Molecular regulation of visual system development: more than meets the eye

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Vertebrate eye development has been an excellent model system to investigate basic concepts of developmental biology ranging from mechanisms of tissue induction to the complex patterning and bidimensional orientation of the highly specialized retina. Recent advances have shed light on the interplay between numerous transcriptional networks and growth factors that are involved in the specific stages of retinogenesis, optic nerve formation, and topographic mapping. In this review, we summarize this recent progress on the molecular mechanisms underlying the development of the eye, visual system, and embryonic tumors that arise in the optic system.

For humans, the visual system is a principal conduit for acquiring external sensory information. Thus, “quality of vision” is intimately tied with “quality of life.” Despite extensive clinical and laboratory investigation, many diseases that impair vision, ranging from congenital abnormalities to sporadic forms of retinal degeneration, lack effective treatments. One hope is that improved understanding of development of the visual system, from the eye to the visual cortex, will provide insight into methods for attenuating or reversing these disorders. Development of the neural retina and visual system, especially the mechanism of axon remodeling during synaptogenesis, is complex. Studies have shown that numerous genes are involved in the differentiation and formation of the retina acting at specific stages of the development of visual system. In this review, we will summarize recent progress on the molecular mechanisms underlying the development of the eye and visual system.

Anatomy of eye development

The basic components of the complex optic system are derived from four embryonic sources: forebrain neuroectoderm, intercalating mesoderm, surface ectoderm, and neural crest (Fig. 1). The neuroectoderm differentiates into the retina, iris, and optic nerve; the surface ectoderm gives rise to lens and corneal epithelium; the mesoderm differentiates into the extraocular muscles and the fibrous and vascular coats of the eye; and neural crest cells become the corneal stroma sclera and corneal endothelium. The vertebrate eye originates from bilateral telencephalic optic grooves. In humans, optic vesicles emerge at the end of the fourth week of development and soon thereafter contact the surface ectoderm to induce lens formation. When the lens placode invaginates to form the lens vesicle, the distal part of optic vesicle begins to invaginate to form the optic cup. The retinal fissure normally closes at ∼7 wk of development, and proximal parts of the hyaloid vessels persist to form the central artery and vein of the retina, a branch of the ophthalmic artery. Defects in closure of the fissure result in coloboma, defined as defects of the iris, retina, choroid, and optic nerve, depending on their extent. The retina develops from the walls of the optic cup with the outer, thinner pigmented layer forming the retinal pigment epithelium (RPE) and the inner, thicker neural layer differentiating into the neural retina. The neural layer contains photoreceptors (rods and cones) and other neural cell types, such as bipolar and ganglion cells [Fig. 2]. The axons of retinal ganglion cells [RGCs] residing in the surface layer of the neural retina grow proximally into the wall of the optic stalk to the brain, and gradually form the optic nerve. The pathfinding and orientation of the retinal ganglion innervation at the superior colliculus [SC] or dorsal lateral geniculate nucleus [dLGN] reflects the stereotypic orientation of the neuronal somata within the retina.

The neural retina

The vertebrate retina is composed of six types of neurons and one type of glia [Müller glia], which constitute three...
nuclear layers: RGCs in the ganglion cell layer (GCL); horizontal, amacrine, bipolar, and Müller glial cells in the inner nuclear layer (INL); and rod and cone photoreceptors in the outer nuclear layer (ONL) (Fig. 2). The cell types are produced in an orderly manner that is generally conserved in vertebrates (Cepko 1999; Marquardt and Gruss 2002; Hatakeyama and Kageyama 2004). During retinogenesis, these seven cell types derive from a common population of retinal progenitor cells residing in the inner layer of the optic cup. There are four important steps in the process of generating the mature retina from retinal progenitor cells. Retinal progenitor cells must expand through cell division, exit the cell cycle, commit to a particular cell fate, and then execute the differentiation program for the committed cell type. Lineage analyses have revealed that retinal progenitor cells are multipotent and retain their ability to generate different cell types up to the final cell division (Turner and Cepko 1987; Holt et al. 1988; Wetts and Fraser 1988; Turner et al. 1990). As summarized in Table 1, numerous recent misexpression and loss of function studies have identified that retinal development is controlled primarily by transcription factors of the basic helix–loop–helix (bHLH) and homeobox families (Marquardt and Gruss 2002, Hatakeyama and Kageyama 2004). It is thought that homeodomain factors regulate layer specificity while bHLH activators determine cell fate within the homeodomain-factor-specified layers [Figs. 2, 3]. For example, both Math5 and Pax6 are expressed by RGC progenitors and required for RGC formation (Brown et al. 2001; Marquardt et al. 2001; Wang et al. 2001). Adjacent, early progenitor cells that coexpress Math3 and NeuroD (Inoue et al. 2002) together with Pax6/Six3/Prox1 (Dyer et al. 2003) or Pax6/Six3/Lim1 (Liu et al. 2000) adopt the amacrine or horizontal cell fate in the INL. Coexpression of NeuroD/Mash1 and Otx2/Crx may induce photoreceptor development in the ONL (Furukawa et al. 1997).

