Pathophysiology of Neurodegeneration in Retinal Diseases as Glaucoma and Diabetic Retinopathy and Potential Mechanisms of Retinal Neuroprotection

Anindya Sen[*1], Asima Adak[2]

[*1]Professor, Department of Electronics and Communication Engineering, Heritage Institute of Technology, Kolkata, West Bengal, India,

[2]Assistant Professor, Department of Electronics and Communication Engineering, Heritage Institute of Technology, Kolkata, West Bengal, India

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ABSTRACT

Retinal cell neurodegeneration relates to glaucoma, diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa. Early stages of such disease are preceded by retinal neurodegeneration or angiogenesis in retinal vessels. It is a well established fact that total or partial vision loss is caused by abnormal retinal degeneration of the photo receptors or the inner retinal neurons, as well as unusual growth of cells forming extra retinal venules and arterioles. However the reasons and mechanisms behind the abnormal retinal cell deaths or unusual cell growths remains unknown and is considered an area of active research.

This paper reviews contemporary research on retinal disease citing reasons for a typical retinal vessel cell growth, unusual death of retinal cells, and ways to repair the retinal damaged cells under various degrees of impairment.

Knowledge about the mechanism behind the sudden change in cell pattern behavior will help to track and better understand the reasons behind early start and rate of progression for such retinal diseases, and how to harness an quick control over disease progression, with help to prognosis and complete recovery.

Neurodegeneration of RGC (retinal ganglion cell) is due to Glutamate excitoxicity and a few other factors. Neovascularization occurs from increased VEGF presence in vitreous of eye. Precise cellular repair is done on retina using derived information.

Keywords – Glaucoma, diabetic retinopathy, macular degeneration, retinitis pigmentosa and neuro degeneration.

I. INTRODUCTION

Vision loss is caused by the death of retinal neurons, however the causes and the mechanisms leading to neuronal death are far from being fully elucidated. Neurodegeneration is a distinctive trait of retinal pathologies like Glaucoma, diabetic retinopathy, age related macular degeneration, and retinitis

pigmentosa. Both apoptosis and necrosis with retinal cells occur under different circumstances and involve different steps, which results in the loss of the sensory cells of the retina, the photoreceptors. Angiogenesis with the retinal cells due to VEGF (vascular endothelial growth factor) plays a critical role in growth of abnormal retinal vessels. Ongoing research is mostly dedicated with detection of retinal disease relating outer features and boundary parameters [1-9]. This work relates the pathophysiology of retinal neurodegeneration with the progression of ocular disease.

1.1. Neural paths

The cells of the visual pathways are organized to handle information about line, contrast, movement and color. They do not however, form a picture in the brain. Rather they form a spatial and temporal pattern of electrical activity. Neuron is the specialized nerve cell used for transmitting information through electrical and chemical signals. Three main parts of neuron are the i) cell body (soma or neurons core), ii) Axon (tail like structure which joins the cell body at a junction called axon hillock), and iii) Dendrites (fibrous roots that branch out of the cell body). Neurons signals among each other using AP (action potentials) which is generated as a shift in the neurons electric potential caused by the flow of ions in and out of the neural membrane.

Chemical and electrical synapses can be triggered by APs where a synapse (Figure 1) is a gap between two neurons. Presynaptic endings, synaptic clefts, and post synaptic endings make up synapses. Synapses might be chemical or electrical in nature. Neurons interact via AP using the synaptic gap in a chemical synapse. The AP is carried along the axon to the presynaptic end. This causes the release of neurotransmitters, which are chemical messengers. These chemicals pass through the synaptic cleft and bind to receptors in the dendrite's post synaptic terminal. The postsynaptic

neuron can be excited by neurotransmitters, causing it to create its own potential. They can also block the post synaptic neuron, which results in no AP being formed.

Retinal neurons transmit electrical signals that is converted from light, from the lens to brain, using AP.
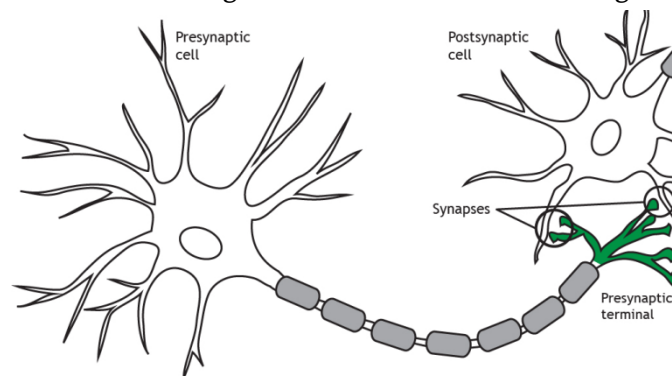

Figure 1. The terminals of a presynaptic neuron in close proximity with a post synaptic unit, displaying the synapse.

