Chapter 9
Axonal Degeneration

Yasushi Kitaoka

Abstract Axonal degeneration often leads to the death of retinal ganglion cell (RGC) bodies. The pattern of localized retinal nerve fiber layer defects observed in glaucoma patients suggests that axonal degeneration may occur first, followed by sequential RGC body loss in this pathological condition. The molecular mechanism of axonal degeneration in the optic nerve is still unclear. The tumor necrosis factor injection model and the hypertensive glaucoma model may be useful in understanding the mechanism of axonal degeneration of RGCs because axon loss precedes RGC body loss in both models. There is a growing body of evidence that glaucoma may be correlated with Alzheimer's disease. Autophagy impairment may be involved in neurodegenerative diseases including Alzheimer's disease and glaucoma. Thus, the modulation of these signaling pathways will lead to a new concept of axonal protection.

Keywords Alzheimer's disease • Autophagy • Glaucoma • Tumor necrosis factor

9.1 Amyloidogenic Pathway and Axonal Degeneration

Alzheimer's disease (AD) is a neurodegenerative disorder in which axonal degeneration may precede cell body death [1]. The deposition of β-amyloid (Aβ) in neuronal cells is a hallmark of AD. The unfavorable metabolism of amyloid precursor protein (APP) leads to Aβ production. APP is proteolytically cleaved by β-secretase, generating a short C-terminal fragment (CTFβ) of 99 amino acids. The CTFβ fragment of APP is then cleaved by γ-secretase into an Aβ peptide and a cytosolic APP intracellular domain in the amyloidogenic pathway [2]. Although

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mutations in the APP or presenilin (PS) genes have been implicated in familial AD [3], the physiopathological events underlying chronic Aβ production/clearance imbalance may be different in sporadic AD and familial AD [4]. Nonetheless, an increase in PS1 and subsequent Aβ accumulation have been found in the hippocampus of senescence-accelerated mice (SAMP8), suggesting the involvement of PS1, one of the γ-secretase complexes, in sporadic AD [5]. It has also been suggested that overexpression of *PS1* in vivo is sufficient to elevate γ-secretase activity and that upregulation of PS1/γ-secretase activity could contribute to increased risk for late-onset sporadic AD [6]. Thus, elucidating the mechanism of the amyloidogenic pathway remains a potential target for discovering a treatment for sporadic AD.

APP has been reported to accumulate in the optic nerve in rat and mouse glaucoma models [7, 8]. Aβ was also found to accumulate in retinal ganglion cells (RGCs) in a rat glaucoma model [9]. Although some studies found no positive association between glaucoma and AD [10, 11], other supported the correlation of these two neurodegenerative diseases [12, 13]. A very recent study has demonstrated that biomarkers of AD, such as apolipoprotein E and transthyretin, were increased in the aqueous humor in glaucoma patients compared with those in a control cataract patients group [14], suggesting that there is a linking pathophysiology in both diseases.

As another linking factor in the pathophysiology of AD and glaucoma, tumor necrosis factor (TNF), a cytokine that is synthesized and released from astrocytes and microglia, has been proposed. For example, TNF has been implicated in the pathogenesis and progression of AD [15, 16]. A meta-analysis demonstrated that AD is accompanied by an inflammatory response, particularly higher peripheral concentrations of TNF, interleukin (IL)-6, IL-1β, transforming growth factor-β, IL-12, and IL-18 [17]. Recent studies have demonstrated that the inhibition of TNF signaling reduces multiple hallmark of AD, including APP, Aβ peptide, and Aβ plaque [18], and prevents pre-plaque amyloid-associated pathology, cognitive deficits, and the loss of neurons in a mouse model of AD [19]. Similar to the findings of its crucial roles in AD, TNF has also been shown to have pivotal roles in the pathogenesis of glaucoma [20]. Glial production of TNF is increased in the glaucomatous optic nerve and TNF-mediated neurotoxicity is a component of neurodegeneration in glaucoma [20]. Increases in TNF have been demonstrated in the retina [21] and optic nerve [22] in hypertensive glaucoma models. A recent study of the aqueous humor has demonstrated that a significantly higher percentage of patients in the glaucoma group were positive for TNF compared with the cataract group [23]. A more recent study of the proteomic data from human glaucoma has shown a prominent upregulation of TNF/TNFR1 signaling in the glaucomatous retina [24]. A meta-analysis demonstrated that patients with open-angle glaucoma may have higher TNF levels in the aqueous humor compared with the control group, and the TNF-308G/A polymorphism is significantly associated with the risk of high-tension glaucoma [25]. Taken together with the finding that APP and Aβ accumulate in the optic nerve and RGCs in glaucoma models, it is possible that

