Photoreceptors are highly specialized primary sensory neurons that sense light and initiate vision. This critical role is well demonstrated by the fact that visual impairment accompanies photoreceptor loss or dysfunction in many human diseases. With the remarkable advances in stem cell research, one therapeutic approach is to use stem cells to generate photoreceptors and then engraft them into diseased eyes. Knowledge of the molecular mechanisms that control photoreceptor genesis during normal development can greatly aid in the production of photoreceptor cells for this approach. This article will discuss advances in our understanding of the molecular mechanisms that regulate photoreceptor fate determination during development. Recent lineage studies have shown that there are distinct retinal progenitor cells (RPCs) that produce specific combinations of daughter cell types, including photoreceptors and other types of retinal cells. Gene regulatory networks, in which transcription factors interact via cis-regulatory DNA elements, have been discovered that operate within distinct RPCs, and/or newly postmitotic cells, to direct the choice of photoreceptor fate.

Keywords: photoreceptor fate determination, retinal development, gene regulatory network, transcription factors, cell lineages

The vertebrate retina is a highly evolved organ that captures and processes visual information within the eye, and delivers the resultant signals to the brain. More than 60 retinal cell types interact within circuits that transform the information conveyed by light, processing it to extract features of relevance to an organism, and then delivering that information to the brain. Among these, photoreceptor cells carry out phototransduction to initiate the process of vision. Unfortunately, photoreceptors are relatively vulnerable to environmental perturbations and genetic insults, possibly due to their high metabolic activity and delicate structure. In many human retinal diseases, such as retinitis pigmentosa and macular degeneration, visual impairment is due to photoreceptor loss or dysfunction. Recent lineage studies have shown that there are distinct retinal progenitor cells (RPCs) that produce specific combinations of daughter cell types, including photoreceptors and other types of retinal cells. Gene regulatory networks, in which transcription factors interact via cis-regulatory DNA elements, have been discovered that operate within distinct RPCs, and/or newly postmitotic cells, to direct the choice of photoreceptor fate.

Distinct RPCs Produce Rod or Cone Photoreceptors

All retinal cells, including photoreceptors, are derived from RPCs. A longstanding question in this field is whether RPCs differ in terms of their ability to produce specific types of retinal cells, as has been discussed in a recent review. Lineage studies have shown that the descendants of single RPCs, that is, clones, often comprise many retinal cell types, indicating that RPCs can be multipotent. In the mouse and rat, which have a conserved temporal order, along with other cell types in the retina. In most species, cones are born before rods, but there can be overlap in their birthdates. In mice, the production of cones starts at around embryonic day 10 (E10), peaks at E14, and finishes before birth at E18. Rods are born over a longer period of time during development, starting at around E15, reaching a peak at birth, and continuing until postnatal day 7 (P7). At different developmental stages, different numbers of rods and cones are generated. The number of newborn cells fated to be rods exceeds that of cones quickly after the start of rod genesis; and by E14, there are more cells fated to be rods than there are cells fated to be cones. Upon completion of development, rods comprise approximately 70% of all cells in the mature retina, while cones comprise approximately 2%. These studies lay the groundwork for understanding rod and cone fate determination, and suggest that different molecular mechanisms may control photoreceptor fate decisions at distinct developmental stages. One aspect of the mechanisms used is the role played by retinal progenitor cells (RPCs), the mitotic cells that produce retinal cells. These cells, and/or their newly postmitotic progeny, are the cells in which cell fate decisions are made. It is thus important to consider the nature of RPCs at different stages, as well as the gene regulatory networks (GRNs) that operate within them and/or their newly postmitotic progeny at different developmental stages. Recent advances that define these aspects of photoreceptor determination will be presented here.
indicate that some NPCs are committed to produce only photoreceptors whereas other NPCs are multipotent. Recent studies have probed this question by using molecular markers that distinguish among NPCs, and then tracking the type of progeny that such NPCs make. The results from these studies provide strong evidence for intrinsic differences between those NPCs that produce rods and those that produce cones.

