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Trends in Neurosciences

Feature Review

Retinal ganglion cell circuits and glial interactions in humans and mice

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Retinal ganglion cells (RGCs) are the brain's gateway for vision, and their degeneration underlies several blinding diseases. RGCs interact with other neuronal cell types, microglia, and astrocytes in the retina and in the brain. Much knowledge has been gained about RGCs and glia from mice and other model organisms, often with the assumption that certain aspects of their biology may be conserved in humans. However, RGCs vary considerably between species, which could affect how they interact with their neuronal and glial partners. This review details which RGC and glial features are conserved between mice, humans, and primates, and which differ. We also discuss experimental approaches for studying human and primate RGCs. These strategies will help to bridge the gap between rodent and human RGC studies and increase study translatability to guide future therapeutic strategies.

Highlights

Retinal ganglion cells (RGCs) are crucial for vision, and they interact across species with broadly conserved cell types that include neural partners, astrocytes, and microglia in the retina and the brain.

Humans have approximately half as many ganglion cell types as mice, and human high-acuity vision relies on only a few RGC types within the fovea, a structure that is absent in mice.

RGCs communicate with microglia and astrocytes to impact glial biology, and glial cells in turn modulate ganglion cell connectivity and function.

Emerging models for studying the human visual system may uncover human-specific differences in neural development and neuron–glia interactions that may drive specialized features of human brain development more broadly.

Mouse and human retina exhibit distinct cellular and organizational properties

Studies in neuroscience rely heavily on mice and other model organisms to discover principles that are hoped to be useful in understanding the human nervous system and perhaps treating its diseases. This extends to studies of sensory systems such as the visual system. Vision begins in the retina, and the importance of studies in mice and other animal models in increasing our understanding of retinal circuitry cannot be overstated. However, recent data have uncovered a surprising degree of human-specific specialization in retinal cell diversity, wiring, and functional variability relative to mouse models. Understanding these differences is crucial given that the relatively 'simple' retinal circuit has been used to discover generalizable neural principles.

In this review we focus on RGCs and their interactions with retinal and brain neurons, as well as with two key glial cell types, microglia and astrocytes. We begin by outlining the development and organization of RGCs and these glial types in both mice and humans or primates. Next, we discuss RGC interactions with their presynaptic partners in the retina and postsynaptic partners in the brain, and highlight the roles of microglia and astrocytes in shaping these connections. We then examine the similarities and differences between RGCs and glial cell types in mice and humans or primates and explore potential reasons for the differences across species. Finally, we address the challenges of studying human- and primate-specific RGC and glial features, and evaluate experimental approaches to overcome the significant variability between species.

RGC and glia organization across the retinal surface

Diurnal primates are the only mammalian species that have a retinal structure known as the fovea, which is important for high-acuity vision (Figure 1). The fovea lies at the center of the macula. Both structures represent <5% of the retinal area, but in many foveated species these regions are responsible for nearly 50% of the visual information passed to the brain [1,2]. Visual acuity declines rapidly outside the fovea, and primates have evolved eye movements to direct the fovea to regions of interest in the visual scene [3]. Many diseases cause the fovea to degrade, and any

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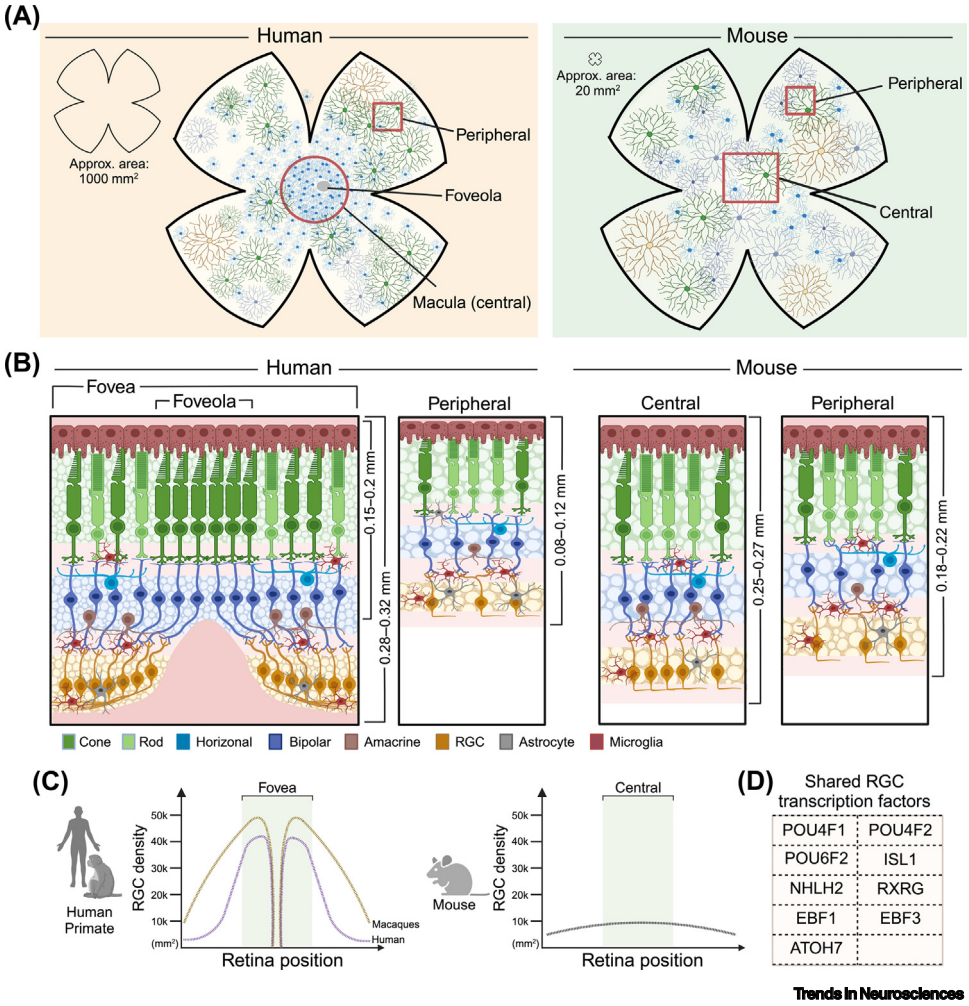

Figure 1. Retinal ganglion cell (RGC) densities and topography in primate and mouse. (A) Schematic of a flat mount retina in humans and mouse. The human retina is larger than the mouse retina, shows lower RGC subtype diversity, and has a macula and fovea. The primate macula has a much higher RGCs density than the peripheral retina. The mouse retina lacks a macula and fovea, but displays slightly higher RGC densities in the retina center compared to the periphery. (B) Cross-section schematic and the retinal thickness of the human and mouse retina [4]. In both species the retina has three cellular layers, two synaptic layers, and a retina nerve fiber layer. Rod and cone photoreceptor nuclei reside in the outermost layer, whereas horizontal, bipolar, most amacrine, and Müller glia nuclei (not shown) reside in the inner nuclear layer. RGC and displaced amacrine nuclei reside in the ganglion cell layer, and RGC axons and astrocytes reside in the retina nerve fiber layer. Microglia processes are enriched in the synaptic layers. The primate fovea shows a characteristic displacement of inner retina neurons such that light has direct access to the dense cones populating this region. (C) Approximate spatial distributions of RGC densities in primates versus mice. RGCs are most numerous in the primate macular region and absent from the foveola, whereas in mouse RGC density is only moderately higher in the central retina (modified from [9]). (D) Shared transcription factors contribute to RGC specification in mouse and primates [39]. Figure created with BioRender.

therapy that aims to preserve or restore high-acuity vision must target the fovea. For this reason, rodents and other widely accessible animal models that lack a fovea are less effective for modeling the development or diseases of this important retinal region.