Later, progenitor cells that express Mash1/Math3 with Chx10 differentiate into bipolar cells (Tomita et al. 2000; Hatakeyama et al. 2001). Still other, misexpression studies using retrovirus have shown that bHLH repressors Hes1/Hes5 promote generation of Müller glial cells from later progenitor cells at the expense of neural differentiation (Furukawa et al. 2000; Hojo et al. 2000). Thus, bHLH factors have critical regulatory functions from progenitor cells to each of the emergent differentiated cell types.

Another important modulator of retinal progenitor cell competence is the growth and differentiation factor 11 (GDF11), a member of transforming growth factor-β (TGFβ) superfamily. GDF11 does not affect progenitor proliferation, but controls the duration of expression of various bHLH and homeobox genes including Math5, Pax6, and Prox1 [Fig. 3, arrows]. In so doing, GDF11 ultimately controls the temporal window of competence and thus the relative numbers of retinal cell types (Kim et al. 2005). For example, GDF11 down-regulates Math5 expression causing progenitor cells to lose competence to form RGCs. Instead, they now acquire competence to produce later-born cell types. Consistent with this, GDF11-null mice show an increased number of RGCs at the expense of amacrine cells and photoreceptors (Kim et al. 2005). Proliferation of retinal progenitors may also be partly controlled by extrinsic cues such as ciliary neurotrophic factor (CNTF), bone morphogenetic protein (BMP), and fibroblast growth factor (FGF) molecules; however, these effects appear independent of fate and differentiation cues among both early and late progenitor cells (Cepko 1999, Yang 2004).

Figure 1. Embryonic lineages that contribute to the eye. [Blue] Forebrain neuroectoderm; [green] surface ectoderm; [yellow] mesoderm; [pink] neural crest. Note that the layers of the optic cup fuse to form the RPE and the neural retina, and extend anterior to form the ciliary body and iris.

Table 1. Expression of homeobox and bHLH genes in the retinal progenitor cells

| Gene  | Group      | Cell type     | Reference                  |
|-------|------------|---------------|---------------------------|
| pax6  | homeobox   | ganglion      | Marquardt et al. 2001     |
|       |            | amacrine      |                           |
|       |            | horizontal    |                           |
| six3  | homeobox   | amacrine      | Oliver et al. 1995        |
|       |            | horizontal    |                           |
| chx10 | homeobox   | bipolar       | Liu et al. 1994           |
| prox1 | homeobox   | amacrine      | Dyer et al. 2003          |
| lim1  | homeobox   | horizontal    | Liu et al. 2000           |
| crx   | homeobox   | cone/rod      | Chen et al. 1997,         |
|       |            |               | Furukawa et al. 1997      |
| otx2  | homeobox   | cone/rod      | Nishida et al. 2003       |
| rax   | homeobox   | Müller         | Furukawa et al. 2000      |
| math5 | bHLH       | amacrine      | Brown et al. 2001,        |
|       |            | cone/rod      | Wang et al. 2001          |
| neuroD| bHLH       | amacrine      | Morrow et al. 1999        |
|       |            | cone/rod      |                           |
| math3 | bHLH       | amacrine      | Tomita et al. 2000        |
|       |            | bipolar       |                           |
| mash1 | bHLH       | amacrine      | Tomita et al. 1996b       |
|       |            | cone/rod      |                           |
| hes1  | bHLH       | Müller         | Tomita et al. 1996a       |
| hes5  | bHLH       | Müller         | Hojo et al. 2000          |
| hes2  | bHLH       | Müller         | Satow et al. 2001         |

