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Retinal Ganglion Cell Death

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1. Introduction

1.1 Topographic and cellular organization of the retina

The retina is the thin (0.2 mm) lining of the back of the eye that gathers light focused on it by the cornea and lens. The retina has a complex laminar organization; cells are organized into layers (Fig. 1). These layers are named by reference to the middle of the eyeball; the innermost layers are located nearest the vitreous chamber, whereas the outermost lie adjacent to the retinal pigment epithelium and choroid. The most important layers, progressing from the inner to the outer, are: **(1) the inner limiting membrane** (formed by astrocytes and the conical end-feet of Müller cells); **(2) the nerve fiber layer**, composed of the axons of ganglion cells; **(3) the ganglion layer**, containing the cell bodies of ganglion cells; **(4) the inner plexiform layer**, composed of synapses formed between bipolar, amacrine, and ganglion cells; **(5) the inner nuclear layer**, containing the cell bodies and nuclei of horizontal, bipolar, and amacrine cells; **(6) the outer plexiform layer**, composed of synapses connecting photoreceptor cells from the outer nuclear layer with bipolar and horizontal cells from the inner nuclear layer; **(7) the outer nuclear layer**, containing the synapses and cell bodies of two classes of photoreceptors, namely the rods and cones; **(8) the outer limiting membrane**, a junction line between photoreceptor cells and Müller cells; **(9) the photoreceptor layer**, which contains the light-sensitive outer segments of the photoreceptors; and **(10) the retinal pigment epithelium (RPE)**, which is a monolayer of melanin-containing cells forming part of the blood/retina barrier. Although the RPE is not a component of the neural retina, this layer provides critical metabolic support to photoreceptors and the integrity thereof is fundamental in terms of proper retinal function [Bok, 1993; Krstić, 1997].

Retinal tissue contains both neuronal and non-neuronal elements, which work together to enable vision and to maintain retinal homeostasis

Neurons: The retina contains five types of neurons: (1) photoreceptors (cone and rod cells); (2) bipolar cells (of the flat, midget, and rod types); (3) horizontal cells; (4) amacrine cells; and, (5) ganglion cells [Krstić, 1997]. Photoreceptors are photosensitive neurons that absorb photons from the field of view and, using a specific complex biochemical pathway, turn this information into electrical signals via the process termed phototransduction [Sung & Chuang, 2010] to bipolar cells. Horizontal cells connect rods and cones that horizontally convey information within the retina. The horizontal cells receive input from one or more photoreceptors and transmit information to other photoreceptors and to bipolar cells [Poche & Reese, 2009]. Amacrine cells modulate signaling between bipolar and ganglion cells. The amacrine cells receive inputs from one or more bipolar cells and contact ganglion cells that

in turn accept inputs from other bipolar cells. As with the horizontal cells, amacrine cells release inhibitory neurotransmitters in a graded manner, hyperpolarizing ganglion cells with which they are they contact, rendering it less likely that such cells will fire action potentials [Forrester, 2002]. Bipolar cells transmit signals from photoreceptors or horizontal cells, and pass such signals on to ganglion cells either directly or indirectly (via amacrine cells). Ganglion cells are the only retinal cells that produce action potentials; the release of glutamate by (a) bipolar cell(s) in contact with such cells is sufficient to depolarize the ganglion cells to threshold levels. These action potentials are transmitted to the brain via the fibers of the optic nerve.

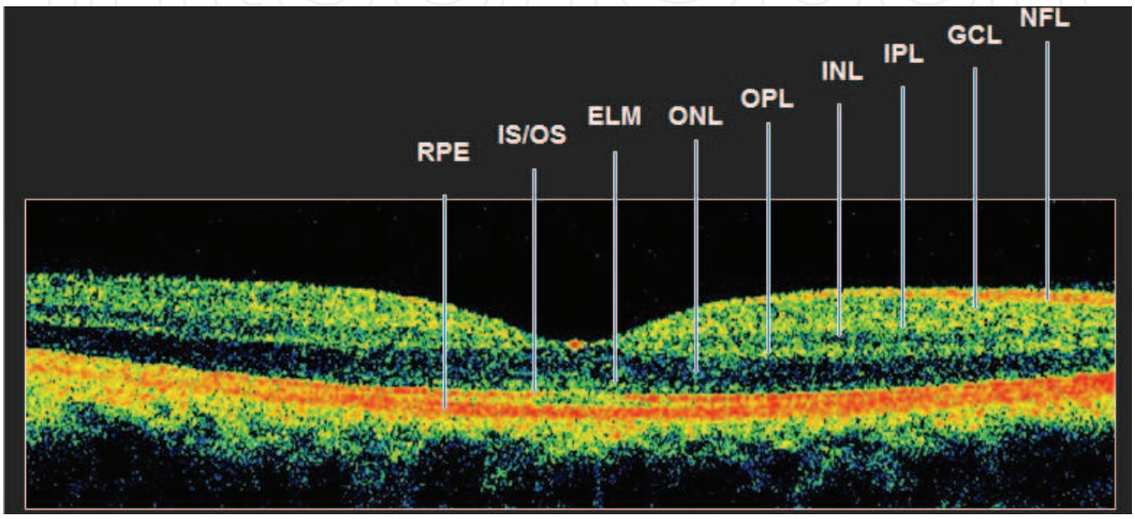


Fig. 1. Several layers can be resolved and have been labeled in the optical coherence tomography image of a normal human retina: Retinal pigment epithelium (RPE), inner segment/outer segment intersection of photoreceptors (IS/OS), external limiting layer (ELM), outer nuclear layer (ONL), outer plexiform layer (ONL), nerve fiber layer (NFL), ganglion cell layer (GCL), inner plexiform layer (IPL), inner nuclear layer (INL)

Some retinal cells have regulatory, nutritional, and immunomodulatory functions

Glial cells (Müller cells and astrocytes) are non neuronal cells that serve as an interface between neurons and the vasculature and provide support and nutrition, maintain homeostasis of the retinal extracellular milleu [Bringman *et al*., 2006]. **Müller cells** form the majority of glial cells within the retina, and are arranged in a parallel manner. These cells span the entire thickness of the retina, projecting from the vitreous humor (the viscous fluid in the back of the eye) to the rear of the retina. These tubular cells wrap all retinal neurons and act as living optical fibers within the eye, funneling light to rod and cone cells [Franze *et al*., 2007]. **Astrocytes** are confined principally to the retinal fiber layer, wherein they wrap ganglion cell axons and axon bundles that ultimately form the optic nerve. Other astrocytes line the inner surface of the retina and surround the blood vessels. Astrocytes vary in morphology, depending on their precise retinal location and their interaction with surrounding cells [Trivino *et al*., 1992; Chang & Stone, 1991].

Retinal pigment epithelium cells (also termed melanosomes) are cuboidal cells that are arranged in a monolayer, and are easily recognized because they are pigmented [Bok, 1993].

Microglial cells are phagocytic cells within the retina that play important roles in defense

against invading microorganisms, in immunoregulation, and in tissue repair [Chen *et al*., 2002]. **Vascular endothelial cells and pericytes** provide nutritional support to, and aid in waste product removal from, the inner retina [Hosoya & Tomi, 2005].

Retinal topography

The retina may be divided into several regions that differ in structure; these regions contain neurons of different types. The **macula lutea** is in the center of the retina, and includes the fovea and surrounding tissue. The **fovea** is a small depression within the retina. In the fovea, the retina is thinner than elsewhere, consisting only of cones that are longer and thinner than the other cones of the eye. All **neurons** and **capillaries** originating elsewhere become compacted around the edges of the fovea. In the region surrounding the fovea, a gradual decrease in cone density is apparent, whereas rod density gradually rises. Finally, the eye contains a region in which there are no receptors, but rather an accumulation of ganglion cell axons, forming the optic nerve. This region, termed the **optic disc**, contains the point where the optic nerve emerges from the retina. Because no photoreceptors are present in this region, a break in the visual field (the so-called blind spot) may be noted. The optic disk is also the point of entry of the major blood vessels that supply the retina [Forrester, 2002].

2. Glaucoma and retinal ganglion cell death

Glaucoma is a neurodegenerative disease characterized by progressive, irreversible loss of vision [Gupta & Yücel, 2007]. Retinal ganglion cells are the only neurons affected in glaucoma; cells of other regions of the inner and outer retina remain unaffected, as confirmed by electroretinographic tests and histopathological studies [Aldebasi *et al*., 2004; Glovinsky *et al*., 1991; North *et al*., 2010; Quigley *et al*., 1998].

Retinal ganglion cells (RGCs) are the output neurons of the retina. The dendrites of these cells receive synapses from bipolar and amacrine cells in the inner plexiform layer. The cell somata reside in a narrow ganglion cell layer, and the axons of the cells travel through the optic nerve to retinorecipient structures in the brain, wherein the axons form glutamatergic synapses [Masland, 2001; Mu & Klein, 2004; Nassi & Callaway, 2009; Wassle, 2004]. Although RGCs share many features with other neurons, the former cell type vary significantly in terms of size, interconnections, and responses to visual stimulation. More than 12 types of ganglion cells have been distinguished in the mammalian retina studies [Rockhill, 2002]. It remains unclear whether some ganglion cells are more susceptible to apoptosis than are others, under glaucomatous conditions [Quigley, 1999]. Early studies indicated that large ganglion cells (magnocellular ganglion cells) and nerve fibers were selectively lost in experimental glaucoma models in nonhuman primates, and in human glaucoma patients [Quigley *et al.,* 1988]. In support of these observations, another work found selective loss of anterograde axonal transport to the magnocellular layer of the dorsal lateral geniculate nucleus, which is the region containing the largest RGCs [Dandone *et al.,* 1991]. There are also observations that doesnot support the hypothesis that selective loss of RGC occurs in glaucoma [Morgan *et al.,* 2000].

The axons of RGCs are non-myelinated from the retina to the lamina cribrosa, but become myelinated thereafter. In unmyelinated axons, action potentials propagate by depolarization along the membrane; this process consumes more energy than does the saltatory conduction of myelinated axons [Wang *et al.,* 2003]. Therefore as an adaptive process to the increased

energy need, the axons of RGCs are characterized by many varicosities filled with mitochondria [Wang *et al.,* 2003].
RGCs have very long axons, thus increasing cell vulnerability to various disorders. Axon regions are likely to encounter metabolic stress such as hypoxia, and to be exposed to free radicals and mechanical compression (e.g., in the lamina cribrosa). These insults induce RGC death [Schmidt *et al.,* 2008]. To deal with these stressors, RGCs have a high antioxidant capacity (attributable to endogenous antioxidant defenses including expression of all of catalase, superoxide dismutase, glutathione peroxidase, and peroxiredoxins) compared with other neurons [Fatma *et al.,* 2008; Kortuem *et al.,* 2000], but the cells remain more vulnerable to stressors than, for example, Müller or vascular cells. [Schmit *et al.,* 2008].

