A Neurological Perspective on Glaucoma

How neurodegenerative diseases and glaucoma could be similar.

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That glaucoma is considered foremost a disease of the anterior eye arises primarily from two facts: (1) elevated IOP is the only modifiable risk factor for the disease and (2) managing IOP either pharmacologically or surgically is the overwhelmingly prevalent clinical course of treatment. Although managing IOP can slow the progression of the disease, it is not a cure, and the loss of vision due to glaucoma often continues unabated despite this therapy. Enigmatically, lowering IOP in patients with nominally normal pressures can effectively reduce their risk of the neuropathy associated with glaucoma. These observations suggest that we should consider glaucoma a disease in which neurological susceptibility to IOP-related and other stressors is formative. This consideration underscores the need for probing the mechanisms linking IOP to optic neuropathy in glaucoma and for identifying new strategies that directly target these mechanisms.

Vision loss in glaucoma occurs through the degeneration of retinal ganglion cells (RGCs) and their axons, some 1.5 million of which compose the optic nerve (Figure 1). Their deterioration represents a substantial loss of neural activity in the brain, because approximately 50% to 60% of the cerebral cortex spread over roughly 40 to 45 identified visual areas represents visual function. Ultimately, the degeneration of RGCs in glaucoma entails downstream caspase- and mitochondrial-dependent apoptotic cascades. Unfortunately, this information offers little in the way of neuroprotective intervention. Because apoptosis is complex and defined by a multitude of interlacing and redundant components, focusing on arresting the process pharmacologically, as one would for the human disease, is a daunting proposition.

Neuroscientists are therefore intensely engaged in probing the earliest, pre-apoptotic events involved in the physiological response of RGCs and their axons to insults like elevated IOP and age, which is, in fact, the greatest risk factor for the disease. Because RGCs and the optic nerve are integral components of the central nervous system (CNS), it is useful to draw comparisons between glaucoma and other age-related and/or progressive neurological diseases such as Alzheimer’s, Parkinson’s, and amyotrophic lateral sclerosis. Cross-fertilization between...
the disciplines involved in studying these diseases and in testing new interventions will lead to a better understanding of glaucoma and, one hopes, to a preventive treatment for the associated neuropathy.

**AXONOPATHY IN PROGRESSIVE NEURODEGENERATIONS**

Progressive neurodegenerative disorders are of heterogeneous etiology. Whatever the triggering events, these diseases are joined by several common threads. Key among these is general axonopathy, which includes the early and progressive loss of axonal transport, the dissipation of presynaptic active zones at axonal targets, and distal degeneration and/or retraction.\(^{12,13}\) Comparative studies of axonopathy across diseases have led to a revision of the classic viewpoint of neuronal death in which dendritic and axonal degeneration occur subsequent to an injury to the cell body (or soma). There is a growing consensus that distal axonal processes and their synapses are uniquely vulnerable in disease, regardless of the site of initial neuronal stress. For example, in Alzheimer’s disease, impaired transport along axons early in the disorder raises the production of amyloid-\(\beta\) peptide in the axonal terminals; the increase has been linked to a loss of synaptic connections with their target neurons.\(^{14}\) These signs of axonopathy precede the large-scale loss of neurons in the brain that is so endemic of the disease.\(^{15}\) Similarly, in Parkinson’s disease, a loss of neurons in the substantia nigra is preceded by synaptic loss and axonal dystrophy, particularly in the longest axons.\(^{36}\) Finally, in amyotrophic lateral sclerosis, the neuromuscular junction becomes denervated through distal degeneration prior to the extensive death of motor neurons; again, there is a loss of axonal transport and a depletion of presynaptic structures.\(^{17}\)

The axon of the RGC, like other axons in the CNS, normally transports amyloid precursor protein to distal synaptic targets, where it is involved in the processing and release of amyloid-\(\beta\). Thus, levels of amyloid precursor protein that are high enough for detection using protein markers are a sign of abnormal axonal transport, and such levels have been noted in glaucomatous retinas.\(^{18}\) Furthermore, targeting the deposition of amyloid-\(\beta\) in RGCs is effective at reducing apoptosis in an acute animal model of glaucoma.\(^{19}\) A prominent feature of the progressive degeneration of RGCs in the DBA2J mouse model of hereditary, closed-angle glaucoma is axonal atrophy and the modulation of axonal transport proteins.\(^{20,21}\) Importantly, deficits in axonal transport occur prior to the loss of RGC bodies in the retina.\(^{22}\) This “somatic persistence” is also apparent with the transgenic inactivation of the pro-apoptotic gene Bax in the DBA2J, which prevents the loss of RGC bodies but does not slow the progression of axonal degeneration in the nerve.\(^{23}\) Similarly, in a mouse model of Parkinson’s disease, the elimination of Bax promotes somatic survival more so than axonal survival.\(^{24}\) These findings suggest that axonal and somatic survival can be compartmentalized, so the two may represent distinct therapeutic targets.\(^{25-27}\)

**WHERE IS THE FIRST SIGN OF INJURY?**

RGC axonal degeneration in the optic nerve must be closely linked to somatic intracellular cascades (and vice versa). Indeed, there is nothing to suggest that somatic events in the retina do not initiate axonopathy or at least influence axonal survival. A key distinction is that the initial site of degeneration need not correspond to the locus of the original stressor or response to stress. Conforti and colleagues eloquently made this point in their recent review of neuronal degeneration:

> We need to consider what we mean by the “first neuronal events” because the first cellular structures to degenerate are often not where the first molecular events occur. Neuronal subcompartments depend heavily upon one another for survival. … The site of degeneration is not a reliable indicator of where the initial defect occurred.\(^{13}\)

Along these lines, an important hypothesis in glaucoma is that axonal transport blockade occurs early at the laminae zone in the optic nerve head (Figure 1). There, RGC axons pass unmyelinated from the retina to the nerve and are putatively most vulnerable to IOP-related insults such as mechanical deformation.\(^{26}\) This idea is supported by studies showing changes in transported proteins in this zone.\(^{28,29}\) Other evidence, however, suggests that axonal degeneration is worse distally in the nerve,\(^{30}\) which raises the possibility that earlier deficits in RGC axonal transport could actually occur more distally in the relay centers of the brain (Figure 1). Such a progression would certainly be more in line with other CNS diseases. The key is a better understanding of the molecular mechanisms through which RGCs become susceptible to glaucomatous stressors such as IOP and age and of how that susceptibility sets the pace for degeneration.

At the risk of oversimplification, a central theme emerging from comparisons of progressive CNS diseases is that important commonalities in pathogenesis (such as distal axonopathy) arise despite heterogeneous etiologies. Perhaps the most appropriate first question to pose, then, is not whether neurodegeneration in glaucoma could be similar to that of other CNS diseases but rather why we would expect it to be any different.
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