Table 1. Expression of homeobox and bHLH genes in the retinal progenitor cells.
During development, nearly half of RGCs experience programmed cell death (PCD) [Perry et al. 1983]. Many transcription factors, neurotrophic factors, cell death-regulating factors, and caspases have all been implicated in the regulation of developmental RGC death [Isemann et al. 2003]. Neurotrophins induce neural cell survival and differentiation during retinal development through the high-affinity tyrosine kinase (Trk) receptors [von Bartheld 1998]. Additional reports have suggested that NGF binding to the low-affinity neurotrophin receptor p75 (p75NTR) might induce PCD in the early phase of retinal development [Frade and Barde 1999]. There are two periods of cell death in the developing murine retina. The first peak occurs during embryonic days 15–17 [E15–E17], and is the main onset of neurogenesis, neural migration, and initial axon growth. Recent evidence identifies post-mitotic RGCs at the optic nerve exit un

Figure 2. Retinal cell fates. Three major divisions—GCL, INL, and ONL—give rise to seven retinal cell types that arise from common multipotent progenitors in a fixed order. The RGC is the first neuronal cell type and Müller glia appear last. Homodomain and bHLH transcription factors cooperate as intrinsic regulators to define the layer specificity and the neuronal cell fate. Hes1 inhibits neuronal differentiation and maintains progenitor cells. The cells that sustain Hes1/Hes5 expression during neurogenesis stages adopt the final available cell fate of Müller glial cells. [Bottom right] The relative timing of cell appearance is for mouse development.

Adult retinal stem cells

Retinal stem cells can be isolated from the pigmented ciliary margin of the adult mouse and human eyes [Tropepe et al. 2000]. Although the number is small in the adult ciliary margin, Wnt3a can increase the self-renewal of retinal stem cells via the canonical pathway [Inoue et al. 2006]. In addition, a glycogen synthase kinase3 (GSK3) inhibitor mimics the proliferative effect of Wnt3a, which is partly dependent on FGF signaling. These results may provide a novel therapeutic strategy for in vitro pooling or in vivo activation of retinal stem cells derived from the adult ciliary margin. Thus, the understanding of developmental retinogenesis and its stenotopic molecular codes described above may one day lead to production of specific neuronal subtypes from retinal stem cells as well as embryonic stem cells [Ikeda et al. 2005].

Müller glial cells may also have progenitor-like regenerative potential after mild injury and trophic factor stimulation [Ooto et al. 2004; Fischer 2005]. Müller cells are thought to carry out many of the functions provided by radial glia, astrocytes, and oligodendrocytes in the CNS [Harada et al. 2000]. Thus, the retinogenic potential may be closely related to neurogenic function of the radial glial cells in the cerebral cortex [Campbell and Gotz 2002; Alvarez-Buylla and Lim 2004].

Retinal polarity

In addition to the ordered appearance of retinal cell types, another important genetic influence on retinal progenitor cells is their positional identity as reflected in the inner retinal development (Cellerino et al. 1997; Harada et al. 2005). Thus, neurotrophins and their receptors seem to be differentially involved in RGC apoptosis according to the developmental stage. Additional studies to determine the functions of both mature neurotrophins and proneurotrophins [Nykjaer et al. 2004; Teng et al. 2005; Woo et al. 2005] may uncover the detailed mechanisms of RGC number control and axon remodeling.
the subsequent organization of polarity and topographic maps. Although the direct comparison between humans and other species is difficult, several transcription factors have recently been identified that establish nasal-temporal (N–T) and the dorsal-ventral (D–V) retinal polarity [Peters 2002; McLaughlin et al. 2003a]. Pax6 has a principal role, since it is required for the normal regulation of both N–T and D–V axis regulatory genes, thus exerting its importance beyond the early development of the eye cup [Baumer et al. 2002]. As summarized in Figure 4, the N–T axis is set earlier than the D–V axis. First, polarized expression of the two winged-helix transcription factors, brain factor-1 [BF1] and BF2, divides the optic stalk and the retina into nasal and temporal domains [Hatini et al. 1994]. Misexpression of BF1 or BF2 results in misprojection on the chick tectum, showing that these transcriptional factors control the positional identity in RGCs along the N–T axis [Yuasa et al. 1996]. Next, two homeobox containing genes, SOHo1 and GH6, are expressed in a nasal-high and temporal-low pattern (Schulte and Cepko 2000). Thereafter, EphA5 and EphA6 are expressed in a high-to-low T–N gradient [Brown et al. 2000].

