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REVIEW

Intrinsic control of mammalian retinogenesis

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Abstract The generation of appropriate and diverse neuronal and glial types and subtypes during development constitutes the critical first step toward assembling functional neural circuits. During mammalian retinogenesis, all seven neuronal and glial cell types present in the adult retina are specified from multipotent progenitors by the combined action of various intrinsic and extrinsic factors. Tremendous progress has been made over the past two decades in uncovering the complex molecular mechanisms that control retinal cell diversification. Molecular genetic studies coupled with bioinformatic approaches have identified numerous transcription factors and cofactors as major intrinsic regulators leading to the establishment of progenitor multipotency and eventual differentiation of various retinal cell types and subtypes. More recently, non-coding RNAs have emerged as another class of intrinsic factors involved in generating retinal cell diversity. These intrinsic regulatory factors are found to act in different developmental processes to establish progenitor multipotency, define progenitor competence, determine cell fates, and/or specify cell types and subtypes.

Keywords Retinogenesis · Retinal progenitor cell · Transcription factor · Non-coding RNA · Dll4-Notch signaling · Foxn4

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Introduction

The mammalian retina is a delicate multilayered sensorineural epithelium composed of six major types of neurons and one type of glia, the Müller cells (Fig. 1c). The neuronal types include the rod and cone cells as photoreceptors, the horizontal, bipolar and amacrine cells as interneurons, and the retinal ganglion cells (RGCs) as output neurons. Except for rods, all major types of retinal neurons consist of two or more subtypes that differ in morphologies, physiological properties, and/or sublaminar positions, with amacrine cells and RGCs as the most diversified cell types [1–4]. During embryogenesis, retina originates from the optic vesicle, a protrusion of the neuroepithelium of the neural tube at the diencephalon level. Following invagination of the optic vesicle, a double-layered optic cup is formed with the inner layer containing multipotent retinal progenitor cells (RPCs) capable of differentiating into any of the seven neuronal and glial cell types (Fig. 1a, b). Producing proper types and quantity of retinal cells constitutes the critical first step toward assembling a functional retinal circuitry. A central question in retinal development is, thus, how these diverse cell types and subtypes are specified and differentiated from the multipotent RPCs.

During retinogenesis, the seven major cell types are generated from multipotent RPCs following a loose and overlapping temporal order [5–7] (Fig. 1d). It has been proposed that both intrinsic and extrinsic factors together determine the choice of retinal cell fates and that RPCs may pass through successive and distinct states of competence for the ordered generation of different cell types [8–10]. Extrinsic factors such as FGFs, EGFs, CNTF, Shh, thyroid hormone, and Notch/Delta are all known to affect retinal cell fates [8–11]. For instance, constitutively

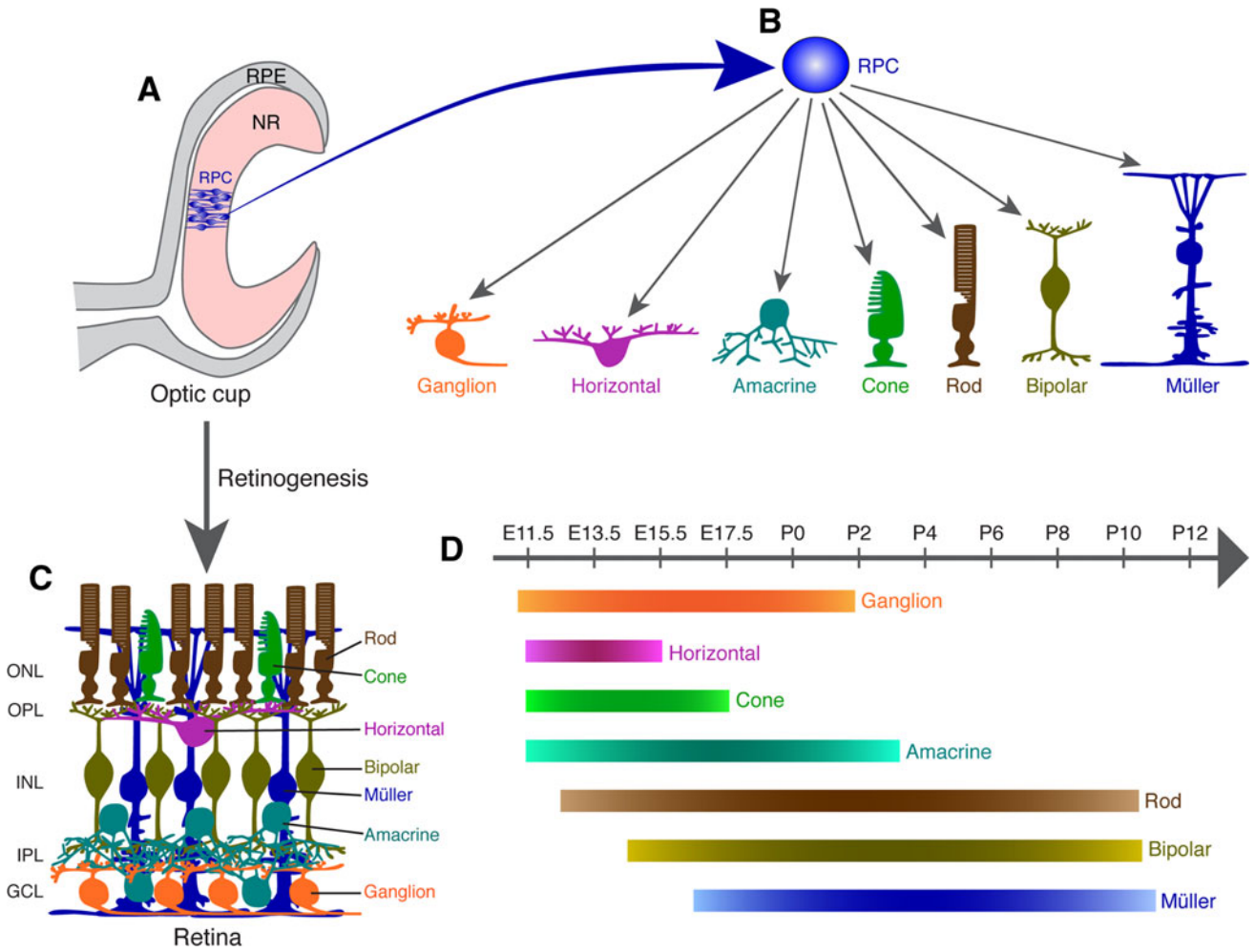

Fig. 1 Retinal development from multipotent progenitor cells. **a**, **b** Schematic illustration of the double-layered optic cup. The inner layer harbors multipotent retinal progenitors that are capable of differentiating into the ganglion, horizontal, amacrine, cone, rod, bipolar, and Müller cells. **c** Schematic of the retinal structure assembled from the seven cell types produced from multipotent progenitors. **d** Order of birth of mouse retinal cell types. Birthdating analysis has revealed a loose temporal sequence of generation of the six neuronal and one glial cell types in the mouse retina. *GCL* ganglion cell layer, *INL* inner nuclear layer, *IPL* inner plexiform layer, *ONL* outer nuclear layer, *OPL* outer plexiform layer, *RPC* retinal progenitor cell, *RPE* retinal pigment epithelium, *NR* neural retina

