Intrinsically photosensitive retinal ganglion cell

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INTRINSICALLY PHOTOSENSITIVE RETINAL GANGLION CELL

GRADUATE THESIS

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Abbreviations and their explanations

1. CNS - central nervous system
2. ipRGCs - intrinsically photosensitive retinal ganglion cell
3. S - skin
4. C - conjunctiva / choroid
5. F - follicles
6. M - striated muscle/myoepithelial cells
7. T - tarsus
8. TG - tarsal glands
9. D - ducts
10. LP - lamina propria
11. A - acini
12. V - blood vessels
13. ECM - extracellular matrix
14. LASIK - laser assisted in situ keratomileusis surgery
15. IOP - intraocular pressure
16. PE - pigmented epithelium
17. NE - non pigmented epithelium
18. LC - lens capsule
19. DLF - differentiating lens fibers
20. MLF - mature lens fibers
21. VB - vitrous body
22. ILL - the inner limiting layer

23. NFL - the nerve fiber layer
24. GL - the ganglionic layer
25. IPL - the inner plexiform layer
26. INL - the inner nuclear layer
27. OPL - the outer plexiform layer
28. ONL - the outer nuclear layer
29. OLL - the outer limiting layer
30. RCL - the rod and cone layer

Contents

1. Summary

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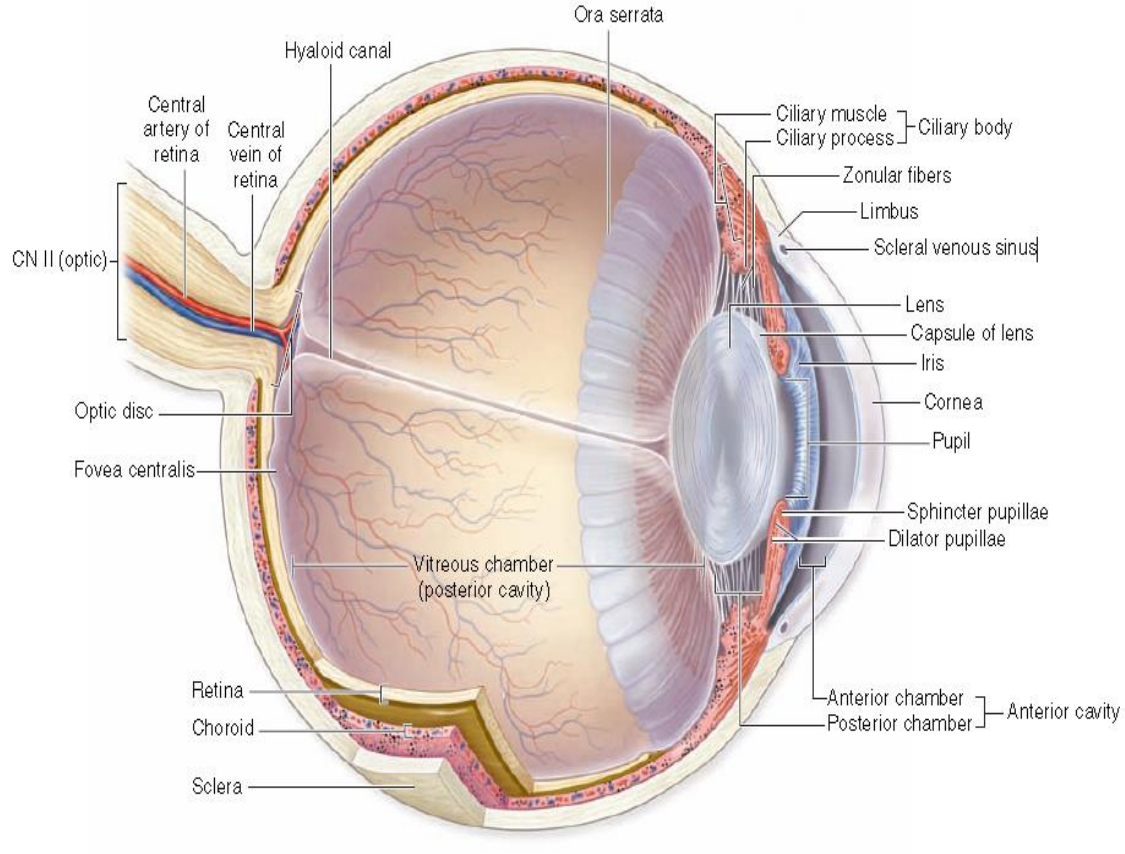
This graduation paper presents the histology of the eyes many segments, which include: conjunctiva, eyelids, lacrimal glands, scelra, cornea, limbus, choroid, ciliary body, iris, lens, vitreous body and the retina. With outlined medical or surgical correlations where appropriate. Featuring a greater emphasis on a particular type of retinal ganglion cell, known as the intrinsically photosensitive retinal ganglion cell. Intrinsically photosensitive retinal ganglion cells are a type of ganglion cell within the mammalian retina which act as a standalone photoreceptor. They are unique in regards to the current dogma of the classical rod and cone photoreceptors. They communicate directly to the brain, their function is not oriented to visual perception, but to physiological responses like the pupillary light response and circadian rhythm synchronization in response to the intensity of environmental illumination. They also seem to have a unique photopigment, the most likely candidate is melanopsin. Five different subtypes of intrinsically photosensitive retinal ganglion cell have been identified and their impact on health and interaction with certain pathological mechanism is under study. The intrinsically photosensitive retinal ganglion cells show great potential for future diagnostic and possible therapeutic options in medicine and may have a greater impact on the overall human environment in regards to environmental illumination.

Key words: ipRGCs, eye, photoreceptor, ophthalmology, circadian photoreceptor

2. Introduction

2.1. The Eye

The eyes are complex paired organs, used for capturing electromagnetic radiation of wavelengths in between 390-700 nm and to convey this information to the CNS, where it gives rise to form, intensity, and color of electromagnetic radiation reflected from objects and providing the sense of sight, but is also found to be a crucial key component of the circadian rhythm and physiological responses to the time of day, as presented by Anthony L. Mescher (2013), p.479-497. and Cecie Starr (2010) and Berson DM (Berson 2003). The eyes are located within the orbits of the skull which are formed by parts of the frontal, lacrimal, sphenoid, zygomatic, ethmoid, maxillary and palatine bones, containing adipose cushions, as presented by Anthony L. Mescher (2013), p.479-497. and Doxanas MT (1984). Individually an eyeball is formed by three distinct layers: a tough external fibrous layer consisting of the sclera and the transparent cornea, a middle vascular layer that includes the choroid , ciliary body, iris and an inner sensory layer, the retina, which communicates with the cerebrum through the posterior optic nerve. In addition, the lens is a perfectly transparent biconvex structure held in place by a circular system of zonular fibers that attach it to the ciliary body and by close apposition to the posterior vitreous body. Partly covering the anterior surface of the lens is an opaque pigmented extension of the middle layer called the iris , which surrounds a central opening, the pupil. Located in the anterior portion of the eye, the iris and lens are bathed in clear aqueous humor that fills both the anterior chamber between the cornea and iris and the posterior chamber between the iris and lens. Aqueous humor flows through the pupil that connects these two chambers. The posterior vitreous chamber, surrounded by the retina, lies behind the lens and its zonular fibers and contains a large gelatinous mass of transparent connective tissue called the vitreous body. This structures work in harmony to give eyes shape, turgor, metabolic nourishment and enable their physiological function, as presented by Anthony L. Mescher (2013), p.479-497.



