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Retinal neural progenitors express topographic map markers

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ABSTRACT

Transplantation of neural stem cells for replacing neurons after neurodegeneration requires that the transplanted stem cells accurately reestablish the lost neural circuits in order to restore function. Retinal ganglion cell axons project to visual centers of the brain forming circuits in precise topographic order. In chick, dorsal retinal neurons project to ventral optic tectum, ventral neurons to dorsal tectum, anterior neurons to posterior tectum and posterior neurons to anterior tectum; forming a continuous point-to-point map of retinal cell position in the tectal projection. We found that when stem cells derived from ventral retina were implanted in dorsal host retina, the stem cells that became ganglion cells projected to dorsal tectum, appropriate for their site of origin in retina but not appropriate for their site of implant in retina. This led us to ask if retinal progenitors exhibit topographic markers of cell position in retina. Indeed, retinal neural progenitors express topographic markers: dorsal stem cells expressed more Ephrin B2 than ventral stem cells and, conversely, ventral stem cells expressed more Pax-2 and Ventroptin than dorsal stem cells. The fact that neural progenitors express topographic markers has pertinent implications in using neural stem cells in cell replacement therapy for replacing projecting neurons that express topographic order, e.g., analogous neurons of the visual, auditory, somatosensory and motor systems.

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1. Introduction

Transplantation of neural stem cells for replacing neurons after neurodegeneration requires that the transplanted stem cells accurately reestablish the lost neural circuits in order to restore function. Topographic order of projecting neurons is maintained in many of the neural circuits of the nervous system. Retinal ganglion cell axons, for example, project to visual centers of the brain forming circuits in topographic order (DeLong and Columbre, 1965; Sperry, 1963). Similarly, analogous projecting neurons of the auditory (Knudsen and Knudsen, 1983), somatosensory (Schlaggar and O'Leary, 1994) and motor (Lance-Jones and Landmesser, 1980) systems maintain topographic order when forming circuits.

Topographically graded/distributed molecular markers of cell position have been shown to direct proper projection of axons to form appropriate neural circuits in these brain systems. We reported the first topographically graded molecule, TOP_{DV}, in 1978 (Trisler et al., 1981) and we reported an orthogonal gradient of TOP_{AP} molecules in 1990 (Trisler, 1990). Subsequently, a host of topographical marker molecules have been reported in the visual system: retina, optic nerve, optic chiasm, optic tract and optic tectum (Fig. 1). In retina, topographically graded cell surface molecules TOP_{DV} (Fig. 1 and Refs. Trisler, 1990; Trisler and Collins, 1987; Trisler et al., 1981), JONES (Constantine-Paton et al., 1986), Ephrin B1 and Ephrin B2 (Braisted et al., 1997) are more abundant in dorsal retina than in ventral retina as are transcription factors Tbx-5 (Koshiba-Takeuchi et al., 2000) and Xvent2 and diffusible morphogens BMP-4 (Hogan, 1996) and Radar (Rissi et al., 1995). Conversely, cell surface receptor EphB2 (Braisted and et al., 1997) as well as transcription factors Pax-2 (Mey and Thanos, 2000) and Vax2 (Barbieri and et al., 1999) and diffusible morphogens Sonic hedgehog (Ekker and et al., 1995) and retinoic acid (Wagner et al., 2000) are more abundant in ventral retina than in dorsal retina. Similarly, there are comparable graded molecules along the anterior–posterior axis of retina. Together, these orthogonally graded molecules can be used to identify cell position in the innate retinal map.

In order to study the feasibility of using fetal neural stem cells or fetal neurons for replacing lost neuronal circuits in topographically ordered neural systems and the involvement of molecular maps in this order, we transplanted embryonic chick retinal cells derived from ventral retina into host retina. We found that when cells derived from ventral retina were implanted in dorsal host