What organizational properties of the fovea underlie high-acuity vision? Viewed in cross-section, both mouse and primate retina have a conserved stereotypic laminar organization consisting of

three cellular layers, two synaptic layers, and an axonal layer. Photoreceptor nuclei reside in the outer nuclear layer, whereas horizontal cell, amacrine, and bipolar cell nuclei reside in the inner nuclear layer, and RGC and displaced amacrine nuclei reside in the ganglion cell layer. The outer plexiform layer (OPL) is composed of synapses between photoreceptors and bipolar and horizontal cells, and the inner plexiform layer (IPL) consists of synapses between RGCs and bipolar and amacrine cells. RGC axons and astrocytes reside in the retina never fiber layer (RNFL). In primates and humans, the fovea is ~1.5 mm in diameter and covers 5° of the visual field. Within the fovea resides the foveal pit, or foveola [4]. This 350 μm diameter region represents 1° of the visual field and shows altered laminar organization [2,5]. The inner retina layers are displaced to the side and blood vessels are absent, creating the foveal avascular zone [6] (Figure 1B). This arrangement allows light to directly reach foveal cones without first traversing cell bodies and synapses. In addition to these modifications, foveal cones are connected to dedicated bipolar cells and ganglion cells. Primates have the highest macular RGC densities (~50 000 RGCs per mm^2 in macaques), with up to eight layers of ganglion cell bodies [7]. Two RGC types, called midget and parasol RGCs, are the most abundant in the human and primate retina and occupy the majority of the fovea and macula. RGC density is lower in the primate peripheral retina, with ~10 000 cells per mm^2 [8,9]. Humans RGC densities range from ~40 000 RGCs per mm^2 in the fovea to 3000 in the periphery [8]. Human retinal thickness also varies from ~0.3 mm in the parafovea to ~0.1 in the periphery [10] (Figure 1B,C). Although rodents lack a macula and fovea, they display slightly higher RGC densities in the retina center versus the periphery (from 10 000 to 5000 RGCs per mm^2, respectively). Retinal thickness also varies from the center to periphery, but less so than in humans, ranging from ~0.26 mm in the center to ~0.2 mm in the periphery (Figure 1B,C). Mouse RGCs are arranged in a monolayer [11].

Mouse RGC somas and processes are adjacent to glia cells, an arrangement that is conserved in humans. These glial populations include microglia, which are retina-resident immune phagocytes, astrocytes, and Müller glia. This review focuses on the former two populations (Müller glial function is reviewed in [12]). In humans, microglia comprise ~30% of the cells in the retina [13]. Among other roles, microglia modulate RGC survival and connectivity [14]. At the transcriptional level, mouse and human microglia show a high degree of similarity [15]. In adult primate retinas, microglia are sparse in the foveal center, and these cells are mainly found in the RNFL, IPL, and OPL (Figure 1B). IPL and OPL microglia density peaks in the parafoveal region and decreases toward the periphery. Parafoveal microglia processes are also more complex than their peripheral counterparts [16]. RNFL microglia density is relatively uniform across the retina compared to other layers, suggesting the potential for specialized RNFL microglia functions, such as supporting the superficial vasculature. In addition, primate microglial density increases with age, especially in the fovea and macula [16].

RNFL-localized astrocytes also interact with RGCs by providing metabolic support, aiding vessel growth, and participating in retina–blood barrier formation [17,18]. GFAP-positive cells are present in the human and primate foveola, but whether these are astrocytes or Müller cells is less clear [19,20]. Modern single-cell labeling methods reveal variations in the stereotypical 'star-like' astrocyte morphology. It is presently unclear whether these structural variations have biological relevance [17]. Astrocyte density in the human retina also varies: the highest concentration occurs near the optic nerve head, and lower numbers are present in less vascularized peripheral regions [21]. Astrocytes are also absent from areas with very thin nerve fiber layers, such as the retina–ciliary body junction [21].

RGC and glia development across human and mouse

Eye formation begins early in embryonic development. The eye field is present in mice at embryonic day 8 (E8) and in humans at fetal day 21 (Figure 2A,F) [22,23]. In both species, retinal neurons

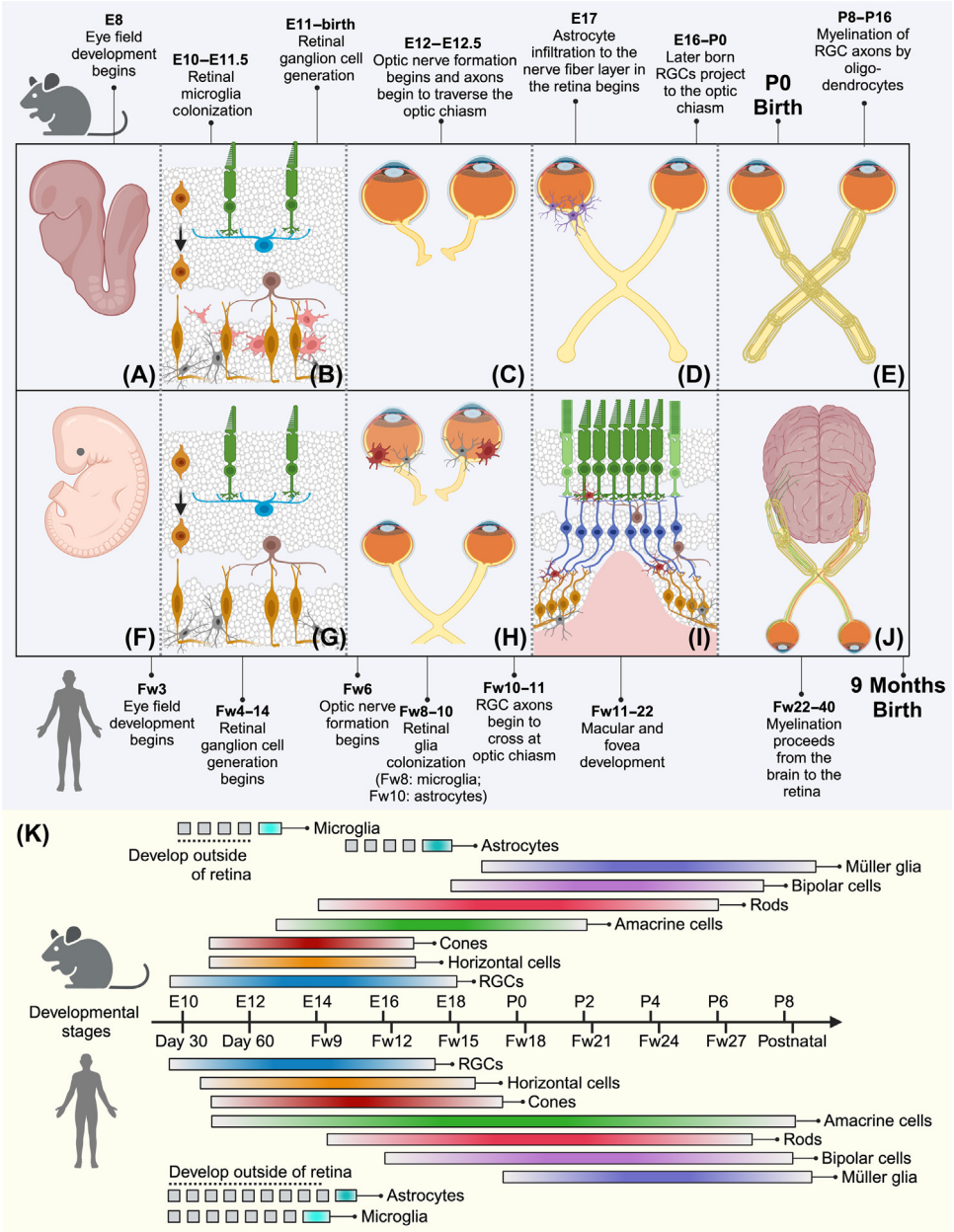

Figure 2. Timeline of key events in human and mouse retinal ganglion cell (RGC) and retinal development. (A) In mice, eye field specification begins at embryonic day 8 (E8). (B) RGCs are born from retinal progenitor cells in the outer retina beginning at E11, peaking at E14.5, and ending immediately before birth [26]. Microglia are born in the yolk sac and colonize the retina at E10–E11. (C) Mouse RGCs begin to extend axons at E12. (D) Mouse astrocytes are born in the optic disc progenitor zone. (E). Mouse RGC axons are myelinated by oligodendrocytes starting from the optic disc between postnatal day 8 (P8) and P16. (F) In humans, eye field development begins at fetal week 3 (Fw3). (G) Human RGCs are born between Fw4 and Fw14 and, as in mice, are specified from retinal progenitor cells. (H) Starting at Fw6, human optic nerve formation begins, followed by retinal glia colonization. RGC axons cross the optic chiasm at Fw10–Fw11. (I). Human macula and fovea development begins at Fw11. (J) RGC axon myelination begins in the brain at Fw22 and reaches the optic nerve head by Fw36–Fw40. (K) Schematic of a timeline depicting the birth order of retinal neuron and glia cell types in mouse and human. The relative order in which retina cell types are born is conserved between human and mice, and all

