Review

Metabolic Shift and Increased Osmotic Pressure Underlie Age-Related Macular Degeneration: A Review

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Review

Metabolic Shift and Increased Osmotic Pressure Underlie Age-Related Macular Degeneration: A Review

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Abstract: In our previous papers, we demonstrated that inflammation and aging are the common roots of cancer and Alzheimer's disease (AD). In both diseases, there is an inhibition of the mitochondria. In cancer, the alkaline intracellular pH (pHi) is associated with cell proliferation; acidic pHi causes apoptosis in AD. This difference is because cancer feeds on chemically neutral glucose, while neurons feed on acidic lactic acid. Increased uptake of lactic acid is responsible for acidic pH and cell death.Similarly, to AD, inflammation is responsible for metabolic shifts in age-related macular degeneration (AMD). In AD, there is hyperosmolarity responsible for increased lactic secretion by glial cells. Increased lactic secretion will cause neo-angiogenesis and neural cell death. Drugs increasing hyperosmolarity (Polyethylene Glycol) cause neo-angiogenesis and drusen-like structures in rodents. The link between AMD and inflammation is reinforced by the fact that treatments aiming at restoring mitochondrial activity, such as lipoic acid and/or methylene blue, have been experimentally shown to be effective in each set of diseases. The role of osmolarity has been demonstrated in the pathologies of the anterior segment of the eye, such as dry eye, corneal ulceration, cataracts, and glaucoma. The role of increased osmolarity in age-related macular degeneration (AMD) has been largely overlooked. We herein suggest that metabolic shift, inflammation, and hyperosmolarity are key players in the pathogenesis of AMD.

Keywords: macular degeneration; osmotic pressure; pHi; apoptosis; mitochondria; lipoic acid; methylene blue

1. Introduction

The past few decades have seen limited successes in the fight against age-related macular degeneration (AMD), cancer, and Alzheimer's disease (AD). In each set of diseases, the paradigm has been centered on genomic alterations. Cancer and AD, or AMD, are widely considered to be different sets of diseases with different prognoses, sites of origin, patterns of spread, and treatments. Cancer, AD, or AMD can be seen at both opposite ends of a biological pattern. In cancer, there is unrelenting cell division. In AD or AMD, there is prominent apoptotic cell death. These diseases are different entities but share multiple common epidemiological and biological features [1–3]. Cancer and Alzheimer's disease can be considered metabolic diseases [4,5]. Similarly, AMD can be seen as a disease with features common to cancer and AD [6,7].

Our work aims to highlight the underlying unity of these diseases and that metabolic shifts and increased osmotic pressure are also pivotal in the development of AMD. Increased osmotic pressure is well known to cause inflammation [8] and play a key role in cancer and Alzheimer's disease [9].

We hypothesize that increased osmotic pressure because of inflammation of the posterior segment results in the increased secretion of lactic acid -by the Muller glial cells- which will feed the

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retinal cells. The retina cannot metabolize this lactic acid, resulting in acidic intracellular pH, synaptic dysfunction, extracellular deposition (Drusen), and ultimately apoptosis.

2. Overview

Age-related macular degeneration (AMD) is an eye condition strongly associated with aging. It can result in significant vision loss and blindness [10–12]. Age-related macular degeneration (AMD) is a chronic eye illness that mostly affects individuals over 50, while it can sometimes strike younger people in industrialized countries [13,14].

AMD is a retinal disease that typically affects the macula and gradually impairs vision in the central region of the field of vision. The primary clinical symptoms of early-stage AMD include drusen and changes to the retinal pigment epithelium [15].

Four stages can be distinguished in AMD [16–18]. The initial phase consists of typical aging changes with no aberrant pigmentation and just a little drusen. At this point, the drusen's diameter is less than 63 mm. While some intermediate drusen with diameters of 63 and 124 mm are in the second stage of AMD, no abnormalities are related to the RPE cells. The third stage is marked by RPE anomalies, at least one big drusen (diameter 125 mm; intermediate AMD), extensiveness, and moderateness. Advanced AMD, or stage 4, is characterized by geographic atrophy (GA) of the fovea or other age-related features of neovascular macular degeneration (nAMD) that lead to vision loss [15,19].