activated Notch and elevated Dll signals are shown to suppress neuronal differentiation whereas inhibiting Notch signaling has the opposite effect [12–17]. Notch signaling is also required to promote the Müller glial fate but inhibit the photoreceptor fate [18–21]. Despite the involvement of extrinsic factors, however, recent evidence suggests that intrinsic factors are the primary determinants of retinal fate choices. Retinal clones generated in serum-free clonal-density cultures of late rat RPCs were found to be indistinguishable in composition and size from clones generated in explants of retina of the same age [22]. Moreover, lineage tracing by time-lapse microscopy in such clonal culture as well as in zebrafish developing retina revealed that individual clones exhibit great variations in size, composition, and division mode, but as a population, fit a simple stochastic model in which equipotent RPCs have certain probabilities of division and differentiation [23, 24]. One underlying mechanism for such stochasticity may be the extreme heterogeneity exhibited by RPCs in their expression of transcription factors (TFs) [25].

In the past two decades, experiments that perturb normal expression of TFs have shed fundamental new light on the molecular basis of retinal cell fate commitment and differentiation. Not only have a variety of TFs and cofactors been identified that control the competence states of RPCs and/or participate in their specification and differentiation, but many of them are found to have multiple roles in different developmental contexts (Fig. 2). For instance, Neurod1 is involved in the determination of bipolar, amacrine, and horizontal cells, the specification of M-cones, and

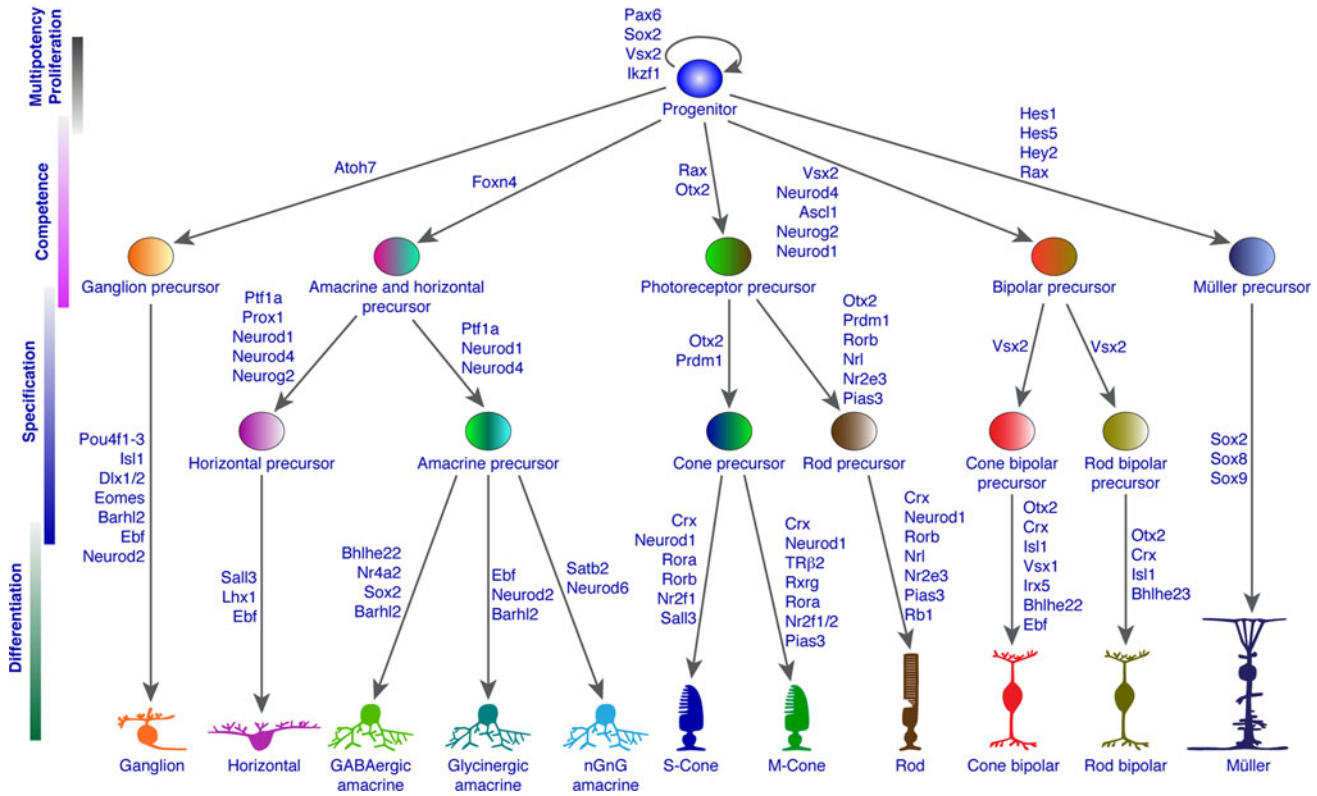

Fig. 2 Known transcription factors and cofactors involved in retinal progenitor multipotency and competence as well as in the specification and differentiation of different retinal cell types and subtypes

in terminal differentiation and survival of photoreceptors (see below and Fig. 2). More recently, non-coding RNAs (ncRNAs) have emerged as another important family of intrinsic factors involved in regulating retinal cell development. In this review, I will focus on these two families of intrinsic molecules, with an emphasis on their functions in RPC competence, specification, and differentiation.

