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Mitochondrial Dysfunction in Retinal Diseases

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Abstract

The mitochondrion is a vital intracellular organelle for retinal cell function and survival. There is growing confirmation to support an association between mitochondrial dysfunction and a number of retinal degenerations. Investigations have also unveiled mitochondrial genomic instability as one of the contributing factors for age-related retinal pathophysiology. This review highlights the role of mitochondrial dysfunction originating from oxidative stress in the etiology of retinal diseases including diabetic retinopathy, glaucoma and age-related macular degeneration (AMD). Moreover, mitochondrial DNA (mtDNA) damage associated with AMD due to susceptibility of mtDNA to oxidative damage and failure of mtDNA repair pathways is also highlighted in this review. The susceptibility of neural retina and retinal pigment epithelium (RPE) mitochondria to oxidative damage with ageing appears to be a major factor in retinal degeneration. It thus appears that the mitochondrion is a weak link in the antioxidant defenses of retinal cells. In addition, failure of mtDNA repair pathways can also specifically contribute towards pathogenesis of AMD. This review will further summarize the prospective role of mitochondria targeting therapeutic agents for the treatment of retinal disease. Mitochondria based drug targeting to diminish oxidative stress or promote repair of mtDNA damage may offer potential alternatives for the treatment of various retinal degenerative diseases.

Keywords

Mitochondria; Diabetic retinopathy; Glaucoma; Retinal degeneration; Age-related macular degeneration

INTRODUCTION

The mitochondrion is a critical organelle for cell function and survival. Its primary roles are adenosine triphosphate (ATP) production, control of cellular metabolism and regulation of apoptosis (programmed cell death). It consists of inner and outer membranes composed of phospholipid bilayers containing numerous integral proteins. Mitochondrial density varies among different cell types and is expressed abundantly in highly metabolic active cell types such as retinal pigment epithelium (RPE).[1] Due to its critical functioning, mitochondrial dysfunctions may severely affect tissue homeostasis. Oxidative damage induced

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mitochondrial dysfunction has been proposed as a most prevalent ageing theory.[1–4] Furthermore, involvement of mitochondrial DNA (mtDNA) damage and mitochondrial theory of ageing has been observed in age-related macular degeneration (AMD).[5]

Acute and chronic mitochondrial dysfunctioning is associated with a number of age-related degenerative diseases including Parkinson's, Alzheimer's and AMD. In this review, we will summarize recent developments in understanding the role of the mitochondrion as a weaker link in the antioxidant defenses of retinal cells and a potential contributor to the pathogenesis of retinal degenerations such as diabetic retinopathy, glaucoma and AMD. We will further highlight the mechanistic basis of mtDNA damage associated to AMD. Moreover, the potential role of mitochondria targeting agents for the treatment of retinal diseases will be outlined at the end of the review.

Diabetic Retinopathy

Diabetic retinopathy is the most prevalent microvascular complication of diabetes, and remains a leading cause of vision loss in many developed countries. The development of this microvascular disease occurs gradually and silently in as many as 50% of type I and 10% of type II diabetic patients within 15 years of diagnosis.[6,7] Chronic hyperglycemia and other risk factors (hypertension, dyslipidaemia) are believed to trigger a cascade of biochemical and physiological changes that lead to microvascular damage and retinal dysfunction. The retinal manifestations of diabetes mellitus are broadly classified as either non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR). The progression of NPDR, which covers only intraretinal microvascular changes, starts from mild non-proliferative abnormalities (altered retinal vascular permeability) to moderate and severe NPDR (vascular closure). The eventual progression of PDR is characterized by new blood vessel formation and sometimes fibrous band proliferation on the retinal surface. Macular edema, characterized by retinal thickening from leaky blood vessels, can develop in both stages of retinopathy due to increased retinal vascular permeability which leads to fluid accumulation in the retina.[8–10]

