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5th International Conference on
Clinical & Experimental Ophthalmology
August 04-06, 2015 Valencia, Spain



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Investigación en Retina y Ciencias de la Visión
Research in Retina and Vision Sciences

Pathogens

Traumatisms

Chemical Substances

Immune Response

Hypoxia

Environmental Agents



OCULAR STRESS

Eye Damage

Reversible Changes

Irreversible Changes

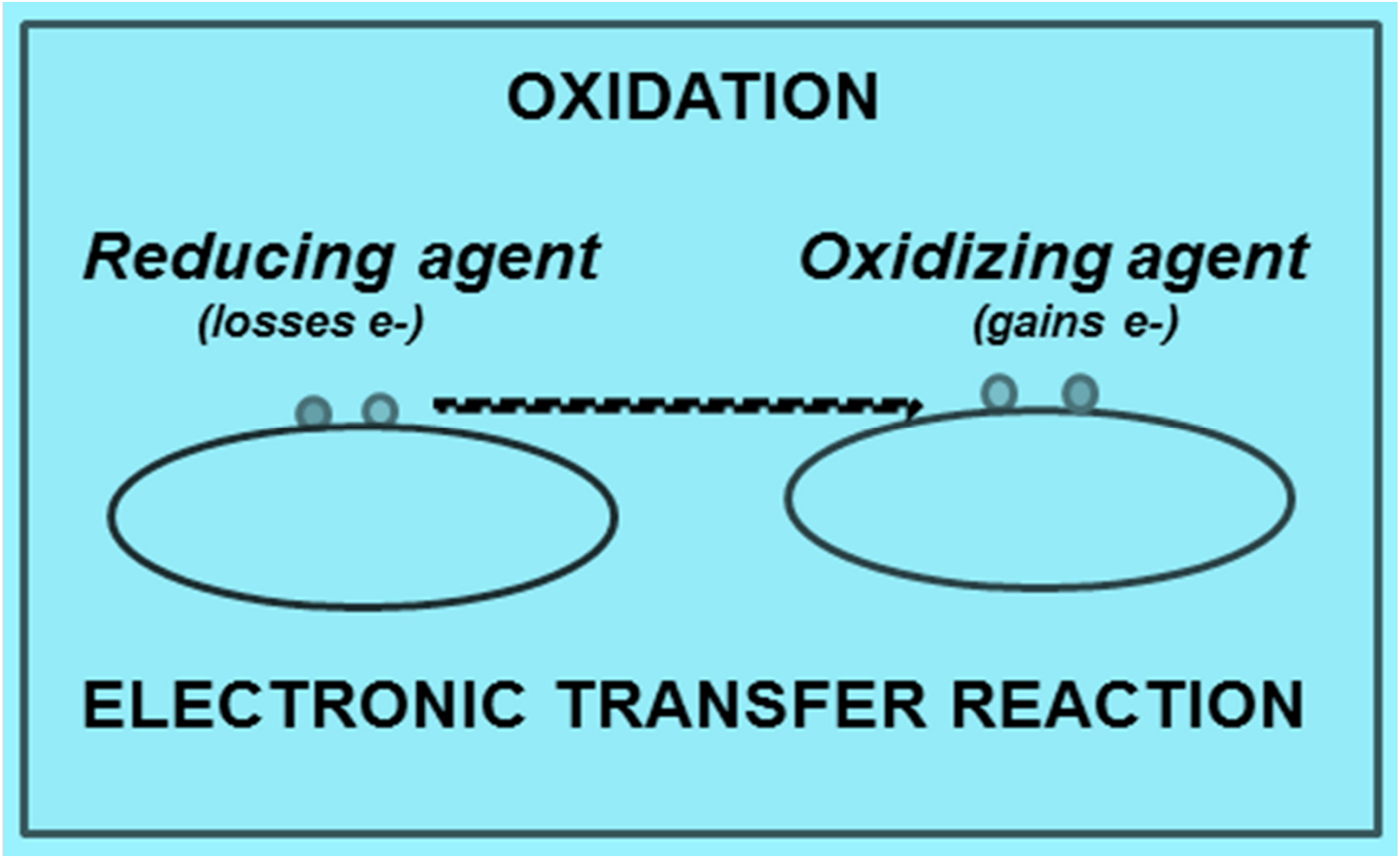
REPAIRING

DEGENERATION

EYE DISEASES

VISUAL IMPAIRMENT

VISUAL LOSS



- **Reduction-oxidation (redox)** concepts are based on the electron transfer events.
- Compounds capable of “accepting” electrons are <u>oxidizing agents</u> and those able to “assign” electrons are <u>reducing agents</u>

Under normal conditions (during aerobic metabolism) the O_2 undergoes tetravalent reduction to water (H_2O).