1.2. Visual setup

The lens divides the anterior chamber, which contains the aqueous humor, from the posterior chamber, which contains the viscous vitreous fluid. These two colorless substances enable light to pass through the eye and onto the retina. The aqueous humor is generated by the ciliary muscle's unique vascular tissue. Increased pressure within the eye occurs when the aqueous humor is generated quicker than it is cleared. This is linked to damage to the eye's nerve fibres and causing visual loss, giving rise to a condition known as glaucoma.

Starting from the rear to the front of the retina, where light is initially incident, the retinal nerve fibre layer (RNFL) is made up of rods, cones, bipolar cells, and ganglion cells. Defects in the retinal nerve fibre layer have been recognized as an essential diagnostic indicator of glaucoma for decades, as they manifest clinically early in the disease with anticipation of vision loss. Traditional clinical procedures such as ophthalmoscopy and photography, on the other hand, may identify a minimum loss of RNFL of 50 to 70 mm, or up to 50% of normal tissue thickness. As a result,

new advances in imaging techniques are intended to improve glaucoma identification and care by providing reliable, sensitive, and quantitative measurements of the RNFL [10].

Scanning laser polarimetry (SLP) and optical coherence tomography (OCT) are the two most commonly used techniques for this purpose.

1.3. Cellular road map for vision

Because of the forms of their light-sensitive tips, photoreceptor cells in the retina are referred to as rods and cones. The photoreceptor cells' light-sensitive part faces away from the incoming light. The rods are incredibly sensitive and respond to very low levels of illumination, whereas the cones are much less sensitive and only respond to light that is brighter than twilight.

Photopigment molecules absorb light and are found in photoreceptors. One of the four photopigments in the retina is rhodopsin, which is found in the rods and one in each of the three types of cones. A protein called opsin surrounds and binds the chromophore molecule in each photo pigment. The chromophore, or light-sensitive portion of the photopigment, is retinal, a vitamin A variation, and is identical in each of the four photopigments. Each of the four types has a different opsin (Figure 2) [11] that filters the light that reaches the retina. Each of the four photopigments absorbs light more effectively at a different region of the visible spectrum due to the varied opsins. One of the photopigment may absorb wavelengths in the range of red light best, whereas another absorbs wavelength in the range of green light best.

Photopigments are arranged in layered membranes parallel to the retina within photoreceptor cells. Each photoreceptor's repeated layers of membranes may contain over a billion photopigment molecules, making it effective to trap light.

After a molecule of retina is activated by light it changes form. This alteration makes it easier for protein opsin to attach to a G protein, which activates the phosphodiesterase enzyme. This enzyme then hydrolyzes cyclic GMP (cyclic 3',5'-guanosine monophosphate, or cGMP), lowering its concentration. Photoreceptor cyclic GMP concentrations are low in the presence of light, and plasma-membrane ion channels mediated by this second messenger are closed. The cell hyperpolarizes as the plasma membrane continues to push calcium ions ($Ca2++$) out of the photoreceptor.
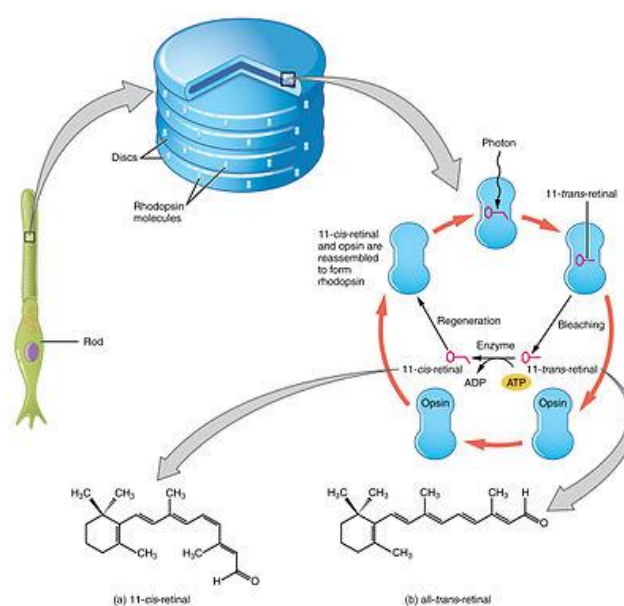

Figure 2. A photon of light is absorbed by the retinal molecule inside an opsin protein. When a photon is absorbed, the retinal molecule transforms from its 11-cis-retinal isomer to its all-trans-retinal isomer state. This shift in retinal structure pushes against the outer opsin protein, triggering a signal cascade that could lead to chemical signaling being delivered to the brain as visual perception. The body next re-shapes the retinal molecule back to its original shape, allowing signaling to resume.