Single-cell expression profiling of NPCs has been carried out using microarrays to probe whether NPCs differ from each other.13 These data showed many differences among NPCs across development, as well as at a single time in development. One gene that varied was the bHLH gene, *Olig2*, which showed variation in expression among NPCs across time, and at one time. Hafler et al.14 followed the cell types produced by *Olig2*-expressing NPCs, and showed that they were terminally dividing and produced specific pairs of neurons at different developmental stages in mice. When the daughters of E13.5 to E14.5 *Olig2*-expressing NPCs were clonally labeled by retroviral infection, only cones and horizontal cells were marked. When day P0 or P3 *Olig2*-expressing NPCs were marked by viral infection, only rods and amacrine cells were labeled. The *Olig2*-minus NPCs made clones comprising rods and bipolar cells, as well as rods and Müller glial cells (Fig. 1A). Interestingly, though *Olig2*-expressing NPCs clearly can make both rods and cones, the *Olig2*-derived clones never comprised both rods and cones, even at E13.5 to E14.5, when the birthdates for rods and cones overlap.

A study in zebrafish tracked the progeny of NPCs that expressed a reporter for a cone marker, *Thrb* (also known as *Nr1a2*), by live imaging.15 These *Thrb*-expressing NPCs produced predominantly long (L) cones in terminal divisions. In addition to these terminal divisions, a few *Thrb*-expressing NPCs produced 4-cell clones. One such clone comprised 2 L cones and 2 horizontal cells, each made by symmetrical terminal divisions. Additional types of divisions were observed as well, but no clones of rods and cones were observed (Fig. 1B). The authors also examined the *Crx*-expressing NPCs by using a reporter based upon *Crx*, which is expressed in NPCs, rods, cones, and bipolar cells.16 *Crx*-expressing NPCs also showed homotypic patterns from terminal divisions, producing pairs of cones expressing the same opsin type (i.e., the
Regulates the expression of Vsx2 negatively regulates and induce expression of Blimp1 through at least two enhancers.\cite{9,54,55} Newly postmitotic cells made by any of these RPCs are likely to require additional steps to determine their fates; for example, they need to escape Notch signaling and set the proper level of Otx2. Additional genes expressed by the RPCs and/or newly postmitotic cells that are also important in induction, or repression, of the rod and cone fate are Rax, Pax6, Blimp1, RORγ, Vsx2, and multiple bHLH genes. (B) GRN that regulates the binary fate choice of rod versus bipolar cell. As cells exit mitosis, Otx2 and RORγ are expressed and induce expression of Blimp1 through the B108 enhancer.\cite{39} During and after cell cycle exit, Blimp1 levels rise, whereupon Blimp1 negatively regulates the expression of Otx2 through the ECR2 enhancer\cite{9} as well as its own expression. through a Blimp1 3' UTR element.\cite{59} Blimp1 also negatively regulates Vsx2 through at least two enhancers.\cite{57,54,55} Otx2 primes expression of Vsx2\cite{58,59} and Notch represses, directly or indirectly, the level of Blimp1.\cite{20,56} Cells that have low Otx2 and no (or low) expression of Otx2 and Vsx2 achieve the rod fate, whereas those with high Otx2 and Vsx2 achieve the bipolar fate. The mRNA levels of Otx2 and Blimp1 are dynamic throughout this period via feedforward and feedback regulation. Part (B) reprinted with permission from Wang S, Sengel C, Emerson MM, Cepko CL. A gene regulatory network controls the binary fate decision of rod and bipolar cells in the vertebrate retina. Dev Cell. 2014;30:513–527. Copyright 2014 Elsevier, Inc.