The non-dividing human retinal pigment epithelium (RPE) is a cell that performs several vital tasks for the survival of photoreceptor cells. As aging progresses, the RPE experiences several alterations that eventually result in the formation of drusen, a clinically noticeable localized yellow deposit of extracellular, polymorphous material at the interface between RPE and the inner collagenous zone of Bruch's membrane. The primary indicator of AMD is the presence of drusen inside the macula. In contrast, people with tiny drusen who do not have any other ocular abnormalities have a lower chance of developing the disease's more severe manifestations [11,17].

AMD patients exhibit a highly varied clinical appearance associated with drusen features and pigmentary abnormalities, including hypo- and hyperpigmentation. Numerous diseases can lead to geographic atrophy (GA) or choroidal neovascularization (CNV) AMD, often known as dry or wet AMD, respectively. These pathologies include focal detachment of the RPE, outer retinal atrophy, and new blood vessel growth between Bruch's membrane and the retina [11].

AMD is typically categorized based on the size of the drusen in clinically applied categorization methods that evaluate the severity of the non-sight-threatening early phases of this illness. Large drusen are classed as "intermediate" AMD and medium-sized drusen are regarded as "early" AMD. The likelihood of experiencing geographic atrophy (GA) and/or neovascular AMD, is highest when drusen are vast in area and accompanied by pigmentary changes [20].

3. Epidemiology

It has been estimated that 1.75 million Americans aged 40 and above have AMD, making the overall prevalence of neovascular AMD and geographic atrophy 1.47%. With more than 15% of White women over 80 years old having neovascular AMD and/or geographic atrophy, the prevalence of AMD rose with age. Over 7 million people were at significant risk of getting AMD because they had drusen that measured 125 microns or greater. The aging population is expected to lead to a 50% increase in AMD cases, reaching 2.95 million by 2020. White people had a considerably higher prevalence of age-related macular degeneration than did Black people [21].

The highest disease burden is seen in non-Hispanic White Europeans; however, the prevalence of AMD varies significantly by ethnicity. In a recent study, Wong et al. computed the pooled prevalence of population-based studies of AD across ethnically varied age groups (45–85 years) and found that the highest prevalence was found among people of European heritage, ranging from 12.3 to 30% as age increased [22]. The disease burden among Asians (7.4%), Africans (7.5%), and Hispanics (10.4%) is very high, despite a minor decrease (14). Nevertheless, the illness burden in the US has

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been estimated by some researchers to be lower, with non-Hispanic White Europeans having the highest prevalence at roughly 7.3% [15,23].

The incidence of age-adjusted dry AMD ranged from 0.3% to 0.4% in a population-based cohort research that integrated data from three population-based cohort studies (mean age: 60.1-65.7 years), with follow-up times ranging from 4.8 to 6.5 years. A higher incidence was associated with late-stage AMD disease. The incidence of dry AMD was also correlated with baseline drusen status in a North American study (N = 3,549). Patients with large bilateral drusen at baseline (n = 241) had a 10-year incidence risk of dry AMD diagnosis of 9.9%; patients with large bilateral drusen and RPE changes at baseline (n = 44.3%); and patients with late AMD (dry or wet) in one eye at baseline (n = 390) had a 10-year incidence risk of 53.9% [15,24].

Approximately 20 million Americans and 196 million people worldwide suffer from age-related macular degeneration. AMD is a major contributor to severe visual impairment in the elderly and is predicted to impact 288 million individuals globally by 2040. Furthermore, AMD affects 0.3 out of every 1000 persons in the 55 to 59 age group and 36.7 out of every 1000 people in the 90+ age group each year. It is estimated that 71% of late-stage AMD cases are heritable [25].

4. Risk Factors

Numerous factors, both modifiable and non-modifiable, have been associated with an elevated risk of AMD development. Aging, ethnicity, and genetics are some of the multiple risk factors contributing to advanced AMD development [11,26].

Extracellular debris deposits known as drusen are seen in the space between Bruch's membrane (BM) and the retinal pigment epithelium (RPE). The primary indicator of AMD is the presence of drusen inside the macula. The number of drusen overall, as well as the area or volume of drusen assessed, are risk factors for the development of GA and nAMD [27–29]. Additionally, the placement of the drusen has prognostic significance for the course of the disease; that is, eyes that have drusen close to the fovea are more likely to develop late AMD than eyes that have drusen farther from the fovea [30–32]. According to a recent study, the development of drusen may initiate an inflammatory cascade that contributes to the advancement of AMD [26,33].