2.1 In glaucoma, the mechanisms of cell death differ in retinal ganglion cell bodies and axons

2.1.1 Cell body death

RGC cell body death occurs via apoptosis or necrosis [Farkas & Grosskreutz, 2001; Kuehn *et al.,* 2005; Tatton *et al.,* 2001]. **Apoptosis** is an active genetic process whereby a cell undergoes an organized series of events culminating in self-destruction. All animal cells are programmed to self-destruct when they are not further required, or when damaged. Because cells play an active role in their own death, apoptosis is often termed "cell suicide". Apoptosis is in play during development and neurodegeneration, facilitating cell destruction without affecting neighboring cells that are destined to survive.
Whatever the initiating insult, actual cell death (the last step in apoptosis) features a final common pathway characterized by an orderly pattern of inter-nucleosomal DNA fragmentation, chromosomal clumping, cell shrinkage, and membrane blebbing. Eventually, the cell dies and marks itself for phagocytosis by nearby macrophages [Mace & Riedl, 2010].
Necrosis is another mechanism of cell body death. It is accidental in nature, and serves to eliminate cells that have been severely damaged. Unlike apoptosis, necrosis is a passive process during which the cell membrane is rapidly destroyed and toxic cellular components spill into the extracellular space, potentially injuring nearby cells [Dawson, 2005]. A low ATP concentration or impaired ATP generation predisposes cells to necrosis [Nicotera *et al.,* 1998]. The cell membrane becomes permeable early during this process. Organelles may become dilated, and ribosomes dissociate from the endoplasmic reticulum. The nucleus disintegrates later. Proteases play major roles in cell degradation during necrosis. As a consequence, cellular contents are libareted into the intracellular space and evoke an inflammatory response (Fig. 2). Although a growing body of evidence supports the idea that apoptosis serves as the primary mechanism of ganglion cell death in glaucoma patients, necrosis contributes to cell death in the late phase of the disease, as observed in rats subjected to optic nerve transection [Bien *et al.,* 1999]. RGC necrosis also has been reported to occur immediately after ischemic injury induced by imposition of high-level intraocular pressure [Joo *et al.,* 1998] and under intense excitotoxic conditions [Bonfocco *et al.,* 1995].

2.1.2 Axon death

Axon death occurs via either of two basic mechanisms: Wallerian degeneration and die-back [Borgens, 1988; Coleman & Freeman, 2010].
Wallerian degeneration, classically defined as degeneration of axons distal to an injury, is generally noted in severely damaged axons, and results in atrophy and rapid loss of structure throughout the entire length of the axon. At the cellular level, initial segmentation

of the myelin sheath is apparent, followed by swelling of the axolemma, disorganization of neurofilaments and microtubules, and mitochondrial swelling. The remaining axonal fragments then undergo phagocytosis by glial cells and macrophages. The cell body can live for a number of days, but ultimately undergoes apoptosis [Saxena & Caroni, 2007].

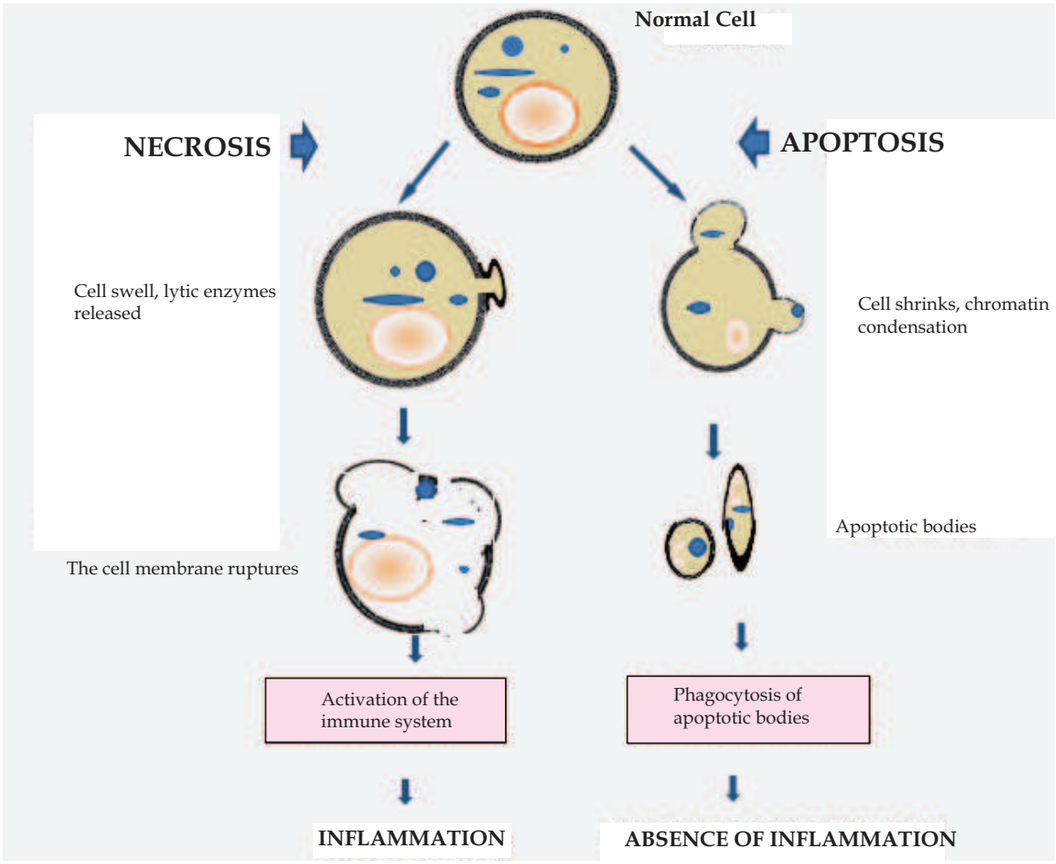


Fig. 2. Scheme representing necrosis and apoptosis

Die-back occurs in axons that experience more moderate injury, and is characterized by slower retrograde degeneration with a distal-to-proximal progression (thus from the synapse to the soma) [Seif *et al*., 2007]. Milder insults may allow greater functional connectivity between the soma, proximal and distal axonal segments and die-back death can occur over several months.

2.2 Morphological features of apoptosis and apoptotic process in RGCs

Examination of apoptotic cells by light microscopy allows evaluation of morphological features including condensation of chromatin and cytoplasm, cell fragmentation, and apoptotic body formation [Kerr *et al*., 1972].

Electron microscopy has shown that the earliest detectable ultrastructural change of apoptosis is chromatin condensation, which commences peripherally along the nuclear membrane and leads to the formation of a crescent or ringlike structure [Cummings *et al*., 1997]. This is followed by nuclear changes including convolution of the nuclear outlines and peripheral nuclear chromatin breakdown. Early in apoptosis, and contemporaneously with

the described nuclear changes, cells cease to contact neighboring cells, usually accompanied by loss of special membrane structures such as microvilli and desmosomes, and apoptotic cells begin to exhibit protrusions of the plasma membrane [Wyllie,1997].
Apoptosis is accompanied by cell volume decreases, cell density increases, more compact cytoplasmic organelles, and convolution of both cellular and nuclear outlines [Cummings *et al*., 1997; Kerr *et al*., 1994]. Concommitantly, cytoplasmic changes may be detected, including aggregation of cytoskeletal filaments, clumping of ribosomal particles, and rearrangement of the rough endoplasmic reticulum. Cytoplasmic and nuclear condensation is followed by production of numerous membrane protuberances, resulting in development of membrane-bound apoptotic bodies with well-preserved cytoplasmic organelles [Cummings *et al*. 1997; Kerr *et al*., 1994; Wyllie, 1997]. Finally, the protrusions detach from the cells, forming apoptotic bodies densely packed with cellular organelles and nuclear fragments, which are phagocytosed by neighboring cells in the absence any inflammatory reaction. The latter feature is crucial, because it allows cell death to occur without damage to adjacent cells [Cummings *et al*., 1997; Kerr *et al*., 1994; Wyllie 1997].

Biochemical features of apoptosis

Cleavage of chromosomal DNA into oligonucleosomes is a biochemical hallmark of apoptosis. During the early stage of the process, DNA is broken into large fragments (50-300 kb in size) [Bortner *et al*., 1995], which are subsequently cleaved into nucleosomal units (180 bp in size) [Zhang *et al*., 2010].
Another biochemical feature of apoptosis is expression of cell surface markers that result in recognition and eventual phagocytosis of apoptotic cells, but with minimal damage to surrounding tissue. This is achieved by externalization of phosphatidylserine from the normal location on the inner leaf of the plasma membrane lipid bilayer to the outer leaf [Bratton *et al*., 1997]. Normally, viable cells show asymmetric distributions of particular phospholipids between the inner and outer leaflets of the plasma membrane. Early in apoptosis, however, loss of such plasma membrane asymmetry, accompanied by phosphatidylserine externalization, occurs in all cell types [van Engeland *et al*., 1998].
Condensation of the cytoplasmic space resulting in cell shrinkage is a universal characteristic of apoptosis [Wyllie, 1986]. Apoptotic cell shrinkage is associated with a decrease in [Na+]i and [K+]i which occurs after chromatin condensation and internucleosomal DNA fragmentation, and prior to apoptotic body formation [Mc Carthy & Cotter, 1997]. Coupled with this loss of intracellular ions, the cell may also lose the ability to take up ions, as exemplified by an early inhibition of the Na^+/K^+-ATPase in certain model systems [Bortner *et al*., 2007]. This dramatic decrease in intracellular ions results in a cellular ionic environment permitting the activation of various cell death enzymes including caspases and apoptotic nucleases. The presence of high extracellular potassium prevents cell shrinkage by inhibiting the efflux of this ion, indicating that the normal intracellular ionic environment has a repressive effect on the apoptotic process [Bortner *et al*., 2007].

2.3 The apoptotic process

Apoptosis is an active, energy-requiring process which can be separated into three distinct phases: (a) signaling, (b) commitment, and (c) execution.
In the signaling phase pro-apoptotic stimuli (ligand-induced activation of the death receptors, cellular stress signals *etc*..) initiate the sequence of events that leads to cell death. **The commitment phase** is the step by which the cell either commits to apoptosis or activates mechanisms stopping the signaling cascade initiated during the signaling phase. **The**

execution phase begins after the cell fully commits to apoptosis. This is the point of no return for the cell, which is now irreversibly committed to die. Enzyme systems become activated; these actions result in the biochemical and morphological features of apoptosis. The enzyme systems cleave proteins, externalize phosphatidylserine, and degrade DNA. During this phase, the cell membrane begins to bleb, forming vesicles that contain high concentrations of cellular components that were formerly distributed in a more widespread manner with the cell [Mills, 2001; Hengartner, 2000]. At the end of the execution phase, vital cell structures and functions are destroyed. Externalization of phosphatidylserine serves as an "eat-me" signal to phagocytosing cells, which ingest newly dead cells without causing inflammation.