**FIGURE 2.** Models for photoreceptor fate determination. (A) A model for rod versus cone development wherein distinct RPCs produce cones and rods.\cite{14,44} RPCs that express Olig2, Otx2, and Oc1 are present in the early retina. Both Otx1 and Otx2 are required for expression of the early cone marker, Thrb, and to produce cones. These early RPCs also can produce horizontal cells, which upregulate Otx1, while cones downregulate Otx1. Rods are produced by RPCs that express Olig2 and Otx2, but not Otx1. The newly postmitotic cells are modeled to be distinct from the point of genesis from those made by the Otx1-expressing RPC. Newly postmitotic cells made by any of these RPCs are likely to require additional steps to determine their fates; for example, they need to escape Notch signaling and set the proper level of Otx2. Additional genes expressed by the RPCs and/or newly postmitotic cells that are also important in induction, or repression, of the rod and cone fate are Rax, Pax6, Blimp1, RORγ, Vsx2, and multiple bHLH genes. (B) GRN that regulates the binary fate choice of rod versus bipolar cell. As cells exit mitosis, Otx2 and RORγ are expressed and induce expression of Blimp1 through the B108 enhancer.\cite{39} During and after cell cycle exit, Blimp1 levels rise, whereupon Blimp1 negatively regulates the expression of Otx2 through the ECR2 enhancer\cite{9} as well as its own expression. through a Blimp1 3' UTR element.\cite{59} Blimp1 also negatively regulates Vsx2 through at least two enhancers.\cite{57,54,55} Otx2 primes expression of Vsx2\cite{58,59} and Notch represses, directly or indirectly, the level of Blimp1.\cite{20,56} Cells that have low Otx2 and no (or low) expression of Otx2 and Vsx2 achieve the rod fate, whereas those with high Otx2 and Vsx2 achieve the bipolar fate. The mRNA levels of Otx2 and Blimp1 are dynamic throughout this period via feedforward and feedback regulation. Part (B) reprinted with permission from Wang S, Sengel C, Emerson MM, Cepko CL. A gene regulatory network controls the binary fate decision of rod and bipolar cells in the vertebrate retina. Dev Cell. 2014;30:513–527. Copyright 2014 Elsevier, Inc.

Medium [M], short [S], long [L], or ultraviolet [UV] cone opsins (Fig. 1C).

Both of these studies suggest that there are distinct types of terminally dividing RPCs that produce rods or cones. Further examination of the heterogeneity of RPCs and characterization of their lineage history will be needed to fully understand the lineage trees that result in these terminally dividing cells.

**GRNs INVOLVED IN CONE OR ROD GENESIS**

The lineage experiments described above suggest that the decision to be a photoreceptor, that is, the determination event, occurs in terminally dividing cells and/or their newly postmitotic progeny, and may occur over a period of several days. Many genes have been shown to be involved in photoreceptor fate determination, including Notch1.\cite{17,22} Rax,\cite{23,26} Otx2,\cite{27,29} bHLH genes,\cite{30–35} Vsx2,\cite{40–42} Foxn4,\cite{45} and Otx1.\cite{44} Loss of function of these genes leads to a reduction in the number of photoreceptors, with a concomitant increase in one or more other cell types. Given that multiple genes are involved in the fate determination events, it is likely that GRNs are at work in the retina to effect the timely production of the correct number of each type of photoreceptor. Recent studies have started to dissect how transcription factors (TFs) interact within GRNs in distinct RPCs to control rod and cone photoreceptor fate determination.

As in zebrafish, Thrb is an early marker of cones in mice and chicks.\cite{45} Through discovery of an enhancer that regulates Thrb in these species, along with the cognate TFs that regulate the enhancer, a TF that is important for cone determination, Onecut 1 (Oc1), was discovered.\cite{44} An understanding of the role of Oc1 has aided in the definition of a GRN for cones versus rods. Otx2, which was previously shown to be important for rod and cone genesis,\cite{27} and Oc1 were shown to combinatorially regulate the Thrb gene via direct binding to the ThrbCRM1 enhancer, which is active in an RPC that generates horizontal cells and photoreceptors. Oc1 was found to be expressed in chick and mouse RPCs during the period when cones are generated, but not in the postnatal mouse retina, when only rods, and not cones, are produced (Fig. 2A). Misexpression of Oc1 in the postnatal mouse retina, where Otx2 is expressed, induced the formation of immature cones, along with horizontal cells. This induction was dependent upon Otx2, as removal of a conditional allele of Otx2 prevented this induction. These data suggest that Otx2 and Oc1 together promote the fates of cones and horizontal cells. A model for Oc1 and Otx2 action in the retina was also proposed.\cite{44} The CRM1-active RPCs divide to give rise to cones and horizontal cells. In cone precursor cells, the level of Oc1 declines and Otx2 is maintained, while in horizontal cell precursors, the level of Otx2 increases and Otx2 decreases. More interestingly, Oc1 probably plays an important role in cone versus rod fate determination, as the repression of Oc1 led to increased rod genesis. Specifically, electroporation of the chick retina with a construct in which a transcriptional repressor domain was fused to Oc1 led to a reduction in Thrb expression. This construct also led to an upregulation of MafA,
the chick homologue of Nrl, a key gene in rod differentiation. The Ocl-repressor domain fusion also led to premature expression of rhodopsin, in keeping with an increase in the production of rods. Moreover, in Ocl knockout mice, a reduction in Thrb mRNA and an upregulation in Nrl mRNA were seen. These data all point to a role of the Ocl gene (and possibly Ocx2, which has high homology to Ocl) in regulating the cone versus rod fate decision. In summary, this study indicates that coexpression of Otx2 and Ocl may be able to drive early events in cone genesis, leading to cone induction from stem cells.

