Shedding light on the importance of autophagy in AMD

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Novel concept: inner choroid/outer retina neurovascular unit

Autophagy is a protective process that prevents oxidative damage in the eye. Recognition of this provides researchers with a new pathway to deal with age-related macular degeneration (AMD) and other retinal pathologies, according to Roberto Pinelli, MD, CEO and founder of the Switzerland Eye Research Institute, Lugano, Switzerland.

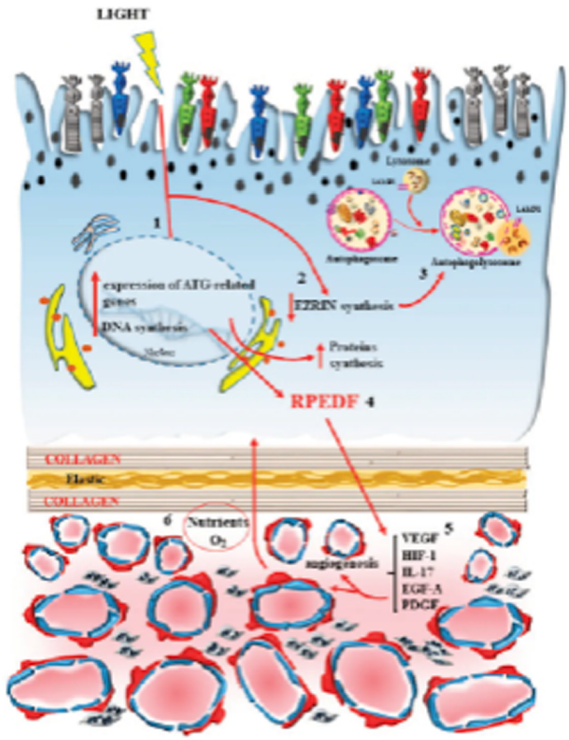

Figure 1. *Autophagy, which is induced during the process of photo-transduction, plays a seminal role in sustaining retinal integrity during AMD. Image courtesy of Dr Roberto Pinelli*

He described the latest ideas about the function of light in the retina in AMD and potentially other retinal diseases.

"Light and photobiomodulation are the new horizon for treating AMD and reveal a new way to consider retina management," he commented.

Dr Pinelli discussed the essential role of light in the functioning of autophagy in the outer retina, ie, the retinal pigment epithelium (RPE) and the outer segment of the photoreceptors, and the inner choroid, ie, Bruch's membrane, endothelial cells, and the pericytes of the choriocapillaris.[1]

In the outer retina and inner choroidal neurovascular unit, Dr Pinelli explained that the "autophagy machinery is fundamental in promoting visual processing and preserves the integrity of the outer retinal segments (**Figure 1**). This is mainly due to light-dependent biochemical cascades placed downstream of autophagy activation, which consist of various pathways mostly within the RPE."

Other structures at the choroidal-retinal border are also modulated by light, where autophagy and actual photo-transduction take place. At this level, there is need for trophic support and high protein/organelle turnover to sustain light stimulation. This activity contributes to defining the inner choroid/outer retina as the "morpho-functional unit," referred to as the retinal neurovascular unit, he said.

Specific autophagy-related structures in baseline and degenerating retina

Although autophagy alterations can vary in several types of retinal degeneration, the relevance of autophagy in the outer retina is that it deals with the site-specific pathology of AMD, which mostly affects the outer retina.

The relevance of autophagy in RPE cells is evident in experimental models, Dr Pinelli explained, in which specific autophagy-inducing genes are knocked out.[2] This is key at the onset and during the course of genetically induced experimental AMD. In fact, when knocking down autophagy-related genes, specifically in RPE cells, the occurrence of retinal abnormalities mimicking those described in human AMD is consistently documented. These similarities include stagnant vacuoles in altered RPE cells, which modify their shape and size along with the amount of pigmentation, and the occurrence of frank RPE cell death.

Synergism of autophagy in the outer retina/inner choroid

Therole of autophagy in the inner choroid is also relevant to the understanding of the mutual interactions between the outer retina and inner choroid.

Long wavelength light is important and beneficial.

"The seminal role of autophagy in sustaining retinal integrity during AMD is likely to be naturally induced by long wavelength light pulses and light-sensitive phytochemicals, which in addition to maintaining retinal structure and visual acuity, also counteract retinal degeneration," Dr Pinelli said. Numerous studies have documented this early on in AMD,[3,4] among others.

In contrast, short wavelength light and metabolic dysfunctions may induce deleterious effects by altering a number of chemical species that undergo conformational changes and in so doing derange organelles that are affected during the high metabolic turnover of this part of the retina. "In this case, autophagy is key to counteracting the deleterious effects of light by removing damaged structures, which require powerful and fast replacement,"[5] he said.

This applies to proteins, lipids and sugars and extends to specific autophagy-dependent organelles such as mitochondria. All these structures may be targets of deleterious short wavelength light, which may produce free radicals, alter DNA integrity, disrupt tissue structure, and sustain retinal degeneration.

