1.12 Mammalian Retina Development

Daniel Kerschensteiner[a,b,c,d], [a] John F. Hardesty, MD Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, Saint Louis, MO, United States; [b] Department of Neuroscience, Washington University School of Medicine, Saint Louis, MO, United States; [c] Department of Biomedical Engineering, Washington University School of Medicine, Saint Louis, MO, United States; and [d] Hope Center for Neurological Disorders, Washington University School of Medicine, Saint Louis, MO, United States

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1.12.1 Abstract

In the mammalian retina, approximately 150 different types of neurons are connected in approximately 40 distinct circuits. These circuits convert the pixel representation of photoreceptors into parallel feature representations of ganglion cells, the sole output neurons of the retina, which drive reflexive behaviors, support conscious visual perception, and mediate non-image forming functions of light. In this chapter, I discuss how diverse retinal neurons arise from uniform progenitor cells, migrate to specific positions, elaborate intricate axon and dendrite arbors, and establish precise patterns of connections. For clarity and consistency, I focus, when possible, on the retinal development of mice.

This chapter is divided into sections that represent different steps along the way to retinal circuit assembly. Although these steps are presented in sequence, many of them occur simultaneously during development (Fig. 1).

1.12.2 Progenitor Proliferation and Neurogenesis

One of the most striking features of the mature retina is its cellular diversity; within seven cell classes (rods, cones, horizontal cells, bipolar cells, amacrine cells, ganglion cells, and Müller glia) more than 150 cell types have been identified (Fig. 2). Cellular diversity serves functional specificity and allows the retina to parse information contained in the influx of photons to the eye into distinctive feature representations of the environment. These feature representations are communicated to the brain through the spike trains of retinal ganglion cells. In mice, large-scale surveys of morphology (Bae et al., 2018; Helmstaedter et al., 2013), function (Baden et al., 2016), and gene expression (Rheaume et al., 2018; Tran et al., 2019) identified more than 40 ganglion cell types. Thus, more than

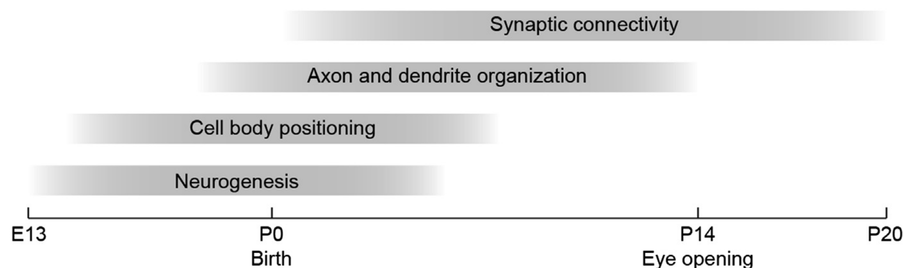

Figure 1 Timeline of Retinal Development in Mice. The timing of the important steps in retinal circuit assembly is shown as a function of embryonic (E) and postnatal (P) age in mice (in days).

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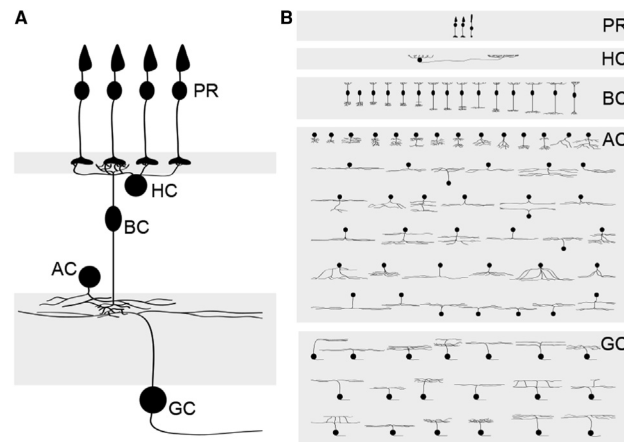

Figure 2 **Retinal Neuron Classes and Neuron Types**. (A) Schematic of a retinal cross-section illustrating the classes of retinal neurons (PR: photoreceptors, combining rods and cones, HC: horizonal cells, BC: bipolar cells, AC: amacrine cells, GC: ganglion cells). (B) Schematic illustrating the diversity of neuron types within these classes based on several recent morphological surveys (Bae et al., 2018; Greene et al., 2016; Helmstaedter et al., 2013; Sabbah et al., 2018). For amacrine and ganglion cells, only a subset of cell types are depicted. The style of the illustration is inspired by Masland (2001).

40 parallel streams of information, their content shaped by synaptic interactions of manifold neurons upstream of ganglion cells, leave the eye. This section summarizes our understanding of how the diverse cells of the retina are generated during development.

Not only are cell types of the retina morphologically, functionally, and transcriptionally diverse, they vary greatly in their numbers. For example, the mouse retina contains ~6.4 million rods (Jeon et al., 1998) but only ~730 M1 intrinsically photosensitive ganglion cells (Hattar et al., 2002), and the human retina, contains ~90 million rods (Curcio et al., 1990) but only ~15,000 M1 cells (Morgia et al., 2016). Therefore, we need to ask not just how a wide range of cell types is generated, but how each is produced in precisely the right number.

All neurons of the retina and Müller glia arise from a common pool of multipotent retinal progenitor cells (RPCs) (Turner et al., 1990; Turner and Cepko, 1987). RPCs can undergo three types of divisions: (1) symmetric proliferative divisions, which give rise to two RPCs, (2) asymmetric neurogenic divisions, which give rise to one neuron (or Müller glia) and one RPC, and (3) symmetric neurogenic divisions, which give rise to two neurons (or Müller glia). It follows that symmetric proliferative divisions expand the pool of RPCs, asymmetric neurogenic divisions maintain it, and symmetric neurogenic divisions deplete it. During early retinal development, RPCs undergo symmetric proliferative divisions to expand the progenitor pool and support mature retinal cell numbers. The transcription factors PAX6, CHX10, and SOX2 promote RPC proliferation and mutations in the respective genes can cause microphthalmia (i.e., small eyes) or anophthalmia (i.e., a lack of eyes) (Burmeister et al., 1996; Marquardt et al., 2001; Taranova et al., 2006). As development progresses, RPCs begin to divide asymmetrically. Different retinal cell types emerge in overlapping waves from these asymmetric divisions as RPC competence shifts over time (Livesey and Cepko, 2001). Finally, RPCs undergo symmetric neurogenic divisions and the cellular composition of the retina is finalized. The timing of terminal symmetric divisions is regulated by the cell-cycle machinery, NFI (Nuclear Factor I) transcription factors, and NOTCH signaling (Clark et al., 2019; Del Bene et al., 2008; Dyer and Cepko, 2001).

At a population level, the different retinal cell classes are generated in a stereotypical and evolutionarily conserved sequence, ganglion cells first and Müller glia last (Livesey and Cepko, 2001) (**Fig. 3**). Heterochronic transplantation experiments revealed that changes in competence over time are intrinsic to RPCs. Thus, early RPCs transplanted into late retinal environments give rise to early cell fates (Belliveau and Cepko, 1999), whereas late RPCs transplanted into early retinal environments give rise to late cell fates (Belliveau et al., 2000). Similarly, when RPCs are isolated from their environment and put in culture, they give rise to cell fates that reflect their age (Austin et al., 1995; Cayouette et al., 2003; Gomes et al., 2011; Reh and Kljavin, 1989). In spite of the ordered progression at the population level, at each timepoint, RPCs can produce a variety of cells (He et al., 2012). This raises the question of whether RPCs are heterogeneous and dedicated to specific fates or whether they are homogenous and stochastically generate postmitotic fates. Single-cell RNA sequencing (scRNA-Seq) revealed diversity among RPCs (Cepko, 2014; Clark et al., 2019; Lu et al., 2019; Sridhar et al., 2020). Based on their RNA expression profiles, RPCs appear to mature and diverge gradually along trajectories that merge with the major retinal cell classes, suggesting increasing RPC dedication (Clark et al., 2019; Lu et al., 2019; Sridhar et al., 2020). Consistent with this interpretation, lineage tracing and live imaging studies identified RPCs expressing specific markers that give rise to stereotypic daughter cell types (Godinho et al., 2007; Hafler et al., 2012; Suzuki et al., 2013).