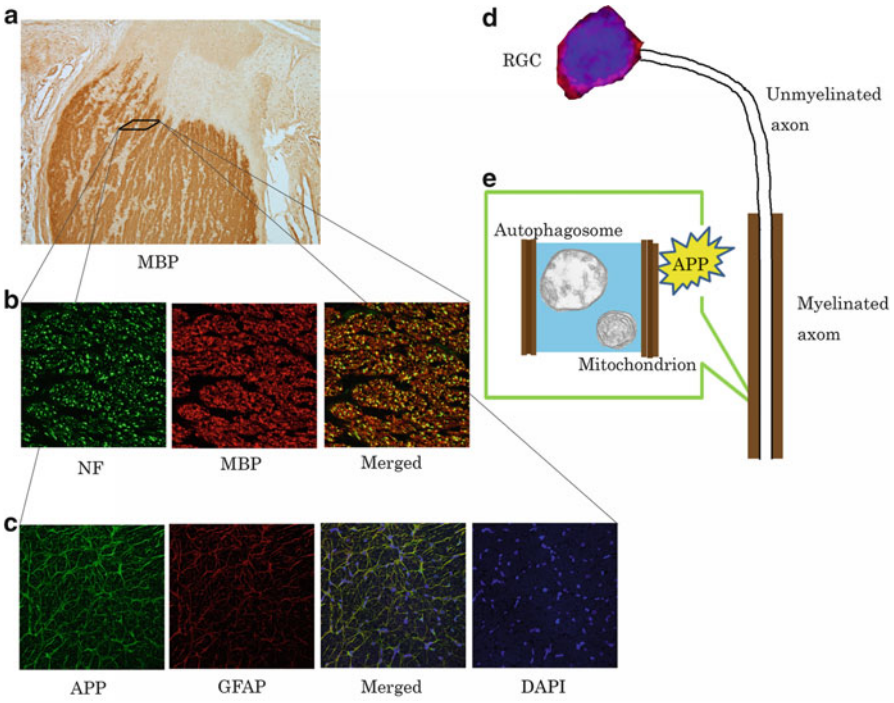

Fig. 9.1 (**a**) Myelin basic protein (MBP) immunostaining in normal rat optic nerve. (**b**) Immunohistochemistry of neurofilament (NF) and MBP in cross sections of the optic nerve. (**c**) Immunohistochemistry of amyloid precursor protein (APP) and glial fibrillary acidic protein (GFAP) in cross sections of the optic nerve. (**d**) Schema of RGC axons in unmyelinated and myelinated areas. (**e**) High-magnification schema of a myelinated axon

TNF signaling and the amyloidogenic pathway are involved in the pathophysiology of both AD and glaucoma.

In longitudinal sections of normal rat optic nerve, myelinated axons can be recognized as myelin basic protein (MBP)-positive staining starting around the laminar portion (Fig. 9.1a, d). In myelinated areas, neurofilament is located inside (green dots) and MBP is located outside rings (red rings) in cross sections (Fig. 9.1b). In TNF-induced optic nerve degeneration, there is an increase in phosphorylated PS1 located in astroglial cells, thereby leading to a subsequent increase in γ-secretase activity in the optic nerve [26]. APP is also located in astroglial cells, because there is substantial colocalization of APP and glial fibrillary acidic protein in cross sections of the optic nerve (Fig. 9.1c, e). The cleavage of APP by the activation of γ-secretase occurs mostly in glial membranes in the optic nerve in this TNF-induced neurodegeneration model [26], which displays primary axonal degeneration with sequential RGC body death [27]. Taken together, the activation of the amyloidogenic pathway in glial cells may be involved in nearby axonal degeneration.