Various hyperglycemia-induced metabolic abnormalities, including increased activity of the polyol pathway, advanced glycation end products (AGEs) and protein kinase C (PKC) activation are implicated in the progress of diabetic retinopathy. These metabolic pathways are considered to be interconnected and may mediate oxidative stress. Elevated oxidative stress plays a major role in the pathogenesis of diabetic complications.[11,12] Oxidative stress is the accumulation of reactive oxygen species (ROS) beyond the capacity of a cell to defend, because of increased generation or impaired removal of ROS.[13] The presence of a high content of polyunsaturated fatty acids, high oxygen uptake and glucose oxidation renders the retina more susceptible to oxidative stress relative than any other tissue.[14] Critical events suggested in the pathogenesis of diabetic retinopathy are hyperglycemia, changes in the redox homeostasis and oxidative stress. Increased oxidative stress is reported in diabetic retina of animal models (diabetic and galactosemic rats).[15] Elevated retinal levels of lipid peroxides, superoxide and hydrogen peroxide and down-regulation of the mRNA of the enzymes responsible for scavenging superoxide, superoxide dismutase (SOD), and glutathione reductase were reported in diabetic rat and mouse models.[16–18] A decreased

level of intracellular antioxidant (GSH) and impairment of antioxidant defense enzymes in the retina was also reported in diabetic rats.[19–20] Furthermore, increased oxidative stress is also observed in bovine retinal endothelial cells (BREC) and pericytes incubated in high glucose medium and in other non-vascular retinal cells including transformed retinal Muller cells (rMC-1) and photoreceptors.[16,21] These experiments clearly suggested an important role of oxidative stress in the development of retinopathy in diabetes. Moreover, animal studies have confirmed that oxidative stress not only contributes to the development of diabetic retinopathy but also offers resistance to reversal of the conditions after glycemic control.[22] However, the mechanism by which oxidative stress can contribute to the pathogenesis of diabetic retinopathy remains to be elucidated.

Mitochondrial Dysfunction in Diabetic Retinopathy

Mitochondria are considered to be the prime endogenous source of superoxides, peroxynitrite, and hydroxyl radicals, and are also a target for damaging effect of oxidants, suggesting the existence of a vicious cycle of oxidative damage.[23] Chronic overproduction of ROS in the retina results in abnormal mitochondrial functions in diabetes (Figure 1).[13,14,24] Inhibition of antioxidant scavengers is one of the ROS-induced dysfunctions in mitochondria that may lead to enhanced sensitivity of retinal cells to oxidative stress. The isoform of SOD in the mitochondria (MnSOD) along with GSH may be suppressed in the diabetic and high glucose-cultured retinal mitochondria.[25–27] Increased mitochondrial DNA damage has been reported in the diabetic retina of an animal model.[28] ROS mediated damage to the mitochondrial lipid membrane enhances permeability of the mitochondrial membrane which represents another cellular dysfunction caused by ROS. Increased swelling of the mitochondria was observed in the retina of diabetic mice.[26] It is widely accepted that apoptosis of retinal cells is the most common incident in diabetic retinopathy. Kowluru et al. have demonstrated that the release of cytochrome c from mitochondria to the cytoplasm and Bax translocation from the cytoplasm to mitochondria that could drive cell apoptosis were increased in retinal capillary cells in diabetes.[29] Thus, it is evident that mitochondria play a crucial role in the development of retinopathy in diabetes, and oxidative stress can modulate mitochondrial cytochrome c release resulting in increased retinal capillary cell death.

Diabetic Retinopathy Treatments Targeted to Mitochondrial Dysfunction

Diabetic retinopathy is a complex disease which is difficult to treat due to its multifactorial nature. An efficient therapy will probably be a combination of drugs targeting multiple pathways involved in the pathogenesis of diabetic retinopathy. Since the disease pathogenesis is partially attributed to mitochondrial dysfunction, treatment options should also consider restoring normal mitochondrial function. Oxidative stress is the significant instigator of hyperglycemia-induced mitochondrial damage. Therefore, treatment strategies to improve mitochondrial function by lowering oxidative stress may be an appropriate alternative.[15,24] Sheu et al. has described a number of antioxidants which can be transported into mitochondria but only a few have been tested in diabetic retinopathy.[30] Considering the role of superoxides in the development of diabetic retinopathy, SOD mimetics may represent a class of treatment to counter the effect of oxidative stress. MnSOD mimics are low-molecular weight, manganese containing, non-peptide molecules with similar function, and catalytic rates of native SOD enzymes. Kowluru et al.[24,29] have shown that MnTBAP