Picture 1.The sagittal section of an eye shows the interrelationships among the major ocular structures. According to Anthony L. Mescher. Junqueira's Basic Histology.thirteenth edition, Lange, 2013, p.480, with permission (Department of Histology and Embryology of the School of Medicine University of Zagreb, 2015)

2.2.Intrinsically photosensitive retinal ganglion cell

The intrinsically photosensitive retinal ganglion cells are a subgroup of retinal ganglion cells, which are located in the retinal ganglion layer. Their existence was speculated for many years, due to the eyes ability to have certain light responses in the absence of rod and cone cells, that exists in blind patients, as presented by Berson DM (Berson 2003). Definitive proof of their existence was absolutely confirmed, after the discovery of their unique photopigment melanopsin. In the form and function, the intrinsically photosensitive retinal ganglion cells show phototransduction resembling that found in invertebrates, rather that the vertebrate one, as presented by Pickard GE and Sollars PJ (Pickard & Sollars 2012). This finding could perhaps be an indicator of its evolutionary age. Nowadays, up to five distinct subtypes of intrinsically photosensitive retinal ganglion cells have been observed, as presented by Xiwu Z and et al. (Xiwu and et al. 2014). They have several important functions, which include: circadian rhythm synchronization depending on environmental illumination levels, pupillary light responses and have been speculated to have a role in vision, as presented by Berson DM (Berson 2003) Strange vision and Pickard GE, Sollars PJ (Pickard & Sollars 2012). So far, their role in the global development of functional vision from an embryonic point has also been established, as presented by Shih-Kuo C and et al. (Shih-Kuo & et al. 2013). There is an increasing number of papers being published, which show clinical correlations between intrinsically photosensitive retinal ganglion cells and ocular pathology, as presented by Berson DM (Berson 2003) Strange vision and Carolina PB Gracitelli, et al. (Gracitelli & et al. 2014) and Esquiva G, et al. (Esquiva & et al. 2013). Intrinsically photosensitive retinal ganglion cells are a new element in clinical ophthalmology and will require translational research from multidisciplinary teams, in order to find future medical applications of the knowledge available.

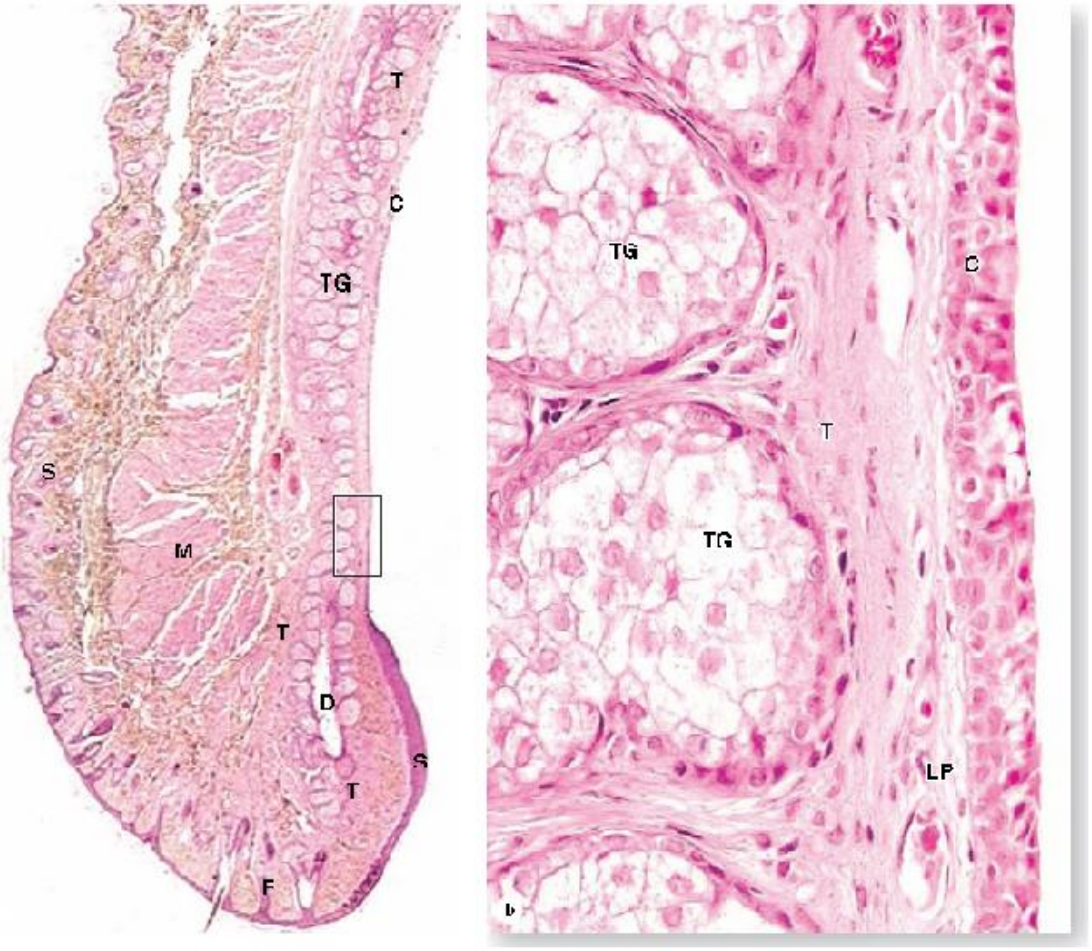
3. Accessory Structures of the Eye

3.1. Conjunctiva

The conjunctiva is a thin transparent membrane which covers the anterior portion of the eye, over the sclera and joining it at a common end point at the corneal limbus. It consists of a stratified columnar epithelium, with numerous small goblet cells, supported by a thin lamina propria of loose vascular connective tissue, as presented by Anthony L. Mescher (2013), p.479-497. The conjunctiva extends as a continuous unbroken sheet up against over the inner part of the eyelid, which enables physiological containment of the tear film. This forms a smooth surface for the lids to rub against the anterior portion of the eye, acts as natural bandage should the conjunctival part over the eye get damaged, prevents foreign particles that enter the eye from going over the eyes into the orbit and by this same mechanism has allowed the development and use of contact lenses as a refractory, astigmatic and therapeutic correction. Mucous secretions from conjunctiva cells are added to the tear film that coats this epithelium and the cornea, as presented by Anthony L. Mescher (2013), p.479-497 and Mann A And Tighe B (Mann & Tighe 2013). This is clinically important, since a pathology which renders the mucus secreting ability of the conjunctiva ineffective, will have a profound impact on the whole tear film, even if the lipid and aqueous components are intact, which may lead to dry eye syndrome (~30 % adult population) as presented by Jandroković S, et al. (Jandroković & et al. 2013) and Kaštelan S, et al. (Kaštelan & et al. 2013). Conjunctivitis, or pink eye, is a condition in which the conjunctiva is inflamed usually due to bacterial or viral infection or to allergies. The inflammation increases the discharge of mucus and enlarges the microvasculature of the sclera, causing the white sclera to have a reddish appearance. Bacterial and viral conjunctivitis are contagious but have little effect on vision, as presented by Anthony L. Mescher (2013), p.479-497.

