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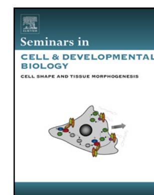

Review

Guidance of retinal axons in mammals

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ABSTRACT

In order to navigate through the surrounding environment many mammals, including humans, primarily rely on vision. The eye, composed of the choroid, sclera, retinal pigmented epithelium, cornea, lens, iris and retina, is the structure that receives the light and converts it into electrical impulses. The retina contains six major types of neurons involving in receiving and modifying visual information and passing it onto higher visual processing centres in the brain. Visual information is relayed to the brain via the axons of retinal ganglion cells (RGCs), a projection known as the optic pathway. The proper formation of this pathway during development is essential for normal vision in the adult individual. Along this pathway there are several points where visual axons face 'choices' in their direction of growth. Understanding how these choices are made has advanced significantly our knowledge of axon guidance mechanisms. Thus, the development of the visual pathway has served as an extremely useful model to reveal general principles of axon pathfinding throughout the nervous system. However, due to its particularities, some cellular and molecular mechanisms are specific for the visual circuit. Here we review both general and specific mechanisms involved in the guidance of mammalian RGC axons when they are traveling from the retina to the brain to establish precise and stereotyped connections that will sustain vision.

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1. Introduction

Retinal ganglion cells (RGCs) are the neurons in the mammalian retina that collect all the visual information perceived by the eyes and send it to the brain where it will be processed. Axons from these neurons are located in the inner layer of the retina where

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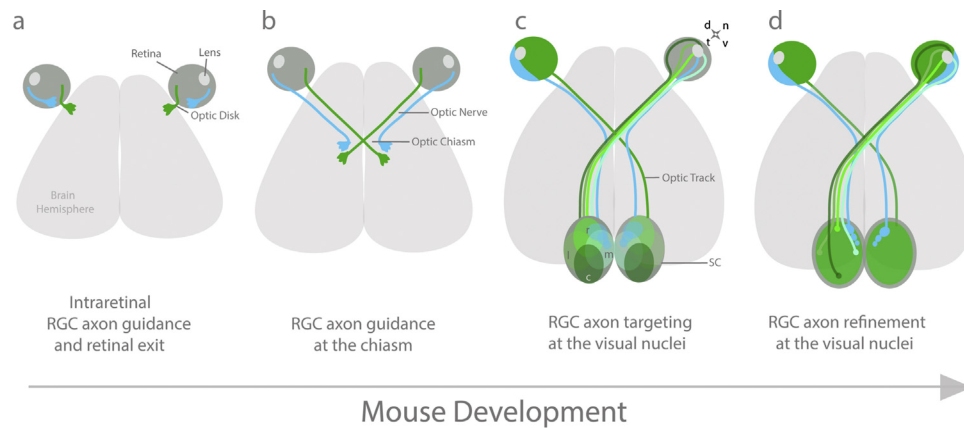

Fig. 1. Development of the visual pathway in mice.
The formation of the visual pathway takes place in several phases:
a. Beginning around E10.5, RGCs begin to differentiate and extend their axons within and out of the retina. From the outset growth is oriented towards the optic disc. The first RGCs to differentiate are located in dorscocentral retina (green), with later generated axons including those from ventrotemporal retina (blue) which gives rise to the mature ipsilateral projection.b. From E13 to E17 RGC axons navigate the optic chiasm region. A group of RGC axons originating from ventrotemporal retina (blue) reach the midline at this stage but turn away from it to project into the ipsilateral optic tract. In contrast, axons originating from other retinal regions cross the midline (green) to project into the same optic tract. The ipsilateral axons fasciculate with the contralateral axons coming from the other side forming the optic tract, where they then grow towards the different visual targets.c. At postnatal stages RGC axons target the different visual nuclei. By birth, most axons have reached the different visual targets, including the superior colliculus (SC). The rest of the nuclei are not shown for simplification. Once in the appropriate target, axons arborize extensively following a rough topographic map: axons from the nasal retina go to the caudal collicular areas, temporal axons to rostral areas, axons from the dorsal retina to lateral areas and ventral axons to the medial colliculus. At this initial stage, axonal terminations overlap extensively (large coloured circles). Contralateral axons (green) and ipsilateral (blue) terminals also intermingle profusely.d. By the second postnatal week, after an extensive refinement process, RGCs have established their final projection pattern. Axons originating in the nasal retina terminate in the caudal SC, temporal axons project into the rostral colliculus, dorsal axons map to the lateral SC and ventral axons terminate in the medial SC. Final termination zones are represented as small coloured circles. This final topographic arrangement occurs bilaterally but the projections of RGCs from different areas of the retina along the rostro-caudal and medio-lateral axis are shown only in the left SC for simplicity. In the right SC, ipsilateral axonal terminations (blue) form restricted patches at the rostro-medial collicular areas while contralateral terminals (green) fill the rest of the SC.
d, dorsal; v, ventral; n, nasal; t, temporal; r, rostral; c, caudal; m, medial; l, lateral.

they show typical neuronal polarity. RGC axons are basally oriented towards the optic fibre layer at the inner surface of the retina while dendrite arborizations extend on the opposite pole of the cell. The development of the visual pathway starts just after RGC differentiation, when visual axons initiate their trip towards visual targets by growing on the basement membrane of the retina in the direction of the optic nerve to exit the eye. Once they are out of the retina and into the optic nerve, visual axons continue their journey to approach the optic chiasm region. In mammalian species, many, if not all, RGC axons cross the midline at the chiasm to grow into the contralateral optic track. Depending on the degree of binocular overlap in the visual fields, a variable number of axons (~3% in mice, ~45% in humans) do not cross, but instead make a 45° turn away from the midline and project ipsilaterally, fasciculating with contralaterally projecting axons from the opposite eye. Through evolution, the percentage of this ipsilateral projection correlates with the extent of binocular vision. Additionally, the axons of a special type of RGCs, the intrinsically photosensitive retinal ganglion cells, ipRGCs, instead of entering the optic tracks, arborize into a non-image forming center, the suprachiasmatic nucleus, at the level of the optic chiasm. RGCs project to a large number of retinorecipiant brain regions (~46 in mice) [1] with the majority extending through the optic tracts and terminating in the lateral geniculate nucleus (LGN) and the superior colliculus (SC). In these targets, RGC terminals initially arborize extensively forming fuzzy topographic maps in an eye-specific segregation manner. Finally, after a refinement process that includes massive pruning, retinal axon terminals establish connections only with the right partners (Fig. 1).

During development, RGC axons therefore have to complete a long trip that initiates in the retina and ends at the different visual targets in the brain. Axon pathfinding along this complicated journey is possible because of the existence of special proteins called axon guidance molecules. In combination with cell–cell interaction mechanisms, these guidance molecules orient RGC axons along the pathway until they reach their targets and establish consolidated synapses in a multistep process critical to allow vision. In this article, we review the current knowledge about guidance molecules and mechanisms directing mammalian (mainly mouse) RGC axons from the retina to the brain.

