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Mechanisms of Retinal Ganglion Cell Injury and Defense in Glaucoma

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Abstract

Glaucoma is a disease in which retinal ganglion cells (RGCs) die leading ultimately to blindness. Over the past decade and a half, information has begun to emerge regarding specific molecular responses of the retina to conditions of elevated intraocular pressure (IOP). It is now clear that the state of the RGC in glaucoma depends on a balance of pro-survival and pro-death pathways in the retina and details of these responses are still being worked out. In this review, we will discuss the evidence supporting the involvement of specific apoptotic cascades as well as the insults that trigger RGC apoptosis. In addition, we will present evidence supporting the existence of endogenous protective mechanisms as well as exogenous neuroprotective strategies.

Introduction

Glaucoma is a chronic degenerative optic neuropathy in which retinal ganglion cells (RGCs) die leading to gradual vision loss and ultimately blindness. RGC death is most commonly a consequence of elevated intraocular pressure (IOP), although it can also happen under normal IOP. Due to the limited understanding of the molecular mechanisms of the disease, so far IOP has been the only clinically modifiable causative factor, and all the current medical and surgical treatments of glaucoma are aimed at reducing IOP (Kwon et al., 2009). However, information regarding the molecular events in response to elevated IOP has begun to emerge in animal research in the past decade and a half. The advanced knowledge of the molecular mechanisms of glaucoma could potentially lead to more specific and effective treatments in clinic. This review briefly discusses the mechanisms of RGC death and the insults that trigger RGC death in glaucoma, as well as endogenous defense mechanisms and the exogenous neuroprotective interventions.

RGCs die by apoptosis

In glaucoma, RGCs ultimately die via apoptosis regardless of the mechanisms of the insults, such as neurotrophin deprivation, glial activation, excitotoxicity, ischemia, oxidative stress, to name a few. Apoptosis is a cascade of cellular events that causes programmed self-destruction of a cell. It is characterized by DNA fragmentation, chromatin condensation, formation of apoptotic bodies, loss of mitochondrial membrane potential and changes in plasma membrane composition. In axotomy and optic nerve crush models (Garcia-

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Valenzuela et al., 1994; Berkelaar et al., 1994; Quigley et al., 1995; Li et al., 1999; Hänninen et al., 2002), experimental glaucoma models (Garcia-Valenzuela et al., 1995; Quigley et al., 1995; Huang et al., 2005a, b; Libby et al., 2005a; Calandrella et al., 2007) and human glaucoma (Kerrigan et al., 1997), dying RGCs display many of these characteristics.

Apoptosis is controlled by caspases

Apoptosis is controlled by the caspase family of cysteine proteases. Due to their potential destructive power, the caspases are usually present as inactive pro-enzymes in healthy cells and only become active upon removal of the pro-domain by limited proteolysis. There are also caspase inhibitors present in the cells, which bind to the caspases and suppress their activity. To date, fourteen caspases have been identified in animals, twelve in humans. Caspases -2, -3, -6, -7, -8, -9, -10, -12 and -14 are centrally involved in apoptosis, while caspases -1, -4, -5 and -11 play roles in inflammation (Slee et al., 1999a; Ho and Hawkins, 2005).

The extrinsic pathway of apoptosis

In mammalian cells, apoptosis can be triggered extrinsically or intrinsically. The extrinsic pathway, also known as the death receptor pathway, is initiated by Fas ligand (FasL) or tumor necrosis factor (TNF) binding to death receptors (i.e., Fas, TNFR) located on the cytoplasmic membrane. The death domains of the death receptors form clusters with procaspase-8 via adaptor proteins and cleave it to activated caspase-8 (Ashkenazi et al., 1998; Yang et al., 1998). Activated caspase-8 can activate caspases-3 and -7, caspase-3 activates caspases-6 and -2, and caspase-6 then activates caspases-8 and -10 (Hirata et al., 1998; Slee et al., 1999b). Upon activation, the downstream “executioner” caspases digest the cellular contents and cause the demolition of the cell.

