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Therapeutic potential of co-enzyme Q10 in retinal diseases

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Abstract

Coenzyme Q10 (CoQ10) plays a critical role in mitochondrial oxidative phosphorylation by serving as an electron carrier in the respiratory electron transport chain. CoQ10 also functions as a lipid-soluble antioxidant by protecting lipids, proteins and DNA damaged by oxidative stress. CoQ10 deficiency has been associated with a number of human diseases including mitochondrial diseases, neurodegenerative disorders, cardiovascular diseases, diabetes, cancer, and with the ageing process. In many of these conditions CoQ10 supplementation therapy has been effective in slowing or reversing pathological changes. Oxidative stress is a major contributory factor in the process of retinal degeneration. In this brief review, we summarize the functions of CoQ10 and highlight its use in the treatment of age-related macular degeneration and glaucoma. In light of these data we propose that CoQ10 could have therapeutic potential for other retinal diseases.

Keywords co-enzyme Q10, oxidative stress, retina, age related macular degeneration, glaucoma, retinitis pigmentosa, diabetic retinopathy, protection

1. Introduction

Coenzyme Q10 (CoQ10), first identified by Crane et al, is a 1,4-benzoquinone-containing molecule with a hydrophobic tail harbouring 10 isoprenyl units (1). CoQ10 is ubiquitously distributed in various tissues and blood and presents in all cell membranes (2, 3). It is synthesized in the mitochondrial matrix and at least 12 genes are required for its biosynthesis; mutations in some of these genes have been reported to cause CoQ10 deficiencies (4). CoQ10 exists in more than one state within the body: oxidized (ubiquinone), partially reduced (semiquinone radical) and reduced (ubiquinol) forms (Figure 1A); the ratio of oxidized and reduced forms in various cellular membranes is dependent on the metabolic state of individual cells. Within the inner mitochondrial membrane, the CoQ10 pool is found in two main forms: approximately 30% is protein bound and principally participates in oxidative phosphorylation; the remainder is not protein-bound and contributes to different functions, the major one being as a lipophilic antioxidant (5). CoQ10 is required for cellular ATP generation by shuttling electrons from complexes I and II to complex III in the mitochondrial respiratory chain (Figure 1 B) (6). The oxidized form of CoQ10 is able to undergo two electron reductions in a reaction involving complex I and complex II, resulting in the formation of ubiquinol: subsequently, electrons are passed to complex III. Typically, tissues that are heavily reliant on oxidative metabolism, such as the myocardium, present a high concentration of CoQ10. It is the only naturally occurring endogenous lipid-soluble antioxidant which, in its reduced and active form ubiquinol, may act as a direct free radical scavenger, inhibiting the oxidation of lipids, proteins and DNA (6) or may act synergistically with other antioxidants, such as vitamin E, regenerating its oxidised form, tocopheryl radical. CoQ10 also demonstrates a regulatory role in the expression of genes involved in cell signalling, metabolism and nutrition transport (7). Moreover, it has been shown to exert an anti-inflammatory effect by reducing LPS-induced secretion of TNF-α, possibly via the NFkB1-dependent pathway (8).

CoQ10 deficiency is mainly associated with encephalomyopathy, infantile multisystemic disease, cerebellar ataxia, pure myopathy, and cardiofaciocutaneous syndrome. The causes of CoQ10 deficiencies are primarily due to mutations in ubiquinone biosynthesis genes (*COQ2*, *PDSS1* and *2*, and *ADCK3*) or in genes indirectly related to CoQ10 biosynthesis (*APTX*, *BRAF*, and *ETFDH*). However, the causes of CoQ10 deficiency still remain unknown in a large number of patients (4). Lowered levels of CoQ10 have been reported in different clinical conditions, including cardiovascular disease, diabetes, cancer, and neurodegenerative disease. More generally, a subliminal deficit of CoQ10 might also be observed in

paraphysiological states such as ageing: synthesis in human is known to peak around the third decade of life and subsequently decreases with age. Moreover, the use of commonly prescribed drugs that interfere with the mevalonate pathway, such as statins, are known also to impact cellular coenzyme Q10 level. Interestingly, intracellular content of CoQ10 is close to the Km of the respiratory complexes, implying that even slight variations in the CoQ10 content translate into dramatic changes in the mitochondrial bioenergetics that is known to be a major site of production of reactive oxygen species. Oral CoQ10 therapy has been applied to different forms of CoQ10 deficiency, with resulting significant clinical improvements (4). Oxidative stress plays an important role in the pathogenesis of vascular diseases, diabetes and neurodegenerative disease. Due to its antioxidant properties, CoQ10 supplementation has been beneficial in the treatment of the above diseases. Numerous studies have reported that CoQ10 administration improved cardiovascular function (2,9,10). CoQ10 supplementation in three separate clinical trials of dyslipidemic type 2 diabetic patients showed raised plasma CoQ10 levels, improved endothelial function, and decreased blood pressure and glycosylated haemoglobin (HbA1C) (11-13). CoQ10 has been used in different neurodegenerative diseases, including Parkinson's disease, Huntington's disease, and Alzheimer's disease. CoQ10 supplementation seemed to slow progression of Parkinson's disease (9, 14).