Apoptosis occurs via two major pathways: the intrinsic and extrinsic pathways

The **intrinsic pathway** is initiated from within the cell when intracellular stress is sensed. This pathway is controlled by the balance of activity of pro- and anti-apoptotic members of the *Bcl2* gene family and involves regulation of mitochondrial membrane permeability. In response to pro-apoptotic signals, cytochrome c, apoptotic protease activating factor 1 (APAF-1), and caspase-9 are released from the mitochondrial membrane and form apoptosomes [Hengartner, 2000], which in turn activate caspase cascades. In contrast, the **extrinsic pathway** is initiated by cell surface signaling following binding of an extracellular ligand to a "death receptor". Formation of the death-induced signaling complex (DISC) directly stimulates the caspase cascade via activation of caspase-8, without any mitochondrial involvement. Caspase-8 acts on pro-caspase-3, generating active caspase-3, which in turn cleaves the DNA fragmentation factor (DFF) [Hengartner, 2000]. The active (cleaved) form of the latter factor induces internucleosomal DNA strand cleavage at 200 bp intervals, a hallmark of apoptosis [Nagata, 2000].

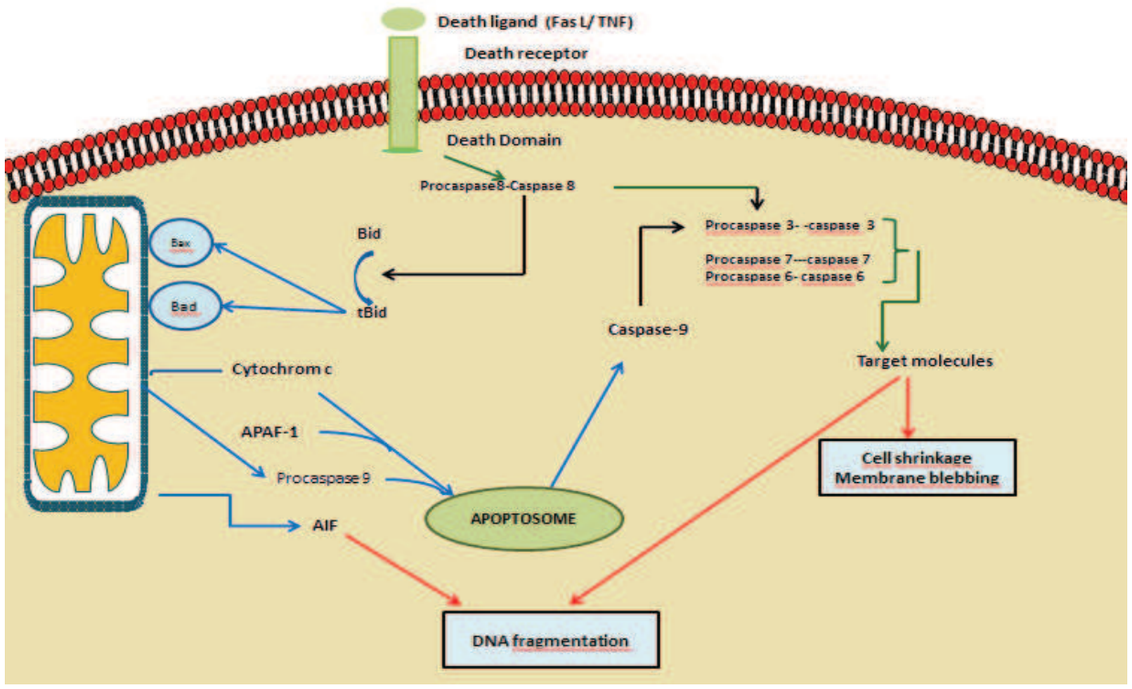


Fig. 3. Intrinsic and extrinsic pathways of apoptosis

Links between the extrinsic and the intrinsic pathway exist at several levels (Fig 3). Upon death receptor triggering, activation of caspase-8 may result in cleavage of Bcl-2 interacting domain (BID), which in turn translocates to the mitochondria to release cytochrome c [Cory & Adams, 2002; Yin, 2000]. In addition, cleavage of caspase-6 (a downstream component of the mitochondrial pathway) may generate feedback to the receptor pathway, via cleavage of caspase-8 [Cowling & Downward, 2002]. The extrinsic and intrinsic pathways share a common endpoint at the level of caspase-3 activation [Guerin *et al*., 2006].

2.3.1 Direct signal transduction (death receptors)

Death receptors are cell surface molecules that transmit apoptotic signals initiated by specific death ligands from the extra- to the intra-cellular environment, and play central roles in initiation of apoptosis. In addition, all death receptors contain a homologous cytoplasmic aminoacid sequence termed the "death domain" [Itoh & Nagata, 1993; Tartaglia *et al*., 1993]. Death receptors belong to the tumor necrosis factor **(TNF)** receptor family. Eight members of the death receptor family sharing homologous cytoplasmic death domains have been characterized to date; these are Fas/Apo-1/CD95, TNF-R1 [tumor necrosis factor (TNF) receptor 1], DR3 (death receptor 3), TRAIL-R1 (TNF-related apoptosis-inducing ligand receptor 1), TRAIL-R2, DR6, p75-NGFR (p75-nerve growth factor receptor), and EDAR (ectodermal dysplasia receptor) [Lavrik *et al*., 2005].

Binding of a death-inducing ligand to the appropriate receptor can result in release of ceramide, typically produced by the action of acid sphingomyelinase [Gulbins, 2003], that in turn rapidly forms ceramide-enriched signaling platforms within the cell membrane [Zhang *et al*., 2009]. Such platforms result in clustering of receptor molecules, which greatly enhances apoptotic signaling. Indeed, this effect is so marked that death receptor signaling in the absence of receptor clustering is rarely able to activate the full apoptotic process. Binding of the appropriate ligand to a death receptor typically causes a conformational change in the intracellular region of the receptor that in turn results in the death domain motif becoming accessible [Zimmermann *et al*., 2001]. Such exposure allows various adaptor proteins to bind to the receptor to form a death-inducing signalling complex (DISC). The adaptor proteins, such as FADD (Fas-associated death domain) contain motifs described as death effector domains, which permit recruitment of pro-caspases, typically pro-caspase 8, to the DISC [Kaufmann *et al*., 2002]. Activation of caspase 8 follows, and apoptosis is initiated within seconds after ligand binding.

TNF receptor-1, a death receptor, has recently been identified to be one mediator of the RGC death evident in patients with various neurodegenerative injuries [Tezel *et al*., 2004]. Immunohistochemical studies and in situ hybridization have shown that the level of TNF receptor-1 is greater in glaucomatous eyes than in age-matched control eyes [Tezel *et al*., 2001]. RGCs of glaucoma patients were usually positive when immunostained for TNF-α receptor-1. It is tempting to speculate that the relatively selective expression of this receptor in RGCs may in part explain the increased vulnerability of such cells to apoptosis during glaucomatous optic nerve degeneration [Tezel *et al*., 2001].

Fas is a transmembrane protein expressed by numerous cells. Components of the FAS/FAS-ligand system represent the prototypical receptor-mediated apoptosis pathway [Love, 2003]. Fas-Associated protein with death domain (FADD) is an adaptor molecule that bridges the Fas death receptor, to caspase-8. In rats with elevated intraocular pressure, FADD immunoreactivity was evident in Müller glial cells and RGCs [Ju *et al*., 2006].

2.3.2 Mitochondrial abnormalities

Mitochondrial dysfunction leads to RGC death via caspase-dependent and -independent pathways, initiated by the loss of mitochondrial membrane potential, release of cell death mediators, and/or oxidative stress [Tezel *et al*., 2004]. Members of the Bcl-2 protein family regulate the mitochondrial pathway. This protein family is subdivided into two protein groups: anti-apoptotic proteins, such as Bcl-2 and Bcl-XL; and pro-apoptotic multidomain proteins, such as BAX and "BH3 domain-only" proteins [Antonnsson, 2001]. Mitochondrial membrane integrity is maintained by the actions of the anti-apoptotic group members. Internal stimuli from cell damage sensors (e.g., p53) can stimulate mitochondrion-driven apoptosis by activation of the pro-apoptotic proteins. Protein p53 and members of the Bcl-2 family are active in retinal ganglion cells in glaucoma [Nichells, 1999].

Protein localization studies suggest that, upon activation of cell death, Bcl-2-associated X protein (BAX) is recruited from the cytoplasm to the mitochondrial outer membrane [Nichells, 1999]. The transition to membrane permeability and the release of cytochrome c are critical events in terms of the subsequent steps taken toward apoptosis. Release of cytochrome c activates the caspase cascade via protein association with pro-caspase 9 and apoptosis protease activating factor-1 (Apaf-1) [Adams & Cory, 2007; Danial & Korsmeyer, 2004].

Several studies have found that BAX is a major effector of apoptotic ganglion cell death in the retina after exposure to ischemia, excitotoxicity, or axotomy; and during retinal degeneration [Chen *et al.,* 2003; Isenmann *et al.,* 1997; Isenmann *et al.,* 1999; Zhang *et al.,* 2002]. Complete BAX deficiency of the DBA/2J mouse line prevented RGC somal death during glaucoma development [Libby et al., 2005].

Mitochondrial permeability transition pores (MPTPs)

The mitochondrial permeability transition pore (MPTP) is a pore protein that spans the inner and outer mitochondrial membranes, allowing the passage of any molecule <1,500 Da in size [Crompton *et al.,* 1987]. MPTP induction can lead to mitochondrial swelling and cell death, and plays an important role in some types of apoptosis. Mitochondrial calcium overload, oxidative stress, adenine nucleotide depletion, depolarization, and/or elevated phosphate concentration, results in opening of the MPTP. This leads to osmotic swelling of the mitochondrial matrix as water influx is followed by compression of the intercristal space. It is presumed that cytochrome c and other apoptogenic factors, including apoptosis-inducing factor (AIF), are released through the pores, [Zoratti *et al.,* 2005] although the mechanism of mitochondrial membrane permeabilization remains unclear.

Release of cytochrome c

Cytochrome c is an electron carrier of the respiratory chain, normally located in the space between the inner and outer mitochondrial membranes. The protein is released by the mitochondria to the cytosol in response to pro-apoptotic stimuli. Such release activates the caspase-dependent apoptotic pathway. Once in the cytosol, cytochrome c forms a complex with apoptotic protease-activating factor 1 (APAF-1) and caspase-9 to form the apoptosome [Cain *et al.,* 2002], which initiates a cascade of proteolytic cleavages.

2.4 Signaling mechanisms protecting RGCs from apoptosis

Bcl-2, an anti-apoptotic protein of mitochondria, has been shown to inhibit cytochrome c release and to protect against oxidative stress-induced apoptosis [Takahashi *et al.,* 2004]. The

actions of members of the Bcl-2 protein family thus counterbalance the effects of proapoptotic BAX proteins [Antonnsson, 2001]. When BAX species are predominant, apoptosis occurs. However, if Bcl-2 levels are higher, cell survival is favored. For example, if a rise in intraocular pressure leads to neurotrophin insufficiency, this will in turn cause downregulation of Bcl-2 and upregulation of BAX, resulting in apoptosis.