Once N–T polarity is determined, D–V polarity develops initially through the opposing actions of dorsally restricted BMP4 and ventrally derived sonic hedgehog (Shh) signals regulating the growth and specification of the optic primordium [Zhang and Yang 2001]. Ventrotin, a ventrally localized BMP4 antagonist, also negatively regulates the dorsalizing effect of BMP4 [Koshiba-Takeuchi et al. 2000; Sakuta et al. 2001; Mui et al. 2002]. For example, Vax2 has a shallow N–T gradient in addition to its strong D–V gradient [Mui et al. 2002]. BF1 mutant mice exhibit both N–T and D–V patterning defects associated with ectopic expression of BF2 and specific loss of Shh, respectively [Huh et al. 1999]. Thus, current understanding places Pax6 at the beginning of a hierarchy that is followed by N–T axis specification followed by D–V alignment. Disruption of preceding regulatory steps apparently has consequences on all subsequent events.

**The optic nerve and ganglion cell axon pathfinding**

The RGC is the only retinal neuron that projects and conveys visual information to the brain. Once retinal polarity is established, RGCs extend axons to the optic nerve head at the central retina, form the optic nerve and chiasm, and establish retinotopic maps in the SC. Here again, Shh signaling appears to hold important roles. Shh is expressed in the center of the prechordal plate and up-regulates Vax1 and Pax2 in the optic stalk. The induction of these two genes negatively controls the expression of Pax6 in the optic cup [Macdonald et al. 1995; Hallonet et al. 1999]. Later, Shh secreted from RGCs maintains Pax2 in the optic stalk and disc via Vax1 expression, which is necessary for their specification as glial cells [Bertuzzi et al. 1999; Dakubo et al. 2003].
The optic nerve undergoes gliogenesis similar to general CNS gliogenesis. Oligodendrocyte type-2 astrocyte precursor cells (O-2As) are born in the floor of the third ventricle and migrate into the optic nerve toward the eye (Ono et al. 1997). During migration, O-2As differentiate into oligodendrocyte precursor cells (OPCs) and type-2 astrocyte precursor cells. Migratory direction of OPCs is regulated by attractive guidance molecule netrin-1, secreted from cells concentrated in the optic disc and in the temporal quadrant of the optic nerve (Spassky et al. 2002). OPCs are inhibited from migrating into the retina beyond the optic nerve head, while type-2 astrocyte precursor cells distribute in the retina (Watanabe and Raff 1988; Sugimoto et al. 2001). Type-1 astrocytes are derived from optic stalk neuroepithelium and represent the largest glial cell population in the optic nerve. These astrocytes are thought to provide a structural support for RGC axons and a scaffold for OPC migration (Tsai and Miller 2002). The projecting RGC axons provide Shh signal for expansion of the astrocyte precursor cell population in the embryonic optic nerve (Dakubo et al. 2003) and additional growth/trophic factors for the proliferation of type-1 astrocytes in the first postnatal week (Burne and Raff 1997).

During the long distance of axon pathfinding, RGC growth cones are navigated by a succession of different guidance cues expressed in their local environment (Oster and Sretavan 2003; Rashband et al. 2003; Mann et al. 2004; Williams et al. 2004). The first pathfinding task for RGCs is to exit the eye through the optic nerve. Chondroitin sulphate proteoglycan inhibits RGC axon growth and controls the initial direction of axons (Brittis et al. 1992). As shown in Figure 5, a ring of chondroitin sulphate prevents RGC axons from spreading toward the peripheral retina, thus confining extension toward the central optic disc. In addition, axon guidance molecules, such as L1, netrin-1, and laminin-1, are involved in retinal axon exit at the optic disc leading to optic nerve formation (Mann et al. 2004). L1 is a member of immunoglobulin family of cell adhesion molecules, and blockade of L1 function severely disrupts radial growth cone orientation and rate of outgrowth (Brittis et al. 1995). In netrin-1-deficient retinas, many RGC axons fail to exit into the optic nerve, resulting in optic nerve hypoplasia (Deiner et al. 1997). Similar abnormalities are observed in mice mutant for the netrin-1 receptor, deleted in colorectal cancer (DCC), which is expressed on RGC axons (Deiner et al. 1997). Interestingly, laminin-1 changes netrin-1 attraction to repulsion at the entrance of the optic nerve head, which may help steer retinal axons into the optic nerve (Hopker et al. 1999). In addition to these guidance cues, Eph receptor tyrosine kinases have redundant functions in RGC axon pathfinding. RGC axons from dorsal retina bypass the optic disc in EphB2, EphB3 double mutants, without affecting the expression of other guidance cues (Birgbauer et al. 2000, 2001). Similar intraretinal guidance errors are not detected in single knockout of EphB1–3 or EphB1, EphB2 double mutants (Williams et al. 2003). Thus, a proper balance of repulsion and attraction helps RGC axons to navigate in the correct direction toward the optic disc.