TFs involved in conferring/maintaining neurogenic competence and multipotency of RPCs

Prior to retinogenesis, neuroepithelial cells in the optic cup must acquire multipotency and establish competence for the generation of the full range of retinal cell types. Accumulating evidence has indicated that maintaining a precise ratio of Sox2 and Pax6 levels in RPCs is essential for establishing and/or maintaining neurogenic competence and multipotency of RPCs (Fig. 2). Pax6 is a paired-type homeodomain TF required for early patterning of eye development. Its mutations or overexpression resulted in a range of ocular phenotypes including small eyes, absence of eyes, cataract, or aniridia in the mouse and human [26–30]. Conditional ablation of *Pax6* from mouse RPCs caused loss of all retinal cell types except for GABAergic amacrine cells, suggesting a requirement of Pax6 by RPCs to acquire and/or maintain their multipotent state [31]. Pax6 controls RPC multipotency by regulating the expression of multiple retinogenic bHLH and homeodomain TFs which are key intrinsic regulators of cell type specification [31–33]. Pax6 is also highly expressed in iris and ciliary body epithelium and crucially required for their differentiation [34].

At the optic cup stage of retinal development, Pax6 and Sox2, a HMG-box TF, are expressed in opposite gradients, with Sox2 displaying a central-high to peripheral-low gradient but Pax6 a peripheral-high to central-low gradient [35]. *Sox2* inactivation in RPCs resulted in loss of neurogenic competence and a switch to non-neural ciliary epithelial fate, accompanied by loss of Notch1 and neurogenic factor expression, and simultaneous increase in expression of Pax6 and ciliary epithelial markers [35, 36]. The maintenance of *Rax/Rx* and *Vsx2/Chx10* homeobox gene expression in *Sox2* null RPCs [35] indicates that, despite its necessity, Pax6 is insufficient to maintain neurogenic competence of RPCs even in the presence of Rax and Vsx2. In contrast, ablating *Sox2* on a *Pax6* heterozygous background partially rescued the *Sox2* mutant phenotype, suggesting that a proper ratio of Sox2 to Pax6 levels is key to the maintenance of RPC neurogenic

competence and multipotency [35]. Consistent with this hypothesis, both *Sox2* and *Pax6* mutant phenotypes are sensitive to their gene dosage [26, 28, 30, 36], and similar to *Pax6*, *Sox2* mutations are associated with anophthalmia and microphthalmia in humans and mice [36, 37]. Aside from Sox2, Vsx2 is also required to prevent RPCs from differentiating into the ciliary body and pigmented epithelium by repressing the expression of *Mitf*, a bHLH leucine zipper TF gene involved in retinal pigment epithelium differentiation [38–40]. *Vsx2* mutation caused RPC fate switch to pigmented cells and *Mitf* upregulation whereas misexpressed Vsx2 led to *Mitf* downregulation and nonpigmented epithelium [38]. Thus, the maintenance of RPC neurogenic competence depends on precise and coordinated regulation of Pax6, Sox2, and Vsx2 TFs during retinogenesis.

The multipotent RPCs are thought to gradually change their competence states as retinogenesis progresses from embryonic to postnatal stages [8, 9]. It has been demonstrated that the Ikzf1/Ikaros zinc finger TF plays a key role in establishing the early temporal competence states responsible for generating early-born cell types [41]. Inactivating *Ikzf1* caused loss of early-born neurons including ganglion, amacrine, and horizontal cells without affecting late-born cell types. On the other hand, while suppressing late-born cell types including bipolar and Müller cells, Ikzf1 misexpression in postnatal RPCs was sufficient to confer them with prenatal competence to generate early-born neurons [41]. The intrinsic factor(s) responsible for conferring late temporal competence states still remains elusive, but its identification will help to more completely elucidate the molecular mechanism underlying neurogenic competence and multipotency of RPCs.

TFs involved in retinal cell diversification

Photoreceptors

A cascade of TFs acts combinatorially for the determination and differentiation of rod and cone cells (Fig. 2). Their fate commitment and differentiation require the function of three paired-type homeodomain TFs, Rax, Otx2, and Crx. Conditional inactivation of *Otx2* in mouse RPCs resulted in a failure to generate rods and cones while causing a fate-switch to amacrine cells, whereas its misexpression in RPCs promoted a photoreceptor cell fate [42]. Otx2 determines the photoreceptor fate in part by activating the expression of *Crx* [42], which has been shown by gene targeting and overexpression analyses to be essential for maturation but not for specification of photoreceptor cells [43, 44]. In the human, mutations in *CRX* are associated with retinal diseases including cone-rod dystrophy, retinitis pigmentosa, and Leber congenital amaurosis [45–48]. Otx2 may also have a role in terminal differentiation of photoreceptors, as $Otx2^{+/-}Crx^{-/-}$ mice exhibited a more severe photoreceptor phenotype than either $Otx2^{+/-}$ or $Crx^{-/-}$ animals [49]. Rax, a retinal field specifier [50], has turned out to be a crucial upstream regulator of *Otx2* [51]. It binds directly to the embryonic *Otx2* enhancer to activate its expression in photoreceptor precursors, and this expression can be severely attenuated by genetic ablation of *Rax* in RPCs [51]. Thus, Rax may have a role in photoreceptor competence acquisition and/or fate determination.

The PR domain zinc finger TF Prdm1/Blimp1 is also involved in photoreceptor specification as its inactivation caused a decrease of photoreceptors with a concomitant fate change to bipolar and Müller cells while its misexpression suppressed the bipolar cell fate [52, 53]. It inhibits the bipolar fate by repressing the expression of Vsx2 and Vsx1 [53], two homeodomain TFs involved in bipolar cell development as discussed below. Besides Crx, Neurod1, a bHLH TF, is required for terminal differentiation and survival of photoreceptors. Inactivating *Neurod1* resulted in shortened inner and outer segments, abnormal synapses, and degeneration of rods and cones [54]. The maturation of rods additionally depends on the retinoblastoma protein Rb1. Genetically ablating *Rb1* or biochemically inactivating its protein activity caused loss of rod marker expression, deformed rod inner and outer segments, and defective rod pedicles [55]. Despite the downregulation of rod determination genes *Nrl* and *Nr2e3* in *Rb1* null retinas, it is unclear whether Rb1 has any role in specifying the rod fate because its absence causes no S-cone increase, normally seen in *Nrl* and *Nr2e3* mutants [55] (see below).