Hyperpolarization is carried passively to the photoreceptor cell's terminal, where it slows the release of neurotransmitters from the cell. The photoreceptor's synapse neurons receive a signal from

the lower neuro transmitter concentration that light has been absorbed by the receptor. The receptor potential of photoreceptors is hyper-polarized in response to light.

In the dark, photoreceptors have a high level of cyclic GMP. In the dark, the plasma-membrane ion channels are open, allowing Na+ and Ca2+ to enter the cell and depolarize the membrane, resulting in increased transmitter release. The retinal molecule changes form back to its resting shape after being activated by light. This is accomplished through enzyme-mediated activities. Intracellular Ca2+ regulates cyclic GMP levels, allowing for light adaption.

The activation of photopigments in cone receptor cells is the first step in colour vision. Human retinas include three types of cones, each of which contains photopigments that are sensitive to red, green, or blue light. Different wavelengths of light absorb and respond optimally to certain pigments. The red pigment is frequently referred to as the yellow pigment because it is more sensitive to the wavelengths that correlate to yellow. Although each type of cone responds best to light of a specific wavelength, it can also be activated by light of other wavelengths. The three cone kinds are activated to varying degrees for any given wavelength of the visible spectrum. The M type ganglion cells respond to a wide range of wave lengths for color vision. They gather information from all three types of cones and transmit a broad brightness signal rather than a single color. Colors are coded by P type ganglion cells. They're also known as opponent color cells since one type of cone receptor receives excitatory input while another receives inhibitory input. As a result, when stimulated by blue light, a cell's rate of firing may be highest, followed by red and white light in decreasing order for rate of firing.

People with color blindness lack either red or green pigments, making it difficult to distinguish between red and green.

Rods and cones are at the start of the visual neuronal circuits. These photoreceptors communicate with one another as well as second-order neurons such as bipolar cells (Figure 3). Color, intensity, form, depth, and movement are all properties of visual images that bipolar cells respond to differently. These different properties are transported all the way to the cerebral cortex by parallel visual pathways. Both neurons that transmit information horizontally from one section of the retina to another (provide direct link between photoreceptor terminals) and ganglion cells synapse (still within the retina) are the bipolar cells. Amacrine cells mediate lateral interactions between bipolar cell terminals and the dendrites of ganglion cells. The parvocellular (P) and magnocellular (M) types of ganglion cells are concerned with various aspects of the visual signal. The parvocellular (P) type is best suited to dealing with fine details and responds well to small stationary stimuli in the centre of the visual image. The magnocellular (M) type is most suited to assessing the physical aspects of a stimulus and detecting motion since it responds to larger moving stimuli towards the periphery of the visual image. Color information is also transmitted by the P cells. Action potentials are produced by ganglion cells in response to activation, whereas graded potentials are produced by the rods, cones, and other retinal neurons.

The output of the retina to the optical nerve is formed by the axons of the ganglion cells (Figure 3). The lateral geniculate nucleus in the thalamus is where the information from P and M ganglion cells is kept separate. Optical nerve fibres project to many structures in the brain, the majority of which pass to the lateral geniculate nucleus in the thalamus. AP is sent from the lateral geniculate nucleus to the visual cortex. The visual cortex is divided into multiple sub

divisions, each of which represents the whole visual field that is stimulated by the retina at any one time.

There is a classification of data and a point-to-point projection of a certain group of data. The transmission of information from the retina to the visual cortex follows a perfect point-to-point projection pattern, with adjacent retinal regions projecting to adjacent visual cortex subdivisions.

The visual cortex preserves the separate individual functions of cells that began in the retina. The lateral geniculate is responsible for separating and relaying distinct types of visual information from the retina to different cortical zones. As a result, most neurons in one sub division of the neural visual cortex respond solely to stimuli that are oriented in a specific direction in the visual field, a trait that is critical in the development of an object's form. Movement of an object across the visual field is most receptive to neurons in another subdivision. In addition, some neural groupings may respond best to color, while others may respond exclusively to certain inputs from both eyes, which could be a clue to depth perception. The input received by different kinds of ganglion cells determines the functional distinctions between various parts of the visual cortex.

Figure 3: Structure of the retina. (A) Section of the retina showing overall arrangement of retinal layers.

(B) Diagram of the basic circuitry of the retina. A three-neuron chain—photoreceptor, bipolar cell, and ganglion cell—provides the most direct connection to optic nerve for transmitting visual information to the brain [41].

