Neurogenesis and Specification of Retinal Ganglion Cells

Kim Tuyen Nguyen-Ba-Charvet * and Alexandra Rebsam *

Institut de la Vision, Sorbonne Université, INSERM, CNRS, 17 rue Moreau, F-75012 Paris, France
* Correspondence: kim.charvet@inserm.fr (K.T.N.-B.-C.); alexandra.rebsam@inserm.fr (A.R.)

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Abstract: Across all species, retinal ganglion cells (RGCs) are the first retinal neurons generated during development, followed by the other retinal cell types. How are retinal progenitor cells (RPCs) able to produce these cell types in a specific and timely order? Here, we will review the different models of retinal neurogenesis proposed over the last decades as well as the extrinsic and intrinsic factors controlling it. We will then focus on the molecular mechanisms, especially the cascade of transcription factors that regulate, more specifically, RGC fate. We will also comment on the recent discovery that the ciliary marginal zone is a new stem cell niche in mice contributing to retinal neurogenesis, especially to the generation of ipsilateral RGCs. Furthermore, RGCs are composed of many different subtypes that are anatomically, physiologically, functionally, and molecularly defined. We will summarize the different classifications of RGC subtypes and will recapitulate the specification of some of them and describe how a genetic disease such as albinism affects neurogenesis, resulting in profound visual deficits.

Keywords: retinogenesis; retinal progenitor cell; fate control; competence; stochastic; development; RGC subtype; albinism

1. Introduction

Retinal ganglion cells (RGCs) are the sole output neurons from the retina and thus integrate and transmit all visual information to the brain. How are these RGCs generated during development? We will first review the main sequences of retinal neurogenesis, and how multipotent retinal progenitor cells (RPCs) can generate the seven retinal cell types. These cells populate different layers. From the apical side of the eye, the outer nuclear layer (ONL) is composed of cone and rod photoreceptors. Then, the inner nuclear layer (INL) comprises the interneurons (bipolar, horizontal and amacrine cells, and Müller glial cells (MG)). Finally, The ganglion cell layer (GCL) contains RGCs. (Figure 1a). The histogenesis of the neural retina proceeds with RPCs within the germinial zone located at the apical surface near the retinal pigmented epithelium (RPE), giving rise progressively to all seven retinal cell types in appropriate proportions and a specific order corresponding to the layer order. We will discuss how extrinsic and intrinsic factors control this neurogenesis and their relative contribution. Furthermore, we will examine more in detail how the specific combination of transcription factors will determine the fate of RGCs. Strikingly, despite generic features, RGCs also acquire subtype-specific properties that are strictly related to particular functions. So far, in mice, 30 to 40 subtypes of RGCs have been characterized based on various criteria [1,2] that we will review here. While these RGC subtypes are at the basis of the multiple visual functions, the mechanisms underlying this diversity are still unclear, but we will discuss the few studies addressing the differentiation of selected RGC subtypes.
2. Timing of RGC Neurogenesis

All vertebrate retinal neurons are produced in a definite temporal order from a pool of multipotent progenitor cells (Figure 1b) [3–7]. The timing of retinal neurogenesis is an integral part of the differentiation. Rat RPCs, when isolated at E14, differentiate into RGCs, but form rods when isolated at P1 [8]. Later, Brzezinski et al. showed that RPCs could be divided into at least two categories: early RPCs that are Ngn2+ and give rise to RGCs, and late RPCs that are Ascl1+ and differentiate into the other types of retinal neurons [9]. In 1985, Young adapted birth dating data from earlier studies [10,11] to his results from tritiated-thymidine injection and produced the first differentiation time-course of mouse retinal neurons (Figure 1b) [12]. It showed that RGCs start to differentiate after E10 and that they represent 2.7% of the retinal cells, the most numerous one being rods (72.3%). In vertebrates, RGCs are always the first-born retinal neurons or amid the earliest. Moreover, they were often around the future localization of the optic nerve. For instance, in chick, the first RGCs were found around the optic nerve head at E2 [13], while in the zebrafish embryo, the first BrdU-positive postmitotic cells were detected at 28 h post-fertilization in the GCL of the ventronasal retina, next to the optic stalk [14]. In *Xenopus laevis*, similar tritiated-thymidine injection studies have situated the birthdate of RGCs between stages 24 and 29 [4,15]. In mice, cumulative labeling with BrdU injection and rhodamine-dextran tracing showed that the first RGCs appear between E11 and E12 [16]. Both in chick and mice, first-born RGCs initially form a small patch around the future optic nerve head in the central retina [13,16]. Thus, RGC differentiation starts in the central retina and then proceeds towards the periphery of the retina. Finally, in the rhesus monkey, RGC genesis begins at E30 and continue until E70 [17]. In the human and mouse early embryonic retina, transcriptomic results show exceptional analogy in the developmental stages, and human RGC neurogenesis starts at D52 [18].

![Figure 1. Layer distribution and genesis of the different retinal cell types.](image-url)
3. Extracellular Differentiation Signals

What are the triggers for the RPCs to switch from symmetric amplifying division to asymmetric division and differentiate into RGCs? After the initiation of neurogenesis, RPCs are thus confronted with two choices: to produce a post-mitotic neuron or to remain in cycle as a progenitor cell. The coordination of cell cycle exit and re-entry is essential, in order to ensure a balanced production of early versus late retinal cell types, but how are these events regulated?

Various studies in different species have pointed toward extracellular differentiation factors. For instance, in vitro, isolated early RPCs can develop into RGCs [8,20] or cones [21]. However, when a few early RPCs are mixed with postnatal RPCs in vitro, the young progenitors differentiate into rods instead of RGCs [22]. Moreover, signals from surrounding tissue control the spread of neuronal differentiation across the zebrafish retina [23].

Extrinsic factors can regulate RGC differentiation at two levels. They can provide feedback inhibition to control RPC cell fate. For instance, in vitro, rat amacrine cells influence RPC differentiation [24]. Besides, the presence of feedback signals controlling RGC number has also been shown in the frog [25]. Still, in vitro, E9 chick retinal cells inhibit RGCs differentiation of E4 retinal cells. This effect can be reversed by depleting the E9 retinal cells [26]. Ablating RGCs in vivo in the GCL at E4 in chick leads to an anachronic production of RGCs, rescued by exogenous nerve growth factor (NGF) [27]. Thus, it has been postulated that NGF, expressed in RGCs, was regulating the production of RGCs in chick, by signaling through the p75 receptor present on the young migrating RGCs [27,28]. Nevertheless, contrary to the chick, in mice, migrating RGCs expressed TrkA, while p75 is present in the GCL [29], advocating that the regulation of RGC number is different in birds and mammals. In vivo, Atoh7:GFP RPCs transplanted in the Lakritz zebrafish mutant (Atoh7^{−/−}) generate two RGCs instead of one when transplanted in a wild-type zebrafish, suggesting that the environment can somehow affect the regulation of RPC fate [30]. Hence, extrinsic factors must play a role in neurogenesis and RGC differentiation, and we will review the different extracellular molecules identified.

3.1. Notch

Notch is a multifunctional signaling pathway involved in numerous physiological and pathological processes during development and in adulthood [31]. In the developing retina, Notch signaling maintains neural progenitor cells by a lateral inhibition signal that eases progenitor cell growth and inhibits neuronal differentiation [32,33]. Two types of ligands have been described that bind to the Notch receptor, Delta-Deltalike, and Serrate-Jagged-Lag1 [34]. Ligand-receptor binding activates a sequence of proteolytic actions, that liberates the receptor intracellular domain to then build a multi-protein complex with Maml and Rbpj, which translocates to the nucleus and regulates gene expression [35]. Throughout retinal development, this Notch protein complex directly controls Hes1 and Hes5, two anti-proneural basic helix-loop-helix (bHLH) transcription factors (TFs) that block neurogenesis [36]. Three Delta-like genes are expressed in the retina, Dll1, Dll3 and Dll4 [37], but studies using conditional knock-out mice revealed that only Dll1 and Dll4 participate in retinal development [38,39]. Most importantly, loss of function for Notch pathway components, including Notch1 [40,41], Rbpj [42,43], Delta-like1 [38] and Hes1 [44], as well as pharmacological inhibition of Notch signaling leads to early cell cycle exit, amplified retinal neurogenesis, and a particular excess of RGCs. Conversely, misexpression of Hes1 or Notch blocks RPC differentiation [45–48]. Recently, Ha et al. suggested that part of the Notch signal comes from two different sources. Notch signaling from the RPE induces RPC proliferation, while the one from the GCL inhibits RGC differentiation [49]. Surprisingly, although the role of Notch signaling in the retina has been studied for more than two decades, the expression patterns of the different components of Notch signaling in the different retinal cells and their changes during development are still confusing [49–51]. Last but not least, it is noteworthy to mention that epigenetic mechanisms regulate retinal Notch signaling. In the zebrafish retina, the histone deacetylase and the Tets enzymes control the Notch pathway [52,53]. Moreover, Brm, an enzyme responsible for chromatin remodeling, has been shown to block Notch signaling [54].
3.2. Sonic Hedgehog

The hedgehog (Hh) family of morphogens encodes secreted proteins essential for cell fate decisions during embryogenesis and to maintain tissue homeostasis in most species. The first member of this family, Hh, was identified in drosophila [55], followed by its vertebrate orthologs Sonic Hh (Shh), Indian Hh and Desert Hh [56]. Hh proteins bind to Patched (Ptc) [57], which will trigger Smoothened (Smo) therefore inducing signal transduction [58,59]. The Hh signaling pathway is one of the main regulators of retinal development. It has been implicated in many steps from optic disk development [60] to proliferation [61], laminar organization [62] and RGC axon guidance [63]. Shh was found in RGCs in mice [61], zebrafish [64], frog [65] and chick [66]. Hh signaling from newly generated RGCs is one of the signals inducing RPC proliferation. When Shh is removed from RGCs, retinas are much smaller [60–62,67]. In mouse as well as in chick retina, the Shh pathway acts as a negative feedback controller of RGC neurogenesis. More precisely, Shh from young born RGCs regulates RGC differentiation within a normal period of retinogenesis [66,68].

Interestingly, the sonic-you (syu) mutant zebrafish, which has a deletion in the Shh gene, exhibit delayed photoreceptor and RGC differentiation [69,70]. Another study where Hh signaling was blocked showed that both cell cycle exit and RGC maturation were inhibited. The difference between mice and zebrafish may originate from the different sources of Shh. In mice, Shh is only secreted by RGCs, while in the zebrafish, Shh is also detected in the RPE [69]. An alternative explanation could be that the photoreceptor delay is secondary to the RGC differentiation defect [71].

3.3. Fibroblast Growth Factors

Much less is known about the role of fibroblast growth factor (FGF) in retinal neurogenesis. Nevertheless, several studies in different species showed that FGF signaling during retinogenesis contributes to RPC fate decisions. The first evidence came from the chick retina in vitro. When using a protein kinase inhibitor to block FGF signaling, RGC neurogenesis was delayed. Conversely, FGF1 but not FGF8 treatment stimulates RGC differentiation [72]. Overexpression of FGF2 in Xenopus RPCs led to a 35% increase in the number of RGCs [73]. In the chick and the zebrafish retina, different FGFs were involved. FGF8 activated retinal neurogenesis from the optic stalk. Moreover, both FGF3 and FGF8 regulate the secretion of Shh from RGCs [74]. It is then possible that these growth factors stimulate RPC cell cycle exit and differentiation into RGCs through Shh signaling [64,74,75].

In conclusion, these studies exploring the role of extrinsic factors in RGC neurogenesis clearly show that these molecules are essential to regulate retinal cell differentiation. Nevertheless, the mechanism at stake is likely different between fish, birds and mammals.

4. Competence and Stochastic Model of Retinal Cell Fate

Three decades ago, retinal lineage analysis in several species, revealed that early RPCs were able to give rise to clones containing highly variable cell types and were thus multipotent [3–6]. However, clones at early time points are usually larger than later ones, [3,4] and late RPCs in rodents mainly generated a restricted number of retinal cell types [3]. For instance, very few RGCs are produced after P0 [3,6]. At that period, the “competence model” [76] suggested that early RPCs were able to give rise to all retinal cell types, then over time, RPCs were going through a deterministic cascade of competence state, changing the ability of RPCs to produce certain retinal cell types as in drosophila neuroepithelial cells [77].

What could trigger this temporal control of cell fate? One possibility is that extrinsic signals from the environment could modulate this competence. However, graft experiments showed that early RPCs maintain their multipotency even in older environments [24,78,79]. Furthermore, in vitro explants of RPCs taken at different time points recapitulate the size and composition of temporally similar clones in vivo [80]. Thus, it is more likely that intrinsic mechanisms regulate the competence of RPCs and the future fate of their progeny. Interestingly, when the progeny of RPC clones was studied
in detail both in vitro [80,81] and in vivo using time-lapse imaging [82], it revealed a large variety of clones in size and fate composition even at a given developmental time, illustrating a substantial variability in RPC division and competence. It became less evident to link a clear competence state of RPCs with a specific developmental time.