CoQ10 is detectable in both choroid and retina, though levels are relative low when compared to other oxygen-demanding tissues (15, 16). Similarly to other tissues, the level of CoQ10 in the retina declines with age (15). There is increasing evidence that CoQ10 protects retinal cells *in vitro* and *in vivo*, therefore the age-related CoQ10 decrease might exacerbate the risk of retinal disease, while supplementation could have a preventative role. Here we provide an overview of the therapeutic roles of CoQ10 in retinal diseases.

2. Structure and function of mammalian retina

The neural retinal is a unique structure, consisting of three major cellular layers (outer nuclear layer, ONL; inner nuclear layer, INL; ganglion cell layer, GCL), separated by synaptic layers (Figure 2) (17). An outer monolayer, the retinal pigment epithelium (RPE), underlies the retina and supports photoreceptor function. ONL contains the light-sensitive photoreceptors, rods and cones. Rods are sensitive to dim light, whereas cones function in bright light and colour vision. In the central retina of primates, there is a small cone-enriched area, the 'macula', which is functionally specialised for high acuity vision. The central pit of the macula is the fovea (Figure 2), which contains only cones and provides the sharpest vision (18). In the retinae of most mammalian species, about 95% of photoreceptors are rods.

The adult human retina has about 91 million rods and 5 million cones (18). INL is composed mainly of bipolar cells, although amacrine cells and horizontal cells are also localized in this layer. Bipolar cells receive synaptic input from photoreceptors and are responsible for transmitting the signals to ganglion cells directly or indirectly via amacrine cells. Horizontal cells provide feedback to photoreceptor cells and possibly bipolar cells. Amacrine cells are inhibitory neurons and interact with retinal ganglion cells via their dendritic arbors (17). The ganglion cells have long axons, which form the optic nerve, and are responsible for the transmission of signals from photoreceptors to brain.

The retina has the highest oxygen consumption rate (per gram tissue) in the body, which results in the production of a large amount of reactive oxygen and nitrogen species (RONS) that pose a risk for subsequent cellular damage (19, 20). The retina, particularly the macula, is also subjected to high light exposure, making photosensitizing molecules, such as retinoids, vulnerable to light damage. In addition, photoreceptor outer segments are extremely lipid-rich: about 15% of wet weight content is lipid compared with 1% of wet weight in other types of cells (21). The photoreceptor outer segments also have a high level of the very-long-chain polyunsaturated fatty acid (PUFA), which is vulnerable to RONS and are easily oxidisable to malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) (20). Cellular systems present several defence lines against oxidative damage. However, oxidative imbalances occurring as a result of the ageing process promote oxidative damage that might contribute to the pathogenesis of retinal diseases.

Clinical data have demonstrated oxidative stress contributes the pathogenesis of retinal diseases. Lower total antioxidant capacity has been reported in aqueous humor and sera from patients with retinitis pigmentosa (RP) (22). In patients with diabetic retinopathy (DR), lipid peroxidation in serum was significantly increased when compared to that of patients with diabetes (but with no retinopathy) and there is positive correlation between lipid peroxidation and disease severity (23, 24). Furthermore, patients with proliferative DR have a markedly increased serum MDA level compared to that of non-proliferative DR patients (25). Recently increased oxidative stress level and decreased antioxidant defence have been identified in the sera from patients with primary open angle glaucoma, pseudoexfoliative glaucoma and primary angle-closure glaucoma (26, 27). Due to the central role of oxidative stress in the progression of these diseases, antioxidant therapies may play a role in counteracting retinal degeneration. Actually antioxidant supplementation in patients with nonproliferative DR demonstrated retardation of disease progress and maintenance of plasma antioxidant capacity (28).

3. Protection of retinal diseases by co-enzyme Q10

3.1 Age related macular degeneration

Age-related macular degeneration (AMD) is the most common cause of blind registration in the developed world (29). Early AMD is characterized by drusen formation and pigmentary changes. Late AMD is characterized by geographic atrophy (dry AMD) and / or choroidal neovascularisation (CNV, wet AMD). Wet AMD presents newly formed immature blood vessels growing from the choroid through Bruch's membrane toward the outer retina. Wet AMD accounts only for about 10-15% of cases, but for 80-90% of resultant blindness. Anti-VEGF (vascular endothelial growth factor) therapies dramatically halt progression of CNV in the majority of wet AMD patients but there is no effective treatment for AMD patients with geographic atrophy. An important pathological feature of AMD is the accumulation of both focal (drusen) and diffuse extracellular (basal) deposits in the macula, between the retinal pigment epithelium (RPE) and the adjacent Bruch's membrane. These deposits lead to dysfunction and subsequent death of RPE and associated photoreceptors (30). It is well recognized that oxidative damage plays an important role in AMD and that antioxidant supplementation can protect against the condition (31).

Blasi et al. measured CoQ10 in plasma and platelets of 19 patients with exudative AMD and 19 age-matched controls (32). They found that most AMD patients had a lower level of plasma CoQ10 than that of most controls, suggesting a link between CoQ10 level and AMD (32). Fourteen early AMD patients treated with a mixture including polyunsaturated fatty acids (1320 mg/day), acetyl-L-carnitine (500 mg/day), CoQ10 (30 mg/day), and vitamin E (30 mg/day) showed slight improvement in visual functions after three months of treatment; the improved visual functions remained relatively steady until 24 months. By contrast, the visual functions of controls treated with vitamin E only (30 mg/day) slowly worsened (33). The same research group continued to evaluate the treatment efficacy of a combination of acetyl-L-carnitine, n-3 fatty acids and CoQ10 in early AMD patients for 12 months (34). 106 patients were randomly allocated to two groups: the treated group (51 patients) and the placebo group (55 patients); four efficacy parameters including visual field mean defect (VFMD), visual acuity, foveal sensitivity and fundus alteration were measured. The treated group showed significant improvement in visual function, demonstrating a significant difference in VFMD, visual acuity and foveal sensitivity when compared to that of the placebo group. Only 2% of the treated group exhibited clinically related worsening in VFMD while 17% of the control group showed further deterioration by the end of the trial (34).