**Optic glioma**

The most common tumor of the optic tract is the optic glioma or pilocytic astrocytoma. This is usually a benign (WHO type I) tumor whose growth can impair visual function. Formation of optic glioma typically occurs in childhood and is connected to abnormal gliogenesis during embryonic and early postnatal periods (Maher et al. 2001; Zhu and Parada 2002). The majority (70%) of childhood optic gliomas are associated with the genetic disease Neurofibromatosis type 1 (NF1) (Listernick and Gutmann 1999). NF1 acts as a tumor suppressor by inhibiting Ras activity and suppressing Ras-mediated cell growth. Conditional knockout (Cre/lox) strategies have been employed to model NF1-initiated optic gliomas in mice. These studies have provided evidence that induction of NF1-associated optic gliomas requires the heterozygous state of nontumor tissues in addition to loss of NF1 in astrocyte lineage (Bajenaru et al. 2002; Zhu et al. 2005). Thus, as known for other NF1-associated tumors,
amplified paracrine interplay between sources of mitotic stimulus in the microenvironment and the NF1-nullizygous cells may be at the root of tumor induction. Further studies to reveal the detailed mechanisms in the formation of optic glioma may produce more widespread benefit in the management of NF1.

Retinal axon guidance and formation of the optic chiasm

The optic chiasm is the structure where partial contralateral crossover of RGC axons occurs. Netrin-1 likely exerts its attractant influence on RGC axons after they exit the eye [Fig. 5]. However, netrin-1 is not present around the chiasm midline where RGC axons come under the influence of repulsive molecules such as Sema5A and Slit/Robo [Fig. 5]. Sema5A is expressed at the optic disc and along the optic nerve, and blockade of Sema5A eliminates the ipsilateral projection in mice. The EphB1 receptor is specifically expressed in RGCs in the mouse ventrotemporal (VT) retina indirectly control ipsilateral projections through regulation of ephrin-B2 and/or EphB1. For example, in Vax2-null mice, ephrin-B2 expression is extended to the ventral retina, but EphB2 is almost absent [EphB1 expression was not examined] [Barbieri et al. 2002]. In addition to such a molecular dorsalization of the developing retina [see Fig. 4], Vax2 mutant mice were reported to have almost complete absence of ipsilateral projections [Barbieri et al. 2002]. This phenotype was not reproduced in an independent study [Mui et al. 2002]. Another candidate for regulating ipsilateral projections is the zinc-finger transcription factor Zic2 that is expressed in dif-

Figure 5. RGC axon guidance. In the retina, axons are repelled from the periphery by chondroitin sulfate. At the optic disc, RGC axons exit the retina into the optic nerve using a mechanism based on attractive netrin/DCC-mediated action. Within the optic nerve, RGC axons are kept within the pathway through semaphorin distribution and by inhibitory Slit/Robo interaction. Slits also contribute to positioning the optic chiasm by creating zones of inhibition. Zic2-expressing RGCs in the VT retina project EphB1-expressing axons, which repel ephrin-B2 at the optic chiasm and terminate ipsilateral targets.

In the former section, we reviewed recent progress on the mechanism of optic chiasm formation and contralateral crossing over of retinal axons. However, in most mammals, RGC axons derived from the temporal retina avoid the midline and project ipsilaterally [Jeffery 2001]. The degree of uncrossed axons is <5% in the mouse, but nearly 50% in humans. This arrangement at the level of the optic chiasm is necessary for acquiring high-quality binocular vision and stereopsis. Efrin-B2 and EphB1 control axon divergence at the optic chiasm [Williams et al. 2003]. Efrin-B2 is expressed in radial glial cells at the optic chiasm concurrent with the development of the ipsilateral projections, and the blockade of ephrin-B2 eliminates the ipsilateral projection in mice. The EphB1 receptor is specifically expressed in RGCs in the mouse ventrotemporal (VT) retina that give rise to the ipsilateral projection [Fig. 5] and EphB1 mutants reveal a strong reduction in the number of ipsilateral projections [Williams et al. 2003]. EphB1, EphB2, EphB3 triple mutants exhibit no more severe phenotype compared with the EphB1 single mutant, indicating an absence of redundancy such that only EphB1 may be up-regulated in growth cones as they enter the chiasm region [Williams et al. 2003].