In situations inducing an incomplete reduction, very unstable and reactive species are formed, the so called reactive oxygen species (ROS).

National Park EL TEIDE, Canary Islands



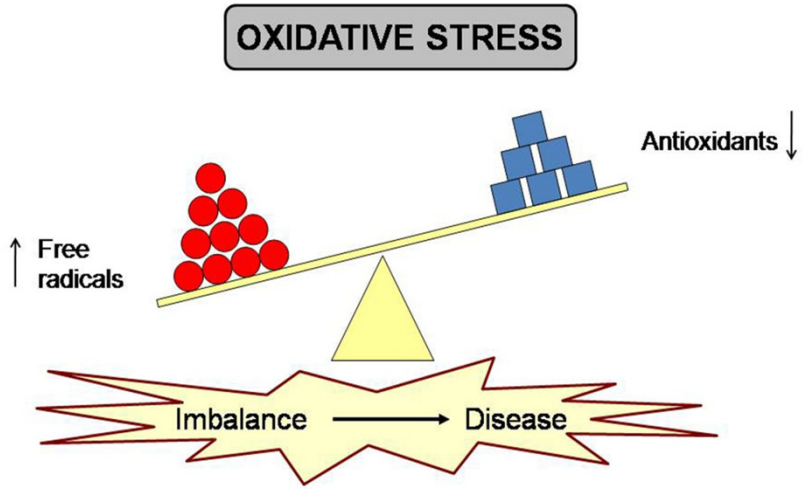
National Park LA ALBUFERA, Valencia

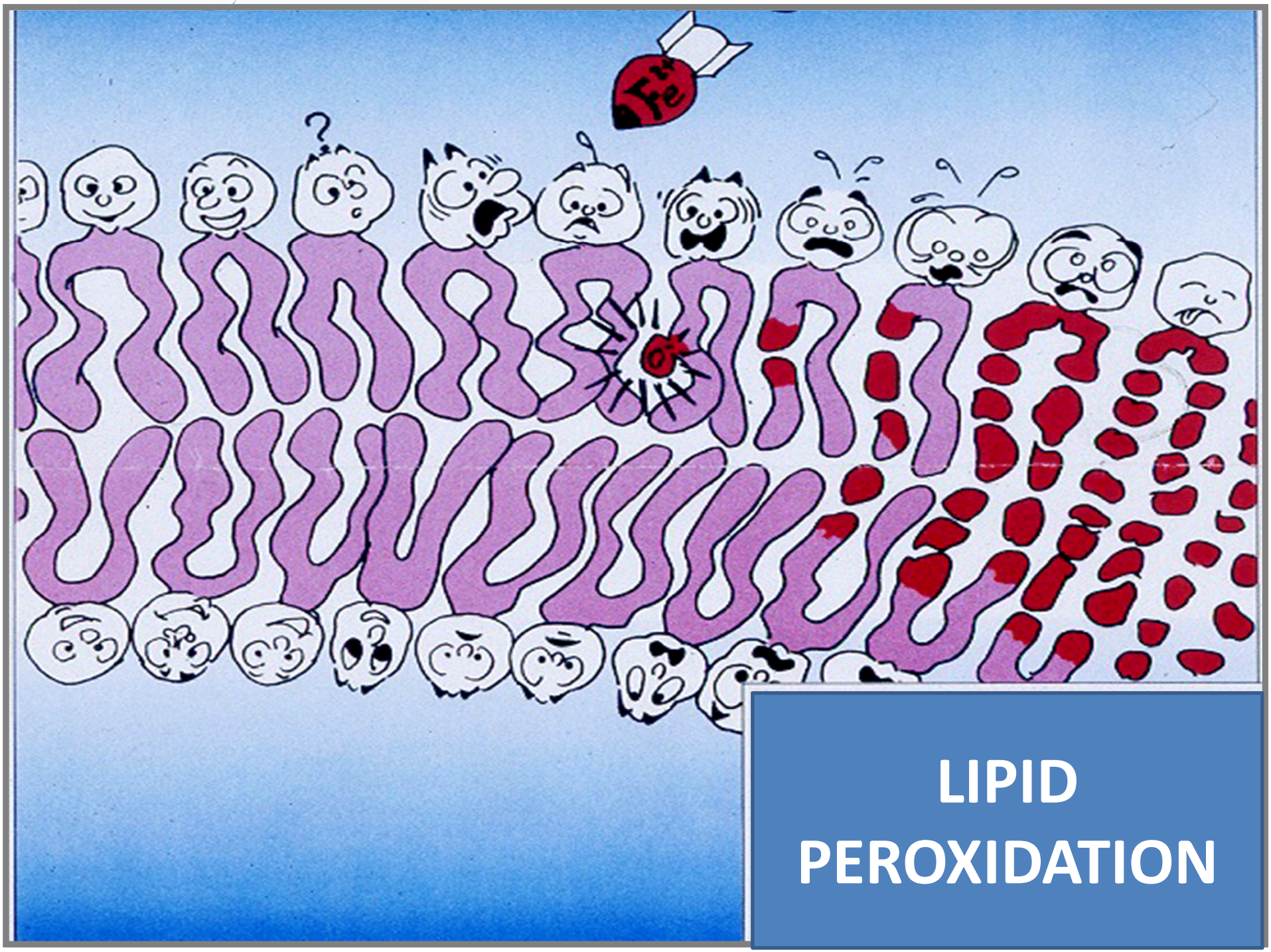


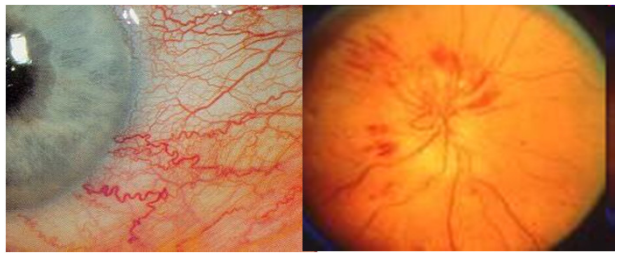
- **Superoxide anion (O2 •):** Formed in multiple processes. Most abundant among the ROS (it possesses a half-life of millisec.). It is not reactive enough to directly attack macromolecules, but it can start ROS chain formation.
- **Hydrogen peroxide (H_2O_2):** A non-radical ROS with the ability to generate other ROS. A small molecule that diffuses easily, passing through cell membranes, propagating its effects farther than other ROS.
- **Hydroxyl radical (OH •):** Most powerful/harmful of all ROS. Its short half-life (10 sec) is a limiting condition to the diffusion. It is formed from $O_2^{\cdot -}$ and H_2O_2 in the presence of iron during the sequential **reactions of Haber-Weiss and Fenton**:

$$O_2 \bullet^- + H_2O_2 \longrightarrow O_2 + OH \bullet + OH^-$$
$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH \bullet + OH^-$$

- There are endogenous and exogenous **defense mechanisms** against oxidative attack.
- Cells maintain a reducing environment by the corresponding enzymes and the constant supply of metabolic energy. 
- **Oxidative stress** and its biomarkers are the biochemical end point of the imbalance between the ROS production and the ability of antioxidant biological systems to counteract the effects of ROS metabolites.