3.2. Eyelids

The eyelids are relatively mobile structures consisting of skin, muscle, and the conjunctiva that cover and protect the eyes. The skin is loose and elastic, lacks fat, and has only very small hair follicles and fine hair, except at the distal edge, where large follicles with eyelashes are present. Associated with the follicles of eyelashes are sebaceous glands and modified apocrine sweat glands. Eyelids contain the puncta through which the tears flow into the lacrimal drainage system, as presented by Anthony L. Mescher (2013), p.479-497. Folliculitis of the eyelashes, also know as a sty or external hordeolum, is common problem encountered in primary care medicine, the most common pathogen is found to be *Staphylococcus aureusas* presented by Lindsley K, et al. (Lindsley & et al. 2010). Usually a conservative treatment is effective, but occasionally surgery may be indicated. Internal hordeolums usually require surgical excision. Beneath the skin are striated fascicles of the orbicularis oculi, innervated by the seventh nerve, and levator palpebrae muscles that are innervated by the third nerve (folds the eyelids), as presented by Bruce J (2011), p.3-4. Damage to this structures may result in what is know as ptosis. Adjacent to the conjunctiva is a dense fibroelastic plate called the tarsus that supports the other tissues. The tarsus surrounds a series of 20 to 25 large sebaceous glands, each with many acini secreting into a long central duct that opens among the eyelashes. Oils in the sebum produced by these tarsal glands, also called Meibomian glands, form a surface layer on the tear film, reducing its rate of evaporation, and help lubricate the ocular surface, as presented by Anthony L. Mescher (2013), p.479-497. A fundamental understanding of the eyelid histology should be mandatory for blepharoplasty. The failure to respect histological architecture of the eyelids and neighbouring structures can lead to astigmatism, which besides blurry vision may lead to an inability to use contact lenses and dry eye syndrome, as presented by Shao W, et al. (Shao & et al. 2004). Examples like this demonstrate the need for a closer interaction between basic sciences and clinical or surgical practice.



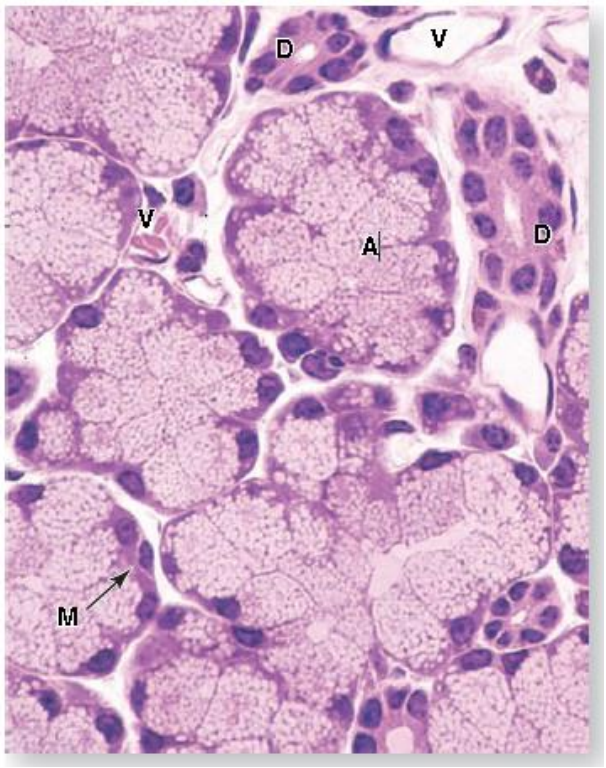
Picture 2. Eye Lid. According to Anthony L. Mescher. Junqueira's Basic Histology.thirteenth edition, Lange, 2013, p.496, with permission (Department of Histology and Embryology, School of Medicine University of Zagreb, 2015). A: “The eyelid is a pliable tissue with skin (S) covering its external surface and smooth conjunctiva (C) lining its inner surface. At the outer rim of the eyelid are a series of large hair follicles (F) for the eyelashes. Associated with these hair follicles are small sebaceous glands and modified apocrine sweat glands. Internally eyelids contain fascicles of striated muscle (M) comprising the orbicularis oculi muscle and closer to the conjunctiva a thick plate of fibroelastic connective tissue called the tarsus (T). This tarsal plate provides structural support for the eyelid and surrounds a series of large sebaceous glands, the tarsal glands (TG), with acini secreting into long central ducts (D) that empty at the free edge of the eyelids." X12.5. H&E. B: "At higher magnification, only the inner aspect of the eyelid is seen, and it shows that the conjunctiva (C) is a mucous membrane consisting of a stratified columnar epithelium

with small cells resembling goblet cells and resting on a thin lamina propria (LP). Large cells undergoing typical holocrine secretion are shown in the tarsal gland acini (TG), and the fibrous connective tissue in the tarsus (T) surrounding the acini. Sebum from these glands is added to the tear film and helps lubricate the ocular surface." X200. H&E , as presented by Anthony L. Mescher (2013), p.479-497.

3.3. Lacrimal glands

The paired lacrimal glands are located in the superior-temporal portion of the orbit, as presented by Bruce J (2011), p.88-95. They have a continuous production and supply of the tear film, with the major roles of providing easy lubrication for the conjunctiva and cornea, as well as metabolic role as an oxygen supplier to the cornea, as presented by Anthony L. Mescher (2013), p.479-497. Tear fluid has a major role in the innate immunity of the eyes, "it contains various metabolites, electrolytes, and proteins of innate immunity such as lysozyme", as presented by Anthony L. Mescher (2013), p.479-497. The main lacrimal glands have several observable lobes. They are released through excretory ducts, into the superior fornix, located between the eyelids and the eye. The lacrimal glands are composed of acini, large serous cells, which contain secretory granules. They are in turn enveloped by myoepithelial cells and a vascular stroma, as presented by Anthony L. Mescher (2013), p.479-497. Sjögren's syndrome is autoimmune disorder, which may affect the eye and cause a reduction of the tear film volume and dry eyes syndrome, as presented by Akpek EK, et al. (Akpek & et al. 2015). "Tear film moves across the ocular surface and collects in other parts of the bilateral lacrimal apparatus: flowing through two small round openings (0.5 mm in diameter) to canaliculi at the medial margins of the upper and lower eyelids, then passing into the lacrimal sac, and finally draining into the nasal cavity via the nasolacrimal duct", as presented by Anthony L. Mescher (2013), p.479-497. The canaliculi that drain the film are lined by stratified squamous epithelium proximal, but the more extending sac and duct are lined by pseudostratified ciliated epithelium , as presented by Anthony L. Mescher (2013), p.479-497. Dacryocystitis is an infection of the lacrimal sac, secondary to obstruction of the nasolacrimal duct at the junction of lacrimal sac. This obstruction may be either pathological, such as an bacterial abscess or due to congenital underdevelopment of the canaliculi or lacrimal duct. Treatment is usually antimicrobial for acquired cause

or surgery for complicated or congenital causes, which usually involves dilatation and reconstruction of the nasolacrimal apparatus. A contrasting procedure may be done, when the puncta are closed by silicon plugs, to prevent tear film removal in patients with low tear film producing or excessive evaporative pathology, as presented by Eshraghi B, et al. (Eshraghi & et al. 2014).



Picture 3. Lacrimal Gland. According to Anthony L. Mescher. Junqueira's Basic Histology.thirteenth edition, Lange, 2013, p.497, with permission (Department of Histology and Embryology, School of Medicine University of Zagreb, 2015). “Lacrimal glands secrete most components of the tear film that moisturizes, lubricates, and helps to protect the eyes. The glands have acini (A) composed of secretory cells filled with small, light-staining granules and myoepithelial cells (M). Connective tissue surrounding the acini contains blood vessels (V) of the microvasculature and intra- and interlobular ducts (D) converging as excretory ducts that empty into the superior conjunctival fornix between the upper eyelid and the eye". X400. H&E , as presented by Anthony L. Mescher (2013), p.479-497.