Neural circuits also organize what and where visual information is sought. Even after leaving the visual cortex, some of the information is maintained independent. Some routes send data straight from the visual cortex to the temporal lobe, which processes the identification of objects in the visual field - assessing the "what" of the visual stimuli. Other pathways lead to the parietal lobe, which analyses the "where" of the visual stimuli by processing information about the localization of objects in the visual field. The frontal cortex receives information from both the temporal and parietal lobes and uses it to direct "activities." As a result, distinct pieces of visual information are conveyed in parallel routes and processed in a variety of ways in different sections of the cerebral cortex before being reintegrated to produce conscious sight sensation.

The suprachiasmatic nucleus, which controls a number of circadian behaviours, receives a portion of the visual input. This nucleus serves as a "biological clock," synchronizing neural clocks based on diurnal cycles of light intensity. Other visual information is sent to the brain stem and cerebellum, where it helps with eye and head coordination, gaze fixation, and pupil constriction. This is brief overview of human visions regular cellular road map to brain.
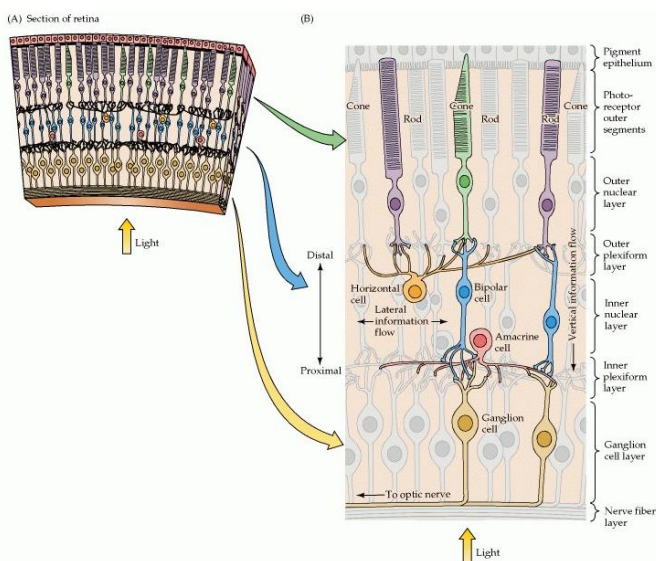
II. GLAUCOMA OCCURRENCE

The anterior chamber, which contains aqueous humor, and the posterior chamber, which contains vitreous humor, in the eye are separated by a lens. The transmission of light from the front of the eye to the retina is enabled by these two colorless substances. The aqueous humor is made up of vascular tissue that resides above the ciliary muscle. In rare

cases, the aqueous humor is generated quicker than it is cleared, resulting in an increase in eye pressure. Glaucoma causes an increase in intraocular pressure. Raised intraocular pressure is the primary issue or pathology in glaucoma. The optic nerve is compressed and damaged by this increased pressure. When the optic nerve is injured, it stops transmitting visual information to the brain, causing vision loss.

The exact pathophysiology that contributes to this optic nerve (Figure 4, 5) injury is not clearly understood and needs investigation. The increased pressure on the retina is thought to cause the sensitive retina's cells and nerve ganglions to die (retinal ganglion apoptosis). This increased pressure, also compress the retina's small blood veins, depriving it of nourishment. This leads to a clinically gradual loss of peripheral vision and, eventually, eyesight [12].
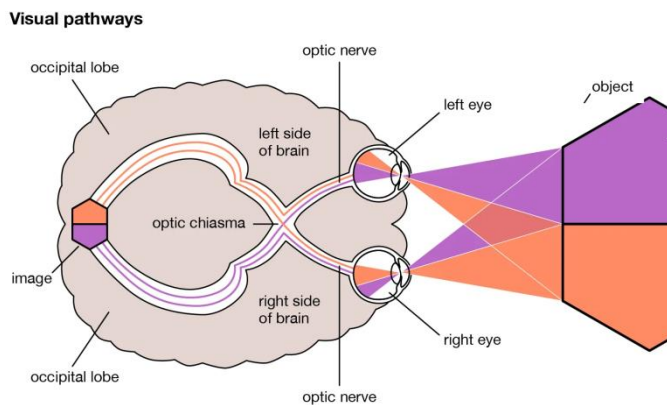

Figure 4: Depicts the optic nerve, connecting the retina to the visual cortex in the back of the brain. Increased intracranial pressure, tumours, and increased vascular pressure in the eye are some mechanisms by which the optic nerve gets damaged, impairing vision [45].