The differentiation of retinal neurons and Müller glia is controlled by gene regulatory networks in late RPCs and early postmitotic cells. Gene regulatory networks involve feedforward and feedback interactions between transcription factors, activators, and repressors. In the retina, the gene regulatory networks that differentiate rods from cones and rods from bipolar cells have been studied intensely (Cepko, 2015), and differences in the *cis*-regulatory elements that drive gene expression in these cells have

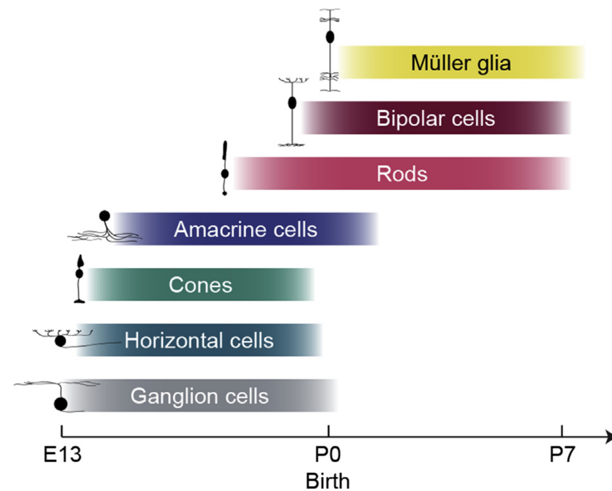

Figure 3 Timeline of Neurogenesis in the Mouse Retina. The order and timing of neurogenesis of the retinal cell classes shown as a function of embryonic (E) and postnatal (P) age in mice (in days). This figure summarizes data from Rapaport et al. (2004) and Young (1985).

been uncovered (Hsiau et al., 2007; Murphy et al., 2019; Wang et al., 2014). Knowledge of the gene regulatory networks that control differentiation opens the possibility of reprogramming cells in mature circuits. This possibility was demonstrated in mice, in which reprogramming of rods into cones halted retinal degeneration in a model of retinitis pigmentosa, a disease primarily affecting rods (Montana et al., 2013). In common with the distinctions between cell classes (e.g., rods vs. cones) the differentiation of closely related cell types depends on gene regulatory networks. For example, ON and OFF starburst amacrine cells are differentiated by cell-types-specific expression of the transcription factor FEZF1, which drives expression of ON starburst genes and suppresses expression of OFF starburst genes (Peng et al., 2019).

The cellular composition of the retina depends not only on the birth of neurons and Müller glia but also on their death. Programmed cell death in the developing retina occurs in two phases (Braunger et al., 2014; Buss et al., 2006; Linden and Reese, 2006). The first phase, during embryonic development in mice, adjusts the RPC pool size. The second phase coincides with synaptogenesis and occurs during postnatal development in mice. How the second phase of programmed death is distributed across retinal cell classes remains uncertain (Linden and Reese, 2006). There is convincing evidence that programmed cell death is most abundant among ganglion cells, more than 60% of which vanish during development (Galli-Resta and Ensini, 1996; Strom and Williams, 1998). Based on the patterns of pyknotic nuclei, programmed cell death affects all other retinal cell classes, with the possible exception of cones (Johnson et al., 1999; Williams et al., 1990), to varying degrees and at different times (Young, 1984). Programmed cell death results in part from competition for limited trophic support (e.g., neurotrophins and insulin-like growth factor) from the local environment or, in the case of ganglion cells, from their downstream targets (Bovolenta et al., 1996; Cusato et al., 2002; Ma et al., 1998). In addition, cytotoxic signals between cells can induce programmed cell death. Thus, starburst amacrine cells are sensitive to extracellular ATP, released by their neighbors (Resta et al., 2005). Starburst amacrine cells express purinergic $P2X_7$ receptors, which form large pores in response to prolonged elevations of extracellular ATP and trigger cell death (Adinolfi et al., 2005; Resta et al., 2005). Similarly, interactions mediated by Down Syndrome Cell Adhesion Molecule (DSCAM) or DSCAM-like 1 (DSCAML1) promote cell death, evidenced by an overabundance of retinal neurons in *Dscam* and *Dscaml1* mutants (Fuerst et al., 2008, 2009; Keeley et al., 2012). Thus, both competition for support and hostile interactions between neurons regulate mature retinal cell numbers.

1.12.3 Cell Body Positions

Retinal circuits are organized in part by the positions of their constituent cells. This section reviews the development of three fundamental features of the spatial layout of retinal neurons: specific laminar positions, regular lateral distributions (i.e., retinal mosaics), and species-specific regional specializations (e.g., the human fovea).

1.12.3.1 Cell Body Lamination

Retinal cell bodies are distributed in three nuclear layers. The outer nuclear layer (ONL) contains rods and cones, the inner nuclear layer (INL) horizontal cells, bipolar cells, and amacrine cells, and the ganglion cell layer (GCL) amacrine cells and ganglion cells. This arrangement separates connections between retinal neurons into two synaptic layers and two sequential stages of visual processing. Neurons of the ONL and INL connect in the outer plexiform layer (OPL), whereas neurons of the INL and GCL connect in the inner plexiform layer (IPL).

Most RPCs divide near the apical surface of the retina (i.e., the outer edge of the future ONL) (Turner et al., 1990). As a result, most neurons must migrate some distance toward their final laminar position. Unlike in cortex, where neurons are stacked in order of their appearance from the apical to the basal surface (Greig et al., 2013), the laminar positions of retinal neurons do not reflect their birth order. Thus, other cues must define laminar targets in the retina. The class-specific trajectories of retinal neurons have been mapped (**Fig. 4**), but the mechanisms that guide their migration and signal where to stop are poorly understood.

Ganglion cells are born first and migrate from the apical to the basal side of the retina by somal translocation (**Fig. 4**) (Hinds and Hinds, 1974; Icha et al., 2016; Morest, 1970). RPCs have bipolar morphologies with two processes connecting them to the basal and apical surface, respectively. During somal translocation, newborn ganglion cells retain apical and basal processes and shift their cell body toward the basal side. Somal translocation of ganglion cells is followed, after retraction of the apical process, by a second phase that adjusts ganglion cell positions laterally (Icha et al., 2016).

Rods and cones are born at different times: cones early and rods late in development. Both ultimately reside close to where they are born and there is little evidence that rods migrate along specific trajectories. By contrast, the cell bodies of cones are distributed throughout the ONL during early development and then migrate to the apical surface (Rich et al., 1997). Cone axon terminals (i.e., cone pedicles) contact postsynaptic partners before cone nuclei reach their final positions by somal translocation (**Fig. 4**) (Huckfeldt et al., 2009; Rich et al., 1997). The upward motion of cones fails and their nuclei sink to their pedicles when interactions between the nuclear envelope and the cytoskeleton are disrupted (Razafsky et al., 2012). Intrinsically photosensitive ganglion cells respond to light before rods and cones. During development, intrinsically photosensitive ganglion cells send dendrites into the OPL, where they contact cone terminals and dendrites of dopaminergic amacrine cells (Renna et al., 2015; Sondereker et al., 2017; Tufford et al., 2018). Most of these dendrites are subsequently pruned. When intrinsically photosensitive ganglion cells are ablated during development, a subset of cones mislocalize; their nuclei fail to translocate to the apical surface of the ONL and some migrate into the INL and GCL. This effect depends in part on the light-evoked activity of the intrinsically photosensitive ganglion cells and dopaminergic signaling (Tufford et al., 2018). Thus, signals from ganglion cell photoreceptors relayed by transient dendritic collaterals contribute to cone lamination.

Amacrine cells and horizontal cells are born during early development, overlapping with ganglion cells and cones (**Fig. 3**). Although horizontal cells end up closer to their birthplace than amacrine cells, they take a longer route to get there (**Fig. 4**). Both amacrine and horizontal cells migrate in a mixture of modes, using somal translocation and unconstrained migration (Deans et al., 2011; Godinho and Link, 2006; Huckfeldt et al., 2009; Ray et al., 2018). They first move from the apical side to the basal margin of the emerging INL. In *lakritz* mutant zebrafish, which lack ganglion cells, amacrine cells migrate all the way to the basal surface of the retina (i.e., the inner limiting membrane), indicating that ganglion cells serve as a stop signal for amacrine cell migration (Kay et al., 2004). Whereas amacrine cells remain adjacent to the emerging IPL, horizontal cells migrate back apically to the border between the INL and the ONL and eventually form synapses with rods and cones in the OPL (Edqvist, 2004; Huckfeldt et al., 2009; Liu et al., 2000). This second leg of the horizontal cell journey depends on their expression of the homeodomain transcription factor LIM1. In *Lim1* knockout mice, horizontal cells remain at the basal margin of the INL and send processes in the IPL, highlighting the importance of laminar cell body positions for retinal circuit organization (Poché et al., 2007).