4. Fibrous Layer

4.1 Sclera

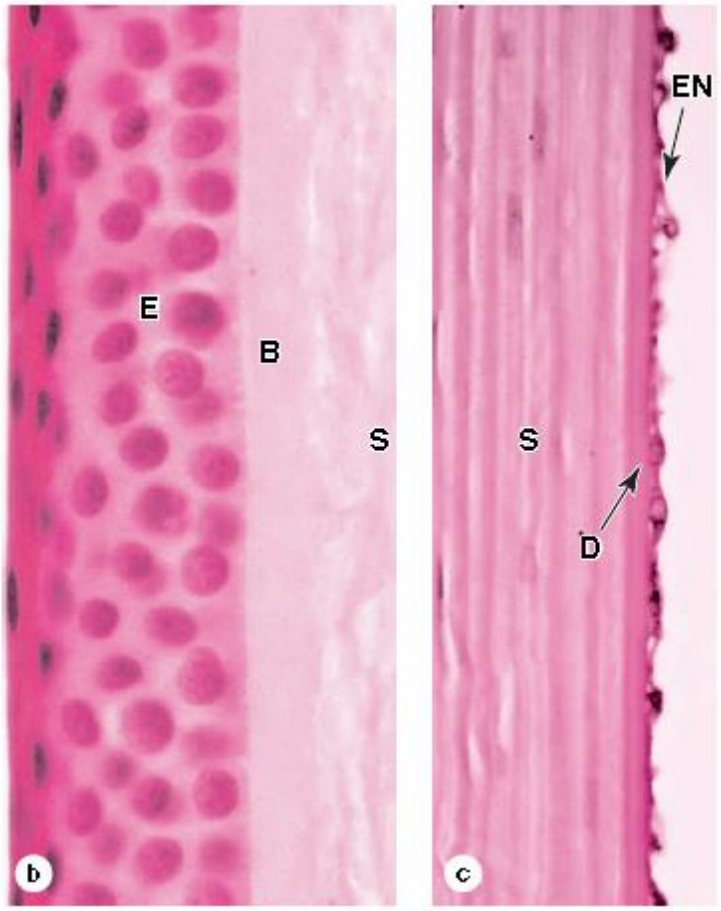
The sclera is a firm fibrous capsule that gives shape the eye, protection of the internal structures of the eye and is a base for the ocular muscle attachment, thus enabling movement and fixation of the globe. The sclera is a white structure rich in type 1 collagen, dense irregular connective tissue, that covers the posterior five-sixth of the eye, and joins anteriorly with the cornea at the stem cell rich region called the limbus. The sclera forms an enclosed region of about 22mm for adults, with an average thickness of 0.5mm. Microvasculature becomes visible near its outer surface. The thickest area of the sclera is near the optic nerve, where it is about 1mm thick. The sclera joins the epineurum of the optic nerve. At the point where it surrounds the choroid a distinct area may be seen called the suprachoroid lamina, which contains more cellular components compared to the ECM. The site of muscle tendon attachment is near the anterior portion of the sclera, as presented by Anthony L. Mescher (2013), p.479-497.

4.2. Cornea

The cornea is located at the anterior one sixth of the eye, it continues where the sclera ends at the limbus, it is a transparent structure with both protective and refractive properties. It also has an intrinsic role in the tear film regulation. It is highly innervated by free nerve endings. It is completely avascular and the anterior or external surface gains O_2 by diffusion from the air. Histologically, it is devided into five distinct layers. An external stratified squamous epithelium, an anterior limiting membrane (Bowman's membrane), which is the basement membrane of the external stratified epithelium, the thick stroma, a posterior limiting membrane (Descemet's membrane), which is the basement membrane of the endothelium and an inner simple squamous endothelium. The external stratified epithelium is not keratinized, five to six cell layers thick, is highly regenerative due to stem cell in the corneoscleral limbal proximity, and forms about one tenth of the corneal structure. The flat epithelial cells have microvilli which help contain the tear film: water, lipid and glycoprotein components. The basement membrane of this epithelium, often called Bowman's membrane, is very thick (8-10 μm) and contributes to the stability and strength of the

cornea, helping to protect against infection of the underlying stroma. The stroma, also known as substantia propria makes up most of the cornea, about nine tenths of the corneal thickness. It is about sixty layers of highly organised parallel collagen bundles at right angles to each other and together with its water component, contribute to the transparency of this unique avascular tissue. Between the collagen lamellae are cytoplasmic extensions of flattened fibroblast-like cells called keratocytes. The ECM of this this cells contains many proteoglycans like lumican, with keratin sulfate, chondroitin sulfate, which contribute to the organisation and functinal transparency of the cornea. The shape or curvature of the cornea can be changed surgically to improve certain visual abnormalities involving the ability to focus. in the common ophthalmologic procedure, laser - assisted in situ keratomileusis (LASiK) surgery, the corneal epithelium is displaced as a flap and the stroma reshaped by an excimer laser which vaporizes collagen and keratocytes in a highly controlled manner with no damage to adjacent cells or ECM. After reshaping the stroma, the epithelial flap is repositioned and a relatively rapid regenerative response reestablishes normal corneal physiology. LASiK surgery is used to correct myopia or hyperopia, as presented by Anthony L. Mescher (2013), p.479-497. The corneal surface is subject to many surgical procedures, with attempts of correcting astigmatism, keratoconus, etc. Corneal grafts are among the most successful transplants, due to the corneas lack of blood supply and lymphatic drainage. The eyes local immune tolerance and antigen presenting cells and immunomodulatory factors all contributed to this success. The posterior surface of the corneal stroma is lined by a membrane called Descemet’s membrane. It supports the internal simple samous endothelium. This endothelium is the most metabolically active component of the cornea. It contains the sodium/potassium atpase pump, which helps the more posterior part of the cornea get nourishment from the aqueous humor and help to pump water into the corneal stroma, where it is crucial for forming the collagen architecture, which enables transparency, as presented by Anthony L. Mescher (2013), p.479-497. This simple sqamous endothelium is a crucial structure. It only repairs by hypertrophic mechanisms and not by hyperproliferation, so if it gets damaged, its surface thins in response, as presented by Bruce J (2011), p.97-113. If the surface becomes too thin, the corneal stroma may lose form and dilate, does the cornea may become cloudy and less refractive. Knowledge of this histological fact contributes to how and where

incisions are made during surgery, to avoid damage to this endothelium as presented by Anthony L. Mescher (2013), p.479-497. and can be seen by Tojo N, et al. (Tojo & et al. 2015).



Picture 4. The cornea. According to Anthony L. Mescher. Junqueira's Basic Histology, thirteenth edition, Lange, 2013, p.483, with permission (Department of Histology and Embryology, School of Medicine University of Zagreb, 2015). B: In the picture, one can see the epithelium (E), which rests on its Bowman's membrane (B), and the anterior segment of the stroma, cut to fit the image. C: The posterior portion of the stroma rests on Descemet's membrane (D) and finally the simple squamous endothelium which forms the posterior corneal surface and is highly metabolically active. X400. H&E, as presented by Anthony L. Mescher (2013), p.479-497.

4.3. Limbus

The limbus is a transitional zone where the transparent cornea meets the non-transparent sclera. It forms a ring surrounding the cornea. Here Bowman's membrane ends and the surface epithelium becomes more stratified as the conjunctiva that covers the anterior part of the sclera. As mentioned previously, stem cells located at the limbus surface give rise to rapidly dividing progenitor cells that move centripetally into the corneal epithelium. The stroma becomes vascular and less well-organized at the limbus, as the collagen bundles merge with those of the sclera. At the limbus, the Descemet's membrane and its simple endothelium is switched with a system of irregular endothelium-lined channels called the trabecular meshwork. This system enables collection and drainage of the aqueous humor, from the anterior chamber of the eye. The fluid moves from the channels to larger canal called the canal of Schlemm, also known as the scleral venous system. This drains into scleral small veins, as presented by Anthony L. Mescher (2013), p.479-497.