For patients with normal tension glaucoma there is no increase in intraocular pressure. These patients have problems with retinal blood vessels and perfusion, as well as immune system derangements (autoimmune causes), which could result in optic nerve injury.

According to certain research, the optic nerve heads (Figure 5) of these patients are very susceptible, with damage happening at considerably lower intraocular pressures than in healthy people. As a result, drugs that lower intraocular pressure may be beneficial in their treatment.

2.1. Raised intraocular pressure

Normally, the aqueous humor aids in nutrient delivery and waste elimination for the retinal cells. The ciliary body epithelium produces it, which drains out through the trabecular meshwork at the anterior chamber angle.
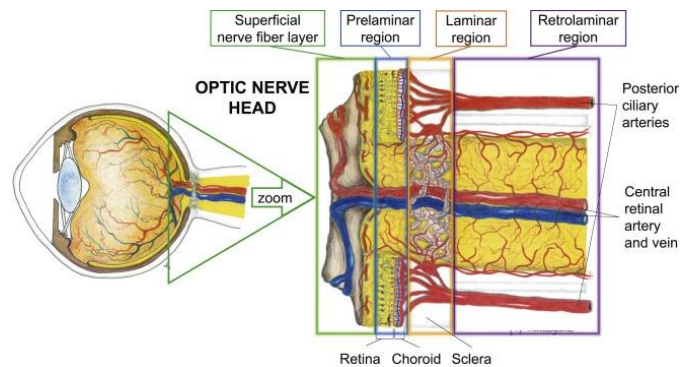

Figure 5. Optic nerve head in detail

When this flow is disturbed, pressure builds up inside the eye. This can happen in one of two ways: -
· Blockage of the trabecular meshwork drainage (in open angle glaucoma)
· Narrowing of the draining angle (in angle closure glaucoma)

2.2. Glaucoma with age

The most common cause of aqueous flow interruption is old age. The trabecular meshwork cells become less effective with age, resulting in an accumulation of aqueous humour in the anterior chamber of the eye. The lens also hardens and grows in size as it gets older. The anterior chamber of the eye is narrowed even more, and the anterior chamber angle is physically narrowed. Although much of the

pathophysiology is unknown, age over 40, African American or Hispanic heritage, family history, myopia, and elevated intraocular pressure (IOP) are all risk factors for glaucoma [13]. The precise process by which elevated IOP affects glaucomatous changes in the eye is not clearly understood.

For decades, retinal nerve fibre layer (RNFL) defects have been recognized as an important diagnostic sign of glaucoma because they appear clinically early in the disease and are predictive of vision loss later on [14–16]. Traditional clinical procedures such as ophthalmoscopy and photography, on the other hand, may identify a minimum loss of RNFL of 50% to 70% in terms of original thickness, or up to 50% of normal tissue thickness [17, 18]. As a result, current advances in imaging techniques are hoped to improve glaucoma identification and management by providing accurate, sensitive, and quantitative assessments of the RNFL. However this do not provide underlying reason about the cause of the defects in the RNFL layer.

2.3. Effect of retinal ganglion cell (RGC)

Glaucoma is a category of diseases also characterized by the death and degeneration of retinal ganglion cells (RGCs). Mitochondrial malfunction and oxidative stress both have a role in the mortality of glaucomatous RGCs. Mitochondrial uncoupling protein 2 (Ucp2) is a well-known oxidative stress regulator that improves cell survival in acute oxidative stress scenarios. However, the effect of Ucp2 on cell survival in subacute and chronic neurodegenerative diseases is yet unknown.

Degeneration of the optic nerve (the second cranial nerve) due to direct or indirect damage to these particular retinal ganglion cells, whose axonal projections collectively make up the optic nerve, results in optic atrophy [46]. The function of the optic nerve is to carry visual data from the retina of the eye to the lateral geniculate body (a relay station in the centre of the brain) for transmission to a cortical area at the back of the brain called the occipital cortex. Common causes of optic atrophy include glaucoma, or tumors that press on the optic nerve, vascular diseases, trauma, and exposure to various drugs and toxins.

The retinal ganglion cell (RGC) is the type of neuron found near the inner surface of the retina (the ganglion cell layer). Bipolar cells and retina amacrine cells are two types of intermediary neuron that receive visual information from photoreceptors (Figure 3). Amacrine cells in the retina, particularly narrow field cells, are critical for forming functional subunits within the ganglion cell layer and allowing ganglion cells to detect a small dot moving a short distance [33]. Retinal ganglion cells jointly transfer image-forming and non-image-forming visual information from the retina to numerous locations in the thalamus, hypothalamus, and mesencephalon in the form of action potential.