3.2 Glaucoma

Glaucoma is a leading cause of irreversible blindness, affecting more than 70 million people worldwide (35). It is characterized by the progressive degeneration of retinal ganglion cells. Intraocular pressure (IOP) is higher in many glaucoma patients and regarded as an important factor for initiating neuronal damage in these patients. Previous studies demonstrated that elevated acute and chronic IOP induced oxidative stress in the retina (36-38), resulting in the oxidative modification of proteins, lipids and DNA (39-41). Primary and secondary hypoxia (the latter subsequent to elevated IOP) result in oxidative stress and glutamate excitotoxicity, both of which contribute to ganglion cell dysfunction in glaucoma (42). Histological studies on glaucomatous eyes from patients and different animal models demonstrated that ganglion cells were degenerated through apoptosis (43-47). The death of ganglion cells is mainly caused by oxidative damage via multiple pathogenic mechanisms (42,48). Antioxidants (n-3 PUFAs, α-Lipoic acid and mitochondrially-targeted SKQ1) treatment in glaucoma animal models showed protection of retinal ganglion dysfunction (49-52).

CoQ10 has also been used to protect retinal ganglion cell function in the glaucomatous condition. *In vitro* studies demonstrated that CoQ10 treatment increased survival of RGC-5 cells (a rat ganglion cell line) from apoptosis when exposed to H_2O_2, radiation, antimycin (the complex III inhibitor) or serum starvation (53-55). Administration of CoQ10 in high intraocular pressure-induced ischemia rat model prevented ganglion cell loss (56). The protection of ganglion cell death by CoQ10 in ischemic retina was through ameliorating oxidative stress, blocking apoptosis, preserving mitochondrial function and inhibiting microglial activation (57). In untreated mouse ischemic retina, the level of superoxide dismutase 2 (SOD2) and heme oxygenase 1 (HO-1) was significantly increased at 12h after transient retinal ischemia when compared to non-ischemic control retina; however, CoQ10 treatment preserved SOD2 and HO-1 at levels similar to those of non-ischemic retina. The level of apoptosis-associated protein Bax was significantly increased in ischemic retina, but CoQ10 treatment markedly decreased Bax expression. In addition, the expression of glial fibrillary acidic protein (GFAP, a marker for astroglial cells) and Iba-1 (a marker for microglial cells) was significantly decreased in CoQ10-treated ischemic retina when compared to that of non-treated ischemic retina, demonstrating the inhibition of astroglial and microglial cell activation (57).

Glutamate excitotoxicity can cause ganglion cell death in glaucoma through the N—methyl-D-aspartate (NMDA) receptor-activated influx of extracellular calcium into cells, which regulates the activities of cell-death-associated enzymes (42,58). Significantly

increased retinal extracellular glutamate was detected in pressure-induced ischemic rat model; intraocular administration of CoQ10 markedly minimized the increase (56). In an intravitreally NMDA-injection-induced retinal damage mouse model, oral administration of CoQ10 (10 mg/kg) for 14 days showed that CoQ10 exerted neuroprotective effects by decreasing ganglion cell death significantly when compared to that of untreated ischemic retina (53). When CoQ10 was administered as eye drops on mouse cornea, it reached the choroid/ retina in a dose- and time-dependent manner (55). Moreover, in patients undergoing vitrectomy CoQ10 administered by eye drops has been shown to penetrate the vitreous body, where it could function on the retinas (59). In a retinal damage mouse model made by intravitreal injection with kainite (a glutamate agonist), CoQ10 eye drop treatment significantly reduced ganglion cell death by inhibiting caspase-dependent apoptosis (55). Lee et al investigated the neuroprotective effects of CoQ10 in a glaucoma mouse model (DBA/2J) by feeding the glaucomatous mice with CoQ10 for 6 months (60). The survival of ganglion cells was markedly increased in the CoQ10 treated mouse retina when compared to that of mouse fed with a control diet. Similar to the data from retinal ischemic mouse model (57), the protection of ganglion cell death by CoQ10 also resulted from ameliorating glutamate excitotoxicity, blocking oxidative stress, maintaining mitochondrial function and inhibiting astroglial activation (60). Most recently, open-angle glaucoma (OAG) patients treated with eye drops containing CoQ10 and vitamin E (in addition to a β-blocker monotherapy) for 12 months showed beneficial effects on function of the inner retina (assessed by pattern electroretinogram) and enhanced visual cortical response (assessed by pattern visual-evoked potential) (61).