5. Vascular Layer

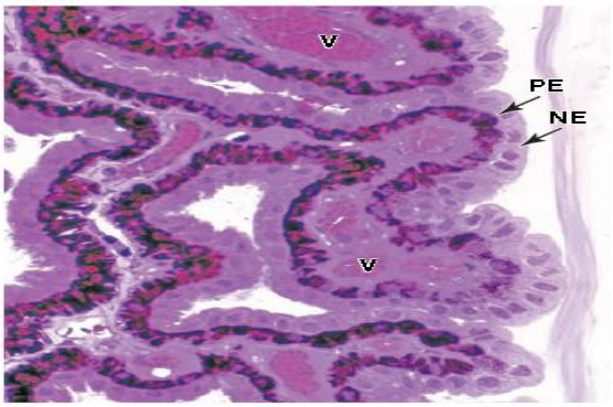
5.1. Choroid

The choroid consists of a highly vascularised, loose connective tissue. It is localized at the posterior two thirds of the eye and conatins many melanocytes. This enables the choroid to prevent any light from entering the eye, except at the pupil, as presented by Anthony L. Mescher (2013), p.479-497. The choroid is located between the retina and sclera and provides a protective and metabolic medium for structures in the close proximity. Histologically, two distinct layers can be observed, the choroid-capillary lamina and Brusch's membrane. The choroid-capillary lamina is rich in microvasculature and provides metabolic nutrition to the outer retinal layers. The Bruch's membrane is composed of collagen and elastic fibres. Forming extracellular sheets that envelops the microvascular layers and the pigmented retinal layer, as presented by Anthony L. Mescher (2013), p.479-497.

5.2. Ciliary Body

The ciliary body is the anterior portion of the uvea and lies posterior to the limbus. It surrounds the lens, and is supported structurally by the scera. The ciliary body has several important structures associated with it. These structures include the ciliary muscle, the ciliary processes and the ciliary zonule, as presented by Anthony L. Mescher (2013), p.479-497. The ciliary muscle can be divided into three layers and forms the most of the mass of the ciliary body. By contraction of the ciliary muscles, tension is released on the ciliary zonules and the lens curves up, a process called accomodation, which is necessary for near vision. This definition may be confusing, since contraction means reduction in volume-surface area, a common mechanism how regular skeletal muscle acts on bones as lever pulling on it. But, the ciliary muscle when depolarised (contraction) actually expands in volume-surface area and in the process resolves the tension on the ciliary zonules by pushing them, as presented by Anthony L. Mescher (2013), p.479-497 and by , as presented by Bruce J (2011), p.10-11. This is the reason why patients can have headaches and discomfort when using using eyes at a close distance for a prolonged time since, the ciliary muscles are contracted, as presented by Vincent AJ, et al. (Vincent & et al. 1989). The ciliary zonules are made of radially oriented fibers which mostly consists of fibrillin 1 and fibrillin 2, produced by the non-pigmented portion of the ciliary process. The fibers form gives in between the ciliary processes and bind the lens surface. This forms a firm attachment for the lens and enables accommodation and relaxing of the lens, as presented by Anthony L. Mescher (2013), p.479-497. The ciliary processes are about 75 ridges extending from the highly vascularized portion of the ciliary body. The surface area formed is quite extensive and is covered by a dual layer of low columnar cells, called the columnar epithelium. The inner epithelial layer contains abundant amounts of melanin and is continuous with the the anterior projection of the pigmented retina epithelium. The surface epithelial layer that lacks melanin is continuous with the sensory layer of the retina. This area is highly metabolically active, with many Na+/K+-ATPase pumps which help in the active secretion of the aqueous humor. The aqueous humor has an inorganic ion composition similar to that of plasma but almost has no protein content, as presented by Anthony L. Mescher (2013), p.479-497. The aqueous humor is secreted into the

posterior chamber and flows through the pupil into the anterior chamber, where it is absorbed by the trabecular meshwork at the iridocorneal angle, which drains into the canal of Schlemm. The canal of Schlemm in turn drains into the venous system. Since the aqueous humor is produced continuously, obstruction of any kind may lead to a condition called acute angle glaucoma. This may occur if there is an intrinsic pathology within the trabecular meshwork and its extension or if the flow of the aqueous humor is impeded by the lens occluding the pupillary opening with the iris. Since acute angle closure glaucoma is a medical emergency, it must be addressed fast and it usually requires a surgical intervention, such an iridectomy, where small holes are punctured in the iris to produce a secondary drain for the aqueous humor, and pressure lowering drugs like mannitol. Otherwise, IOP will rise and induce a compresive neuropathy to the optic nerve. Chronic glaucoma may be addressed by aqueous humor production lowering drugs, or drugs which attempt to decrease the drainage, as presented by Anthony L. Mescher (2013), p.479-497. in Bruce J (2011), p.146-162. and is found in Jovina LS, et al. (Jovina & et al. 2011).



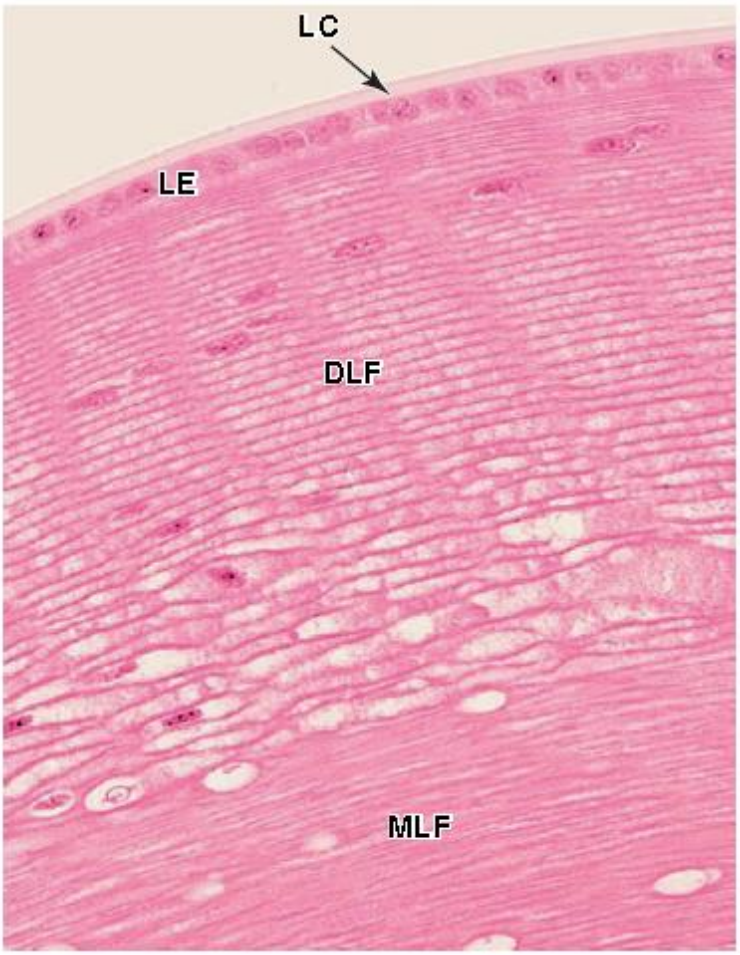
Picture 5. Epithelium of the ciliary processes. According to Anthony L. Mescher. Junqueira's Basic Histology.thirteenth edition, Lange, 2013, p.486, with permission Department of Histology and Embryology, School of Medicine University of Zagreb, 2015). Two layers can be observed, the pigmented (PE) inner portion and the exterior non-pigmented layer (NE). Below the core of the layers are numerous small blood vessels (V) which are the source for the components of the aqueous humor. X200. PT., as presented by Anthony L. Mescher (2013), p.479-497.