2. Mechanisms controlling growth of RGC axons within the retina and out of the eye

2.1. Growth into the optic fibre layer

Shortly after their final cell division, newly generated RGCs extend their axons into the optic fibre layer at the inner surface of the retina. Within the optic fibre layer the axons then extend in a radially-oriented, highly-directed fashion centrally towards the optic disc, their exit point from the eye. Growth into the optic fibre layer is controlled, at least in part, through inhibitory signalling (Fig. 2a). Slits are secreted proteins that are potent inhibitors of RGC axon outgrowth. In the developing rodent retina two members of the leucine-rich repeat superfamily, *Slit1* and *Slit2*, are expressed in the RGC and inner nuclear layer of the retina, whereas one of their receptors, *Robo2* is expressed by most, if not all, RGCs [2–4]. In mice lacking *Slit1;Slit2* or *Robo2* a subset of RGC axons, originating predominately in ventral retina, grow aberrantly into the outer retina. Surprisingly, although located out with the optic fibre layer, these aberrantly located axons still extend towards the optic disc and exit the eye, demonstrating that the signals for disc-directed growth are not located exclusively in the optic fibre layer [5,6]. Secreted frizzled related proteins (Sfrps) also help prevent growth of RGC axons into the outer retina. *Sfrp1* is expressed in the retinal pigmented epithelium (RPE), ciliary margin zone (CMZ) and RGC layer, whereas *Sfrp2* is expressed in the outer retina and proximal optic stalk. In mice lacking *Sfrp2*, and to a greater extent *Sfrp1;Sfrp2* knockout

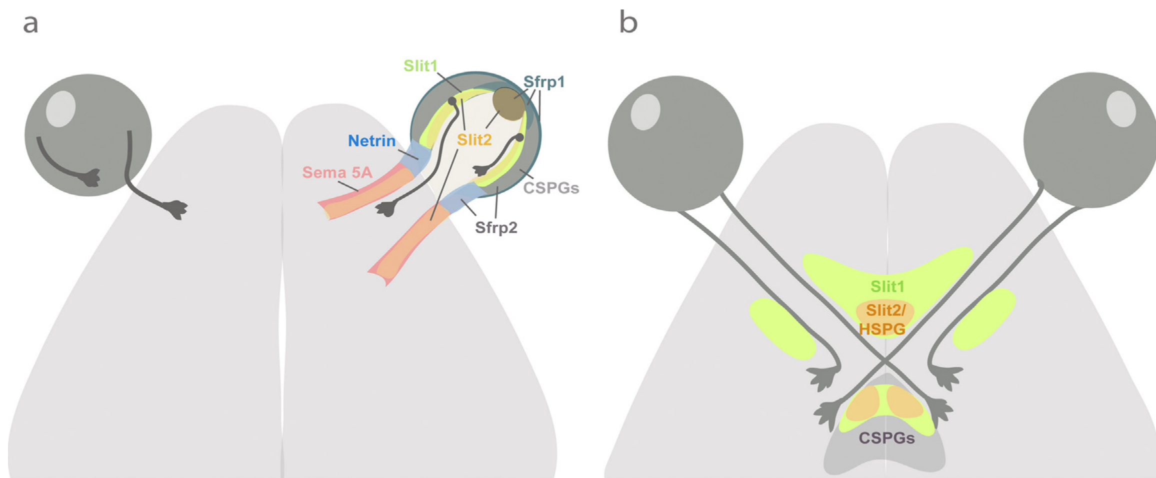

Fig. 2. Molecular mechanisms underlying early navigation of RGC axons.
a. Exiting the retina and going into the optic nerve. Growth into the optic fibre layer and towards the optic disc is regulated through a combination of inhibitory molecules, such as Slits and Sfrps, expressed in the RGC axon environment and cell adhesion molecules expressed by the RGC axons. Netrin, expressed at the optic disc, directs growth out of the eye, and inhibitory factors, such as Sema5A and Slits, channel the RGC axons through the optic nerve.
b. Navigation at the optic chiasm. Inhibitory factors, such as Slits and CSPGs, help channel the RGC axons through the optic chiasm and ensure they remain on their correct trajectory. Extracaellular matrix molecules such as HSPGs are also important for directed growth through the chiasm and may act, at least in part through modulating Slit localisation and signalling.

mice, a subset of RGC axons stray aberrantly into the outer retina, where, similar to in *Slit* mutants, they extend towards the optic disc and exit the eye [7]. Sfrp1 can act directly to modulate the rate and direction of growth of chicken and *Xenopus* RGC axons [8] suggesting that Sfrps may act directly on mouse RGC axons as a guidance signal to help preventing growth into the outer retina. However, the similarity in the phenotype of *Slit1;Slit2* and *Sfrp1;Sfrp2* mutants raises the possibility that Sfrps may also regulate intraretinal guidance through modulating Slit signalling. In addition to having direct effects on RGC axons, Sfrps act as negative modulators of the metalloprotease ADAM10 [9,10] and Kuzbanian (Adam10 in *Drosophila*), promotes cleavage of Robo, important for Slit-mediated axon repulsion [10]. However, no evidence has been found for modification of Robo2 processing in *Sfrp* mutants, although increased proteolytic processing of N-cadherin, which forms a multimeric complex with Robo receptors important for Slit-mediated repulsion, has been reported [7,11,12]. The planar cell polarity protein Vangl2, which localises to developing RGC axons, is also essential for normal orientation of RGC axons into the optic fibre layer. In mice lacking *Vangl2* many axons project aberrantly through the outer retina and accumulate in the subretinal space [13]. Further work will be required, however, to determine the mechanism(s) by which Vangl2 controls intraretinal axon guidance.

2.2. Growth towards the optic disc

In addition to helping prevent growth of RGC axons into the outer retina, Slit and Sfrp-signalling is also important for controlling the normal disc-directed growth of RGCs axons within the optic fibre layer. In mice lacking *Slit2*, its receptor *Robo2*, or *Sfrp1;Sfrp2* the normal disc-directed growth of RGC axons is disrupted with many axons projecting aberrantly towards the retinal periphery or orthogonal to their normal direction of growth. However, many of these aberrant axons are subsequently able to correct their direction of growth and reach the optic disc [6,7,14]. A source of Slits thought to be important for preventing growth into the retinal periphery is the lens. In vitro the lens secretes factors that are inhibitory to RGC axon outgrowth [5,15], and this inhibitory activity is attenuated in lenses from *Slit* mutants [5]. Through inhibitory signalling, chondroitin sulphate proteoglycans (CSPGs) also help direct growth centrally, away from the retinal periphery. During the period when RGC are generated, CSPGs localise in a receding central-peripheral wave in the rat retina, with newly generated RGCs located central to the CSPG-positive domain. Disrupting CSPG localisation in the retina with chondroitinase ABC results in precocious differentiation of RGCs in the peripheral retina and random orientation of RGC axons, including towards the retinal periphery [16].