Bipolar cells and Müller glia, which are born late, retain the bipolar morphology of their precursors and, other than adjusting the position of their nuclei within this morphology, do not appear to migrate (Goldman, 2014; Morgan et al., 2006). Thus, the freedom of neuronal movements is determined in part by their birth order.

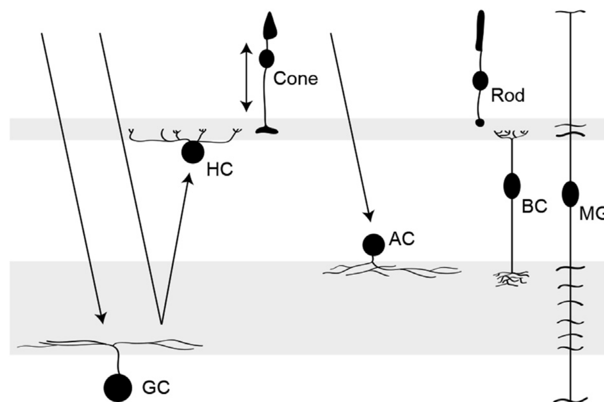

Figure 4 Migration Patterns of Developing Retinal Neurons. Schematic illustrating migration trajectories of different retinal neuron classes. Neurons are shown in order of their generation from left to right. Whereas early-born cells migrate along various vertical and lateral trajectories, late-born cells (i.e., rods, bipolar cells, and Müller glia) move little.

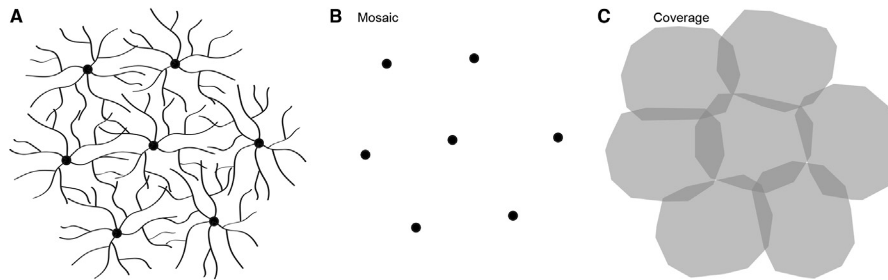

Figure 5 Lateral Distributions of Retinal Cell Bodies and Neurites. (A) Schematic illustrating the distribution of cell bodies and neurites of neurons of the same type. (B, C) Cell body mosaic (B) and regular neurite territory coverage.

1.12.3.2 Cell Body Mosaics

In the plane of their laminar targets, the cell bodies of many retinal neurons are evenly distributed (i.e., retinal mosaics) (**Fig. 5**). In each retinal mosaic, the cell bodies of one neuron type are separated by preferred distances from their nearest same-type neighbors and are surrounded by exclusion zones devoid of same-type cells (Reese and Keeley, 2015; Wässle and Riemann, 1978). This arrangement serves to distribute the computations implemented by the respective cell types evenly across visual space.

Lineage tracing revealed that clonally related rods, bipolar cells, and Müller glia align in narrow columns marking their origin, whereas cones, horizontal cells, amacrine cells, and ganglion cells disperse laterally from their birthplace (Reese et al., 1995, 1999). Rods, bipolar cells, and Müller glia are not arranged in mosaics. The mosaics of cones, horizontal cells, amacrine cells, and ganglion cells are shaped, to varying degrees, by the positions of their birth, lateral migration, and cell death (Eglen, 2006).

The regularity of cone arrays varies drastically across species. At one extreme, cones in the zebrafish retina form crystalline mosaics with precisely repeated motifs of four spectral cone types (Allison et al., 2010). At the other extreme, short (S), medium (M), and long wavelength-sensitive (L) cones of humans are randomly distributed in the central retina (Roorda et al., 2001; Roorda and Williams, 1999). The development of highly ordered cone mosaics in zebrafish appears to involve lateral induction of cell fates, similar to photoreceptors in fruit flies, and migration, with little or no contribution from cell death (Frankfort and Mardon, 2002; Mochizuki, 2002; Zou et al., 2012).

Homotypic interactions (i.e., interactions between neurons of the same type) during migration guide the development of horizontal cell mosaics. As horizontal cells migrate apically (i.e., during the second leg of their bidirectional journey), they elaborate vertical processes. The vertical processes of neighboring horizontal cells occupy non-overlapping territories, and if one horizontal cell is ablated with a laser, its neighbors move toward the ablation site as their processes fill in the vacated territory (Huckfeldt et al., 2009). Similarly, when a subset of horizontal cells is arrested at the basal margin of the INL by deletion of *Lim1*, the remaining apically migrating cells spread out evenly into lower-density mosaics (Poche et al., 2008). Thus, homotypic repulsion of vertical migratory processes shapes horizontal cell mosaics. Repulsive homotypic interactions between horizontal cells are mediated by two related transmembrane proteins: MEGF10 and MEGF11. In *Megf10 Megf11* double knockout mice, the number of horizontal cells is unchanged, but their lateral distribution is disorganized (Kay et al., 2012). When horizontal cells reach their final laminar destination in wild-type mice, they retract vertical and elaborate lateral processes. These lateral processes are not territorial and overlap sixfold among neighbors (Huckfeldt et al., 2009; Reese et al., 2005).

The mosaics of different amacrine cell types depend differently on lateral migration vs. cell death. Newborn starburst amacrine cells space themselves evenly by lateral migration (Galli-Resta et al., 2002). The regularity of their distribution remains fixed during the subsequent period of programmed cell death (Galli-Resta and Novelli, 2000), and is unchanged when naturally occurring cell death is disrupted (Resta et al., 2005). Similar to horizontal cells, homotypic repulsion mediated by MEGF10 drives the lateral dispersion of starburst amacrine cells (Kay et al., 2012). By contrast, dopaminergic amacrine cells appear not to migrate laterally, and cell bodies lose their mosaic distributions and tend to cluster when programmed cell death is disrupted (Keeley et al., 2012; Raven et al., 2003; Strettoi and Volpini, 2002).

Homotypic repulsion controls dendritic territories of ganglion cells, and loss of such interactions can disrupt ganglion cell mosaics and lead to cell body clustering (Fuerst et al., 2008, 2009). However, although dendritic repulsion is required for ganglion cell mosaics, it does not instruct their formation. Thus, even when ganglion cell density is reduced to a point where the dendrites of same-type cells no longer touch, the remaining cells form mosaics (Lin et al., 2004). There is some evidence that ganglion cell mosaics are shaped by programmed cell death (Chen et al., 2013; Jeyarasasingam et al., 1998), but the signals involved remain unknown.

1.12.3.3 Regional Specializations of Cell Densities

Retinal mosaics regularize cell distributions locally, but on a global scale, many retinas exhibit inhomogeneities in the distribution of cells. Thus, most retinas contain acute zones in which ganglion cell densities are increased. In these acute zones, dendrite arbors of ganglion cells are proportionally smaller increasing the spatial resolution (i.e., acuity) of vision (Baden et al., 2019; Cronin et al., 2014; Hughes, 1985). The shapes and positions of acute zones are adapted to the visual environments and viewing strategies of each animal (Baden et al., 2020; Cronin et al., 2014; Hughes, 1985).

Color and luminance contrast are unevenly distributed across the visual fields of many animals, and their retinas show corresponding anisotropies in the distribution of cells and their functional properties (Baden et al., 2013; Haverkamp et al., 2005; Zimmermann et al., 2018). In addition to inhomogeneities of scene statistics across the visual field, specializations in cell distributions and wiring may be driven by region-specific behavioral requirements (e.g., the need to detect looming aerial predators in the sky) (Zhang et al., 2012).