Astrocytes are the major type of glial cell in the optic nerve head (ONH) and provide support for axon function (61). During the progression of glaucoma, astrocytes become activated and are involved in the ONH remodelling associated with the condition (62, 63). Oxidative stress is known to reactivate ONH astrocytes and is implicated in the pathogenesis of glaucoma (64, 65). When rat ONH astrocytes were treated with CoQ10 and H_2O_2, cell viability and ATP in these cells were both significantly increased, while ROS production was markedly reduced, when compared to that of cells treated with H_2O_2 alone. The GFAP, SOD2 and HO-1 proteins in CoQ10 treated cells were significantly decreased compared to those of H_2O_2-treated cells. CoQ10 treatment preserved mitochondrial morphology and biogenesis by upregulating the expression of the mitofilin and PGC-1α proteins, respectively (66). These data suggest that CoQ10 can protect ONH astrocytes from oxidative stress mainly through maintenance of mitochondrial function.

4. Potential of CoQ10 for the treatment of retinitis pigmentosa and diabetic retinopathy

As oxidative stress also plays a critical role in the pathogenesis of retinitis pigmentosa and diabetic retinopathy, so CoQ10 has potential for the treatment of both diseases.

4.1 Retinitis pigmentosa

Retinitis pigmentosa (RP, MIM #268000) is a heterogeneous group of conditions involving progressive degeneration of photoreceptor cells and affects 1/4000 individuals worldwide (67). The early clinical feature of RP is night blindness, often starting in adolescence, followed by progressive loss of peripheral vision and late loss of central vision. The characteristically clinical feature is bone spicule pigment deposits presented in the retinal fundus (Figure 3). RP may occur alone, as non-syndromic RP, without other clinical features, or as syndromic RP with different clinical phenotypes. Most RP cases are presumed to result from a mutation in one or more genes and may show autosomal dominant, recessive, X-linked, or mitochondrial inheritance, although about one-half of all cases are sporadic. Mutations in more than 62 genes have been reported to cause non-syndromic RP, including 23 genes associated with autosomal dominant RP, 36 genes associated with recessive RP, and 3 genes associated with X-linked RP (68).

Death of rod cells in RP occurs through both caspase-dependent and -independent apoptosis, while death of cone cells occurs primarily through necrosis (69, 70). Oxidative damage plays a critical role in the death of photoreceptors (69). Photoreceptors have one of the highest rates of oxygen consumption in the body and this is particularly high in the parafoveal region of primates, where rod density is highest (71). Our previous work showed that severe oxidative stress was present in the retinas of four RP mouse models ($Pde6b^{rd1/rd1}$, $Pde6b^{atrd1/atrd1,}$ $Rho^{-/-}$ and $Prph2^{rds/rds}$) evidenced by significantly reduced retinal complex I activities (14-29% of wildtype) at a stage when significant photoreceptor loss has not yet occurred (72). In RP, oxidative damage is also a major contributing factor to cone death subsequent to the death of rod cells. Further antioxidants have been shown to slow/reduce cone cell death in different RP animal models (73). Upregulation of antioxidant defences by over-expression of both superoxide dismutase 2 (SOD2) and catalase in photoreceptor mitochondria also reduces cone cell death in RP mouse models (74).

It is desirable to develop new candidates with the potential of reducing reactive oxygen species (ROS) production and/or upregulating antioxidant defences, which in turn can potentially slow down retinal degeneration in RP.

4.2 Diabetic retinopathy

Diabetic retinopathy (DR) refers to the irreversible damage of retinal cells and structures as a result of chronic diabetes. DR is a progressive disease that is influenced by the duration and control of diabetes, and its development is believed to occur gradually with different degrees of disease severity. DR is classified into five stages: no diabetic retinopathy, background diabetic retinopathy, non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME) (75, 76). The first stage, no diabetic retinopathy (Figure 4A), is characterized by normal retinal histology with absence of any abnormal neovascularization and microvascular abrasions. The second stage, background DR (Figure 4B), is the earliest stage of DR and is associated with the presence of low grade of microaneurysm, retinal hemorrhage and exudate. The third stage, non-proliferative diabetic retinopathy (NPDR), itself includes three phases: mild NPDR (Figure 4C) which involves microaneurysm; moderate NPDR (Figure 4D) which involves less severe microaneurysm, intraretinal haemorrhage and microvascular occlusion; and severe NPDR (Figure 4E) which is characterized by severe and increased rate of intraretinal haemorrhage, microvascular abnormalities and venous beading. The fourth stage, proliferative diabetic retinopathy (PDR, Figure 4F), is considered to be a severe phase and is defined by retinal ischemia and increased rate of abnormal neovascularization in the retina, optic disc and iris with vitreous or pre-retinal haemorrhage. The fifth stage, diabetic macular edema (DME, Figure 4G), is associated with relatively increased retinal thickness at the centre of the macula, vascular permeability and leakage, hard exudate, breakdown of blood-retina barrier (BRB) and retinal detachment (75, 76).