Grafting experiments in chicken have demonstrated that there is an inherent polarity in the retina, with growth preferred towards and away from the optic disc, but not perpendicular to this direction. Moreover, the optic disc does not appear to attract axons from a distance. Instead local cues within the neuroepithelium direct growth towards the optic disc [17]. In keeping with this idea, cell adhesion molecules and contact with previously formed axons have been implicated in directing RGC axon growth centrally in the mammalian retina. The cell adhesion molecule L1 promotes RGC axon growth in an FGF receptor-dependent fashion and is concentrated at sites of contact between RGC axons. Blocking L1 or FGF receptor function disrupts the normally disc-directed growth of RGC axons [18]. In mice lacking the activated leukocyte cell adhesion molecule (ALCAM; also known as BEN, SCI, DM-GRASP, neurolin), the fasciculation and disc-directed growth of a subset of RGC axons is perturbed [19]. Blocking Sonic hedgehog signalling in RGCs also perturbs disc-directed growth, with axons turning in aberrant directions including towards the retinal periphery [20]. The expression of all these axon guidance molecules must be orchestrated by transcription factors. To date, few transcription factors have been described as regulators of intraretinal guidance. In mice lacking *the* POU class 4 transcription factor *Brn3b (Pou4f2)* RGC axons defasciculate in the retina and follow abnormal trajectories to the optic disc, with axons failing to reach the optic disc [21]. In chicken embryos, the zinc finger transcription factor Zic3 and the homeobox transcription factor Irx4 are expressed in the RGC layer and control intraretinal axon trajectory [22,23]. However, whether these factors are important for guidance in the mammalian retina remains to be established.

2.3. Exit from the eye

Once RGC axons reach the optic disc, their next challenge is to exit the eye. A key player in this process is netrin-1 which is

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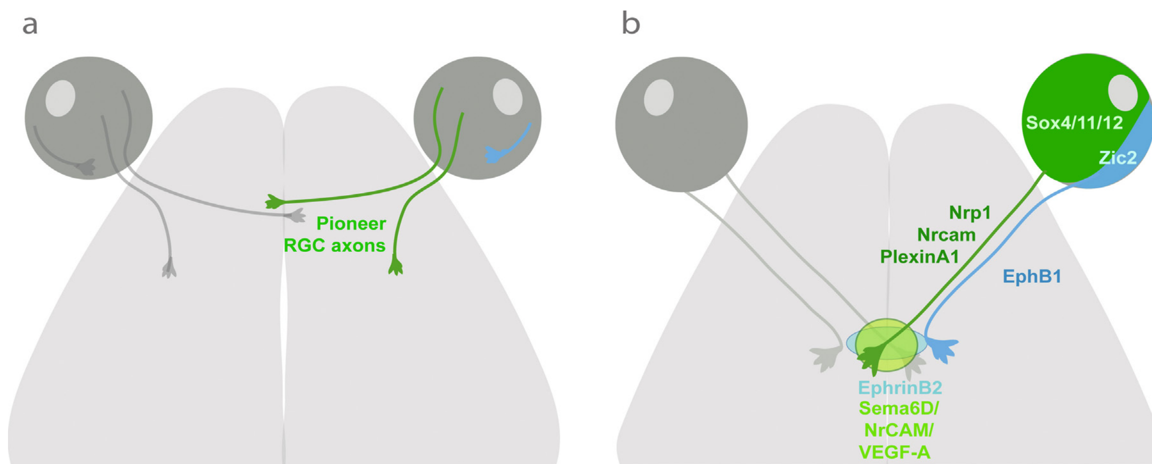

Fig. 3. Mechanisms determining axonal laterality at the mouse optic chiasm.
a. At E12, early pioneer RGC axons arising in the dorsocentral retina grow into the diencephalon projecting either contralaterally or ipsilaterally. However, these early ipsilateral axons do not approach the optic chiasm midline, but instead remain more laterally, and project directly into the ipsilateral optic tract and will later disappear. At E14, RGC axons from the ventrotemporal retina, that will establish the permanent ipsilateral projection, (turquoise line) start to extend within the retina and will reach the midline at later stages.
b. Around E15-E16, axons from the ventrotemporal retina that express the EphB1 receptor (turquoise line) induced by the transcription factor Zic2, are repelled by ephrin-B2 that is expressed by glial cells at the chiasm midline. As a consequence of EphB1/ephrin-B2 interaction, ipsilateral axons turn to project to targets on the same side. Contralateral axons (green lines) do not express EphB1 and ignore Ephrin-B2. Instead, they express Neuropilin1 (NRP1) and are attracted by VEGF-A expressed at the midline. Additionally, contralateral but not ipsilateral axons express NrCAM and PlexinA1. PlexinA1, NrCAM and Sema6D are also expressed at the midline and contribute to promoting midline crossing.
For simplicity only one side is coloured, the opposite axons are labelled in grey. There are other proteins reported to be specifically expressed in the ipsilateral or the contralateral population such as, Boc or Brn3a/Isl2 respectively. However, they have not been included here because their function in axon midline decisions is still not clear.

expressed by the glial cells of the optic disc (Fig. 2a). In mice lacking Netrin-1 or its receptor DCC, expressed normally by RGCs, RGC axons fail to exit the eye resulting in optic nerve hypoplasia [24]. Although Down syndrome cell adhesion molecule (DSCAM), which is also expressed by RGCs, has been implicated as a netrin receptor [25–27] DSCAM is not required for the guidance of RGC axons out of the eye [28]. Netrin normally is attractive for RGC axons. However, through modulating growth cone cAMP levels, it has been proposed that laminin localised to the optic disc converts the netrin response to repulsion, driving growth out of the eye [29]. Because of the key role of netrin in promoting growth out of the eye, mouse mutants with impaired optic disc development, for example heterozygous *Krd* and *Bst* mutants, mutants that lack *Shh* in RGCs and *Tbx2* mutants, display defects in RGC axon exit from the eye [30–32]. Other factors important for growth out of the eye include EphBs and Bmp receptor 1b. In mice lacking *EphB2;EphB3* or *Bmpr1b* subsets of axons in dorsal and ventral retina respectively fail to exit the eye [33,34].

Heparan sulphate proteoglycans (HSPGs) modulate the localisation and signalling of multiple guidance signals including Slits and Netrin-1 [35–41]. Accordingly, disrupting Heparan Sulphate biosynthesis in the retina results in intraretinal pathfinding errors similar to those seen in *Slit* and *netrin-1* mutants, including growth into the outer retina disrupted central-peripheral guidance and failure to exit the eye [42]. Thus, guidance of RGC axons in the retina, as well as other parts of the optic pathway (see below), is dependent not only on the presence of specific guidance cues but also other factors in their environment, including the composition of the extracellular matrix.

3. Growth of RGC axons through the optic nerve

Once RGC axons exit the eye they extend in the optic nerves towards the ventral midline of the diencephalon (future hypothalamus) where they meet to form the optic chiasm. Inhibitory signals such as Slit2 and Sema5a, which are expressed around the optic nerve, help restrict axons to the optic nerve [43,44] (Fig. 2a). Sfrp-signalling also helps control the tight bundling together of RGC axons in the optic nerve [7] whereas Sonic hedgehog signalling promotes the rate and direction of growth of RGC axons as they extend through the optic nerve [20]. The homeodomain protein Vax1 is essential for growth of RGC axons from the optic nerve into the chiasm. In the absence of *Vax1* RGC axons stall at the junction of the optic nerve with the ventral diencephalon and fail to progress further along the optic pathway [45]. Initially it was thought that Vax1 controls RGC axon growth by regulating the transcription of guidance cues such as netrin-1, expressed at the optic nerve/diencephalon junction. More recently, however, it has been demonstrated that Vax1, secreted by ventral diencephalon cells, acts directly on RGC axons as an attractive guidance signal, independent of it transcriptional activity, to promote growth towards the optic chiasm [46].