Spotlighting the RPE

The RPE is the centre of the universe in AMD.

"The RPE cells possess the highest autophagy rate in the retina.[6] In fact, autophagy in the RPE is key in removing various chemical species and subcellular organelles. Most proteins and lipid clearance is autophagy-dependent, which is supported by the fact that autophagy defects lead to accumulated misfolded proteins and lipid droplets. This extends to cell organelles, since autophagy failure alters the structures and amount of various organelles in the RPE," Dr Pinelli explained.

When the process is dysfunctional, misfolded proteins, lipids, and organelles can accumulate in giant lysosomes, where proteins tend to bind sugars to produce advanced glycation end products and lipids, to generate lipofuscin, which may further bind melanosomes to form melanolipofuscin. These structures, including mitochondria, are cellular debris, which produce the building blocks of drusen.

Dysfunctional autophagy in the inner choroid/outer retina: paramount in AMD

The retinal degeneration in AMD occurs in different retinal areas but involvement of the macula is paramount. In dry AMD, solid drusen are predominant and in the wet form,soft drusen occur in the context of retinal exudates and newly formed blood vessels.

Clinically, AMD is characterised by loss of visual acuity and contrast sensitivity as the result of selective impairment ofthe macular vision, a typical symptom of which is distorted, wavy lines along horizontal and vertical axes (metamorphopsia). The mechanisms of decreased visual acuity are thought to result from loss of retinal planarity and a loss of foveal cones, which suppresses contrast sensitivity. Massive loss of photoreceptors is eventually responsible for these symptoms.[7]

Dr Pinelli suggested that impaired vision likely occurs early in the disease course despite the preserved photoreceptor integrity. "This is likely to depend on the failure in the biochemical cascades generating the visual physiology. In fact, the massive involvement of an autophagy failure in the physiopathology of AMD should first alter the turnover of the photo-pigments."[7]

A number of disorders are involved in the pathogenesis of AMD, ie, retinal-specific autophagy alterations,[8,9] blue light-induced autophagy failure leading to excessive oxidised substrates,[10,11] and systemic metabolic disorders suppressing retinal autophagy such as diabetes[12,13] and familial dyslipidemia.[14,15]

Site-specific autophagy suppression in the retina leads to AMD. Specifically, the retinal site where autophagy is fundamental in preventing AMD is the outer retina and this area extends to the inner choroid, passing through Bruch's membrane.[6,9] The specific cells are the outer photoreceptors, RPE, endothelial cells, and pericytes of the choriocapillaris, and very likely also scattered fibroblasts in Bruch's membrane.

The relevance of the RPE status in AMD is established, but novel findings in the inner choroid pinpoint specific choroid cells and mechanisms are involved in AMD development.[16-18] Particularly, dysfunctional autophagy in the choroid may be responsible for delivering abnormal substrates to the outer retina and may start deposition of drusen on the outer aspect of Bruch's membrane.

Loss of autophagy in RPE cells in AMD occurs when autophagy is inhibited when the lysosomes cannot degrade the metabolic by-products. This is typical in early AMD when excessive stagnant lysosomes are seen to contain nondigested material (lipofuscins or lipomelano-fuscin).[19]

Lipofuscin in turn blocks lysosomal enzymes and constrains these organelles to release their content below the plasma membrane, where this material aggregates to form drusen.

An autophagy defect within RPE may lead to a number of downstream deleterious events. In fact, altered organelles and misfolded proteins, sugars and lipids are expected to trigger direct toxicity in the cell. This is likely to occur at short time intervals. The late fate of these aggregates is more questionable, since a number of reports range from a detrimental mechanical effect to an inert role as innocent bystanders, simply witnessing a previous dynamic of the disease.

Inner choroid/outer retina neurovascular unit: connecting photoreceptor stimulation with metabolic activity and blood supply

Light and photobiomodulation are the new horizon for treating AMD and reveal a new way to consider retina management.

The concept of the neurovascular unit is an orchestrated activity of the blood vessels in the inner choroid to supply the metabolic demand of the RPE cells and outer photoreceptors in a coordinated manner. When high energy demand occurs in the outer retina, a cross-talk between the RPE and inner choroid generates an appropriate modulation of blood flow and clearance of retina-dependent catabolites. Similarly, the status of the inner choroid is expected to modulate the activation of the outer retina through specific signalling. Therefore, the inner choroid/outer retina unit should be considered a functional unit, meaning an area in which the RPE and the inner choroid work in synergy.

This hypothesis makes the inner choroid/outer retina unit similar to the neurovascular unit recently described in the central nervous system.[20] Along this line, in the retina the rate of autophagy within rods varies according to the diurnal regulation of the light cycle.[21] This occurs according to the metabolic requests induced by vision. It is therefore is possible to define a so-called "inner choroid/outer retina" neurovascular unit, where the activity of the outer segment of the photoreceptors and RPE cells are coordinated with blood supply through the choriocapillaris.[22]

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