2.5 Killing of RGCs by activated proteolytic caspases

Many signals and pathways cause apoptosis, but the only cell killing mechanism is the organized degradation of cellular organelles by activated proteolytic caspases. The enzymes belong to the cysteine proteases that upon activation through the intrinsic and/or extrinsic pathways destroy essential cellular proteins. In a healthy cell, caspases are held in inactive zymogenic states, thus as pro-caspases, and do not become functional until proteolytically processed. Caspases can be divided into two groups; the initiator (e.g., caspases 8 and 9) and effector (e.g., caspases 3, 4, and 7) caspases [Alenzi *et al.,* 2010]. Initiator caspases activate effector caspases in response to specific cell death signals, and effector caspases in turn cleave other protein substrates within the cell resulting in apoptotic process [Chang & Yang, 2000].

Caspase activation in mammalian cells is mediated via two main routes, often referred to as 'the intrinsic pathway and 'the extrinsic pathway [Hengartner, 2000]. Enzymes at the upper end of the cascade include caspase-8, 10 and caspase-9. Caspase-8 is the initial caspase of the extrinsic pathway, thus representing the cellular response to triggering of receptors with death domains. While caspases 8 and 10 act as initiator caspases of the extrinsic apoptosis pathway, caspase 9 acts as an initiator caspase of the intrinsic apoptosis pathway [Kuida K. 2000]. The intrinsic pathway commences with release of cytochrome c from mitochondria, which then interacts with apoptosis protease activating factor-1 (Apaf-1), resulting in self-cleavage and activation of caspase-9. Caspase 3 is considered to be the main effector caspase involved in both intrinsic and extrinsic pathways. Caspases-3, -6, and -7 are downstream enzymes that are activated by upstream proteases, and act to cleave cellular targets. These caspases are responsible for destruction of key cytoskeletal proteins, causing the morphological changes typically observed in cells undergoing apoptosis. Caspases activate DNAses, inhibit DNA repair enzymes, and break down nuclear structural proteins [Kitazumi & Tsukahara 2011].

To prevent unnecessary cell death, cells synthesize inhibitors of apoptosis proteins (IAPs); these proteins are grouped into a family that modulates initiator and effector caspase activity.

Several studies have found that caspase-3 is involved in the apoptotic death of RGCs induced by ischemia [Lam *et al.,* 1999; Tezel & Wax, 1999], excitotoxicity [Tezel & Wax, 1999], and chronic ocular hypertension [McKinnon *et al.,* 2003]. Inhibition of caspase-3 activity reduced the level of apoptotic cell death induced in retinal cells by either excitotoxicity or ischemia [Lam *et al.,* 1999, Chen *et al.,* 2001].

3. Mechanisms of RGC death

3.1 Mechanical stress

Optic nerve axons exit the eye at the lamina cribrosa. At this site, the glial-wrapped axon bundles are confined within the rigid pores of the laminar cribriform plates, termed the lamina cribrosa pores. Axon bundles are thought to be vulnerable to mechanical stress in the

region of passage through the laminar pores. It has been suggested that compression at the level of the lamina cribrosa (often caused by elevated intraocular pressure) damages RGC axons [Quigley & Addicks, 1981]. Although differences in lamina cribrosa pore shape in glaucomatous eyes have been observed in glaucoma patients, it remains unknown whether such alterations precede the onset of RGC loss [Tezel *et al*, 2004].

It is hypothesized that the force exerted by extrinsic intraocular pressure on the optic nerve results in backward bowing of laminar support tissues, distortion of laminar plates, misalignment of laminar pores, and nerve cell damage caused by direct mechanical compression or interruption of axoplasmic flow [Quigley *et al.,* 1980]. It is also possible that mechanical distortion of extracellular matrix plates contributes to glaucoma, as blood vessels are thereby affected [Quigley & Addicks, 1981]. Importantly, the extracellular matrix plates of the lamina are covered by astrocytes that provide the axons with support that is both neurotrophic in nature and otherwise.

Elevated intraocular pressure may obstruct the retrograde transport that is thought to inhibit delivery of neurotrophic substances to RGCs, thereby triggering apoptosis [Quigley, 1999]. An alternative hypothesis is that intraocular pressure elevation alters glial cells in some manner, resulting in damage to RGC axons [Hernandez *et al.,* 2000]. Loss of glial support functions may also be important in terms of neuronal compromise [Lappe & Siefke, 2003].

In addition, RGC death induced by elevated intraocular pressure involves caspase activation (including that of caspases-3,8 and -9) in experimental rat models of glaucoma [Hanninen et al., 2002; Huang et al., 2005; McKinnon et al., 2002;].

3.2 Hypoxia-ischemia

Dysregulation of blood flow, causing tissue hypoxia, either secondary to or independent of intraocular pressure elevation, has been suggested to cause retinal damage in glaucoma patients [Cioffi,2001; Flammer et al., 2002; Osborne et al., 2001]. The structural and functional integrity of the retina depends on a regular supply of oxygen. The inner retinal layers exhibit the highest sensitivity to hypoxic challenge, whereas the outer retina is more resistant to hypoxic stress [Kaur et al., 2008].

RGCs have been reported to be particularly sensitive to acute, transient, and mild systemic hypoxic challenge [Kergoat et al., 2006]. RGC death has been found to occur in many different models of induced retinal ischemia [Adachi et al., 1996, Lafuente et al., 2002]. Analysis of the expression of a hypoxia-induced transcription factor, HIF-1α, the synthesis of which is tightly regulated by cellular oxygen concentration, has provided direct evidence that hypoxia occurs in the retina and optic nerve head of glaucomatous eyes, and hypoxic signaling is likely to be one pathogenic mechanism involved in glaucomatous neurodegeneration [Tezel & Wax, 2004]. Hypoxia induces HIF-1α synthesis; the target genes of this transcription factor include those encoding vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS) [Levy et al., 1995]. NOS is the the enzyme responsible for production of nitric oxide (NO), an important cellular signaling molecule.

Upregulated expression of VEGF and NOS in the retina has been reported following hypoxic injury [Kaur et al., 2006], as well as in the glaucomatous retina [Tezel & Wax, 2004]. NO synthesis by NOS contributes to the cytotoxicity that culminates in cell death and axonal damage. In addition to generating free radicals, NO induces the pro-apoptotic cascade by enhancing phosphorylation of Bcl-2 [Mishra et al., 2004; Seminara et al., 2007], which in turn results in the loss of anti-apoptotic potential.

Hypoxia-ischemia causes accumulation of reactive oxygen species (ROS), which have been shown to be cytotoxic to RGCs [Tezel & Yang, 2004]. ROS are chemically-reactive molecules containing oxygen. ROS cause necrotic cell death via direct oxidative damage to cellular constituents. ROS also trigger apoptotic death, as they participate in the signal transduction pathway characteristic of apoptosis [Kortuem et al., 2000, Levkovitch-Verbin et al., 2000, Lieven *et al*., 2003]. Hypoxia activates microglia, the immune effector cells of the retina, resulting in release of TNF-α (an inflammatory cytokine) [Kaur *et al*., 2008].

Abnormally high-level release of the excitatory amino acid glutamate under hypoxic-ischemic conditions has been implicated in hypoxic and ischemic neuronal death [Benveniste et al., 1984], and glaucoma [Sucher *et al*., 1997]. RGCs are very sensitive to the toxic effects of elevated glutamate, but the mechanism by which this response is mediated remains unclear. Upon hyperstimulation of one or more glutamate receptors, neuronal cell death is induced by excitotoxins; the process is complex and is not yet fully understood. Several studies have found that both the apoptotic and necrotic pathways of cell death can be activated under such conditions [Ankarcrona *et al.,* 1995].

3.3 Free radical-induced damage

The source of reactive oxygen species (ROS) may be either exogenous (the extracellular fluid) or endogenous. ROS are created in the eye by sunlight, mitochondrial respiration, and intra- and extra-cellular metabolic reactions [Roth, 1997]. The major producers of ROS in RGCs are mitochondria. The lamina cribrosa contains more mitochondria than are present in other regions of the RGC axon. As the number of mitochondria increases, more oxygen is consumed, and ROS synthesis rises. ROS initiate many metabolic cascades that have a wide variety of downstream effects. In vitro studies with RGC-5 cells (RGC-5 is a clonal rat RGC line) showed that oxidative stress perturbs calcium homeostasis, activates pro-apoptotic caspases, depletes glutathione levels, and increases the extent of DNA fragmentation, suggesting that a final common pathway of oxidative stress-induced cell death may exist [Maher & Hanneken 2005a, Maher & Hanneken 2005b].

3.4 Excessive glutamate stimulation

Glutamate, the excitatory neurotransmitter of the retina, is released by photoreceptors, bipolar cells, and ganglion cells, and mediates the transfer of visual signs from the retina to the brain [Wong *et al*., 2007]. However, when glutamate levels are elevated, neuronal death can occur via either apoptosis or necrosis [Ankarcrona *et al*., 1995]. Thus, appropriate clearance of synaptic glutamate is required if retinal excitatory synapses are to function normally, and to prevent neurotoxicity. Glial cells surround glutamatergic synapses; such cells express glutamate transporters and the glutamate-metabolizing enzyme glutamine synthetase. Together, these enzymes convert glutamate to the non-toxic amino acid glutamine [Bringmann *et al.,* 2009].

Glutamate interacts with numerous receptor subtypes; these fall into two major classes. One class is coupled to G-proteins (the metabotropic class), the other class connect directly to transmembrane channels (the ionotropic class, including the amino-methyl-propionic-acid [APMA], NMDA, and kainate glutamate receptors). The toxic effects of elevated glutamate levels are predominantly mediated by overstimulation of receptors for the glutamate analog N-methyl-D-aspartate (NMDA). Activation of NMDA receptors by glutamate results in overloading of intracellular Ca^{2+}, which in turn activates calcium-dependent enzymes and

leads to principally necrotic cell death [Shen *et al.,* 2006]. Excess glutamate, which may result from ischemia, can trigger apoptosis. It has been shown that glutamate, acting via the ionotropic receptors, significantly elevates the levels of neuronal nitric oxide synthase (nNOS), TNF-α, and interleukin-1β [Kaur *et al.,* 2009]. This results in influx of Na^+ and Cl^- ions, in turn inducing osmotic swelling and glutathione depletion.
Glutamate release has been implicated as a mechanism of RGC death in glaucoma [Levin & Peeples 2008, Osborne *et al.,* 1999, Levkovitch-Verbin *et al.,* 2001]. Although numerous studies have examined the role played by glutamate in acute ischemia, the relevance of glutamate excitotoxicity in glaucoma remains doubtful.