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and Müller glia are derived from retinal progenitor cells, and RGCs are the first neuronal type specified [24] (Figure 2K). As RGCs mature, they grow dendrites, connect with inner retina neurons, and extend axons toward the nerve fiber layer. RGC axons then exit from the retina via the optic disk and bundle together to from the optic nerve, which passes through the optic chiasm. RGC axonal terminals can collateralize and contact several retinorecipient targets in the brain [25]. The timing of RGC developmental events has been well characterized in mice (Figure 2A–E,K). RGCs are generated over a 10 day period, beginning at ~E11. Their production peaks at E14.5, and the final RGCs form immediately before birth [26]. Newborn RGCs exit the cell cycle near the apical retina and migrate to the basal ganglion cell layer (Figure 2B) [27–29]. RGCs begin to extend axons at E12 and cross the developing optic chiasm starting at E12.5 [30,31] (Figure 2C). By ~E15, RGC axons form an X-shaped optic chiasm where a portion of axons from each eye cross to target the opposite (contralateral) brain region (Figure 2D) [32]. Later-born RGC axons also project to the brain, a process that continues until birth. The optic nerve becomes myelinated by oligodendrocytes starting from the optic disc between postnatal day 8 (P8) and P16 (Figure 2E) [33]. Mouse eye opening occurs between P12 and P14, before which retina development is largely complete.

The overall sequence of RGC developmental events is thought to be conserved between mice and humans, but the timing and duration differ significantly (Figure 2F–J). Mouse retina development is complete in ~3 weeks, covering both pre- and postnatal periods. By contrast, most human retina development occurs prenatally over 35 weeks. Human RGCs can be observed at fetal week 4 (Fw4) (Figure 2G) [23]. Optic nerve formation starts as early as Fw6, and by Fw10 RGC axons begin to cross the optic chiasm (Figure 2H) [34]. The macula develops between Fw11 and Fw13 [35], and the fovea starts to form at Fw11 (Figure 2I) and continues to mature until ~4 years of age [35,36]. Unlike mice, myelination of human RGCs appears to progress from the brain to the eye, beginning in the lateral geniculate nucleus (LGN) at Fw22 and ending at Fw36 (Figure 2J) [34]. At birth, infant visual acuity is poor but improves relatively rapidly. Trichromatic color detection emerges at ~3 months of age, coinciding with cone maturation [37,38]. Human retinal connectivity refines over the first 2 years, and the visual system has matured fully by early adolescence [34].

Recent advances in single-cell sequencing enable the comparison of retinogenesis processes between species. Human RGCs share a set of well-characterized transcription factors that influence RGC development in mice (Figure 1D) [39]. Mouse RGCs at E12–E14 align with human RGCs at fetal days 52–57, whereas mouse RGCs at E16 to P0 match human RGCs at fetal days 67–107 [23]. However, there are there are notable differences in developmental cell birth order and patterning between mice and humans (Figure 2K). For example, astrocytes are born in a narrower window in mice (~E13–P0) relative to humans (day 60 to ~Fw27), even when accounting for species-specific gestational differences [40].

Conserved developmental events extend to RNFL glia. Microglia are derived from the yolk sac, and these cells play important roles in regulating retina neurogenesis and RGC axon refinement, and in facilitating vessel growth. In mice, microglial development commences at E8.5–E9.5 [41]. Newborn microglia migrate to the nascent central nervous system and arrive in the mouse retina by E11.5. In the human retina, microglia are present by Fw10 [42] (Figure 2A,B). Although the

cell types are born in windows that span weeks (mice) to months (humans). In mice, some retinal cell types are born postnatally, whereas in humans all cells are generated before birth. In both mice and humans, astrocytes and microglia develop outside of the retina and migrate into the retina early in development. The overall developmental stages are similar between monkeys and humans. Data adapted from [175]. Figure created with BioRender.

molecular mechanisms by which microglia home to the central nervous system are not fully clear, these cells are thought to arrive in part via the growing circulatory system [41]. At Fw12, human microglia appear denser in the deeper retinal layers and may be more abundant in the periphery. By Fw20, retinal microglia are distributed relatively evenly [42]. The adult foveola is largely devoid of microglia, suggesting that, like many other cells, microglia are displaced from this region [42,43].

Microglia positioning and arrangement are closely tied to the progression of retinal neuron and synapse development. Most mouse microglia first appear in the IPL and then migrate to the OPL, consistent with their role in synapse refinement [44]. In adult mice and humans, microglia processes remain enriched in the synaptic layers, with an equal distribution between the IPL and OPL in mice [44]. Microglia abundance also correlates with the peak of retinal neuron development. In mice, retina microglia numbers increase from P1 to P7, and levels reach twice those in adults. Microglia numbers then decrease and are maintained at a steady state starting at P28 [45]. Whether similar patterns are present in humans awaits further study.

Astrocytes originate from the optic disk progenitor zone at the junction of the optic nerve stalk and the retinal cup [17,46]. Astrocyte colonization of the RNFL begins at E17 in mice and ~Fw9 in humans (Figure 2D,H) [47,48]. Astrocytes then migrate outward from the optic nerve head in a radial pattern [17]. Studies in mice have identified two key factors that promote astrocyte migration: the inner limiting membrane (ILM) and RGC axons. The ILM is formed by astrocytes and Müller glia end feet, and demarks the retina and vitreous boundary. The ILM guides astrocyte migration because ILM disruption in mice significantly alters astrocyte organization, reduces their coverage, and alters astrocyte morphology [49]. The ILM also serves as a substrate for RGC axon growth cones, and directs their growth towards the optic disc [50]. In turn, RGC axons provide astrocytes with centrifugal guidance cues that help to orient astrocyte migration to the outer retina. In RGC axon-guidance mutants, astrocytes fail to polarize properly and form migratory chains along misrouted RGC axons, suggesting that RGC axons may dictate astrocyte migration trajectories [18]. To our knowledge, similar mechanisms have not yet been investigated in primates.

RGC interactions with cellular partners

Presynaptic interactions

RGCs receive visual information through their synapses with amacrine and bipolar cell partners in the IPL, which are arranged in at least five synaptic sublaminae (S1–S5, Figure 3C) [51]. This organization facilitates preprocessing of visual information before it is transmitted to the brain. In mice, inhibitory amacrine synapses start to form at P3, before bipolar excitatory synapses emerge at P10 [52]. By contrast, primate IPL synapses begin to appear at fetal day 55, and excitatory bipolar cell synapses form before inhibitory amacrine synapses, which emerge at fetal day 78 [36]. Primates have ~12 bipolar cell types that largely overlap with the 14 types identified in mice, and seven mouse types map to a single macaque type [8,53,54]. By contrast, primates possess ~30 amacrine cell types, whereas mice have >60, and several are conserved between the species [8,53,55,56]. In both mice and humans, RGC dendrites in the top IPL receive input from OFF cone bipolar cells and respond to light decrements (OFF response), whereas those in the bottom IPL receive input from ON cone bipolar cells and respond to light increments (ON response) [51]. In mice, the processes by which dendrites segregate to distinct synaptic lamina vary across RGC types [57]. For some types, dendrites initially extend throughout the IPL before being restricted to a specific sublamina, whereas for other types branches are specifically added or removed [57]. Dendritic refinement in mice occurs from ~P1 to P14, and the OFF pathway matures earlier than the ON pathway [58]. This pattern is consistent with observations in