Although several clinical trials of γ-secretase inhibitors (GSIs) for AD treatment have not achieved success so far, some clinical trials are still ongoing [28]. GSIs decreased Aβ production in the human central nervous system [29] and decreased the appearance of new amyloid plaque and the growth of preexisting plaque in APP/PS1 mice [30]. It has been suggested that synapses are the initial target in AD and that learning and memory deficits occur before the formation of plaque [31]. Instead of plaque, soluble Aβ impaired memory function [32], and the GSI LY-411575 reduced soluble Aβ and rescued the neuronal dysfunction in the hippocampus of a mouse model of AD [33]. Therefore, it is likely that GSIs have beneficial effects on neurons including synapses through the inhibition of both amyloid plaque and soluble Aβ. Moreover, the novel GSI ELN594 attenuated the formation and growth of new plaque and led to a normalization of the enhanced dynamics of synaptic structures close to plaque [34]. Furthermore, the GSI N-[N-(3,5-difluorophenacetyl)-L-alanyl]-S-phenylglycine *t*-butyl ester (DAPT) induced neural differentiation of human Müller stem cells into RGC precursors and increased the number and length of neurites in cultured cells [35]. Since a recent study has suggested that RGC dendritic atrophy precedes cell loss in a mouse model of AD [36], preventing dendrite atrophy as well as axonal degeneration of RGCs before cell death is important in both AD and glaucoma. In axons, it was shown that DAPT injection immediately after axotomy increased axon regeneration in mature *Caenorhabditis elegans* neurons [37]. In optic nerve axons, treatment with the GSI BMS299897 significantly prevented axonal loss in TNF-induced optic nerve degeneration [26]. These findings suggest that GSIs can protect synapses and axons that are the early manifestation sites in AD and glaucoma. Further studies will be needed to clarify notch conditions after administration of GSIs to examine whether local applications for optic nerve diseases may be feasible.

9.2 Autophagy and Axonal Degeneration

Autophagy is a self-digestion system that is a cellular pathway involved in protein and organelle degradation. Alteration of autophagy is associated with several conditions, including cancer, infectious and immunity disease, liver disease, heart disease, myopathy, and neurodegenerative disease [38]. In the central nervous system (CNS), a previous study suggested that the induction of autophagy serves as an early stress response in axonal dystrophy and may participate in the remodeling of axon structures in Purkinje cells [39]. It was also suggested that autophagy is required for normal axon terminal membrane trafficking and turnover, and an essential role of local autophagy in the maintenance of axonal homeostasis and prevention of axonal degeneration in Purkinje cells was demonstrated [40]. In contrast, in superior cervical ganglion neurons, the autophagy inhibitor 3-methyladenine (3-MA) efficiently suppressed neurite degeneration by protecting neurites from the loss of viability and mitochondrial function [41], suggesting that autophagy may play several distinct roles in axons depending on different types of

neuron or different types of injury. Autophagosomes inside axons can move toward cell bodies, and this movement is dependent on a dynein motor [42]. Therefore, it is possible that axonal transport may affect autophagosome clearance.

In the eyes, the existence of microtubule-associated protein light chain 3 (LC3)-II, an autophagic marker, in RGCs and its transient upregulation after optic nerve transection have been demonstrated [43]. That study showed that the inhibition of autophagy with bafilomycin A1, 3-MA, and wortmannin in RGC-5 cells under serum-deprived conditions decreased cell viability by approximately 40 %, suggesting the activation of autophagy in RGCs after optic nerve transection and its protective role in RGC-5 cells maintained under conditions of serum deprivation [43]. Those findings are consistent with the results of a recent study demonstrating that decreased Brn-3a-immunopositive RGCs in flat-mounted retinas after optic nerve transection were significantly increased by rapamycin, an autophagy inducer [44]. In addition, rapamycin decreased intracellular reactive oxygen species (ROS) production and increased cell viability in RGC-5 cells with the ROS-inducing agent paraquat [44]. That study also showed that the autophagy inhibitor 3-MA increased ROS production and reduced cell viability in RGC-5 cells, implying that autophagy induction protects RGC-5 cells from mitochondrial damage and cell death, whereas autophagy inhibition promotes ROS production and cell death [44]. In contrast, another study demonstrated that decreased 4′,6-diamidino-2-phenylindole (DAPI)-positive cells after intraocular pressure (IOP) elevation in the RGC layer were significantly increased by 3-MA [45]. Thus, the role of autophagy in RGC death is still controversial, although the fact that about 50 % of DAPI-positive cells in the RGC layer are displaced amacrine cells in rats and mice may affect the RGC survival estimation. Nonetheless, all of the above studies and a very recent study in a nonhuman primate chronic hypertensive glaucoma model [46] support the concept that autophagy is activated in RGCs in response to damage such as glaucoma and other optic nerve injuries.