One possibility derived from mathematical models is that the proliferation and fate of RPCs could be partially stochastic [80]. In this model, individual RPCs are multipotent, but the probability that they produce an early retinal cell type (such as RGC) decreases over time, whereas the probability of producing late retinal cell types (such as rod photoreceptor) increases over time. Furthermore, their type of division could also be probabilistic. Initially, there is a high probability for proliferative division (to divide symmetrically, generating two progenitors), then, a higher probability for asymmetric division (generating one progenitor and one differentiated cell). Later on, differentiative divisions of RPCs will likely give rise to two differentiated cells (similar or different). In this model, there is still a slight probability of generating two differentiated cells at early stages and two progenitors at late stages, accounting for lineage analysis experimental data observed [80,82]. Furthermore, the general order of cell birth is not conserved within individual lineages. In some cases, for example, a bipolar cell was generated before an amacrine cell within the same clone. Also, Müller glia can be produced after rod photoreceptors in a few clones, suggesting that RPCs do not lose their neurogenic potential once they have generated a glial cell [80]. However, the fate determination of retinal cells is probably not purely stochastic as the frequency of some clonal composition is much higher than what would be expected (such as some same type pairs, or the fact that the sister cell of a RGC is often a RPC), suggesting that these stochastic events can be skewed in certain directions. This stochastic model, with changes in probabilities over time, considers the majority of cells produced but also experimentally observed oddities.

5. Factors Controlling the Competence of Progenitors

A perfect molecular candidate to control the changing states of competence or probability needs to be expressed in RPCs and to change over time. One such factor is Ikaros family zinc finger protein 1 (Ikzf1 or Ikaros), a vertebrate ortholog of hunchback in drosophila. Ikzf1 is expressed in early proliferative RPCs [83] (Figure 2), and its lineage was determined using ikzf1-cre mouse lines can label all retinal cell types (early and late) in an unbiased manner [84]. However, when ikzf1 is overexpressed, RPC production is biased toward early fates, and in \(^{ikzf1}\) mutant mice, fewer early-born cell types are produced [83]. Another factor, Casz1, is a vertebrate ortholog of drosophila temporal identity factor castor. Casz1 is expressed in mid/late stage RPCs in murine retina and controls the fate of these mid/late neurons [85]. Indeed, the conditional deletion of Casz1 in RPCs increases the production of early-born neurons at the expense of later-born ones [85]. However, no change in clonal size distribution was observed in loss or gain of function experiments suggesting that Casz1 alters RPC fate independently of proliferation or cell death [85].

Furthermore, the ectopic expression of Casz1 promotes the production of mid/late-born retinal neurons. Interestingly, casz1 is repressed by Ikzf1, similarly as in drosophila with castor and hunchback [85]. Thus, the same molecules are controlling temporal fate patterning in mouse retina and drosophila neuroblasts. However, only two homologs of the drosophila temporal fate transcription cascade have been characterized as temporal fate transcription factors (TFs) in mice. It remains to be seen whether other orthologs such as Krüppel or Pdm that are intermediate in the TF cascade in drosophila between Hunchback and Castor, are also part of the same gene regulatory network in mice retinogenesis [77]. One difference, though, is that in drosophila, the temporal fate patterning is completely deterministic while it is probabilistic in the mouse. Hence, other molecular players are likely at stake.
6. Intrinsic Control of RGC Specification

6.1. Transcription Factors

These competence-controlling factors could change the probability to express (or not) particular sets of genes that control the specification of the different retinal cell types. In this review, we will focus on the TFs that control the generation of retinal ganglion cells. Other sets of TFs are also controlling the generation of the other retinal cell types and are reviewed in [19,86,87]. All RPCs express during the early proliferative phase of retinal development, the TFs Pax6, Sox2 and Vsx2 (previously named Chx10) (Figure 2), that are important for their multipotent state and their self-renewal [88,89]. At this time Vsx2 inhibit the basic helix–loop–helix (bHLH) TF Atoh7 (formerly Ath5 or Math5 in mice) and Vsx1 [90]. Then, Vsx2 is downregulated in almost all RPCs and Atoh7 starts to be upregulated in RPCs that will become RGCs (Figure 2), as shown using lineage tracing in the zebrafish retina [90].

![Figure 2. Transcription factors participating in the specification of RGCs from early retinal progenitor cells (RPC) to committed progenitors that will later produce postmitotic RGCs.](image)

#### 6.1.1. Atoh7

Atoh7 is transiently expressed in the mouse retina starting at E11 [91] and is necessary for the generation of RGCs (Figure 2), but not sufficient on its own [92–94]. Loss of Atoh7 leads to an 80% reduction in RGCs in the mouse [92] and an increase in amacrine cells and cone photoreceptors [92,93]. In the zebrafish Atoh7 mutant (lakritz), there is an almost complete loss of RGCs [95]. Lineage analysis of Atoh7 expressing cells shows that Atoh7 cells give rise to multiple retinal cell types, including RGCs, amacrine, horizontal, and photoreceptor cells in mouse and zebrafish [30,96–98]. In the absence of Atoh7, early RPCs fail to exit the cell cycle and keep proliferating [94,97]. The expression of Atoh7 is spatiotemporally regulated by the competition or cooperation of different bHLH proteins such as Ngn2, Hes1, NeuroM and Atoh7 itself on evolutionarily conserved sequences of Atoh7 promoter [99].

#### 6.1.2. POU Domain, Class 4, Transcription Factors

Atoh7 is the main TF regulating the fate of RGCs, but several other TFs, downstream of Atoh7 are also crucial for the specification of RGCs. For instance, Atoh7 functions upstream of the family of POU domain, class 4, transcription factors (Pou4f, previously named Brn-3) to promote retinal ganglion cell development (Figure 2) [100]. During mouse retinogenesis, Atoh7 is responsible for the initiation of Pou4f2 (previously Brn-3b) expression in postmitotic RGCs, which in turn activates the expression of Pou4f1 (Brn-3a) and Pou4f3 (Brn-3c) in respectively around 80% and 20% of developing RGCs [100–103]. The expression of Pou4f2 in differentiated RGCs is then maintained by a combination of auto-activation and feedback regulation by Pou4f1 and Pou4f3 [100]. Pou4f2 is necessary for the terminal differentiation and survival of most RGCs but was not thought to be required for their
initial specification [102, 104–106]. However, later experiments using Pou4f2b−/− mice showed that these cells produced amacrine and horizontal cells as well as late-born RGCs, but few early-born RGCs. Thus, Pou4f2 can act as a RGC specifier gene by promoting RGC differentiation and by suppressing non-RGC differentiation programs (Figure 2) [107]. Pou4f3−/− mice show no visible retinal defects [104, 108], but Pou4f3 is required for RGC differentiation and can partially compensate for the loss of Pou4f2 as Pou4f2/Pou4f3 double knockout mice were more severely affected than Pou4f2 knockout mice [109]. Loss of Pou4f1 leads to a very modest RGC loss and an increase in the ratio of bistratified to monostratified RGCs, suggesting a role for Pou4f1 in the RGC subtype specification, rather than an early role on RGC specification [110]. Pou4f2 also regulates directly Shh [106] and Tbr2 (also called eomes or eomesodermin) [111].

Besides, Atoh7 regulates the expression of Insulin gene enhancer protein 1 (Isl1 or islet1), a LIM homeodomain TF that defines a distinct but overlapping subpopulation of RGCs with Pou4f2 [112–115]. Similarly, Pou4f2 and Isl1 cooperate for RGC differentiation and survival [102, 104, 105, 108, 113, 116] and function downstream of Atoh7 for RGC specification. Indeed, the ectopic expression of Pou4f2 and Isl1 in the Atoh7-null retina is sufficient to rescue RGC specification [117]. Thus, the Atoh7-Pou4f2/Isl1 pathway specifies a population of RGCs (Figure 2). In the human embryonic retina, ATOH7 and POU4F2 are highly expressed between D52 and D57 [18], suggesting potentially conserved mechanisms.

6.1.3. Dlx Family of Transcription Factors

The distal-less homeobox family of TFs is also important for RGC differentiation and survival, especially Dlx1 and Dlx2. A Dlx regulatory region is a direct target of Atoh7 in chick retina [118]. Indeed, dlx1/dlx2−/− mice have reduced RGCs due to the enhanced apoptosis of late-born RGCs [119]. Dlx1 and Dlx2 were also identified as transcriptional activators of Pou4f2 expression (Figure 2) supported by in utero retinal electroporation of Dlx2 and siRNA-mediated knockdown of Dlx2 in primary embryonic retinal cultures [119]. Furthermore, dlx1/dlx2/pou4f2 triple knockout mice show defects that are stronger than the combined effect of pou4f2-KO and dlx1/dlx2−/−, with an almost complete loss of RGCs and a marked increase in amacrine cells in the ganglion cell layer (GCL) [120]. Therefore, the regulation of Pou4f2 by Dlx1 and Dlx2 is required for RGC differentiation in the vertebrate retina [120].

6.1.4. SoxC Family of Transcription Factors

Lastly, another set of TFs has been implicated in RGC specification, the SoxC family of proteins. Early progenitor cells express Sox11. Loss of Sox11 resulted in the delayed initiation of ganglion and cone cell neurogenesis without affecting proliferation. However, postnatal development was normal, only a moderate reduction of RGCs was observed, possibly due to the redundant activity of Sox4, which expression starts at postnatal ages [121, 122]. However, loss of both Sox4 and Sox11 in the retina resulted in the absence of RGCs without affecting Atoh7 or Pou4f2 (Figure 2). As Atoh7 removal abolished the expression of Sox4 and Sox11 and overexpression of Sox4 and Sox11 stimulated Pou4f2 expression in vitro, Sox4 and Sox11 function downstream of Atoh7 while upstream of Pou4f2 to regulate the development of RGCs [122].

6.1.5. Other Regulators

Recently, many studies have used bulk RNA sequencing [18, 123] or single-cell RNA sequencing to study the development of the retina in both mice [124, 125] and humans [126]. Some potential new regulators have emerged, such as Eya2, a protein phosphatase involved in protein-protein interactions and post-translational regulation that is a downstream target of Atoh7 and can control Pou4f2 expression in vitro [123]. Also, TFAP2D is a potential candidate found in the human retina, as it is a transcription factor expressed in RPCs and developing RGCs in the human retina from 5 gestational weeks [126], and is also expressed in mouse retina from E13.5 to E16.5 [127]. A role for these molecules in determining RGC identity remains to be shown by functional validation.
In summary, three parallel but potentially cross-regulatory transcriptional pathways seem to play a role in RGC differentiation involving either Atoh7-Pou4f2/Is11, Atoh7-Dlx1/Dlx2-Pou4f2, and Atoh7-Sox4/Sox11-Pou4f2 (Figure 2). Transcriptomics is revealing new transcription factors expressed in RPCs that could potentially direct RGC fate (or the fate of other retinal cell types). However, the functional validation of most of these genes is still required yet impossible in humans. The use of retinal cells generated from human induced pluripotent stem cells (iPSCs) could address this problem, as they are amenable to genetic manipulation [128].

6.2. MicroRNA

MicroRNAs (miRNAs), small nucleotide RNAs that influence gene expression through post-transcriptional regulation of mRNA translation and degradation, have recently emerged as essential regulators in RGC neurogenesis [129,130].

Loss of function experiments in Xenopus embryo suggested that miRNAs could regulate the timing of retinal neurogenesis [131]. Different conditional knock-out mice were used to study Dicer function in the retina and allowed to conclude that miRNAs, and in particular let-7, miR-125, and miR-9, regulate the transition between early RPCs and late RPCs [132–136]. Indeed, early RPCs in Dicer mutant mice did not express the TF Ascl1 and therefore did not switch to the late progenitor state, which resulted in an overproduction of RGCs [132]. Moreover, in vitro re-aggregation experiments showed that this miRNA function is cell-autonomous [135]. In the next RGC differentiation step, Pou4f2 (Brn-3b) is necessary for the terminal differentiation and survival of most RGCs [120]. This TF seems to be down regulated by miR-23a and miR-374 [137].

The exact role of miRNAs has been difficult to decipher, partly because of their instability [138]. Moreover, there are many candidate target genes for a single miRNA [139]. Finally, as miRNA are fine regulators, loss of function studies often showed slight phenotypes [140]. In order to overcome these problems, many studies have chosen to analyze the loss of miRNA regulation. For instance, in the retina, many results came from disrupting the pre-miRNA processing enzyme Dicer.

Thus, a Dicer conditional-knockout (cKO) suppressing miRNA in RPCs showed pathfinding defects in the optic chiasm [141]. Based on this phenotype, the authors hypothesized that Dicer could regulate axon guidance at the midline. However, these Dicer cKO also presented severe microphtalmia even though the eye structure remained normal [141]. Therefore, the pathfinding default might also, in part, results from defects in RGC neurogenesis.