Oxidative stress is a common characteristic of DR secondary to hyperglycemia. Mitochondria are the principal source of energy production. Under normal conditions, mitochondria provide energy through the electron transport chain (ETC) in which oxygen (O_2) is utilized as the main electron donor and then reduced to ROS to maintain cellular functions; any increase of ROS level is neutralized by a specialized antioxidant defence system (77). Mitochondria are the main source of ROS production during diabetes, and studies have shown that hyperglycemia induces mitochondrial ROS overproduction in response to increased activation of the polyol pathway, AGEs, PKC pathway, hexosamine biosynthesis, and poly (ADP-riobose) polymerase. Under physiological conditions excess ROS is eliminated by specific antioxidant scavengers and balanced by mitochondria maintaining redox (77). Several antioxidant scavengers such as catalase, superoxide dismutases (SODs) and glutathione peroxidases (GPXs) have been reported to be involved in oxidative stress during DR (78-81). Accumulated data from diabetic patients, diabetic animal models and

high glucose treated cells has revealed that these anti-oxidants may exhibit different gene expression patterns and activity; the activity of catalase, SODs and GPXs were reported to be low in diabetic patients, animal models and high glucose treated cells compared to normal control (78-81). Thus, a therapeutic strategy to directly decrease ROS production and enhance expression of these anti-oxidants will protect the retina from oxidative stress damage during DR.

5. Conclusion

Oxidative stress causes damage to protein, lipid and DNA, which results in retinal cell dysfunction and death. Mitochondria are the major source of oxidative stress. CoQ10 functions as an electron carrier in the mitochondrial respiratory chain and as an intracellular antioxidant that offers therapeutic potential for neurodegenerative diseases. Furthermore, due to its antioxidant properties CoQ10 has demonstrated a protective role in the neuroretina by counteracting oxidative stress, inhibiting microglia cell activation and maintaining mitochondrial function. In particular, the role of CoQ10 in modulating mitochondrial permeability transition pore has been linked to its beneficial effects in preventing the glutamate-induced cytotoxicity that may contribute to neural degeneration. CoQ10 topical eye preparation