4. Axon pathfinding at the optic chiasm

4.1. Navigating the chiasm region

In mice, the first optic axons entering the diencephalon come from the dorsocentral retina and reach the optic chiasm midline at E12.5. These first-born RGCs, originating in the dorsocentral retina, are the first to enter the optic tract at E12.5. Some of these axons grow straight, crossing the midline, while others follow a more ventrolateral path and do not cross the midline [47–50] (Fig. 3a). Only few of the early-growing non-crossing RGC axons reach the visual targets and they then disappear completely after the refinement process [51,52]. It is possible that this transient population of uncrossed axons are the consequence of guidance mistakes because at the time they reach the midline guidance cues important to induce divergence are not yet expressed. Another, not mutually exclusive, possibility is that transient early ipsilateral fibers form a pioneer pathway that helps guide the later, follower, permanent ipsilateral axons (see later sections). In keeping with this idea,

elegant studies in zebrafish have demonstrated that axon–axon interactions between pioneer and follower axons are essential for guidance at multiple points along the optic pathway, including the optic chiasm [53].

In contrast to these dorsocentral ipsilaterally projecting neurons, early-born crossed axons do not disappear at later stages. At E12.5 they enter a glial palisade at the midline and course close to a border delineated by an early neuronal population that expresses a range of cell-surface proteins, including SSEA-1, CD44, beta-tubulin and CSPGs [50,54] (Figs. 2 and 3b). In utero ablation of these neurons in mouse embryos at E11, before RGC axons have arrived in the ventral diencephalon, results in stalling of the RGC axons in the optic nerves and complete failure to form the optic chiasm and optic tracts [55] demonstrating that these cells are essential for formation of the optic chiasm. Moreover, experiments in vitro incubating retina-diencephalon slices with chondroitinase ABC, an enzyme that degrades CSPGs, produced axonal disorganization, with axons crossing in aberrant locations and growing away from their normal path, indicating that molecules expressed by these cells, and not just physical guidance resulting from cell–cell contact, are essential to guide RGCs along the prospective chiasm [54].

More recently, Slits and their Robo receptors have been reported as essential for keeping RGC axons on their correct tracks while they are invading the chiasm region. In mice two members of the Slit family (*Slit1* and *Slit2*) are expressed around the path followed by RGC axons and one of their receptors, *Robo2*, by most if not all RGCs (Fig. 2b). In vitro Slits are potent inhibitors of RGC axon outgrowth and in mutant mice for Slit-Robo signalling some axons cross the midline in ectopic locations, others grow aberrantly into the contralateral optic nerve and a number of them wander posteriorly along the midline [2,43,56]. Similar to Slits proteins, Islr2, another member of the leucine-rich repeat superfamily contributes to delineating axon guidance at the chiasm. *Islr2* mutant mice display a thicker chiasm along the antero-posterior axis and a greater number of axons enter the opposite optic nerve in these mice. Defasciculation defects in the optic tract were also observed both at ventral and dorsal locations in these mice [57].

As mentioned above, Slit signalling is modulated by different types of molecules. For example, HSPGs are necessary in the axons to respond to Slits [41,58] and are required to localise Slits to the extracellular matrix [40]. Accordingly, mice with disrupted HS biosynthesis display some similar pathfinding errors at the optic chiasm to *slit* and *robo2* mutants [36,38,58,59]. Slit signalling may also be modulated by metalloproteases as demonstrated in *Drosophila* axons [10]. Treatment of an in vitro *Xenopus* brain preparation exposed to metalloprotease inhibitors results in stalling of axons at the optic chiasm, misprojection into the contralateral optic nerve and axon defasciculation [60]. However, whether metalloproteases are essential for guidance in the mammalian optic pathway, through modulation of Slit signalling and/or other guidance molecules, has not yet been established.

The Secreted Frizzled Related Proteins *Sfrp1* and *Sfrp2* localise to RGC axons and, as previously mentioned, are important for guidance and bundling of RGC axons in the retina. Later they seem to play a similar function at the chiasm and optic tracts. At the optic chiasm, RGC axons are more loosely packed in mutant mice for *Sfrp1* and *Sfrp2*. This defect was more evident in *Sfrp1;Sfrp2* double mutant embryos and in 20%, of the cases the phenotype at the chiasm was similar to that described for *Slit1/;Slit2* or *Robo2* embryos. Interestingly, axonal tracings at E13.5, when the first set of RGC axons reach the chiasm, demonstrated a mild anterior dispersion of axons at the double mutant chiasms indicating that late-born axons are more dependent on Sfrp-mediated axon fasciculation/guidance than early generated, pioneer axons. *Sfrp1* and *Sfrp2* are not expressed in the environment of RGC axons as they navigate through the chiasm, suggesting that Sfrps act autonomously in RGCs to control guidance in this region of the optic pathway. Metalloprotease-mediated proteolytic processing of N-cadherin is altered in these mutants [7], but whether this impacts on Slit signalling [11,12] and underlies the guidance errors at the chiasm of *Sfrp* mutants remains to be determined.

Other factors such as Sonic Hedgehog (Shh) also play an important role in confining the RGC axon's path as they grow through the chiasm. If Shh signalling is altered during mouse development, RGC axons exhibit pathfinding defects such as defasciculation, increase of the area occupied by the contralateral axons at the midline region, and contralateral axons aberrantly extending into the ipsilateral tract and the contralateral optic nerve [20]. In spinal commissural axons Shh signalling is mediated via a non-canonical pathway involving local protein translation of ß-actin at the growth cone regulated by zipcode binding protein 1 [61]. Whether this is also true for RGC axons is not known currently.

The Ebf/Olf (Early B-Cell Factors) family of proteins are helix-loop-helix (HLH) transcription factors including four members, Ebf1 through Ebf4. These transcription factors are involved in axon guidance in different systems [62,63], including the visual pathway. At the optic chiasm of *Ebf1* mutant mice, there is an increase in the number of contralateral axons at expenses of ipsilateral axons and an increased projection of RGC axons to the opposite eye. Ebfs are expressed in differentiated RGCs during development [64] in a time that is compatible with the regulation of guidance receptors important for navigating the optic chiasm. However, the identity of the receptors regulated by Ebf remains to be established.