Here we have reviewed the different regulators of RGC neurogenesis extensively. Nevertheless, even if we have mentioned epigenetic regulation of the Notch pathway, we should not forget that variations in histone modifications, changes in DNA methylation and hydroxymethylation patterns have been shown to regulate neurogenesis (reviewed in [142]). For instance, in addition to inhibiting Notch signaling, Brm, an enzyme responsible for chromatin remodeling, also induces cell cycle exit and enables Pou4f2 expression in vitro [54].

7. The Ciliary Marginal Zone, a Source of Neurogenesis in Mammals

Now that we described the neurogenesis in RPCs, we will discuss another source of neurogenesis that originates in the ciliary marginal zone (CMZ), the transition area between the neural retina and the RPE (Figure 3a). The progenitor cells in the CMZ contribute to the establishment of the neural retina by producing new neurons during development and throughout life in many lower vertebrates [5,143–146]. Many studies in non-mammalian vertebrates have pointed out a role of Müller glia and the CMZ as a source of stem cells for adult neurogenesis in the retina, particularly upon lesion [146]. Thus, the addition of neurons generated from the CMZ participates in eye growth [147] in addition to the neurons generated from the main RPCs that are differentiating in a central to peripheral wave in the neural retina [76,145,148,149].

However, in rodents, the CMZ was not considered a stem cell niche for the neural retina. Indeed, previous experiments had shown that the Pax6 removal in the distal CMZ, using a Pax6^{loxfllox}; Tyrp2-Cre
cKO did not impair the neuronal differentiation of the retina [150]. However, recent evidence has shed light on the CMZ contribution to retinogenesis. Time-lapse imaging using a Zic2-GFP reporter mouse line labeling a subset of proximal CMZ progenitors showed that some CMZ cells were migrating to the peripheral neural retina to become RGCs (Figure 3a). Furthermore, Cyclin-D2 was necessary for the generation of some of these RGCs, especially for the ipsilateral Zic2-positive RGCs [151]. The definitive contribution of the CMZ to the different retinal cell types was determined using a lineage tracing approach with Msx1, a TF selectively expressed in the proximal area of the CMZ [152]. Most cells derived from Msx1 progenitor cells were located in the non-pigmented epithelium of the ciliary body and in the iris (Figure 3b).

Nevertheless, some Msx1 progenitor cells can differentiate during embryogenesis into the different types of retinal cells (RGCs, photoreceptors, Müller, amacrine and bipolar cells) (Figure 3b). However, the proportion of retinal cells produced by CMZ-derived Msx1 progenitors differs from the retinal cells produced by the main neural RPCs, with fewer photoreceptors produced for instance [6]. Also, Msx1 progenitors seem to generate selectively part of the ipsilateral RGCs [151], suggesting a different bias in the production of retinal cells from CMZ progenitors compared to neural RPCs. Furthermore, CMZ-derived retinal cells are located at the periphery of the retina and not the central retina [152] (Figure 3b), suggesting that centrally-located retinal cells are generated from RPCs and that retinal progenitors or cells do not migrate over significant distance.

In the future, it would be interesting to identify the mechanisms of cell fate specification for CMZ progenitors, and whether they differ from the main RPCs. Overall, the proximal region of the CMZ in mice is also able to contribute to the generation of the neural retina during development (Figure 3). However, murine CMZ cells are unable to generate neural retinal cells postnatally and in the adult [152].

![Figure 3](image_url)

**Figure 3.** Schematic representation of lineage tracing from progenitors of the ciliary marginal zone (CMZ) or neural retina in mouse. (a) At E14, retinal progenitor cells (RPCs) (magenta) are the main contributor to retinal neurogenesis, but Msx1+ progenitors (green) in the proximal CMZ migrate towards the neural retina and contribute to retinal neurogenesis at the periphery of the retina. (b) At P10, cells derived from Msx1+ progenitors (green) produce most retinal cell types, although with a different ratio than cells derived from RPCs (magenta). Also, Msx1+ progenitors (green) contribute to non-pigmented epithelial cells of the ciliary body and the cells in the iris. RPE: retinal pigmented epithelium, RGC: retinal ganglion cells, BC: bipolar cells, AC: amacrine cells, MG: Müller glia, RP: rod photoreceptors, CP: cone photoreceptors, HC: horizontal cells. Adapted from Marcucci et al., 2016 [151] and Bélanger et al., 2017 [152].

8. RGC Migration

After exiting the cell cycle at the apical side, postmitotic RGCs, migrate toward the GCL all along the apico-basal axis where they will develop their axon (Figure 4). Several decades ago, the migration pattern of RGCs was already described in rodents using Golgi staining and electron microscopy [153,154]. These studies hypothesized that RGCs migrated by translocating their soma. In the chick, the R4 antibody labeling RGCs described a transient bipolar RGC spanning the entire thickness of the retina around E4. In older embryos, these bipolar RGCs disappear and only unipolar
RGCs in the GCL were immuno-stained [155]. Later, time-lapse video-microscopy studies on the zebrafish retina confirmed that the RGC soma was translocated to the GCL while they remained attached to the apical and basal surface of the retina, hence presenting a bipolar shape (Figure 4) [30,156,157].

Little is known about the molecules regulating RGC migration. Recently, it has been shown in mice that the β1-Integrin laminin receptor with Cas signaling-adaptor proteins are necessary for RGCs to find their way to the GCL and arrange into a single cell layer [158].

Thus, this migration of young postmitotic RGCs is required for their final maturation and for the proper organization of retinal cells into layers.

Figure 4. The newborn retinal ganglion cell (RGC) translocates from the apical part of the retina toward the future ganglion cell layer at the basal side. During the entire process, the cell is attached to both sides of the retina. After the migration, the RGC adjusts its position while losing its apical process and send its axon to the optic nerve. INL: inner nuclear layer, IPL: inner plexiform layer. Adapted from Amini et al. [159].

9. Classification of RGC Subtypes

In the next section, we will discuss how RGCs have been classified by anatomy, function and molecular signature and also how their pathfinding and targeting also discriminate the different subtypes.

With rare exceptions, all RGCs have in common their cell bodies positioned in the GCL (Figure 1a). They also develop their dendrites in the INL and their axon toward the brain. Finally, vertebrate RGCs can be identified by pan-RGC markers such as the cell surface protein Thy1 [160], the RNA-binding protein RBPMS [161] and the TFs of the Pou4F family [103,110].

9.1. Morphological Criteria

Santiago Ramon y Cajal was a pioneer at describing the different neurons in order to understand neuronal circuits, and characterized different types of RGCs in detail [162]. Nevertheless, the classification has tremendously changed over the past few years as a result of the advances in new technologies such as single-cell transcriptomics, functional imaging, or large-scale electron microscopy [2,163,164]. Here our purpose is not to debate what defines an RGC cell type. We will recapitulate studies that have described the diversity of RGCs according to different criteria in order to highlight how much is left to decipher the mechanisms of RGC differentiation.

Even if, for a long time, the criteria of morphology and function have been used to look for the different types of RGCs, anatomical classifications have led the field due to the technical limits of defining functional subtypes with receptive field studies. The categorization of RGC dendritic morphologies in the mouse retina based on combined microinjection of Lucifer Yellow and DiI revealed 11 to 14 types of RGCs [165,166]. This classification was not very different from the one established with a genetic method using alkaline phosphatase as a histochemical reporter that yielded 12 different
types of RGC [167]. Later, the injection of neurobiotin increased the number to 22 [168]. In the last
decade, the addition of computational techniques enhanced spatial precision and, combined with the
quantification of the dendritic arbor, categorized 15 types of RGCs [169].

9.2. Functional Criteria

However, based on their function, 21 types of RGCs were found (reviewed in [1]): the ON-OFF
direction-selective ganglion cells (ON-OFF DS RGC) (4 types) [170], the ON direction-selective ganglion
cells (3 types) [171], the alpha RGCs that are Smi-32+ in mice (3 types) [172], the intrinsically
photosensitive RGCs (ipRGCs) that expressed melanopsin (5 types). These neurons have the
particularity to participate in the synchronization of the circadian oscillator [173]. In mice, 13% of the
RGCs close to the center of the visual field are Local Edge Detectors (LED) RGCs (3 types) [174,175].
These neurons correct excitation from both On and Off bipolar cells. Finally, the mouse retina also
contains three types of J-RGCs named after their expression of the junctional adhesion molecule B,
which selectively respond to stimuli moving in a soma-to-dendrite direction [176]. More recently,
optical imaging advances have revolutionized the field (reviewed in [177]). For instance, Baden et al.,
found at least 32 RGC types relying on their light responses and anatomical criteria [163].

9.3. Molecular Criteria

Last but not least, countless studies have classified RGCs following their molecular signature, and
in particular, the presence of determining transcription factors. Recently, Sweeney et al. have proposed
that almost all RGCs could be categorized in three classes depending on their expression of Isl2, Tbr2,
or Satb1/Satb2 and hypothesized that these TFs are responsible for RGC functional identity [178].
Supporting this idea, Isl2 colocalizes with Smi32 a marker of alpha-RGCs [179]. Moreover, Satb1
controls the morphogenesis of ON-OFF DS RGCs, as loss of Satb1 results in mono-stratified dendrites
and a lack of ON input (Figure 5) [180]. However, Satb1 does not affect the generation or survival of
these ON-OFF DS RGCs [180]. Moreover, Tbr2 was found in non-overlapping RGC subtypes that
project to non-image-forming brain areas such as the pretectum, suprachiasmatic nucleus, and ventral
LGN, and include all melanopsin-expressing ipRGCs [181,182]. Furthermore, it is worth noting that
Tbr2 is crucial for the formation and maintenance of ipRGCs (Figure 5), which exclusively express
Opsin 4 (Opn4) [181], and that Pou4f2 and Tbr2 label RGCs that do not overlap [182].

The first single-cell RNA sequencing experiments have raised hope to unify the different
classifications under a universal one combining molecular signature, morphology, and function [2,183].
Such a study would allow characterizing and targeting specific subtypes for modifications with
unprecedented precision, as done using genetic in most invertebrates. The first study using single-cell
RNA sequencing was performed on the whole retina of mice before eye-opening and categorized
40 RGC types [2]. Another study looked for new genes that could define new RGC subtypes among
Parvalbumin-expressing RGCs. However, the clustering into eight subtypes did not reveal a molecule
that could identify a specific RGC subtype without being expressed in other retinal cells. This work
suggests that molecular signatures identifying RGC subtypes are likely composed of a combination of
genesis, rendering their identification and genetic modifications challenging [183].

Further studies are needed to identify a more complex molecular signature than previously
expected, as many fields such as developmental biology, evolution, physiology will benefit from this
unified categorization. For the moment, the categorization choice should relate to the scientific question
asked. However, in the particular case of RGC neurogenesis, a robust technique combining the lineage
tracing with the molecule signature is needed, as recently used in the cortex [184].
9.4. Brain Targeting and Pathfinding at the Optic Chiasm

9.4.1. Brain Targeting

The previous classifications do not take into account the projection site of these RGC subtypes to different nuclei in the brain. In the mouse, 46 different RGC targets have been identified participating in image-forming and non-image forming visual functions [185], which is higher than the number of RGC subtypes identified so far. How can the numerous targets match the number of RGC subtypes? First, a single RGC can project to different targets. For instance, most RGCs that project to the dorsolateral geniculate nucleus, also project to the superior colliculus [186]. However, many studies following RGC targeting have relied on transgenic mouse lines expressing GFP in one specific RGC subtype or a few RGC subtypes. In most cases, these RGC subtypes project to several brain targets rather than a single target. This can result from 2 possibilities: (1) one single RGC projects to several targets that are the same for each subtype; (2) each RGC within a subtype projects to a single brain target or few targets that are not always the same. The second possibility will suggest a further subdivision of RGC subtypes depending on their targets. So far, only single axonal reconstruction is able to identify RGC morphology and clearly link it with precise targeting, but it is painstaking and usually lacks the molecular signature of these RGCs [186]. Thus, it is still an open debate (reviewed in [187,188]).

Interestingly, different RGC populations employ different strategies to achieve accurate axon-target matching. The strategy used correlates with the birthdate of RGCs and the timing of axon growth [189]. Thus, early-born and early-projecting RGCs tend to first innervate multiple targets, to then refine to the appropriate ones (usually several) while later-born and later-projecting RGCs are highly accurate in their initial targeting [189]. However, the existence of a causal relationship between RGCs birthdate and subtype identity remains to be determined. Indeed, their targeting properties could also only be related to the axonal order of arrival in their targets. In this case, early axons would have more possibilities of targeting than later-arriving ones, which would then have to compete for the remaining space.

9.4.2. Pathfinding at the Optic Chiasm

Another criteria that classify RGCs into two distinct classes is their axon guidance decision at the optic chiasm: crossing or not at the midline to project to the opposite (contralateral) or same side (ipsilateral) of the brain [190,191]. This categorization into ipsilateral or contralateral RGCs comprises different subtypes regrouping RGCs that are morphologically different [186,192] and RGCs some that target different brain areas [188].