It has been demonstrated that 34 genetic loci, comprising 52 gene variations, are connected to AMD [34]. Numerous combinations of gene variations have been found in many chromosomes, including chromosomes 1, 6, and 10 [35,36], using genome-wide screening techniques. These responsible genes regulate immune response, inflammatory processes, and retinal homeostasis. Variations in these loci are thought to be responsible for the degree of dysfunction of these responses in AMD patients. High-temperature requirement serine peptidase 1 (HTRA1; also known as age-related maculopathy [ARM] susceptibility 2 [ARMS2]) on chromosome 10 at 10q26, CFB/C2 on chromosome 6 at 6p21.3. and CFH on chromosome 1 at 1q31.3 are the most studied potential genes [11,37,38]. Genetic predisposition has a greater influence than just an individual's increased risk of getting AMD; it can also impact how well an individual respond to treatment. A combination of high-risk alleles in CFH, ARMS2, and VEGFA was shown by Smailhodzic et al.[39] to be linked to an earlier age of onset and a poor response to intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapies in AMD patients. Additionally, variations of the CFH gene polymorphism T1277C were linked to a limited morphological response and a delayed functional response to the initial intravitreal injection of Avastin (bevacizumab) in patients with homozygous CC group, as reported by Medina et al.[26,40,41].

Age is by far the most significant demographic risk factor for AMD [26,30–32] According to a recent meta-analysis that combined data from 14 population-based studies, the prevalence of early AMD increased from 3.5% in individuals 55–59 years old to 17.6% in those 85 and older. These prevalence rates rise from 0.1% to 9.8%, respectively, for late AMD. [10,26]. Age is marginally more strongly related to the development of geographic atrophy (GA) compared to neovascular AMD (nAMD)[42–44]. Furthermore, While AMD is rare in individuals under 50, patients over 75 have a threefold higher risk of developing the condition than those between 65 and 74 years of age. In the United States, 30% of those over 85 have AMD [11].

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The primary significant modifiable risk factor is smoking. AMD is two to four times more common in smokers over 40 than in nonsmokers of the same age [41]. Indeed, smoking has been the most reliable variable linked to neovascular AMD and geographic atrophy. A meta-analysis of five case-control studies, five cross-sectional studies, and six prospective cohort studies has also calculated the risk of smoking. Current smokers exhibited a significantly higher risk of AMD compared to never-smokers [45].

There are still contradictory results on the association of sex with predisposition and progression of AMD. While both men and women can get AMD, some research indicates that females have an increased likelihood of developing early AMD,[43,46] and late AMD [26,47] particularly nAMD [32,48]. Other research, however, indicates that there is no association between sex and the advancement of the illness [26,31,42,49].

Diet, lifestyle, and nutrition play important roles in AMD. The systolic or diastolic blood pressure or the use of antihypertensive drugs was not substantially connected with an increased risk of either early- or late-stage AMD. The French ALIENOR research found that high pulse pressure was linked to an increased risk of late-stage AMD [50]. While monounsaturated fats may be beneficial (30), a high diet of certain lipids, such as trans fats, saturated fats, and omega-6 fatty acids, has been linked to a twofold rise in the prevalence of AMD [26,51].

5. Inflammation as the Driving Force in Cancer, Alzheimer's, and Aging

In cancer, AD, and AMD, there is a small proportion of patients who have inheritable genetically transmissible risk factors [52,53]. Multiple genes are known to be implicated in cancer. Compared with the much more common sporadic cancer, these tumors arise most commonly before the age of fifty [54].

There are also cases of familial AD of autosomal-dominant inheritance, which usually has an onset at an early age [55]. Most autosomal-dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilin 1 and 2 [56,57]. The vast majority of cases of AD do not exhibit autosomal-dominant inheritance and are thus termed sporadic AD. Similarly, a small proportion of AMD appears to have a genetic component [58]. These genetic features are rare in contrast to the most common sporadic ones. The vast majority of cases of AMD are sporadic. AMD, like cancer and Alzheimer's disease, is strongly age-related [35].