4.2. Axon midline crossing at the chiasm

Depending on whether their axons cross or avoid the midline at the chiasm RGCs are called contralateral or ipsilateral RGCs respectively. These two populations express distinct genes in order to cross or not at the midline [65] and consequently respond differently to cellular and molecular cues arrayed at the chiasm midline (Fig. 3b). For instance, contralateral but not ipsilateral RGC axons express Neuropilin1 (NRP1), a receptor for the vascular endothelial growth factor, VEGF-A, that is highly expressed at the midline [66]. Mice lacking either *nrp1* or expressing only a VEGF-A isoform, $VEGFA_{120}$, that cannot signal through NRP1, exhibit an increased number of ipsilateral axons likely as a consequence of the failure of presumptive contralateral axons to cross the midline [66,67]. Conditional deletion of *Nrp1* specifically from RGCs confirmed that NRP1 acts autonomously in RGCs to control contralateral axon growth. However, NRP1 also helps shape RGC axon projections through its role in blood vessel patterning. The presumptive chiasmatic region is normally relatively avascular, creating a passage for contralateral axon growth. In endothelial-specific *Nrp1* mutants and mice expressing only the $Vegfa^{188}$ isoform ectopic vessel sprouts develop in the chiasmatic region. These vessels present a physical barrier to axon growth, but RGC axons are able to activate mechanisms that enable them to navigate around these aberrant vessels to continue towards their target regions, creating gaps or holes in the axon bundles. Thus, NRP1 has a dual role in optic chiasm formation – it acts directly in RGCs axons to promote contralateral axons growth, and impacts indirectly on chiasm formation through controlling neurovascular co-patterning [68]. Sema6D is also expressed at the optic chiasm midline but it does not act as a ligand for NRP1. Instead, it forms a complex with NrCAM, expressed on the midline radial glia, and PlexinA1, expressed on SSEA-1-neurons at the chiasm area, to promote growth of contralateral RGC axons [69].

The transcriptional mechanisms controlling the expression of guidance molecules at the growth cone of contralateral RGCs remained unknown for a long time. Until very recently, only two transcription factors were reported to be expressed specifically in

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contralateral but not ipsilateral RGCs. One of these transcription factors is the LIM-HD transcription factor Isl2. Isl2 is expressed in about 40% of contralaterally projecting RGCs but not in ipsilateral RGCs [70]. In *Isl2* mutant mice there are more ipsilateral axons but this extra ipsilateral projection comes specifically from RGCs located in the ventrotemporal area that normally project contralaterally. RGCs from other retinal areas project correctly to the contralateral side in the *Isl2* mutants suggesting that this transcription factor plays a role in repressing the ipsilateral program in the ventrotemporal retinal quadrant but does not specify contralateral RGCs from the rest of the retina. Recent studies have shown that Isl2-retinal cells are a class of non-ON-OFF direction selective RGCs that have dendritic lamination pattern restricted to a specific sublamina of the inner plexiform layer of the retina (S3) and project axons to image-forming retinorecipient areas [71]. However, the precise function of Isl2 in RGCs from non-ventrotemporal regions of the retina is still unclear. The second transcription factor reported to be expressed in contralateral but not ipsilateral RGCs is Brn3a (Pou4f1), another member of the Pou family [72]. The function of this transcription factor in contralateral RGCs is still unclear but RNA sequencing analysis comparing the transcriptomic profile of Brn3a-labelled neurons with RGCs lacking Brn3a suggest that it may be involved in keeping RGC type specification [73].

To date, SoxCs are the most clear example of a transcription factor family directly controlling contralateral RGC identity. SoxC genes (in particular Sox4, 11 and 12) act during differentiation of contralateral RGCs by binding to Hes5 and repressing Notch signalling which is active in neural progenitors. When SoxC genes are deleted in postmitotic RGCs, Plexin-A1 and Nr-Cam expression is downregulated. Contralateral (but not ipsilateral) axons lacking SoxC grow poorly on chiasm cells in vitro and some of them project ipsilaterally at the chiasm midline in vivo [74], indicating that SoxC genes are essential to determine contralateral RGC fate.

4.3. Axon midline avoidance at the chiasm

In most mammals, the ipsilateral projection arises in the ventral-temporal retina, the site of binocular overlap in the visual field. In mouse, ipsilateral RGCs start to differentiate at E14.5. In contrast to the transient uncrossed RGC axons originated in the central retina, ipsilateral axons coming from the VT retina are maintained in adult mice and express specifically the zinc finger transcription factor Zic2 (Fig. 3b). The number of Zic2-positive RGCs varies between species depending on the extent of binocular vision, suggesting that this transcription factor could be a determinant of axonal ipsilaterality in the visual system of different species. Functional experiments confirmed this hypothesis. Mutant mice for *Zic2* lack ipsilateral projections at the optic chiasm [75] and, conversely, ectopic expression of *Zic2* in contralateral RGCs generates an aberrant misprojection of these axons to the ipsilateral side [76]. Therefore, Zic2 is both necessary and sufficient for specification of ipsilaterally projecting RGCs. It remains unknown how Zic2 is regulated but, recent studies have shown that ipsilateral RGCs may have at least two origins: a subpopulation of Zic2-positive RGCs arise in the CMZ, a region located at the periphery of the retina, and depend on the expression of CyclinD2. A second subpopulation of Zic2-positive RGCs are CyclinD2 independent and originate in the neural retina [77]. Albino mice have fewer Zic2-positive cells than pigmented mice [75], in agreement with the described reduction of ipsilateral axons associated with albinism. Birth-dating experiments have suggested that this reduction in ipsilateral RGCs is due to an imbalance in the generation of ipsi- and contralateral RGCs in albino compared with pigmented retina [78,79] [80,81]. Recent experiments have demonstrated that the Zic2 population generated in the CMZ is reduced in albino mice and therefore, this reduction is dependent on Cyclin D2 [77].

It is likely that, in an indirect manner, the second population of Zic2-positive RGCs that arise independent of CyclinD2 expression derive from neural progenitors located in the ventrotemporal part of the early retina positive for the forkhead transcription factor Foxd1. In the absence of Foxd1, which is expressed normally in the VT retina, Zic2 is downregulated [82].

Zic2 induces the expression of the tyrosine kinase receptor EphB1 to control RGC axon midline avoidance [76] (a detailed description of the Eph family of receptors is included in later sections). EphB1 is highly enriched in ipsilateral RGC axons. When EphB1 expressing RGC axons approach the midline, EphB1 binds to its ligand ephrinB2 that is expressed by midline radial glia cells triggering a repulsive response and inducing a turning to project ipsilaterally [83] (Fig. 3b). The expression of EphB1 in the temporal half of the retina in human embryos [84] suggests that the role of this receptor in provoking axon midline repulsion is conserved through evolution. Recent reports have demonstrated that Zic2 also determines axon midline avoidance in the developing spinal cord [85]. However, here it works through the regulation of a different receptor of the same family, EphA4 [85] which also is a receptor for ephrinB2. Modern next-generation sequencing technologies should provide further information about Zic2 targets in different contexts in the near future.

In addition to EphB/ephrinB signalling other pathways may be involved in axon midline avoidance. Boc, one of the Shh receptors, is expressed specifically in ipsilateral RGCs [20,86,87]. Ectopic expression of Boc in contralateral RGCs induces a change of laterality in a subset of axons [87] suggesting that Boc/Shh signalling is involved in axon guidance. However, because in the absence of Boc ipsilateral RGCs do not differentiate properly and express contralateral RGCs markers instead of ipsilateral RGCs markers [86] it is also possible that the switch induced by Boc in axonal laterality derives from a change in cell fate rather than a defect in axon guidance.