The TF Islet2 is expressed in post-mitotic contralateral RGCs (Figure 5) and represses the ipsilateral program as Islet2 knock-out mice showed an increased ipsilateral projection correlated with fewer ipsilateral RGCs [193]. Recently, the SoxC family of TF (Sox4, 11 and 12) that was previously implicated in RGC neurogenesis [121,122], was identified as a specific regulator for the differentiation of contralateral RGCs [194]. Interestingly, SoxC TFs stimulate contralateral RGC differentiation by antagonizing the Notch signaling pathway [194]. Additionally, SoxC TFs regulate molecules that are important for contralateral axon guidance such as Plexin-A1 and Nrcam [194,195].

We will focus more on the ipsilateral subclass of RGCs as their molecular characterization is currently the best described. Ipsilateral RGCs are located in the ventro-temporal retina in mice and express the TF Zic2 that defines their identity and controls the expression of the guidance receptor EphB1 and the serotonin transporter SERT [196,197]. These genes are transiently expressed, during a specific period of development [198–200]. While involved in the proper refinement of ipsilateral retinal axons in their brain targets, SERT is not necessary for their midline decision [197,201]. Besides, EphB1 loss of function or Zic2 knock-down in mice leads to a reduced ipsilateral projection [198,199], while ectopic expression of Zic2 or EphB1 is sufficient to induce the ipsilateral misrouting of some retinal axons [196,202]. Thus, Zic2 is essential to specify ipsilateral RGCs (Figure 5), while EphB1 controls their guidance decision at the optic chiasm. Indeed, EphB1-expressing axons are repelled at the midline by ephrin-B2, to project ipsilaterally. As previously mentioned, a RPC subpopulation...
within the CMZ that contribute to retinogenesis has been isolated [152]. Hence, Zic2+ progenitors in the CMZ seem to migrate toward the neural retina and generate ipsilateral Zic2+ RGCs [151]. What are the upstream regulators controlling the neurogenesis of ipsilateral RGCs? A microarray screen identified new molecular determinants of ipsilateral and contralateral RGCs at embryonic ages [203]. Among them, Cyclin-D2 (ccnd2), a regulator of the cell cycle, was upregulated in ipsilateral RGCs and also found expressed in the ventral CMZ [151,203]. Ccnd2−/− mice have reduced mitosis in the ventral CMZ and a diminished neurogenesis in the ventral retina affecting both the contralateral and ipsilateral RGCs [151], suggesting that Cyclin-D2 could regulate cell cycle exit and neurogenesis. Another interesting upstream candidate is Foxd1, a TF expressed in the ventral retina at embryonic stages. Foxd1 controls Zic2 expression as foxd1−/− mice lack Zic2 expression in ventro-temporal retina whereas its ectopic expression leads to the ipsilateral misrouting of some Foxd1-expressing axons [204,205]. Furthermore, Shh regulates the specification of ipsilateral RGCs, as Boc−/− mice presented a modification of ipsilateral and contralateral markers [206].

Figure 5. Examples of specific transcription factors that determine the identity of RGC subtypes or subclasses.

10. Altered Neurogenesis in Albinism

A genetic disease with reduced ipsilateral projection has provided some insight into the generation of ipsilateral RGCs and neurogenesis in general: albinism [190]. Albinism is a rare genetic disease characterized by hypopigmentation, affecting mainly eyes (in ocular albinism) or also skin and hair (in oculocutaneous albinism) and results in a profound visual impairment that includes very low visual acuity, photophobia, nystagmus, and abnormal binocular vision (stereopsis) [207–210]. The pigmentation defect occurring at the level of the RPE affects the retinal neurogenesis, resulting in fewer ipsilateral RGCs [211,212] and reduced numbers of photoreceptors [213] in albino mouse models, most likely at the origin of the deficits in binocular vision and visual acuity, respectively. Indeed, the delayed neurogenesis leading to the reduction in the number of ipsilateral RGCs results in a reduced ipsilateral projection and abnormal brain projection [198,211,212,214,215]. How is neurogenesis perturbed in the albino retina? Interestingly, there are fewer Ccnd2+ cells in the CMZ of albino retinas during development [151]. Thus Cyclin-D2 is an interesting candidate, upstream of Zic2 expression, and essential for the specificiation of ipsilateral RGCs. However, how this altered neurogenesis occurs from a pigmentation defect in the adjacent RPE is still a mystery. Several signaling pathways that could alter neurogenesis in albinism have been identified. Wnt signaling in the peripheral RPE has been implicated as a negative regulator of ipsilateral identity and Wnt2b expression is expanded in the central RPE in albino mice instead of being confined to the periphery as in pigmented mice [216]. In addition, activating Wnt signaling with lithium chloride in pigmented mice during pregnancy reduced the number of Zic2+ RGCs to a level comparable to albino retina. This suggests that Wnt signaling could regulate Zic2 expression [216], but the mechanisms at hand are still unknown. Furthermore, the recent discovery that the regulation of Notch signaling in the RPE impacts neurogenesis in the adjacent retina [49] opens up a new avenue of research to decipher the signaling pathways linking RPE and neural retina to regulate neurogenesis, as a means to better understand the role of extrinsic factors on neurogenesis and how it is altered in the albino eye.
11. Conclusions

Over recent decades, much progress has been made to improve the understanding of RGC neurogenesis and differentiation. The current view is that retinal progenitor cells in vertebrates can generate different retinal types in a stochastic manner but with a probabilistic bias for some cell types that change during development. This model could explain why all retinal cell types can be generated at any given developmental time but with a different probability, ending up with RGCs generated mostly early on and rod photoreceptors later. This stochastic model is possibly a general rule for the development of the central nervous system, as suggested by recent data on the neurogenesis of the cerebral cortex [217]. The extrinsic and intrinsic factors that regulate the cell fate determination are being isolated, with compelling evolutionary conserved factors initially identified in the more deterministic neurogenesis of the drosophila eye. However, two aspects remain to be established: (1) how the developmental expression of these factors is regulated, and (2) how the change in cell fate probabilities occur over time. The transcription factors that regulate RGC neurogenesis are identified: Atoh7 and Pou4f2 appear as the key regulators with several transcription factors in between. As RGCs are not a homogeneous population, several studies have tried to identify the molecular determinants and/or markers of RGC subtypes. This characterization was done initially by combinatorial expression of various transcription factors or markers for different types of RGCs. However, the recent emergence of single-cell RNA sequencing technology will hopefully allow the identification of new markers for RGC subtypes but also to determine their specification pathways during development. In the future, studies will undoubtedly link molecular specification of RGC subtypes with their brain connectivity to decipher the molecular mechanisms that are at hand. Finally, understanding the developmental mechanisms determining the specification of retinal cells is crucial for the efficient, targeted generation of retinal cells from induced pluripotent stem cells of patients for research on the human retinal neurogenesis and also potential therapeutic strategies.

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Abbreviations

bHLH basic helic-loop-helix
cckd2 Cyclin-d2
cKO conditional knock-out
CMZ ciliary marginal zone
FGF/Fgf fibroblast growth factor
GCL ganglion cell layer
Hh hedgehog
INL inner nuclear layer
MG Müller glial cells
NGF nerve growth factor
ONL outer nuclear layer
Ptc Patched
RGC retinal ganglion cell
RPC retinal progenitor cell
RPE retinal pigmented epithelium
Shh Sonic hedgehog
Smo Smoothened
TF transcription factor
References

1. Sanes, J.R.; Masland, R.H. The Types of Retinal Ganglion Cells: Current Status and Implications for Neuronal Classification. *Annu. Rev. Neurosci.* 2015, 38, 221–246. [CrossRef]

2. Rheaume, B.A.; Jereen, A.; Bolisetty, M.; Sajid, M.S.; Yang, Y.; Renna, K.; Sun, L.; Robson, P.; Trakhtenberg, E.F. Single cell transcriptome profiling of retinal ganglion cells identifies cellular subtypes. *Nat. Commun.* 2018, 9, 2759. [CrossRef]

3. Turner, D.L.; Cepko, C.L. A common progenitor for neurons and glia persists in rat retina late in development. *Nature* 1987, 328, 131–136. [CrossRef] [PubMed]

4. Holt, C.E.; Bertsch, T.W.; Ellis, H.M.; Harris, W.A. Cellular determination in the Xenopus retina is independent of lineage and birth date. *Neuron* 1988, 1, 15–26. [CrossRef]

5. Wetts, R.; Fraser, S.E. Multipotent precursors can give rise to all major cell types of the frog retina. *Science* 1988, 239, 1142–1145. [CrossRef] [PubMed]

6. Turner, D.L.; Snyder, E.Y.; Cepko, C.L. Lineage-independent determination of cell type in the embryonic mouse retina. *Neuron* 1990, 4, 833–845. [CrossRef]

7. Fekete, D.M.; Perez-Miguelsanz, J.; Ryder, E.F.; Cepko, C.L. Clonal Analysis in the Chicken Retina Reveals Tangential Dispersion of Clonally Related Cells. *Dev. Biol.* 1994, 166, 666–682. [CrossRef]

8. Reh, T.; Kljavin, I. Age of differentiation determines rat retinal germinal cell phenotype: Induction of differentiation by dissociation. *J. Neurosci.* 1989, 9, 4179–4189. [CrossRef]

9. Brzezinski, J.A.; Kim, E.J.; Johnson, J.E.; Reh, T.A. Ascl1 expression defines a subpopulation of lineage-restricted progenitors in the mammalian retina. *Development* 2011, 138, 3519–3531. [CrossRef]

10. Sidman, R. Histogenesis of mouse retina studied with thymidine-H3. In *The Structure of the Eye*; Smelser, G., Ed.; Academic Press: New York, NY, USA, 1961; pp. 487–506.

11. Carter-Dawson, L.D.; Lavail, M.M. Rods and cones in the mouse retina. II. Autoradiographic analysis of cell generation using tritiated thymidine. *J. Comp. Neurol.* 1979, 188, 263–272. [CrossRef]

12. Young, R.W. Cell differentiation in the retina of the mouse. *Anat. Rec.* 1985, 212, 199–205. [CrossRef] [PubMed]

13. Prada, C.; Puga, J.; Perez-Mendez, L.; Lopez, R.; Ramirez, G. Spatial and Temporal Patterns of Neurogenesis in the Chick Retina. *Eur. J. Neurosci.* 1991, 3, 559–569. [CrossRef] [PubMed]

14. Hu, M.; Easter, S.S. Retinal neurogenesis: The formation of the initial central patch of postmitotic cells. *Dev. Biol.* 1999, 207, 309–321. [CrossRef] [PubMed]

15. Jacobson, M. Retinal Ganglion Cells: Specification of Central Connections in Larval Xenopus laevis. *Science* 1967, 155, 1106–1108. [CrossRef]

16. Drager, U.C. Birth Dates of Retinal Ganglion Cells Giving Rise to the Crossed and Uncrossed Optic Projections in the Mouse. *Proc. R. Soc. B Biol. Sci.* 1985, 224, 57–77.

17. la Vail, M.M.; Rapaport, D.H.; Rakic, P. Cytogenesis in the monkey retina. *J. Comp. Neurol.* 1991, 309, 86–114. [CrossRef]

18. Hoshino, A.; Ratnapriya, R.; Brooks, M.J.; Chaitankar, V.; Wilken, M.S.; Zhang, C.; Starostik, M.R.; Gieser, L.; La Torre, A.; Nishio, M.; et al. Molecular Anatomy of the Developing Human Retina. *Dev. Cell* 2017, 43, 763–779. [CrossRef]

19. Cepko, C. Intrinsically different retinal progenitor cells produce specific types of progeny. *Nat. Rev. Neurosci.* 2014, 15, 615–627. [CrossRef]

20. Austin, C.P.; Feldman, D.E.; Ida, J.A.; Cepko, C.L. Vertebrate retinal ganglion cells are selected from competent progenitors by the action of Notch. *Development* 1995, 121, 3637–3650.

21. Adler, R.; Hatlee, M. Plasticity and differentiation of embryonic retinal cells after terminal mitosis. *Science* 1989, 243, 391–393. [CrossRef]

22. Watanabe, T.; Raff, M.C. Diffusible rod-promoting signals in the developing rat retina. *Development* 1992, 114, 899–906. [PubMed]

23. Masai, I.; Stemple, D.L.; Okamoto, H.; Wilson, S.W. Midline Signals Regulate Retinal Neurogenesis in Zebrafish. *Neuron* 2000, 27, 251–263. [CrossRef]

24. Belliveau, M.J.; Cepko, C.L. Extrinsic and intrinsic factors control the genesis of amacrine and cone cells in the rat retina. *Development* 1999, 126, 555–566. [PubMed]
25. Reh, T. Cell-specific regulation of neuronal production in the larval frog retina. *J. Neurosci.* 1987, 7, 3317–3324. [CrossRef]

26. Waid, D.K.; McLoon, S.C. Ganglion cells influence the fate of dividing retinal cells in culture. *Development* 1998, 125, 1059–1066.