has been shown to be an effective means of delivery to the vitreous cavity and retina. However, until now only oxidised CoQ10 (ubiquinone) has been tested. The recent availability of the stable formation of the reduced and active form of CoQ10 (ubiquinol) might represent a ground-breaking innovation in the field. In fact, cellular metabolism is able to efficiently promote reduction of exogenously provided coenzyme Q10, while the activity of reducing systems declines with age.

In conclusion, a significant body of evidence supports a role for CoQ10 in promoting eye health through inhibiting ROS production and protecting neuroretinal cells from oxidative damages (Figure 5), although further studies are required to evaluate potential beneficial effects of ubiquinol eye-drop treatment for patients with retinal diseases, including AMD, DR, RP and glaucoma, which are major causes of blindness in the world.

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Figure legends

Figure 1 Coenzyme Q10 is a redox existing in the cellular membranes and consisting of a quinone ring and 10-isoprenoid-unit tail. There are three states of Coenzyme Q10: fully oxidized form (ubiquinone), semiquinone (ubisemiquinone) and fully reduced form (ubiquinol) (A). Coenzyme Q10 is soluble in phospholipid bilayer of the inner mitochondrial membrane. It is an essential component of the mitochondrial respiratory chain (B). Ubiquinone can adopt one or two electrons from inner mitochondrial membrane complex I and II, transforming into semiquinone or ubiquinol by Q10 reductases. Then Q10 transfers the electrons to complex III. The electron is then passed to complex IV through cytochrome C. A component of Complex III can convert ubiquinol to ubiquinone to recycle Q10.

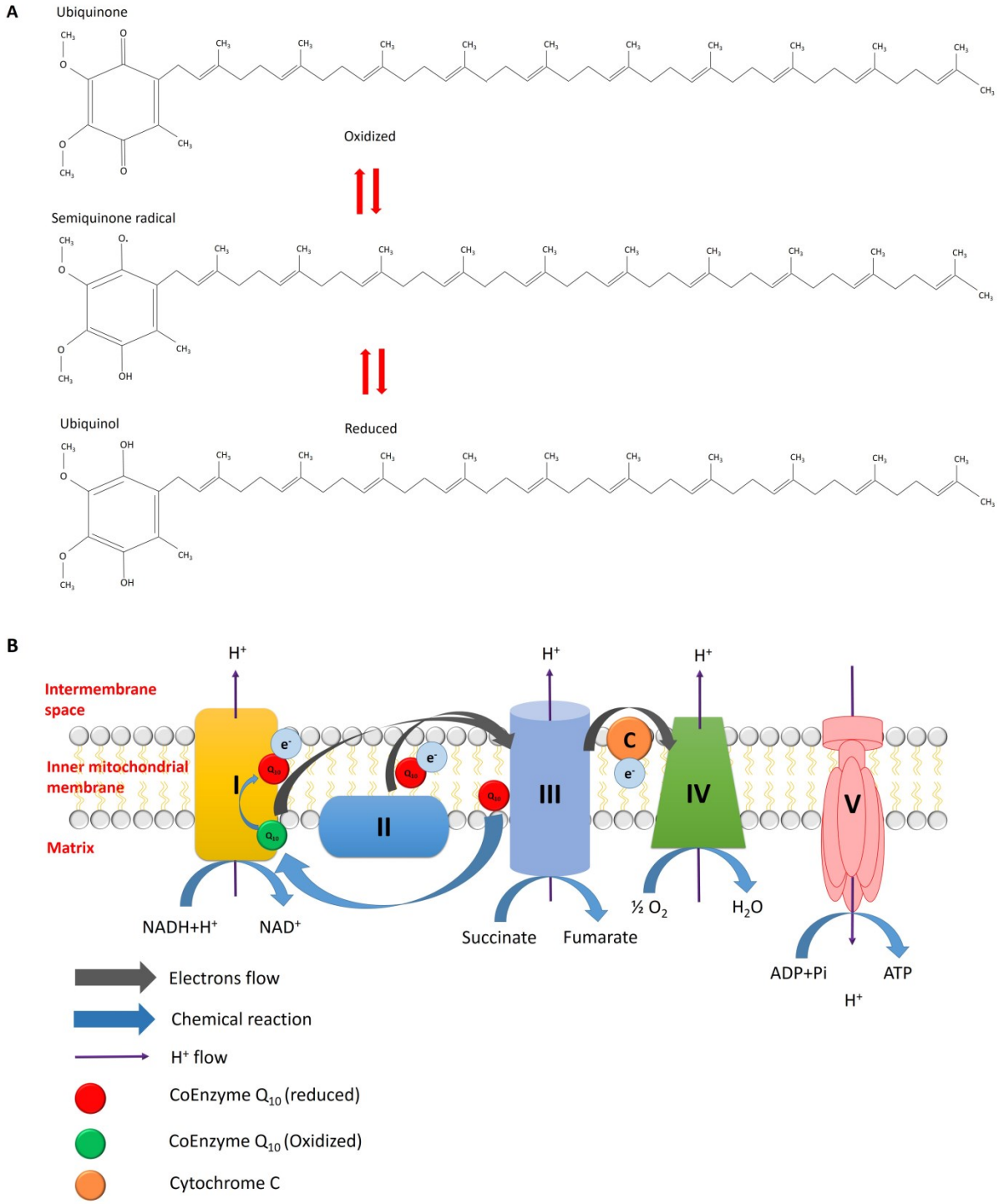
Figure 2 The structure of the retina. (A) Cross-sectional image of the heathy retina obtained by optical coherence tomography (OCT). Scans were taken with the upper panel showing the 64th scan and the lower panel showing the 256th scan. (B) Histological structure of mouse retina obtained by hematoxylin-eosin staining (left panel) and by immunostaining with 1D4 antibody (labelling the rod outer segments, right panel). GCL, ganglion cell layer; INL, inner nuclear layer; IS, inner segment; IPL, inner plexiform layer; L, lens; NFL, nerve fiber layer; ONL, outer nuclear layer; OS, outer segments; RPE, retinal pigment epithelium.