3.5 Activated glial cells

Microglial and macroglial cells (Müller cells and astrocytes) have important immunoregulatory functions and control the extracellular environment of the optic nerve head and retina. In the optic nerve, glial cells include astrocytes, oligodendrocytes (located behind the lamina cribrosa), and microglia [Johnson & Morrison, 2009]. In the retina, Müller cells and astrocytes are predominant. Under normal conditions, glial cells support neuronal function via a variety of mechanisms including structural and nutritional roles as well as the removal of ions and neurotransmitters from the extracellular space [Johnson & Morrison, 2009].
It is possible that activation of glial cells in glaucomatous eyes serves primarily to support neuronal function. However, at some point, triggered by the prolonged stress associated with glaucoma, a shift in cell function seems to occur; the cells are no longer supportive but rather damage neuronal tissue. The injury involves both mechanical insult and changes in the microenvironment. In addition, a growing body of evidence suggests that, under glaucomatous stress conditions, glial cells may even become neurodestructive, releasing increased amounts of neurotoxic substances including TNF-α and nitric oxide (NO) [Tezel, 2006].
Astrocytes become reactive in response to various stimuli, including elevated intraocular pressure, excitotoxicity, and retinal ischemia [Neufeld & Liu 2003, Hernandez et al., 2008]. Reactive astrocytes in glaucomatous optic nerve heads apparently play important roles in the development of local neurotoxicity, confined to the retinal ganglion cell axons, by producing excessive levels of NO in patients with glaucomatous optic neuropathy [Liu & Neufeld 2000]. The use of inhibitors of nitric oxide synthase, such as 3-aminoguanidine, reduced RGC loss in rat eyes with elevated intraocular pressure [Neufeld et al., 1999].
Chronic activation of retinal and optic nerve head glia in glaucomatous eyes also involves activation of the antigen-presenting abilities of such cells, thereby facilitating initiation of an autoimmune process via antigen presentation [Tezel et al., 2007].
In glaucoma patients, microglia become activated and redistributed within the optic nerve head [Neufald et al., 1999], after which cytokines and chemokines are synthesized [Block 2007, Kim 2005]. However, the influence of microglial factors on other retinal cells, including RGCs, is unclear, although such interactions may be relevant to glaucoma pathology. This aspect of the field merits further study.

3.6 Inflammatory cytokines (tumor necrosis factor-α and NO)

Glial production of **tumor necrosis factor- α** (TNF-α) is increased, and the level of TNF receptor-1 upregulated, in RGCs and their axons in glaucomatous donor eyes [Tezel G, 2008]. The two main subgroups of the TNF receptor superfamily, TNF-R1 and TNF-R2,

recognize both the membrane-bound and soluble forms of TNF-α. The current view of TNF-α-mediated signaling is that binding of the factor to TNF-R1 promotes neuronal cell death whereas messages from TNF-R2 trigger proliferative and regulatory signals promoting cell survival. Establishment of a critical balance between the considerable variety of intracellular signaling pathways determines whether an RGC will die or will survive exposure to TNF-α. This factor, secreted by stressed glial cells within glaucomatous tissues, can induce RGC death via induction of a receptor-mediated caspase cascade, mitochondrial dysfunction, and/or oxidative damage. In addition to direct neurotoxic effects on RGCs and axons thereof, TNF-α signaling is likelyto contribute to secondary degeneration of primarily uninjured RGCs [Tezel G, 2008].

TNF-α can induce glial NO production thus the extent of excitotoxic injury. NO induces the proapoptotic cascade in hypoxic neural tissues by enhancing phosphorylation of Bcl-2 [Mishra et al. 2004]. The anti-apoptotic potential of Bcl-2 is lost because the protein can no longer heterodimerize with the pro-apoptotic protein BAX, resulting in BAX-mediated activation of caspases and initiation of apoptosis. Other mechanisms by which NO may contribute to cytotoxicity include peroxynitrite-mediated oxidative injury, DNA damage, and energy failure [StClair et al., 1997].

Involvement of TNF-α in the innate immune response may also have implications in terms of axonal degeneration in glaucomatous eyes. TNF-α signaling may be associated with axonal dysfunction and Wallerian degeneration. One function of TNF-α during the latter type of degeneration has been suggested to be induction of macrophage recruitment for debris removal [Tezel G, 2008].

TNF- α also activates matrix metalloproteinases, which are involved in tissue remodeling within the glaucomatous optic nerve head. The matrix metalloproteinases are a family of proteolytic enzymes secreted by glial cells, and are capable of degrading almost all components of the extracellular matrix. The intensity of immunostaining for matrix metalloproteinases (MMP-1, MMP-2, and MMP-3), was greater in glaucomatous optic nerve heads compared with controls [Yan X *et al.*, 2000]. TNF-α induced matrix metalloproteinase activity has also been shown to facilitate macrophage recruitment by nerves injured during delayed axonal degeneration [Tezel G, 2008].

TNF- α stimulates endothelin-1 synthesis and secretion in optic nerve head astrocytes [Tezel G, 2008]. Endothelin-1 is a vasoconstrictor peptide and along with nitric oxide (NO) regulate optic nerve head, retinal, and choroidal blood flow. Exposure of retinal ganglion cells (RGCs) or RGC-5 cells, a transformed cell line, to endothelin-1 causes apoptic cell death [Salvatore & Vingolo, 2010]

4. Axonal compromise

The human RGC axon travels a distance of approximately 50 mm from the cell body to the target synapse. On leaving the eye, axons turn through 90° to enter the optic nerve head and then traverse the lamina cribrosa to enter the retrobulbar optic nerve [Morgen, 2004]. The lamina cribrosa provides structural and functional support to the RGC axons as they pass from the relatively high-pressure environment in the eye to a low-pressure region in the retrobulbar cerebrospinal space. Within the lamina cribrosa, axonal viability requires adequate delivery of nutrients (assessed in terms of lamellar capillary volume flow) and sufficient diffusion of such nutrients (from lamellar capillaries across endothelial cell basement membranes, through the trabecular extracellular matrix, and across astrocyte

basement membranes) to the centers of axon bundles. The route taken by individual axons can place them at increased risk of damage [Morgen, 2004].
Specifically, compartmental degeneration of axons, synapses, and dendrites can occur independently of somal loss [Whitmore et al., 2005]. Using a murine model of inherited glaucoma, Libby et al [2005] showed that axonal loss occurred independently of somal loss, not just in a spatial sense but via a distinct molecular pathway. The cited authors also found that distinct degeneration pathways were activated in different regions of retinal nerve cells. It was noted that appropriate biochemical function of the nerve cell body, which resides in the retina, required the pro-apoptotic protein BAX (the Bcl2-associated X protein). In contrast, metabolic pathway function in the part of the cell (the axon) that connects the cell body to the brain did not require BAX. In addition, work in a primate model of experimental glaucoma showed that retinal ganglion cells undergo a pattern of degeneration that originates in the dendritic arbor and concludes with shrinkage of the cell soma. In DBA/2J mice, in which intraocular pressure rises spontaneously, axons degenerate before cell bodies, and distal axons appear to be first affected [Schlamp *et al.,* 2006].
The mechanism of vision loss in glaucoma is not understood, but various lines of evidence indicate that RGC axons are critical sites for early pathological changes, including retention of intraretinal RGC axons concomitant with axon loss in the optic nerve [Soto *et al.,* 2008], retrograde degeneration as assessed via axon quantification [Schlamp *et al.,* 2006], and maintenance of RGC somata under circumstances in which retrograde label is lost [Buckingham *et al.,* 2008].
These findings indicate the need to understand axon-specific degeneration pathways in glaucoma, suggesting, first, that distinct somal and axonal degeneration pathways may exist and, second, that both pathways must be to targeted to save vision.

4.1 Axoplasmic flow

RGCs are long projecting neurons, the axons of which form the optic nerve. As with other neurons, ganglion cells must possess a mechanism whereby the cell body remains informed of conditions along the axon and at the synapse, to allow axon size and functions to be maintained. This is accomplished via active axonal transport, a complex energy-driven process that moves molecules from the cell body to the axon terminus (anterograde transport) and also toward the cell body (retrograde transport). Anterograde transport can be divided into fast (50–400 mm/day) and slow (less than 10mm/day) transport. Fast anterograde transport is related to the transport of synaptic vesicles proteins, kinesins, and enzymes involved in the metabolism of neurotransmitters. Slow anterograde transport is given over to the transport of neuronally synthesised proteins that include cytoskeletal components, polymers, and protein complexes that are to be delivered to the axon and its terminal regions. Retrograde transport is classified as fast (200–400 mm/day) and is concerned with the movement of endosomes and lysosomes containing internalised membrane receptors and neurotrophins towards the cell body [Morgan, 2004].
Both anterograde and retrograde transport require integrity of the axonal cytoskeleton, which is composed of microtubules, neurofilaments, and microfilaments. Active axonal transport refers to the process whereby vesicles are transported along microtubules by the dynein and kinesin motor molecules; the kinesins drive anterograde transport and the dyneins retrograde transport. Kinesins typically contain two heavy chains with motor heads which move along microtubules via a pseudo-processive asymmetric walking motion. In comparison with kinesin, the size of a dynein is much larger. Dyneins don't seem to follow

paths that are parallel to protofilament direction but they move across the microtubule surface [Ross *et al*., 2008]. The dynein and kinesin motor molecules acquire energy by hydrolysis of ATP produced by mitochondria. Active axonal transport is essential to ensure communication along axons and interruption thereof is potentially fatal to cells.

Obstruction of axonal transport in RGCs compromises cell viability by preventing delivery of substrates, such as neurotrophic factors, that are necessary for somal survival. Such small growth-enhancing peptides include brain-derived neurotrophic factors (BDNFs), nerve growth factors (NGFs), and neurotrophin-3 (NT-3) and -4 (NT-4) [Funakoshi *et al.,* 1993].

Brain-derived neurotrophin factor (BDNF) is one mediator known to be vital for the buildup and preservation of neurons. BDNF is transported to retinal ganglion cell bodies via retrograde axonal transportation, using synaptic connections within these cells. BDNF has a specific receptor, termed TrkB, which exists in all retinal layers except those of the photoreceptors and the optic nerve. Activation of TrkB directly elicits pro-survival signals during glaucoma progression, and rescues RGCs from death in the context of optic nerve axotomy or glaucoma [Bai, 2010]. Mechanical stress at the level of the lamina cribrosa impairs the retrograde transport of neurotrophins, including BDNF. Thus, retinal ganglion cell somae are deprived of the mediator and the apoptotic cascade is activated [Wong *et al.,* 2011].

4.2 Retrograde degeneration

Wallerian degeneration generally occurs in severely damaged axons and is characterized by a rapid loss of axonal structure throughout the length of the axon. Die-back occurs in axons with more moderate injury and is characterized by a slower retrograde degeneration that proceeds from the synapse to the soma [Levin & Albert 2010]. Although it is not known how axons in a glaucomatous human eye degenerate, clues to this process have come from recent studies in (Wld(S)) mutant rats; suggesting that axonal degeneration in glaucoma follows a Wallerian-like mechanism [Beirowski *et al.,* 2008].

Damage to the optic nerve in mammals induces retrograde degeneration and apoptosis of the retinal ganglion cell (RGC) bodies. The molecular mechanisms responsible for transforming the repellent guidance cue from the damaged axon into a death signal that may affect the cell body are yet to be discovered.

5. References

Adachi M, Takahashi K, Nishikawa M, Miki H, Uyama M. (1996). High intraocular pressure-induced ischemia and reperfusion injury in the optic nerve and retina in rats. *Graefes Arch Clin Exp Ophthalmol*, Vol. 234, No.7, pp. (445-451).