The acute zone of the primate retina is the fovea. Primates, including humans, make frequent saccadic eye movements to focus salient regions of the environment onto the fovea. In the fovea, midget ganglion cells receive private-line input from individual cones (Calkins et al., 1994; Dacey, 2004; Kolb and Marshak, 2003; Polyak, 1941; Sinha et al., 2017; Wässle et al., 1994). As a result, visual acuity and color sensitivity are highest in the fovea. In the human retina, there are $\sim$200,000 mm^{-2} cones in the fovea compared to 7000 mm^{-2} in the periphery (Curcio et al., 1990). By contrast, rods are excluded from the center of the fovea (Curcio et al., 1990). Cone density in the fovea increases during development by lateral migration, while the generation of rods is suppressed in this area (Bringmann et al., 2018; Hendrickson, 1992, 1994; Packer et al., 1990). Bipolar cell distributions follow photoreceptor distributions, with cone bipolar cells abundant in the fovea and rod bipolar cells scarce (Grünert and Martin, 1991; Martin and Grünert, 1992). Similarly, ganglion cell density follows the distribution of cones and peaks toward the fovea (Wässle et al., 1989). The morphogenic signals that determine the extent and position of the fovea and govern the differences in cell densities remain unknown.

All cellular elements of the retina except for cones and Müller glia processes are displaced laterally from the center of the fovea to generate its eponymous pit shape (Bringmann et al., 2018). The displacement of cells reduces the scattering of light on its way to the cone outer segments while the slanted walls of the foveal pit locally magnify the retinal image (Bringmann et al., 2018; Walls, 1942). The foveal pit develops after all neurons have been generated, and synaptic connections have begun to form (Hendrickson, 1992, 1994). Before this time, blood vessels and ganglion cells axons grow around the site of the future foveal pit. The tension of arcuate axon fascicles around the fovea may pull ganglion cells and their presynaptic partners aside and thus excavate the foveal pit (Van Essen, 1997).

Across the mouse retina, the distribution of ganglion cells as a class is relatively flat (Jeon et al., 1998). However, a recent study discovered that the density of alpha ganglion cells rises to a peak in the dorsotemporal retina, which covers the binocular region of visual space in mice (Bleckert et al., 2014). The behavioral significance and development of this cell-type-specific acute zone remain to be studied.

The spectral composition of the visual fields of ground-dwelling rodents differs above (rich in ultraviolet light) and below (low in ultraviolet light) the horizon (Baden et al., 2013). Mice have two types of cones. S cones, which everywhere in the retina express only the ultraviolet-sensitive S opsin, and M/S cones which, in the dorsal retina express predominantly the green-sensitive M opsin and in the ventral retina predominantly S opsin (Haverkamp et al., 2005). The topographic switch from M to S opsin in M/S cones occurs in a narrow band of the retina that aligns with the horizon (i.e., the opsin transitional zone). In this opsin transitional zone, color-opponent receptive fields can arise in ganglion cells without cone-type-specific wiring (Chang et al., 2013; Johnson et al., 2018). Using this mechanism and differences in spectral sensitivities of rhodopsin (i.e., the green-sensitive photopigment of rods) and S opsin (Joesch and Meister, 2016), mice can detect color around and above the horizon (Denman et al., 2018). The nuclear thyroid hormone receptor TRβ2 promotes M opsin expression and suppresses S opsin transcription, and is required for the dorsoventral patterning (Ng et al., 2001). Together with the differentially timed expression of COUP-TF transcription factors under control of the morphogen BMP4, this gives rise to the gradient in ultraviolet- vs. green-sensitive cones across the mouse retina (Hoon et al., 2014; Satoh et al., 2009).

Insights into the regional specializations of retinal circuits, their relationships to visual environments, viewing strategies, and behavioral demands across more species, will provide important insights into the adaptation of biological visual systems, and raise interesting questions about the developmental mechanisms that implement these evolutionary adaptations.

1.12.4 Dendrite and Axon Organization

Retinal neurons form synaptic connections in two layers: the outer plexiform layer (OPL) and inner plexiform layer (IPL). During development, the axons and dendrites of retinal neurons need to target the correct plexiform layers and stratify at specific depths within them. Dendrite and axon lamination narrow the choice of synaptic partners and, thus, support the connective specificity of retinal circuits. Within their laminar targets, axon and dendrite arbors need to grow to an appropriate size and coordinate territories with neighboring cells of the same type to establish even coverage of the retina. Dendrite size correlates with receptive field size, and the relative arbor coverage of different neuron populations determines the ratio in which their signals are combined in specific circuits. The following sections discuss the strategies and mechanisms by which dendrites and axons of retinal neurons become organized vertically (i.e., lamination, **Fig. 6**) and horizontally (i.e., coverage, **Fig. 5**).

1.12.4.1 Dendrite and Axon Lamination

Axons and dendrites are guided to their laminar targets by a combinatorial code of cell surface and secreted cues. No single cell type displays or organizes these cues; instead, order arises from a multitude of interactions between synaptic partners, competitors, and indifferents, each expressing a cell-type-specific set of cues and recognition molecules. As a result, the overall lamination pattern of

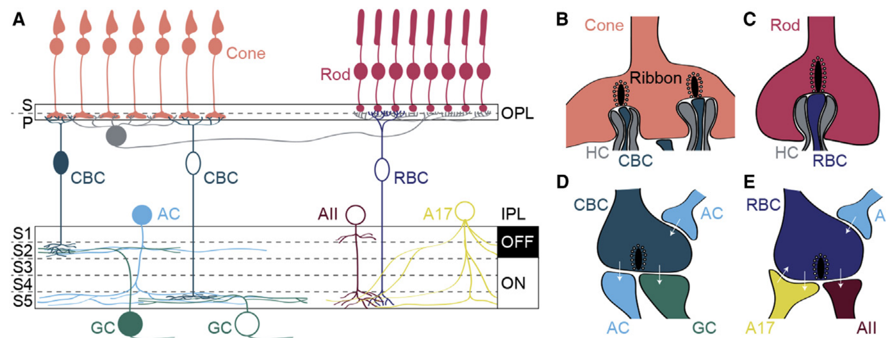

Figure 6 Laminar Architecture and Synaptic Motifs in the Retina. (A) Schematic cross-sectional view of the retina (S: rod spherule layer, P: cone pedicle layer, OPL: outer plexiform layer, CBC: cone bipolar cell, RBC: rod bipolar cell, AC: amacrine cell, AII: AII amacrine cell, A17: A17 amacrine cell, GC: ganglion cell, IPL: inner plexiform layer, S1–S5: sublayers of the IPL). (B–E) Synaptic motifs of cone pedicles (B), rod spherules (C), cone bipolar cell terminals (D), rod bipolar cell terminals (E).

the retina is robust to the ablation of individual cell types (Brown et al., 2001; Green et al., 2003; Günhan-Agar et al., 2000; Kay et al., 2004).

Different components of the combinatorial code define laminar targets at different resolutions. During early postnatal development, cells in the outer neuroblastic layer (i.e., the future ONL) of the mouse retina express class 5 transmembrane semaphorins (SEMA5A and SEMA5B), while cells in the inner neuroblastic layer (i.e., the future INL and GCL) express two plexin receptors (i.e., PLEXA1 and PLEXA3) (Matsuoka, Chivatakarn, et al., 2011a). Deletion of these semaphorins and plexins causes amacrine and ganglion cell dendrites to stray into the OPL and form additional synaptic layers within the INL, indicating that repulsive semaphorin-plexin interactions restrict neurites to the IPL. A similar phenotype is observed in mutants of the atypical cadherin Fat3, in which amacrine cells retain their multipolar migratory morphology and target dendrites to a novel plexus within the INL, in addition to the IPL (Deans et al., 2011). Synaptic partners divert processes to this novel plexus, highlighting the role of adhesive interactions in the stratification of circuits.

Adhesive interactions across the synaptic cleft (i.e., transsynaptic interactions) also help restrict neurites to the OPL. The leucine-rich repeat protein NGL2 on horizontal cell axons interacts transsynaptically with Netrin G2 (NTNG2) in rod axon terminals (or spherules) (Soto et al., 2012). In the absence of NGL2, horizontal cell axons stray into the ONL even when NGL2 is removed in mature circuits (Soto et al., 2012, 2018). Similarly, the auxiliary calcium channels subunit $\alpha2\delta4$ in rods interacts transsynaptically with mGluR6 receptors on rod bipolar cell dendrites, and rod spherules mislocalize to the ONL in *α2δ4* knockout mice (Wang et al., 2017). A recent CRISPR-Cas9 screen revealed that WNT5 secretion from rod bipolar cells helps organize the OPL (Sarin et al., 2018). When *Wnt5* or the genes encoding its receptors in rods, *Ryk* and *Fzd4/5*, are deleted, patches of duplicated OPL appear in the ONL (Sarin et al., 2018).