Fe
LIPID
PEROXIDATION



Genetic variation
Epithelial cells
1
2
3
4
5
6
Oxidants
Antioxidants
Neutrophils
Macrophages
Proteases
Antiproteases
Oxidative stress
Inflammation
Hipersecretion
Apoptosis

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Mol Vis. 2015 May 11;21:555-67. eCollection 2015.

A metabolomic approach to dry eye disorders. The role of oral supplements with antioxidants and omega 3 fatty acids.

Galbis-Estrada C[1], Pinazo-Durán MD[2], Martínez-Castillo S[3], Morales JM[4], Monleón D[5], Zanon-Moreno V[6].

Author information

Abstract

PURPOSE: We used nuclear magnetic resonance spectroscopy of hydrogen-1 nuclei ((1)H NMR S) to analyze the metabolic profile of reflex tears from patients with dry eye disorders.

METHODS: We performed a prospective case-control study involving 90 participants: 55 patients diagnosed with dry eye syndrome (DESG) and 35 healthy subjects (control group, CG). From the DESG, two subgroups were formed: mild DES (n=22) and moderate DES (n=33). Participants were prescribed an oral nutraceutic supplementation containing antioxidants and essential polyunsaturated fatty acids to be taken as three capsules per day for 3 months. Reflex tears (20-30 µl) were collected from the tear meniscus of both eyes of each subject with a microglass pipette. Nuclear magnetic resonance (NMR) spectra were acquired with a standard one-dimensional pulse sequence with water suppression; 256 free induction decays were collected into 64,000 data points with 14 ppm spectral width.