27. Gonzalez-Hoyuela, M.; Barbas, J.A.; Rodriguez-Tebar, A. The autoregulation of retinal ganglion cell number. *Development* 2001, 128, 117–124.

28. Frade, J.M.; Rodriguez-Tebar, A.; Barde, Y.A. Induction of cell death by endogenous nerve growth factor through its p75 receptor. *Nature* 1996, 383, 166–168. [CrossRef]

29. Harada, C.; Harada, T.; Nakamura, K.; Sakai, Y.; Tanaka, K.; Parada, L.F. Effect of p75NTR on the regulation of naturally occurring cell death and retinal ganglion cell number in the mouse eye. *Dev. Biol.* 2006, 290, 57–65. [CrossRef]

30. Poggi, L.; Vitorino, M.; Masai, I.; Harris, W.A. Influences on neural lineage and mode of division in the zebrafish retina in vivo. *J. Cell Biol.* 2005, 171, 991–999. [CrossRef]

31. Diezel, C.; Lendahl, U. Notch Signaling in Development, Tissue Homeostasis, and Disease. *Physiol. Rev.* 2017, 97, 1235–1294. [CrossRef]

32. Louvi, A.; Artavanis-Tsakonas, S. Notch signalling in vertebrate neural development. *Nat. Rev. Neurosci.* 2006, 7, 93–102. [CrossRef] [PubMed]

33. Treisman, J.E. Retinal differentiation in Drosophila. *Wiley Interdiscip. Rev. Dev. Biol.* 2013, 2, 545–557. [CrossRef] [PubMed]

34. Fiuza, U.M.; Arias, A.M. Cell and molecular biology of Notch. *J. Endocrinol.* 2007, 194, 459–474. [CrossRef] [PubMed]

35. Kopan, R.; Ilagan, M.X.G. The Canonical Notch Signaling Pathway: Unfolding the Activation Mechanism. *Cell* 2009, 137, 216–233. [CrossRef]

36. Kageyama, R.; Ohtsuka, T.; Kobayashi, T. Roles of Hes genes in neural development. *Dev. Growth Differ.* 2008, 50, 97–103. [CrossRef]

37. Nelson, B.R.; Hartman, B.H.; Ray, C.A.; Hayashi, T.; Bermingham-McDonogh, O.; Reh, T.A. Acheate-scute like 1 (Ascl1) is required for normal delta-like (Dll) gene expression and notch signaling during retinal development. *Dev. Dyn.* 2009, 238, 2163–2178. [CrossRef]

38. Rocha, S.F.; Lopes, S.S.; Gossler, A.; Henrique, D. Dll1 and Dll4 function sequentially in the retina and pV2 domain of the spinal cord to regulate neurogenesis and create cell diversity. *Dev. Biol.* 2009, 328, 54–65. [CrossRef]

39. Luo, H.; Jin, K.; Xie, Z.; Qiu, F.; Li, S.; Zou, M.; Cai, L.; Hozumi, K.; Shima, D.T.; Xiang, M. Forkhead box N4 (Foxn4) activates Dll4-Notch signaling to suppress photoreceptor cell fates of early retinal progenitors. *Proc. Natl. Acad. Sci. USA* 2012, 109, E553–E562. [CrossRef]

40. Jadhav, A.P.; Mason, H.A.; Cepko, C.L. Notch 1 inhibits photoreceptor production in the developing mammalian retina. *Development* 2006, 133, 913–923. [CrossRef]

41. Yaron, O.; Farhy, C.; Marquardt, T.; Applebury, M.; Ashery-Padan, R. Notch1 functions to suppress cone-photoreceptor fate specification in the developing mouse retina. *Development* 2006, 133, 1367–1378. [CrossRef]

42. Riesenberg, A.N.; Liu, Z.; Kopan, R.; Brown, N.L. Rbpj cell autonomous regulation of retinal ganglion cell and cone photoreceptor fates in the mouse retina. *J. Neurosci.* 2009, 29, 12865–12877. [CrossRef] [PubMed]

43. Zheng, M.H.; Shi, M.; Pei, Z.; Gao, F.; Han, H.; Ding, Y.Q. The transcription factor RBP-J is essential for retinal cell differentiation and lamination. *Mol. Brain* 2009, 2, 38. [CrossRef] [PubMed]

44. Tomita, K.; Ishibashi, M.; Nakahara, K.; Ang, S.L.; Nakanishi, S.; Guillelmet, F.; Kageyama, R. Mammalian hairy and Enhancer of split homolog 1 regulates differentiation of retinal neurons and is essential for eye morphogenesis. *Neuron* 1996, 16, 723–734. [CrossRef]

45. Furukawa, T.; Mukherjee, S.; Bao, Z.Z.; Morrow, E.M.; Cepko, C.L. rax, Hes1, and notch1 promote the formation of Müller glia by postnatal retinal progenitor cells. *Neuron* 2006, 26, 383–394. [CrossRef]

46. Jadhav, A.P.; Cho, S.H.; Cepko, C.L. Notch activity permits retinal cells to progress through multiple progenitor states and acquire a stem cell property. *Proc. Natl. Acad. Sci. USA* 2006, 103, 18998–19003. [CrossRef]
47. Henrique, D.; Hirsinger, E.; Adam, J.; Le Roux, I.; Pourquié, O.; Ish-Horowicz, D.; Lewis, J. Maintenance of neuroepithelial progenitor cells by Delta–Notch signalling in the embryonic chick retina. Curr. Biol. 1997, 7, 661–670. [CrossRef]

48. Bao, Z.Z.; Cepko, C.L. The Expression and Function of Notch Pathway Genes in the Developing Rat Eye. J. Neurosci. 1997, 7, 1425–1434. [CrossRef]

49. Ha, T.; Moon, K.H.; Dai, L.; Hatakeyama, J.; Yoon, K.; Park, H.S.S.; Kong, Y.Y.Y.; Shimamura, K.; Kim, J.W. The Retinal Pigment Epithelium Is a Notch Signaling Niche in the Mouse Retina. Cell Rep. 2017, 19, 351–363. [CrossRef]

50. Zhu, M.Y.; Gasperowicz, M.; Chow, R.L. The expression of NOTCH2, HES1 and SOX9 during mouse retinal development. Gene Expr. Patterns 2013, 13, 78–83. [CrossRef]

51. Riesenberg, A.N.; Brown, N.L. Cell autonomous and nonautonomous requirements for Deltalike1 during early mouse retinal neurogenesis. Dev. Dyn. 2016, 245, 631–640. [CrossRef]

52. Yamaguchi, M.; Tonou-Fujimori, N.; Komori, A.; Maeda, R.; Nojima, Y.; Li, H.; Okamoto, H.; Masai, I. Histone deacetylase 1 regulates retinal neurogenesis in zebrafish by suppressing Wnt and Notch signaling pathways. Development 2005, 132, 3027–3043. [CrossRef] [PubMed]

53. Seritrakul, P.; Gross, J.M. Tet-mediated DNA hydroxymethylation regulates retinal neurogenesis by modulating cell-extrinsic signaling pathways. PLoS Genet. 2017, 13, e1006987. [CrossRef] [PubMed]

54. Das, A.V.; James, J.; Bhattacharya, S.; Imbalzano, A.N.; Antony, M.L.; Hegde, G.; Zhao, X.; Mallya, K.; Ahmad, F.; Knudsen, E.; et al. SWI/SNF Chromatin Remodeling ATPase Brm Regulates the Differentiation of Early Retinal Stem Cells/Progenitors by Influencing Brn3b Expression and Notch Signaling. J. Biol. Chem. 2007, 282, 35187–35201. [CrossRef] [PubMed]

55. Nüsslein-Volhard, C.; Wieschaus, E. Mutations affecting segment number and polarity in Drosophila. Nature 1980, 287, 795–801. [CrossRef] [PubMed]

56. Echelard, Y.; Epstein, D.J.; St-Jacques, B.; Shen, L.; Mohler, J.; McMahon, J.A.; McMahon, A.P. Sonic hedgehog, a member of a family of putative signaling molecules, is implicated in the regulation of CNS polarity. Cell 1993, 75, 1417–1430. [CrossRef]

57. Marigo, V.; Davey, R.A.; Zuo, Y.; Cunningham, J.M.; Tabin, C.J. Biochemical evidence that Patched is the Hedgehog receptor. Nature 1996, 384, 176–179. [CrossRef] [PubMed]

58. van den Heuvel, M.; Ingham, P.W. Smoothening the path for hedgehogs. Trends Cell Biol. 1996, 6, 451–453. [CrossRef] [PubMed]

59. Murone, M.; Rosenthal, A.; de Sauvage, F.J. Sonic hedgehog signaling by the Patched–Smoothened receptor complex. Curr. Biol. 1999, 9, 76–84. [CrossRef] [PubMed]

60. Dakubo, G.D.; Wang, Y.P.; Mazerolle, C.; Campsall, K.; McMahon, A.P.; Wallace, V.A. Retinal ganglion cell-derived sonic hedgehog signaling is required for optic disc and stalk neuroepithelial cell development. Development 2003, 130, 2967–2980. [CrossRef]

61. Jensen, A.M.; Wallace, V.A. Expression of Sonic hedgehog and its putative role as a precursor cell mitogen in the developing mouse retina. Development 1997, 124, 363–371.

62. Wang, Y.P.; Dakubo, G.; Howley, P.; Campsall, K.D.; Mazarolle, C.; Shiga, S.A.; Lewis, P.M.; McMahon, A.P.; Wallace, V.A. Development of normal retinal organization depends on Sonic hedgehog signaling from ganglion cells. Nat. Neurosci. 2002, 5, 831–832. [CrossRef] [PubMed]

63. Sánchez-Camacho, C.; Bovolenta, P. Autonomous and non-autonomous Shh signalling mediate the in vivo growth and guidance of mouse retinal ganglion cell axons. Development 2008, 135, 3531–3541. [CrossRef] [PubMed]

64. Neumann, C.J.; Nuesslein-Volhard, C. Patterning of the Zebrafish Retina by a Wave of Sonic Hedgehog Activity. Science 2000, 289, 2137–2139. [CrossRef] [PubMed]

65. Perron, M. A novel function for Hedgehog signalling in retinal pigment epithelium differentiation. Development 2003, 130, 1565–1577. [CrossRef]

66. Zhang, X.M.M.; Yang, X.J.J. Regulation of retinal ganglion cell production by Sonic hedgehog. Development 2001, 128, 943–957.

67. Levine, E.M.; Roelink, H.; Turner, J.; Reh, T.A. Sonic hedgehog promotes rod photoreceptor differentiation in mammalian retinal cells in vitro. J. Neurosci. 1997, 17, 6277–6288. [CrossRef]
68. Wang, Y.; Dakubo, G.D.; Thurig, S.; Mazzerolle, C.J.; Wallace, V.A. Retinal ganglion cell-derived sonic hedgehog locally controls proliferation and the timing of RGC development in the embryonic mouse retina. *Development* 2005, 132, 5103–5113. [CrossRef]

69. Stenkamp, D.L.; Frey, R.A. Extraretinal and retinal hedgehog signaling sequentially regulate retinal differentiation in zebrafish. *Dev. Biol.* 2003, 258, 349–363. [CrossRef]

70. Stenkamp, D.L.; Frey, R.A.; Prabhudesai, S.N.; Raymond, P.A. Function for Hedgehog Genes in Zebrafish Retinal Development. *Dev. Biol.* 2000, 220, 238–252. [CrossRef]

71. Dakubo, G.D.; Wallace, V.A. Hedghogs and retinal ganglion cells: Organizers of the mammalian retina. *Neuroreport* 2004, 15, 479–482. [CrossRef]

72. McCabe, K.L.; Gunther, E.C.; Reh, T.A. The development of the pattern of retinal ganglion cells in the chick retina: Mechanisms that control differentiation. *Development* 1999, 126, 5713–5724. [PubMed]

73. Patel, A.; McFarlane, S. Overexpression of FGF-2 alters cell fate specification in the developing retina of Xenopus laevis. *Dev. Biol.* 2000, 222, 170–180. [CrossRef] [PubMed]

74. Martinez-Morales, J.R.; Del Bene, F.; Nica, G.; Hammerschmidt, M.; Bovolenta, P.; Wittbrodt, J. Differentiation of the Vertebrate Retina Is Coordinated by an FGF Signaling Center. *Dev. Cell* 2005, 8, 565–574. [CrossRef] [PubMed]

75. Shkumatava, A.; Fischer, S.; Müller, F.; Strahle, U.; Neumann, C.J. Sonic hedgehog, secreted by amacrine cells, acts as a short-range signal to direct differentiation and lamination in the zebrafish retina. *Development* 2004, 131, 3849–3858. [CrossRef] [PubMed]

76. Cepko, C.C.L.; Austin, C.P.; Yang, X.; Alexiades, M.; Ezzeddine, D. Cell fate determination in the vertebrate retina. *Proc. Natl. Acad. Sci. USA* 1996, 93, 589–595. [CrossRef]

77. Li, X.; Chen, Z.; Desplan, C. Temporal Patterning of Neural Progenitors in Drosophila. In *Current Topics in Developmental Biology*; Academic Press Inc.: Cambridge, MA, USA, 2013; Volume 105, pp. 69–96.