In 1863, It was hypothesized that the origin of cancer occurs at sites of chronic inflammation [59]. A demonstration of the carcinogenicity of inflammation is foreign-body carcinogenesis [60]. The physical characteristics of the implant, rather than the chemical composition, are the critical determinants of tumor development. Abrasive, but not smooth, implants are both inflammatory and carcinogenic [60]. Inflammation is also a risk factor for AD [61]. Brain inflammation induced by repeated trauma increases brain levels of proteins associated with neurodegeneration such as amyloid β 1–42, observed in AD, total tau, and α-synuclein observed in Parkinson's disease (PD) [62].

Elderly people express low-level systemic inflammation [63]. Systemic inflammation plays a key role in the diseases of aging [63]. Inflammation, as seen in the process of aging, is a determinant in most of the diseases of the elderly [64]. The role of inflammation in AMD has been partially overlooked and is characterized by complement activation [65]. There are scanty reports about its importance but no clear explanation about its central role in this disease [24]. Another clue to the link between AD and AMD is the presence of beta-amyloid in the brain [66].

6. Inflammation and Increased Osmolarity

Inflammation is a clinical feature that can be caused by factors as diverse as heat, freezing temperature, trauma, or multiple chemicals resulting in vascular leakage [67,68]. Inflammation (a clinical feature) is closely related, if not synonymous, to hyperosmolarity (a physical feature) [8,69]. Animal models of inflammation demonstrate that in inflammatory fluids, whatever the cause, there is protein content, resulting in increased osmolarity. Increased osmolarity, whatever its cause, results in inflammation. Increased extracellular osmolarity stimulates cytokine synthesis and secretion and results in the proliferation and activation of immune cells [8].

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The role of osmolarity has been demonstrated in the pathologies of the anterior segment of the eye, such as dry eye [70], corneal ulceration [71], and glaucoma [72]. Cataracts can also be caused by increased osmotic pressure [73].

7. Osmosis in the Posterior Segment

The posterior segment of the eye has one of the highest metabolic rates, requiring a rich supply of oxygen and other nutrients [74]. While the central retinal artery provides the inner retina's blood supply, most of its oxygen demand (seven times more important than that of the brain at constant weight) is supplied by diffusion from the underlying choroid, which is the sole supply of the avascular fovea. The choroid has the highest rate of blood flow per weight of any tissue [75]. The choroid, because of its intense blood flow and the permeability of the Bruch's membrane, has a major role in the thermoregulation of the macula. The innermost layer of the choroid is the Bruch's membrane, a 2-4μm thick elastic sheet. At a young age, it is permeable to liquids, ions, and small proteins [76].

There is evidence of a dialysis-like phenomenon in the eye. Like in an artificial kidney cartridge, where there is the concomitant circulation of arterial blood and dialysate, the choroidal and the retinal fluid circulation are separated by the Bruch's membrane. The Bruch's membrane is semi-permeable and this membrane is formed of glycated proteins such as heparin. The flow of the choroidal arteries is about 10 to 20 times more important than the flow of the retinal arteries [75,77], increasing the hydrostatic pressure in the retina. The two compartments of dialysis in the eye are the retinal pigment epithelium (RPE) and outer segments of the visual cells (OS) as the dialyzed sector animated by a centripetal flow, and secondary the choroid, which may be equated with a dialyzing bath driven by a centrifugal rather than counter flow. That is, to increase the exchange's surface and to maintain a gradient, reinforce efficiency [78].

8. Aging of the Posterior Segment: Vascular Changes

During aging, there is a clear decrease in the perfusion of the choroid. The normal thickness of the choroid, measured in younger emmetropes (<27 years old) by EDI-OCT, varies from 264 to 436μ [79]. It decreases by 15.6μ per decade[80,81]. The Bruch membrane thickens, further altering exchanges [76]. The choroidal blood flow decreases, as does the porosity of the Bruch membrane. The decreased perfusion will result in ischemia and, therefore, the impairment of retinal pigment epithelium's (RPE) hemodynamic cellular antioxidant properties. The retinal pigment epithelium RPEis is deficient in managing such increased oxidative stress either by the apical synthesis of Reticular Pseudo Drusen (RPD), also named Subretinal Drusenoid Deposit (SDD) or by the more common basal exocytosis of multiple drusen composed of lipofuscin and bis retinoids [65].