Figure 3 Bone spicule pigment deposits are present in the fundus of retinitis pigmentosa patient (right side). Fundus of healthy individual is on the left side. Adapted from Raghpathy et al. (Ref 81)

Figure 4 Clinical classfification of diabetic retinopathy (DR) determined by ophthalmoscopy (fundoscopy). (A) Heathy retina. (B) Background DR. (C) Mild non-proliferative diabetic retinopathy (NPDR). (D) Moderate NPDR. (E) Severe NPDR. (F) Proliferative diabetic retinopathy (PDR). (G) Diabetic macular edema (DME). Adapted from El-Bab et al., 2012 (Ref 82) and Shotliff and Duncan, 2006 (Ref 83).

Figure 5 Diagram illustrating protection of co-enzyme Q10 (CoQ10) via inhibiting ROS production. CoQ10 (ubiquinol) blocks the production of ROS and subsequently attenuates oxidative damage and inflammation, which reduce death of retinal cells (photoreceptors, retinal pigment epithelium cells and ganglion cells) and delays the progression of retinal diseases (age-related macular degeneration, AMD; diabetic retinopathy, DR; retinitis pigmentosa, RP; glaucoma).

Figure 1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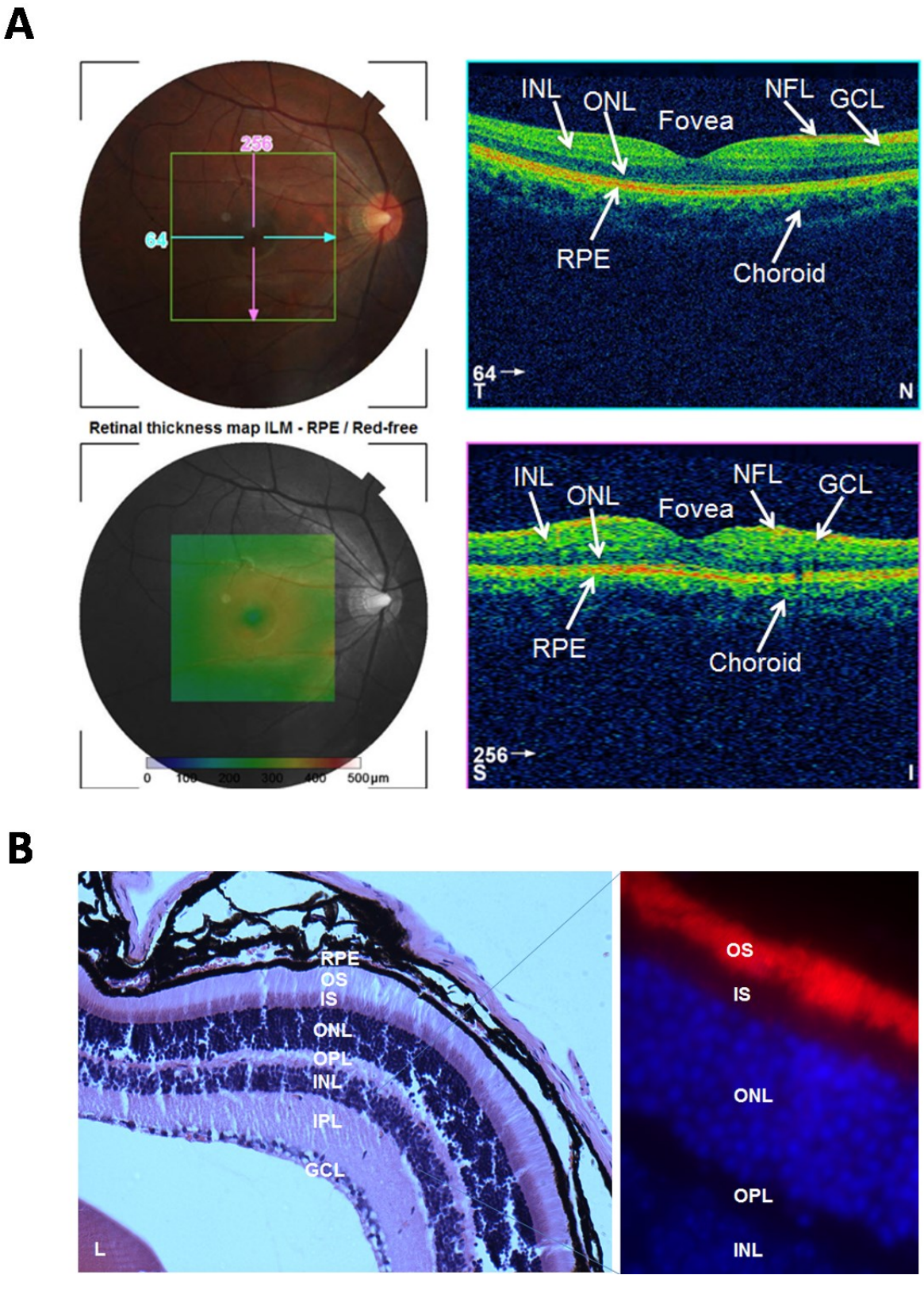
Oxidized
Semiquinone radical
Reduced
Ubiquinol
B
Intermembrane space
Inner mitochondrial membrane
Matrix
H+
I
II
III
IV
V
C
e-
NADH+H+
NAD+
Succinate
Fumarate
½ O2
H2O
ADP+Pi
ATP
Electrons flow
Chemical reaction
H+ flow
CoEnzyme Q10 (reduced)
CoEnzyme Q10 (Oxidized)
Cytochrome C

639 **Figure 2**



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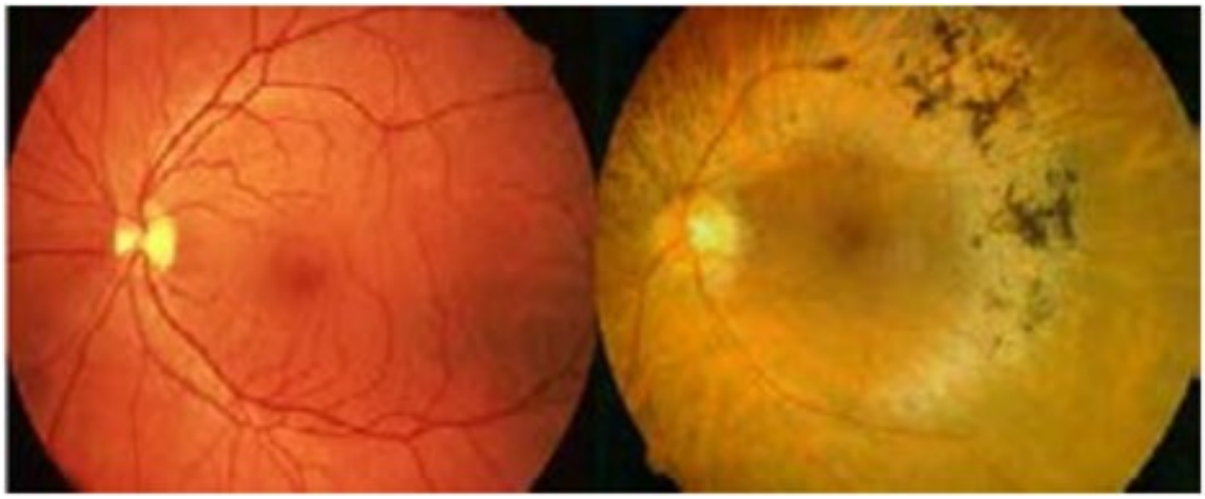
643 **Figure 3**