[manganese (III) meso-tetrakis (4-carboxypheny) porphyrin], a MnSOD mimic, can significantly inhibit glucose-induced decrease in GSH levels and translocation of cytochrome c from mitochondria and Bax into the mitochondria of retinal capillary cells. It can also inhibit apoptosis by suppressing caspase-3 activation.[24,29]

It is therefore essential to recognize treatment strategies that could inhibit superoxide production which might represent a possible direction for clinical research in diabetes. Although the mimetics appear to be very promising, it is not known whether any of these mitochondria-targeted treatments are beneficial in diabetic retinopathy. Furthermore, pharmacokinetics and route of administration also need to be addressed. Additional animal studies and clinical trials can resolve such issues.[15,24]

Glaucoma

Glaucoma is a neurodegenerative disease of the optic nerve characterized by the accelerated death of retinal ganglion cells (RGCs) and their axons which ultimately leads to progressive vision loss. Elevated intraocular pressure (IOP) and age are key risk factors for glaucoma. Reducing IOP is the only current treatment option available to retard glaucoma progression in clinical practice. However, control of IOP by itself may not be sufficient to arrest the progression of glaucoma and strategies that compliment IOP control for protecting the optic nerve are required.[31,32]

MITOC HONDRIA L DYSFUNCTION IN GLAUCOMA

Mitochondrial dysfunction is believed to contribute to the pathogenesis of a number of neurodegenerative disorders. Glaucoma has similar etiology to other neurodegenerative diseases, such as selective loss of a single neuronal cell population, age related incidence, and neuronal cell death. The dense distribution of mitochondria around the optic nerve head, the primary site of glaucomatous axonal injury, reflects a high requirement for ATP.[31,32] Ju et al.[33] have recently demonstrated the induction of mitochondrial fission, abnormal cristae depletion, and cellular ATP reduction in differentiated RGC-5 cells exposed to high hydrostatic pressure over 3 days. This observation suggests that elevated pressure, a major risk factor in glaucoma, may disrupt mitochondrial structure and function in RGCs, possibly leading to apoptosis (Figure 2).[31,33] An association between glaucoma and mitochondrial dysfunction has also been suggested in a recent clinical study where a 20% reduction in mitochondrial respiratory function and an increase in mitochondrial DNA mutation were observed in peripheral blood of primary open-angle glaucoma patients relative to an age-matched control group.[34] The mitochondrion is a key regulator of apoptosis and is implicated as the prime factor responsible for neuronal loss in neurodegenerative diseases. Evidence has also suggested that apoptosis is an important mechanism of cell death in glaucoma neurodegeneration. RGC apoptosis occurs in animal glaucoma models and in the retina of glaucoma patients.[35,36] There is growing evidence to support involvement of mitochondria-mediated ROS-induced RGC injury. ROS generation is noticed in the retina and optic nerve of glaucoma animal models and in retinal ischemia reperfusion models.[37,38] Furthermore, human studies have also confirmed the involvement of mitochondria-mediated oxidative stress in glaucoma due to up-regulation of various antioxidant proteins (serum auto-antibodies, glutathione S-transferase and iron-regulating proteins).[39,40]

GLAUCOMA TREATM ENTS TARGETED TO MITOC HONDRIAL DYSFUNCTION

As a potential neuroprotective therapy, various antioxidants have been studied in neurodegenerative diseases with partial success. Advances have also been made in targeting antioxidants directly to the mitochondria, a major site of ROS production, by conjugating antioxidants to lipophilic cations.[30,41] The mitochondria-targeted cationic plastoquinone derivative SkQ1 (10-(6′-plastoquinonyl) decyltriphenylphosphonium) has been investigated as a prospective tool for treating experimental glaucoma induced by serial injections of 2% hydroxypropyl methyl cellulose to the anterior segment of the rabbit eye. Once, daily drops of 5 μM SkQ1 caused a reduction in glaucomatous changes.[42] SkQ1 appears to be a promising candidate for treating glaucoma. Involvement of mitochondria in glaucoma pathogenesis might therefore represent a new therapeutic target for protecting the optic nerve and preventing vision loss.

