The Cell and Molecular Biology of Glaucoma: Common Neurodegenerative Pathways and Relevance to Glaucoma

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Recent work in our laboratory has shown that glaucoma and Alzheimer’s disease (AD) share similar molecular and cellular pathways that may contribute to neuronal loss in glaucoma. Investigating these shared pathways will yield valuable clues to aid in rational drug design for the treatment of glaucoma.

Classification of Chronic Neurodegenerations

Most neurodegenerations can be classified into one of two categories: Specific genetic mutations cause autosomal dominant (“familial”), early-onset forms of AD, Huntington’s disease (HD), and Parkinson’s disease (PD). Fortunately, the incidence of these familial types of neurodegeneration is low, comprising less than 10% of total cases of AD, HD, and PD. These mutations have been exploited to create transgenic mouse models that have greatly aided in the understanding of the pathobiology of these diseases. The more prevalent category of neurodegenerations includes AD, PD, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease). These sporadic diseases manifest in the later decades of life and are not associated with specific gene mutations, as are the familial forms of the diseases—facts that closely parallel those in open-angle glaucoma. Mounting evidence shows that late-onset neurodegenerations are characterized by a combination of genetic susceptibility and environmental exposure with mechanisms that overlap those in the familial or early-onset forms of the disease.

Alzheimer’s Disease

AD is a progressive, debilitating neurodegeneration and is the most common form of dementia. It causes loss of neurons in the hippocampus and cerebral cortex, leading to short-term memory loss. It is characterized by the formation of aggregated proteins composed of amyloid-β, known as amyloid plaques, and neurofibrillary tangles, composed of hyperphosphorylated tau protein. Amyloid-β is cleaved from the membrane-bound protein amyloid precursor protein (APP) by enzymes termed secretases. The pathologic forms of amyloid-β are cleaved by β- and γ-secretases; these are currently target components of drugs under development for the treatment of AD. A third secretase, the α subtype, cleaves APP to form a soluble form that is important in neuronal survival and synaptic maintenance.

APP is the most abundant protein in the optic nerve. It is rapidly transported in the optic nerve in small vesicles and is transferred to the axon plasma membrane and synapses. The incidence of glaucoma is significantly higher in AD patients than in age-matched controls: 26% versus 5% in a German population and 24% versus 9% in a Japanese population. Furthermore, progression of visual field defects is accelerated in patients with open-angle glaucoma and AD versus patients with open-angle glaucoma without AD. We have shown that APP is abnormally processed, and neurotoxic amyloid-β species are upregulated in the retina of rats and mice exposed to chronically elevated eye pressure. Hyperphosphorylated tau protein has also been detected in the retinas of glaucoma patients. Glaucoma and AD are characterized by synaptic degeneration in the brain, which implies that it is not just a disease of the eye, but of the brain as well.

Memantine, a treatment approved by the U.S. Food and Drug Administration for AD, has been used in a clinical study for the treatment of human glaucoma. Unfortunately, the clinical endpoints (preservation of visual fields) for the study were not reached, probably due to an ineffective mechanism of action. However, directly targeting the formation of amyloid-β has shown promise in preserving retinal ganglion cells (RGCs) in a rat glaucoma model.

Parkinson’s Disease

PD is the most common neurodegenerative movement disorder, caused by loss of dopaminergic neurons in the substantia nigra of the brain. It is characterized by slowness of movement, difficulty in walking, rigidity, and shaking. As with AD, cognitive and behavioral problems and dementia occur in advanced stages of PD. Hereditary forms of PD show mutations in α-synuclein and phosphatase and tensin homolog (PTEN), and pathology shows eosinophilic cytoplasmic inclusions of fibrillar, misfolded proteins termed Lewy bodies.

The synucleins are a family of proteins with unknown function, but a link between α-synuclein and PD and other synucleinopathies has been established. α-Synuclein has been noted to be deposited in a specific area of the optic nerve head where myelin begins to be expressed. A recent study has shown that optic nerve astrocytes digest and process RGC axonal processes, suggesting that optic nerve head astrocytes are important for normal maintenance of RGCs. Axonal material found inside these astrocytes contained a protease-resistant form of γ-synuclein, possibly contributing to the loss of RGCs in glaucoma.