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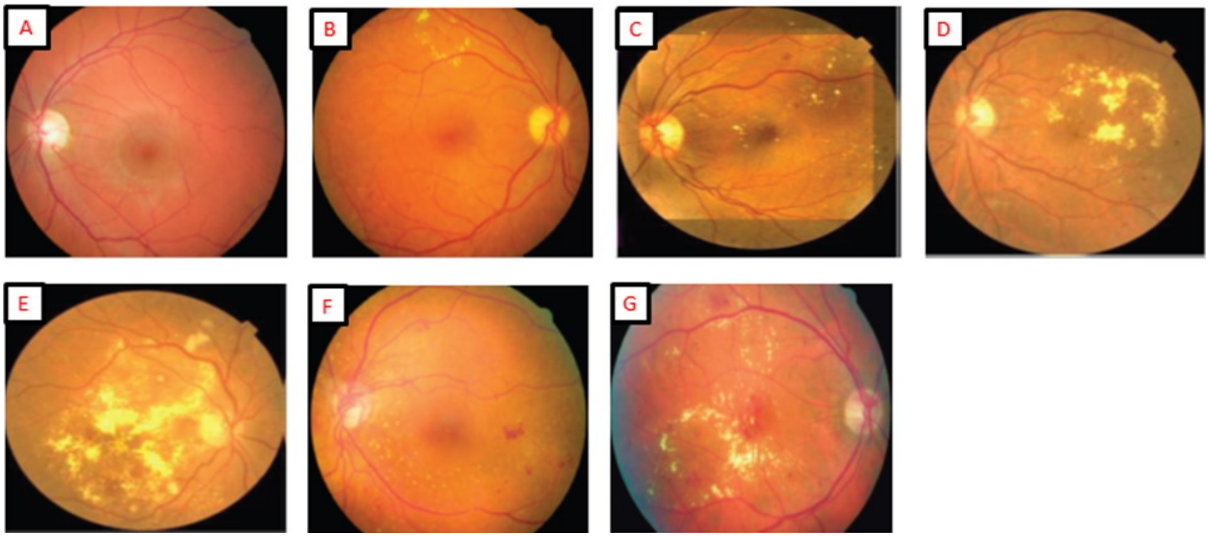
646 **Figure 4**



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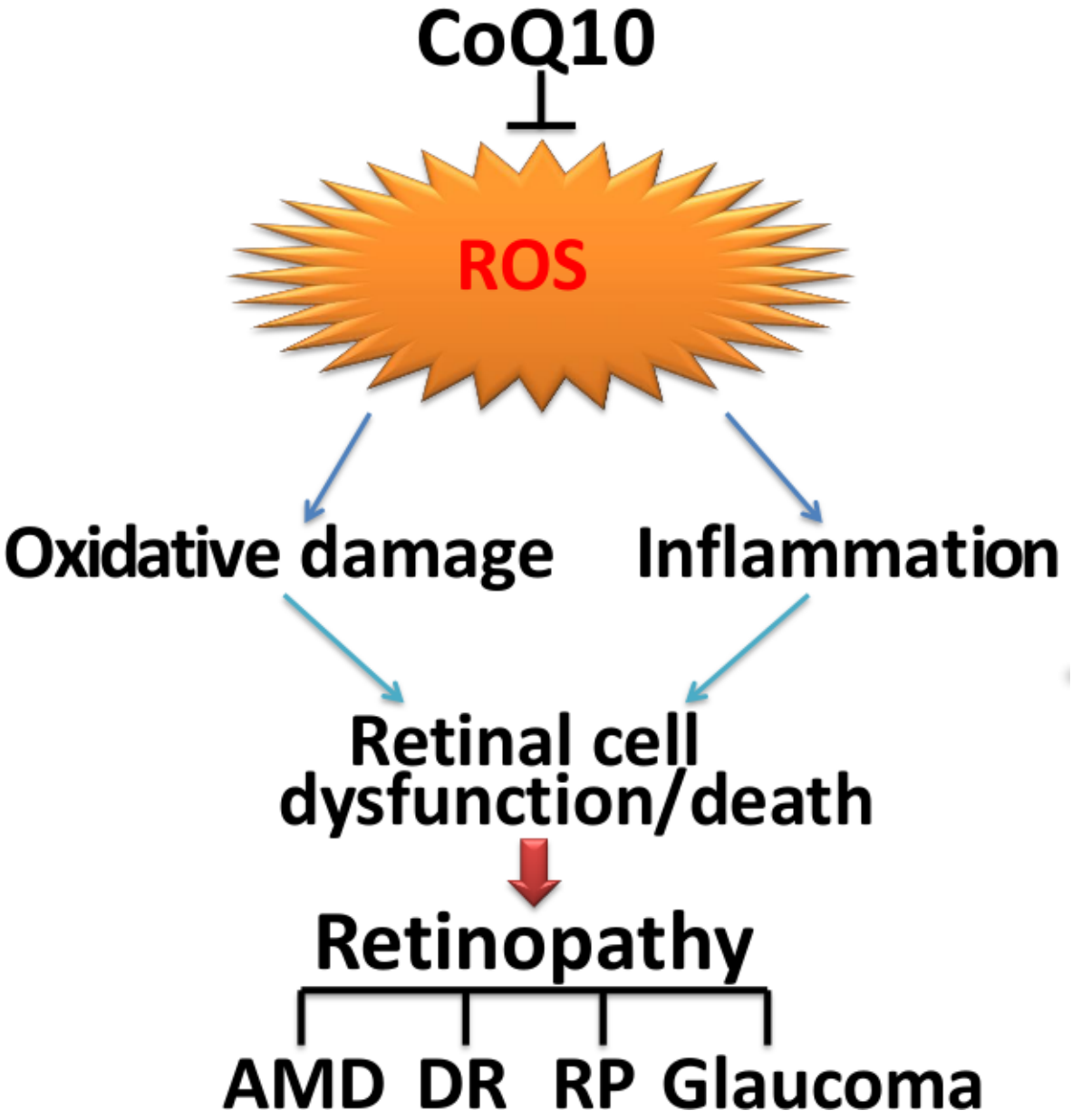
656 **Figure 5**



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