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Molecular guidance of retinotopic map development in the midbrain

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Topographic maps are utilized in many sensory and motor systems to efficiently transfer information between brain regions. The retina's projection to the superior colliculus has served as a model for the identification of molecular cues and mechanistic strategies by which topographic maps are formed. Evidence from both *in vitro* and *in vivo* studies points to graded cell surface cues playing a central role, but support for axon–axon competition and selective degeneration have also been advanced recently. In combination with mathematical models, these studies suggest that topographic maps are established using a complex combination of strategies to ensure precise connectivity.

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Introduction

The organization of neuronal projections into topographic maps is a common strategy employed throughout the nervous system, allowing for efficient transfer of information between brain regions. In topographic maps, the neighbor–neighbor relationships of cell bodies in one region are maintained in their terminations in the target area. This is most easily appreciated in the visual system, where topographic mapping conserves the spatial organization of the visual scene as it is propagated to higher visual centers.

The best understood topographic map is the retina's projection to the optic tectum (OT), or its mammalian equivalent, the superior colliculus (SC). The retina can be divided into two Cartesian axes, the temporal–nasal (T–N) and dorsal–ventral (D–V) axes, which are mapped onto the anterior–posterior (A–P) and lateral–medial (L–M) axes of the OT/SC, respectively (Figure 1). Each of these axes is mapped independently [1], using unique molecular strategies to establish topography. Here, I will discuss current models explaining the molecular forces that drive map formation along each axis, highlighting recent studies elucidating the underlying mechanisms of this process.

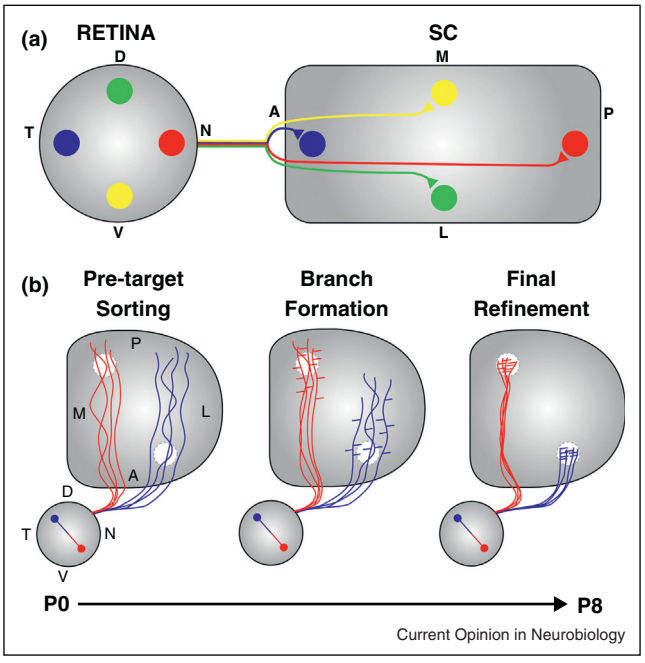
Mapping the T–N retina onto the A–P axis of the SC

Retinal ganglion cell (RGC) projections enter the SC/OT and extend to the posterior-most region, regardless of their positional origin along the T–N axis in the retina (Figure 1) [2,3]. Following this, RGCs extend interstitial branches in the region of their future termination zone (TZ). Finally, branches are selectively pruned or stabilized to establish a mature TZ. Where these branches form along the A–P axis is driven by a balance of forces. Exactly how this balance is achieved remains unclear, but a repulsive force from the posterior SC driven by ephrin-A/EphA forward signaling is widely accepted. Below, I will briefly discuss the evidence for the repulsive ephrin-A force and elaborate the current models explaining how this may be counter-balanced.

Ephrin-As repel EphA-bearing RGCs

Several lines of evidence demonstrate that ephrin-As in the posterior SC/OT serve as repellent cues to EphA-bearing RGCs and mediate topographic mapping along the A–P axis. First, using the *in vitro* stripe assay, Bonhoeffer and colleagues demonstrated that temporal RGCs are repelled by a membrane-bound cue in the posterior SC/OT, which was later identified as ephrin-A5 [4–6]. Later gain-of-function studies demonstrated that a related molecule, ephrin-A2 [7,8], also repelled RGC axons when overexpressed in the chick OT [9]. Ephrin-As and their receptors, the EphAs, were also found to be expressed in gradients along the T–N axis of the retina and A–P axis of the SC/OT in many species (frog: [10,11]; chick: [6,8,12]; mouse: [13–15] human: [16]), making them ideal candidates as the chemical labels posited by Sperry to mediate topographic mapping [17]. Confirming this, genetic deletion of ephrin-A5 results in topographic mapping errors [13], and these errors are enhanced in ephrin-A2/A5 double knockout and ephrin-A2/A3/A5 triple knockout mice [18,19]. Complementing these data, deletion of EphA5 reduces the sensitivity of RGCs to ephrin-As *in vitro* and results in topographic mapping errors *in vivo* [20]. Taken together with EphA receptor gain-of-function studies [21••,22], a repulsive force generated by target-derived ephrin-As signaling through EphAs on RGCs plays a critical role in topographic mapping. However, a single repulsive gradient would be insufficient to establish topography

