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Cellular and Molecular Determinants of Retinal Cell Fate

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Abstract

The vertebrate retina is regarded as a simple part of the central nervous system (CNS) and thus amenable to investigations of the determinants of cell fate. Its five neuronal cell classes and one glial cell class all derive from a common pool of progenitors. Here we review how each cell class is generated. Retinal progenitors progress through different competence states, in each of which they generate only a small repertoire of cell classes. The intrinsic state of the progenitor is determined by the complement of transcription factors it expresses. Thus, although progenitors are multipotent, there is a bias in the types of fates they generate during any particular time window. Overlying these competence states are stochastic mechanisms that influence fate decisions. These mechanisms are determined by a weighted set of probabilities based on the abundance of a cell class in the retina. Deterministic mechanisms also operate, especially late in development, when preprogrammed progenitors solely generate specific fates.

1. INTRODUCTION

The retina has long been used as a model to investigate the determinants of cell fate in the vertebrate central nervous system (CNS). Its peripheral location in the eye, compact structure, and relatively small number of cell classes make the retina a simple and "approachable part of the brain" (Dowling 2012). More recently, however, the impetus for studying retinal cell fate has expanded beyond it being a model for the CNS, focusing instead on the retina itself. The elucidation of molecular pathways that instruct distinct retinal cell fates has greatly aided work aimed at cell replacement therapies with the potential to restore compromised vision (Jorstad et al. 2017, Todd et al. 2021, Yao et al. 2018). Here we review what is known about cell fate acquisition in the vertebrate retina, focusing on the mouse retina, findings from which have been the biggest contributor to this field, but also drawing on work from other vertebrates, including zebrafish, chick, and *Xenopus laevis*.

1.1. Cell Composition of the Vertebrate Retina

Each of the six retinal cell classes occupies stereotypic positions within one of the three cellular layers (**Figure 1*a***). Photoreceptors (PhRs) (the rods and cones) are located in the outer nuclear layer. Three interneuron classes, horizontal cells (HCs), bipolar cells (BCs), and amacrine cells (ACs), reside in the inner nuclear layer (INL), and ganglion cells (GCs) can be found in the

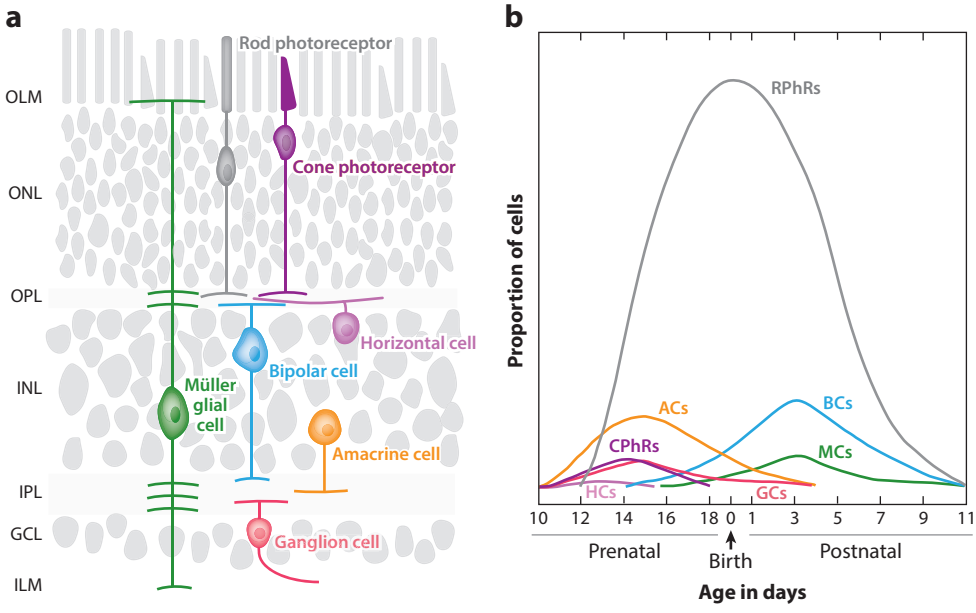


Figure 1

Schematic of the vertebrate retina. (*a*) Five neuronal cell classes and one glial cell class are stereotypically localized in the three nuclear layers: ONL, INL, and GCL. Retinal cells form synaptic connections in the OPL and IPL. MCs contribute to the formation of the OLM and ILM at the apical and basal part of the tissue, respectively. (*b*) The proportion of retinal cell classes that are born (i.e., undergo their last mitosis) from embryonic day 10 until postnatal day 11 in the mouse retina. Panel *b* adapted with permission from Young (1985); copyright John Wiley and Sons. Abbreviations: AC, amacrine cell; BC, bipolar cell; CPhR, cone photoreceptor; GC, ganglion cell; GCL, ganglion cell layer; HC, horizontal cell; ILM, inner limiting membrane; INL, inner nuclear layer; IPL, inner plexiform layer; MC, Müller glial cell; OLM, outer limiting membrane; ONL, outer nuclear layer; OPL, outer plexiform layer; RPhR, rod photoreceptor.

ganglion cell layer. Müller glial cells (MCs), the major glial cell class, span the apico-basal extent of the retina, with their somata localized to the INL. The number of subtypes within each neuronal cell class varies across vertebrates, reflecting the specializations required in distinct visual environments. For instance, whereas the mouse retina contains two subtypes of cone PhRs, sensitive to short (S) and medium (M) wavelengths of light, the zebrafish retina is tetrachromatic with cones sensitive to long (L), M, S, and UV wavelengths (Baden & Osorio 2019). Similarly, whereas the mouse retina has a single type of HC (Peichl & González-Soriano 1994), the zebrafish retina has four (Song et al. 2008).

1.2. Cell Genesis in the Developing Retina

The period of cell genesis varies across species. Thus, whereas retinogenesis is protracted in the mouse, extending from embryonic day 11 until postnatal day 7, a period of almost 2 weeks (Young 1985), it is complete within 2 days in zebrafish (Hu & Easter 1999). Nevertheless, cells are generated in a conserved order. GCs are the first to be generated in all vertebrates studied thus far. In mice, in which the most thorough birth-dating studies have been conducted, the next cell classes generated are cones, ACs, and HCs, followed by rods, BCs, and MCs. Importantly, the time windows during which each of these cell classes is generated overlap considerably. Thus, at any given time point, cells with distinct fates are generated concurrently (**Figure 1*b***). How retinal progenitor cells (RPCs) generate the diverse cell classes that populate the retina has been the subject of intense study over the last three decades.