The size, connections, and reactions to visual stimulation of retinal ganglion cells vary significantly, but they always have a long axon that extends into the brain as a defining feature. The optic nerve, optic chiasm, and optic tract are all made up of axons. A tiny number of retinal ganglion cells do not contribute to vision but are photosensitive; their axons form the retinohypothalamic tract and contribute to circadian rhythms and the pupillary light reflex, which causes the pupil to shrink. RGCs are the sole output neurons in mammals that transport vision signals from the eyes to the brain, and they are divided into at least 40 categories based on morphological, functional, and genetic characteristics.

Glaucoma is a chronic ocular neuropathy marked by axon degradation and cell death in RGCs. Increased pressure in the eye leads to glutamate-induced excitotoxicity, according to one theory for glaucoma damage.

2.4. RGC and Glutamate excitotoxicity

The neurons that carry visual signals from the eyes to the brain involve retinal ganglion cells (RGCs), bipolar cells, and amacrine cell. Degeneration in these cells causes blindness in many retinal illnesses, and growing data suggests that RGCs are type-specific in their vulnerability to diverse traumas. Glutamate excitotoxicity is a degenerative process in which neurons are injured and die as a result of excessive glutamate receptor stimulation, by influx of extracellular calcum, and it is a key factor in the death of neurons in many CNS (central nervous system) and retinal illnesses.

In many retinal illnesses, such as glaucoma, diabetic retinopathy, optic nerve damage, and retinal ischemia, glutamate excitotoxicity is assumed to play a significant role in retinal ganglion cell death. A increasing body of evidence suggests that mitochondrial dysfunction plays a critical role in the aetiology of glaucoma [19–30]. RGC loss has been shown to be caused by mitochondrial malfunction in animal and cultured cell experimental glaucoma models [31, 32].

2.5. Neovascularization

Areas of ischemic retina which characterize a number of ocular pathologies, (like diabetic retinopathy, and retinopathy of prematurity) would produce an unknown agent that stimulates the growth of new blood vessels. Increase of vascular endothelial growth factors (VEGF) [34] in the vitreous of eye has been found in patients with proliferative diabetic retinopathy. VEGF is associated with new vessel growth, is driven by hypoxia, and is able to induce permeability [35]. Several studies have measured levels of proangiogenic molecules in vitreous specimens and shown that patients with retinal neovascularization have elevated levels of several factors including VEGF, insulin like growth factor-1

(IGF-1), interleukin-8, placental growth factor, hepatocyte growth factor, platelet derived growth factor, and leptin. While all these growth factor contribute to the development of the retinal neovascularization, there is strong evidence to support that VEGF plays the main role. Studies suggest that pigment epithelium-derived factor (PEDF) may suppress occular angiogenesis.

Another explanation of ocular neovascularization is by glycosylations of proteins molecules in mammals [36]. The study points to growing evidence showing that glycosylation influences the process of angiogenesis and impacts activation, proliferation, and migration of endothelial cells as well as the interaction angiogenic endothelial cells with other cell types necessary to form blood vessels. Evidence from studies suggest that the members of the galectin class of b-galactoside-binding proteins modulate angiogenesis by novel carbohydrate-based recognition systems involving interactions between glycams of angiogenic cell surface receptors and galectins.

2.6. Cellular repair by tissue engineering

One of the major glial component of the retina are Müller glia, and they are one of the last retinal cell types to be born during retinal development, however their main use is to maintain homeostasis and integrity. The Müller glia structure present in fish, birds and mammals are similar and share function. The main difference between Müller glia in fish and those in mammals is their ability to participate in retinal repair [37]. Unlike those present in birds and mammals, fish Müller glia respond to retinal injury by undergoing a reprogramming event that enables them to acquire the properties of a retinal stem cell and generate multipotent progenitors for repair. Papers understanding the mechanisms underlying Müller glial cell reprogramming and retina regeneration in fish along with studies of Müller glia in other species, such as birds and mammals, may reveal novel

strategies for stimulating retina regeneration in humans.

Tissue engineering is used to repair cells of a damaged retina. Here the first step is to find a group of reliable cells which could generate the cell matrix and the an extra cellular matrix resembling that of the native tissue. Stem cells are widely used in such applications, as they can adapt to a new environment by proliferating and differentiating into various types of mature cell that form tissues. Thus stem cell therapy can replace damaged retinal cell by replacing them with new cells [38].