There is strong evidence indicating that the extrinsic pathway is involved in RGC apoptosis in glaucoma. FasL and Fas associated death domain increase upon elevated IOP (Kim and Park, 2005). Elevated IOP also causes up-regulation of TNF- α , microglial activation, loss of optic nerve oligodendrocytes and loss of RGCs (Nakazawa et al., 2006). Treatment with an antibody neutralizing TNF- α activity or deleting the genes encoding TNF- α or TNFR2 blocked the deleterious effects of ocular hypertension in mice (Nakazawa et al., 2006). The mRNA level of caspases-3 and -8 are up-regulated in glaucomatous eyes, as well as the activated forms of caspases-3 and -8 proteins (Tezel and Max, 1999; McKinnon et al., 2002; Huang et al., 2005a; Kim and Park, 2005; Levkovitch-Verbin et al., 2007).

The intrinsic pathway of apoptosis

There are also many intrinsic factors that can evoke apoptosis without the involvement of the death receptors, such as neurotrophin deprivation and oxidative stress. Although the initial steps of the intrinsic pathways are not clear, they all eventually converge onto the mitochondrion. These insults cause the release of cytochrome *c* from mitochondrial intermembrane space to the cytoplasm (Green and Reed, 1998), as does elevation of IOP (Huang et al., 2005b). The release of cytochrome *c* is regulated by the Bcl-2 family members localized in the mitochondrial outer membrane. Pro-apoptotic Bcl-2 family members such as Bax, Bid and Bad promote the release and anti-apoptotic members Bcl-2 and Bcl-x_L inhibit the release of cytochrome *c* (Nuñez et al., 1998). Once released to the cytoplasm, cytochrome *c* binds to apoptosis inducing factor-1 (Apaf-1) and procaspase-9 forming the apoptosome (Li et al., 1997; Srinivasula et al., 1998; Zou et al., 1999). The apoptosome facilitates the cleavage of procaspase-9 to activated caspase-9, which then can activate caspases-3 and -7, triggering the same downstream caspase cascade as caspase-8 does in the extrinsic pathway (Slee et al., 1999b; Srinivasula et al., 1998).

Blocking the pro-apoptotic factors and promoting the anti-apoptotic factors have been proven neuroprotective upon RGC injury. Bax^{-/-} mice exhibit complete abrogation of RGC soma death after optic nerve crush (Li et al., 2000) and in a chronic glaucoma model (Libby et al., 2005b). However, mutation of the Bax gene does not prevent optic nerve damage (Whitmore et al., 2005). Bcl-2 and Bcl-x transcripts are detected in the retina (Levin et al., 1997; Chaudhary et al., 1999). Overexpression of Bcl-2 prolongs RGC survival after optic nerve lesions (Bonfanti et al., 1996; Cenni et al., 1996), and excess Bcl-x prevents RGC loss in rat axotomy models (Liu et al., 2001; Kretz et al., 2004; Malik et al., 2005). In addition, the transcription of Bax and Bcl-2 genes is regulated by transcription factors such as immediately early genes (IEGs). Changes in IEG expression have been detected in various experimental glaucoma models and they are associated with both RGC apoptosis (Koistinaho et al., 1993; Levkovitch-Verbin et al., 2005; Wang et al., 2005; Kwong and Caprioli, 2006; Levkovitch-Verbin et al., 2007) and RGC survival and regeneration (Hull and Bahr, 1994; Robinson, 1994; Lu et al., 2003).

Both caspase-9 mRNA and procaspase-9 are up-regulated in axotomized rat retinas and retinas exposed to elevated intraocular pressure. Activated caspase-9 is only detected in damaged retinas (Kermer et al., 2000; Hänninen et al., 2002; Huang et al., 2005a; Grosskreutz et al., 2005).

The interaction between the extrinsic pathway and the intrinsic pathway

The extrinsic pathway and the intrinsic pathway are not entirely independent pathways. They cross talk and together they amplify and accelerate the apoptotic cascades. As described above, activated caspase 9 can activate the downstream extrinsic pathway. Meanwhile, activated caspase-8 can cleave BID, a pro-apoptotic member of the Bcl-2 family. Truncated BID is detected in the glaucomatous eyes in a rat experimental glaucoma model (Huang et al., 2005b). Once cleaved, truncated BID translocates from the cytoplasm to the mitochondria and promotes the release of cytochrome *c*, leading to apoptosome formation and activation of caspase-9, triggering the activation of downstream caspases as in the intrinsic pathway (Luo et al., 1998).