2. RETINAL PROGENITOR CELLS

RPCs are regarded to be multipotent, capable of generating more than one cell class. Evidence for this comes from lineage studies that marked single RPCs using retroviral infections or fluorescent tracers and analyzed their ensuing progeny at mature time points. Daughter cell clones arising from these RPCs were variable in size and composition and comprised both neuronal cell classes and Müller glia (Holt et al. 1988, Turner & Cepko 1987, Turner et al. 1990, Wetts & Fraser 1988).What remained unclear from these studies were the patterns of mitosis individual RPCs underwent and which specific cell classes were generated at each division. Cycling RPCs can undergo one of three modes of division: (*a*) Symmetric proliferative divisions are characterized by RPCs that divide to generate daughter cells that return to the cell cycle (**Figure 2*a***). Such divisions occur early during retinal development to increase the RPC pool. (*b*) Asymmetric differentiative divisions that generate an RPC and a postmitotic daughter allow for the generation of distinct retinal cell classes while maintaining the RPC pool (**Figure 2*b***). (*c*) Terminal divisions in which two postmitotic daughters are generated effectively deplete the RPC pool and largely occur toward the end of cell genesis (**Figure 2*c***). If both postmitotic daughters acquire the same fate, these terminal divisions are considered symmetric, whereas the acquisition of distinct fates would render the divisions asymmetric (**Figure 2*d***). Indeed, such asymmetric fate outcomes (e.g., a rod and an AC; Hafler et al. 2012, Turner & Cepko 1987) provide support for the multipotency of RPCs even in terminal divisions. There is, however, also evidence for RPCs committed to a single fate, for example, rods (Turner & Cepko 1987).

2.1. Cellular and Molecular Heterogeneity Among Retinal Progenitors

RPCs are present throughout the period of retinal histogenesis, coexisting alongside newly generated postmitotic cells. Cycling RPCs span the extent of the retinal epithelium and undergo characteristic nuclear translocations along their cytoplasmic processes that are tightly linked to the phase

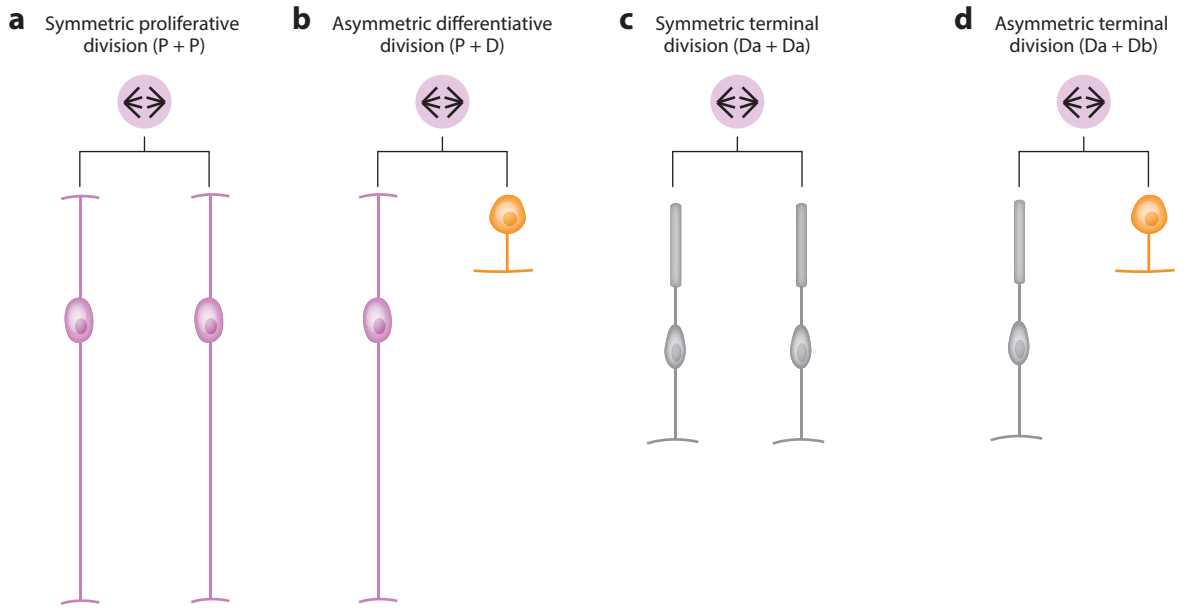


Figure 2

Modes of division of retinal progenitors. (*a*) Symmetric proliferative division produces two progenitor cells (P + P). (*b*) Asymmetric differentiative division generates a progenitor cell and a postmitotic cell that will undergo differentiation (P + D). (*c*) Symmetric terminal division produces two postmitotic cells that will acquire the same fate (Da + Da). (*d*) Asymmetric terminal division generates two postmitotic cells of different fates (Da + Db).

of the cell cycle they are in. Thus, for example, RPC nuclei are located closer to the basal surface during S-phase and at the apical surface at mitosis (Baye & Link 2007, Sauer 1935). This cellular behavior, termed interkinetic nuclear migration, is conserved across vertebrate species and CNS regions. However, not all RPCs resemble these neuroepithelium-spanning cells or exhibit their behavior. In the zebrafish retina, delaminated progenitors exclusively committed to the HC fate undergo terminal mitosis in the forming INL (Godinho et al. 2007, Weber et al. 2014), whereas HC-committed progenitors in the chick retina undergo mitosis at the basal surface (Boije et al. 2009). Terminally dividing BC progenitors in the zebrafish retina also undergo mitotic divisions in the INL (Engerer et al. 2017, Weber et al. 2014).

Although most RPCs are multipotent, they are not a homogeneous population. Gene expression studies of the developing mouse retina (Blackshaw et al. 2004, Trimarchi et al. 2008), including a large-scale single-cell RNA-sequencing (scRNA-seq) effort (Clark et al. 2019), revealed RPC subpopulations with distinct molecular signatures. Broadly, murine retinal RPCs were classified as primary or neurogenic. Although both RPC categories comprise cycling cells, only the neurogenic subpopulation expresses proneural transcription factors (TFs), indicative of an ensuing differentiative mitotic division in which at least one daughter exits the cell cycle. Primary RPCs at a given developmental stage were enriched for cell cycle–related genes and largely molecularly homogeneous (Clark et al. 2019). However, primary RPCs from embryonic versus postnatal time windows exhibited distinct molecular signatures. Among the transcriptional regulators that embryonic primary RPCs expressed were *Fibroblast growth factor 15* (*Fgf15*), *Forkhead Box P1* (*Foxp1*), and *Foxp4*, whereas *Retinaldehyde Binding Protein 1* (*Rlbp1*), *SRY-Box Transcription Factor 8* (*Sox8*), *Argininosuccinate Synthase 1* (*Ass1*), and *Nuclear Factor I* (*Nfi*) TFs were

expressed by postnatal primary RPCs. Neurogenic RPCs from the embryonic and postnatal mouse retina could also be distinguished by the specific proneural TFs they express. For instance, the TF atonal homolog 7 (Atoh7, also known as Math5), which is necessary for specifying the GC fate (see Section 4.5), is expressed by neurogenic RPCs only in the embryonic retina, not in the postnatal mouse retina (Clark et al. 2019). This expression is in line with when GCs are generated and the fact that Atoh7 is pivotal in GC fate specification.