78. Watanabe, T.; Raft, M.C. Rod photoreceptor development in vitro: Intrinsic properties of proliferating neuroepithelial cells change as development proceeds in the rat retina. *Neuron* 1990, 4, 461–467. [CrossRef]

79. Belliveau, M.J.; Young, T.L.; Cepko, C.L. Late retinal progenitor cells show intrinsic limitations in the production of cell types and the kinetics of opsin synthesis. *J. Neurosci.* 2000, 20, 2247–2254. [CrossRef]

80. Gomes, F.L.A.F.; Zhang, G.; Carbonell, F.; Correa, J.A.; Harris, W.A.; Simons, B.D.; Cayouette, M. Reconstruction of rat retinal progenitor cell lineages in vitro reveals a surprising degree of stochasticity in cell fate decisions. *Development* 2011, 138, 227–235. [CrossRef]

81. Cayouette, M.; Barres, B.A.; Raft, M. Importance of Intrinsic Mechanisms in Cell Fate Decisions in the Developing Retina. *Neuron* 2003, 40, 897–904. [CrossRef]

82. He, J.; Zhang, G.; Almeida, A.D.; Cayouette, M.; Simons, B.D.D.; Harris, W.A. How Variable Clones Build an Invariant Retina. *Neuron* 2012, 75, 786–798. [CrossRef]

83. Elliott, J.; Jolicœur, C.; Ramamurthy, V.; Cayouette, M. Ikaros confers early temporal competence to mouse retinal progenitor cells. *Neuron* 2008, 60, 26–39. [CrossRef] [PubMed]

84. Tarchini, B.; Jolicœur, C.; Cayouette, M. In vivo evidence for unbiased Ikaros retinal lineages using an Ikaros-Cre mouse line driving clonal recombination. *Dev. Dyn.* 2012, 241, 1973–1985. [CrossRef] [PubMed]

85. Mattar, P.; Ericson, J.; Blackshaw, S.; Cayouette, M. A Conserved Regulatory Logic Controls Temporal Identity in Mouse Neural Progenitors. *Neuron* 2015, 85, 497–504. [CrossRef] [PubMed]

86. Boije, H.; MacDonald, R.B.; Harris, W.A. Reconciling competence and transcriptional hierarchies with stochasticity in retinal lineages. *Curr. Opin. Neurobiol.* 2014, 27, 68–74. [CrossRef]

87. Swaroop, A.; Kim, D.; Forrest, D. Transcriptional regulation of photoreceptor development and homeostasis in the mammalian retina. *Nat. Rev. Neurosci.* 2010, 11, 563–576. [CrossRef]

88. Marquardt, T.; Ashery-Padan, R.; Andrejevskii, N.; Scardigli, R.; Guillemot, F.; Gruss, P. Pax6 Is Required for the Multipotent State of Retinal Progenitor Cells Genesis, RPCs Appear to Be Retained in a Progenitor State by the Action of Notch-Delta Signaling and Down-Stream Effectors of Notch, like the bHLH Transcription. *Cell* 2001, 105, 43–45.

89. Burmeister, M.; Novak, J.; Liang, M.Y.; Basu, S.; Ploder, L.; Hawes, N.L.; Vidgen, D.; Hoover, F.; Goldman, D.; Kalnins, V.I.; et al. Ocular retardation mouse caused by Chx10 homeobox null allele: Impaired retinal progenitor proliferation and bipolar cell differentiation. *Nat. Genet.* 1996, 12, 376–384. [CrossRef]

90. Vitorino, M.; Jusuf, P.R.; Maurus, D.; Kimura, Y.; Higashijima, S.I.; Harris, W.A. Vsx2 in the zebrafish retina: Restricted lineages through derepression. *Neural Dev.* 2009, 4, 14. [CrossRef]
91. Brown, N.L.; Kanekar, S.; Vetter, M.L.; Tucker, P.K.; Gemza, D.L.; Glaser, T. Math5 encodes a murine basic helix-loop-helix transcription factor expressed during early stages of retinal neurogenesis. *Development* 1998, 125, 4821–4833.

92. Wang, S.W.; Kim, B.S.; Ding, K.; Wang, H.; Sun, D.; Johnson, R.L.; Klein, W.H.; Gan, L. Requirement for Math5 in the development of retinal ganglion cells. *Genes Dev.* 2001, 15, 24–29. [CrossRef]

93. Brown, N.L.; Patel, S.; Brzezinski, J.; Glaser, T. Math5 is required for retinal ganglion cell and optic nerve formation. *Development* 2001, 128, 2497–2508.

94. Le, T.T.; Wroblewski, E.; Patel, S.; Riesenber, A.N.; Brown, N.L. Math5 is required for both early retinal neuron differentiation and cell cycle progression. *Dev. Biol.* 2006, 295, 764–778. [CrossRef] [PubMed]

95. Kay, J.N.; Finger-Baier, K.C.; Roesser, T.; Staub, W.; Baier, H. Retinal ganglion cell genesis requires lakritz, a zebrafish atonal homolog. *Neuron* 2001, 30, 725–736. [CrossRef]

96. Yang, Z.; Ding, K.; Pan, L.; Deng, M.; Gan, L. Math5 determines the competence state of retinal ganglion cell progenitors. *Dev. Biol.* 2003, 264, 240–254. [CrossRef] [PubMed]

97. Feng, L.; Xie, Z.; Ding, Q.; Xie, X.; Libby, R.T.; Gan, L. MATH5 controls the acquisition of multiple retinal cell fates. *Mol. Brain* 2010, 3, 36. [CrossRef] [PubMed]

98. Brzezinski, J.A.; Prasov, L.; Glaser, T. Math5 defines the ganglion cell competence state in a subpopulation of retinal progenitor cells exiting the cell cycle. *Dev. Biol.* 2012, 365, 395–413. [CrossRef] [PubMed]

99. Hernandez, J.; Matter-Sadzinski, L.; Skowronska-Krawczyk, D.; Chiodini, F.; Alliod, C.; Ballivet, M.; Matter, J.M. Highly conserved sequences mediate the dynamic interplay of basic helix-loop-helix proteins regulating retinogenesis. *J. Biol. Chem.* 2007, 282, 37894–37905. [CrossRef]

100. Liu, W.; Mo, Z.; Xiang, M. The Ath5 proneural gene function upstream of Brn3 POU domain transcription factor genes to promote retinal ganglion cell development. *Proc. Natl. Acad. Sci. USA* 2001, 98, 1649–1654. [CrossRef]

101. Pan, L.; Yang, Z.; Feng, L.; Gan, L. Functional equivalence of Brn3 POU-domain transcription factors in mouse retinal neurogenesis. *Development* 2005, 132, 703–712. [CrossRef]

102. Gan, L.; Wang, S.W.; Huang, Z.; Klein, W.H.; Nathans, J. POU Domain Factor Brn-3b Is Essential for Retinal Ganglion Cell Differentiation and Survival but Not for Initial Cell Fate Specification. *Dev. Biol.* 1999, 210, 469–480. [CrossRef] [PubMed]

103. Xiang, M.; Zhou, L.; Macke, J.P.; Yoshioka, T.; Hendry, S.H.C.; Eddy, R.L.; Shows, T.B.; Nathans, J. The Brn-3 family of POU-domain factors: Primary structure, binding specificity, and expression in subsets of retinal ganglion cells and somatosensory neurons. *J. Neurosci.* 1995, 15, 4762–4785. [CrossRef]

104. Erkman, L.; McEvilly, R.J.; Luo, L.; Ryan, A.K.; Hooshmand, F.; O’Connell, S.M.; Keithley, E.M.; Rapaport, D.H.; Ryan, A.F.; Rosenfeld, M.G. Role of transcription factors a Brn-3.1 and Brn-3.2 in auditory and visual system differentiation and cell cycle progression. *Dev. Biol.* 2001, 239, 36–47. [CrossRef] [PubMed]

105. Wang, S.W.; et al. Brn3b in Controlling the Development, Morphology, and Function of Retinal Ganglion Cells. *Neuron* 2002, 36, 603–606. [CrossRef] [PubMed]

106. Mu, X.; Beremand, P.D.; Zhao, S.; Pershad, R.; Sun, H.; Scarpa, A.; Liang, S.; Thomas, T.L.; Klein, W.H. Discrete gene sets depend on POU domain transcription factor Brn3b/Brn-3.2/POU4f2 for their expression in the mouse embryonic retina. *Development* 2004, 131, 1197–1210. [CrossRef] [PubMed]

107. Qiu, F.; Jiang, H.; Xiang, M. A comprehensive negative regulatory program controlled by Brn3b to ensure ganglion cell specification from multipotential retinal precursors. *J. Neurosci.* 2008, 28, 3392–3403. [CrossRef]

108. Xiang, M. Requirement for Brn-3b in early differentiation of postmitotic retinal ganglion cell precursors. *Dev. Biol.* 1998, 197, 155–169. [CrossRef]

109. Wang, S.W.; Mu, X.; Bowers, W.J.; Kim, D.S.; Plas, D.J.; Crait, M.C.; Fedoroff, H.J.; Gan, L.; Klein, W.H.; Wang, S.W.; et al. Brn3b/Brn3c double knockout mice reveal an unsuspected role for Brn3c in retinal ganglion cell axon outgrowth. *Development* 2002, 129, 467–477.

110. Badea, T.C.; Cahill, H.; Ecker, J.; Hattar, S.; Nathans, J. Distinct Roles of Transcription Factors Brn3a and Brn3b in Controlling the Development, Morphology, and Function of Retinal Ganglion Cells. *Neuron* 2009, 61, 852–864. [CrossRef]

111. Mao, C.A.A.; Wang, S.W.; Pan, P.; Klein, W.H. Rewiring the retinal ganglion cell gene regulatory network: Neurod1 promotes retinal ganglion cell fate in the absence of Math5. *Development* 2008, 135, 3379–3388. [CrossRef]
112. Mu, X.; Fu, X.; Beremand, P.D.; Thomas, T.L.; Klein, W.H. Gene regulation logic in retinal ganglion cell development: Is11 defines a critical branch distinct from but overlapping with Pou4f2. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 6942–6947. [CrossRef]

113. Pan, L.; Deng, M.; Xie, X.; Gan, L. ISL1 and BRN3B co-regulate the differentiation of murine retinal ganglion cells. *Development* **2008**, *135*, 1981–1990. [CrossRef]

114. Elshatory, Y.; Deng, M.; Xie, X.; Gan, L. Expression of the LIM-homeodomain protein Is11 in the developing and mature mouse retina. *J. Comp. Neurol.* **2007**, *503*, 182–197. [CrossRef] [PubMed]

115. Elshatory, Y.; Everhart, D.; Deng, M.; Xie, X.; Barlow, R.B.; Gan, L. Islet-1 Controls the Differentiation of Retinal Bipolar and Cholinergic Amacrine Cells. *J. Neurosci.* **2007**, *27*, 12707–12720. [CrossRef] [PubMed]

116. Erkman, L.; Yates, P.A.; McLaughlin, T.; McEvilly, R.J.; Whisenhunt, T.; O’Connell, S.M.; Krones, A.I.; Kirby, M.A.; Rapaport, D.H.; Bermingham, J.R.; et al. A POU Domain Transcription Factor-Dependent Program Regulates Axon Pathfinding in the Vertebrate Visual System. *Neuron* **2000**, *28*, 779–792. [CrossRef]

117. Wu, F.; Kaczynski, T.J.; Sethuramanujam, S.; Li, R.; Jain, V.; Slaughter, M.; Mu, X. Two transcription factors, Pou4f2 and Is11, are sufficient to specify the retinal ganglion cell fate. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E1559–E1568. [CrossRef]

118. Del Bene, F.; Ettwiller, L.; Skowronska-Krawczyk, D.; Baier, H.; Matter, J.M.; Birney, E.; Wittbrodt, J. In Vivo Validation of a Computationally Predicted Conserved Ath5 Target Gene Set. *PLoS Genet.* **2007**, *3*, e159. [CrossRef]

119. de Melo, J.; Du, G.; Fonseca, M.; Gillespie, L.A.; Turk, W.J.; Rubenstein, J.L.R.; Eisenstat, D.D. Dlx1 and Dlx2 function is necessary for terminal differentiation and survival of late-born retinal ganglion cells in the developing mouse retina. *Development* **2005**, *132*, 311–322. [CrossRef]