5.3. Iris

The iris is the anterior part of the uveal tract, covering part of the lens, forming the border between the anterior and posterior chamber and gives rise to the pupil, as presented by Anthony L. Mescher (2013), p.479-497. The anterior layer of the iris is formed by a dense layer of fibroblasts and melanocytes, with their processes. The iris is not a typical structure, for not having any epithelial coverings. The deeper structure of the iris (stroma) is made of some melanocytes and loose connective tissue, containing a sparse microvasculature. The posterior area of the iris forms a two layer continuous surface with the ciliary processes, but is highly packed with the pigment melanin. This melanin prevents any light from entering the eye, besides the pupillary area, as presented by Anthony L. Mescher (2013), p.479-497. The iris also contains epithelial cell, which forms the dilator pupillae muscle and contains the smooth fiber layers, that give rise to the sphincter pupillae muscle. The dilator pupillae muscle receives innervation from the sympathetic nervous system. The sphincter pupillae muscle receives innervation from the parasympathetic nervous system. Their function is to dilate and constrict the pupil. The number and density of melanocytes determines the patient's eye colour. More dense irises give rise to darker brown eyes, while less dense irises give rise to light blue eye, as presented by Anthony L. Mescher (2013), p.479-497.

6. Lens

The lens is a biconcave curved, transparent structure with refractory properties, which helps to transmit the light to the retina. The lens' unique structure is that it is absolutely avascular. It is highly plastic, in the sense that can allow accommodation, but this property is lost with increasing age, as presented by Anthony L. Mescher (2013), p.479-497. The lens has three histological components: the lens capsule, lens epithelium and lens fibers. The lens capsule (10-20 μm), is formed by proteoglycans and type IV collagen, which surrounds the lens and provides sites of attachment for the fibers of the ciliary zonules. This histological fact is important when performing cataract surgery, since a prolapse or extensive damage to the posterior aspect of the capsule may lead to difficulty of intraocular lens implantation, as presented by Anthony L. Mescher (2013), p.479-497. and Budde WM and Jonas JB (Budde & Jonas 1999). The subcapsular layer of the anterior lens epithelium consists of a single layer of cuboidal cells. It has two crucial functions, one is to act as an anchor of attachment between the lens capsule and the inner lens fibers. The other function arises from the fact that the subcapsular layers are continuous to the posterior portion of the lens near the equator, where they turn and are continuous with the lens fibre layer. This is the source of lens growth and this process continues through out the the patients life, as presented by Anthony L. Mescher (2013), p.479-497. The lens fibers are thin, terminally differentiated cells,"lens fibers typically become 7 to 10 mm long, with crosssection dimensions of only 2 by 8 μm", as presented by Anthony L. Mescher (2013), p.479-497. The cytoplasmic area is full of proteins called crystallins, the remaining constituents of the fibers undergo atrophy: organelles and the nucleus. This fibers are pact in a tight manner which enables the lens to have transparent and refractive power, as presented by Anthony L. Mescher (2013), p.479-497. "In the fourth decade of life presbyopia (Gr. presbyter, elder + L. opticus, relating to eyes) normally causes the lenses to lose elasticity and their ability to undergo accommodation", as presented by Anthony L. Mescher (2013), p.479-497.



Picture 6. Lens. According to Anthony L. Mescher. Junqueira's Basic Histology.thirteenth edition, Lange, 2013, p.489, with permission (Department of Histology and Embryology, School of Medicine University of Zagreb, 2015). The lens capsule (LC) can be seen on the margin of the lens. The simple columnar layer of epithelium (LE) may be seen beneath the lens capsule (LC). Differentiating lens fibers (DLF) still need to mature into mature lens fibers (MLF) and contain their nucleus.X200. H&E., as presented by Anthony L. Mescher (2013), p.479-497.

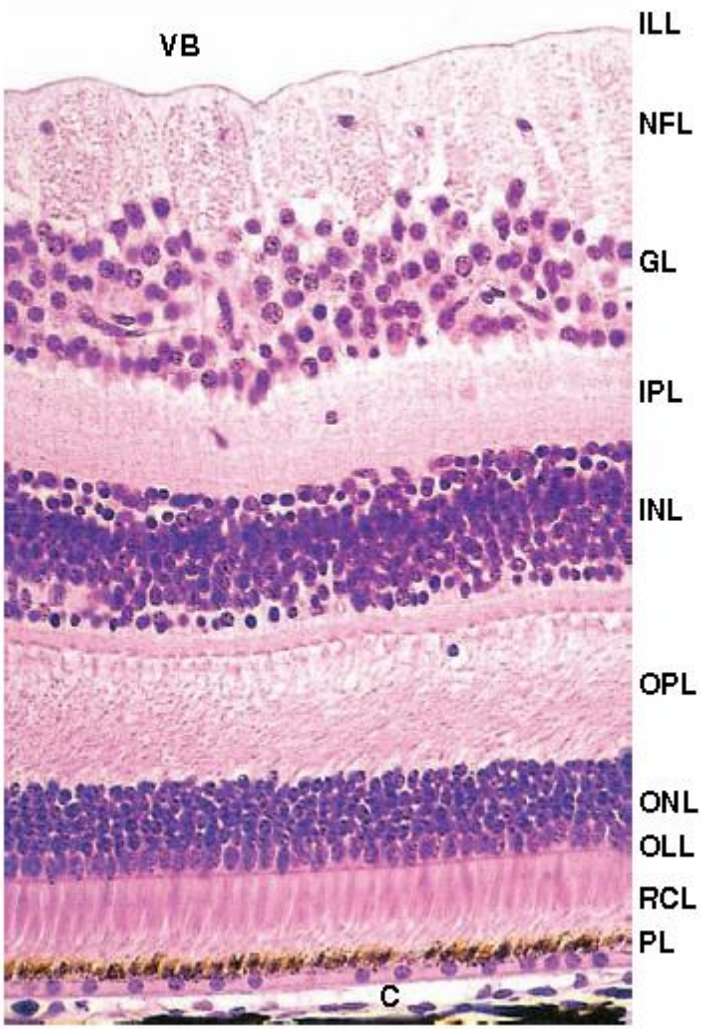
7. Vitreous body

The vitreous body fills and forms the vitreous chamber in the posterior portion of the eye. It is formed by a transparent gel like structure which is made by connective tissue and consists of 99% water. Most of this connective tissue is formed by collagen fibrils and hyaluronate with a few cells, namely macrophages and hyalocytes. Hyalocytes synthesise collagen fibrils and hyaluronate, as presented by Anthony L. Mescher (2013), p.479-497.