Heterogeneity in the RPC population was also reported in an RNA-seq study of the developing zebrafish retina (Xu et al. 2020). Given the speed of retinogenesis in the zebrafish retina—lasting only 2 days from 24 h postfertilization (hpf) until 72 hpf—RPCs were isolated at relatively short intervals and subdivided into clusters based on gene expression patterns. Three of the clusters were common to RPCs originating from distinct developmental time points, 24, 36, and 48 hpf. The gene expression profiles of Clusters 1 and 2 suggested they are akin to the primary RPCs described for the mouse retina, and Cluster 3 was classified as comprising neurogenic RPCs that give rise to the earliest-born cell classes in the zebrafish retina, GCs and ACs. RPCs isolated at 48 hpf were subdivided into four additional clusters: Cluster 4 expressed genes linked to the generation of BCs and PhRs, Cluster 5 represented precursors committed to the HC fate, and Clusters 6 and 7 represented precursors committed to the PhR and MC fates, respectively.

2.2. Temporal Patterning of Progenitors

The differential gene expression patterns between temporally distinct RPC cohorts reflect the prevailing model of cell fate determination. Originally proposed more than two decades ago (Cepko et al. 1996), the competence model suggested that RPCs transition through distinct states in which they can generate a limited repertoire of cell classes. Moreover, transitions between competence states are unidirectional so that once the time window for the generation of a specific cell class has passed, it can no longer be generated (Cepko et al. 1996, Livesey & Cepko 2001).

The competence state an RPC is in is determined by so-called temporal TFs. At distinct developmental time windows, RPCs express specific temporal TFs that are necessary and sufficient to generate early and late cell classes that are born in the embryonic and postnatal retina, respectively. Although temporal TFs do not directly instruct cell fate, they are upstream of transcriptional networks that do (see Section 4). Several temporal factors in the mouse retina have been identified, all of which have counterparts in the *Drosophila* CNS. *Ikaros Family Zinc Finger 1* (*Ikfz1*), a temporal TF, is expressed in embryonic mouse RPCs and confers the competence to generate GCs, ACs, and HCs, three of the four cell classes born prenatally (Elliott et al. 2008). Thus, when *Ikfz1* is experimentally misexpressed in the postnatal mouse retina, RPCs that normally generate PhRs and BCs acquire the competence to generate GCs, ACs, and HCs. Conversely, in the absence of *Ikfz1*, cell classes generated embryonically are reduced in number, whereas those generated in the postnatal retina are unaffected. The temporal TF Castor Zinc Finger 1 (Casz1) is expressed by mouse RPCs at mid-to-late stages of retinogenesis, permitting the generation of rods and BCs (Mattar et al. 2015). Indeed, it has been proposed that through its interactions with the nucleosome remodeling and deacetylase (NuRD) complex and the Polycomb repressor complex, Casz1 promotes the rod fate while suppressing MC fate (Mattar et al. 2021). A recently discovered temporal TF, POU Class 2 Homeobox 1 (Pou2f1), regulates the generation of cones (Javed et al. 2020), all of which are born prenatally in the mouse retina. Notably, Pou2f1 represses Casz1, thus preventing early RPCs from acquiring a late RPC competence state. Thus, temporal TFs not only confer specific competence states to the RPCs in which they are expressed but also regulate the transitions between states.

2.3. Biased Progenitors

In addition to the multipotent RPCs described in Section 2.2, some RPCs are biased, even stereotypic, in the cell classes they generate. This is particularly apparent in RPCs undergoing terminal divisions. For example, in the zebrafish retina, terminal divisions in the late stages of neurogenesis generate pairs of PhRs (He et al. 2012, Suzuki et al. 2013), BCs (Engerer et al. 2017, Weber et al. 2014), or HCs (Godinho et al. 2007, Weber et al. 2014). RPCs in the mouse retina, expressing the basic helix-loop-helix (bHLH) oligodendrocyte transcription factor 2 (Olig2), divide terminally, generating daughters with the same fate, either two cones or two HCs (Hafler et al. 2012). Pairs of HCs of the same subtype in the chick retina have been reported (Rompani & Cepko 2008). Moreover, Cadherin 6 (Cdh6)-expressing RPCs in the mouse retina give rise to multiple cell classes, but the GCs they generate are almost exclusively of a specific subtype: direction-selective GCs that also express Cdh6 (De la Huerta et al. 2012).

3. INTRINSIC VERSUS EXTRINSIC DETERMINANTS OF CELL FATE

Several lines of evidence suggest that intrinsic mechanisms rather than extrinsic cues are key players in determining cell fate in the retina. RPCs isolated from the rat retina and cultured at clonal density divided in predictable modes and gave rise to retinal cell classes in the same order they would have in vivo (Cayouette et al. 2003, Gomes et al. 2011). Moreover, RPCs from the embryonic retina generated cell classes with early fates even when cultured with (Belliveau & Cepko 1999) or transplanted into (Rapaport et al. 2001) a postnatal environment. Similarly, postnatal RPCs did not alter their output when placed in an embryonic retinal environment (Belliveau et al. 2000). Thus, being placed in a heterochronic milieu did not alter the innate capacity of RPCs. Nevertheless, cues from the environment might provide some feedback to RPCs, for example, by inhibiting the generation of more cells from a specific cell class when sufficient numbers have been generated (Waid & McLoon 1998).