Several regulatory genes expressed in the developing retina indirectly control ipsilateral projections through regulation of ephrin-B2 and/or EphB1. For example, in Vax2-null mice, ephrin-B2 expression is extended to the ventral retina, but EphB2 is almost absent [EphB1 expression was not examined] [Barbieri et al. 2002]. In addition to such a molecular dorsalization of the developing retina [see Fig. 4], Vax2 mutant mice were reported to have almost complete absence of ipsilateral projections [Barbieri et al. 2002]. This phenotype was not reproduced in an independent study [Mui et al. 2002]. Another candidate for regulating ipsilateral projections is the zinc-finger transcription factor Zic2 that is expressed in dif-
formed (Herrera et al. 2003). In VT RGCs, Zic2 expression is spatiotemporally identical to that of EphB1 and the loss- and gain-of-function analyses indicate that Zic2 is sufficient to switch the outgrowth behavior of retinal axons from crossed to uncrossed patterns in response to inhibitory cues from chiasm cells. In addition, genetic hypomorphs of Zic2 display reduced ipsilateral projection. The phenotype appears similar to that of EphB1 mutants, although these mice also exhibit abnormal RGC axons that project between the optic nerve and chiasm. These findings suggest that Zic2 may control the ipsilateral projection by directly regulating multiple guidance genes including EphB1. The proportion of Zic2-expressing cells correlates with the spatiotemporal features of the formation of the uncrossed projection in such diverse species as the mouse, ferret, Xenopus, and chick, and reflects the degree of binocularity in each of these species, implicating Zic2 function in patterning binocular vision throughout evolution (Herrera et al. 2003).

Ephrins and molecular control of topographic mapping

Upon crossing the midline, RGC axons project to their major targets: the SC and the dLGN. Topographic mapping of RGC axons occurs along two sets of orthogonally oriented axes. The N–T axis of the retina maps along the posterior–anterior [P–A] axis of the SC, and the D–V retinal axis along the lateral–medial [L–M] SC axis. Accumulating evidence has revealed that ephrin-As and their EphA receptors are required for proper retinal N–T mapping along the SC P–A axis (Brown et al. 2000; Wilkinson 2000; McLaughlin and O’Leary 2005). In mouse retina, EphA5 and EphA6 are expressed in a decreasing gradient from temporal to nasal axons, while ephrin-A2 and ephrin-A5 from the posterior to the anterior SC (Fig. 6). The EphA–ephrinA repellent interactions between RGCs and the SC, impedes high EphA-expressing RGC axons from terminating in the ligand-rich posterior part of the SC (Fig. 6, blue and black axons) while permitting low EphA-expressing RGCs to invade (Fig. 6, red axons). In ephrin-A2, ephrin-A5 double-mutant mice, both temporal and nasal RGCs exhibit mapping defects, and the ectopic terminations of nasal RGCs are found anterior to their correct P–A sites (Feldheim et al. 2000). These results support the idea that EphA gradients in the retina and ephrin-A gradients in the SC may operate in combination with axon–axon competition in map formation. Graded EphA receptor expression in the SC and ephrinA expression in the retina also influences A–P positioning (Fig. 6). For example, EphA7 shows the strongest anterior-high and posterior-low expression in the SC, but is absent in the retina. A recent study showed that EphA7 is a repellent substrate for retinal axon growth in vitro, and topographic mapping of both temporal and nasal axons is disturbed in EphA7 mutant mice (Rashid et al. 2005). One recent study reported that an external gradient of Engrailed-2, a homeodomain transcription factor, repels growth cones of Xenopus axons originating from the temporal retina, but attracts nasal axons (Brunet et al. 2005). In engrailed-misserexpressing chicken tectum, Eph ligand family 1 [ELF-1] and repulsive axon guidance signal [RAGS] that belong to the family of ligands for Eph-related receptor tyrosine kinases are up-regulated (Logan et al. 1996). In addition, axons from nasal retina frequently arborized at various sites including the inappropriate anterior tectum (Itasaki and Nakamura 1996). Taken together, Engrailed-2 may also participate in the formation of P–A axis in the vertebrate SC, possibly by regulating the expression of Eph family members (Drescher et al. 1997).