8. Retina

The retina is the most inner structure of the eye and consists of two distinct sublayers, the structurally and metabolically important outer pigmented layer and the phototransductive inner neural layer. The pigmented sublayer is formed by simple cuboidal epithelium, in connection with Bruch's membrane and the choroidocapillary lamina of the choroid, it is continuous with the epithelium covering ciliary body and posterior iris. The neural is layer rich and stratified with neurons, photoreceptors and accessory structures. Its functional neural and phototransductive parts can only be seen to extend to the border of the ora serata, but as a layer it can be seen to extend to the cuboidal epithelium that sheetes the surface of the ciliary body and posterior iris, as presented by Anthony L. Mescher (2013), p.479-497. The nature of the retina to be formed by less tightly attached sublayers can lead to serious pathology called retinal detachment. It is usually formed at the border of the two sublayers. It may be caused by various causes, such as blunt trauma, a rupture in retina followed by vitreous invagination and retinal edema, to name a few. Retinal detachment requires surgical treatment if there is to be any hope for a recovery, as presented by Anthony L. Mescher (2013), p.479-497. and described by Subhadra J (Subhadra 2003). The pigmented portion of the retina, is formed by cuboidal or low columnar cells which surround the neural part of the retina. The cells of the basal layer are rich in mitochondria, which form numerous invaginations with plentiful gap junctions. The cells apical surfaces form many finger-like projections which extend into the tip of the photoreceptor layer; this area is rich in melanin granules. This area also consists of many phagocytic vacuoles and secondary lysosomes, peroxisomes, and abundant

smooth endoplasmic reticulum, which isomerise vitamin A. This pigmented layer has several important functions which include: absorption of scattered light, formation of the blood-retinal barrier, facilitation of ion transport between these layers, isomerisation of trans retinal to cis retinal, degradation and phagocytosis of shed photoreceptor material, antioxidants function and ATP production for the neural layer, as presented by Anthony L. Mescher (2013), p.479-497. The neural portion of the retina is formed by nine layers. It functions as a CNS output, comprised of well organised neural sublayers and glia. Three functionally most important layers are: the outer nuclear layer (which can be found near the pigmented portion of the retina), which is formed by the cell bodies of the photoreceptors; the inner nuclear layer consists of the core nuclei of many neurons, and among which bipolar cells, amacrine cells and horizontal cells are to be identified, which form an intricate neural network with other cells, most notably the rod and cone cells; it also houses glial cells called Müller cells. The ganglionic layers, just behind the nerve fiber layers formed by ganglion cell axons, is the nearest portion of the neural retina to the vitreous. Ganglion axons (the nerve fiber layer) finally form the optic nerve, which travels to the CNS. The ganglion layer is more or less uniformly one cell layer thick at its periphery, but is more dense near the macular region. Today we know that the ganglion cell layer has many regulatory functions and intrinsic photoreceptors like cells called intrinsically photosensitive retinal ganglion cells, as presented by Anthony L. Mescher (2013), p.479-497. and Berson DM (Berson 2003). In between these three nuclear layers are two plexiform regions, formed by axons and dendrites, in connection by synapses. The outer plexiform layer is more posterior in the eye of the two plexiform layers. It is formed by axons and dendrites of neurons of the inner nuclear layer. The inner plexiform layer is more anterior and is formed by axons and dendrites, which join the inner nuclear layer and ganglion layer. The Müller cells form two thin boundaries. The outer limiting membrane, formed by rigid and coherent junctions at the photoreceptor layer and Müller cell processes. The inner limiting membrane is a terminal expansion of Müller cells processes in ending with the collagenous border of the vitreous. The main two type of photoreceptors are the rod and cone cells, and the light must go passing the obstructing layers to reach them, as presented by Anthony L. Mescher (2013), p.479-497.



Picture 7. Layers of the Retina. According to Anthony L. Mescher. Junqueira's Basic Histology.thirteenth edition, Lange, 2013, p.492, with permission (Department of Histology and Embryology, School of Medicine University of Zagreb, 2015). VB- vitrous body and C- choroid form the borders of the retina. ILL- The inner limiting layer, NFL- The nerve fiber layer, GL- The ganglionic layer, IPL- The inner plexiform layer, INL- The inner nuclear layer, OPL- The outer plexiform layer, ONL- The outer nuclear layer, OLL- The outer limiting layer, RCL- The rod and cone layer, PL(NE)- The non-neural pigmented layer. X150. H&E., as presented by Anthony L. Mescher (2013), p.479-497.

9. Intrinsically photosensitive retinal ganglion cell

9.1. History

Light was known to synchronize circadian phases through the retinohypothalamic tract, which is a tract that connects the suprachiasmatic nucleus with portions of the retinal ganglion layer. It was assumed that all inputs to the ganglion layer originated from the classical photoreceptors, namely rods and cones, as presented by Johnson RF, et al. (Johnson & et al. 1988) and Moore RY, et al. (Moore & et al. 1995) and Sousa-Pinto A and Castro-Correia J (Sousa-Pinto & Castro-Correia 1970). During the 1980s, behavioral studies showed inconsistencies with this classic view and thus opened the window for what would be later called intrinsically photosensitive retinal ganglion cells, as presented by Foster RG (Foster 2002). The light threshold differed from rods and cones and was preserved in rodless and coneless mice and in some blind patients, as shown by the preserved ability to suppress plasma melatonin levels following light exposure, as presented by Takahashi JS, et al. (Takahashi and at al 1984) and Foster RG, et al. (Foster & et al. 1991) and Klerman EB, et al. (Klerman & et al. 2002). This findings may have clinical relevance in regards to enucleation, that is the surgical removal of the eyeball, as presented by Moshfeghi DM (Moshfeghi 2000). Blind eyes that are painful or have a probability to spread a metastatic or infectious agent to the rest of the body are removed. The preserved ability to suppress plasma melatonin levels following light exposure shows that blind eyes are not always dead eyes, given their possible roles outside of spatial vision. Since blind eyes are not dead eyes and if the probability to spread a metastatic or infectious agent is small, the number of enucleations performed should be reconsidered. The possibility of an extraocular mechanism was also abandoned by this finding, because enucleation abolished this phenomenon, as presented by Foster RG, et al. (Foster & et al. 1991). Definitive proof of the intrinsically photosensitive retinal ganglion cells existence was concluded with the discovery of a unique photopigment called melanopsin, which differs from photopigments found in rod and cone cells and was found to be contained within this subgroup of ganglion cells (~1-3)%, as presented by Provencio I, et al. (Provencio & et al. 2000) and Hattar S, et al. (Hattar & et al. 2002). Today, up to five subgroups of ipRGCs are known, typed M1, M2, M3, M4 and M5 and found that they have many more proven and speculated roles in humans than

circadian photoentrainment, as presented by Xiwu Z, et al. (Xiwu & et al. 2014) and Foster RG (Foster 2002). In regards to the history of ipRGCs, an honorable mention is the discovery of luminance units by Barlow and Levick, which seem to be what we call today ipRGCs. They were found as a curiosity as early as 1969, almost forty years before ipRGCs phototransduction was confirmed, as presented by Barlow HB and Levick WR (Barlow & Levick 1969).

9.2. Morphology and function

As mentioned previously, the ganglionic layers, just behind the nerve fiber layers formed by ganglion cell axons, are the nearest portion of the neural retina to the vitreous. In regards to its local organisation, the ganglion layer is more or less uniformly one cell layer thick at its periphery, but is more dense near the macular region, as presented by Anthony L. Mescher (2013), p.479-497. In animal studies, within the ganglion layer, about 1500 ganglion cells were found to contain the photopigment opsin melanopsin. This is about 1-3% of all ganglion cells within the ganglion layer. There is an overall concentration of these cells to the superior region of the retina, occasionally they are also present in the inner plexiform layer, as presented by Hattar S, et al. (Hattar & et al. 2002). If confirmed in human studies, this may have implication on surgical procedures which target the retina by photocoagulation in more advanced forms of diabetic non-proliferative retinopathy; the superior portions of the retina could be treated more conservely to preserve the ipRGCs located there. IpRGCs dendrites form a complex layer in the inner plexiform layer; surprisingly, they are also independently photosensitive and contain the photopigment melanopsin, as presented by Hattar S, et al. (Hattar & et al. 2002) and , and Berson DM et al. (Berson & et al. 2002). IpRGCs dendrites are far more expressed that dendrites of cone and rod cells, with a span of ~500µm and ~1µm, respectively, as presented by Berson DM et al. (Berson & et al. 2002). This phenomenon forms a large receptive field for the IpRGCs, perhaps countering their small numbers. The IpRGCs were found to be selective for pituitary-adenylate-cyclase-activating peptide, which is speculated to have a role in retinohypothalamic tract relay of electrical impulses, as presented by Hannibal J, et al. (Hannibal & et al.