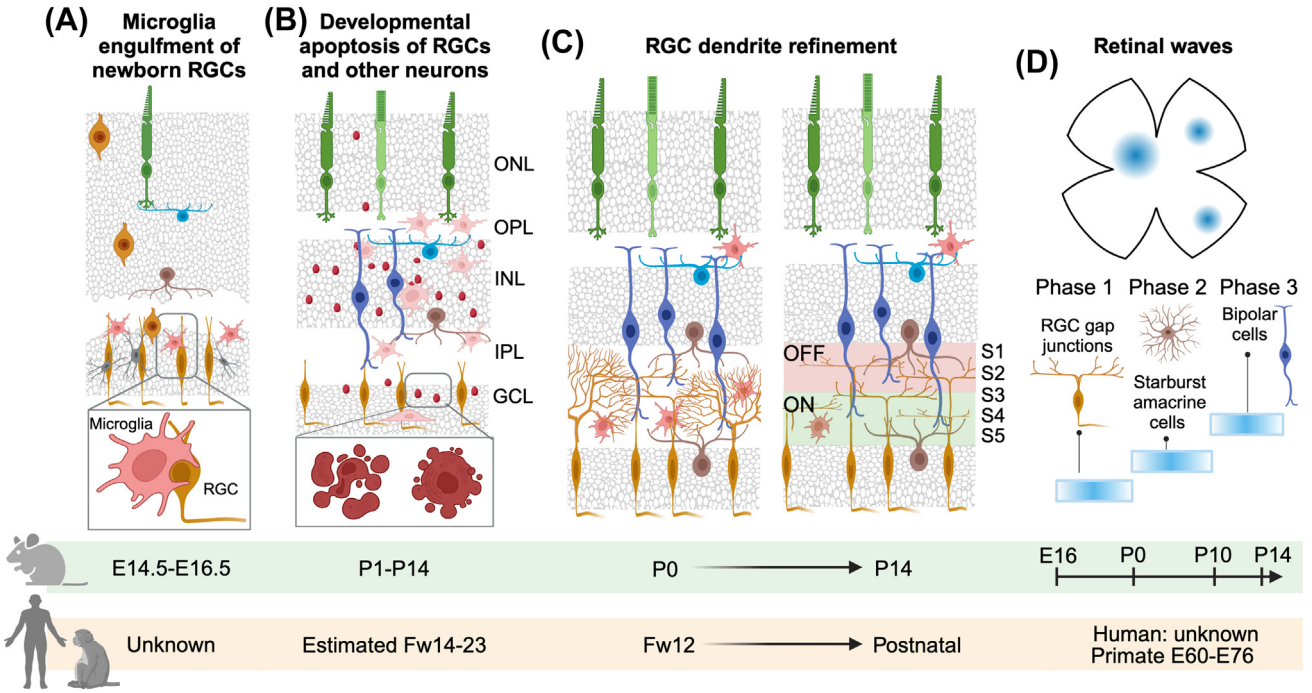

Figure 3. Retinal ganglion cell (RGC) developmental events that impact retinal connectivity and function. (A) In mice, a subset of early born, non-apoptotic RGCs are engulfed by microglia, which reduces overall RGC numbers. The complement molecule C1q appears to help drive this selective engulfment. (B) RGCs, as well as most other retinal neuron types, undergo normal developmental apoptosis, which leads to the death of ~30% of all RGCs that are generated from retinal progenitor cells. (C) RGCs selectively extend their dendrites to specific retinal synaptic layers, and their neurites are further refined through RCG subtype-specific processes that involve selective pruning, sequential addition, and biased dendritic targeting [176]. In some cases the molecular pathways that help to drive laminar selection have been identified in mice, but these pathways are unknown for the majority of RGC types. (D) All RGC survival and dendritic refinement outcomes are complete before mouse eye opening. These processes are impacted by a spontaneous form of activity called retinal waves. Different cells drive three types of retinal waves that follow each other in development from embryonic (E) day E16 to postnatal (P) day P14. Gap junctions between RGCs are thought be important for phase 1 retinal waves, whereas acetylcholine release by a type of amacrine cell known as a starburst amacrine is important for phase 2. Glutamate release from bipolar cells contributes to phase 3 retinal waves [72]. Abbreviations: Fw, fetal week; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; ONL, outer nuclear layer; OPL, outer plexiform layer; S1–5, sublaminae 1–5. Figure created with BioRender.

developing monkey retinas [59]. Notably, retinal microglia are highly active during this period, although their specific role in RGC dendrite refinement remains to be determined [60].

Several molecular pathways have been identified in mice that guide RGC dendrites to specific laminae (Figure 3). These molecules play roles in cell adhesion, dendrite repulsion, dendrite elimination, and subcellular localization (reviewed in [61]). It is believed that a molecular 'code' enables RGC types to identify and connect with their appropriate partners in each sublamina. The molecular nature of this code varies, but there is a notable degree of conservation across species. Families of these specificity molecules include classical cadherins, protocadherins, semaphorins, and sidekicks [61]. Although whether these pathways are conserved in humans is largely unknown, emerging retinal organoid and assembloid approaches may soon facilitate the identification of relevant human RGC guidance and specificity molecules. Such advances could be instrumental in preventing or restoring disruptions of human RGC circuits [62].

Developmental death of RGCs

About 30–50% more RGCs are born than are needed in the adult retina, and the excess RGCs undergo normal developmental cell death, as has been documented in mice, humans, and other species (Figure 3B) [63–65]. In mice, RGC death occurs during the first two postnatal weeks, and removing the

proapoptotic protein Bax leads to a higher number of RGCs persisting into adulthood [63]. These preserved RGCs do not respond normally to injury, indicating that their physiological properties may be disrupted [66]. The factors that promote the survival of some RGCs but the death of others are unclear, but it appears unlikely that the majority of developmental RGC death is due to brain projection errors (Figure 3D) [67]. Microglia also aid in RGC elimination by engulfing a subset of live RGCs shortly after birth (Figure 3A) [68]. In the mouse retina, normal developmental cell death also affects microglia functional specialization because reducing neuronal apoptosis alters microglia transcriptional clustering [69]. Whether similar roles for microglia extend to the human retina is currently unknown.

Early RGC activity and synapse refinement

In the developing visual system, RGCs display periodic action-potential bursts before photoreceptors become light-responsive. In mice, this activity manifests as excitation 'waves' that propagate across the retina from E16 to P14 (Figure 3D) [70,71]. In mice, retinal waves occur in three phases: RGC depolarization mediated by RGC gap-junction coupling (~E16–P0), acetylcholine release from starburst amacrine cells (~P0–P10), and glutamate release from bipolar cells (~P10–P14) (reviewed in [72]). Retinal waves are conserved in primates, but it is unclear whether their types and phases are similar to those in mice [73]. In primates, waves first appear at E60, a week before eye-specific axonal segregation begins, and then decrease rapidly from E67 to E76 [73]. Retinal waves influence both pre- and postsynaptic RGC refinement. For instance, in mice, waves aid the maturation of direction selectivity [74] and retinal vasculature development [75]. However, ON and OFF IPL stratification is not significantly affected by wave activity [76]. Interestingly, RGCs also produce dopamine during the first postnatal week, which inhibits vascular growth through the Notch pathway [77]. In the mouse brain, RGC waves are important for RGC axon targeting, eye-specific segregation, retinotopic mapping, the emergence of motion detection in the superior colliculus, and visual cortex refinement [78–80]. In primates, however, it is unlikely that waves drive RGC axon targeting because this process is completed before E60 when primate waves first appear. The roles of primate waves in eye-specific segregation and other aspects of visual circuit maturation remain to be investigated.

Astrocytes and microglia interact with and influence RGC activity and development both directly and indirectly (Figure 3). In the primate retina, RGC fragments may be found in microglia, even in adults [81]. In mouse, depletion of microglia does not appear to dramatically alter retina development, although modest reductions in a and b wave electroretinography responses are observed over time [82]. Microglia may also affect RGCs indirectly by influencing the vasculature. Both mouse and human retina possess a transient hyaloid vasculature and a permanent trilaminated retina vasculature that support RGC function [83]. Ablation of mouse vitreal macrophages delays hyaloid vasculature removal [84], whereas elimination of retina microglia temporarily reduces vascular branching [85]. Astrocytes also influence vascular development. During the first postnatal week in mice or the third trimester in humans, RNFL astrocytes form ring-shaped patterns that guide the future shape of RNFL capillaries by templating endothelial cell growth [18,48]. Endothelial cells enter the retina at the optic nerve head, and superficial vascular layer angiogenesis progresses from the center to the periphery. Endothelial tip cells extend filopodia along astrocyte arbors to guide vascular growth and align capillaries with the astrocyte network [86]. Therefore, astrocyte numbers are crucial for determining vascular patterns and density, and increased astrocyte numbers can lead to excessive vessel growth and hemorrhage [87]. Microglia help to regulate astrocyte abundance by engulfing live astrocytes [88]. Although similar mechanisms have not yet been demonstrated to our knowledge in primates, the restriction of human astrocytes to vascularized regions of the RNFL suggests a potentially analogous relationship [21].