Three types of photoreceptors, rod, S-cone, and M-cone, are specified from photoreceptor precursors during mouse retinogenesis. Humans are trichromatic with the additional L-cone. The specification of these photoreceptor subtypes relies on a complex network of TFs. Rorb, a retinoic acid receptor-related orphan nuclear receptor TF, acts directly upstream of Nrl, a basic leucine zipper TF, to specify the rod fate. Targeted inactivation of either gene caused a similar phenotype—conversion of rods into S-cones, while misexpressed Nrl was sufficient to promote the rod fate in photoreceptor precursors and partially rescue the *Rorb* mutant phenotype [56–58]. There is complete downregulation of *Nrl* expression in the absence of *Rorb* [58], and Rorb together with Otx2 and Crx directly binds to an *Nrl* enhancer to activate its expression [59, 60]. In the human, missense mutations in *NRL* are associated with autosomal dominant retinitis pigmentosa [61, 62]. Nrl functions to determine rods from precursor cells by activating numerous rod-specific genes as well as by suppressing cone-specific genes in part by directly regulating expression of the *Nr2e3* orphan nuclear receptor gene [56, 63].

Nr2e3 mutation in mice causes the *rd7* retinal degeneration characterized by the presence of hybrid photoreceptors and increased S-cones [64–67], and in humans it is associated with the enhanced S-cone syndrome [68, 69]. Nr2e3 is expressed exclusively in rods to repress the expression of cone-specific/enriched genes [66, 67, 70]. This gene repression program requires Nr2e3 association with and SUMOylation by Pias3, a transcription cofactor and E3 SUMO ligase [71]. Misexpressed Pias3 promoted rod differentiation in the developing retina whereas its reduced expression led to increased S-cone-like cells [71].

M-cone specification critically depends on the concerted action of Neurod1, TRβ2/Thrb (thyroid hormone receptor β2), and Rxrg/RXRγ (retinoid X receptor γ). Inactivating *Neurod1* or *Thrb* in mice caused a complete loss of M-cones and a concomitant increase of S-cones [72, 73]. The absence of *Rxrg* resulted in a similar S-cone increase but a normal pattern of M-opsin expression [74]. Neurod1 appears to directly activate *Thrb* expression to specify M-cones while Rxrg may form a heterodimer with TRβ2 to repress S-opsin expression in M-cones [73, 75]. During late retinogenesis, TRβ2 responds to the dorsal-high to ventral-low gradient of thyroid hormone to promote M-opsin expression while suppressing S-opsin expression in the dorsal retina [75]. TRβ2 and Rxrg specify M-cones by directly binding to the promoter of *Pias3* to selectively activate its expression in M-cones [76]. Pias3 overexpression promoted the M-cone fate at the expense of S-cones whereas its knockdown or SUMOylation-deficient mutant caused the opposite effect [76]. Interestingly, TRβ2 expressed from the *Nrl* locus is sufficient to specify M-cones in *Nrl* null background but not in the heterozygous background, indicating the presence of a common photoreceptor precursor as well as Nrl dominance in specifying the rod fate [77] (Fig. 2). Other TFs involved in M-cone development include Nr2f1/COUP-TFI and Nr2f2/COUP-TFII, two orphan nuclear receptors that are expressed in reciprocal dorsal-to-ventral gradients within the mouse retina and required for suppressing S-opsin expression in the dorsal region [78]. Their genetic ablation resulted in elevated S-cones in the dorsal retina [78].

Besides its role in rod fate commitment, Rorb is also involved in S-cone specification. In association with Crx, it binds directly to the S-opsin gene promoter to activate its expression, and in early postnatal *Rorb* null mutant retinas there is complete loss of S-cones [79]. However, in late postnatal *Rorb* null retinas, S-cones are greatly increased [58], suggesting the presence of additional TFs involved in S-cone development. Rora, another member of the ROR family, also participates in regulating S-opsin expression. Similar to Rorb, Rora binds to the S-opsin gene promoter and acts synergistically with Crx to activate S-opsin gene expression [80]. However, unlike Rorb, its inactivation led to reduced expression of both S- and M-opsins, indicating a role for Rora in differentiation of both S- and M-cones [80]. S-cone subtype specification also depends on the Sall3 zinc-finger TF. It could bind to the promoters of S-cone genes and activate their expression when ectopically expressed, whereas its deficiency caused loss of S-cones [81]. On the other hand, Nr2f1 is required to repress M-opsin expression in S-cones since its ablation caused increased number of M-cones in the ventral retina and eliminated the gradient of M-cone distribution [78].

Bipolar cells

Fate determination of bipolar cells depends on the synergistic activities of Vsx2 and bHLH TFs Ascl1/Mash1, Neurod4/Math3, Neurod1, and Neurog2/Ngn2 (Fig. 2). Loss of *Vsx2* function caused a blockage of bipolar cell specification and RPC proliferation accompanied by a RPC fate switch to photoreceptors and perhaps also Müller cells [82, 83]. *Vsx2* null mutations caused microphthalmia in both mice and humans [82, 84]. Misexpressed Vsx2 in postnatal RPCs promoted bipolar cell formation while inhibiting the photoreceptor fate, whereas its knockdown had the opposite effect [83]. Retinas deficient for both *Ascl1* and *Neurod4* lacked bipolar cells and displayed a fate change to Müller cells [85, 86]. Similarly, bipolar cells were missing and Müller cells increased in retinas deficient for *Neurog2*, *Neurod4*, and *Neurod1* even though bipolar cells were generated in retinas deficient for any two of them [32]. When Ascl1 or Neurod4 was co-expressed with Vsx2 in RPCs, they were able to promote the bipolar cell fate, but they lacked this activity on their own [85], indicating that commitment to a bipolar cell fate requires the combinatorial action of Vsx2 and Ascl1 or Neurod4 in RPCs.

Besides the essential roles of Otx2 and Crx in photoreceptor development, they are also cooperatively required for bipolar cell differentiation. There was a significant decrease of bipolar cells in $Otx2^{+/-}$; $Crx^{-/-}$ double mutant retinas but not in $Otx2^{+/-}$ or $Crx^{-/-}$ single mutant retinas; additionally, marker genes for bipolar cells were more severely downregulated in the double than the single mutants [49, 87]. Conditional ablation of *Otx2* also resulted in loss of mature bipolar cells [49]. Otx2 and Crx appear to control bipolar cell differentiation by directly binding to cis-regulatory sequences of *Vsx2* and other bipolar cell-specific genes to activate their expression [87]. The LIM-homeodomain protein Isl1 is another TF involved in bipolar cell differentiation. Its inactivation did not affect bipolar cell generation but caused loss of multiple bipolar subtypes and greatly reduced expression of Bhlhe23/Bhlhb4 and Vsx1, two TFs required for differentiation of rod and OFF-cone bipolar cells, respectively [88–90].