Although the extrinsic pathway has mitochondrial-independent signal cascade, the mitochondrion can be involved in both the extrinsic and intrinsic pathways. Importantly, mitochondrial dysfunction is lethal to the cell because it results in the loss of ATP production and generation of excessive reactive oxygen species. Therefore, involvement of mitochondrion is usually considered irreversible in apoptosis (Chang et al., 2002; Nickells et al., 2008).

Calcium-dependent apoptotic pathway

Calcium signaling plays critical roles in neuronal function and dysregulation of calcium homeostasis is involved in many neurodegenerative diseases (Wojda et al., 2008). Calcium influx from the extracellular space or calcium released from the endoplasmic reticulum leads to elevation of intracellular Ca²⁺, which in turn activates numerous Ca²⁺-dependent enzymes including calcineurin and calpain. A recent *in vitro* study shows RGC intracellular Ca²⁺ increases significantly upon exposure to elevated hydrostatic pressure and chelation of extracellular Ca²⁺ reduces RGC apoptosis upon elevated pressure (Sappington et al., 2009). This elevation in intracellular Ca²⁺ could trigger the activation of calcineurin and calpain, which contribute to RGC apoptosis in glaucoma.

Calcineurin is a Ca²⁺ calmodulin-dependent serine-threonine phosphatase. It dephosphorylates BAD, a pro-apoptotic member of Bcl-2 family, causing its dissociation with the inhibiting protein 14-3-3 and its translocation to the mitochondrial membrane.

Dephosphorylated BAD binds to the anti-apoptotic Bcl-2 or Bcl-x_L on the outer membrane of mitochondrion and promotes release of cytochrome *c* (Wang et al., 1999; Hekman et al., 2006). Calcineurin is expressed in RGC somas in rat, bovine and human retinas (Nakazawa et al., 2001; Seitz et al., 2002). Calcineurin activation, BAD dephosphorylation, cytochrome *c* release and RGC death are detected in experimental glaucoma (Huang et al., 2005b). Oral administration of the calcineurin inhibitor FK506 blocks each of these effects and is neuroprotective for RGC and the optic nerve in experimental glaucoma (Huang et al., 2005b). Oral administration of FK506 also blocks the cleavage of caspase-9 and reduces RGC death in an optic nerve crush model (Freeman and Grosskreutz, 2000; Grosskreutz et al., 2005).

Calpain is a Ca²⁺-dependent cysteine protease. It is ubiquitously expressed in the central nervous system and is involved in many neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease (Nixon, 2003; Goll et al., 2003). In the retina, calpain is expressed in the RGCs and nerve fiber layer (Blomgren and Karlsson, 1990; Persson et al., 1993; Azuma and Shearer, 2008). Calpain activation is detected in the ganglion cell layer in retina explants after axotomy (McKernan et al., 2007) and in a rat experimental glaucoma model (Huang et al., 2010). Inhibition of calpain significantly protects RGCs from apoptosis after axotomy (McKernan et al., 2007). Inhibition of calpain is also neuroprotective in an acute ocular hypertension/ischemia model in rat (Oka et al., 2006a, b). Cleavage of calcineurin by calpain is detected in a rat experimental glaucoma model (Huang et al., 2010). Calpain cleaves the auto-inhibitory domain of calcineurin and converts full length calcineurin to a constitutively active form. Calpain inhibitors block calcineurin cleavage and protect against excitotoxic neuronal cell death *in vitro* and *in vivo* (Wu et al., 2004). Therefore, calpain may act through calcineurin to promote cell death in glaucoma.

The insults that trigger RGC apoptosis

Although in the end all RGCs are thought to die by apoptosis in glaucoma, there are different insulting mechanisms that lead to the initiation of apoptosis and these mechanisms are not mutually exclusive. Some widely studied and accepted mechanisms include neurotrophin deprivation, glial activation, excitotoxicity, ischemia and oxidative stress.