AGE-RELAT ED MACULAR DEGENERATION

AMD is a progressive neurodegenerative disease that primarily affects the central region of the retina (macula) and is a leading cause of blindness in the elderly. The presence of macroscopically visible soft drusen, with areas of hyper- or de-pigmentation are characteristic early symptoms of AMD, whereas atrophy of photoreceptors and RPE or choroidal neovascularization are evident during later stages of the disease.[43–47]

MITOC HONDRIA L DYSFUNCTION IN AMD

Strong evidence showing mitochondrial dysfunction in AMD has been reported. An association between AMD and a variant of mitochondrial protein (LOC387715/ARMS2 (age-related maculopathy susceptibility 2)) has been identified.[48] In AMD genetic variants at two chromosomal loci, 1q32 and 10q26 confer major disease risks. A consensus from multiple studies is that the 1q32 and 10q26 region simultaneously harbors a first and second major genetic determinant of AMD susceptibility.[49–52] Previous studies have identified chromosome 1q32 as harboring a susceptibility locus (complement factor H) for AMD which does not have any connection to the mitochondrion.[49,50] However, signals at 10q26 overlap two nearby genes, LOC387715/ARMS2 (age-related maculopathy susceptibility 2) and HTRA1/PRSS11 (high-temperature requirement factor A1). The LOC387715/ARMS2 gene produces a protein of unknown function that localizes in the mitochondria, and polymorphisms in LOC387715/ARMS2 alter the risk of AMD by modulating the function of this gene.[48,51–53] Furthermore, changes in the activity or regulation of LOC387715/ ARMS2 are likely to be responsible for the impact on AMD disease susceptibility.[53]

Retinal pigment abnormalities and RPE atrophy similar to those present in the early AMD phenotypes are detected in 75% of individuals with the MELAS A3243G mitochondrial DNA mutation.[54] mtDNA haplogroups which are associated with either increased or decreased prevalence of age-related maculopathy have been identified.[55] So far there is no report available which confirms the association of similar mtDNA haplotypes with AMD.

Based on this finding one can further explore the possible involvement of mtDNA haplogroups in AMD.

In addition, the oxidative stress hypothesis of AMD proposes that cumulative oxidative damage to proteins, lipids, and DNA also leads to disease progression. Changes in selected redox proteins (an indicator of increased oxidative stress) and altered protein expression reflecting impaired mitochondrial biogenesis were found in human donor eyes with the progression of AMD.[56,57] These findings led to the proposition that bioenergetic consequences of mtDNA derangements may be expressed in macular RPE as a maculopathy and contribute to the development of AMD. Evidence of mitochondrial dysfunction from human tissue examination and animal models has also been reported. Feher et al.[58] revealed through morphometric studies a significant diminution in number and area of RPE mitochondria as well as loss of cristae and matrix density with age in AMD specimens. These decreases were significantly greater in AMD than in normal aging. This study has further confirmed that besides changes in mtDNA, alterations of mitochondrial membranes may also play a crucial role in the development of mitochondrial dysfunctions in AMD.[58]

Despite the evidence of mitochondrial dysfunction in AMD where emphasis is focused on the RPE, only a few studies have been focused the role of mtDNA damage and repair in the retina. Barreau et al. has identified mtDNA deletions in aged human retina.[59] Increased mtDNA damage and decreased repair, along with reduced mitochondrial respiration in RPE and choroid of rodents are also observed with progression of ageing.[60–62] Thus, mtDNA damage in RPE is associated with aging and may be a susceptibility factor in the development of AMD.