2002). From an developmental point, IpRGCs were found to require an ordered fashion in their location within the ganglion layer in order to fuction; more specifically , IpRGCs require proximity-dependent Bax-mediated apoptosis to achieve this functional arrangement. In Bax mutant mice, there was a disturbance in IpRGCs architecture and these cells were found to have abnormal localisation of synapses as a consequence, as presented by Shih-Kuo C, et al. (Shih-Kuo & et al. 2013). IpRGCs are found not be a homogeneous group of a subset of retinal ganglion cells, but have their own uniqueness and subtypes; so far, up to five distinct subtypes of IpRGCs have been characterised, M1, M2, M3, M4 and M5. M2-M5 cells are found to be able to detect spatial differences in light intensity, with a possible role in analysing form in vision. M1-M4 cells have demonstrated their transmissions ultimately to the superior colliculus, which is known to detect novel objects in the visual field, leading to more evidence that IpRGCs might have a role in spatial vision as well as many other physiological functions, as presented by Xiwu Z, et al. (Xiwu & et al. 2014). The discovery of IpRGCs originates from their ability to induce photoentrainment of the circadian system and its synchronisation to day time intensity of the ambient light, as presented by Johnson RF, et al. (Johnson & et al. 1988) and Moore RY, et al. (Moore & et al. 1995) and Sousa-Pinto A and Castro-Correia J (Sousa-Pinto & Castro-Correia 1970) and Foster RG (Foster 2002). Circadian rhythm is a sort of a biological clock that has a period which lasts approximately one day. Circadian rhythm regulate sleep, hormonal levels, temperature generation, cognition and many other body functions with daily variations. This rhythms are induced by a certain pacemaker-like group of cells, that are called the suprachiasmatic nucleus and are located within the hypothalamus, as presented by Gillette MU And Tischkau SA (Gillette & Tischkau 1999). Because this phase is not exactly 24 h, it is prone to drift away from the actual day time, so it needs to be entrained by the IpRGCs. This is most pronounced when the patient changes time zones, resulting in what is known as jet lag, as presented by Arendt J (Arendt 2009). Needless to say, a disruption of circadian rhythms is a potential cause of great human morbidity and mortality, and emphasizes the importance of IpRGCs. IpRGCs achieve photoentrainment of the suprachiasmatic nucleus by directly linking to the suprachiasmatic nucleus by the retinohypothalamic tract, as presented by Sousa-Pinto A and Castro-Correia J (Sousa-Pinto & Castro-Correia 1970). Photoentrainment is slow to respond to brief

light exposure, which correlates with the IpRGCs slow response to ambient light, namely IpRGCs are more insensitive that cone and rods to light, but can integrate photic energy for much longer periods of time, as presented by Nelson DE and Takahashi JS (Nelson & Takahashi 1999). There are several differences in phototransduction in IpRGCs compared to the classic ones described in cones and rods. Light induces hyperpolarization of cone and rod cell, while light induces depolarisation of IpRGCs. Isolated IpRGCs have the wavelength sensitivity function for a typical vitamin A based photopigment, like the ones found in rods and cones. This has led to assume that IpRGCs photopigment is also an opsin. But in animal models, this opsin (later confirmed to be melanopsin) has a functionally different wavelength. Namely, IpRGCs are most sensitive at approximately 484 nm, while rat rods are most sensitive at approximately 500 nm and cones 510 nm or 359 nm, respectively, as presented by Barlow HB and Levick WR (Barlow & Levick 1969) and Bridges CDB (Bridges 1959) and Jacobs GH et al. (Jacobs & et al. 2001). Melanopisn was found mostly in cells inervating the retinohypotalamic tract. IpRGCs were found to be cells responsible for innervating the suprachiasmatic nucleus, thus melanopsin was concluded to be the target opsin, as presented by Provencio I, et al. (Provencio & et al. 2000). However, the actual mechanism of this IpRGCs to suprachiasmatic nucleus pathway is not so simple, there is a presence of intraretinal synaptic modulation, most likely from influence by rods, cones, bipolar and amacrine cells. Thus, at least some of the IpRGCs get mixed input and a modulated output to the suprachiasmatic nucleus, as presented by Belenky MA, et al. (Belenky & et al. 2003). It is clear that more effort will be required for more research and insight into this entrainment phenomenon in the future. However, IpRGCs have many other roles besides photoentrainment. Most closely related is the IpRGCs ability to regulate the release of melatonin from the pineal gland. Light induced suppression of otherwise high nocturnal melatonin. The light's wavelength required is consistent with IpRGCs wavelength preference. In addition, this melatonin cycle is preserved in rodless and conless mice, as well as in some blind patients, as presented by Takahashi JS, et al. (Takahashi & et al. 1984) and Foster RG, et al. (Foster & et al. 1991) and Klerman EB, et al. (Klerman & et al. 2002). Short day length may induce seasonal affective disorder. Seasonal affective disorder is treated by bright light exposure therapy, the target for this treatment is unknown, but given this new insight, IpRGCs seam a

probable target candidate, as presented by Avery DH (Avery 1998). Among other important regulated systems by the IpRGCs, of particular mention are: sleep, pupillary light reflex, cortisol regulation and heart rate, as presented by Foster RG (Foster 2002) and Hattar S, et al. (Hattar & et al. 2002). The pupillary light reflex is assumed to arise from the fact that the retina links to the olivary pretectal nucleus and that IpRGCs are connected directly to it. This may also explain why the pupillary light reflex remains intact in rodless and coneless mice, as presented by Hattar S, et al. (Hattar & et al. 2002) and Lucas RJ, et al. (Lucas & et al. 2001). IpRGCs may have a role in the eyes immune response as well, but more research is required to validate this claim further, as presented by VanGelder RN (VanGelder 2001). All of this emerging evidence has managed to catch up to clinical ophthalmology. There is a rapid rise in published articles on the topic of IpRGCs and their possible roles in disease pathogenesis. A positive association was found between IpRGCs and retinal nerve fiber layer thinning as a result of glaucoma, and IpRGCs impairment was found to be associated with late stage retinal degeneration, as presented by Berson DM (Berson 2003) and Carolina PB Gracitelli, et al. (Gracitelli & et al. 2014) and Esquiva G, at al. (Esquiva & et al. 2013).

10. Conclusion

The eyes are complex organs made of distinct compartments, which act in harmony as a single unit. This fact is scientifically fascinating as well as medically daunting. This multicompartmental architecture of the eye has forced ophthalmologist to specialise in particular compartments of the eyes, such as the anterior segment specialist, posterior surgical segment and posterior medical specialist. With the large amount of evidence emerging on the importance of intrinsically photosensitive retinal ganglion cells, there might be a new distinct field of ophthalmology forming in the future. This will hopefully bring new diagnostic as well as treatment options for the associated pathology. In the meantime, more research is required on intrinsically photosensitive retinal ganglion cells, with a multidisciplinary approach.

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13. Biography

Leon Rabatić was born on the 17.1.1991. in Zagreb. In 2009 he graduated from the XV. High school in Zagreb and enrolled into the School of Medicine University of Zagreb. During his studies, from his 1st year, he was awarded a student volunteer status at the Biology department, Epigentics laboratory, under the project of "Epigenetics of breast cancer, cardiac mixoma and aortic valve clacification". In 2nd year of study he became a honorary member of the European association of cancer research (number EACR15803). From his 4th year, he was volunteering with the Ophthalmology department, in Dubrava hospital, Zagreb, and participated in several research studies. From his 6th year, he was a student assistant for the History and physical examination course at KBC Rebro.