Within the OPL and IPL, circuits are organized in specific sublayers (**Fig. 6**). Rod spherules, rod bipolar cell dendrites, and horizontal cell axons target the outer part of the OPL; cone pedicles, cone bipolar cell dendrites, and horizontal cell dendrites target in the inner part of the OPL (Blanks et al., 1974; Olney, 1968). The IPL is partitioned into five sublaminae (S1S5) (**Fig. 6**). The outer two (S1S2) contain axons and dendrites that respond to light decrements (i.e., OFF stimuli); the inner three (S3S5) contain axons and dendrites that respond to light increments (i.e., ON stimuli) (Hoon et al., 2014; Sanes and Zipursky, 2010). Whereas the mechanisms of OPL sublamination have not received much attention (Tanabe et al., 2006), the cues that guide sublaminar targeting in the IPL have been studied extensively (Hoon et al., 2014; Sanes and Zipursky, 2010). Repulsive semaphorin-plexin interactions help divide the IPL into ON and OFF zones. SEMA6A and PLEXA4 show complementary expression in the ON and OFF zone of the IPL, respectively, and genetic deletion of either cue causes mistargeting of axons and dendrites between the two zones (Matsuoka, Nguyen-Ba-Charvet et al., 2011b). Starburst amacrine cells play a critical role in the direction-selective computation of the retina (Wei, 2018). ON and OFF starburst cells stratify their dendrites in two separate plexuses in the respective zones of the IPL. PLEXA2 is expressed in both ON and OFF starburst amacrine cells, whereas SEMA6A is expressed only in ON cells. In *PlexA2* and *Sema6A* knockout mice, the division between the two starburst plexuses is blurred and dendrites of individual cells cross between them (Sun et al., 2013).

Interactions of cell adhesion molecules on the axons and dendrites of synaptic partners mediate targeting to specific sublaminae within the ON and OFF zones of the IPL. For example, homo- and heterophilic interactions of cadherins (CDH6, CDH8, CDH9, and CDH10) direct bipolar cell axons, starburst amacrine cell neurites, and ON-OFF direction-selective ganglion cell dendrites to sublaminae S2 and S4, where OFF and ON components of the circuit, respectively, assemble (Duan et al., 2014, 2018). In addition, ON-OFF direction-selective ganglion cells and ON starburst amacrine cells express the homophilic cell adhesion molecule Contactin 5 (CNTN5) (Peng et al., 2017). When CNTN5 is removed from starburst or ganglion cells, ON-OFF direction-selective ganglion cells lose their ON dendrites (Peng et al., 2017). The homophilic cell adhesion molecule Sidekick 2 (SDK2) appears to play a similar role in the assembly of the object-motion-sensitive circuit of the retina, whose neurites meet in S3 (Krishnaswamy et al., 2015).

As discussed above (see 1. Progenitor Proliferation and Neurogenesis), gene regulatory networks drive the differentiation of retinal neuron types, whose axons and dendrites target specific retinal layers through unique combinations of cues and recognition molecules on their cell surface. This raises the question: which gene regulatory networks control the cell-type-specific expression of cell surface molecules? The transcriptional regulator SATB1 is required for the expression of CNTN5 in ON-OFF direction-selective ganglion cells. ON-OFF direction-selective ganglion cells lose their ON dendrites in *Satb1* knockout mice, as they do in *Cntn5* mutants (Peng et al., 2017). The transcription factor TBR1 is expressed in four ganglion cell types whose dendrites stratify in the OFF zone of the IPL (Liu et al., 2018). In *Tbr1* knockout mice, dendrites of the same cells mistarget, shifting either entirely to the ON zone or elaborating additional arbors there. Furthermore, ectopic expression of TBR1 can redirect dendrites from the ON to the OFF zone of the IPL (Liu et al., 2018). TBR1 appears to guide dendrites of the four ganglion cells to their shared laminar target through different cell surface effectors (Liu et al., 2018), indicating complexity in the translation of the gene regulatory into the cell surface code for laminar targeting.

In some instances, neurotransmitters act as secreted cues for lamination. Thus, bipolar cell dendrites and horizontal cell dendrites and axons send ectopic processes into the ONL, when glutamate release from photoreceptors is disrupted (Dick et al., 2003; Raven et al., 2008; Soto et al., 2012). Activity manipulations have varied effects on the stratification of ganglion cell dendrites, indicating that the function of neurotransmitters may depend on cell type, species, and the nature of the perturbation (Bleckert and Wong, 2011; Bodnarenko et al., 1995; Bodnarenko and Chalupa, 1993; Kerschensteiner et al., 2009; Soto et al., 2012; Tian and Copenhagen, 2003; Xu and Tian, 2007).

1.12.4.2 Dendrite and Axon Coverage

The dendrites and axons of each neuron type cover the retinal surface evenly and with fixed overlap (**Fig. 5**). Even neurite coverage distributes the computations of each cell type homogeneously across visual space, while differences in overlap determine the ratios in which the computations of different cells are combined in specific circuits.

Even neurite coverage of most retinal neurons relies on DSCAM or DSCAML1, which interact homophilically and are expressed in non-overlapping sets of cells (Agarwala et al., 2000, 2001; Fuerst et al., 2008, 2009; Hughes et al., 2007). In *Dscam* and *Dscaml1* mutants, neurites fasciculate, and cell bodies cluster (i.e., retinal mosaics are lost) (Fuerst et al., 2008, 2009). These deficits are cell type specific in two ways: first, only cells that normally express the respective genes are affected, and second, different cell types congregate in distinct clusters and form separate neurite fascicles (Fuerst et al., 2008, 2009). These observations suggest that DSCAM and DSCAML1 provide generic 'nonstick' signals that counteract cell-type-specific adhesion mechanisms (Garrett et al., 2018). Consistent with this hypothesis, deletion of cell-type-specific Cadherins rescues neurite fasciculation and cell body clustering in *Dscam* mutants, and ectopic expression of Cadherins in *Dscam* mutants promotes fasciculation and clustering across cell-type boundaries (Garrett et al., 2018).

Horizontal cells express neither DSCAM nor DSCAML1. Instead, even neurite distributions of horizontal cells rely on repulsive interactions of SEMA6A and PLEXA4 (Matsuoka et al., 2012).

The neurites of individual starburst amacrine cells fan out in radially symmetric arbors and rarely cross each other. The eponymous shape of starburst amacrine cell arbors is critical for their function (Euler et al., 2002; Morrie and Feller, 2018). Yet, the neurites of nearby starburst amacrine cells fasciculate and are reciprocally connected (Ding et al., 2016; Pei et al., 2015; Zheng et al., 2004). Thus, starburst amacrine cells need to distinguish neurites of the same cell from neurites of other cells of the same type (i.e., self/non-self discrimination). The γ-subcluster of protocadherins (*Pcdhg* genes) mediates self/non-self discrimination of starburst amacrine cells (Lefebvre et al., 2012). Through alternative promoters, the *Pcdhg* locus gives rise to 22 cadherin-like proteins, which engage in strictly homophilic *trans* interactions (Schreiner and Weiner, 2010). PCDHGs interact promiscuously in *cis* and form tetrameric complexes that provide >200,000 distinct *trans* interaction interfaces (Schreiner and Weiner, 2010). When all PCDHGs are removed, neurites of starburst amacrine cells fasciculate and connect within cells as they normally do between (Kostadinov and Sanes, 2015; Lefebvre et al., 2012). By contrast, when all starburst cells express the same PCDHG, the neurites of nearby starburst amacrine cells avoid each other as they normally do within cells (Kostadinov and Sanes, 2015; Lefebvre et al., 2012). Thus, uniquely matching combinations of PCDHGs separate the neurites of individual starburst amacrine cells, while differences in the PCDHG combinations of nearby cells allow their neurites to fasciculate and connect. Additional, self-avoidance of ON starburst amacrine cells is mediated by SEMA6A – PLEXA2 interactions (Sun et al., 2013).