In the mouse retina, there exist one type of rod bipolar cells and at least nine types of morphologically and

physiologically distinct cone bipolar cells [91]. At present, little is known about how each of these subtype identities is specified and differentiated from the bipolar precursors. The bHLH TF Bhlhe23 is expressed by all developing rod bipolar cells, and its targeted deletion caused a near complete loss of these cells due to a failure in their terminal differentiation [92]. For cone bipolar cells, the Vsx1 homeodomain TF may be required for differentiation of all OFF-cone bipolar cells, as its inactivation led to diminished OFF-cone bipolar marker expression and disrupted photopic OFF responses [89, 90]. Acting in parallel with Vsx1, the Irx5 homeodomain TF controls the differentiation of Type 2 and 3 OFF-cone bipolar cells [89, 90, 93]. On the other hand, the bHLH TF Bhlhe22/Bhlhb5 functions upstream of Vsx1 to specify the Type 2 OFF-cone bipolar cells, as retinas deficient for *Bhlhe22* displayed a failure in their generation and decreased Vsx1 expression [94]. The Ebf (Ebf1–4) HLH TFs are also involved in specifying Type 2 OFF-cone bipolar cells. Their misexpression in RPCs promoted the differentiation of this cone bipolar subtype whereas their loss-of-function suppressed its differentiation [95].

Ganglion cells

The competence state for RGC generation has been shown to be conferred by the bHLH TF Atoh7/Math5 (Fig. 2). Atoh7 is transiently expressed in a subset of RPCs during or after their terminal cell cycle [96, 97]. Its mutation in the zebrafish *lakritz* mutant leads to a complete loss of RGCs, and in the human, deletion of the *ATOH7* remote enhancer causes optic nerve aplasia in the nonsyndromic congenital retinal nonattachment (NCRNA) disease [98, 99]. Targeted disruption of *Atoh7* in mice resulted in near complete loss of RGCs and overproduction of amacrine, cone, horizontal, and Müller cells [100–102]. Atoh7 is required only for conferring RPCs with the competence of RGC generation since genetically marked Atoh7-expressing RPCs are multipotential, being able to generate all major cell types present in the adult retina [96, 103]. That Atoh7 overexpression in mouse retinal progenitors/precursors did not favor the RGC fate or prolong RGC birth further demonstrated a permissive-only role for Atoh7 in RGC development [104]. By contrast, Atoh7 misexpression in *Xenopus* and chick RPCs was shown to promote the RGC fate and activate expression of the RGC differentiation TF Pou4f2/Brn3b or equivalent [105, 106], implicating a species difference. Atoh7 controls RGC competence in part by directly activating the expression of *Pou4f2* and *Isl1*, two homeobox TF genes involved in RGC specification and differentiation [107, 108]. In addition, gene expression profiling analysis has revealed that Atoh7-regulated genes include the two branches of genes controlled by Pou4f2 and Isl1 [108, 109].

The LIM-homeodomain TF Isl1 and POU-domain TF Pou4f2 appear to act in parallel to control RGC specification and differentiation. During mouse retinogenesis, they are co-expressed in migrating newborn RGCs as well as differentiated RGCs [107, 110]. Inactivating either *Pou4f2* or *Isl1* caused optic nerve hypoplasia, a loss of ~70 % of RGCs, delayed RGC axon growth, RGC axon guidance errors, and RGC nerve fiber defasciculation [107, 108, 110–115]. Distinct but redundant functions are implicated between Pou4f2 and Isl1 or other Pou4f TFs during RGC development because more severe RGC loss and axon growth defects were seen in *Pou4f2* and *Isl1* or *Pou4f3* double mutant mice [107, 116]. Correspondingly, Pou4f2 and Isl1 regulate overlapping but distinct groups of genes and they co-occupy the promoters of shared RGC genes [107, 108]. Similarly, despite RGC loss in both *Pou4f1* and *Pou4f2* conditional knockout mice, conditional ablation of *Pou4f1* changed dendritic morphology and stratification of RGCs whereas conditional inactivation of *Pou4f2* caused RGC transdifferentiation and central projection defects but no alteration in RGC dendritic stratification [117, 118].

Pou4f2 specifies RGCs from early retinal precursors not only by promoting RGC differentiation but also by inhibiting non-RGC differentiation programs. It suppresses the expression of TF genes involved in the specification and differentiation of amacrine, horizontal, and late-born ganglion cells, and correspondingly, *Pou4f2* inactivation results in overproduction of these cells [119]. On the other hand, Pou4f2 misexpression led to increased RGC differentiation but decreased non-RGC cell types [119, 120]. Gene expression profiling has revealed that Pou4f2 regulates a large set of genes involved in RGC development, among them the T-box TF gene *Eomes*, homeobox TF gene *Barhl2*, and HLH TF genes *Ebf1–4* [95, 119, 121–123]. The expression of *Eomes* and *Ebf3* is directly activated by Pou4f2 through the promoter or enhancer, although it remains to be determined whether this is also the case for *Barhl2* [95, 122]. Inactivation of *Eomes* or *Barhl2* caused a phenotype resembling that of *Pou4f2* mutants, which includes a 30 % decrease in RGC number and optic nerve size [122, 123]. Ebf factors appear to be necessary but insufficient for RGC differentiation as a dominant-negative form of Ebf suppressed RGC formation whereas the wild-type Ebf1 had no effect [95].

The Dlx1 and 2 homeodomain TFs are co-expressed with Pou4f2 in developing RGCs during retinal development and play a key role in the differentiation of late-born RGCs [124, 125]. Mice deficient for both *Dlx* genes exhibited a mild optic nerve hypoplasia, a loss of ~30–40 % of RGCs, and aberrant expression of the photoreceptor TF gene *Crx* in the RGC layer of the retina [125]. Late-born RGCs failed to generate, whereas there was essentially normal production of early-born RGCs in

the double mutant retina [125]. Neurod2, a bHLH TF expressed in a small population of RGCs [126] might be involved in RGC subtype specification. It induced RGC differentiation when misexpressed in postnatal RPCs [126].