120. Zhang, Q.; Zagozewski, J.; Cheng, S.; Dixit, R.; Zhang, S.; de Melo, J.; Mu, X.; Klein, W.H.; Brown, N.L.; Wigle, J.T.; et al. Regulation of Bm3b by DLX1 and DLX2 is required for retinal ganglion cell differentiation in the vertebrate retina. *Development* **2017**, *144*, 1698–1711. [CrossRef]

121. Usui, A.; Mochizuki, Y.; Iida, A.; Miyauchi, E.; Satoh, S.; Sock, E.; Nakauchi, H.; Murakami, A.; Wegner, M.; et al. The early retinal progenitor-expressed gene Sox11 regulates the timing of the differentiation of retinal cells. *Development* **2013**, *140*, 740–750. [CrossRef]

122. Jiang, Y.; Ding, Q.; Xie, X.; Libby, R.T.; Lefebvre, V.; Gan, L. Transcription Factors SOX4 and SOX11 Function Redundantly to Regulate the Development of Mouse Retinal Ganglion Cells. *J. Biol. Chem.* **2013**, *288*, 18429–18438. [CrossRef]

123. Gao, Z.; Mao, C.A.; Pan, P.; Mu, X.; Klein, W.H. Transcriptome of Atoh7 retinal progenitor cells identifies new Atoh7-dependent regulatory genes for retinal ganglion cell formation. *Dev. Neurobiol.* **2014**, *74*, 1123–1140. [CrossRef] [PubMed]

124. Clark, B.S.; Stein-O’Brien, G.L.; Shiau, F.; Cannon, G.H.; Davis-Marcisak, E.; Sherman, T.; Santiago, C.P.; Hoang, T.V.; Rajaii, F.; James-ESposto, R.E.; et al. Single-Cell RNA-Seq Analysis of Retinal Development Identifies NFI Factors as Regulating Mitotic Exit and Late-Born Cell Specification. *Neuron* **2019**, *102*, 1111–1126. [CrossRef] [PubMed]

125. Lo Giudice, Q.; Leleu, M.; La Manno, G.; Fabre, P.J. Single-cell transcriptional logic of cell-fate specification and axon guidance in early born retinal neurons. *Development* **2019**, *146*. [CrossRef] [PubMed]

126. Hu, Y.; Wang, X.; Hu, B.; Mao, Y.; Chen, Y.; Yan, L.; Yong, J.; Dong, J.; Wei, Y.; Wang, W.; et al. Dissecting the transcriptome landscape of the human fetal neural retina and retinal pigment epithelium by single-cell RNA-seq analysis. *PLoS Biol.* **2019**, *17*, e3000365. [CrossRef] [PubMed]

127. Zhao, F.; Lufkin, T.; Gelb, B.D. Expression of Tfap2d, the gene encoding the transcription factor Ap-2δ, during mouse embryogenesis. *Gene Expr. Patterns* **2003**, *3*, 213–217. [CrossRef]

128. Reichman, S.; Terray, A.; Slembruck, A.; Nanteau, C.; Orieux, G.; Habeler, W.; Nakauchi, H.; Aburatani, H.; Murakami, A.; Elshatory, Y.; Everhart, D.; Deng, M.; Xie, X.; Barlow, R.B.; Gan, L. Islet-1 Controls the Di
132. Georgi, S.A.; Reh, T.A. Dicer Is Required for the Transition from Early to Late Progenitor State in the Developing Mouse Retina. *J. Neurosci.* 2010, 30, 4048–4061. [CrossRef]

133. Georgi, S.A.; Reh, T.A. Dicer is required for the maintenance of notch signaling and gliogenic competence during mouse retinal development. *Dev. Neurobiol.* 2011, 71, 1153–1169. [CrossRef]

134. Davis, N.; Mor, E.; Ashery-Padan, R. Roles for Dicer1 in the patterning and differentiation of the optic cup neuroepithelium. *Development* 2011, 138, 127–138. [CrossRef] [PubMed]

135. Iida, A.; Shinoe, T.; Baba, Y.; Mano, H.; Watanabe, S. Dicer plays essential roles for retinal development by regulation of survival and differentiation. *Investig. Ophthalmol. Vis. Sci.* 2011, 52, 3008–3017. [CrossRef] [PubMed]

136. La Torre, A.; Georgi, S.; Reh, T.A. Conserved microRNA pathway regulates developmental timing of retinal neurogenesis. *Proc. Natl. Acad. Sci. USA* 2013, 110, 2362–2370. [CrossRef] [PubMed]

137. Rasheed, V.A.; Sreekanth, S.; Dhanesh, S.B.; Divya, M.S.; Divya, T.S.; Akhila, P.K.; Subashini, C.; Chandrika Sivakumar, K.; Das, A.V.; James, J. Developmental wave of Brn3b expression leading to RGC fate specification is synergistically maintained by miR-23a and miR-374. *Dev. Neurobiol.* 2014, 74, 1155–1171. [CrossRef] [PubMed]

138. Krol, J.; Loedige, I.; Filipowicz, W. The widespread regulation of microRNA biogenesis, function and decay. *Nat. Rev. Genet.* 2010, 11, 597–610. [CrossRef] [PubMed]

139. Friedman, R.C.; Farh, K.K.H.; Burge, C.B.; Bartel, D.P. Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res.* 2009, 19, 92–105. [CrossRef]

140. Baek, D.; Villén, J.; Shin, C.; Camargo, F.D.; Gygi, S.P.; Bartel, D.P. The impact of microRNAs on protein output. *Nature* 2008, 455, 64–71. [CrossRef]

141. Pinter, R.; Hindges, R. Perturbations of MicroRNA Function in Mouse Dicer Mutants Produce Retinal Defects and Lead to Aberrant Axon Pathfinding at the Optic Chiasm. *PLoS ONE* 2010, 5, e10021. [CrossRef]

142. Seritrakul, P.; Gross, J.M. Genetic and epigenetic control of retinal development in zebrafish. *Curr. Opin. Neurobiol.* 2019, 59, 120–127. [CrossRef]

143. Fischer, A.J.; Reh, T.A. Identification of a proliferating marginal zone of retinal progenitors in postnatal chickens. *Dev. Biol.* 2000, 220, 197–210. [CrossRef]

144. Johns, P.R. Growth of the adult goldfish eye. III. Source of the new retinal cells. *J. Comp. Neurol.* 1977, 176, 343–357. [CrossRef] [PubMed]

145. Straznicky, K.; Gaze, R.M. The growth of the retina in *Xenopus laevis*: An autoradiographic study. *J. Embryol. Exp. Morph.* 1971, 26, 67–79. [PubMed]

146. Fischer, A.J.; Bosse, J.L.; El-Hodiri, H.M. The ciliary marginal zone (CMZ) in development and regeneration of the vertebrate eye. *Exp. Eye Res.* 2013, 116, 199–204. [CrossRef] [PubMed]

147. Hitchcock, P.; Raymond, P. Retinal regeneration. *Trends Neurosci.* 1992, 15, 103–108. [CrossRef]

148. Hollyfield, J.G. Differential growth of the neural retina inXenopus laevis larvae. *Dev. Biol.* 1971, 24, 264–286. [CrossRef]

149. Livesey, F.J.; Cepko, C.L.C. Vertebrate neural cell-fate determination: Lessons from the retina. *Nat. Rev. Neurosci.* 2002, 109–118. [CrossRef]

150. Davis, N.; Yoffe, C.; Raviv, S.; Antes, R.; Berger, J.; Holzmann, S.; Stoykova, A.; Overbeek, P.A.; Tamm, E.R.; Ashery-Padan, R. Pax6 dosage requirements in iris and ciliary body differentiation. *Dev. Biol.* 2009, 333, 132–142. [CrossRef]

151. Marcucci, F.; Murcia-Belmonte, V.; Wang, Q.; Coca, Y.; Ferreira-Galve, S.; Kuwajima, T.; Khalid, S.; Ross, M.E.; Mason, C.; Herrera, E. The Ciliary Margin Zone of the Mammalian Retina Generates Retinal Ganglion Cells. *Cell Rep.* 2016, 17, 3153–3164. [CrossRef]

152. Bélinger, M.C.C.; Robert, B.; Cayouette, M. Msx1-Positive Progenitors in the Retinal Ciliary Margin Give Rise to Both Neural and Non-neural Progenies in Mammals. *Dev. Cell* 2017, 40, 137–150. [CrossRef]

153. Moster, D.K. The pattern of neurogenesis in the retina of the rat. *Z. Anat. Entwickl.* 1970, 131, 45–67. [CrossRef]

154. Hinds, J.W.; Hinds, P.L. Early ganglion cell differentiation in the mouse retina: An electron microscopic analysis utilizing serial sections. *Dev. Biol.* 1974, 37, 381–416. [CrossRef]

155. McLoon, S.C.; Barnes, R.B. Early differentiation of retinal ganglion cells: An axonal protein expressed by premigratory and migrating retinal ganglion cells. *J. Neurosci.* 1989, 9, 1424–1432. [CrossRef] [PubMed]
157. Icha, J.; Kunath, C.; Rocha-Martins, M.; Norden, C. Independent modes of ganglion cell translocation ensure correct lamination of the zebrafish retina. *J. Cell Biol.* 2016, 215, 259–275. [CrossRef] [PubMed]

158. Riccomagno, M.M.; Sun, L.O.; Brady, C.M.; Alexandropoulos, K.; See, S.; Kurokawa, M.; Kolodkin, A.L. Cas Adaptor Proteins Organize the Retinal Ganglion Cell Layer Downstream of Integrin Signaling. *Neuron* 2014, 81, 779–786. [CrossRef] [PubMed]

159. Amini, R.; Rocha-Martins, M.; Norden, C. Neuronal Migration and Lamination in the Vertebrate Retina. *Front. Neurosci.* 2018, 11, 742. [CrossRef]

160. Barnstable, C.J.; Dräger, U.C. Thy-1 antigen: A ganglion cell specific marker in rodent retina. *Neuroscience* 1984, 11, 847–855. [CrossRef]

161. Rodriguez, A.R.; de Sevilla Müller, L.P.; Brecha, N.C. The RNA binding protein RBPMS is a selective marker of ganglion cells in the mammalian retina. *J. Comp. Neurol.* 2014, 522, 1411–1443. [CrossRef]

162. Ramón y Cajal, S. La rétine des vertébrés. *Cellule* 1892, 1, 119–257.

163. Baden, T.; Berens, P.; Franke, K.; Román Rosón, M.; Bethge, M.; Euler, T. The functional diversity of retinal ganglion cells in the mouse. *Nature* 2016, 529, 345–350. [CrossRef]

164. Helmstaedter, M.; Briggman, K.L.; Turaga, S.C.; Jain, V.; Seung, H.S.; Denk, W. Connectomic reconstruction of the inner plexiform layer in the mouse retina. *Nature* 2013, 500, 168–174. [CrossRef] [PubMed]

165. Coombs, J.; van Der List, D.; Wang, G.Y.; Chalupa, L.M. Morphological properties of mouse retinal ganglion cells. *Neuroscience* 2006, 140, 123–136. [CrossRef] [PubMed]

166. Kong, J.H.; Fish, D.R.; Rockhill, R.L.; Masland, R.H. Diversity of ganglion cells in the mouse retina: Unsupervised morphological classification and its limits. *J. Comp. Neurol.* 2005, 489, 293–310. [CrossRef]

167. Badea, T.C.; Nathans, J. Quantitative analysis of neuronal morphologies in the mouse retina visualized by using a genetically directed reporter. *J. Comp. Neurol.* 2004, 480, 331–351. [CrossRef] [PubMed]

168. Völgyi, B.; Chheda, S.; Bloomfield, S.A. Tracer coupling patterns of the ganglion cell subtypes in the mouse retina. *J. Comp. Neurol.* 2009, 512, 664–687. [CrossRef] [PubMed]

169. Sümbül, U.; Song, S.; McCulloch, K.; Becker, M.; Lin, B.; Sanes, J.R.; Masland, R.H.; Seung, H.S. A genetic and computational approach to structurally classify neuronal types. *Nat. Commun.* 2014, 5, 3512. [CrossRef]

170. Weng, S.; Sun, W.; He, S. Identification of ON-OFF direction-selective ganglion cells in the mouse retina. *J. Physiol.* 2005, 562, 915–925. [CrossRef] [PubMed]

171. Sun, W.; Deng, Q.; Levick, W.R.; He, S. ON direction-selective ganglion cells in the mouse retina. *J. Physiol.* 2006, 576, 197–202. [CrossRef] [PubMed]

172. Pang, J.J.; Gao, F.; Wu, S.M. Light-Evoked Excitatory and Inhibitory Synaptic Inputs to ON and OFF α Ganglion Cells in the Mouse Retina. *J. Neurosci.* 2003, 23, 6063–6073. [CrossRef]

173. Hattar, S.; Liao, H.W.; Takao, M.; Berson, D.M.; Yau, K.W. Melanopsin-Containing Retinal Ganglion Cells: Architecture, Projections, and Intrinsic Photosensitivity. *J. Physiol.* 2005, 562, 915–925. [CrossRef] [PubMed]