Adams JM, Cory S. (2007). The Bcl-2 apoptotic switch in cancer development and therapy. *Oncogene*, Vol. 26, No.9, pp. (1324–1337).

Aldebasi YH, Drasdo N, Morgan JE, North RV. (2004). S-cone, L + M-cone, and pattern, electroretinograms in ocular hypertension and glaucoma. *Vision Res*, Vol. 44, No 24, pp. (2749-2756).

Alenzi FQ, Lotfy M, Wyse R. (2010) Swords of cell death: caspase activation and regulation. *Asian Pac J Cancer Prev*, Vol.11, No 2, pp. (271-280).

Ankarcrona M, Dypbukt JM, Bonfoco E, Zhivotovsky B, Orrenius S, Lipton SA, Nicotera P. (1995). Glutamate- induced neuronal death: a succession of necrosis or apoptosis depending on mitochondrial function. *Neuron*, Vol. 15, No.4, pp. (961-973).

Antonsson B. (2001). Bax and other pro-apoptotic Bcl-2 family "killer-proteins" and their victim the mitochondrion. *Cell Tissue Res*, Vol. 306, No 3, pp. (347-361).

Artal-Sanz M, Tavernarakis N. (2005). Proteolytic mechanisms in necrotic cell death and neurodegeneration. *FEBS Letters*, Vol. 579, No. 15, pp.(3287-3296).

Benveniste H, Drejer J, Schousboe A, Diemer NH. (1984). Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. *J Neurochem*, Vol. 43, No. 5, pp. (1369-1374).

Beirowski B, Babetto E, Coleman MP, Martin KR. (2008) The WldS gene delays axonal but not somatic degeneration in a rat glaucoma model. *Eur J Neurosci,* Vol (28) No.,(6), pp. (1166-1179).

Bien A, Seidenbecher CI, Böckers TM, Sabel BA, Kreutz MR.(1999) Apoptotic versus necrotic characteristics of retinal ganglion cell death after partial optic nerve injury. *J Neurotrauma*, Vol. 16, No. 2, pp. (153-163).

Bok D. (1993) The retinal pigment epithelium: a versatile partner in vision. *J Cell Sci*, Vol.17, pp (189-195).

Bonfocco E, Krainic D, Ankarcrina M, Nicotera P, Lipton SA. (1995). Apoptosis and necrosis: two distinct events induced, respectively, by mild and intense insults with N-methyl-D-aspartate or nitric oxide/superoxide in cortical cell cultures. *Neurobiology*, Vol. 92, pp. (7162–7166).

Borgens RB. (1988) Voltage gradients and ionic currents in injured and regenerating axons. *Adv Neurol*, Vol 47, pp. (51-66).

Bortner CD, Oldenburg NBE, Cidlowski JA. (1995). The role of DNA fragmentation in apoptosis. *Trends Cell Biol*, Vol. 5, No. 1, pp (21-26).

Bratton DL, Fadok VA, Richter DA, Kailey JM, Gutrie LA Henson PM. (1997). Appearance of Phosphatidylserine on Apoptotic Cells Requires Calcium-mediated Nonspecific Flip-Flop and Is Enhanced by Loss of the Aminophospholipid Translocase. Vol. 17, No. 272, pp . (26159–26165).

Bringmann A, Pannicke T, Biedermann B, Francke M, IIandiev I, Grosche J, Wiedemann P, Albrecht J, Reichenbach A. (2009). Role of retinal glial cells in neurotransmitter uptake and metabolism. *Neurochem Int,* Vol *54,* No *3-4*, pp. (143-160).

Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, Osborne NN, Reichenbach A. (2006). Muller cells in the healthy and diseased retina. *Prog Retin Eye Res,* Vol.25, No.4, pp.(397–424).

Bringmann A, Pannicke T, Grosche J, Francke M, Wiedemann P, Skatchkov SN, Osborn NN, Bortner CD, Cidlowski JA. (2007). Cell shrinkage and monovalent cation fluxes: role in apoptosis. *Arch Biochem Biophys*, Vol 15, No 462 (2): pp. (176-188).

Cain K, Bratton SB, Cohen GM. (2002). The Apaf-1 apoptosome: a large caspase-activating complex. *Biochimie,* Vol. 84, No 2-3, pp. (203-214).

Chang L.T, Stone J. (1991). Factors determining the morphology and distribution of astrocytes in the cat retina: a 'contact-spacing' model of astrocyte interaction. *J Comp Neurol,* Vol 15, No.303(3), pp. (387-399).

Chang HY , Yang X. (2000). Proteases for Cell Suicide: Functions and Regulation of Caspases. *Microbiol Mol Biol Rev*, Vol 64, No 4, pp. (821–846).

Chen L, Yang P, Kijlstra A. (2002). Distribution, markers, and functions of retinal microglia. *Ocul Immunol Inflamm*, Vol.10, No.1, pp. (27-39).

Chen ST, Hsu JR, Hsu PC, Chuang JI. (2003). The retina as a novel in vivo model for studying the role of molecules of the Bcl-2 family in relation to MPTP neurotoxicity. *Neurochem Res*, Vol. 28, No.6, pp. (805–814).

Chen TA, Yang F, Cole GM, Chan So. (2001). Inhibition of caspase-3-like activity reduces glutamate induced cell death in adult rat retina. *Brain Res Vol*, 904, No.1 pp. (177–188).

Cioffi GA. (2001). Three common assumptions about ocular blood flow and glaucoma. *Surv Ophthalmol*, Vol.45 No (suppl 3), pp.(325–331)

Coleman MP, Freeman MR. (2010). Wallerian degeneration, wld(s), and nmnat. *Annu Rev Neurosci*, Vol.33, pp. (245-267).

Cory S, Adams JM. (2002). The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer*, Vol. 2, No.9, pp. (647-656).

Cowling V, Downward J. (2002). Caspase-6 is the direct activator of caspase-8 in the cytochrome c-induced apoptosis pathway: absolute requirement for removal of caspase-6 prodomain. *Cell Death Differ*, Vol. 9, No.10, pp. (1046-1056).

Crompton M, Costi A, Hayat L. (1987). Evidence for the presence of a reversible Ca2+-dependent pore activated by oxidative stress in heart mitochondria. *Biochem J*, Vol. 245, No. 3, pp. (915-918).

Cummings MC, Winterford CM, Walker NI. (1997). Apoptosis. *Am J Surg Pathol*, Vol.21, No.1, pp.(88-101)

Dandona L, Hendrickson A, Quigley HA. (1991). Selective effects of experimental glaucoma on axonal transport by retinal ganglion cells to the dorsal lateral geniculate nucleus. Invest Ophthalmol Vis Sci, Vol. 32, No. 5, pp. (1593-1599).

Danial NN, Korsmeyer SJ. (2004). Cell death: critical control points. Cell. 116:205–219.

Dawson VL. 2005 Molecular mechanisms in neuronal and axonal apoptosis and necrosis. *Adv Stud Med*, Vol. 5, No.4, pp. (387-391).

Fatma N, Kubo E, Sen M, Agarwal N, Thoreson WB, Camras CB, Singh DP. (2008). Peroxiredoxin 6 delivery attenuates TNF-α-and glutamate-induced retinal ganglion cell death by limiting ROS levels and maintaining Ca^{2+} homeostasis. *Brain Research,* Vol. 1233, No 3: pp. (63-78).

Farkas RH, Grosskreutz CL. (2001). Apoptosis, neuroprotection, and retinal ganglion cell death: an overview. *Int Ophthalmol Clin,*. Vol.41, No 1, pp. (111-130).

Flammer J, Orgül S, Costa VP, Orzalesi N, Krieglstein GK, Serra LM, Renard JP, Stefennsson E .(2002) The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res,* Vol. 21, No 4, pp. (359–393).

Franze K, Grosche J, Skatchkov SN, Schinkinger S, Foja C, Schild D, Uckermann O, Travis K, Reichenbach A, Guck J. (2007). Muller cells are living optical fibers in the vertebrate retina. *Proc Natl Acad Sci USA*, Vol. 104 No. 20, pp. (8287-8292).

Forrester JV. (2002) The eye: basic sciences in practice

Funakoshi H, Frisen J, Barbany G, et al. (1993). Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve. *J Cell Biol,* Vol (123) pp. (455-465).

Glovinsky Y, Quigley HA, Dunkelberger GR. (1991). Retinal ganglion cell loss is size dependent in experimental glaucoma. *Invest Ophthalmol Vis Sci,* Vol. 32, No . 3, pp. (484–491).

Guerin MB, McKernan DP, O'Brien CJ, Cotter TG. (2006). Retinal ganglion cells:dying to survive. *Int J Dev Biol*, Vol.50, No 8, pp. (665-674).

Gulbins E. (2003). Regulation of death receptor signaling and apoptosis by ceramide. *Pharmacol Res*, Vol. 47, No 5, pp. (393-399).

Gupta N, Yücel YH. (2007). Glaucoma as a neurodegenerative disease *Current Opinion in Ophthalmology*, Vol. 18, No 2, pp.(110-114).

Hanninen VA, Pantcheva MB, Freeman EE, Poulin NR, Grosskreutz CL. (2002). Activation of caspase 9 in a rat model of experimental glaucoma.*Curr Eye Res*, Vol. 25, No 6, pp. (389-395).

Hengartner MO. (2000). The biochemistry of apoptosis. *Nature* Vol. 407, No 12 pp. (770-776).

Hernandez MR, Miao H, Lukas T (2008). Astrocytes in glaucomatous optic neuropathy. *Prog Brain Res,* Vol. 173, pp. (353–373).

Hernandez MR, Pena JD, Selvidge JA, Salvador- Silva M, Yang P. (2000) Hydrostatic pressure stimulates synthesis of elastin in cultured optic nerve head astrocytes.*Glia,* Vol. 32, No 2 pp. (122-136).

Hosoya K, Tomi M. (2005) Advances in the Cell Biology of Transport *via* the Inner Blood-Retinal Barrier: Establishment of Cell Lines and Transport Functions. *Biol Pharm Bull*, Vol. 28,No.1, pp.(1-8).

Huang W, Dobberfuhl A, Filippopoulos T, Ingelssson M, Fileta JB, Poulin NR, Grosskreutz CL. (2005) Transcriptional up-regulation and activation of initiating caspases in experimental glaucoma. *Am J Pathol*, Vol. 167, No 3, pp. (673-681).

Krstić RV. (1997) Human microscopic anatomy: an atlas for students of medicine and biology.

Kuida K. (2000) Caspase-9. *Int J Biochem Cell Biol*, Vol. 32, No 2, pp. (121-124).

Isenmann S, Wahl C, Krajewski S, Reed JC, Bähr M. (1997) Up-regulation of Bax protein in degenerating retinal ganglion cells precedes apoptotic cell death after optic nerve lesion in the rat. *Eur J Neurosci,* Vol. 9, No 8, pp. (1763–1772).

Isenmann S, Engel S, Gillardon F, Bahr M. (1999) Bax antisense oligonucleotides reduce axotomy-induced retinal ganglion cell death in vivo by reduction of Bax protein. *Cell Death Differ*, Vol. 6, No.7, pp. (673–682).