Amacrine and horizontal cells

A common set of TFs including the forkhead/winged-helix TF Foxn4 and bHLH TFs Neurod1, Neurod4, and Ptf1a are involved in the specification of both amacrine and horizontal cells, suggesting the presence of a possible intermediate amacrine and horizontal precursor at early stages of retinogenesis (Fig. 2). Inactivating *Foxn4* eliminated horizontal cells and caused loss of the majority of amacrine cells (Fig. 3a), whereas its overexpression strongly promoted amacrine cell differentiation and horizontal cell marker expression, indicating that Foxn4 is required by RPCs for amacrine and horizontal cell competence and specification [127, 128]. Foxn4 specifies RPCs into amacrine cells in part by activating the expression of *Neurod1*, *Neurod4*, and *Ptf1a* (Fig. 3c) [21, 127, 129]. Neurod1 and Neurod4 are redundantly required for determining the amacrine cell fate. In mice deficient for both *Neurod1* and *Neurod4*, a complete loss of amacrine cells was accompanied by a fate-switch of RPCs to RGCs and Müller cells [130], whereas amacrine cell differentiation was essentially normal in their single mutants [130, 131]. Ptf1a is independently required for specifying the amacrine cell fate, for its ablation resulted in near complete loss of amacrine cells with concomitant increase of RGCs [129, 132]. Although Neurod1 alone or in combination with Pax6 is able to promote amacrine cell differentiation [130, 131], Neurod4 alone lacks this activity and it is capable of doing so only in the presence of Pax6 [130]. Thus, Pax6 may be also involved in specifying amacrine cells apart from its key role in establishing the RPC multipotency.

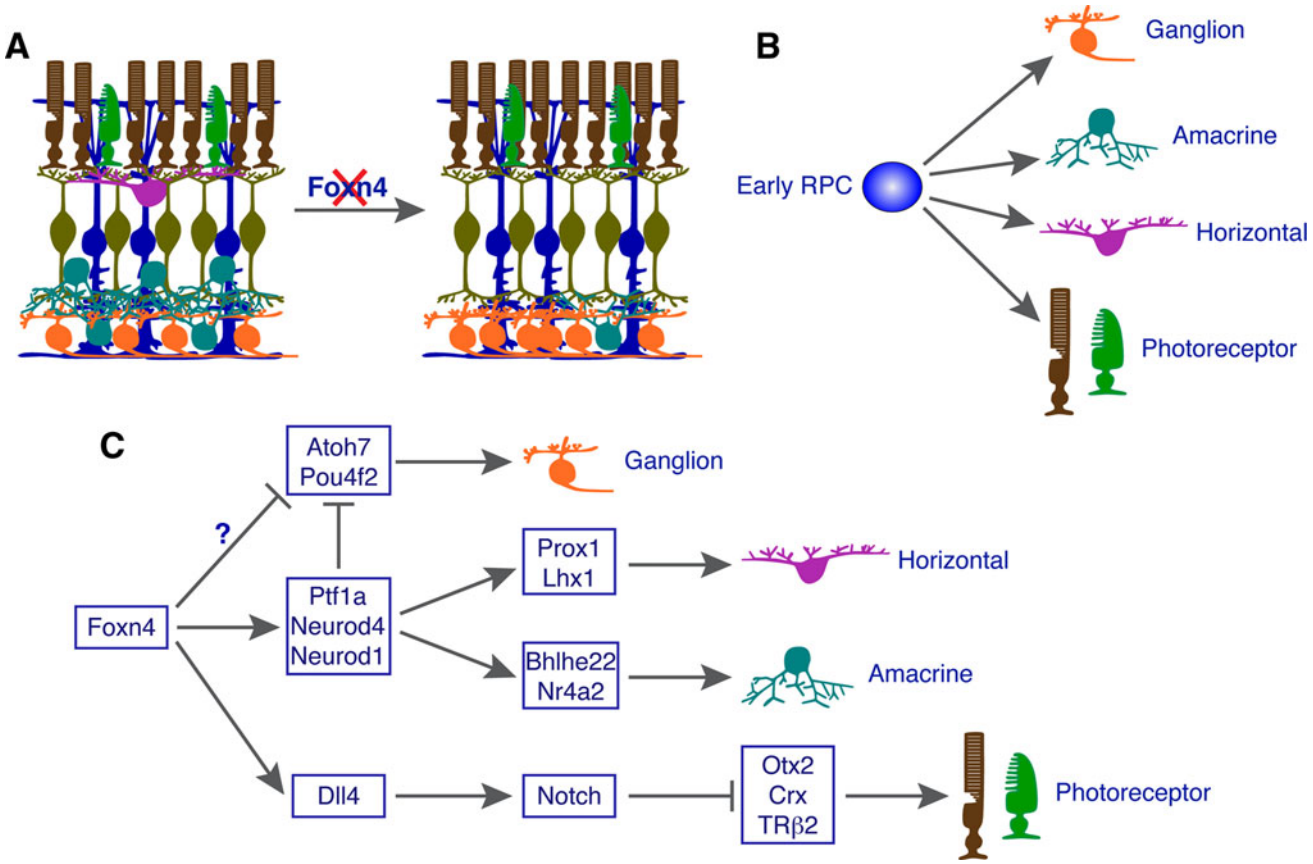

Fig. 3 Model by which Foxn4 promotes the amacrine and horizontal cell fates but suppresses the alternative photoreceptor and ganglion cell fates in early retinal progenitor cells (RPCs). **a** Schematic illustration of retinal phenotype in *Foxn4* null mutant mice. **b** Early RPCs are capable of generating ganglion, amacrine, horizontal, and photoreceptor cells. **c** Foxn4 specifies early RPCs into amacrine and horizontal cells by activating the expression of Ptf1a, Neurod1, and Neurod4, three bHLH transcription factors (TFs) involved in the specification of these two cell types. Meanwhile, Foxn4 may simultaneously suppress the ganglion fate also by activating the expression of these three bHLH factors due to their activity to repress the expression of Atoh7 and Pou4f2. Another possibility is that Foxn4 may directly repress Atoh7 and Pou4f2 expression. Foxn4 suppresses photoreceptor fates by directly activating Dll4-Notch signaling which in turn represses the expression of Otx2, Crx, TRβ2, and perhaps other TFs involved in photoreceptor fate determination and differentiation