Neurotrophin deprivation

Neurotrophins are a family of small secreted peptides that regulate the development, function and survival of neurons. Four neurotrophins have been identified in mammals: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). The cell surface receptors for the neurotrophins are the tropomyosin-related kinase (Trk) receptor family and the p75 NT receptor (p75NTR) (Huang and Reichardt, 2001). Upon binding, the Trk receptors evoke the survival pathways, while p75NTR is a distant member of the TNFR family and promotes apoptosis via the mitochondrial pathway (Dhanasekaran and Reddy, 2008). However, p75NTR can also promote cell survival through nuclear factor kappa B (Nykjaer et al., 2005).

The main neurotrophin supply for the retina is from the brain. The long-range retrograde transportation of neurotrophins is carried out by signaling endosomes. Upon binding of neurotrophins, Trk receptors at the axon terminal are activated, internalized by endocytosis and retrogradely transported up the axon to reach the cell body (Ibáñez, 2007; Cosker et al., 2008). Under conditions of elevated intraocular pressure, the retrograde transport of BDNF and its receptor TrkB is obstructed at the optic nerve head, which is thought to result in the deprivation of neurotrophic support at RGC somas (Pease et al., 2000; Quigley et al., 2000). Although the detailed molecular events are still under investigation, it is believed that

neurotrophin deprivation activates the intrinsic apoptotic pathway. Therefore, exogenous supply of neurotrophin has been an attractive strategy to protect RGCs after injury. A recent study shows NGF eye drops reduce RGC death in a rat glaucoma model and improved visual function in glaucoma patients (Lambiase et al., 2009). Intravitreal injection of BDNF prolongs RGC survival (Mey and Thanos, 1993; Mansour-Robaey et al., 1994; Peinado-Ramon et al., 1996; Ko et al., 2001; Chen and Weber, 2001) and preserves dendritic integrity (Weber and Harman, 2008) in axotomy and optic nerve crush models. Long-term adenoviral delivery of neurotrophin is also effectively protective (Di Polo et al., 1998; Isenmann et al., 1998; Martin et al., 2003; Leaver et al., 2006; Pease et al., 2009). However, in most of the cases, the protection is only temporary, rather than permanent (Clarke et al., 1998; Di Polo et al., 1998). In addition to receiving the retrograde delivery of the neurotrophin and neurotrophin receptors from the brain, the retina also produces them locally (Perez and Caminos, 1995; Lambert et al., 2001; Vecino et al., 2002). The expression levels of BDNF and Trk receptors are both increased after optic nerve injury, but the increase is also only transient (Gao et al., 1997; Cui et al., 2002). The decrease of Trk receptor upon exogenous neurotrophin supply (Chen and Weber, 2004) could be one of the reasons that current strategies fail to rescue RGCs permanently. The response of the neurotrophin pathways to elevated IOP is very complex (Guo et al., 2009) that long-term RGC protection requires a better understanding of the delicate balance of cell survival and death pathways.

Glial activation

There are three types of glial cells in the inner retina: astrocytes, Müller cells and microglia. They provide metabolic and neurotrophic support to the RGCs, maintain the homeostasis of extracellular ions and neurotransmitters, and also function as phagocytic cells upon retinal injury. The expression level of glial cell marker, glial fibrillary acidic protein (GFAP), increases in multiple experimental glaucoma models indicating the activation of glial cells (Wang et al., 2000; Woldemussie et al., 2004; Ahmed et al., 2004; Steele et al., 2006; Xue et al., 2006; Huang et al., 2007). However, the involvement of glial cells in glaucoma is very complex and their effects have been hypothesized to be both injurious and protective.

Glial cells can trigger RGC apoptosis through the extrinsic pathway. A study of cocultured RGCs and glial cells under elevated hydrostatic pressure showed that TNF- α secreted by glial cells facilitated caspase activation and RGC apoptosis (Tezel and Wax, 2000). *In vivo*, both the mRNA and the protein level of TNF- α and TNFR1 are elevated in glaucomatous eyes compared to the control eyes. The up-regulation of TNF- α is more detectable in glial cells and the up-regulation of TNFR1 is more in RGC somas and axons (Yan et al., 2000; Tezel et al., 2001). The expression level of Fas and FasL also increases in glial cells in a rat chronic ocular hypertension model (Ju et al., 2006). A strong increase in nitric oxide synthetase (NOS) is detected in astrocytes near the optic nerve head in human glaucomatous eyes (Liu and Neufeld, 2000) and in a rat experimental glaucoma model (Shareef et al., 1999), but not in another rat glaucoma model (Morrison et al., 2005; Pang et al., 2005). Therefore, the exact role of NOS in glaucoma is still unresolved.