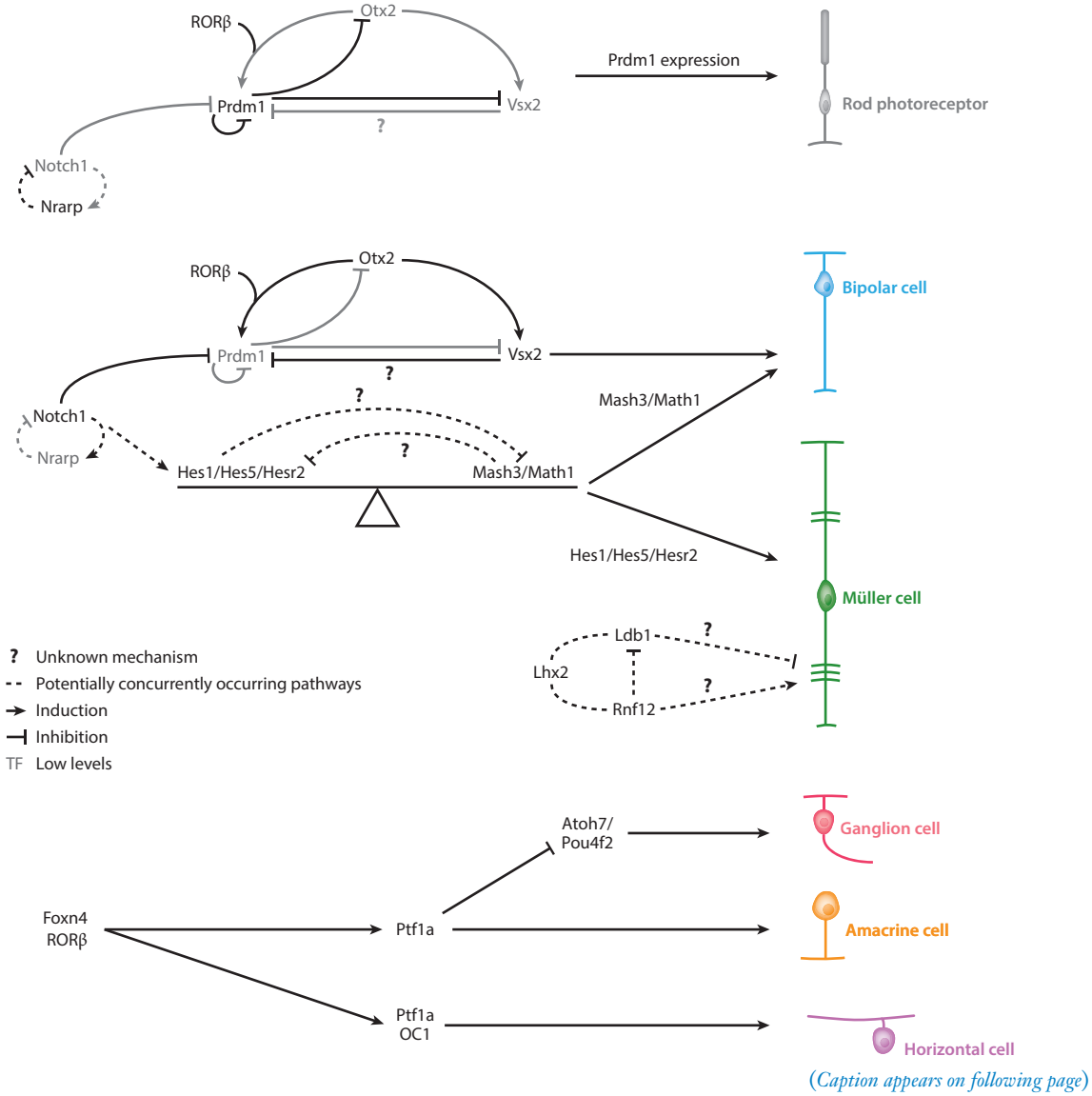
Intrinsic mechanisms that instruct cell fate involve specific TF cascades that are downstream of the competence factors described in Section 2.2. In Section 4, we describe the gene regulatory networks involved in the specification of each retinal cell class (**Figure 3**). The role that specific TFs play has been investigated largely through gain- and loss-of-function approaches. Cre recombinase–based fate mapping and sophisticated retroviral tools have enabled specific lineages to be targeted for labeling or manipulation (Hafler et al. 2012). Time-lapse imaging in vivo in the zebrafish retina (Engerer et al. 2021, Godinho et al. 2007, He et al. 2012, Jusuf et al. 2011, Poggi et al. 2005) and in vitro in postnatal rat RPCs (Gomes et al. 2011) has provided direct observations of dividing RPCs and their progeny in physiological conditions and following manipulation. Further, scRNA-seq studies of the developing mouse (Clark et al. 2019), human (Lu et al. 2020), and zebrafish retina (Wang et al. 2020, Xu et al. 2020) are providing detailed insights into the developmental programs that generate the diversity of retinal cell fates.

4. GENE REGULATORY NETWORKS INVOLVED IN FATE DETERMINATION

4.1. Photoreceptors

The subtypes and proportions of PhRs vary in different species. In zebrafish, rods make up a small proportion of the entire PhR population, with cone subtypes dominating (Baden & Osorio 2019). By contrast, in nocturnal mammals such as mice, rod PhRs dominate (Young 1985). In mice, rods are generated throughout the period of retinogenesis, peaking around birth. Given their abundance, almost every clone contained rods in lineage-tracing studies of mice and rats (Turner &

Cepko 1987, Turner et al. 1990), with some clones exclusively comprising rods. Cones are generated only prenatally in mice, and in many vertebrate species cone genesis is initiated prior to the commencement of rod genesis (Carter-Dawson & Lavail 1979, Sidman 1961, Young 1985). Both PhR types can be generated by terminal divisions in the mouse (Hafler et al. 2012) and zebrafish (He et al. 2012) retina. However, whereas these terminal divisions can generate heterotypic progeny in mice, homotypic PhR pairs are generated in zebrafish (Suzuki et al. 2013). Retrovirus-based clonal analysis of RPCs in mice expressing Olig2 suggested that they divide terminally, generating different combinations of two-cell clones comprising a PhR and an interneuron (Hafler et al. 2012). At embryonic time points, these two-cell clones comprise two cones, one cone and one HC, or two HCs. At postnatal ages, Olig2$^+$ RPCs generated two rods or one rod and one AC.