During mouse retinogenesis, early RPCs give rise to several cell types including ganglion, amacrine, horizontal, cone, and rod cells (Fig. 3b). Foxn4 appears to select the amacrine and horizontal cell fates from early RPCs, not only by promoting these two fates but also by suppressing alternative fates available to the multipotent RPCs. Foxn4 normally inhibits the photoreceptor fate and thus there is a significant increase of photoreceptors and *Crx* expression in *Foxn4* null retinas (Fig. 3a) [127]. Our group has shown by expression profiling and in situ hybridization analyses that *Dll4* expression dramatically decreased in the absence of *Foxn4* and that its overexpression greatly induced *Dll4* expression in retinal explants [21]. Foxn4 colocalizes with Dll4 in RPCs and can directly bind to a *Dll4* enhancer to activate gene expression. Conditional ablation of *Dll4* significantly increased photoreceptors and photoreceptor marker gene expression despite the reduction of other non-photoreceptor cell types [21]. Thus, Foxn4 appears to suppress photoreceptor fates in early RPCs by directly activating Dll4-Notch signaling (Fig. 3c). Similarly, microarray profiling and in situ hybridization analyses have demonstrated that Neurod1, Neurod4, and Ptf1a all depend on Foxn4 for their expression, and that these bHLH TFs all have the activity to suppress RGC generation and *Atoh7* and *Pou4f2* expression [21, 127, 129, 130, 132]. Thus, Foxn4 may limit the competence of early RPCs to generate RGCs by directly and/or indirectly activating the expression of *Ptf1a*, *Neurod1*, and *Neurod4* (Fig. 3c). It is unclear whether Foxn4 directly represses *Atoh7* and *Pou4f2* expression to inhibit the RGC fate (Fig. 3c).

Amacrine cells constitute the most diversified retinal cell class that contains at least 28 subtypes with characteristic morphologies, sublaminar positions, physiological properties, and functions [3, 133, 134]. Based on the neurotransmitters used, they can be grouped into two major subtypes, GABAergic and glycinergic, and a small subtype named nGnG (non-GABAergic non-glycinergic) [135, 136]. Barhl2 is involved in specifying subpopulations of both GABAergic and glycinergic amacrine cells since its inactivation resulted in significant loss of both subtypes and its overexpression elevated glycinergic amacrine cell production [123, 137]. Bhlhb22 and the orphan nuclear receptor Nr4a2 are specifically required for specifying subsets of GABAergic amacrine cells that include the dopaminergic neurons, and misexpressed Nr4a2 was capable of promoting their formation [94, 138]. In addition, overexpression and knockdown experiments have implicated a role for Sox2 in specifying GABAergic neurons [139]. The cholinergic amacrine cells, which comprise a subset of GABAergic neurons, depend on Isl1 for their specification as the absence of *Isl1* caused near complete loss of them [88]. For glycinergic amacrine cells, Ebf TFs were able to promote the non-AII glycinergic amacrine cell fate whereas their dominant-negative form or knockdown had the opposite effect [95]. By contrast, Neurod2 is required for specifying a subset of AII cells and its misexpression promoted the glycinergic amacrine cell fate [126]. Additionally, Pax6 may have a specific role in specifying glycinergic amacrine cells such that its ablation led to near complete loss of this subtype [31].

The identity of nGnG amacrine cells is specified by Neurod6 and the special AT-rich sequence binding protein Satb2. These two TFs were found to be selectively expressed in nGnG amacrine cells by sorting transgenically marked nGnG neurons followed by inventorying and comparing the genes they expressed by microarray profiling [136]. Loss of *Neurod6* function caused a fate change from nGnG to glycinergic amacrine cells, whereas its misexpression led to increased generation of nGnG amacrine cells [136]. Acting upstream of Neurod6, Satb2 promotes *Neurod6* expression as well as the nGnG cell fate [136].

As aforementioned, Foxn4 is required for the competence and genesis of horizontal cells as retinas deficient for *Foxn4* failed to generate any of these cells [127]. It fulfills this function in part by activating the expression of *Ptf1a*, *Prox1*, *Neurod1*, *Neurod4*, and *Neurog2* (Fig. 3c) [21, 127, 129]. Ptf1a plays an essential role in specifying horizontal cells such that its absence in mice abolished these cells [129, 132]. Acting downstream of Ptf1a, the homeodomain TF Prox1 also functions to determine the horizontal cell fate (Fig. 3c) [140]. Its inactivation caused near complete loss of horizontal cells accompanied by a fate-switch to rod and Müller cells, while its overexpression strongly promoted the horizontal cell fate [140]. Neurod1, Neurod4, and Neurog2 appear to act redundantly with each other and in parallel with Ptf1a to specify horizontal cells [32, 129, 132]. Their triple mutants lacked horizontal cells whereas these cells were generated in all double mutants between them [32]. The LIM homeodomain TF Lhx1/Lim1 acts downstream of Ptf1a to control the migration and laminar position of horizontal cells (Fig. 3c) [141]. Lhx1 is found to depend on Sall3 for the maintenance of its expression, therefore inactivating *Lhx1* or *Sall3* resulted in similar mutant phenotypes including inner displacement of horizontal cells and reduced expression of mature horizontal cell markers [81, 141, 142]. Consistent with a role in horizontal cell differentiation, Sall3 overexpression could only induce a partial horizontal phenotype but was unable to specify the horizontal cell fate [81, 142].

Müller cells

It has been shown that committing RPCs to Müller glial cells involves the closely related bHLH transcriptional

repressors Hes1, Hes5, and Hey2/Hesr2 as well as the homeodomain TF Rax (Fig. 2). Hes1, Hes5, and Hey2 are all expressed early in RPCs but later restricted to Müller cells, and their overexpression strongly promoted the Müller cell fate at the expense of neurons [18, 143, 144]. Conversely, *Hes5* inactivation resulted in decreased generation of Müller cells [143]. Rax and the HMG-box TFs Sox2, Sox8, and Sox9 are expressed in a spatiotemporal pattern closely resembling that of the Hes TFs during retinogenesis [18, 139, 145, 146]. Similar to the Hes TFs, Rax potently promotes the Müller cell fate and does so in part by directly activating *Hes1* expression [18]. Sox9 is required for Müller cell differentiation as its conditional ablation and knockdown led to loss of Müller cell marker expression [145, 146]. Similarly, Sox8 knockdown resulted in diminished Müller cell differentiation [146]. Sox8 and 9 appear to mediate Notch-dependent Müller cell development as their expression could be upregulated by activated Notch but downregulated by a Notch inhibitor [18, 146]. They are insufficient to specify Müller cells since overexpression of either TF failed to promote this cell fate [146]. By contrast, Sox2 might play a role in Müller cell specification because its misexpression in postnatal RPCs promoted the Müller and amacrine cell fates at the expense of rod cells [139].

