Back to basics—ephrins, axonal guidance, neuroprotection and glaucoma

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Links between developmental axonal guidance and neuroprotection may well establish ephrins as a major new area of future glaucoma research

Neuroscientists have long been fascinated by the mechanisms by which the nervous system has evolved to enable it to manage activities on each side of the body. During development, as axons reach the midline, specialised cells regulate whether they cross to the opposite side or migrate longitudinally along the same side.[1] This is well-illustrated in animals with binocular vision, where the crossing of retinal ganglion cell (RGC) axons at the optic chiasm is regulated by a group of developmental axonal guidance molecules called the ephrins and the Eph receptors.[2]

Eph receptors comprise the largest known family of receptor tyrosine kinases, with at least 14 members in mammals. Based on the structure of their extracellular domain and ligand binding specificity, Ephs are divided into two subclasses: EphA and EphB. Their ligands (ephrins) also fall into two subclasses: ephrinA is tethered to the membrane through a glycoslylphosphatidyl inositol (GPI) anchor and ephrinB contains a transmembrane domain and cytoplasmic tail. In general, EphA binds preferentially to ephrinA and EphB to ephrinB.[3] Since both Ephs and ephrins are membrane-bound molecules, binding results in the formation of multimeric adhesive complexes that, by endocytosis or cleavage by metalloproteases, can be converted to repulsion and termination of signalling. Another notable feature of Eph–ephrin signalling is that it is bidirectional and can result in the propagation of intracellular signals in either the Eph-expressing or ephrin-expressing cell, referred to as forward and reverse, signalling respectively.[4]

Signalling by Eph/ephrin is critical for normal formation of the optic pathway. Reverse signalling by EphB acting as guidance cues helps direct retinal axons to the optic disc and out of the eye.[5 6] Forward signalling through EphB1, which is expressed specifically by ispsilaterally projecting retinal axons, and its ligand ephrinB2 at the chiasmatic midline directs the hemispheric routing of the axons at the optic chiasm.[2] Finally, in the target, EphA/ephrinA and EphB/ephrinB control the organisation of the axons into topographic maps along the anterior-posterior and medial-lateral axes, respectively.[7]

In addition to their role in developmental axonal guidance, Eph receptors and ephrins have been shown to have a role in CNS injury in adults. Their upregulation is believed to directly inhibit regrowth of regenerating axons by stimulating growth cone collapse. However, ephrins also stimulate astrocyte activation and gliosis—but this is a double edged sword, with glial scar formation acting as a ''seal'' to the injury site at the same time as providing a physical barrier to neuronal regeneration.[8]

In this issue of *BJO*, Schmidt's group have investigated for the first time the changes in ephrin and EphB receptor expression in glaucoma (***see page 1219***), and show that ephrins are activated in early and moderate disease.[9] They suggest that the dual actions of ephrins in CNS injury is similar in glaucomatous disease—on the one hand playing a protective role by limiting axonal damage and inflammatory cell invasion, yet on the other preventing axonal regeneration.

Although Eph/ephrin have not been analysed before in experimental glaucoma, there have been a large number of studies in models of optic nerve (ON) transection, where limited regeneration of RGC axons has been clearly documented.[8] However, the axomitised rat models show that although RGC axons do not regenerate, axonal guidance is preserved through the expression of ephrins in the superior colliculus. Unlike the rat, goldfish are able to regenerate axons after ON transection, and this has been attributed to a gradient level of expression of ephrins in the retina, which appears lost in adult rats.[10]

Recent work has also implicated ephrin/Eph receptors in the pathophysiology of neuronal degeneration. In fact, ephrins have been shown to interact with both ionotropic (NMDA and AMPA) and metabotropic receptors, and disruption of their effects offer a new strategy to preventing effects of neurodegeneration.[11] This has particular relevance to glaucoma, with experimental results having clearly demonstrated the important neuroprotective aspects of glutamate modulation.[12]

In summary, although Eph/ephrin signalling can inhibit axonal regeneration, modulation of Eph receptor expression or signalling could provide a new approach in neurodegenerative diseases. The links between developmental axonal guidance and neuroprotection may well establish ephrins as a major new area of future glaucoma research.

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