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Molecular mediators of cell fate in the vertebrate retina. Gene regulatory networks involved in the fate determination of different cell classes are depicted. In the mouse retina, the acquisition of rod PhR and BC fates is linked, controlled by a TF network involving Otx2, Vsx2, and Prdm1. Otx2 is expressed by a subset of postmitotic precursors and activates Vsx2 and Prdm1, which are instructive for BC and rod PhR fates, respectively. Vsx2 and Prdm1 cross-repress each other to establish which TF will prevail and thus impact which cell fate is specified. Acquiring a definitive rod PhR fate requires the activation of Nrl (not shown). Otx2 and RORβ bind to Nrl in postmitotic PhR precursors to solidify the rod PhR fate. Notch signaling, in concert with its negative regulator Nrarp, also plays an important role in the rod PhR versus BC fate decision. High levels of Notch activation lead to the inhibition of Prdm1 and thus the BC fate. Conversely, low levels of Notch signaling favor the rod PhR fate at the expense of BCs. Notch signaling is also key to regulating the balance between neurogenesis (rod PhR and BC fates) and gliogenesis (MC fate). The Notch effector genes *Hes1*, *Hes5*, and *Hesr2*, which are important for MC fate specification, repress TFs such as Math3 and Mash1 that act in concert with Vsx2 to instruct the BC fate. A gene regulatory network involving Lhx2, its co-activator Ldb1, and Rnf12 has also been implicated in MC fate. The temporal TF Foxn4, together with RORβ, activates Ptf1a, which is essential for AC fate determination. Ptf1a, in combination with Oc1, also a Foxn4 downstream target, is important for HC fate determination. The bHLH TF Atoh7, acting together with its downstream target Pou4f2, is key to GC fate specification and differentiation. Abbreviations: AC, amacrine cell; Atoh7, atonal homolog 7; BC, bipolar cell; bHLH, basic helix-loop-helix; Foxn4, winged helix/forkhead; GC, ganglion cell; HC, horizontal cell; Hesr2, Hes-Related Repressor Protein 2; Hes1,5, Hes Family BHLH Transcription Factor 1,5; Ldb1, LIM Domain Binding 1; MC, Müller glial cell; Nrarp, Notch-regulated ankyrin repeat protein; Nrl, neural retina leucine zipper; Oc1, onecut 1; Otx2, orthodenticle homeobox 2; PhR, photoreceptor; Pou4f2, POU domain class 4 transcription factor 2; Prdm1, PR domain zinc finger protein 1; Ptf1a, pancreas transcription factor 1a; Rnf12, RING Finger Protein 12; RORβ, retinoid-related orphan nuclear receptor β; TF, transcription factor; Vsx2, visual system homeobox 2.

Notably, rods and cones were never immediate siblings. Moreover, not all rods are generated by the Olig2$^+$ RPCs; two-cell clones comprising one rod and one BC or one rod and one MC are generated by Olig2$^-$ RPCs at postnatal time points. The TF orthodenticle homeobox 2 (Otx2), which is upregulated in RPCs as they exit the cell cycle, lies at the heart of rod and cone fate determination (Nishida et al. 2003). In the absence of Otx2, both types of PhRs fail to form.

4.1.1. Cone photoreceptors. Cone fate in mice relies on Otx2 and onecut 1 (Oc1), an atypical homeodomain TF. In combination with Otx2, Oc1 binds enhancer elements of thyroid hormone receptor β2 (Thrβ2), which is active in RPCs that generate cones (as well as HCs). The timing of OC1 expression correlates with when cones, not rods, are generated. Indeed, OC1 is a key element in deciding whether a cone or a rod PhR is fated. Repression of OC1 allows rod PhR generation. Conversely, induced expression of Oc1 in Otx2$^+$ cells in the postnatal mouse retina, when cone generation is normally long completed, results in the generation of cones (Emerson et al. 2013).

In the zebrafish retina, cones are generated in terminal divisions (He et al. 2012), with distinct cone subtypes sensitive to L, M, S, and UV wavelengths of light generated as homotypic pairs by dedicated progenitors (Suzuki et al. 2013). For example, Thrβ2$^+$ L cones are generated by Thrβ2$^+$ progenitors. Knockdown of *Thrβ2* reduced the number of L cones and increased the number of UV cones. Similarly, in mice, the absence of Thrβ2 led to a loss of M cones and an increase in S cones, which are phylogenetically similar to zebrafish UV cones (Ng et al. 2001). UV cones in zebrafish are specified by the T-box TF Tbx2b; in its absence, UV cones are reduced significantly in number with a concomitant increase in rod number (Alvarez-Delfin et al. 2009). Thus, Tbx2b specifies UV cone fate and represses the rod fate.

4.1.2. Rod photoreceptors. At postnatal stages of mouse retinal development, Otx2$^+$ postmitotic precursors are bipotential, capable of adopting rod or BC fates. Otx2 directly activates the transcriptional repressor PR domain zinc finger protein 1 (Prdm1), also called B lymphocyte-induced maturation protein-1 (Blimp1), and visual system homeobox 2 (Vsx2), also called Ceh-10 homeodomain-containing homolog (Chx10). Prdm1 is associated with rod fate specification, and Vsx2 is linked to the BC fate. Prdm1 and Vsx2 cross-repress each other to establish which TF will prevail. The levels of each of these TFs thus critically determine which cell fate will be chosen. Prdm1 also inhibits Otx2. Once the rod or BC fate is specified, a transient period occurs during

which a switch can be induced by the experimental overexpression of the appropriate TF. However, once mature they are no longer amenable to fate changes. Acquiring a definitive rod fate requires activation of the TF neural retina leucine zipper (Nrl) (Mears et al. 2001) or its target, nuclear receptor subfamily 2 group E member 3 (Nr2e3) (Chen 2005). Otx2 and the protein encoding the retinoid related orphan nuclear receptor β (Rorβ) gene directly bind to Nrl in postmitotic PhR precursors to instruct the rod fate. If *Nrl* is knocked out, cones are generated at the expense of rods (Mears et al. 2001). Experimental induction of Nrl or Nr2e3 can transform cone precursors into rods (McIlvain & Knox 2007, Oh et al. 2007). Thus, rod fate specification requires repression of cone-specific genes.

4.2. Bipolar Cells

Acquisition of the BC fate is closely linked with the rod fate (described in Section 4.1.2) and is controlled by a network of TFs in which Otx2, Prdm1, and Vsx2 play key roles. In *Otx2*$^{-/-}$ mutant mice in which PhRs fail to form, BCs are also significantly decreased, implicating a role for Otx2 in PhR and BC fates (Koike et al. 2007). Vsx2 is instructive for the BC fate (Burmeister et al. 1996, Green et al. 2003, Horsford et al. 2004) and inhibits the acquisition of the PhR fate by suppressing the expression of PhR-related genes (Dorval et al. 2005, Livne-Bar et al. 2006). Conversely, Prdm1 represses BC-related genes in Otx2^{+} cells (Brzezinski et al. 2010, 2013; Katoh et al. 2010; Park et al. 2017). In the absence of Prdm1, increased numbers of BCs are observed at the expense of rods. Thus, Prdm1 and Vsx2 suppress each other to solidify the rod PhR versus BC fate (Brzezinski et al. 2010, 2013; Goodson et al. 2020a,b; Katoh et al. 2010; Kim et al. 2008a; Mills et al. 2017; Wang et al. 2014). Recent studies reported newly found upstream regulatory sequences in the *Otx2* and *Vsx2* loci, specific to BCs (Chan et al. 2020, Norrie et al. 2019), displaying another level of specificity in the activation of these factors.