Cell culture studies have shown damage to mtDNA but not to nuclear DNA (nDNA) of human RPE cells when exposed to oxidizing or alkylating agents.[63] Furthermore, nDNA damage repair appears to be rapid relative to mtDNA repair in the RPE, which appears to be slow and relatively inefficient. The lack of evidence for mtDNA repair in response to oxidative stress further suggests that the mitochondrion is a weaker link in the RPE cell's defense against oxidative damage.[5,64,65] A collective outcome of mtDNA damage will be the reduction in metabolic activity and/or an increased propensity for apoptosis. However, mtDNA repair capacity appears to be overwhelmed, resulting in diminished mtDNA repair which may play a significant role in the commencement of AMD.[5,60] Further evidence has shown that human RPE cells treated with H_2O_2 resulted in mtDNA damage, which leads to compromised mitochondrial redox function due to impaired repair mechanism.[5,63] This impaired repair mechanism clearly explains the susceptibility of mtDNA to oxidative damage in human RPE cells, together with the age-related decrease of the cellular antioxidant system.[5]

The susceptibility of RPE mtDNA to oxidative damage along with failure of mtDNA repair provides an intriguing and plausible mechanism for a mitochondria-based model of AMD and retinal degeneration. Figure 3 summarizes the possible mechanisms of AMD.[1,5,66]

AMD TREATM ENTS TARGETED TO MITOC HONDRIAL DYSFUNCTION

Treatment of AMD has always been a challenge for ophthalmologists. Therapeutic strategies targeted to the VEGF-signaling pathway has shown some success in the treatment of neovascular wet AMD, however, there are no proven medical treatments for the more common ‘dry’ AMD. Potential use of antioxidants for delaying later stage progression of AMD has been confirmed by the AREDS study.[67] However, success of this study was likely limited by the choice of dietary antioxidants (which was later addressed in a new NEI funded clinical trial) and the subsequent realization that dietary antioxidants provide differential subcellular protection in the epithelial cells.[68] In support of the therapeutic concept for retinal degeneration, a study by Jarrett et al. has further confirmed that dietary interventions can provide oxidative protection to hippocampal mtDNA and can lower ROS levels in rats.[69] Reports have further proven that Bcl-2 overexpression, melatonin, ascorbic acid and glutathione-S-transferase can prevent mtDNA damage in cultured RPE.[68,70–72] Several studies have also reported that SOD2 up-regulation, resveratrol, N-tertbutyl hydroxylamine, a-crystallin and l-carnitine have the ability to protect against mitochondrial dysfunction in the RPE.[73–77] Whether these antioxidants simply act by reducing ROS levels or act by a more direct effect on mtDNA is yet to be fully elucidated.

An alteration of mitochondrial membranes in AMD has immediate clinical significance as several *in vitro* and *in vivo* studies showed that mitochondrial membranes may be a target for the treatment of mitochondrial dysfunctions. Compounds with specific affinity for mitochondrial membranes (mitochondriotropic) can restore mitochondrial functions.[42] Alterations of mitochondrial membranes are accompanied by considerable accumulation of lipofuscin which may account for oxidative damage to the RPE.[78] It may result in impaired lipid metabolism and apoptosis, characteristics of late AMD.[79] Improvement in lipid metabolism in the RPE may be an innovative therapeutic approach for preventing AMD. As mitochondria and peroxisomes are implicated in both lipid biosynthesis and catabolism, Feher et al.[80] suggested that the most effective dietary intervention may be achieved by targeting these organelles. These researchers developed a new metabolic approach by combining mitochondriotropic compounds including acetyl-l-carnitine (ALC), n-3 fatty acids, coenzyme Q_{10} and vitamin E for improvement of retinal function in early AMD. Clinical studies have confirmed this finding, since a combination of ALC, ω-3 fatty acids and coenzyme Q_{10}, after an initial improvement, stabilized several visual functions in early AMD.[80] Recently, these preliminary results were confirmed by a randomized, double-masked, placebo controlled, clinical trial that showed improvement in both visual functions and fundus alterations in early AMD.[81] These results on restoration of mitochondrial function are certainly very promising for a new therapeutic approach for the treatment of AMD.