Non-coding RNAs in retinal cell development

Apart from TFs, evidence has been accumulating to implicate non-coding RNAs (ncRNAs) as a group of important intrinsic regulators for retinal cell development. MicroRNAs (miRNAs) are single-stranded 19- to 25-nt small ncRNA molecules processed from larger pri-miRNAs by the Drosha and Dicer double-stranded RNA endonucleases. As part of the RNA-induced silencing complex, they pair with target sites located primarily within the 3′ untranslated region of mRNAs to suppress gene expression by inhibiting translation or inducing RNA degradation [147, 148]. miRNA profiling and in situ hybridization analyses have shown that numerous miRNAs are expressed in the mammalian retina during development and at the adult stage in overlapping and distinct patterns [149–152]. A collective role for miRNAs in retinal development has been demonstrated by conditional ablation of *Dicer* in RPCs [153, 154]. *Dicer* inactivation caused selective loss of miRNAs, increased and prolonged production of early-born cell types such as RGCs, a failure to express late RPC markers including Sox9 and Ascl1, and a failure to generate late-born cell types including rod and Müller cells [153, 154]. These results indicate that loss of *Dicer* function traps RPCs at an early competence state and that miRNAs are collectively required for RPCs to make a proper transition from the early to late competence state. Although *Dicer* ablation resulted in diminished Notch and Hedgehog signaling [154, 155], transgenic expression of the Notch intracellular domain (NICD) failed to rescue major *Dicer* mutant phenotypes [155], suggesting a minor role for Notch signaling in mediating miRNA function in retinal development.

miRNAs are additionally required for patterning the distal optic cup and maintaining long-term survival of retinal cells. The presence of a mixture of neuronal and non-neuronal progenitors in the distal retina of *Dicer* mutants suggests that miRNAs may have a role in partitioning or maintaining the retina–ciliary body boundary [154]. A function for miRNAs in retinal maintenance has been implicated by the observed progressive degeneration of retinal cells resulting from *Dicer* inactivation and further confirmed by *miR-124a* ablation [153, 156, 157]. The absence of *miR-124a* caused mislocalization of M- and S-cones and their degeneration by apoptosis, a phenotype that could be rescued by transgenic expression of *miR-124a* [157]. *miR-124a* is required for preventing cone dislocation and degeneration by targeting *Lhx2* mRNA to inhibit its translation [157]. Downregulation of Lhx2 is necessary for cone survival because its overexpression caused cone apoptosis whereas its knockdown partially rescued cone loss in *miR-124a*-deficient retinas [157].

The long non-coding RNAs (lncRNAs) comprise another large class of ncRNAs whose functions are largely unknown but are currently being actively explored [158, 159]. *Tug1* (taurine upregulated gene 1), which was identified in a microarray screen for genes induced by taurine in cultured retinal cells, is the first lncRNA known to play a key role in mammalian retinal development [160]. Its knockdown in RPCs caused decreased rods and missing or shortened outer and inner segments, accompanied by reduced Otx2 and Crx expression but increased cones and apoptosis [160], suggesting a crucial role for *Tug1* in rod fate determination, differentiation, and survival. Both knockdown of another lncRNA *RNCR2/Miat* and overexpression of its dominant-negative form in RPCs promoted the differentiation of amacrine and Müller cells at the expense of photoreceptors [161]. It is therefore likely that *RNCR2* may be normally required for specification of the photoreceptor fate but inhibiting the amacrine and glia fates. The mechanism of how *Tug1* and *RNCR2* control photoreceptor development remains to be determined.

Many lncRNAs are transcribed in opposite orientation of a protein-coding gene and often overlap with the promoter but not the transcribed region of the coding gene. Over one-third of retina-expressed TFs are associated with these opposite-strand transcripts (OSTs) [158, 162]. *Six3OS* represents such a lncRNA which appears to genetically interact with Six3 in a complex manner to control retinal cell development [163]. Six3 when

overexpressed in postnatal RPCs led to increased amacrine cells and diminished bipolar cells, but co-expression with *Six3OS* was able to rescue this phenotype [163]. Knockdown of either *Six3OS* or *Six3* increased Müller cells at the expense of bipolar cells, but simultaneous knockdown of both rescued this phenotype while reducing amacrine cells [163]. Additionally, Six3 overexpression was able to rescue the phenotype of *Six3OS* knockdown whereas the opposite was not true [163]. Interestingly, *Six3OS* does not appear to exert its retinal developmental function by regulating *Six3* expression. Instead, it was found to directly interact with Ezh2, SMARCE1, and Eya family members, suggesting a possibility that *Six3OS* may act as a molecular scaffold to recruit chromatin remodeling factors and TFs [163].

Future perspectives

Rapid advances made over the past two decades have uncovered a complex mechanism of retinal cell specification and differentiation. Molecular genetic studies coupled with bioinformatic approaches have yielded a wealth of information about TFs and cofactors as intrinsic regulators leading to the establishment of RPC multipotency and eventual differentiation of various retinal cell types and subtypes (Fig. 2). These powerful approaches are continuing to reveal the regulatory gene networks in which these TFs participate as well as new classes of intrinsic factors for retinal cell development such as ncRNAs. Despite the tremendous progress, however, there are still numerous questions that remain to be answered. For instance, how do TFs and signaling molecules interact and cooperate at cellular and transcriptional levels to establish RPC competence and drive RPC differentiation? What TFs are responsible for specifying the numerous subtypes of amacrine cells and RGCs? What miRNAs are involved in modulating RPC competence and what is the regulatory relationship between them and the TFs in this process? Are there any lncRNAs involved in RPC competence and how do they interact with TFs at the molecular level to control retinal cell fate and differentiation? Progress in these and other areas promises to yield many more exciting findings in the near future.

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