Another family of membrane proteins that have been proposed to play a role in axonal laterality at the midline are the Teneurins (Ten-m/Odz). Ten-m proteins are a family of type II transmembrane proteins that mediate adhesion by homophilic recognition [88]. The member of the Ten family, Ten-m2, is expressed in the RGC layer. In the absence of this protein there is a 40% reduction in the number of RGC axons projecting to the ipsilateral side. Although the expression of Zic2 is unaltered in *Ten-m2* mutants, EphB1 expression is diminished specifically in the ventral but not in the temporal retina of these mice [89–91] suggesting that Ten-m2 may influence midline axon guidance by alterating the expression of EphB1.

4.4. Guidance through the optic tracts

In comparison to amphibians and fish, much less is known about the mechanisms that control guidance through the mammalian optic tracts. Growth from the chiasm into the optic tracts requires Growth Associate Protein 43 (GAP-43) function. GAP-43 is required autonomously in RGCs for interaction with guidance cues at the proximal region of the optic tracts [92]. In mice lacking GAP-43, RGC axons navigate through the chiasm but fail to enter the optic tracts, with axons either stalling as they exit the chiasm or following aberrant paths within the diencephalon, including back across the midline [93]. The identity of the GAP-43-dependent signals required for growth into the optic tracts is not known currently. Similar to other regions of the mouse optic pathway, inhibitory Slit signalling helps restrict RGC axons to the optic tracts and in the absence of *Slit1;Slit2* or *Robo2* RGC axons stray away from the optic tracts into the telencephalon, widely throughout the diencephalon, and across the dorsal diencephalic midline [14,56]. Several factors have been identified that control the fasciculation of mammalian RGC axons in the optic tracts, including Sfrps, Islr2 and VEGF-A/NRP1 signalling [7,57,66,68]. In the case of VEGF-A/NRP1

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signalling mutants the defasciculated appearance of the optic tracts likely results from misrouting of axons at the optic chiasm, and the resultant co-mingling of ipsilaterally and contralaterally-specified RGC axons in the ipsilateral optic tract, rather than a direct role in controlling axon fasciculation [68]. DSCAM provides permissive, but not guidance, signals that help drive the growth of RGC axons through the optic tracts. Both in vitro and in situ DSCAM provides growth promoting signals to RGC axons, and is required both in the RGC axons and their environment for promotion of axon growth. In *Dscam* mutants, RGC axons follow their normal trajectory through the optic tracts but extend slower than in wild-type embryos and are delayed in reaching their targets. Conversely, overexpressing DSCAM results in exuberant growth in the early optic tract [28]. Further work is required, however, to determine if disrupting the timing at which RGC axons reach their target region contributes to the eye-specific segregation defects in the lateral geniculate nucleus of *Dscam* gain- and loss-of function mutants [94,95].

All along their pathway to the targets, RGC axons use diverse regulatory mechanisms to express, activate and transduce the signalling of the different axon guidance receptors we have reviewed here. Local protein synthesis at the growth cone has been also proposed as one of the most appealing regulatory mechanisms involved in axon pathfinding. mRNAs can be transported to the growth cone enabling rapid changes in the local proteome through local translation. Recent profiling studies in mice have revealed that growing axons possess surprisingly complex and dynamic transcriptomes, suggesting that axonal mRNA localization is highly regulated and likely has an important role during axon pathfinding (reviewed in [96].

5. Targeting to the visual nuclei

In addition to the RGCs transmitting visual information to the main targets in the brain, a subset of RGCs (ipRGCs) instead project to non-image forming visual processing nuclei such as the suprachiasmatic nucleus (SCN) or the olivary pretectal nuclei implicated in circadian rhythms or pupillary reflexes respectively. ipRGCs are intrinsically photosensitive because they express the photopigment melanopsin and are essential to conveying luminance signals to the brain for non-image forming visual processing [97,98]. ipRGCs have elaborate innervation patterns throughout the entire SCN and a single ipRGC can bilaterally innervate the SCN. In addition, a single SCN projecting ipRGC can send collateral inputs to many other brain regions, but the size and complexity of the axonal arborizations into non-SCN regions are less elaborated than those in the SCN [99]. The molecular mechanisms controlling the targeting of ipRGCs to the SCN are largely unknown. Because ipRGCs projections follow the same contralateral:ipsilateral ratio as conventional RGCs, one possibility is that contralateral and ipsilateral ipRGCs use similar programs to other RGCs for pathfinding at the midline. However, the bilateral innervation of the SCN by subsets of ipRGCs is incompatible with the existence of repulsive molecules for these axons expressed at the midline. The SCN is fully innervated by retinal fibers only 10 days after birth [100] and it has been proposed that the targeting of the ipsilateral SCN by bilaterally projecting ipRGCs occurs later in development, once repulsive signals at the midline have been down-regulated.

The guidance mechanisms controlling the arborisation of ipRGCs to the SCN have not been elucidated. However, some of the mechanisms controlling RGC axon targeting to other non-image forming nuclei in mammals are now starting to be described. For instance, the adhesion molecule Cadherin-6 as well as Reelin signalling are important for RGC targeting into non-image forming nuclei [101,102]. Another subtype of RGC project to the accessory optic system (AOS) which generates compensatory eye movements that stabilize images during slow visual field motion. The AOS consists of the nucleus of the optic tract/dorsal terminal complex (NOT) and the dorsal terminal nucleus (MTN) [103–105]. Again, not much is known about the guidance mechanisms of the different RGC axons to any of these specific targets but recent works have shed some light on this process. In the absence of contactin 4 (CNTN4) or one of its binding partners, amyloid precursor protein (APP), a subset of direction selective RGCs fail to target the NOT [106]. Another subset of on direction-selective RGCs express Sema6A and are attracted to the PlexinA2/A4-expressing MTN nucleus where they project [107].

A detailed picture of the different proteins involved in regulating how subsets of RGC axons reach their different targets is far from being complete but, as mentioned above, important advances have been achieved in the last few years. Recent work has also proposed a more general theory about the mode by which RGC select their targets. First arriving axons initially innervate multiple targets, with most of these connections subsequently removed. In contrast, later arriving axons are highly accurate in their target choices. These results led to the proposal that target selection varies according to birthdate and timing of axon ingrowth [95], and appears to depend on the extent of axonal occupancy in the targets.