Notch signaling is an additional important component of the rod versus BC fate decision, affecting cell specification postmitotically (Mizeracka et al. 2013a). Inactivation of the Notch1 receptor in late retinal progenitors in the mouse retina increased the number of rod PhRs at the expense of BCs, whereas Notch1 ablation in early progenitors favored the production of cone PhRs (Jadhav et al. 2006b, Yaron et al. 2006). Microarray analysis of *Notch1* conditional knockout retinae revealed the downregulation of Notch target genes and effectors along with an upregulation of rod precursor–specific genes, including *Prdm1* (Mizeracka et al. 2013b). Collectively, these data suggest a model in which BCs require the action of Notch1 in order to directly or indirectly reduce the levels of Prdm1. Low Prdm1 levels alleviate the inhibition of *Otx2* and *Vsx2* genes and permit their expression and action. When the effect of Notch signaling subsides, the balance favors the expression of proneuronal genes, such as *Math3* [additionally known as *atonal BHLH Transcription Factor 3* (*Atoh3*) or *Neuronal Differentiation 4* (*NeuroD4*)] and *Mash1* [also known as achaete-Scute Family BHLH Transcription Factor 1 (*Ascl1*)], that act along with *visual system homeobox 2* (*Vsx2*) to specify the BC fate (Hatakeyama et al. 2001, Tomita et al. 2000). In *Otx2*$^{+}$ cells in which Notch signaling is not active, *Prdm1* levels are high. As a result, the expression of *Otx2* and *Vsx2* are low or eliminated, leading the cell toward the rod PhR fate.

Additional TFs induce subtype specification of BCs in the rodent retina. Among these are *Vsx1* (Chow et al. 2001, 2004; Ohtoshi et al. 2001, 2004; Shi et al. 2011), basic helix-loop-helix domain containing class B 4 protein (*Bhlhb4*) (Bramblett et al. 2004, Kim et al. 2008b), *Bhlhb5* (Feng et al. 2006, Huang et al. 2014), iroquois Homeobox 5 (*Irx5*) (Cheng et al. 2005), insulin gene enhancer protein 1 (*Isl1*) (Elshatory et al. 2007a,b), PR/SET Domain 8 (*Prdm8*) (Jung et al. 2015), FEZ Family Zinc Finger 2 (*Fezf2*) (Suzuki-Kerr et al. 2018), and jumonji domain-containing protein-3 (*Jmjd3*) (Iida et al. 2014), which are differentially expressed in ON- and OFF-cone BCs as well as rod BCs and affect different aspects of cellular specification.

BC fate specification in the zebrafish retina has not been thoroughly investigated. Nonetheless, Vsx1 and Vsx2, which play important roles in BC fate specification in the mouse retina, are also key players in the zebrafish retina. Most zebrafish BCs express *vsx1* (Engerer et al. 2017, 2021; Passini et al. 1997; Vitorino et al. 2009; Weber et al. 2014) and a smaller population (types S4 and S5) expresses *vsx2* (Barabino et al. 1997, Passini et al. 1997, Vitorino et al. 2009). In zebrafish, *vsx2* signals the BC fate (Vitorino et al. 2009) and acts as transcriptional repressor of *vsx1* as in the mouse retina (Clark et al. 2008, Dorval et al. 2005, Passini et al. 1997, Vitorino et al. 2009).

4.3. Müller Glial Cells

Notch signaling is key for MC fate specification and differentiation across vertebrate species (Bao & Cepko 1997, Furukawa et al. 2000, Jadhav et al. 2006a, Perron et al. 1998, Scheer et al. 2001). Overexpression of the constitutively active form of the Notch1 receptor induced the expression of MC markers (Bao & Cepko 1997, Furukawa et al. 2000, Jadhav et al. 2006a, Scheer et al. 2001). Conversely, inhibition of Notch signaling led to a failure of MCs to differentiate (Bernardos et al. 2005, Scheer et al. 2001). Furthermore, sustained Notch signaling is essential for maintaining the MC identity (Nelson et al. 2011). Three Notch effectors, Hes Family BHLH Transcription Factor 1 (*Hes1*), *Hes5*, and HES-Related Repressor Protein 2 (*Hesr2*), all of which are bHLH transcriptional regulators, play a vital role in MC specification. Retrovirus-mediated overexpression of *Hes1* in the mouse retina led to an increase in cells expressing glial markers; expression of a dominant negative form of *Hes1* led to a decreased number of MCs accompanied by a decrease in BCs (Furukawa et al. 2000). Overexpression of *Hes5* or *Hesr2* also increased the number of MCs, but at the expense of rods (Hojo et al. 2000, Satow et al. 2001), without inducing cell proliferation or death. Thus, *Hes5* and *Hesr2* promote glial fate in precursor cells while inhibiting neuronal fate. Manipulations that target MC fate affect both rods and BCs, retinal classes generated late during development (Young 1985). Thus, inactivation of the Notch1 receptor in late retinal progenitors led to an increased number of not only rod PhRs at the expense of BCs (as described in Section 4.2) but also MCs (Jadhav et al. 2006b). Notch-regulated ankyrin repeat protein (*Nrarp*), a downstream Notch target gene, is a negative regulator of Notch signaling (Krebs et al. 2001, Lamar et al. 2001, Pirot et al. 2004). When *Nrarp* is overexpressed in vivo, increased numbers of rod PhRs were generated at the expense of MCs, while BCs remained unaffected (Mizeracka et al. 2013a). Conversely, in the absence of *Prdm1*, increased numbers of MCs and BCs were seen at the expense of rods (Brzezinski et al. 2010, 2013). Collectively, Notch signaling appears key to achieving a balance between neurogenesis and gliogenesis via downstream effectors that repress proneurogenic bHLH TFs. Accordingly, retinae lacking bHLH neuronal specification factors displayed increased MC genesis (Akagi et al. 2004; Inoue et al. 2002; Tomita et al. 1996, 2000).

In addition to Notch signaling, a gene regulatory network centered on the LIM homeodomain TF *Lhx2* plays an important role in balancing neurogenesis and gliogenesis. *Lhx2*-deficient animals display a significant reduction of the variable Notch components, including Notch1 receptor (de Melo et al. 2016b), and of proneuronal bHLH factors such as NeuroD1 (de Melo et al. 2018). Recent work revealed that Lhx2 and LIM Domain Binding 1 (Ldb1), the transcriptional (co)activator of Lhx2, inhibit MC production, whereas in combination with another factor, RING Finger Protein 12 (Rnf12), they induce gliogenesis. Rnf12 is a negative regulator of Ldb1 and both are expressed in tandem in retinal progenitors (de Melo et al. 2016b,a, 2018), controlling Lhx2 action, which in turn coordinates chromatin accessibility (Zibetti et al. 2019). Downstream targets of Lhx2 act to specify different gliogenic properties of MCs (de Melo et al. 2016a). Coelectroporation of the Lhx2–Ldb1 complex increased PhRs at the expense of BCs and MCs (de Melo et al.