Axonal guidance and postsynaptic interactions in the retinogeniculate circuit

RGC axons are guided by several molecular pathways as they exit the retina. They must (i) navigate to the optic disc, exit the eye, and form the optic nerve; (ii) determine whether to project

ipsilaterally or contralaterally through the optic chiasm; and (iii) establish connections with specific postsynaptic targets in distinct brain regions (Figure 4) [89]. Eph receptors and their and ephrin binding partners serve as repulsive and attractive cues, and direct axon pathfinding throughout these stages. Detailed reviews of these mechanisms are available elsewhere [89]. Mouse and human RGCs differ significantly in their ipsilateral and contralateral projections. In mice, most RGC axons project contralaterally, with only a small fraction targeting the ipsilateral side (Figure 4A). By contrast, humans RGC axon projections are binocular, and ~45% project ipsilaterally and 55% contralaterally [90]. There are also differences between mouse and human RGCs in the brain regions they innervate, particularly regarding the superior colliculus. In mice, 90% of RGCs project to the superior colliculus, whereas only ~10% of RGCs in humans and primates target this region. In addition, most RGCs that project to the mouse superior colliculus have axon collaterals that extend to the LGN, resulting in ~75% of RGCs projecting to the LGN [91,92]. In primates, 90% of RGCs project to the LGN, but the extent of axonal collateralization is this context remains unknown [93,94].

RGC axon maturation regulates both local and long-range developmental events. In mice, RGC axons locally refine and mature over the first two postnatal weeks. Initially, ipsilateral and contralateral inputs to the LGN overlap significantly, but by P8 eye-specific target regions are refined, minimizing overlap between ipsilateral and contralateral axons (Figure 4B). As eye opening approaches, mouse RGC axonal arbors grow smaller, and remaining synaptic contacts are strengthened (Figure 4C) [95,96]. In primates, RGC axonal refinement begins during embryogenesis and follows a different timeline. In monkeys, optic nerve axons reach the dorsal LGN (dLGN) as early as Fw7, shortly after crossing the optic chiasm [34]. Retinogeniculate axonal terminal arbors show increasing complexity from Fw12 to Fw16 [97], contrasting with mice, where axonal arbors first increase in complexity before decreasing [95] (Figure 4C,D).

The organizational principles of the dLGN vary dramatically between mice and higher primates. In mice, the dLGN has two regions – a peripheral region which receives contralateral input and a central region which receives ipsilateral input (Figure 4B) [96,98]. By contrast, the dLGN of macaques, squirrel monkeys, and humans is layered, with six principal layers and six koniocellular layers. Each of these layers receives either contralateral or ipsilateral input. The first two layers are magnocellular, receive input from parasol RGCs, and project to the primary visual cortex (V1) layers 4Cα and 6. The remaining four layers (3–6) are parvocellular, receive inputs from midget RGCs, and project to layers 4Cβ and 6 of V1. The koniocellular layers receive sparse, heterogeneous inputs from RGCs and project axons to the superficial layers of the visual cortex. In primates, RGC axonal terminals are confined to the dLGN by Fw11 before the formation of the dLGN layers, which begins at Fw13. RGC axon refinement could thus contribute to dLGN layer specification (Figure 4C,E) [99,100]

The cellular and molecular processes that drive dLGN refinement remain incompletely understood, although mouse studies offer some insights. Mouse microglia facilitate dLGN synapse refinement in part through the classical complement pathway molecule C1q and its target C3 [101]. Altering microglia function delays the segregation of contralateral and ipsilateral RGC inputs, indicating that microglia engulfment is crucial for mouse RGC axon refinement [101,102]. These processes are activity-dependent: reducing RGC activity in one eye increases microglia engulfment of less active inputs [102], whereas decreasing retinal waves reduces microglial engulfment and elimination of retinogeniculate synapses [103]. These findings support a model in which complement may bind to less active synapses and promote their removal in response to early RGC depolarizations. However, the mechanisms by which complement, a secreted protein, tags specific synapses for removal are not fully understood. It also remains unclear whether similar processes

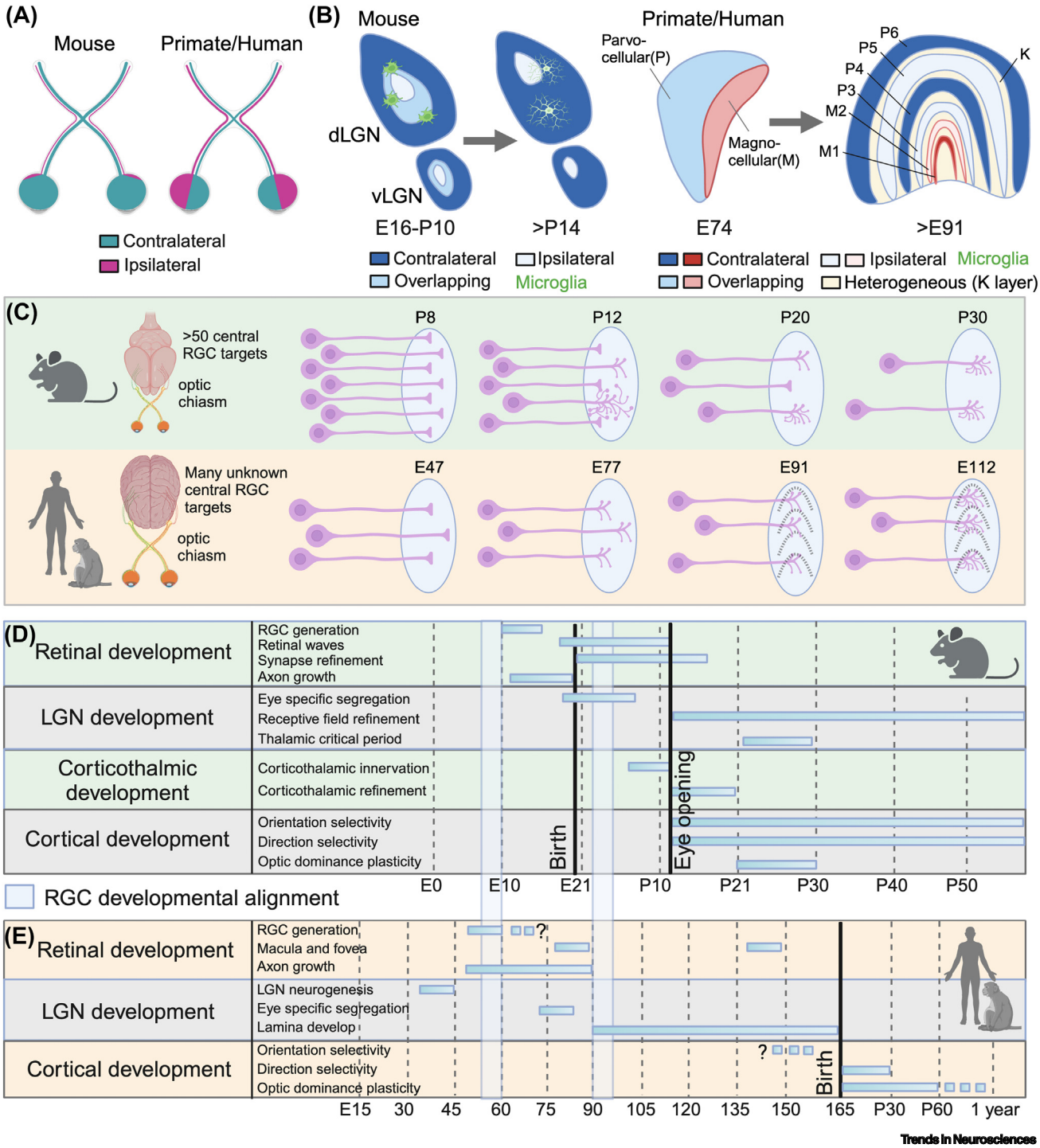

Figure 4. Development of eye–brain connectivity in primates and mouse. (A) Approximate distributions of contralateral and ipsilateral retinal ganglion cell (RGC) axonal projections from the eye to the brain. (B) Structural schematic of the mouse and primate lateral geniculate nucleus (LGN). In mice, the LGN is composed of a central region innervated by ipsilateral RGC axons and a surrounding region that receives contralateral axons. These areas first overlap but then become segregated through the activity of microglia, retinal waves, and intrinsically photosensitive RGCs (ipRGCs). The primate LGN differs significantly from that of mouse. The developing primate LGN is arranged into two layers – the parvocellular and the magnocellular. In adults, the LGN has a highly layered organization with 12 laminae. Among these, layers 2, 3, and 5

(Figure legend continued at the bottom of the next page.)

drive primate dLGN refinement. Future research could utilize histological tools to investigate complement pathway components and microglia phagocytosis properties over the course of primate dLGN refinement. Such knowledge could help to identify therapeutic targets for modulating microglia-mediated refinement of RGC dendrites and axons.