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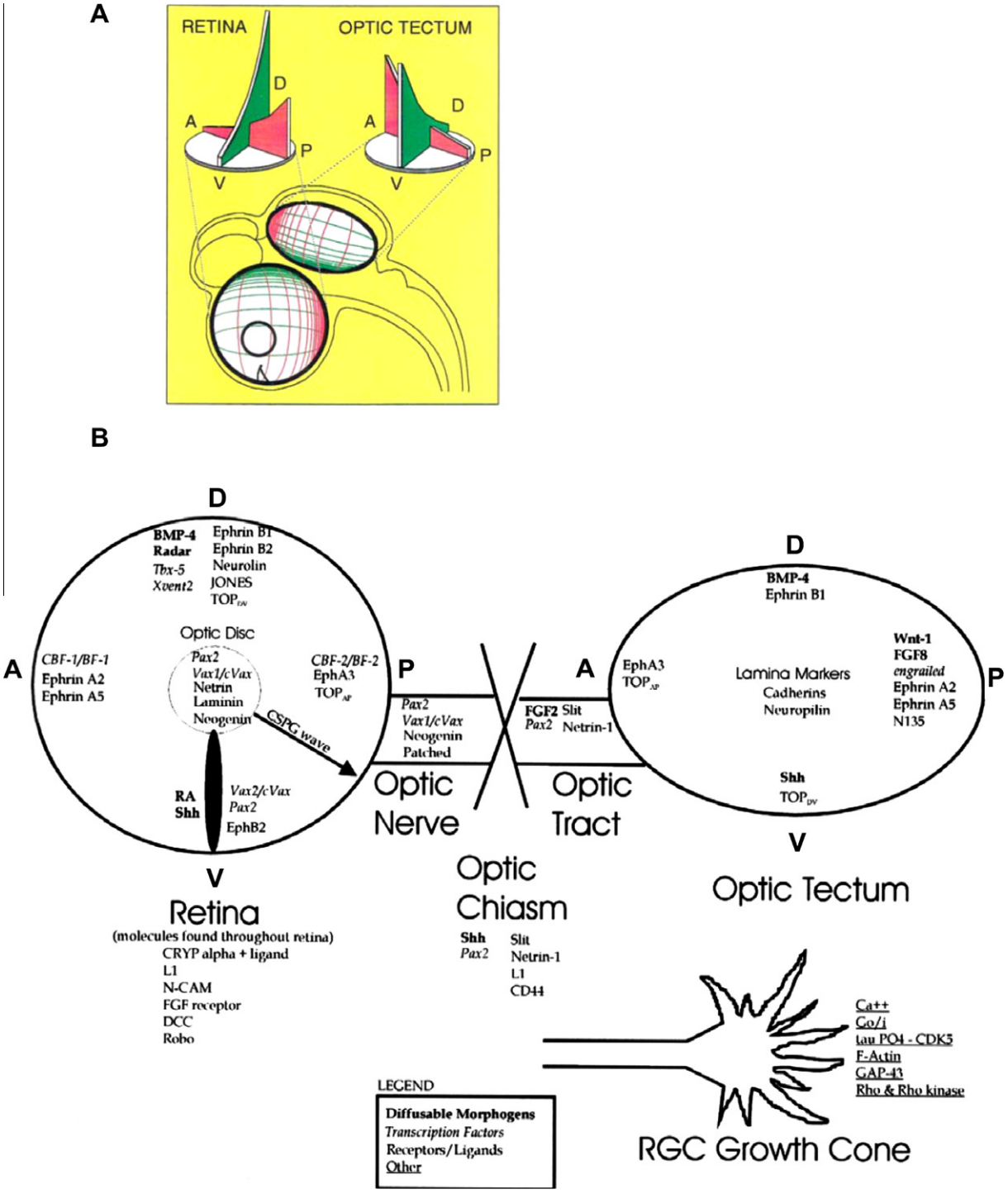

Fig. 1. Topographic molecules can be used to identify cell position in the chick retina and optic tectum. (A) Orthogonal topographic gradients of TOP_{DV} and TOP_{AP} molecules are present in retina and complementary inverted gradients are present in the optic tectum. (B) Topographically distributed diffusible morphogens (boldface), transcription factors (italics) and cell surface effector molecules (normal type) have been reported in the visual system. The individual molecules are shown at their site of highest concentration in either dorsal (D), ventral (V), anterior (A) or posterior (P) retina and optic tectum and along the projection pathway from retina to tectum via the optic nerve, optic chiasm and optic tract (Goolsby, 2004).

retina, the cells that became ganglion cells projected to dorsal tectum, appropriate for their site of origin in retina but not appropriate for their site of implant in retina. This led us to ask if retinal progenitors express topographic markers of cell position in retina. Indeed, we found that retinal neural progenitors express topographic markers: dorsal retinal stem cells expressed more Ephrin B2 than ventral stem cells and ventral stem cells expressed more Pax-2 and Ventroptin than dorsal stem cells.

2. Results

2.1. Topographic projection of implanted retinal ganglion cell axons to optic tectum

Retinal cells derived from embryonic day 8 (E8) ventral retina were labeled with a fluorescent dye (Cell Tracker Orange) and injected into the vitreal space of host E6 chick eyes, 3 days after