2018), implying that multiple mechanisms affecting fate decisions are in place and might occur concurrently.

Vsx2 (*Chx10*), described in Section 4.1.2 in the context of BC fate specification, also plays a role in MC fate determination (Burmeister et al. 1996, Green et al. 2003, Horsford et al. 2004). In the rodent retina, *Vsx2* is expressed in progenitors and at maturity in BCs and a subset of MCs (Liu et al. 1994, Rowan & Cepko 2004). In the zebrafish retina, the reverse pattern is observed: *vsx2* is expressed in MCs and a subset of BCs (Passini et al. 1997, Vitorino et al. 2009). Although it is not clear how *Vsx2* expression in progenitors and MCs is regulated, there are regulatory sequences upstream of the *Vsx2* locus that are specific to BCs and potentially to MCs as well (Norrie et al. 2019). Current evidence suggests that *Vsx2* is permissive for but not necessarily instructive of the glial fate (Hatakeyama et al. 2001, Livne-Bar et al. 2006). Thus, further studies are required to elucidate the importance of *Vsx2* in MC fate determination.

4.4. Horizontal Cells and Amacrine Cells

HCs and ACs are inhibitory interneurons that occupy distinct positions in the INL. Across vertebrate species examined thus far, both cell classes share common gene regulatory networks and arise from an RPC subpopulation that expresses the winged helix/forkhead TF Foxn4 (Li et al. 2004), which has been proposed to be a temporal TF. *Foxn4* confers progenitors with the competence to generate not only HCs and ACs but also cones and rods (Liu et al. 2020). Foxn4 together with retinoid-related orphan nuclear receptor β1 (RORβ1) acts to activate the expression of the bHLH TF pancreas transcription factor 1a (*Ptf1a*) (Liu et al. 2013), which is required for AC fate determination (Dullin et al. 2007, Fujitani et al. 2006, Jusuf et al. 2011, Nakhai et al. 2007). *Oc1* is a downstream target of *Foxn4* and together with *Ptf1a* is required for the acquisition of HC fate (Wu et al. 2013). Postmitotic precursors that express *Ptf1a* and *Oc1* are thus committed to the HC fate and begin to express markers of differentiating HCs, including the TFs LIM homeobox 1 (Lim1) (Poché et al. 2007) and Prospero Homeobox 1 (Prox1) (Dyer et al. 2003), while precursors solely expressing *Ptf1a* are committed to the AC fate. In the absence of *Ptf1a*, both ACs and HCs fail to form and an increase in the number of GCs is observed (Fujitani et al. 2006). This finding suggests an additional role for Ptf1a in repressing the GC fate.

4.5. Ganglion Cells

Atoh7 has long been identified as a key molecular player in GC fate specification (Brzezinski et al. 2012, Mu et al. 2005, Yang et al. 2003). Across vertebrate species a subset of neurogenic RPCs expressing Atoh7 was competent to generate GCs. In the absence of Atoh7, an almost complete loss of GCs was observed (Brown et al. 2001, Kay et al. 2001, Wang et al. 2001). Recent work, however, has called into question the role that Atoh7 plays in GC fate specification, suggesting instead that it promotes GC survival and axon pathfinding within the retina (Brodie-Kommit et al. 2021). When apoptosis was blocked [BCL2 Associated X, Apoptosis Regulator ($Bax^{-/-}$)] in *Atoh7*-deficient mice, GCs were largely specified, with only a 20% reduction in numbers compared with controls. TFs such as Isl1 and Pou domain class 4 transcription factor 2 (Pou4f2), normally regarded to be downstream of Atoh7 and to stabilize GC fate and differentiation (Gan et al. 1999, Pan et al. 2008, Wu et al. 2015), were expressed even in the absence of Atoh7. Thus, in addition to Atoh7, other unknown molecular regulators must work upstream of Isl1 and Pou4f2. A new model for GC fate has emerged in which Atoh7 specifies a small cohort of early-born retinal GCs that might be the source of prosurvival factors and pathfinding cues for later-born GCs. In parallel, TFs such as NeuroD1 (Mao et al. 2013), Sox4 (Jiang et al. 2013), and Oc1 and Oc2 (Sapkota et al. 2014) specify most GCs.

5. STOCHASTIC MECHANISMS IN CELL FATE DETERMINATION

As described in Section 2.2, the competence state of RPCs and the activation of specific downstream TF cascades contribute to cell fate specification. However, about a decade ago, two studies (Gomes et al. 2011, He et al. 2012) brought to the fore the concept that stochastic mechanisms also played a major role during retinogenesis. This notion did not imply randomness but rather that different modes of division or fate choices occurred with a fixed range of probabilities over the course of development and could not always be predicted. Both studies involved long-term time-lapse imaging of individual RPCs either in vitro in postnatal rat RPCs or in vivo in the zebrafish retina, quantitatively analyzing the modes of RPC mitotic divisions over multiple rounds and ascertaining the fate of the progeny at each division. In line with previous, now classical, lineage studies, the researchers found variability in the size and composition of RPC-derived clones. Was this variability a result of endogenously distinct RPC subpopulations, each generating specific cell classes in a deterministic manner? Or were there stochastic mechanisms operating on equivalent progenitors to yield different fate outcomes? Both mechanisms seem to operate during retinogenesis. The mode in which RPCs divided (symmetric proliferative, asymmetric differentiative, or symmetric differentiative; see **Figure 2**) was stochastic, that is, determined by a fixed set of probabilities. For example, in the developing zebrafish retina, at early stages all RPC divisions were symmetric and proliferative. At the next phase, all three division modes had an equal probability of occurring, and in the last phase symmetric differentiative divisions dominated. Similarly, stochastic mechanisms also dictated cell fate outcomes, with the probability for the acquisition of a specific fate being determined by the abundance of a particular cell class in the mature retina. Nevertheless, some cell fates are clearly generated by deterministic mechanisms. This is particularly true for late stages of retinogenesis, at least in the zebrafish retina. For example, rods, cones, BCs, and HCs in the zebrafish retina were almost entirely generated by terminal symmetric differentiative divisions (e.g., pairs of HCs or BCs). The frequency of such outcomes was much higher than would be expected if stochastic mechanisms were at play.