Figure 6. Regulation by Eph/ephrin in retinocollicular topographic mapping. RGC axons are distributed to specific target zones by responding to gradients of ephrin ligands in SC. The high-to-low PA gradient of ephrin-As in SC inhibits the posterior extension of growth cones at various positions, depending on RGC EphA level. Axons from temporal retina, which express high levels of EphA receptors, map to the anterior part in SC [blue and black axons] while low-EphA-expressing RGCs from nasal retina can invade into the more posterior part [red axons]. On the other hand, the attractant effect of EphB/ephrin-B interactions is responsible for L-M mapping. Axons from ventral retina, which express high levels of EphB receptors, map to the medial part in SC [blue axons] while low-EphB-expressing RGCs from dorsal retina map to the lateral part [black and red axons]. [D] Dorsal; [V] ventral; [N] nasal; [T] temporal; [A] anterior; [P] posterior; [L] lateral; [M] medial.
Ephrin-Bs in the SC and their EphB receptors in the retina are also required for proper D–V mapping along the L–M axis [Hindges et al. 2002; McLaughlin and O’Leary 2005]. EphBs are expressed in a low-to-high D–V gradient by RGCs, and ephrin-B1 is expressed in a low-to-high L–M gradient in the SC [Fig. 6]. EphB2, EphB3 double mutants exhibit topographically aberrant projections along the L–M axis [Hindges et al. 2002]. The phenotype is equivalent or more severe in mice in which the kinase domain and C terminus of EphB2 is replaced with LacZ, indicating that forward signaling dominates over reverse signaling. These findings imply that EphB-expressing axons are attracted medially by ephrin-B1, in contrast to the repulsive effect of ephrin-B2 at the optic chiasm [Williams et al. 2003]. As mentioned in the former section, in Vax2-null mice the expression of D–V retinal markers is altered, including a reduced expression of EphB2 and EphB3 in ventral retina, and VT RGCs show a complete shift in their target zones from medial to lateral SC [Barbieri et al. 2002; Mui et al. 2002]. The defects in VT RGC mapping in Vax2 mutants are more severe than EphB2, EphB3 double-mutant mice reflecting the transcriptional regulation of Ephs by Vax2 [Hindges et al. 2002]. The cell adhesion molecule L1 is transiently expressed by RGC axons during pathfinding and mapping, and L1-null mice have defects in both P–A and L–M mapping in the SC [Demyanenko and Maness 2003]. Thus, L1 function is likely required for the accurate performance for EphA and EphB mediated positioning.

Additional work has indicated that in the dLGN, Eph/ephrin gradients also contribute to RGC topographic target recognition and together with neural activity act to control patterning of eye-specific retinogeniculate layers [Feldheim et al. 2000; McLaughlin et al. 2003a; Garel and Rubenstein 2004; Pfeiffenberger et al. 2005]. RGC projections from both eyes initially intermingle, but then segregate postnatally and form eye-specific layers in the dLGN. Ephrin-A2 and ephrin-A5 are expressed in ventral–lateral–anterior-high and dorsal–medial–posterior-low gradients, whereas ephrin-A3 is expressed in small amounts in the dLGN. In ephrin-A2, ephrin-A5 double mutants and ephrin-A2, ephrin-A3, ephrin-A5 triple mutants, eye-specific inputs segregate but the shape and location of eye-specific layers are profoundly disrupted [Pfeiffenberger et al. 2005]. Mice lacking the β2 subunit of nicotinic acetylcholine receptor do not segregate eye-specific inputs and lack correlated RGC spiking and calcium waves [McLaughlin et al. 2003b]. Inhibition of correlated neural activity by a nicotinic acetylcholine receptor antagonist in ephrin-A2, ephrin-A3, ephrin-A5 triple mutants leads to overlapping retinal projections that are located in inappropriate regions of the dLGN, suggesting that regions of the dLGN that are normally occupied by the contralateral eye become competent for innervation from either eye [Pfeiffenberger et al. 2005].