In optic nerve axons, a previous study showed an increase in autophagosomes inside axons until 6 h after optic nerve crush [47]. That electron microscopy finding is consistent with the electron microscopy findings of a recent study demonstrating that abnormal mitochondria and autophagic vacuoles were noted inside axons 3 weeks after glaucoma induction [48]. Thus, autophagosomes and mitochondria move inside axons (Fig. 9.1d, e). Similar to the findings in RGC body death, the role of autophagy in optic nerve axonal degeneration is still controversial. For example, it was shown that the application of 3-MA, an autophagy inhibitor, resulted in a significant delay in axonal degeneration during the acute phase after optic nerve crush [47], while the application of 3-MA exaggerated axonal degeneration induced by IOP elevation [48].

It is interesting to note that the upregulation of autophagy may aid in oligodendrocyte survival in the Long-Evans shaker (les) rat, which has a mutation in MBP that results in severe CNS dysmyelination and subsequent demyelination during development [49]. Because oligodendrocyte loss was observed in the optic nerve after IOP elevation [21], how autophagy in oligodendrocytes can alter axon survival may be particularly interesting. It was shown that the neuroprotective effect of

brain-derived neurotrophic factor (BDNF) was mediated by autophagy through the PI3K/Akt/mTOR pathway, although in cortical neurons rather than oligodendrocytes [50]. Moreover, exogenous BDNF can protect optic nerve axons by recruiting endogenous BDNF located in oligodendrocytes [51]. Oligodendrocytes seem to be sources of BDNF for nearby axons. One hypothesis posits that autophagy induction in oligodendrocytes with the possible involvement of BDNF has beneficial effects on nearby optic nerve axons.

p62, which is also called sequestosome 1, is a multifunctional protein that acts as a critical ubiquitin chain-targeting factor shuttling substrates for proteasomal degradation [52] and interacts with LC3-II, an autophagic marker. p62 is normally degraded by the lysosomal proteases through the interaction with LC3-II [53]. A recent study has shown the accumulation of p62 and LC3-II in the chronically compressed spinal cord, and the forced expression of p62 and the inhibition of autophagy decreased the number of neuronal cells [54]. It has been demonstrated that the inhibition of autophagy is correlated with increased levels of p62 in neuronal cells [39] and that autophagy deficiency leads to the abnormal accumulation of p62 and neurodegenerative changes in the cerebellum [55]. Thus, increased p62 protein levels including autophagic flux impairment may lead to neurodegeneration. An increased p62 protein level was observed in the optic nerve in a hypertensive glaucoma model [48]. Under pathological conditions with impaired autophagy, there is a constitutively high level of p62, thereby leading to the accumulation of damaged mitochondria and subsequent ROS production [56].

Although LC3-II is known as an autophagic marker, it increases not only under autophagy activation but also under autophagy flux impairment [57]. Therefore, increases in both p62 and LC3-II observed in the optic nerve after IOP elevation imply that autophagy flux impairment may be involved in axonal degeneration in glaucoma models [48]. In addition, rapamycin, an autophagy inducer, increased LC3-II further and decreased p62 levels in the optic nerve and exerted axonal protection in a glaucoma model [48]. These findings are in agreement with those of a previous study demonstrating that LiCl, an autophagy inducer, increased the expression of LC3-II under hypoxic stress and decreased the expression of p62 under normoxia and hypoxic stress in a neuronal cell culture [54]. Furthermore, these findings are also supported by a recent study demonstrating that the activation of autophagy increased protein levels of LC3-II and Beclin1 and decreased p62 in neuroblastoma SH-SY5Y cells [58]. Thus, the modulation of autophagy may be a potential strategy against degenerative optic nerve disease.

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