Studies in mice also highlight the crucial role of RGC axons in brain cell and circuit maturation (Figure 4D). First, RGCs influence dLGN circuit maturation and the recruitment of layer-specific dLGN inhibitory interneurons via retinal wave-induced RGC depolarization [104,105]. Second, RGC axons provide secreted cues and a physical scaffold for activity-dependent dLGN maturation, in part by stimulating astrocytes to produce fibroblast growth factor 15, which recruits inhibitory interneurons [106]. Third, RGCs impact the remodeling of thalamocortical relay neurons and dLGN interneurons [107,108] by limiting corticothalamic axon innervation of the dLGN through inhibiting aggrecan degradation. [109,110]. Fourth, RGCs are essential for appropriate cholinergic neuron innervation of the dLGN, which originates from the parabigeminal nucleus of the brainstem [111]. Finally, removing a RGC type called intrinsically photosensitive RGCs (ipRGCs) causes defects in dLGN eye-specific segregation [112], which may reflect the role of ipRGCs in retinal wave propagation [113]. It is unknown which, if any, of these mechanisms extend to humans. Experimental systems that model human eye–brain connectivity, such as pluripotent stem cell-derived retinal–thalamic assembloids [62], could help to resolve these questions. These models will be valuable for understanding developmental disorders of the human visual system and for determining how changes in postsynaptic brain neurons might influence the reinnervation properties of therapeutically transplanted RGCs.

RGC and glial diversity in humans and mice

Are there functionally conserved RGC types in mice and humans despite structural variations?

RGC diversity varies significantly between humans and mice. RGC types are defined by conserved dendritic and axonal morphology, laminar arborization in the IPL, transcriptomic profiles, mosaic pattering, the production of cell type-specific proteins, and the retinorecipient regions that their axons target in the brain [9,114–117]. RGCs of the same subtype also share similar physiological light responses and encode features such as contrast, feature size, local movement direction, light intensity, color, and orientation. Based on these criteria, there are ~45–47 distinct RGCs types in mice [116,118]. Primates have about half as many RGC types, and have only ~18 distinct transcriptional types (Figure 5) [7,56]. In mice, each RGC subtype constitutes <10% of the total RGC population. By contrast, in humans, midget RGCs make up >60% of the total RGC population, and parasol RGCs constitute the next most abundant group at ~10% [8].

Three categories of RGC types are currently known to be conserved between humans and mice: ipRGCs, mouse αRGCs (which most closely correspond to midget and parasol RGCs in primates and humans), and direction-selective RGCs [53,119–124]. Most is known about the first two categories. ipRGCs express melanopsin (OPN4) and play roles in both image-forming and non-image-forming vision [121,125–127]. In mice, there are at least six types of ipRGCs (M1–M6)

receive ipsilateral RGC input while layers 1, 4, and 6 receive contralateral input. The koniocellular layers (K) receive sparse and heterogeneous RGC input. LGN patterning emerges after embryonic (E) day E91 in fetal rhesus monkeys. (C) Timing and organization of RGC axon projections to the mouse and human LGN. In mouse, RGC axons are initially numerous and complex. As RGCs undergo developmental cell death, the number of RGC axon terminal decreases, and the remaining arbors are developmentally refined. Mouse RGC axons reach adult complexity by postnatal (P) day P30. By contrast, primates RGC axonal terminal arbors show a consistent increase in complexity during fetal weeks 12–16. Mouse data adapted from [95]. (D,E) Timing and duration of key events during visual circuit maturation in mouse and primates. RGC transcriptomes in mice at embryonic (E) days E12–E14 and E16–P0 align with human fetal RGCs at days 52–57 and 67–107, respectively. In general, the order of maturation events is conserved between species. Abbreviations: dLGN, dorsal LGN; vLGN, ventral LGN. Data adapted from [177]. Figure created with BioRender.

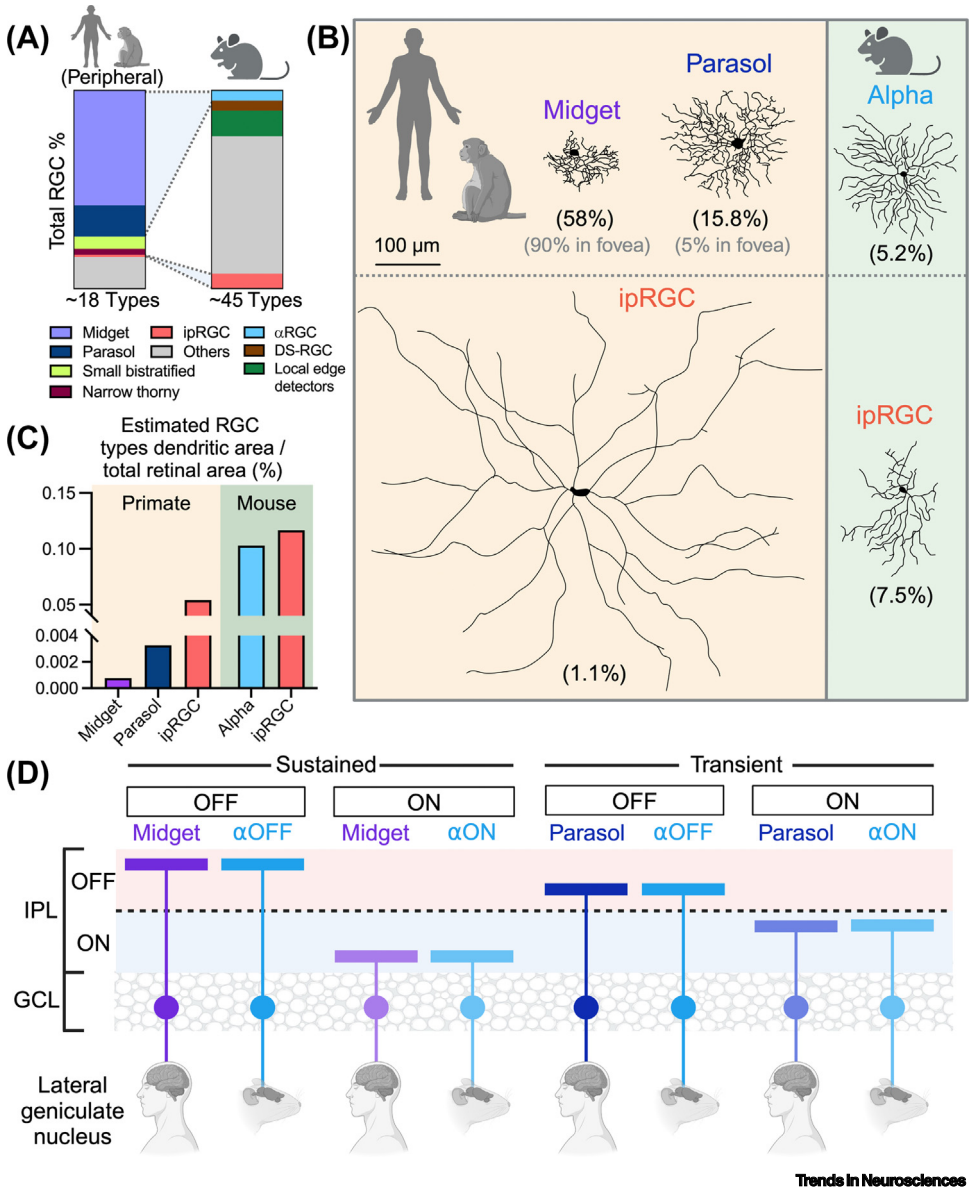

Figure 5. Retinal ganglion cell (RGC) subtype diversity in primates and mice. (A) Schematic of the ratio of RGC types in primate and mouse. Primates have ~18 known RGC types, the majority of which are midget RGCs (60% on average, but 90% in the fovea) and parasol RGCs (16%). By contrast, mice have ~50 RGC types, most of which comprise a small percent of the total. (B) '*En face*' structural schematic of dendrites for a subset of RGC types and estimated abundance relative to the total number of RGCs. (C) Estimated RGC dendritic area as a percentage of the total retinal area for the most conserved types in mouse and human. Although αRGCs most closely align with midget and parasol RGCs at the transcriptional level, their dendritic structures and relative coverage area differ dramatically. A single midget cell dendritic area spans ~0.001% of the human retina, whereas a single αRGC occupies ~0.1% of the mouse retina. By contrast, in humans, intrinsically photosensitive RGCs (ipRCGs) are ~tenfold larger than those in mouse. Dendritic tracing images are adapted from [119,178,179]. (D) Schematic of mouse αRGCs and their transcriptionally closest partner among human RGCs, depicting the conservation of their laminar targeting, general functional properties (ON versus OFF, sustained versus transient), and brain targeting to the lateral geniculate nucleus (LGN). Abbreviation: DS-RGC, directionally selective RGC. Figure created with BioRender.

distinguished by their levels of melanopsin expression, morphology, lamination, and functional properties [128]. In humans, there are at least two types of ipRGCs equivalent to mouse M1 and M2 types, although their size and dendritic coverage within the retina vary significantly between species (Figure 5B,C) [125,129]. ipRGCs are best known for regulating the pupillary light reflex and mediating entrainment of circadian rhythms, primarily through their projections to the suprachiasmatic nucleus [130].

