal fields are also restricted to specific stripes (Ruigrok 2011). This patterned afferent input results in functional differences between stripes (witness the physiological classification of stripes/microzones: Apps and Hawkes 2009), and recent studies have also identified intrinsic functional differences between PC subtypes (e.g., Xiao et al. 2014; Zhou et al. 2014). The significance of cerebellar architecture to overall cerebellar function remains unclear: one speculation is that molecular differences between stripes may reflect alternative modes of long-term depression (Hawkes 2014).

14.2 Pattern Formation

The zone and stripe architecture of the adult cerebellum is established early in development (Fig. 14.1: Dastjerdi et al. 2012). PCs undergo terminal mitosis (E10–E13: Miale and Sidman 1961) within a *Ptf1a*+ expression domain in the ventricular zone of the fourth ventricle (Hoshino et al. 2005; Zordan et al. 2008). Birthdating studies reveal a direct correlation between PC birthdates and their final stripe location, suggesting that both subtype specification and positional information are acquired at this time (e.g., Hashimoto and Mikoshiba 2003; Chung et al. 2008).

Between E14 and E17, PCs undergo a choreographed migration into a reproducible array of numerous clusters that can be distinguished on the basis of differential expression of molecules (e.g. calbindin, engrailed, cadherins and neurogranin: Fujita et al. 2012; Armstrong and Hawkes 2013). These clusters are the targets of specific afferents and specify the adult connectivity (Sillitoe and Joyner 2007).

The PC clusters disperse between E18 and P20, triggered by Reelin secreted by the external granular layer (D'Arcangelo et al. 1995). Because dispersal is restricted to the rostrocaudal plane, each cluster is drawn out into a long, parasagittal stripe.

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