Figure 1



Organization and developmental time course of retinocollicular map formation. **(a)** The retina can be divided into the dorsal–ventral (D–V) and temporal–nasal (T–N) axes, which map along the lateral–medial (L–M) and anterior–posterior (A–P) axes of the SC. As such, the spatial relationships of cell bodies in the retina are maintained in their terminations in the target. **(b)** Rather than projecting directly to their termination zones, retinal ganglion cells (RGCs) innervate the SC and refine to a final topographic map over the first postnatal week in the mouse. RGC axons are present in the SC at birth (postnatal day 0, P0), where they already display pre-target sorting along the L–M axis. Over the next week, RGCs extend interstitial branches in the area of their future termination zone (dashed circle), which are directed by molecular cues expressed in gradients along each axis of both the retina and SC. During the final stages, correlated activity patterns direct the final refinement of RGC branches into a tight termination zone.

and would require a counter-balancing force, for which three models have been proposed (Figure 2).

Dual-gradient model

First, a dual-gradient model posits that a repulsive force originating from the anterior SC/OT could balance out the ephrin-A repulsive signal. Indeed, EphAs/ephrin-As are expressed in counter-gradients in both the retina and SC/OT, and signaling can be initiated in both the EphA-bearing (forward) and ephrin-A-bearing (reverse) cell. The most convincing support for this model comes from *in vivo* loss-of-function experiments. Rashid *et al.* knocked out EphA7, which is expressed in the SC, but not the retina, thus disrupting reverse signaling in RGCs. They found that nasal RGCs made topographic mapping errors in EphA7$^{-/-}$ mice and that nasal axons avoided EphA7 membranes in the *in vitro* stripe assay [23•]. Furthermore, a recent study demonstrated that EphA3 prevents branch formation by nasal axons and is required in the OT for proper mapping of nasal RGCs [24]. In another clever set of experiments, Carreres *et al.* expressed a constitutively active EphA6 (EphA6EE) in RGCs by electroporation, resulting in TZs located anterior to the topographically appropriate location. This function was blocked by co-expression of ephrin-A5, suggesting that reverse signaling can counter-balance the effect of EphA6EE [25•].

These data support reverse signaling, but since ephrin-As do not have a transmembrane domain, the mechanism by which this is mediated remains unclear. Recent studies identify candidate molecules that could serve this function. First, Lim *et al.* showed that the p75 neurotrophin receptor (p75^{NTR}) was expressed in RGCs, able to bind co-expressed ephrin-As, and required for avoidance of EphA7 in an *in vitro* stripe assay [26••]. The authors went on to show that conditional deletion of p75^{NTR} from RGCs resulted in topographic mapping errors of the nasal-most RGCs *in vivo*. In addition to p75^{NTR}, the neurotrophin receptor TrkB may function as a co-receptor. In *in vitro* assays, Marler *et al.* demonstrated that TrkB forms a complex with ephrin-A5 and promotes brain-derived neurotrophic factor (BDNF)-induced branching [27].

Servomechanism model

A second model incorporates *in vitro* evidence that low to moderate levels of ephrin-A2 or ephrin-A5 can increase outgrowth from nasal retinal explants [28•]. In this model, ephrin-As expressed in the SC are bifunctional, such that each RGC axon terminates where the ephrin-A attraction and repellent activities balance out. Indeed, others have posited that branch formation is induced where the balance of EphA/ephrin-A signaling in the RGC is achieved to allow for BDNF-induced branching. Traditionally, this has been thought of as intracellular signals in the RGC driven by cues in the target, but evidence for *cis* interactions on the RGC axon has also been proposed [29,30]. Recently, Gebhardt *et al.* combined mathematical modeling with a novel ''double cue'' *in vitro* stripe assay to provide novel insight into the mechanism of mapping [31•]. In their model, RGCs are bound by the guidance restraint of balancing forward and reverse EphA/ephrin-A signals generated by fiber–target, fiber–fiber and *cis* interactions. The authors simulate an experiment in which outgrowing axons encounter alternating stripes of EphA3 and ephrin-A2, finding that modeled axons from nasal retina prefer stripes of ephrin-A2, while temporal RGCs prefer stripes of EphA3. These predictions were replicated in a subset of *in vitro* experiments, although in a majority of assays all RGCs preferred either ephrin-A2 or EphA3 stripes.

Competition model

A third model invokes axon–axon competition for synaptic territory or trophic factors. Here, temporal RGCs

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