Transcriptomic analyses of 17 vertebrate species revealed that midget and parasol RGCs most closely correspond to the four types of mouse RGCs known as αRGCs (Figure 5A,D) [121]. Although the structures of αRGCs and midget/parasol cells differ significantly, at the transcriptional level, mouse ON and OFF sustained αRGCs align most closely with ON and OFF midget RGCs, whereas mouse ON and OFF transient αRGCs correspond more closely to ON and OFF parasol cells [121]. In addition, these cells receive inputs from the same bipolar orthotypes in mice and primates. Mouse αRGCs heavily innervate the dLGN, as do midget and parasol cells [131,132]. This suggests that midget and parasol RGCs precursors may have been present in early mammalian evolution, potentially providing a selective advantage to ancient primates [121].

Why does RGC diversity decrease in primates relative to mice?

Humans have a larger retina, more RGCs, and a higher RGC density than mice (Figure 1). Although some RGC orthologs are observed between mice and humans, human RGC types are notably less diverse. The reasons for this disparity are not fully understood, but several theories have been proposed. First, primate RGCs are highly concentrated in the macula, which is crucial for high-acuity vision. In addition, primates exhibit a strict division in RGC projections: RGCs from the nasal retina innervate contralateral brain targets, whereas those from the temporal retina innervate ipsilateral brain targets. This division is necessary for binocular visual tasks. By contrast, mouse vision is less dependent on spatial acuity and binocular processing, and mice lack a clear division between RGC projections and only a subset of temporally localized RGCs project ipsilaterally (Figure 4A). Second, it is possible that diverse RGC types in primates may have been displaced to peripheral retinal regions to permit the enhanced acuity and spatial processing afforded by the macula and fovea. This could also mean that current single-cell RNA-seq datasets may underestimate the true diversity of RGC types in primates because non-midget and non-parasol RGCs comprise only ~5% of primate RGCs in the fovea and ~20% of RGCs in the periphery (Figure 5A). Third, the human visual cortex has greater processing capacity relative to the mouse, potentially resulting in the need for less retina computation in humans (the 'complex' brain, 'simple' retina model [133]). Lastly, RGC types may have emerged to optimize the efficient coding of natural scenes [134]. However, it remains unclear how this theory applies to primates because human RGC diversity is mostly present outside the retinal area used for high-acuity vision.

Is mouse microglia and astrocyte diversity conserved in humans?

Unlike neurons, whose transcriptional diversity largely reflects cell type differences, microglia and astrocytes are highly dynamic cells that can exhibit rapidly changing structural, molecular, transcriptional, and functional specializations. This can make it difficult to determine whether glial transcriptional diversity truly represents different cell subtypes or instead represents one or a few populations that can alter their morphology and transcriptome depending on their context. In adults, microglia are long-lived cells, and mouse brain microglia have a median lifespan of >15 months, and human microglia average 4.2 years [135,136]. In adult mice, 85% of microglia remain viable after 1 year [137]. Emerging evidence suggests that transcriptionally distinct microglial populations may influence specific cell types and circuit outcomes [138]. Developmental profiling studies of mouse retinal microglia identify between six and ten distinct cell clusters

[69]. These clusters likely represent different microglia functional states because developmental processes, such as neuronal apoptosis, alter the relative number of microglia within these clusters [69]. Also in accord with this notion, transcriptional clusters of microglia are enriched for the expression of genes associated with different microglial functions, including immune responses and the phagocytosis of dying neurons [69]. Whether similar subclusters exist among human microglia remains to be determined through further sequencing and bioinformatic analyses. By comparison, research on astrocyte diversity in the retina is less extensive. In mice, single-astrocyte labeling techniques have revealed morphological diversity based on proximity to veins or arteries: larger astrocytes tend to cluster around veins near the optic nerve head, whereas smaller astrocytes are more concentrated around arteries [139]. In humans, two types of astrocyte morphologies have been reported: star-shaped astrocytes located in the ganglion cell layer and elongated astrocytes in the nerve fiber layer [140]. It remains unclear whether these astrocyte populations differ in their functional specialization, and if so, how.

Barriers and models for the study of human retinal cells and their diseases

When evaluating mouse models for their utility in understanding human RGC development, diseases, and degeneration, several challenges must be considered (Figure 6). First, human and mouse RGC types have distinctive cellular features, even among conserved types. Second, mice do not normally develop common forms of RGC-related blinding diseases such as glaucoma. To address this, methods to artificially elevate ocular pressure in mice and models of axonal injury, such as nerve crush, have been developed [141] (Figure 6A). Third, genetic risk factors for human glaucoma, such as mutations in *OPTN* [142] and *SIX6* [143], do not always cause significant glaucoma phenotypes in mice [144,145]. For instance, the E50K mutation in *OPTN* leads to severe disease in humans [146], but transgenic mice carrying this mutation exhibit only mild glaucoma, even in older age [144]. This discrepancy may be because the expression levels of human glaucoma risk factors, such as *OPTN* [142] and *SIX6* [145], *GAS7* [147], *MAP3K1* [148], and *CDHR1* [149], could potentially vary between mouse and human RGC types (Figure 6B). Conversely, some gene deletions or mutations that cause glaucoma phenotypes in mice (e.g., the Dba2/j model, which contains numerous mutations, and the *Glast* deletion model) may not be genetically linked to human glaucoma [150,151], whereas others are more conserved (e.g., *ANGPT1* [152]). Mouse and human RGC types may thus differ in their susceptibility to disease risk factors and in their regenerative capacities. Finally, although the commonly used optic nerve crush model is valuable, it does not accurately represent the most common RGC axonal dystrophies. Because neuronal responses vary between humans and mouse disease models, secondary glial responses may also not be conserved.

How might these challenges be addressed? One approach is to increase the use of primates for vision research, although such studies are costly and primate access is limited. Alternatively, culturing whole retinas or retinal pieces from post-mortem human eye donors has proved to be effective for some research goals, such as optimizing adeno-associated virus (AAV) vectors for human foveal delivery [153]. Human retina sample availability, however, remains a challenge. A more accessible option is the use of human retinal organoids (Figure 6A). Generated from human pluripotent stem cells (hPSCs) derived from healthy individuals or those with disease-associated mutations, retinal organoids closely mimic human retinogenesis [154–156]. These organoids can be used to model human retinal development and connectivity. More recently, thalamic and cortical retinal assembloids have also enabled the study of human eye-to-brain connectivity [62]. One limitation of this system, however, is that RGCs within human retinal organoids (hRGCs) begin to die around culture day ~80, possibly due to their deeper location within the organoid where they may become metabolically deprived [155,157]. This challenge can be addressed by labeling hRGCs with fluorescent reporters and isolating them from organoids for long-term culture [158]. Under the right conditions, isolated