The retinal pigment epithelium (RPE) separates the retinal (apical) and choroidal (basal) environments and contributes to a blood-retinal barrier (BRB), which provides a proper environment for photoreceptor cells. The osmolality on the choroidal side is higher than on the retinal side in physiological conditions [82]. Thus, the osmotic gradient from the apical to basal sides is thought to elevate transepithelial electric resistance (TER). TER reflects ion permeability across the epithelia [83]. So, gradients illustrate the direction of epithelia function or pathological changes according to apical and basal osmotic conditions through hydrostatic pressure (HP) [82]. The accumulation of these multiple deposits and wastes of various molecules will also result in a significant increase in osmolarity [8].

9. Increased Osmolarity and AMD

To the best of our knowledge, osmolarity has not been measured in any pathology of the posterior segment, but there is indirect and direct evidence of its importance in AMD. AMD is characterized by multiple features, such as infiltration of the retina by inflammatory cells, proliferation of fibroblasts, and new blood vessel formation. In the neovascular subfoveal

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membranes, the proliferation of fibroblasts goes along as a conjunctival tissue wearing the new vessel network [84].

The secretion of vascular growth factors that leads to wet macular degeneration by the retinal human pigment cells is increased by osmolarity [85,86]. Retinal detachment can be induced by the intravitreal injection of a hyperosmotic solution [87]. Fibroblast proliferation could be a consequence of increased osmolarity [88].

The best demonstration of the key role of osmolarity in AMD comes from animal models [89]. The retina can be damaged by either blue light or a laser. This results in vascular damage and, in turn, increased osmolarity because of an extravascular protein leak. Polyethylene Glycol (PEG) is a chemically inert but osmotically active chemical. PEG is not metabolized in vivo [90]. The subretinal injection of PEG results in choroidal neovascularization [90] and the formation of structures resembling drusen [91].

10. Metabolic Shift Because of Increased Pressure

To perform their normal physiological functions, cells must maintain the intracellular pH (pHi) within the physiological range. Intracellular enzyme activity, cytoskeleton component integration, and cellular growth and differentiation rates are all closely associated with pHi [92]. A fall in pHi decreases neuronal activity and is responsible for apoptosis [93].

In AD, there is a shift toward intracellular acidosis and apoptosis. It has been demonstrated that neurons feed on lactate secreted by glial cells [9]. In the case of AD, there is increased secretion of lactic acid as measured by spinal fluid [94].

he increased secretion of lactate by glial cells results in increased uptake by neurons and intracellular acidosis [9]. This is the inverse of Warburg's effect, as first described by [95]. The fall in pHi will result in neuronal cell death.

A similar scenario is probably at stake in macular degeneration. Neurons feed on lactate released by glial cells, and similarly, retinal cells feed on lactate released by Muller glial cells [96]. Müller cells, akin to glial cells in the brain, metabolize glucose to lactate, which is preferentially taken up by photoreceptors as a fuel for their oxidative metabolism [97]. Even in the presence of glucose and oxygen, cultured human Müller cells obtain most of their ATP, principally from glycolysis, and display a low rate of oxygen consumption [98]. They feed lactate to the retinal cells. Indeed, the increased secretion of lactic acid will have multiple consequences: increased urinary secretion of lactate [99], increased secretion of markers of inflammation [100], and VEGF [101]. The acidic pH plays a crucial role in retinal cell death [102].

The increased secretion of lactic acid is a consequence of inflammation. In inflammation, whatever its cause, there is increased secretion of lactate, resulting in increased serum and urine levels of lactate [103,104]. It has been shown that in response to osmotic stress, cells display acute metabolic remodeling through the control of pyruvate dehydrogenase phosphorylation through direct osmosensing in mitochondria [105]. The correlations between inflammation, hyperosmolarity, and metabolic changes in AMD are shown in Figure 1.