Neurite overlap is the product of cell density and arbor size. It varies significantly between retinal neuron types, from bipolar cells, whose axons and dendrites tile the retinal surface with little overlap (i.e., coverage ≈ 1), to starburst amacrine cells, whose arbors overlap extensively (coverage ≈ 40) (Helmstaedter et al., 2013; Keeley et al., 2007; MacNeil and Masland, 1998; Wässle et al., 2009). For most neuron types, neurite coverage is constant across the retina, as arbor size scales inversely with regional differences in cell density (Bleckert et al., 2014; Dacey, 1993; Peichl, 1991). Arbor size also varies inversely with cell density across mouse strains and with experimentally induced changes in cell numbers (Chen et al., 2013; Huckfeldt et al., 2009; Johnson et al., 2017; Keeley et al., 2014). This inverse relationship suggests that homotypic signals restrict arbor growth. These signals appear to be different from those that establish cell body mosaics and even neurite distributions, as deletion of homotypic cues that distribute cell bodies and neurites evenly do not result in increased arbor size (Fuerst et al., 2008, 2009; Kay et al., 2012; Sun et al., 2013). Starburst amacrine cells and rod bipolar cells express the leucine-rich repeat domain cell adhesion molecule AMIGO2 (Soto et al., 2019). In *Amigo2* mutants, dendrite arbors of starburst amacrine cell and rod bipolar cell expand without changes in cell

body mosaics or neurite distributions (Soto et al., 2019). This identifies AMIGO2 as a cell-type-specific dendrite scaling factor. Similar cues likely mediate homotypic interactions that control the arbor size of other neurons in the retina.

1.12.5 Synaptic Connectivity

Specific patterns of synaptic connections parse and process distinct visual information in parallel pathways. Parallel processing begins at the first synapse of the visual system, in the OPL of the retina. There, rod spherules and cone pedicles form ribbon synapses with dendrites of rod and cone bipolar cells, respectively (**Fig. 6**). In addition to these feedforward connections, rods and cones receive feedback from horizontal cell axons and dendrites, respectively, at the same synapses. Rod signals reach the inner retina through three parallel pathways: (1) via rod bipolar cells, (2) via gap junctions with cones and their connection with cone bipolar cells, and (3) via a subset of cone bipolar cells, whose dendrites directly contact rods. The three rod pathways function at different light levels, with rod bipolar cells mediating vision near its absolute threshold (Bloomfield and Dacheux, 2001; Field et al., 2005). In mice, cone signals diverge to 13 bipolar cell types (Franke et al., 2017; Greene et al., 2016; Helmstaedter et al., 2013; Shekhar et al., 2016). Of these, eight are activated by light increments (ON) and five by light decrements (OFF) (Franke et al., 2017). One ON cone bipolar cell type selectively connects to S cones, and one OFF cone bipolar cell type selectively connects to M/S cones; all others do no distinguish between the two cone types (Behrens et al., 2016; Breuninger et al., 2011). In the IPL, the axons of rod and cone bipolar cells target different sublaminae, rod bipolar cells the innermost S1, ON cone bipolar cells S1S3, and OFF cone bipolar cells S4S5 (Euler et al., 2014; Franke et al., 2017). Bipolar cell axons form dyadic ribbon synapses with specific pairs of ganglion cells, amacrine cells, or amacrine and ganglion cells (Dowling and Boycott, 1966; Raviola and Dacheux, 1987; Raviola and Raviola, 1967) (**Fig. 6**). In addition, amacrine cells form synapses with bipolar cell axons and ganglion cell dendrites.

In mice, retinal synapses develop during the first three weeks of life (Hoon et al., 2014). To assemble parallel pathways that extract specific information, developing retinal neurons need to select appropriate partners, form the right number of synapses with them, and localize the correct proteins to pre- and postsynaptic specializations. This section reviews the mechanisms that determine the specificity, number, and molecular architecture of retinal synapses.

Synaptic specificity emerges from interactions between potential partners involving varying degrees of trial and error (Dunn and Wong, 2012; Kerschensteiner et al., 2009). When preferred partners are removed or silenced, some retinal neurons switch synaptic allegiances (Haverkamp et al., 2006; Okawa et al., 2014; Tien et al., 2017). Thus, synaptic specificity is relative, not absolute. A few signals that promote synapse formation between specific partners have recently been identified. The homophilic cell adhesion molecule Sdk2 is expressed on VGLUT3-expressing amacrine cells and W3 ganglion cells. Sdk2 is required for synapse formation between these cells, but not between either cell and its other partners (Krishnaswamy et al., 2015). Synaptic specificity can extend beyond cell type, to subcellular compartments. Horizontal cell axons selectively form synapses with rods, whereas horizontal cell dendrites selectively connect to cones. NGL2 localizes to the tips of horizontal cell axons and interacts transsynaptically with NTNG2 on rod spherules (Soto et al., 2013). In *Ngl2* knockout mice, horizontal cell axons lose most synapses with rods and stray into the ONL. In addition, ribbon assembly in rod spherules is disrupted, indicating that transsynaptic interactions mediate bidirectional signals that promote pre- and postsynaptic maturation at the contact site (Soto et al., 2013). However, the connections of horizontal cell dendrites with cones are unaffected by *Ngl2* deletion, and functional deficits are limited to dim light signaling (Soto et al., 2013).

Subcellular synaptic specificity is also at the heart of the direction-selective circuit of the retina (Wei, 2018). Each of the four to six primary neurites of a starburst amacrine cell, together with its daughter branches, functions as an independent sensor that responds strongly to centrifugal motion (i.e., from cell body to neurite tip) and weakly to centripetal motion (i.e., from neurite tip to cell body) (Euler et al., 2002). Asymmetric subcellular connectivity translates centrifugal motion preference of starburst neurites into direction-selective ganglion cell responses. Starburst amacrine cell neurites pointing to the nasal side of the retina form inhibitory synapses only with dendrites of ganglion cells that prefer motion to the temporal side, and so on (Briggman et al., 2011; Fried et al., 2002; Wei et al., 2011; Yonehara et al., 2011). Starburst amacrine cells express FRMD7, a potential mediator of signals from the plasma membrane to the cytoskeleton (Yonehara et al., 2016). In *Frmd7* knockout mice, starburst amacrine cell neurites aligned with the horizontal axis of the retina lose their subcellular specificity, and direction-selective ganglion cells that normally prefer nasal or temporal motion receive equal inhibition in both directions and become untuned (Yonehara et al., 2016). A subclass of direction-selective ganglion cells (i.e., the ON direction-selective ganglion cells) project to nuclei of the accessory optic system and drive gaze stabilizing eye movements. In *Frmd7* knockout mice, gaze stabilizing horizontal eye movements are disrupted (Yonehara et al., 2016). The role of FRMD7 in the development of the retinal direction-selective circuit appears to be conserved in humans. Patients with mutations in *FRMD7* lack horizontal gaze stabilization and exhibit spontaneous oscillatory eye movements (i.e., nystagmus). Indeed, *FRMD7* mutation are found in 70% of patients with idiopathic congenital nystagmus (Tarpey et al., 2006).

Synapse numbers increase gradually during the first three postnatal weeks in mice (Fisher, 1979; Morgan et al., 2008). Excitatory and inhibitory synapses on ganglion cell dendrites rise in parallel and are locally coordinated within individual arbors, presumably to maintain balance between these inputs and stabilize activity across development and visual space (Bleckert et al., 2013; Soto et al., 2011). Although neurotransmission is not absolutely required for synapse formation (Varoqueaux et al., 2002; Verhage et al., 2000), the number of synapses between bipolar and ganglion cells is determined by

neurotransmission. Tetanus toxin is a protease that cleaves the vesicle-associated membrane protein 2 (VAMP2) (Schiavo et al., 1992). In mice in which ON bipolar cells express tetanus toxin (*Grm6-TeNT*), the number of synapses between their axons and ganglion cell dendrites is halved (Kerschensteiner et al., 2009). Conversely, synapse numbers are increased in mice with elevated bipolar cell activity (i.e., *Crx* knockout mice) (Soto et al., 2012), indicating that neurotransmission regulates synaptogenesis in a bi-directional manner. The effects of neurotransmission are pathway-specific even when pathways converge onto the same cell. Thus, bipolar cells synapses are reduced on the ON arbor but not the OFF arbors of ON-OFF ganglion cells in *Grm6-TeNT* retinas (Kerschensteiner et al., 2009).

Synaptogenesis in the inner retina, as in many parts of the nervous system, is a high-turnover process. At postnatal day nine, ganglion cells form about 30% new input synapses each day but also eliminate approximately 20% of their connections (Kerschensteiner et al., 2009; Morgan et al., 2011). Neurotransmission could, therefore, alter synapses numbers by regulating the formation of new synapses, the stability of existing synapses, or a combination of both. Live imaging experiments in *Grm6-TeNT* and *Crx* knockout mice revealed that neurotransmission selectively affects the rate of synapses formation but not synapse elimination (Kerschensteiner et al., 2009; Soto et al., 2012).