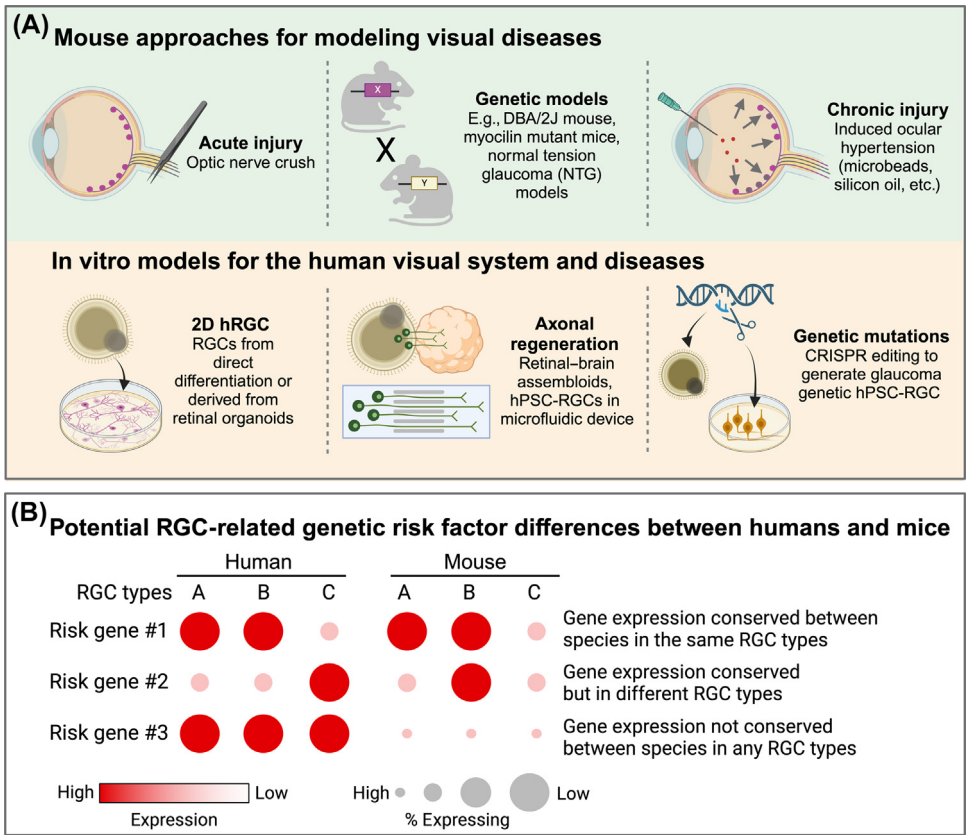

Figure 6. Current experimental models in mice and humans for understanding visual development and disease. (A) Schematic showing mouse (upper panel) and human (lower panel) experimental system alternatives for modeling the visual system and its diseases. In mice, axon injury is often modeled using optic nerve crush. Genetically modified mice can also be used to model human visual diseases by either expressing known human mutations associated with these conditions or by the induction of disease-related changes, even if their causal models or mutations are not directly linked to human disease. For example, mice do not normally develop glaucoma or most other retinal ganglion cell (RGC)-related visual diseases, prompting the development of chronic injury models and induced ocular hypertension models. For studies on human (h) RGCs, human retinal organoids from human pluripotent stem cells (hPSCs) can be used. Alternatively, RGCs can be purified for study in a dish or in transplantation models. Human RGC axon regeneration can be modeled by using microfluidic chambers or assembloid strategies in which retinal organoids are paired with brain organoids. Human disease-related mutations can be introduced into hPSCs from which retinal organoids or RGCs can be derived. (B) Cartoon representation illustrating potential differences in genetic risk factor expression between human and mouse RGCs across different RGC-related diseases. In some cases a conserved RGC type may express a genetic risk factor that is shared between both species. In other cases the risk factor may be conserved in mouse RGCs but is expressed in a RGC type different from that in humans. Alternatively, both the expression of the risk factor and the RGC type in which it is expressed may not be conserved across species. Figure created with BioRender.

hRGCs can grow segregated dendrites and axons, enabling detailed studies of human RGC biology and connectivity [62]. hRGCs facilitate various additional experimental approaches, including RGC transplantation studies, modeling RGC axonal connectivity, and *in vitro* disease models [62,159–162]. Although hRGCs can help to address issues of species and genetic diversity [157,159], it is important to note they are most representative of fetal RGCs, and developing methods to promote hRGCs maturation into an adult-like state is therefore a key goal.

RGC-associated glia are also implicated in retinal diseases. In mouse models of glaucoma, microglial activation precedes RGC loss [163]. Similarly, clusters of activated microglia are

observed in humans with optic nerve head damage [164]. Whether microglia are protective or pathogenic under these conditions and how their roles may change over the course of disease or in particular genetic backgrounds is less clear. For example, some studies suggest that microglia can contribute to RGC degeneration through the production of proinflammatory factors [165], whereas others suggest that *Apoe* and *Lgals3* production may contribute to microglia activity, but these changes can be prevented in the presence of the human *APOE ε4* allele [166]. Reactive astrocytes have also been identified in the optic nerve head of glaucoma patients [167]. Like microglia, astrocytes may exhibit both protective and pathogenic roles, potentially through distinct subpopulations (reviewed in [168]).

The diverse roles played by microglia and astrocytes in specific mouse models used to mimic human conditions may be influenced by variations in the extent and duration of the disease modeled. An alternative approach involves using systems that incorporate human microglia and/or human retinal organoids. For instance, hybrid mice can be created by depleting mouse microglia and replacing them with human microglia [169]. Although primarily used in brain research, similar methods may be applicable to the retina. In addition, human microglia and astrocytes can now be directly derived from hPSCs and introduced into human organoids or neuronal coculture systems [170–174]. These advanced models hold potential for enhancing our understanding of glial human visual diseases.

Concluding remarks and future perspectives

Since the cellular components of the retina were first described over 150 years ago, our understanding of RGCs and their interactions with astrocytes and microglia has advanced significantly. The field has progressed from general morphological descriptions of these cells to detailed knowledge of functionally specialized RGC and microglia subsets and astrocytes. Although human and mouse RGCs both transmit visual information to the brain, their morphological properties, light responses, organizational structures, and developmental timelines differ markedly. Because mouse RGCs, astrocytes, and microglia communicate together in ways that impact both RGC connectivity and survival, as well as on glial function and distribution, it is easy to envisage how these interactions may extend in potentially novel ways to human RGCs types and their glial counterparts. In the coming years we expect that crucial details regarding the molecular basis of human RGG fate, organization, connectivity, and glial communication will be uncovered that will shed light on human-specific visual function and disease susceptibility (see Outstanding questions). Such studies have the potential to leverage the long history of the retina in revealing fundamental neural principles to identify human-specific features of neuron–glia interactions, which in turn may contribute to the prolonged period of brain development characteristic of humans. Recent technical advances, including human retinal organoids, assembloids, eye–brain connectivity models, and the integration of human retinal neurons and glia into mouse systems, will be crucial for these investigations.

Outstanding questions

What factors influence the development, identity, pre- and postsynaptic wiring, organization, and function of human-specific RGC types?

What molecular pathways guide the development of the macula and fovea, and how do these pathways contribute to the enrichment of specific ganglion cell subtypes in these regions?

What are the human-specific factors in RGCs or their partners that prolong their development and synaptic refinement periods relative to those in mice?

How does the resilience of human ganglion cell types compare to that of mice, and can these resilience mechanisms be harnessed to improve the survival of human neurons in visual diseases?

How do retinal ganglion cell types in mice and humans project to and establish connections with specific retinorecipient areas in the brain?

Can circuit tracing of primate or human RGC types determine whether these neurons project to same variety of brain regions as mouse RGCs?

Can alternative differentiation and maturation protocols be developed that promote human retina organoids and related models to adopt neuronal and glial states more closely resembling those of adult retina?

Do human microglia and astrocytes modulate the same biological processes as they do in mice (e.g., synapse refinement and vascular growth)?

Are there species-specific subsets of astrocytes and microglia that regulate distinct functional outcomes in the retina and retinorecipient areas of the brain?

Acknowledgments

We thank Drs Fabrizio Gabbiani, Jeremy Kay, Yi-Rong Peng, Nicholas Tran, and Matthew Rasband for advice, comments, and suggestions on this manuscript. We also thank Molly Rhodes for proofreading the manuscript. This work was supported by the National Institutes of Health (NIH, grants R01EY0332, R01EY035254, R01EY032566, R01EY030458, and R21AG074163 to M.A.S.), the Mallinckrodt Foundation, the BrightFocus Foundation, and the Foundation Fighting Blindness (to M.A.S.). This work was also supported by the RReSTORE Consortium (to K.H).

Declaration of interests

M.A.S has filed a preliminary patent on regulators of microglia state. The other authors declare no competing interests in relation to this work.

Declaration of generative AI and AI-assisted technologies in the writing process

During the revision of this work the authors used ChatGTP to improve readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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