The replacement of retinal tissue cells lost due to a major disease is also done by [39] retinal pigment epithelial (RPE) cell replacement. There is evidence of promising potential applications for treating retinal degenerative diseases using this cell therapy. For example with dry age related macular degeneration (AMD), the formation of drusen is observed between the retinal pigment epithelial (RPE) and Bruch's membrane (BM), causing RPE and photoreceptor cell degeneration. Wet AMD is characterized by the invasion of abnormal, leaky choroidal blood vessels and the accumulation of macrophages in the RPE cell layer, which also lead to degeneration of the RPE and photoreceptor cells. Hence the proposed RPE cell replacement therapy is applied in such cases and found to give satisfactory results.

In [40] there is an example of regenerating the whole destroyed retina of a zebra fish using retinal ganglion cell regeneration method. This is a spatiotemporal process of embryonic ganglion cell neurogenesis.

III.CLASSIFICATION

Vision loss is primarily caused by the death of retinal neurons, and the causes and the mechanisms leading to neuronal death is divided into three broad classes; i) effects on rods and cones, ii) effects on the bipolar cells, iii) effect on retinal ganglion cells.

3.1. Effect of Rods and Cones

A rod cell is sensitive to respond to a single photon of light [42 - 43] and nearly hundred times more sensitive to a single photon than cones. Since rods require less light to function than cones, they are the primary source of scotopic vision (visual information at night). Cone cells, on the other hand, require tens to hundreds of photons to become activated. Additionally, multiple rod cells converge on a single interneuron, collecting and amplifying the signals. However, this convergence comes at a cost to visual acuity (or image resolution) because the pooled information from multiple cells is less distinct than it would be if the visual system received information from each rod cell individually [41].

Retinitis pigmentosa in all forms, is an genetic disease, where a huge number of cell mutations cause degeneration of the rod photoreceptors [42-43] first, followed by slow and characteristic degeneration of the cone photoreceptors. The mechanism of the rod cell death depends on the type of the cell being muted. Also the rate of degeneration of the rod cells is an important prognostic feature as the degeneration of the cone cells starts only after total degeneration of rod cells. Death of only the rod cells causes night blindness, but the death of the cones causes blindness in daylight. Hence it is important to determine how it occurs. There is a misbalance in oxygen usage after complete degeneration of the rod cells. As the rods cells do not exist so there is reduced oxygen usage in that area leaving high tissue levels of O2 in the outer retina area. The excess oxygen stimulates production of superoxide radical in cone cells by mismatches in the electron transport chain in mitochondria and by stimulation of NADPH oxidase activity in cytoplasm. The high levels of superoxide radicals override the antioxidant defense system and generate more reactive species including peroxynitrite which is extremely damaging and difficult to detoxify. This causes progressive oxidative damage in cones, contributing to cone cell death and loss of function

because drugs or gene transfer that reduce oxidative stress promote cone survival and maintenance of function. Compared with aqueous humor samples from control patients, those from patients suffering with Retinitis pigmentosa show significant elevation of carbonyl content on proteins indicating oxidative damage and a reduction in the ratio of reduced to oxidized glutathione indicating depletion of a major component of the antioxidant defense system from ongoing oxidative stress.

3.2. Effect of Retinal Bipolar Cells (RBC)

Retinal [p2] bipolar cells serves as an intermediary between the rods, cones and the retinal ganglion cells, the amacrine cells. Differences in the glutamate subtypes given by different classes of bipolar cells is used to segregate visual information into two parallel pathways, the ON and OFF pathway. In particular, the ON pathway is mediated by rod bipolar cells (RBCs) which receive input exclusively from rods, and ON cone bipolar cells (ON-CBCs) which collect input from cones, both respond to light increments with membrane depolarization.

Retinal bipolar cells, which send visual signal to RGCs, have been largely overlooked in previous studies of glaucoma. This study [], demonstrated that a decline of the presynaptic rod bipolar cells (RBCs) response precedes RGCs loss and a decrease of protein kinase Cα (PKCα) protein expression in RBCs dendrites, using whole-cell voltageclamp, electroretinography (ERG) measurements, immunostaining and co-immunoprecipitation.

In humans, several clinical studies have reported scotopic ERG changes in advanced glaucoma 35–37. This study[] show that RBCs are functionally affected as early, or earlier than RGCs, and provide evidence that the early dysfunction of RBCs is associated with the degradation of PKCα in RBCs, possible through the complex of NR2B–PICK1–PKC dependent ubiquitin-proteasome system.

Glaucoma has traditionally been considered a disease that is limited to the loss of RGCs. However, recent studies suggest that retinal pathology in glaucoma may involve degeneration of retinal amacrine cells[38–40]. This study provide evidence that the cellular function of RBCs was disrupted in several mouse models, of neurodegeneration, as the function of RBCs (presented as the ERG b wave) was significant affected prior to any observable dysfunction in RGCs. Using patch-clamp recording, we also show that the rod, but not cone bipolar cell transduction current was diminished. These results suggest that examination of RBCs, in particular the ERG b wave, could potentially be an early diagnostic approach for glaucoma patients.