A GRN that controls the binary fate decision between rod photoreceptor and bipolar cells in postnatal RPCs has also been recently discovered. At postnatal stages in the mouse retina, several TF genes were known to regulate the rod versus bipolar fate choice, including Notch1,17,20 Otx2,28 RORβ,36,37 Vsx2 (Otx10),40 and Blimp1.36,37 Otx2 has been strongly implicated to be a direct regulator of Vsx256,49 and Vsx2 to be a direct target of Blimp1.37 As Blimp1 could be considered as a node in this GRN, the enhancer(s) that regulates Blimp1 in the postnatal mouse retina was of interest. An enhancer for Blimp1 of only 108 base pairs (B108) was identified. The new method of Cas9-genome editing was used to delete B108 from the mouse genome in vivo using electroporation. B108 deletion recapitulated the retinal loss of function phenotype for Blimp1, thereby establishing that B108 is required for Blimp1 activity in the retina. Feedforward and feedback interactions were then worked out using electroporation of enhancer constructs for Otx250 and Blimp1, as well as gain and loss of function experiments for other TFs of this GRN. Quantification of mRNA levels for some of the genes in the network was accomplished using the single-molecule fluorescent in situ hybridization method of Raj and van Oudenaarden.51 These studies revealed that the critical output of this GRN is the level of expression of Otx2 and Vsx2 (Fig. 2B). High Otx2 and no (or low) Vsx2 are required for the rod fate, whereas high Otx2 and Vsx2 are required for the bipolar fate.

These studies provide examples of GRNs that drive photoreceptor fate determination and highlight the complexity of such networks, showing both feedforward and feedback loops of regulation. They also underscore the complexity of interactions that will need to be teased apart for an understanding of cell fate decisions in complex tissues, as well as the need to use quantitative assays for gene expression levels, given that the levels of these TFs are critical in directing the fate choice.

SUMMARY AND FUTURE ISSUES

Work over the last several years has greatly contributed to our understanding of the fate determination of rods and cones. Rather than rods and cones being produced as a generic type of photoreceptor, that later chooses to be a rod or a cone, it appears that each type of photoreceptor is produced as a rod or a cone by its RPC. Distinct types of RPCs that are terminally dividing produce the different types of cones as homotypic pairs. There are likely many types of RPCs with different GRNs in operation that produce rods, in combination with different types of siblings in terminal divisions; for example, Olig2-expressing RPCs can produce a rod and an amacrine cell while Olig2-negative RPCs can produce a rod and a bipolar cell. These recent data raise several questions for future research as well as providing possibilities for stem cell therapies. First, the GRNs that dictate the formation of rods versus cones, and of different cone types, will need to be characterized. The determination events will need to be linked to regulatory events, for example, chromatin configuration and microRNAs (e.g., see Busskamp et al.52) that direct and/or maintain specific gene expression in differentiating cells. Second, the heterogeneity of RPCs needs to be further explored. The RPCs that are upstream of the terminally dividing RPCs that produce different types of daughter cells will need to be defined to determine if there are distinct lineages that include more than the terminally dividing RPCs. Third, the GRNs that control photoreceptor maturation and function will need to be uncovered to understand how these GRNs are dysregulated in retinal diseases.

By addressing these issues, we would gain a more comprehensive understanding of photoreceptor development, which can lead to novel strategies for the efficient generation of photoreceptor cells or precursors with better transplantation potential from stem cells. For example, it might be possible to label and enrich for distinct RPCs that are biased to produce cones or rods during directed differentiation of stem cells. We may also be able to monitor and manipulate the in vitro differentiation process in a stage- and cell type-specific manner by utilizing cis-regulatory elements that integrate regulatory information within GRNs.

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