Itoh N, Nagata S. (1993). A novel protein domain required for apoptosis: mutational analysis of human Fas antigen. *J Biol Chem,* Vol.268, No 15, pp. (10932–10937).

Johnson EC, Morrison JC. (2009) Friend or Foe? Resolving the Impact of Glial Responses in Glaucoma. *Glaucoma,* Vol.18, No 5, pp. (341-353).

Joo C, Choi JS, Ko HW, Park KY, Sohn S, Chun MH, Oh YJ, Gwag BJ. (1998) Necrosis and apoptosis after retinal ischemia: involvement of NMDA-mediated excitotoxicity and p53. *Invest Ophthalmol Vis Sci*, Vol. 40, No 3 pp. (713–720).

Ju KR, Kim HS, Kim JH, Lee NY, Park CK. (2006) Retinal glial cell responses and Fas/FasL activation in rats with chronic ocular hypertension. *Brain Res,* Vol.1122, No. 1, pp. (209-221).

Kaufmann M, Bozic D,Briand C, Bodmer JL,Zerbe O,Kohl A, Tschopp J, Grütter MG. (2002) Identification of a basic surface area of the FADD death effector domain critical for apoptotic signaling. *FEBS Lett*, Vol. 527, No. 1-3, pp. (250-254).

Kaur C, Foulds WS Ling EA. (2008) Hypoxia-ischemia and retinal ganglion cell damage. *Clin Ophthalmol*, Vol.2 No4, pp. (879–889).

Kergoat H, Hérard ME, Lemay M. (2006) RGC sensitivity to mild systemic hypoxia. *Invest Ophthalmol Vis Sci*, Vol. 47 No. 12, pp. (5423-5427).

Kerr JF, Wyllie AH, Currie AR. (1972) Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer,* Vol. 26, No. 4, pp.(239-257).

Kerr JF, Winterford CM, Harmon BV. (1994) Apoptosis. Its significance in cancer and cancer therapy. *Cancer,* Vol. 73, No. 8, pp. (2013-2026).

Kim Kortuem, Geiger LK, Levin LA. (2000) Differential Susceptibility of Retinal Ganglion Cells to Reactive Oxygen Species. *IOVS*, Vol. 41, No 10, pp. (3176-3186).

Kitazumi I, Tsukahara M. (2011) Regulation of DNA fragmentation: the role of caspases and phosphorylation. *FEBS J.* Vol. 278, No.3, pp. (427-441).

Kortuem K, Geiger LK, Levin LA. (2000) Differential susceptibility of retinal ganglion cells to reactive oxygen species. *Invest Ophthalmol Vis Sci*, Vol.41, No.10, pp. (3176-3182).

Kuehn MH, Fingert JH, Kwon YH. (2005) Retinal Ganglion Cell Death in Glaucoma: Mechanisms and Neuroprotective Strategies. *Ophthalmol Clin N Am,* Vol.18, No 3, pp.(383 – 395).

Lam TT, Abler AS, Tso MO. (1999) Apoptosis and caspases after ischemia-reperfusion injury in rat retina. *Invest Ophthalmol Vis Sci,* Vol. 40, No. 5, pp (967-975)

Lafuente MP, Villegas-Pérez MP, Sellés-Navarro I, Mayor-Torroglosa S, Miralles de Imperial J, Vidal-Sanz M. (2002) Retinal ganglion cell death after acute retinal ischemia is an ongoing process whose severity and duration depends on the duration of the insult. *Neuroscience,* Vol.109, No.1, pp. (157-168).

Lappe-Siefke C, Goebbels S, Gravel M, Lee J, Braun PE, Griffiths IR, Nave KA. (2003). Disruption of Cnp1 uncouples oligodendroglial functions in axonal support and myelination. *Nat Genet,* Vol. 33, No. 3, pp. (366–374).

Lavrik I, Golks A, Krammer PH. (2005). Death receptor signaling. *J Cell Sci*, Vol.118, No. 2, pp.(265-267).Leist M, Nicotera P. (1998) Apoptosis versus necrosis: the shape of neuronal cell death. *Results Probl Cell Differ.* Vol. 24, pp.(105-135).

Levin L, Albert DM. (2010). Ocular Disease: Mechanisms and Management. Elsevier Inc.

Levin LA, Peeples P. (2008). History of neuroprotection and rationale as a therapy for glaucoma. *Am J Manag Care,* Vol.14, No.1 Suppl, pp. (11-14).

Levkovitch-Verbin H, Quigley HA, Kerrigan-Baumrind LA, D' Anna SA, Kerrigan D, Pease ME. (2001). Optic nerve transection in monkeys may result in secondary degeneration of retinal ganglion cells. *Invest Ophthalmol Vis Sci*, Vol.42, No. 5, pp. (975-982).

Levkovitch-Verbin H,Harris-Cerruti C,Groner Y, Wheeler LA, Schwartz M, Yoles E. (2000). RGC death in mice after optic nerve crush injury: oxidative stress and neuroprotection. *Invest Ophthalmol Vis Sci,* Vol. 41, No. 13, pp.(4169-4174).

Levy AP, Levy NS, Wegner S, Goldberg MA. (1995). Transcriptional regulation of the rat vascular endothelial growth factor gene by hypoxia. *J Biol Chem*, Vol. 270, pp.(13333–13337)

Lewin, B. (2000). Genes VII. New York: Oxford University Press.

Libby RT, Li Y, Savinova OV, Barter J, Smith RS, Nickells RW, John SWM. (2005). Susceptibility to neurodegeneration in glaucoma is modified by Bax gene dosage. *PLoS Genet,* Vol.1, No. 1, pp. (17-26).

Lieven CJ, Vrabec JP, Levin LA. (2003) The effects of oxidative stress on mitochondrial transmembrane potential in retinal ganglion cells. *Antioxid Redox Signal,* Vol. 5, No.5, pp. (641-646).

Liu B, Neufeld AH. (2000) Expression of nitric oxide synthase-2 (NOS-2) in reactive astrocytes of the human glaucomatous optic nerve head. *Glia,* Vol. 30, No.2, pp. (178-186).

Love S. (2003) Apoptosis and brain ischaemia. *Prog Neuropsychopharmacol Biol Psych*, Vol. 27, pp. (267–282).

Mace PD, Riedl SJ. (2010) Molecular cell death platforms and assemblies. *Curr Opin Cell Biol*, Vol. 22, No. 6, pp. (828-836).

Maher P, Hanneken A. (2005) The molecular basis of oxidative stress-induced cell death in an immortalized retinal ganglion cell line. *Invest Ophthalmol Vis Sci*, Vol. 46, No. 2, pp.(749-757).

Maher P, Hanneken A. (2005) Flavonoids Protect Retinal Ganglion Cells from Oxidative Stress–Induced Death. *Invest Ophthalmol Vis Sci,* Vol.46, No.12, pp. (4796-4803).

Masland RH. (2001). The fundamental plan of the retina. *Nat Neurosci*, 4 No 9, pp. (877-886).

Masland RH. (2001) Neuronal diversity in the retina. *Curr Opin Neurobiol*, Vol.11, No. 4, pp. (431-436).

McCarthy JV, Cotter TG. (1997) Cell shrinkage and apoptosis: a role for potassium and sodium ion efflux. *Cell Death Differ*,Vol. 4, No 8, pp.(756-770).

McKinnon Sj, Lehman DM, Kerrigan-Baumrind LA,Merges CA, Pease MF, Kerrigan DF, Ransom NL, Tahzib NG, Reitsamer HA, Levkovitch-Verbin H, Quigley HA, Zack DJ. (2002) Caspase activation and amyloid precursor protein cleavage in rat ocular hypertension. *Invest Ophthalmol Vis Sci,*Vol. 43, No 4, pp. (1077-1087)

Mills JC. (2001). Mechanisms underlying the Hallmark features of the execution-phase of apoptosis. *Advances in Cell Aging and Gerontology,* Vol. 5, pp. (1-38).

Mishra OP, Delivoira Papadopoulos M. (2004). Effect of hypoxia on protein tyrosine kinase activity in cortical membranes of newborn piglets--the role of nitric oxide. *Neurosci Lett,* Vol. 372, No. 1-2, pp. (114-118).

Mishra OP, Zubrow AB, Ashraf QM. (2004). Nitric oxide-mediated activation of extracellular signal-regulated kinase (ERK) and c-jun N-terminal kinase (JNK) during hypoxia in cerebral cortical nuclei of newborn piglets. *Neuroscience,* Vol. 123, No. 1, pp. (179- 186).

Morgan JE, Uchida H, Caprioli J. (2000). Retinal ganglion cell death in experimental glaucoma. *Br J Ophthalmol*, Vol. 84, No. 3, pp. (303-310).

Morgan JE. (2004). Circulation and axonal transport in the optic nerve. *Eye,* Vol. 18, pp. (1089-1095).

Mu X, Klein WH. (2004). A gene regulatory hierarchy for retinal ganglion cell specification and differentiation. *Semin Cell Dev Biol,* Vol. 15, No. 1, pp. (115-123)

Nagata S.(2000) Apoptotic DNA fragmentation. *Exp Cell Res,* Vol. 256, No. 1, pp. 12-18.

Nassi JJ, Callaway EM. (2009). Parallel processing strategies of the primate visual system. *Nat Rev Neurosci*, Vol. 10, No.5, pp. (360-372).

Neufeld AH. (1999) Microglia in the Optic Nerve Head and the Region of Parapapillary Chorioretinal Atrophy in Glaucoma *Arch Ophthalmol.* Vol. 117, No. 8, pp.(1050-1056).

Neufeld AH, Liu B. (2003) Glaucomatous optic neuropathy: when glia misbehave. *Neuroscientist,* Vol. 9, No. 6, pp. (485-495).

Neufeld AH, Sawada A, Becker B. (1999) Inhibition of nitric-oxide synthase 2 by aminoguanidine provides neuroprotection of retinal ganglion cells in a rat model of chronic glaucoma. *Proc Natl Acad Sci USA,*. Vol. 96, No. 17, pp. (9944-9948).

Nicotera P, Leist M, Ferrando-May E. (1998). Intracellular ATP, a switch in the decision between apoptosis and necrosis.*Toxicol Lett*, Vol. 102-103, pp. (139-142).

Nickells RW. (1999) Apoptosis of Retinal Ganglion Cells in Glaucoma: An Update of the Molecular Pathways Involved in Cell Death. *Surv Ophthalm*, Vol. 43 No.1, pp.151-161

North RV, Jones AL, Drasdo N, Wild JM, Morgen JE. (2010). Electrophysiological evidence of early functional damage in glaucoma and ocular hypertension. Invest *Ophthalm Invest Ophthalmol Vis Sci*, Vol. 5, No. 2, pp. (1216-1222).

Osborne NN, Melena J, Chidlow G, Wood JP. (2001). A hypothesis to explain ganglion cell death caused by vascular insults at the optic nerve head: possible implication for the treatment of glaucoma. *Br J Ophthalmol,* Vol. 85, No. 10, pp. (1252–1259).