CONCLUSION

Mitochondria are attractive targets for drug-delivery because of their roles in cellular energy metabolism, programmed (apoptotic) cell death, and cell signaling. This review highlights the importance of mitochondria derived oxidative stress and to some extent mtDNA damage in the etiology of various retinal diseases (diabetic retinopathy, glaucoma and AMD).

substantial efforts must be devoted to developing strategies to target small and large therapeutic molecules to mitochondria. A number of possibilities exist for mitochondrial targeted drug delivery such as (i) therapeutic drug targeting based on negative inner membrane potential of mitochondria, (ii) mitochondrial based enzyme catalyze drug release from prodrugs, and (iii) mitochondrial localized transporter or receptor mediated prodrug delivery (Figure 4).[82–86] Continued research in this exciting area will undoubtedly provide a greater understanding of how oxidative stress and deficiencies of the mtDNA contribute to the pathogenesis of neurodegenerative retinal diseases. Future therapeutic strategies should target mitochondria with the ultimate goal of blocking or retarding the effects of chronic mitochondrial dysfunction.

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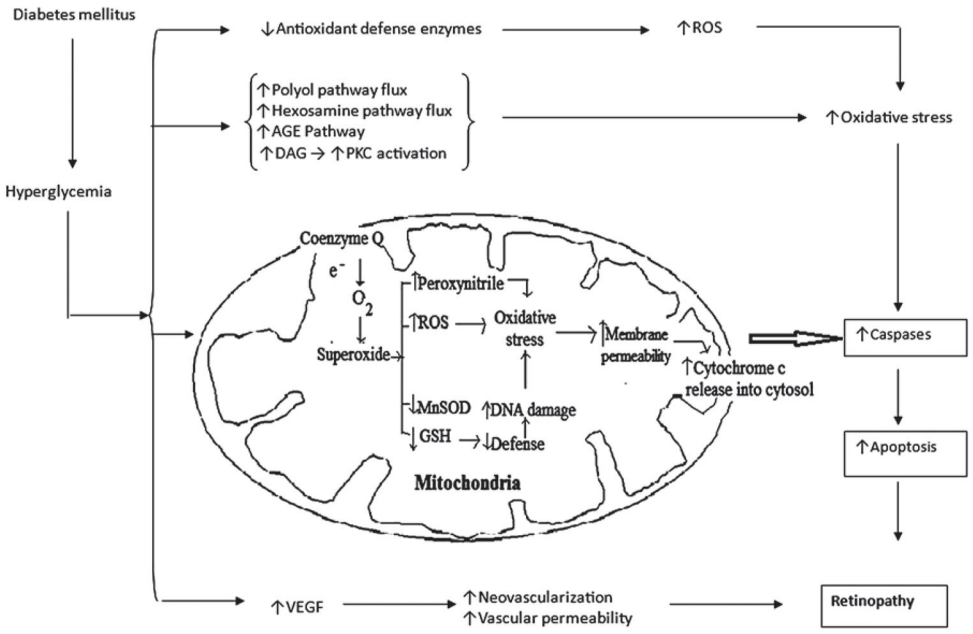

FIGURE 1.

Hyperglycemia mediated mitochondrial dysfunctioning in diabetic retinopathy.