The signals and interactions that control the molecular synapse architecture have been studied most extensively in the outer retina, particularly in the connections of rod spherules with rod bipolar and horizontal cells (Hoon et al., 2014; Martemyanov and Sampath, 2017). The leucine-rich repeat protein ELFN1 is expressed selectively in rods and interacts transsynaptically with MGLUR6 (*Grm6*) receptors on rod bipolar cells dendrite tips (Cao et al., 2015). In *Elfn1* knockout mice, MGLUR6 receptors fail to localize to synapses between rods and rod bipolar cell dendrites (Cao et al., 2015). This causes loss of the transduction channel TRPM1 and other signaling components from the postsynapse, similar to *Grm6* mutant mice (Cao et al., 2009). Thus, MGLUR6 receptors appear to nucleate assembly of the postsynaptic specialization and ELFN1 anchors this complex to the presynapse. Like MGLUR6 in the postsynapse, the voltage-gated calcium channel CAV1.4 is required for the assembly of the molecular machinery of the presynapse (Cao et al., 2015; Mansergh et al., 2005). Finally, distinct surfaces of the auxiliary calcium channel subunit α2δ4 interact with CAV1.4 and ELFN1, to link pre- and postsynaptic organizers and align transmitter release sites and receptors (Wang et al., 2017). In addition to rod bipolar cell dendrites, horizontal cell axons form synapses with rod spherules. The leucine-rich repeat protein NGL2 localized selectively to the tips of horizontal cell axons where it likely interacts with NTNG2 on the rod membrane (Soto et al., 2013, 2018). This not only ensures that horizontal cell feedback is appropriately localized, but transsynaptic signals also promote synapse maturation evidenced by an abundance of immature ribbons precursors in rod spherules of *Ngl2* knockout mice (Soto et al., 2013).

In addition to direct interactions between synaptic partners, interactions with the extracellular matrix shape the architecture of rod synapses. Pikachurin is an extracellular matrix protein with an array of protein-protein interaction domains, which is produced and secreted by photoreceptors (Sato et al., 2008). Dystroglycan at the photoreceptor presynapse interacts with the Laminin G motifs of pikachurin (Omori et al., 2012). Interactions between dystroglycan and pikachurin are required to localize both components to photoreceptor synapses (Omori et al., 2012; Sato et al., 2008). Pikachurin also interacts with the orphan receptor GPR179 in the rod and ON cone bipolar cells postsynapse, and dystroglycan and pikachurin are required to maintain contact between photoreceptors and these bipolar cells (Omori et al., 2012; Orlandi et al., 2018; Ray et al., 2014; Sato et al., 2008). Thus, direct (ELFN1-MGLUR6) and indirect (dystroglycan-pikachurin-GPR179) transsynaptic bridges guide the assembly and localization of the pre- and postsynaptic molecular machineries and maintain contact between them. Two additional leucine-rich repeat proteins, LRIT3 in rod photoreceptors and Nyctalopin in rod bipolar cells) contribute to the transsynaptic signaling complex (Demas et al., 2006; Hasan et al., 2019; Neuillé et al., 2015, 2017; Pearring et al., 2011). Their interaction partners remain to be identified.

Neurotransmission also shapes the molecular architecture of developing synapses. In mice in which rod photoreceptors express tetanus toxin, MGLUR6 fails to localize to the postsynaptic specialization of rod bipolar cells (Cao et al., 2015). A similar phenotype is observed when mice are dark reared from birth, indicating that visually evoked changes in transmitter release are key (Dunn et al., 2013). Experience-dependence of the MGLUR6 localization is limited to the rod bipolar pathway, and MGLUR6 retains its normal position in the ON cone bipolar cell dendrites of dark-reared mice (Dunn et al., 2013).

In the mouse inner retina, axons of type 6 bipolar cells form unique multisynaptic appositions, which contain multiple aligned pre- and postsynaptic specializations within a single extended contact surface with ONα ganglion cell dendrites (Morgan et al., 2011). These multisynaptic appositions are particularly susceptible to changes in activity in *Grm6-TeNT* and *Crx* knockout mice (Kerschensteiner et al., 2009; Morgan et al., 2011; Soto et al., 2012).

Most molecular cues that guide the formation of synapses continue to be expressed in mature circuits, raising the questions whether they are necessary to maintain synapses and whether they can be used to restore connectivity in circuits disrupted by neurodegeneration or injury. Advances in viral and genome engineering have made these questions more readily addressable (Adli, 2018; Li and Samulski, 2020). Using adeno-associated virus (AAV-) mediated CRISPR/Cas9, a recent study found that NGL2 is required to maintain synapses in mature circuits. When *Ngl2* is deleted in horizontal cells of one- or five-months-old mice, synapses with rods are lost by two and six months, respectively (Soto et al., 2018). Furthermore, viral expression of NGL2 in horizontal cells of 1-months-old *Ngl2* knockout mice restores regular synapse numbers by two months (Soto et al., 2018). Similarly, viral expression of LRIT3 in rods of adult *Lrit3* knockout mice rescues transsynaptic deficits in receptor localization (Hasan et al., 2019). Thus, at least a subset of the cues that guide synapse formation is required for synapse maintenance and hold promise for therapeutic circuit restoration.

1.12.6 Homeostatic Plasticity

Homeostatic plasticity refers to the drive and mechanisms by which neurons return to an activity set point following perturbation. Recent studies indicate that homeostatic plasticity regulates many of the processes discussed so far to ensure the development of stably functioning circuits (Tien and Kerschensteiner, 2018; Turrigiano and Nelson, 2004).

Homeostatic plasticity in the developing retina is remarkable in its ability to overcome significant perturbations, its coordination of diverse mechanisms, and the quantitative accuracy of the functional preservation it achieves. In transgenic mice in which more than half of the rod bipolar cells are removed during development, the dendrites of the remaining rod bipolar cells expand to cover vacated inputs (Johnson et al., 2017). This increase in input territories, although desirable from a population standpoint, runs the risk of overwhelming the response range of individual neurons. However, rod bipolar cells with expanded dendrite territories adjust their synapse ultrastructure to downregulate connectivity with each rod. These balancing adjustments of dendrite territories and synapse ultrastructure preserve retinal function in dim light (Johnson et al., 2017).

ONα ganglion cells respond to contrast approximately linearly and with high sensitivity. They inherit these response properties from their excitatory bipolar cell inputs (Grimes et al., 2014; Pang et al., 2003; Schwartz et al., 2012; Tien et al., 2017). In wild-type mice, ONα ganglion cells receive dominant (approximately 70%) input from type 6 bipolar cells (Morgan et al., 2011; Schwartz et al., 2012; Tien et al., 2017). When type 6 bipolar cells are removed from the developing retina, ONα ganglion cells rewire with other bipolar cells in a cell-type-specific manner. They promote a previously minor input type to the dominant one, form synapses with other input types de novo, while maintaining stable connectivity with some input types (Tien et al., 2017). This cell-type-specific homeostatic rewiring accurately preserves the characteristic function of ONα ganglion cells (Tien et al., 2017). Given its ability to compensate for extensive cell loss during development, it would be interested to test whether homeostatic plasticity declines with age, and, if so, whether this decline can be reversed to preserve function in neurodegenerative diseases of the retina.

1.12.7 Development of Retinal Activity

For much of its development, the retina generates wave-like patterns of spontaneous activity (i.e., retinal waves) (Meister et al., 1991) that regulate the proliferation of RPCs, promote the development of synapses in the retina and refine the projections from the retina to the brain (Kerschensteiner, 2014; Kirkby et al., 2013). Across species, retinal waves mature in three stereotypic stages (I–III), in which different signaling mechanisms give rise to distinct patterns of activity that serve specific functions in circuit refinement (Ackman and Crair, 2014; Wong, 1999) (**Fig. 7**).