On the other hand, glial cells can protect RGCs in many different ways. Glial cells provide neurotrophins locally and rescue RGCs after injury (Di Polo et al., 1998). The transcription factor hypoxia inducible factor-1 α (HIF-1 α) is found to be up-regulated in human glaucomatous retina and optic nerve head (Tezel and Wax, 2004) and in Müller cells and astrocytes in a rat experimental glaucoma model (unpublished data). Its gene targets include heat shock protein (Hsp) and erythropoietin (Epo). Hsp expression increases in glial cells in response to elevated IOP and is found neuroprotective in several experimental glaucoma models (Park et al., 2001; Ishii et al., 2003; Huang et al., 2007). Exogenous supply of Epo rescues RGCs under chronic ocular hypertension (Tsai et al., 2005; Fu et al., 2008).

Interleukin-6 secreted by microglia also rescues RGCs from apoptosis in primary cell cultures exposed to elevated pressure (Sappington et al., 2006).

Excitotoxicity

Glutamate is the major excitatory neurotransmitter in the retina. It evokes Ca^{2+} influx from extracellular space through glutamate receptors such as N-Methyl-D-Aspartate (NMDA) receptor. Prolonged or excessive activation of glutamate receptors causes the accumulation of intracellular Ca^{2+} , which activates proteases and turns on detrimental cell signaling pathways including the Ca-dependent apoptotic pathway. RGCs are highly vulnerable to glutamate induced excitotoxicity both *in vitro* and *in vivo* (Caprioli et al., 1996; Lucas and Newhouse, 1957; Sisk and Kuwabara, 1985). Elevated levels of extracellular glutamate were reported in human patients and in a primate glaucoma model (Dreyer et al., 1996). However, later studies failed to confirm this elevation in human (Honkanen et al., 2003), primates (Carter-Dawson et al., 2002; Wamsley et al., 2005) and rats (Levkovitch-Verbin et al., 2002).

Ischemia and oxidative stress

Retinal ischemia is another mechanism that could contribute to RGC death in glaucoma. Reduced ocular perfusion causes oxygen and nutrient deprivation, leading to disruption of cellular energy metabolism and accumulation of free radicals. In normal retina, free radicals are generated during the metabolic process and are terminated by antioxidant enzymes and chemicals. In glaucomatous eyes, large amount of free radicals are generated and overwhelm the ability of the antioxidant system to neutralize them (Kumar and Agarwal, 2007). Excessive free radicals cause oxidative stress, damage lipid, protein and DNA, and ultimately lead to cell death. For extensive discussions on ischemia and oxidative stress, please refer to the companion reviews by Schmetterer and Tezel.

Conclusion

RGC death is an extremely complicated process that all of the mechanisms mentioned above could be involved and interact with each other. For example, dysfunctional Müller cells fail to take up glutamate and convert glutamate to glutamine efficiently, lead to accumulation of glutamate in the synaptic cleft, and therefore glutamate excitotoxicity occurs (Adachi et al., 1998; Danbolt, 2001). Consequently, excitotoxicity-induced Ca^{2+} elevation generates large amount of nitrogen and oxygen free radicals and causes oxidative stress (Tezel, 2006). Regardless the routes, all these mechanisms eventually could cause RGC death through apoptosis. However, the retina has endogenous self-protective mechanisms such as the up-regulation of the pro-survival BDNF and Trk receptors after optic nerve injury (Gao et al., 1997; Cui et al., 2002), the expression of anti-apoptotic Bcl-2 and Bcl-x genes (Levin et al., 1997; Chaudhary et al., 1999) and the increased expression of Hsp (Huang et al., 2007). Therefore, the progression of the disease depends on the balance of pro-survival and pro-death pathways. Comprehensive interventions are necessary to delicately tilt the balance towards the pro-survival direction in order to achieve long term and effective neuroprotection in glaucoma treatment.

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