What could account for the stochastic nature of cell fate decisions in the retina? Several possibilities include variability at the level of gene expression and translational, posttranslational (Kærn et al. 2005), and epigenetic mechanisms (Hu et al. 2012, Raeisossadati et al. 2021). Indeed, the independent activation of specific core TFs, Atoh7, Ptf1a, and Vsx1, in RPCs early during retinogenesis in zebrafish was sufficient to explain the variability in clone composition. The TF or TF combinations individual RPCs expressed constrained their potential and thus the cell classes they produced (Boije et al. 2015).

6. WHEN IS CELL FATE DETERMINED?

Pinpointing exactly when a specific cell fate is determined is difficult. For cell classes that are exclusively generated by terminal symmetric mitotic divisions, one might assume that fate assignments must have already occurred at the level of the RPC. For other cell classes, the consensus is that fate determination occurs immediately prior to or soon after cell cycle exit. There appears to be a brief time window in nascent postmitotic cells during which they are malleable and amenable to fate switches, as shown for rod and BC fates in the murine retina (Goodson et al. 2020b). We recently showed in the zebrafish retina that at least some nascent BCs of the *vsx1* lineage switch to an AC fate during normal development and that this transdifferentiation is mediated by Notch signaling (Engerer et al. 2021). Indeed, Notch signaling has been implicated in binary fate decisions extensively across species and CNS regions, including in asymmetric terminal divisions in the mouse retina (Kechad et al. 2012). How differential Notch signaling is achieved in the daughter cells of

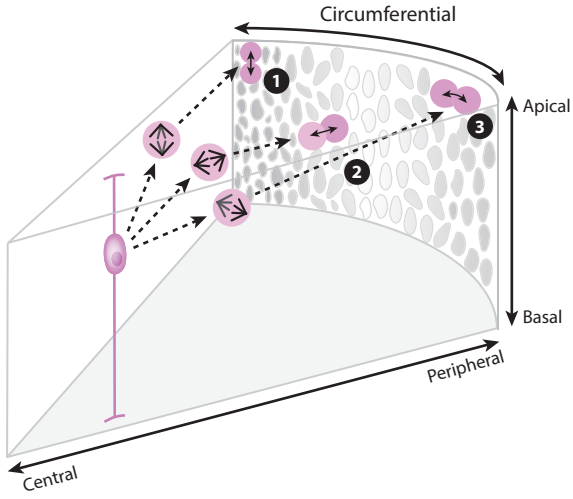


Figure 4

Angles of division. Mitotic divisions along the ① apical-basal axis, ② central-peripheral axis, and ③ circumferential axis. Figure adapted with permission from Cayouette et al. (2006); copyright Elsevier.

terminally dividing RPCs remains to be fully understood. In the mouse retina, the asymmetric inheritance of the Notch signaling antagonizer Numb was proposed to mediate distinct fates following terminal divisions (Kechad et al. 2012), but this mechanism does not seem to operate in the zebrafish *vsx1* lineage. Other, still unknown, mechanisms must therefore operate to underlie the asymmetric Notch activity. The unequal partitioning of a fate determinant in an RPC to its daughters relies both on the distribution of the determinant within the RPC and on the subsequent angle of cleavage at mitosis. In the mouse retina, Numb has a polarized distribution within RPCs and a cleavage plane that distributes it unequally to the emerging apically and basally located daughter cells, permitting diverging fates to emerge (Cayouette & Raff 2003, Kechad et al. 2012). In the zebrafish retina, mitotic divisions occur along multiple axes (**Figure 4**), but at least to date, no evidence has emerged to correlate asymmetric inheritance of a fate determinant and distinct fates.

7. CONCLUDING REMARKS

In the last few decades much progress has been made in our understanding of how different cell classes in the vertebrate retina are generated. The tools employed have expanded beyond classical gain- and loss-of-function experiments and have become increasingly sophisticated so that more intricate details of gene regulatory networks and epigenetic regulatory mechanisms are being revealed. Further, different model systems have provided insights into the evolutionarily conserved mechanisms of development across vertebrates. More recently, there have even been forays into directly understanding human retinal development, through scRNA-seq of fetal tissue and organoids. The insights gained from such investigations of cell fate regulators will undoubtedly contribute to regenerative medicine. Indeed the targeted generation of specific retinal cell types through either induced pluripotent cells or the coaxing of endogenous sources of cell replacement (e.g., MCs) is no longer a distant reality (Jorstad et al. 2017, Todd et al. 2021, Yao et al. 2018).

SUMMARY POINTS

1. The retina is an accessible part of the CNS. Its peripheral location, stereotypic cytoarchitecture, and readily identifiable cell classes make it particularly suitable to the investigation of mechanisms underlying cell fate acquisition.
2. Although the length of retinogenesis varies across vertebrates, retinal cell classes are generated in a conserved, albeit overlapping, order. Cells with distinct fates that are destined for different layers can be generated concurrently.
3. Retinal progenitor cells are largely multipotent but not molecularly homogeneous, suggesting that distinct lineages coexist. At any given time, individual retinal progenitors are competent to generate only a small repertoire of cell classes based on the specific transcription factor(s) that they express.
4. In addition to multipotent progenitors, progenitors that are biased to generate specific cell classes and those committed to the exclusive generation of particular cell classes exist.
5. Retinal cell classes can be generated via asymmetric mitotic divisions, in which their immediate sibling is a progenitor, or via terminal divisions, in which another postmitotic cell is their sibling. Terminal divisions can be further divided into symmetric or asymmetric modes depending on whether the daughter cells adopt the same or distinct fates, respectively.
6. Cell intrinsic mechanisms involving temporal transcription factors and downstream gene regulatory networks play major roles in instructing cell fate. By comparison, extrinsic cues play minor roles.
7. The gene regulatory networks instructing distinct retinal cell fates are beginning to be revealed in increasing detail. The use of scRNA-seq to analyze retinal development has expanded our knowledge of the molecular diversity of progenitors and the gene regulatory networks that mediate cell fates.

FUTURE ISSUES

1. The ways in which subtypes within retinal cell classes are generated should be investigated.
2. scRNA-seq analysis should be expanded to allow for the detection of mRNA isoforms of genes that likely play distinct roles in different contexts.
3. Newly emerging technologies in spatial genomics should be used to examine the expression of multiple transcripts at the single-cell level in developing retinal tissue.
4. Protein expression at the single-cell level during retinal development should be investigated.
5. New genetic sensors of key signaling pathways (e.g., the Notch pathway) should be generated, or existing sensors should be improved, to allow for more temporally resolved analysis of the activity of these pathways in in vivo or in vitro imaging contexts.

6. The link between lineage and connectivity should be explored to answer the question of whether cells that are born together or are clonally related preferentially form synaptic connections.

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