Stage I waves are mediated by electrical coupling and adenosine signaling among RPCs and early-born neurons, including ganglion cells (Singer et al., 2001; Syed et al., 2004). They precede the formation of chemical synapses, prevail in the embryonic retina, and, in mice, are replaced by stage II waves around birth (Bansal et al., 2000). Stage I waves propagate rapidly (~400 μm s^{-1}) and recruit nearby cells indiscriminately. They lack refractory periods, causing colliding waves to superimpose (Syed et al., 2004). Gap junctions and a variety of neurotransmitters are released from RPCs and newborn neurons during stage I waves and may regulate RPCs proliferation and neurogenesis directly and/or via interkinetic nuclear migration, which is coupled to cell-cycle progression (Del Bene et al., 2008; Martins and Pearson, 2008; Norden et al., 2009; Pearson et al., 2005). Stage I retinal waves overlap with the growth of ganglion cell axons toward and initial innervation of subcortical visual areas (Godement et al., 1984; Osterhout et al., 2014). The contributions of stage I waves to these processes remain to be elucidated.

Stage II waves are mediated by a network of cholinergic starburst amacrine cells (Feller et al., 1996). The dendrites of starburst amacrine cells stratify in two narrow bands within the inner plexiform layer (IPL). Stage II waves start from the intrinsic pacemaker activity of SACs and propagate laterally (100–300 μm s^{-1}) through reciprocal excitation in the SAC network (Ford et al., 2012; Zheng et al., 2006). During early stage II waves, acetylcholine (ACh) and GABA mediate this reciprocal excitation (Zheng et al., 2004). Later, as intracellular chloride concentrations drop, GABA becomes inhibitory, and the patterns of stage II waves change (Demas et al., 2003; Maccione et al., 2014; Wong et al., 2000; Zheng et al., 2004). Ganglion cells and other amacrine cells are recruited into stage II waves by cholinergic volume transmission (Ford et al., 2012; Wong et al., 2000). SACs anywhere in the retina can start stage II waves, but in vivo recordings in mice revealed a preference for wave initiation in the ventrotemporal retina, which

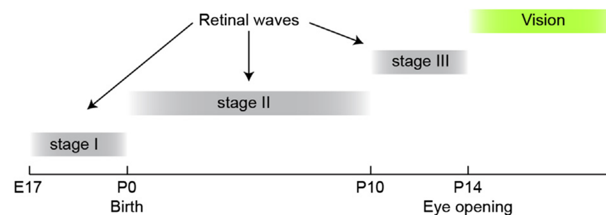

Figure 7 Timeline of Retinal Activity. The timing of the different stages of retinal waves and the onset of vision shown as a function of embryonic (E) and postnatal (P) age in mice (in days).

covers the binocular visual field (Ackman et al., 2012). Slow afterhyperpolarizations endow SACs with prolonged refractory periods (~1 min) that cause colliding wavefronts to annihilate (Feller et al., 1996; Zheng et al., 2006). Although mice do not open their eyes until approximately postnatal day 14 (~P14), light can penetrate closed eyelids and increase the duration of action potential bursts and the robustness of stage II waves through intrinsically photosensitive retinal ganglion cells (ipRGCs) (Kirkby and Feller, 2013; Renna et al., 2011). After GABA switches from excitation to inhibition (~P7), stage II waves are disassembled by the removal of nicotinic acetylcholine receptors from SACs (~P10) (Baldridge, 1996; Zheng et al., 2004), which eliminates reciprocal excitation in the network.

Stage II waves overlap with the later phases of progenitor cell proliferation and the specification of late-born neurons in the retina (Ford and Feller, 2012; Martins and Pearson, 2008). Via M1 muscarinic receptors, ACh released during stage II waves can elevate calcium in progenitor cells and newborn neurons, which may influence their proliferation and differentiation, respectively (Martins and Pearson, 2008; Syed et al., 2004; Wong et al., 1995). Stage II waves also coincide with the morphological development of early-born retinal neurons (Ford and Feller, 2012). Aside from delaying the stratification of some ganglion cell types, however, perturbations of stage II waves appear to have little impact on neuronal maturation and circuit formation in the retina (Bansal et al., 2000; Stacy et al., 2005). By contrast, activity correlations imposed by stage II waves, which propagate through the visual system (Ackman et al., 2012; Siegel et al., 2012), instruct the eye-specific segregation and retinotopic refinement of RGC projections in the brain. The impact of retinal waves on the brain lies outside the scope of this chapter. Interested readers are encouraged to consult excellent recent reviews of this topic (Ackman and Crair, 2014; Cang and Feldheim, 2013; Kirkby et al., 2013).

Stage III waves are mediated by glutamatergic signals from bipolar cells and last from the end of stage II waves to eye opening (i.e., P10P14 in mice). Stage III waves propagate laterally at 150–200 μm s^{-1}, spreading repetitively through patches that shift across the retina over time (Blankenship et al., 2009; Gribizis et al., 2019; Maccione et al., 2014). In vivo, stage III waves exhibit a strong preference for propagation toward the dorsolateral pole of the retina (i.e., the same direction but a more pronounced bias than stage II waves) (Gribizis et al., 2019). Based on their preference for light increments or decrements, bipolar cells can be divided into ON and OFF types, respectively (Euler et al., 2014). Stage III waves are generated and propagate laterally through reciprocal excitation between neighboring ON bipolar cells (Akrouh and Kerschensteiner, 2013; Blankenship et al., 2009). Excitation is mediated by ionotropic glutamatergic signaling and gap-junctional coupling, either directly or indirectly via intervening amacrine cells (Akrouh and Kerschensteiner, 2013). A unique feature of stage III waves is that they recruit ganglion cells with opposite light responses in a fixed sequence: ON before OFF (Kerschensteiner and Wong, 2008). This activity sequence is generated by vertical inhibitory pathways through which ON bipolar cells delay glutamate release from OFF bipolar cells (Akrouh and Kerschensteiner, 2013; Kerschensteiner, 2016). Glutamate uptake maintains separation between signals from ON and OFF bipolar cells on their way to ganglion cells (Akrouh and Kerschensteiner, 2013), and Müller glia, the presumptive agents of this uptake, exhibit wave-associated calcium transients (Rosa et al., 2015). Light penetrating closed eyelids can trigger stage III waves but does not affect their patterns (Tiriac et al., 2018). Effects of light on stage III waves are mediated by conventional photoreceptors (i.e., rods and cones) whose synapses with bipolar cells are the last to form in the retina (Hoon et al., 2014; Tiriac et al., 2018). With the maturation of these synapses around eye opening, light begins to dominate activity in the inner retina and waves disappear. The disappearance of waves does not require visual experience but does require normal synaptic transmission from photoreceptors to bipolar cells (Demas et al., 2003, 2006).

Stage III waves coincide with a period of rapid synapse development in the inner retina (Fisher, 1979; Morgan et al., 2008; Soto et al., 2011) during which glutamate release shapes the connectivity of bipolar and ganglion cells in a bidirectional manner (i.e., increases in activity increase synapse numbers and decreases in activity decrease synapse numbers) (Kerschensteiner et al., 2009; Soto et al., 2012). Live imaging studies revealed that glutamate release regulates selectively the rate of synapse formation, but not elimination (Kerschensteiner et al., 2009; Soto et al., 2012). The effects of activity on synapse development are cell-type-specific (Morgan et al., 2011; Okawa et al., 2014; Schubert et al., 2013; Soto et al., 2012). In addition to synapses, stage III waves may affect the dendritic development of some ganglion cell types (Kim et al., 2010; Xu et al., 2010). The asynchronous activity of ON and OFF ganglion cells (Kerschensteiner and Wong, 2008), in conjunction with burst-time-dependent plasticity rules in retinorecipient targets (Butts et al., 2007; Shah and Crair, 2008), suggests that stage III wave may drive ON/OFF segregation in the dorsolateral geniculate nucleus of the thalamus (Kerschensteiner, 2016). Circumstantial evidence supports this hypothesis, which remains to be experimentally tested (Cramer and Sur, 1997; Gribizis et al., 2019; Hahm et al., 1991; Hooks and Chen, 2007).

1.12.8 Summary and Conclusions

Retinal cells need to take many steps to go from proliferating progenitors to mature neurons connected to specific partners in circuits with distinct functions. This chapter reviewed the mechanisms that guide each step, focusing on insights gained in mice. Disruptions of different steps along the way to retinal circuit assembly cause characteristic deficits from small or absent eyes to circuit-specific dysfunctions (e.g., nystagmus). Such deficits occur both in mouse mutants and human patients. To alleviate suffering in the future, it is important now to study human retinal development and explore to what extent mechanisms are conserved from mice to humans.

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