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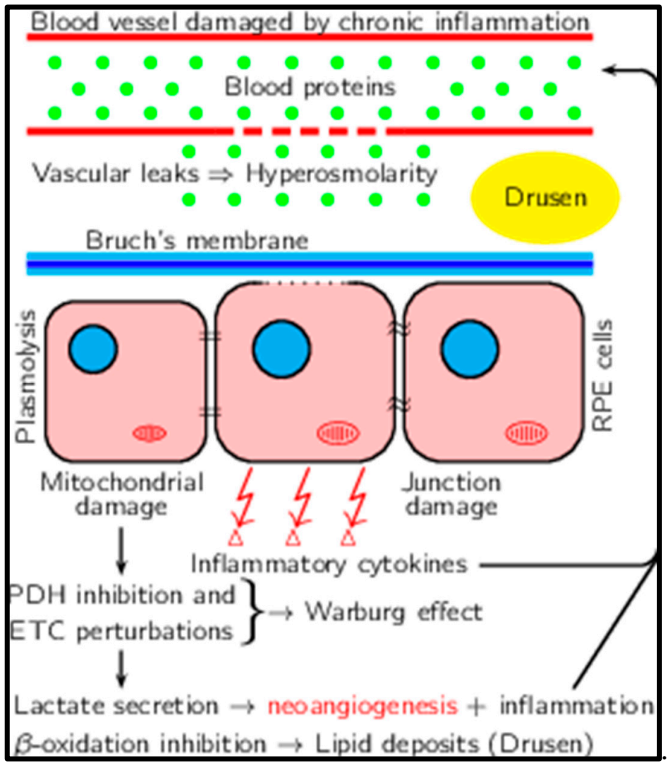

Figure 1. Correlations between inflammation, hyperosmolarity, and metabolic changes in AMD.

The increased secretion of lactate is a consequence of hyperosmolarity. Exposure to increased osmotic pressure has major effects on the metabolic profile of the target cells. Hamraz exposed normal Chinese Ovarian cells (CHO cells) to increased osmotic pressure and showed that these cells expressed increased anaerobic glycolysis, decreased oxidative phosphorylation, and enhanced lactate secretion—the so-called Warburg effect [106]. Table 1 summarizes the metabolic similarities and differences between cancer, Alzheimer's disease, and AMD.

Table 1. Comparison of metabolic characteristics of cancer, Alzheimer's disease and Macular degeneration.

Characteristic	Cancer	Alzheimer disease	Macular degeneration
Extracellular osmolarity	Increases	Increases	Increases
Oxidative phosphorylation	Decreases in cancer cells	Decreases in neurons	Decreases in photoreceptors
Extracellular lactate concentration	Increases	Increases	Increases
Intracellular pH	Increases in cancer cells	Decreases in neurons	Decreases in photoreceptors
Cell ecosystem	Cancer cells + Tumor Associated Macrophages + stroma	Neurons + glial cells	Photoreceptors + Müller cells

11. Shift to Alternative Energy Sources

There is very limited data on the metabolic pathways involved in macular degeneration. The crucial enzymatic activities of most enzymes in glycolysis and mitochondria have not been measured. It is probable that the metabolic patterns are the same in AMD as in Alzheimer's disease or even cancer. However, it has been recently shown that homocysteine causes a metabolic shift from

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mitochondrial respiration to a high rate of glycolysis in RPE cells in AMD. A high rate of glycolysis was demonstrated by a high lactate/pyruvate ratio. This led to the activation of angiogenesis via increased levels of VEGF [107].

In cancer and Alzheimer's disease, there is a decrease in mitochondrial activity. There is a decrease in the activity of the pyruvate kinase, which conveys pyruvate into acetyl coA. Pyruvate dehydrogenase (PDH) is a complex set of subunits. It converts pyruvate into acetyl-CoA. This complex enzyme connects glycolysis, which takes place in the cytoplasm, and the mitochondria, where the Krebs cycle takes place. The activity of the PDH is decreased in both cancer and AD [7,8]. Lipoic acid is a cofactor of the second subunit of PDH.

In AMD, supplementation with lipoic acid improves long-term vision [108], suggesting the key role of pyruvate dehydrogenase. Methylene blue, a century-old drug, can receive two electrons from NADH in the presence of complex I and donate them to cytochrome C, providing an alternative electron transfer pathway in defective mitochondria [109]. The addition of Methylene Blue decreases Warburg's effect induced by increased osmolarity and lowers the secretion of lactic acid [110].

Methylene blue provides a protective effect in neurons and astrocytes against various insults in vitro, like superoxide production. In humans, methylene blue appears effective in the treatment of early-stage AD and memory loss [109–111]. In animal models of AMD, methylene blue prevents neurodegeneration caused by rotenone in the retina [111].

12. Conclusions

This work strongly suggests that macular degeneration, like inflammation, is a straightforward consequence of increased osmotic pressure. In animals, drugs that increase osmotic pressure cause AMD. Increased pressure results in intracellular acidosis and apoptosis. Treatment should aim at normalizing the pressure and limiting the metabolic consequences of increased pressure. Drugs normalizing metabolic abnormalities such as those seen in AMD appear to be promising.

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