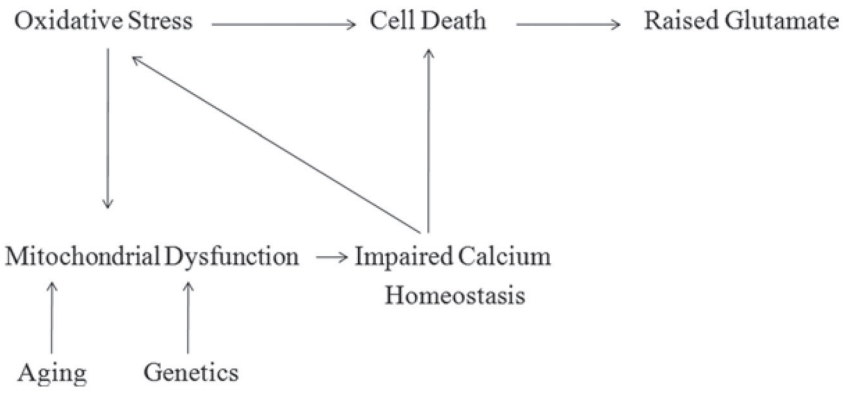

FIGURE 2.
Involvement of mitochondrial dysfunctioning in glaucoma pathogenesis.

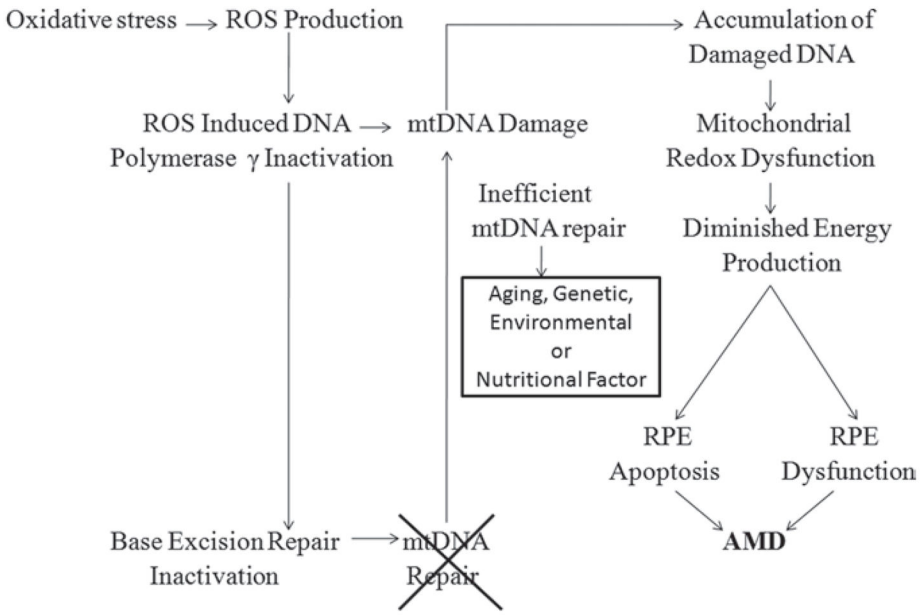

FIGURE 3.
ROS-induced mtDNA damage based model for development of AMD (1,5,66).

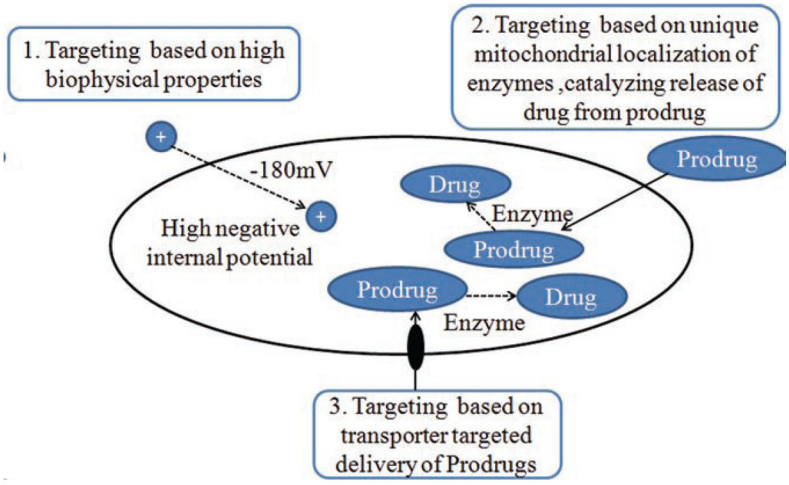

FIGURE 4.
Strategies for targeted delivery of drugs to Mitochondria.