### Thalamocortical (TC) projections

In the mammalian brain, reciprocal connections between sensory nuclei of the dLGN and visual cortical area of the neocortex are essential for the relay and processing of visual information [Garel and Rubenstein 2004]. Recent studies have shown that activity-dependent mechanisms may not be required for the generation of topography of somatosensory and visual cortical maps [Crair 1999; Katz and Crowley 2002]. These results suggest that activity-independent mechanisms must be required for the generation of topographic maps in the cortex. During development, TC axons grow into the subcortical telencephalon (ST), where postnatally they continue on their paths to the cortex. Recent studies have suggested the requirement of some guidance cues in the ST, which may have a key role in controlling the initial topography of thalamic projections to the neocortex. For example, Ebf1, a bHLH transcription factor that is expressed in the dorsal thalamus [DT], ST, and marginal zone of the cerebral cortex, specifies the mapping of TC axons [Fig. 7]. Ebf1 mutant embryos project dLGN axons abnormally into the amygdalar region or become trapped in the ST. Ebf1-null TC axons outside the dLGN reach the cerebral cortex but show a global caudal shift in topography [Garel et al. 2002]. This shift occurs in the absence of an apparent change in thalamic or neocortical reorganization, and is preceded by a shift in the positions of thalamic axons in the ST. The Dlx1 and Dlx2 homeodomain transcription factors are expressed in the ventral thalamus and ST, but are absent from the DT and

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**Figure 7.** Developmental pathfinding of TC axon projections. Ebf1, Dlx1, and Dlx2 expressed in the thalamus and ST affect the relative positioning of TC axons during embryonic development. In addition, EphAs in the DT and ephrin-As in the ST may control the targeting of the dLGN axons to the visual cortex (VC). After birth, TrkC-expressing dLGN axons target to layer 4 of the visual cortex where neurotrophin-3 (NT-3) is expressed. (dLGN) Dorsal lateral geniculate nucleus; (DT) dorsal thalamus; (VT) ventral thalamus; (ST) subcortical telencephalon.
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cortical neurons. In Dlx1, Dlx2 double-mutant embryos, some thalamic axons including axons from the dLGN fail to grow and remain in the ST, and the other axons reach the cortex but exhibit a similar shift in topography, as observed in Ebf1 mutants [Garel et al. 2002]. On the other hand, EphAs in the thalamus and ephrin-As in the ST are involved in the regulation of TC projections in the somatosensory area in the frontal cortex [Dufour et al. 2003]. These findings suggest that various genes affecting the relative positioning of TC axons within the ST may modify the cortical area, including the visual cortex.

Neurotrophins also influence the process of formation of TC connections. Both BDNF and NT-3 are expressed in the cerebral cortex during the critical period when TC axons invade the cortical plate and establish layer-specific synaptic connections with cortical neurons [Lein et al. 2000]. Infusion of BDNF or blockade of TrkB signaling inhibits the formation of ocular dominance columns in the cat visual cortex [Cabelli et al. 1997]; however, eye-specific segregation of visual inputs to the SC and the dLGN is normal in BDNF knockout mice and conditional mutant in which BDNF expression is absent in the CNS [BDNFfloxflox;nestin-Cre mice] [Lyckman et al. 2005]. The absence of BDNF might be compensated by other trophic factors such as NT-4/5. NT-3 is specifically expressed in the layer 4 of the cat visual cortex, both before and during the critical period of TC synapse formation [Lein et al. 2000], and in mice is abundant in specific cortical subregions from P0 until early adulthood [8 wk], whereupon it greatly reduces [Vigers et al. 2000]. Conditional mutants in which NT-3 is completely deleted in the cerebral cortex result in reduction of TC projections to the visual cortex, and show a phenotype of impaired visual function, which is one of relative cortical blindness [Ma et al. 2002]. These findings implicate neurotrophins in the critical stage of precise TC projections to the visual cortex and show a phenotypic of impaired visual function, which is one of relative cortical blindness [Ma et al. 2002]. These findings implicate neurotrophins in the critical stage of precise TC projections to the visual cortex and show a phenotype of impaired visual function, which is one of relative cortical blindness [Ma et al. 2002].

Conclusions

Recent studies have shown that stage- and site-specific intrinsic molecules and extrinsic growth/trophic factors control the early eye formation, retinal differentiation, RGC axon path finding, and topographic mapping. These experimental molecular and genetic findings begin to provide a comprehensive picture of the intricate interplay between transcription factors and signaling at the cell membrane that leads to the complex and precise wiring achieved by the visual system.

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