3.3 Effect of Retinal Ganglion Cells (RGC)

The RGC forms the interconnection between the rods, cones, RBCs and the optic nerve head. Their axons, which make up the optic nerve, project from the retina to the brain (Figure 3).
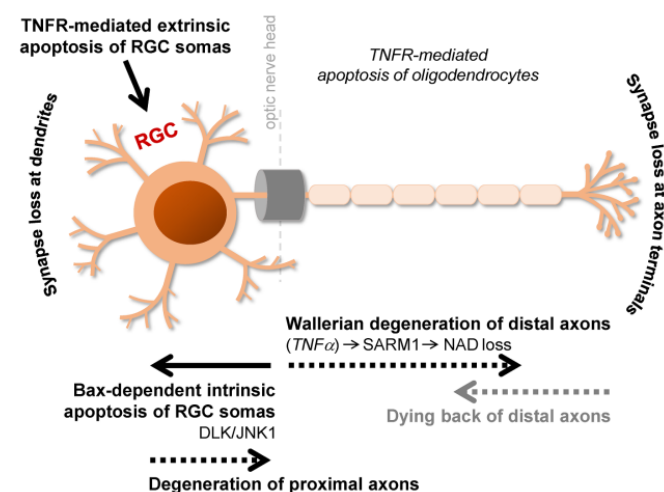

Figure 6: Molecular actions regulate somatic and axonal degeneration of RGCs in glaucoma. Glaucomatous neurodegeneration involves RGC axons, somas, and synapses at dendrites and axon terminals. Optic nerve head is a critical site of injury, and early axonal insults may originate distal and proximal

signals for axonal and somatic degeneration of RGCs. A distal axonopathy is processed through Wallerian degeneration and dying back, while degeneration of proximal axons is secondary to the apoptosis of RGC somas. The apoptotic death of RGCs is processed through intrinsic/mitochondrial and extrinsic/dead receptor-mediated pathways [47].

Progressive degeneration of retinal ganglion cells (RGCs) in glaucoma involves somatic apoptosis in the retina, axonal degeneration in the optic nerve, and synaptic loss at dendrites and axon terminals [47]. There is an interconnected network of pathogenic processes for RGC degeneration. The degradation process includes biomechanical disruption of axonal transport, neurotrophin deprivation, mitochondrial dysfunction,metabolic failure, oxidative stress, calcium imbalance, vascular dysregulation, and neuroinflammation. It is increasingly recognized that beyond IOP and age-related stress, many other factors affect the vulnerability of RGCs to biomechanical, vascular, metabolic, oxidative, and inflammatory injury in glaucomatous eyes. Despite available molecular programs for somatic and axonal degeneration, mitochondrial dysfunction and glia-driven neuroinflammation present interdependent processes with widespread impacts in the glaucomatous retina and optic nerve. The optic nerve head is a critical site of injury in glaucoma, where IOP-dependent or -independent insults can originate distal and proximal signals for axonal and somatic degeneration of RGCs. The health of RGC axons, somas, and synapses are ultimately dependent on one another, and the visual function can only be maintained with an intact neuronal connectivity. However, axonal self-destruction and somatic apoptosis are regulated by molecularly distinct pathways. The self-autonomous destruct pathways for different RGC compartments include Wallerian degeneration of distal axons and Bax-dependent apoptosis of RGC somas (Figure 6) [47].

IV. CONCLUSION

Glaucoma is the second leading cause of blindness worldwide. To date, treatment of glaucoma has focused on lowering intraocular pressure (IOP) though there are other mechanisms that might damage the optic nerve, leading to characteristic visual field loss. Endothelin, a potent vasoconstrictor, is believed to play a role in the pathogenesis of glaucomatous optic neuropathy. In this review paper We have discussed about Glaucoma, diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa are all diseases that are related with neuro degeneration of retinal cells. In retinal cells, both apoptosis and necrosis occur under various conditions and early detection of such effect on retinal ganglion cell (RGC) could help for early detection for retinal disease. Early detection of neovascularization is another feature. For repair of damaged cells in retina there is progressive work using tissue engineering and stem cell therapy. Successful experiments on fish have regenerated a whole destroyed retina. Results indicate that successful application should be possible for regeneration of a whole destroyed retina in human using tissue engineering in near future. Research results shows encouraging work is done as blind people may get full or partial restored vision back.

V. ACKNOWLEDGEMENT

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