174. Jacoby, J.; Schwartz, G.W. Three Small-Receptive-Field Ganglion Cells in the Mouse Retina Are Distinctly Tuned to Size, Speed, and Object Motion. *J. Neurosci.* 2017, 37, 610–625. [CrossRef] [PubMed]

175. Zhang, Y.; Kim, I.J.; Sanes, J.R.; Meister, M. The most numerous ganglion cell type of the mouse retina is a selective feature detector. *Proc. Natl. Acad. Sci. USA* 2012, 109, 2391–2398. [CrossRef] [PubMed]

176. Kim, I.J.; Zhang, Y.; Yamagata, M.; Meister, M.; Sanes, J.R. Molecular identification of a retinal cell type that responds to upward motion. *Nature* 2008, 452, 478–482. [CrossRef] [PubMed]

177. Vlasis, A.L.; Euler, T.; Franke, K. Function first: Classifying cell types and circuits of the retina. *Curr. Opin. Neurobiol.* 2019, 56, 8–15. [CrossRef] [PubMed]

178. Sweeney, N.T.; James, K.N.; Lorig-Roach, R.M.; Feldheim, D.A. Expression of transcription factors divides retinal ganglion cells into distinct classes. *J. Comp. Neurol.* 2019, 527, 225–235. [CrossRef] [PubMed]

179. Triplett, J.W.; Wei, W.; Gonzalez, C.; Sweeney, N.T.; Huberman, A.D.; Feller, M.B.; Felldheim, D.A. Dendritic and axonal targeting patterns of a genetically-specified class of retinal ganglion cells that participate in image-forming circuits. *Neural Dev.* 2014, 9, 2. [CrossRef] [PubMed]

180. Peng, Y.R.R.; Tran, N.M.; Krishnaswamy, A.; Kostadinov, D.; Martersteck, E.M.; Sanes, J.R. Satb1 Regulates Contactin 5 to Pattern Dendrites of a Mammalian Retinal Ganglion Cell. *Neuron* 2017, 95, 869–883. [CrossRef]
181. Mao, C.A.; Li, H.; Zhang, Z.; Kiyama, T.; Panda, S.; Hattar, S.; Ribelayga, C.P.; Mills, S.L.; Wang, S.W. T-box Transcription Regulator Tbr2 Is Essential for the Formation and Maintenance of Opn4/Melanopsin-Expressing Intrinsically Photosensitive Retinal Ganglion Cells. *J. Neurosci.* 2014, 34, 13083–13095. [CrossRef]

182. Sweeney, N.T.; Tierney, H.; Feldheim, D.A. Tbr2 Is Required to Generate a Neural Circuit Mediating the Pupillary Light Reflex. *J. Neurosci.* 2014, 34, 5447–5453. [CrossRef]

183. Laboissonniere, L.A.; Goetz, J.J.; Martin, G.M.; Bi, R.; Lund, T.J.S.; Ellson, L.; Lynch, M.R.; Mooney, B.; Wickham, H.; Liu, P.; et al. Molecular signatures of retinal ganglion cells revealed through single cell profiling. *Sci. Rep.* 2019, 9, 15778. [CrossRef]

184. Kuwajima, T.; Yoshida, Y.; Takegahara, N.; Petros, T.J.; Kumanogoh, A.; Jessell, T.M.; Sakurai, T.; Mason, C. Optic Chiasm Presentation of Semaphorin6D in the Context of Plexin-A1 and Nr-CAM Promotes Retinal Axon Midline Crossing. *Neuron* 2012, 74, 676–690. [CrossRef] [PubMed]

185. Garcia-Frigola, C.; Carreres, M.I.; Vegar, C.; Mason, C.A.; Herrera, E. Zic2 Promotes Axonal Divergence at the Optic Chiasm Midline by Specifying the Uncrossed Retinal Projection. *Cell Rep.* 2018, 24, 291–328. [CrossRef] [PubMed]

186. Hong, Y.K.; Kim, I.J.; Sanes, J.R. Stereotyped axonal arbors of retinal ganglion cell subsets in the mouse superior colliculus. *J. Comp. Neurol.* 2011, 519, 1691–1711. [CrossRef]

187. Dhande, O.S.; Huberman, A.D. Retinal ganglion cell maps in the brain: Implications for visual processing. *Curr. Opin. Neurobiol.* 2014, 24, 133–142. [CrossRef] [PubMed]

188. Dhande, O.S.; Stafford, B.K.; Lim, J.H.A.; Huberman, A.D. Contributions of Retinal Ganglion Cells to Subcortical Visual Processing and Behaviors. *Annu. Rev. Vis. Sci.* 2015, 1, 291–328. [CrossRef] [PubMed]

189. Morin, L.P.; Studholme, K.M. Retinofugal projections in the mouse. *J. Comp. Neurol.* 2014, 522, 3733–3753. [CrossRef] [PubMed]

190. Hong, Y.K.; Kim, I.J.; Sanes, J.R. Stereotyped axonal arbors of retinal ganglion cell subsets in the mouse superior colliculus. *J. Comp. Neurol.* 2011, 519, 1691–1711. [CrossRef]

191. Morin, L.P.; Studholme, K.M. Retinofugal projections in the mouse. *J. Comp. Neurol.* 2014, 522, 3733–3753. [CrossRef] [PubMed]

192. Rompani, S.B.; Müllner, F.E.; Wanner, A.; Zhang, C.; Roth, C.N.; Yonehara, K.; Roska, B. Divergence and Axon Guidance at the Midline: Chiasmatic Misrouting and Consequences. *Neuron* 2012, 74, 676–690. [CrossRef] [PubMed]

193. Pak, W.; Hindges, R.; Lim, Y.S.; Pfaff, S.L.; O’leary, D.D.M. Magnitude of Binocular Vision Controlled by Islet-2 Repression of a Genetic Program that Specifies Laterality of Retinal Axon Pathfinding. *Cell* 2004, 119, 567–578. [CrossRef]

194. Kuwajima, T.; Soares, C.A.; Sitko, A.A.; Lefebvre, V.; Mason, C. SoxC Transcription Factors Promote Contralateral Retinal Ganglion Cell Differentiation and Axon Guidance in the Mouse Visual System. *Neuron* 2017, 93, 1110–1125. [CrossRef] [PubMed]

195. Hong, Y.K.; Kim, I.J.; Sanes, J.R. Stereotyped axonal arbors of retinal ganglion cell subsets in the mouse superior colliculus. *J. Comp. Neurol.* 2011, 519, 1691–1711. [CrossRef]

196. Hong, Y.K.; Kim, I.J.; Sanes, J.R. Stereotyped axonal arbors of retinal ganglion cell subsets in the mouse superior colliculus. *J. Comp. Neurol.* 2011, 519, 1691–1711. [CrossRef]

197. Pak, W.; Hindges, R.; Lim, Y.S.; Pfaff, S.L.; O’leary, D.D.M. Magnitude of Binocular Vision Controlled by Islet-2 Repression of a Genetic Program that Specifies Laterality of Retinal Axon Pathfinding. *Cell* 2004, 119, 567–578. [CrossRef]

198. Herrera, E.; Brown, L.; Aruga, J.; Rachel, R.A.; Dolen, G.; Mikoshiba, K.; Brown, S.; Mason, C.A. Zic2 Patterns Binocular Vision by Specifying the Uncrossed Retinal Projection. *Cell* 2003, 114, 545–557. [CrossRef]

199. Williams, S.E.; Mann, F.; Erskine, L.; Sakurai, T.; Wei, S.; Rossi, D.J.; Gale, N.W.; Holt, C.E.; Mason, C.A.; Henkemeyer, M. Ephrin-B2 and EphB1 Mediate Retinal Axon Divergence at the Optic Chiasm. *Neuron* 2003, 39, 919–935. [CrossRef]

200. Upton, A.L.; Salichon, N.; Lebrand, C.; Ravary, A.; Blakely, R.; Seif, I.; Gaspar, P. Excess of serotonin (5-HT) alters the segregation of ipsilateral and contralateral retinal projections in monoamine oxidase A knock-out mice: Possible role of 5-HT uptake in retinal ganglion cells during development. *J. Neurosci.* 1999, 19, 7007–7024. [CrossRef]
201. Upton, A.L.; Ravary, A.; Salichon, N.; Moessner, R.; Lesch, K.P.; Hen, R.; Seif, I.; Gaspar, P. Lack of 5-HT1B receptor and of serotonin transporter have different effects on the segregation of retinal axons in the lateral geniculate nucleus compared to the superior colliculus. *Neuroscience* 2002, 111, 597–610. [CrossRef]

202. Petros, T.J.; Shrestha, B.R.; Mason, C.A. Specificity and sufficiency of EphB1 in driving the ipsilateral retinal projection. *J. Neurosci.* 2009, 29, 3463–3474. [CrossRef]

203. Wang, Q.; Marcucci, F.; Cerullo, I.; Mason, C. Ipsilateral and Contralateral Retinal Ganglion Cells Express Distinct Genes during Decussation at the Optic Chiasm. *eNeuro* 2016, 3. [CrossRef]

204. Herrera, E.; Marcus, R.; Li, S.; Williams, S.E.; Erskine, L.; Lai, E.; Mason, C. Foxd1 is required for proper formation of the optic chiasm. *Development* 2004, 131, 5727–5739. [CrossRef] [PubMed]

205. Carreres, M.I.; Escalante, A.; Murillo, B.; Chauvin, G.; Gaspar, P.; Vegar, C.; Herrera, E. Transcription Factor Foxd1 Is Required for the Specification of the Temporal Retina in Mammals. *J. Neurosci.* 2011, 31, 5673–5681. [CrossRef] [PubMed]

206. Sanchez-Arrones, L.; Nieto-Lopez, F.; Sanchez-Camacho, C.; Carreres, M.I.; Herrera, E.; Okada, A.; Bovolenta, P. Shh/Boc Signaling Is Required for Sustained Generation of Ipsilateral Projecting Ganglion Cells in the Mouse Retina. *J. Neurosci.* 2013, 33, 8596–8607. [CrossRef] [PubMed]

207. Abadi, R.; Pascal, E. The recognition and management of albinism. *Ophthalmic Physiol. Opt.* 1989, 9, 3–15. [CrossRef]

208. Apkarian, P. Chiasmal crossing defects in disorders of binocular vision. *Eye* 1996, 10, 222–232. [CrossRef]

209. Holder, G.E. Electrophysiological assessment of optic nerve disease. *Eye* 2004, 18, 1133–1143. [CrossRef]

210. von dem Hagen, E.A.H.; Hoffmann, M.B.; Morland, A.B. Identifying human albinism: A comparison of VEP and fMRI. *Investig. Ophthalmol. Vis. Sci.* 2008, 49, 238–249. [CrossRef]

211. Ilia, M.; Jeffery, G. Delayed neurogenesis in the albino retina: Evidence of a role for melanin in regulating the pace of cell generation. *Brain Res. Dev. Brain Res.* 1996, 95, 176–183. [CrossRef]

212. Bhansali, P.; Rayport, I.; Rebsam, A.; Mason, C. Delayed neurogenesis leads to altered specification of ventrotemporal retinal ganglion cells in albino mice. *Neural Dev.* 2014, 9, 11. [CrossRef]

213. Jeffery, G.; Brem, G.; Montoliu, L. Correction of retinal abnormalities found in albinism by introduction of a functional tyrosinase gene in transgenic mice and rabbits. *Dev. Brain Res.* 1997, 99, 95–102. [CrossRef]

214. Averaimo, S.; Assali, A.; Ros, O.; Couvet, S.; Zagar, Y.; Genescu, I.; Rebsam, A.; Nicol, X. A plasma membrane microdomain compartmentalizes ephrin-generated cAMP signals to prune developing retinal axon arbors. *Nat. Commun.* 2016, 7, 12896. [CrossRef] [PubMed]

215. Rebsam, A.; Bhansali, P.; Mason, C.A. Eye-Specific Projections of Retinogeniculate Axons Are Altered in Albino Mice. *J. Neurosci.* 2012, 32, 4821–4826. [CrossRef] [PubMed]

216. Iwai-Takekoshi, L.; Balasubramanian, R.; Sitko, A.; Khan, R.; Weinreb, S.; Robinson, K.; Mason, C. Activation of Wnt signaling reduces ipsilaterally projecting retinal ganglion cells in pigmented retina. *Development* 2018, 145. [CrossRef] [PubMed]

217. Llorca, A.; Ciceri, G.; Beattie, R.; Wong, F.K.; Diana, G.; Serafeimidou-Poulou, E.; Fernández-Otero, M.; Streicher, C.; Arnold, S.J.; Meyer, M.; et al. A stochastic framework of neurogenesis underlies the assembly of neocortical cytoarchitecture. *Elife* 2019, 8, e51381. [CrossRef]

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