Osborne NN, Wood JP, Chidlow G, Bae JH, Melena J, Nash MS. (1999) Ganglion cell death in glaucoma: what do we really know *Br J Ophthalmol*,Vol. 83, No.8, pp.(980-986).

Poche RA, Reese BE. (2009). Retinal horizontal cells: challenging paradigms of neural development and cancer biology. Development Vol. 136, No. 13, pp. (2141-2151).

Quigley HA, Flower RW, Addicks EM,McLoad DS. (1980). The mechanism of optic nerve damage in experimental acute intraocular pressure elevation. *Invest Ophthalmol Vis Sci*, Vol. 19, No. 5, pp. (505-517)

Quigley HA, Addicks EM. (1981). Regional differences in the structure of the lamina cribrosa and their relation to glaucomatous optic nerve damage. *Arch Ophthalmol*, Vol. 99, No. 1, pp. (137-143).

Quigley HA, Dunkelberger GR, Green WR. (1988). Chronic human glaucoma causing selectively greater loss of large optic nerve fibers. *Ophthalmol*,Vol. 95, No. 3, pp. (357–363).

Quigley HA. (1999). Neuronal death in glaucoma *Prog Retin Eye Res,* Vol. 18, No. 1, pp. (39-57).

Rockhill RL, Daly FJ, MacNeil MA, Brown SP, Masland RH. (2002). The diversity of ganglion cells in a mammalian retina. *J Neurosci*, Vol. 22, No. 9, pp. (3831-3843).

Ross JL, Shuman H, Holzbaur ELF, Goldman YE. (2008). Kinesin and dynein-dynactin at intersecting microtubules: motor density affects dynein function. *Biophy J,* Vol. 94, No. 8, pp. (3115-3125).

Roth E. (1997). Oxygen free radicals and their clinical implications. *Acta Chir Hung*, Vol. 36, No.1-4, pp. (302–305).

Salvatore S, Vingolo EM. (2010). Endothelin-1 Role in Human Eye: A Review. *J Ophthalmol,* 354645. Saxena S, Caroni P. (2007). Mechanisms of axon degeneration: from development to disease. *Prog Neurobiol*, Vol. 83, No.3, pp. (174-191).

Schmidt KG, Bergert H, Funk RHW. (2008) Neurodegenerative Diseases of the Retina and Potential for Protection and Recovery. *Curr Neuropharmacol*, Vol. 6, No. 2, pp. (164–178).

Schlamp CL, Li Y, Dietz JA, Janssen KT, Nickells RW. (2006). Progressive ganglion cell loss and optic nerve degeneration in DBA/2J mice is variable and asymmetric. *BMC Neurosci,* Vol. 3, No. 7, pp. 66.

Seif GI, Nomura HM, Tator C H. (2007). Retrograde axonal degeneration "dieback" in the corticospinal tract after transection injury of the rat spinal cord: a confocal microscopy study. *J Neurotrauma,* Vol. 24, No. 9, pp. (1513-1528).

Seminara AR, Ruvolo PP, Murad F. (2007). LPS/IFNgamma-induced RAW 264.7 apoptosis is regulated by both nitric oxide-dependent and -independent pathways involving JNK and the Bcl-2 family. *Cell Cycle,* Vol. 6, No. 14, pp. (1772-1778).

Shen Y, Liu XL, Yang XL. (2006) N-methyl-D-aspartate receptors in the retina. Vol. 34, No. 3, pp. (163-179).

St Clair EG, Anderson SJ, Oltvai ZN. (1997). Bcl-2 counters apoptosis by Bax heterodimerization-dependent and -independent mechanisms in the T-cell lineage. *J Biol Chem,* Vol. 272, No. 46, pp. (29347-29355).

Sucher NJ, Lipton SA, Dreyer EB. (1997). Molecular basis of glutamate toxicity in retinal ganglion cells. *Vision Res,* Vol. 37, No. 24, pp. (3483-3493).

Tartaglia LA, Ayres TM , Wong GHW, Goeddel DV. (1993). A novel domain within the 55 kd TNF receptor signals cell death. *Cell,* Vol.74, No. 5, pp.(845–853).

Takahashi A, Masuda A,Sun M, Centonze VE, Herman B. (2004) Oxidative stress-induced apoptosis is associated with alterations in mitochondrial caspase activity and Bcl-2-dependent alterations in mitochondrial pH (pHm). *Brain Res Bull*, Vol. 62, No. 6, pp. (497-504).

Tatton NA, Tezel G, Insolia SA, Nandor SA, Edward PD, Wax MB. (2001). In situ detection of apoptosis in normal pressure glaucoma. a preliminary examination. *Surv Ophthalmol*, Vol. 45, No. 3, pp. (268-272).

Tezel G. (2006). Oxidative Stress in Glaucomatous Neurodegeneration: Mechanisms and Consequences. *Prog Retin Eye Res*. Vol. 25, No. 5, pp. (490–513).

Tezel G. (2008). TNF-α signaling in glaucomatous neurodegeneration. *Prog Brain Res.* Vol.173, pp. (409-421).

Tezel G, Li LY, Patil RV, Wax MB. (2001). TNF-alpha and TNF-alpha receptor-1 in the retina of normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci*, Vol.42,No.8, pp. (1787-1794).

Tezel G, Yang X, Luo C, Peng Y, Sun SL, Sun D. (2007). Mechanisms of Immune System Activation in Glaucoma: Oxidative Stress-Stimulated Antigen Presentation by the Retina and Optic Nerve Head Glia. *Invest Ophthalmol Vis Sci,* Vol. 48, No2 pp. (705-714).

Tezel G, Yang X, Yang1 J, Wax MB. (2004) Role of tumor necrosis factor receptor-1 in the death of retinal ganglion cells following optic nerve crush injury in mice. *Brain Res,*Vol. 996, No.2, pp. (202–212).

Tezel G, Wax MB. (1999) Inhibition of caspase activity in retinal cell apoptosis induced by various stimuli in vitro. *Invest Ophthalmol Vis Sci,* Vol. 40, No.11, pp. (2660-2667).

Tezel G, Wax MB. (2003). Glial modulation of retinal ganglion cell death in glaucoma. *J Glaucoma*, Vol.12, No.1, pp. (63-68).

Tezel G, Wax MB. (2004). Hypoxia-inducible factor 1alpha in the glacomatous retina and optic nerve head. *Arch Ophthalmol*, Vol.122 No. 9, pp.(1348-1356).

Tezel G, Trinkaus K, Wax MB. (2004). Alterations in the morphology of lamina cribrosa pores in glaucomatous eyes. *Br J Ophthalmol*, Vol. 88, No. 2, pp. (251–256).

Tezel G, Yang X. (2004). Caspase-independent component of retinal ganglion cell death, in vitro. *Invest Ophthalm Vis Sci,* Vol.45, No 11, pp. 4049-4059.

John E. (1987)The retina: an approachable part of the brain

Trivino A, Ramirez JM, Ramirez AI, Salazar JJ, Garcia- Sanchez J. (1992) Retinal perivascular astroglia: an immunoperoxidase study. *Vision Res*, Vol. 32, No. 9, pp. (1601-1607).

van Engeland M, Nieland LJ, Ramaekers FC, Schutte B, Reutelingsperger CP. (1998). Annexin V-affinity assay: a review on an apoptosis detection system based on phosphatidylserine exposure. *Cytometry,*. Vol. 31, No.1, pp. (1-9).

Tombran-Tink J, Barnstable CJ. (2008). Visual Transduction and Non-Visual Light Perception.

Wang L, Dong J, Cull G, Fortune B, Cioffi GA. (2003) Varicosities of Intraretinal Ganglion Cell Axons in Human and Nonhuman Primates. *Invest Ophthalmol Vis Sci*, Vol. 44 No. 1, pp. (2–9).

Wässle H. Parallel processing in the mammalian retina. (2004). *Nat Rev Neurosci*, Vol. 5, No.10, pp. (747-757).

Whiteman AL, Klauss G, Miller PE, Dubielzig RR. (2002). Morphologic features of degeneration and cell death in the neurosensory retina in dogs with primary angle-closure glaucoma. *Am J Vet Res*, Vol. 63, No. 2, pp. (257-261).

Whitmore AV, Libby RT, John SWM. (2005). Glaucoma: Thinking in new ways—a rôle for autonomous axonal self-destruction and other compartmentalised processes. *Prog Retin Eye Res*, Vol. 24, No. 6, pp. (639-662).

Wong KW, Dunn FA, Graham DM, Berson DM. (2007) Synaptic influences on rat ganglion-cell photoreceptors. *J Physiol*, Vol.582, No. 1, pp. (279–296).

Wong VH, Bui BV, Vingrys A J. (2011). Clinical and experimental links between diabetes and glaucoma. *Clinical and Experimental Optometry*, Vol. 94, pp. 4–23.

Wyllie AH. (1997). Apoptosis: an overview. *Br Med Bull*, Vol. 53, No. 3, pp. (451-465).

Wyllie AH. (1986). What is apoptosis? *Histopathology,* Vol.10, No. 9, pp. (995-998).

Yan X, Tezel G, Wax MB, Edward DP. (2000) Matrix metalloproteinases and tumor necrosis factor α in glaucomatous optic nerve head. *Arch Ophthalmol,* Vol. 118, pp.(666-673)

Yin XM. (2000) Signal transduction mediated by Bid, a pro-death Bcl-2 family proteins, connects the death receptor and mitochondria apoptosis pathways. *Cell Res*, Vol. 10, No. 3, pp. (161-167).

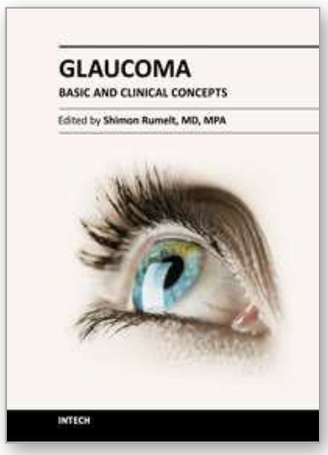
Zhang C, Rosebaum DM, Shaikh AR, Li Q, Rosebaum PS,Pelham DJ,Roth S. (2002) Ischemic preconditioning attenuates apoptotic cell death in the rat retina. *Invest Ophthalmol Vis Sci*, Vol. 43, No. 9, pp. (3059–3066).

Zhang L, Zhang M, Yang S, Cao Y, Zhang SB, Yin L, et al. (2010). A new biodosimetric method: branched DNA-based quantitative detection of B1 DNA in mouse plasma. *Br J Radiol,* Vol. 83, No. 992, pp. (694 - 701).

Zhang Y, Li X, Becker KA, Gulbins E. (2009). Ceramide-enriched membrane domains-structure and function. *Biochim Biophys Acta*, Vol. 1788, No1, pp.(178-183).

Zimmermann KC, Bonzon C, Green DR. (2001). The machinery of programmed cell death. *Pharmacol Ther*, Vol. 92, No. 1, pp. (57-70).

Zoratti M, Szabo I, De Marchi U. (2005). Mitochondrial permeability transitions: how many doors to the house? *Biochim Biophys Acta,* Vol. 1706, No. 1-2, pp. (40-52).



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