6. Topography and refinement at the targets

RGC axons project in the main image-forming nuclei, the LGN and the SC, according to two main features: topography and axonal laterality. These characteristics are also present in other visual targets but likely because of their large size, the SC and the LGN are the most intensely studied visual structures in order to understand how topography and eye-specific projections are established. Initially, RGC axons grow into the SC in a non-topographic manner and then topographic mapping is established in different steps. In mice, this process takes place during the first two postnatal weeks. In the early phase RGC axons enter the SC from the anterior end to reach the most caudal part. After this initial phase of expansion, interstitial branches start to form around the future termination zone (TZ) and, at the same time, the primary axon retracts towards its TZ (Fig. 1c). Further extensive arborization and the removal of topographically inappropriate branches eventually leads to the formation of a mature, highly focused TZ [108] (Fig. 1d). In the mature targets, axons coming from neighbour RGCs in the retina will project to neighbouring TZs, creating a point-to-point representation of the retina in the target. In the adult SC, RGCs axons from the nasal (N) retina project to the caudal (C) region, whereas RGCs in the temporal (T) retina project into rostral (R) areas. RGCs located into the dorso-ventral (D-V) axis of the retina map along the latero-medial (L-M) axis with dorsal RGCs projecting into the lateral SC and ventral RGCs into the medial areas.

6.1. Molecular mechanisms of map topography

Interstitial branching of RGC axons in the SC is promoted by brain-derived neurotrophic factor (BDNF)/tyrosine-related kinase B (TrkB) signalling. This BDNF axon branching is mediated by the microRNA miRNA-132, which downregulates p250GAP, a GTPase-activating protein that suppress Rac function [109]. This signalling does not control map topography *per se*, but multiple molecular gradients and mechanisms act together to influence it. The best understood are the family of tyrosine kinases membrane proteins Ephs and ephrins. It appears that ephrinAs interact with the BDNF receptor, p75 [110] to inhibit BDNF/TrkB signalling and antagonize BDNF-mediated branching.

The function of Ephs and ephrins in topography is conserved through evolution. In fact, their role in the establishment of topo-

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graphic maps was first described in frog and chicken embryos and then confirmed in mammals [111] [112]. The specific members of the Eph/ephrin family involved in mapping vary between species, but the general principle mediating this process is highly conserved. The Eph family is composed of at least 15 members, named after the erythropoietin-producing hepatocellular carcinoma (EPH carcinoma) where they were described for the first time [113]. Based on sequence homology and binding affinity there are two main types of Eph receptors, A and B [114]. There are 9 class A receptors (EphA1 to −A8 and EphA10) and 6 class B receptors (EphB1 to −B6). The ligands for Eph receptors are the ephrins (Eph receptor Interacting proteins). Ephrins are also subdivided into A and B classes on the basis of sequence homology. There are five ligands for EphAs (ephrin-A1 to −A5) and three for EphBs (ephrin-B1 to −B3). In general, ephrin-A proteins bind to EphA receptors, while ephrin-Bs bind to EphB receptors but there are some exceptions to this rule. Independently of the subfamily they belong to, all Eph receptors have a similar structure. They are transmembrane receptor tyrosine kinase proteins containing an ephrin binding domain on the N-terminal region, which determines their affinity to ephrins. In contrast, the ephrins have structural differences depending on the family they belong to. Ephrin-As are short membrane tethered proteins composed by an extracellular Eph specific domain attached to the membrane by a short GPI anchor. Ephrin-Bs also feature a N-terminal Eph specific domain but are transmembrane proteins on the C terminal side and contain an intracellular PDZ binding domain [115]. Upon detection of a ligand, Ephs change their configuration, allowing interaction with others Eph receptors which then start to cluster together [116]. This association allows their own tyrosine kinase domains to phosphorylate each other. Under this new configuration, Eph receptors are able to phosphorylate second messenger proteins starting a signalling cascade. Activated Eph/ephrin complexes tend to form even larger clusters by recruiting other Ephs, forming lipid rafts inside the membrane of the cell [117]. These clusters can contain multiple types of Eph receptors, and may serve as an additional mechanism for crosstalk between −A and −B subclasses [118].

The canonical signal transduction, called forward signalling, is mediated by Eph proteins acting as receptors: upon contact with an ephrin, Ephs initiate an internal signalling cascade that leads to modifications in the cell they are expressed in. Ephrin/Eph reverse signalling has also been described. In this case, upon contact with an Eph protein, ephrins signal intracellularly acting as a receptor [119].

While all members of the −A and the −B families are associated with cell membranes, the extracellular domain of these proteins can be cleaved by metalloproteases of the ADAM family [120]. This cleavage is believed to be the main mechanism to terminate signalling of the receptor and allow cell repulsion. Another mechanism that has been proposed as essential in Eph/ephrin signalling is the endocytosis of the entire Eph/ephrin complex. Endocytosis may happen either in the Eph expressing cell [121] or in the ephrin expressing cell [122] and may also be essential to allow a repulsive response.

In mice, RGCs express a high temporal to low nasal gradient (T > N) of EphA5 and EphA6 [123] while the SC expresses a high rostral to low caudal (R > C) opposing gradient of ephrin-A5 [124]. In some cases, these protein gradients are counterbalanced by opposite gradients in the same tissue. For example, ephrin-A5 is found in the retina in a high nasal to low temporal gradient (N > T). Similarly, gradients of ligands in the SC are countered by opposite gradients of receptors with EphAs expressed in a high-rostral to low-caudal fashion (reviewed in [125])

Manipulation of endogenous levels of both Ephs and ephrins have been very useful to understand the crucial role of these proteins in topography. However, their complex expression patterns in both the retina and the target tissue have made it difficult to uncover their precise mechanisms of action. Genetic deletion of mouse EphA5 leads to a caudal shift of the axons in the SC [126]. Ectopic expression of EphA3 (which is not expressed in RGCs) in a retinal high-temporal to low-nasal gradient lead to a caudal shift of the axons [127]. Genetic deletions of ephrin-As, in either ephrin-A5 mutant mice, ephrin-A2/A5 double mutant mice, or ephrin-A2/A3/A5 triple mutant mice, all result in a caudal shift of retinal axons in the SC, directly proportional to the amount of protein eliminated [128]. More recently, highly sophisticated experiments that conditionally removed ephrinA5 only from the SC or from the SC plus the retina suggest a model in which, as previously thought, temporocentral axons that normally project to the rostrocentral SC do not invade caudal SC positions because of the expression of ephrinAs in caudal SC, but in addition, ephrinA expression in nasal axons plays an important function [128]. In other words, axon–axon repulsion mediated by ephrinAs expressed by the axons is also essential for topographic mapping.

While EphA/ephrinAs establish retinotopic mapping along the rostro-caudal axis, EphB/ephrinBs control topography in the lateromedial axis. EphB1 and EphB2 are both expressed in a very similar high ventral to low dorsal gradient (V > D) in the retina. In fact, it has been proposed that the overall level of EphBs is more important than the identity of a particular EphBs in the establishment of lateromedial mapping [129]. In the SC ephrin-B1 and ephrin–B2 are expressed in a gradient along the medial-lateral (M > L) axis [130] but, as in the case for EphA/ephrinA, ephrinBs and their receptors also exhibit opposing counterbalanced gradients in the same tissues. Ephrin-B1 and −B2 are expressed in a high-dorsal low-ventral gradient (D > V) in the retina and EphBs are expressed in a high lateral to low medial gradient in the SC. The role of these proteins in determining topography along the latero-medial axis was initially proposed because *EphB2/B3* knockout mice exhibit an aberrant lateral shift of the axons in the SC [130]. Similarly, mice lacking either EphB1 or EphB2 or *ephrin-B1/B2* double mutants show a lateromedial displacement of RGCs axon terminals at the targets [131]. In addition, *ephrin-B2* mutants that express a C-terminal, intracellular truncated ephrin-B2–β-gal fusion protein, unable to transduce reverse signals, show defects in lateromedial mapping demonstrating that reverse ephrinB/EphB signalling is also critical in this process [131].