PTEN is a negative regulator of the mammalian target of rapamycin (mTOR) pathway, and in wild-type adult mice, mTOR activity is suppressed and protein synthesis is impaired in axotomized RGCs. Of note, deletion of PTEN promotes axon regeneration after optic nerve crush in mice, and the manipulation of PTEN and mTOR pathways is an exciting new therapeutic approach to promoting axon regeneration after central nervous system injury, both in the eye and in the brain and spinal cord.
Amyotrophic Lateral Sclerosis

ALS is a progressive, fatal motor neuron disease caused by the degeneration of neurons located in the ventral horn of the spinal cord and the cortical neurons that provide their afferent input. It is characterized by rapidly progressive weakness, muscle atrophy, fasciculations, spasticity, dysarthria, dysphagia, and respiratory compromise. Mutations in Cu/Zn superoxide dismutase (SOD1) are known to cause autosomal dominant ALS.2 Mutations in Cu/Zn superoxide dismutase (SOD1) are known to cause autosomal dominant ALS.3

Neuroinflammation

Neuroinflammation is rapidly emerging as a major contributor to the development of chronic neurodegenerations such as AD and PD, as well as glaucoma. Complement proteins are part of the immune system that aid antibodies and phagocytic cells in clearing pathogens. C1q is the first element in the classic complement activation pathway, and it activates several pro tease (C1r, C1s, C2, C3, and C4) that initiate opsonization and anaphylactic reactions that attract phagocytic cells. Increased neuronal C1q expression occurs in AD.45 C1q has been shown to be upregulated in mouse and monkey glaucoma models.6 In a recent study involving a model of inherited mouse glaucoma, the normal developmental mechanism of complement-mediated synapse elimination was aberrantly reactivated in retinal astrocytes.6 The authors conjectured that C1q tags retinal synapses for early elimination and drives dendritic atrophy and axon degeneration that occur in glaucoma.

Tumor necrosis factor (TNF)-α is an inflammatory cytokine, and its receptors TNFR1a and TNFR1b have been noted to be upregulated in the retinas of glaucoma patients.7 In a study of a mouse glaucoma model of elevated IOP, the absence (knockout) of the TNFR1b gene afforded robust neuroprotection of RGCs and their axons. Serum amyloid A is an acute-phase marker of inflammation and infection, and gene-profiling studies of glaucoma have shown upregulation of serum amyloid A in the trabecular meshwork and retina of glaucoma patients.89

Micro-RNA Regulation of Gene Expression in Chronic Neurodegenerations

Because glaucoma and other chronic neurodegenerations share common genetic mechanisms, it is critical to understand how the expression of genes is regulated in the retina and optic nerve in glaucoma, as this knowledge may enable rational drug design for therapeutic intervention. Recent investigations into the regulation of gene expression have focused on micro (mi)RNAs, which are short, endogenously expressed, noncoding RNAs that bind to the 3’ untranslated region of messenger RNA, targeting it for downregulation or degradation.10

Several laboratories have shown significant changes in expression of some miRNAs in the brains of AD patients. Downregulation of these miRNAs is believed to contribute to increased production and accumulation of amyloid-β in these brains. Other miRNAs dysregulated in AD, such as miR-27b, -34a, and -146a, have been hypothesized to contribute to AD pathogenesis by increasing oxidative stress and inducing inflammation.21 In a recent report, human astrocytes from normal individuals were cultured in vitro and treated with interleukin-6 to induce astrogliosis, a detrimental cellular process that occurs in AD brains. Levels of miRNAs were assayed, and miRNA-125b was noted to be upregulated. When miRNA-125b activity was repressed with antisense miRNA-125b, glial cell proliferation and increased expression of CDKN2A (cyclin-dependent kinase inhibitor 2A) were found. CDKN2A is a miRNA-125b target and negative regulator of cell growth. CDKN2A downregulation has been noted in advanced AD and Down’s syndrome brains, disorders associated with astroglia sis. The authors reasoned that miRNA-125b upregulation contributes to cell cycle defects and the astrogliosis that is characteristic of neurodegeneration.22 This finding may be of major importance, given recent reports of a significant association between polymorphisms in CDKN2AS and open-angle glaucoma.23

Given the relationship between AD and glaucoma, we hypothesize that in glaucoma, the retina and optic nerve experience changes in miRNA expression similar to those reported in the brains of AD patients. The observation of changes in expression of specific miRNAs associated with glaucoma should be useful in elucidating the pathogenic mechanisms involved in the loss of RGCs and could identify novel therapeutic targets.

Summary

Glaucoma is an age-related, chronic neurodegeneration of the optic nerve. The molecular and cellular pathologies that characterize the disease are shared by other chronic neurodegenerations such as AD, PD, and ALS. Therapies directed at treating chronic neurodegenerations have potential for use in treating glaucoma; conversely, therapies that are successful in treating glaucoma could be used in treating other chronic neurodegenerations. The following are targets for therapeutic intervention in chronic neurodegenerations and glaucoma:

Axonal transport and integrity
Autophagy and lysosomes
DNA damage and repair
Excitotoxicity and oxidative stress
Gene regulation and miRNA
Mitochondrial function
Neuroinflammation
Programmed cell death (apoptosis)
Protein folding and chaperones
Synaptic function
Ubiquitination and proteasome function

Finally, many of the molecular and cellular pathologies that characterize chronic neurodegenerations could be detected first in the eye, leading to earlier diagnosis and more effective treatments.

References


11. Osborne NN. Recent clinical findings with memantine should not mean that the idea of neuroprotection in glaucoma is abandoned. *Acta Ophthalmol*. 2009;87:450–454.