Because ventral EphBs-expressing RGCs project to ephrinBs expressing areas in the medial SC, it was hypothesized that ephrinBs may attract RGC axon interstitial branches [130], but an attractive response mediated by EphB/ephrin binding has never been reported. However, several adhesion molecules have been proposed to interact with EphB/ephrinBs signalling during the establishment of lateromedial mapping. The adhesion molecule L1 is expressed in RGCs and in the SC and interacts with the cytoskeletal adaptor Ankyrin which in turn interferes with Eph signalling. EphB regulates L1 phosphorylation [132] and mice carrying mutations in the L1 ankyrin-binding motif display abnormal lateromedial mapping of RGC axons, which resembles the phenotype of EphB mutant mice. In addition, the cell adhesion molecule ALCAM is expressed in the SC and has been suggested to interact with L1 in RGC axons to promote branch extension of medial RGC axons [133]. These interactions between Eph/ephrinB signalling and adhesion molecules could account for the projection of ventral axons on ephrinB expressing collicular territories.

In summary, all these studies together demonstrate that in general, EphAs are involved in retinotopic mapping establishment along the nasotemporal retina while EphBs are implicated in mapping along the dorsoventral axis.

The Wnt signalling pathway has also been reported as important in mediating lateromedial mapping. Wnt3 shows a similar expression to ephrinB1 in the SC and Ryk, a Wnt receptor, is highly

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expressed in the ventral mouse retina. Wnt signalling mediated by Ryk may induce the repulsion of ventral axons to the Wnt-expressing medial colliculus. The blockage of Ryk nearly eliminates all laterally directed branches in the SC, leaving only the medially directed branches. This is the opposite phenotype exhibited by *EphB2/B3* double knockout mice in which interstitial branches are found preferentially directed laterally [134]. Although it is unclear currently whether Wnt/Ryk and Eph/ephrin-based signalling interacts or they are independent mechanisms, it seems that Wnt3 and ephrinB1 are opposing guidance activities for regulating interstitial branches in medial-lateral mapping.

As has been previously demonstrated for axon guidance, local protein synthesis at the axon terminals also seems to be an important process during the establishment of topographic maps and subsequent refinement. Using an axon-TRAP-RiboTag approach in mouse followed by deep-sequencing analysis, mRNAs that are being locally translated in RGC axon terminals at the time they are refining at the visual target have been isolated. A high enrichment in mRNAs involved in axon elongation, branching and pruning (among other processes), has strongly supported a role for local translation at the axon terminal while topographic mapping is being established [135].

Ipsilateral and contralateral RGCs project to different areas of the targets according to their topographic location in the retina. Ipsilateral axons are located at the ventrotemporal periphery of the mouse retina and therefore, their corresponding topographic location in the SC is rostromedial areas (Fig. 1c, d). Contralateral RGCs populate the entire retina and their axons topographically fill the SC and the LGN in a complementary pattern with the ipsilateral axons. Therefore, the projection pattern of ipsilateral and contralateral RGCs seems to be mainly determined by general mechanisms controlling topographic mapping. A family of proteins that have been proposed to specifically affect the targeting of ipsilateral RGCs are the Teneurins/Ten_m. Teneurins are implicated in the specification and lamination or RGCs into the retina [136] but they also seem to be essential to guarantee the targeting of ipsilateral axons at the visual nuclei. Genetic removal of *Ten-m3* leads to an alteration of topography that mainly affects the ipsilateral pathway [89,90]. However, since Ten-m3 is not exclusively expressed in ipsilateral RGCs, it is unclear how these proteins specifically affect ipsilateral targeting and further investigations are needed to clarify this issue.

6.2. Mechanisms of axon refinement at the targets

The profuse extension of axon terminals in the area of their future TZ leads them to explore the vicinity in order to later establish correct connections with their proper target cells. After the establishment of a gross topography outlined by guidance molecules, RGC axon terminals undergo extensive refinement at early postnatal stages in a process that depends on spontaneous waves of activity generated in the retina before visual experience is set. The developing retina spontaneously generates retinal waves of correlated activity initiated by sturbust amacrine cells. These waves seem to originate in the ventrotemporal retina [137] and to randomly propagate across the entire retina [138]. It was proposed that spontaneous activity could interfere with Eph/ephrin signalling during the establishment of topographic maps [139]. Increasing evidences now favor the idea that topographic mapping, interpreted as the precise location of the TZ where RGC axons will project, is roughly stablished by Eph/ephrins signalling and interacting proteins. This blurry defined map is later fine-tuned by retinal waves of spontaneous activity. The serum response transcription factor (SRF), which regulates the activity of many immediate early genes such as c-fos in many contexts, participates in axon pruning during visual axons refinement [140] and could be implicated in this activity dependent-refinement processes.

As stated above, this process of spontaneous activity-dependent refinement does not seem to be controlled by guidance molecules [141] or neurotrophic factors such as BDNF [142] and therefore, their mechanisms of action are out of the scope of this review. However, it is worth mentioning that in the case of eye-specific segregation of ipsilateral and contralateral RGCs at the targets, the serotonin transporter SERT plays an important role. SERT, which is controlled by the transcription factor Zic2, and is expressed specifically in ipsilateral but not contralateral RGCs [143] is essential for the refinement of ipsilateral terminals at the SC and LGN [143–145]. In contralateral RGCs, activation of the serotonin receptor 5HT1B, expressed in all RGC axon terminals [146], inhibits cAMP production in the axon terminal because it is negatively coupled to adenylate cyclase 1 (AC1) through G-proteins of the Gi subtype [147]. However ipsilateral axons that express SERT are able to internalize extracellular serotonin and relieve 5HT1B-mediated inhibition, allowing the production of cAMP and promoting ipsilateral axon retraction. Therefore, this seems to be an important mechanisms for ipsi/contra segregation at the visual targets.

7. Conclusions

Since the identification of the first axon guidance molecules much has been discovered on the molecular mechanisms ruling axon guidance and many of these mechanisms have been reported to function in mammalian visual axons. In fact, a considerable number of axon guidance mechanisms were first described in this model. However, there are still many questions to uncover. For instance, it is unclear how the expression of axon receptors and guidance molecules are so perfectly synchronized on time. Or what are the precise regulatory mechanisms that make possible the reuse of the same molecules several times along the pathway. The advent of next generation sequencing technologies combined with new genome editing approaches hold the promise of rapidly increase our current knowledge on the regulatory mechanisms controlling the long trip of RGC axons to their targets during development. The increase of our current understanding on the formation of the visual pathway will have at least two positive consequences: on one hand, it will help us prevent diverse congenital conditions derived from defects in developmental visual miswiring, and, on the other hand, it may contribute to making possible visual axonal reconnection after injury.

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