RESULTS: Basal tears showed a differential metabolomic profile between groups. Almost 50 metabolites were identified by H cholesterol, N-acetylglucosamine, glutamate, amino-n-butyrate, choline, glucose, and formate were detected before supplementation and choline/acetylcholine after supplementation. The metabolic profile of the tears was statistically different between groups, as well as before and after supplementation.

CONCLUSIONS: Our data indicate that DES induces changes in the tear metabolic profile that can be modified with appropriate oral supplementation with antioxidants and essential polyunsaturated fatty acids.

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Acta Ophthalmol. 2014 Dec 28. doi: 10.1111/aos.12629. [Epub ahead of print]

A two-year follow-up of oral antioxidant supplementation in primary open-angle glaucoma: an open-label, randomized, controlled trial.

Garcia-Medina JJ[1], Garcia-Medina M, Garrido-Fernandez P, Galvan-Espinosa J, Garcia-Maturana C, Zanon-Moreno V, Pinazo-Duran MD.

Author information

Abstract

PURPOSE: To evaluate the effect of oral antioxidant supplementation (OAS) on primary open-angle glaucoma (POAG) over a 2-year follow-up period.

PATIENTS AND METHODS: In this open-label, randomized controlled trial, 117 eyes of 117 patients with mild or moderate POAG and intraocular pressure under control with topical antiglaucoma medications were recruited and randomly divided into three groups according to supplementation: (1) OAS with (ICAPS R® - Alcon Laboratories, n = 26); (2) OAS without ω-3 fatty acids (OFTAN MACULA® - Laboratorios Esteve, n = 28); and (3) a control group without OAS (n = 63). They all underwent visual field (VF) tests (Humphrey 24-2) and scans using a Fourier-domain optical coherence tomography (FD-OCT) device (RTVue-100) at the beginning of the study and 2 years later. Mean deviation (MD), standard pattern deviation (PSD), peripapillary retinal nerve fibre layer (RNFL) and macular ganglion cell complex (GCC) parameters were considered for the analysis. Patients were also classified according to MD deterioration (fast deterioration vs. slow deterioration).

RESULTS: Visual field global indices, peripapillary RNFL thickness and macular GCC thickness showed no differences among the groups at the beginning and end of the follow-up. Besides all the comparisons among groups for differences before and after the follow-up of the MD, PSD, RNFL and GCC parameters were also non-significant. The proportions of patients according to MD deterioration were similar among the groups and subgroups ($p > 0.05$ for all the comparisons).

CONCLUSION: Oral antioxidant supplementation with or without ω-3 fatty acids does not appear useful as an adjuvant treatment of mild/moderate POAG in the short term.

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KEYWORDS: antioxidant; ganglion cell; glaucoma; omega-3 fatty acids; optical coherence tomography; oxidative stress

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Eur J Ophthalmol. 2011 Sep-Oct;21(5):637-43. doi: 10.5301/EJO.2010.6212.

A 5-year follow-up of antioxidant supplementation in type 2 diabetic retinopathy.

Garcia-Medina JJ[1], Pinazo-Duran MD, Garcia-Medina M, Zanon-Moreno V, Pons-Vazquez S.

Author information

Abstract

PURPOSE: This study was designed to evaluate the effect of antioxidant supplementation on diabetic retinopathy (DR) over a 5-year follow-up period. To our knowledge, this is the first such clinical trial performed.

METHODS: We recruited 105 type 2 diabetic patients with nonproliferative DR. A complete ophthalmic checkup and a plasma determination of oxidative (malonyldialdehyde [MDA]) and antioxidant parameters (total antioxidant status [TAS]) were obtained as the baseline. One part of the cohort was randomly assigned to oral antioxidant supplementation at nutritional doses. The same examinations were performed with 97 diabetic patients who completed the 5-year follow-up period. The best-corrected visual acuity, DR score, MDA, and TAS values were compared at the beginning and the end of the follow-up.

RESULTS: Best-corrected visual acuity did not change during the follow-up, irrespective of supplementation. However, the retinopathy stage showed a retardation of progression in the subgroup with supplementation, but worsened in the subgroup with no antioxidant supplementation. Furthermore, the antioxidant supplementation group maintained its antioxidant plasma status levels, which was related to decreased oxidative plasma activity.

CONCLUSIONS: Oral antioxidant supplementation could be a useful adjunctive long-term therapy in the treatment of nonproliferative DR.

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J Ophthalmol. 2014;2014:901686. doi: 10.1155/2014/901686. Epub 2014 Jan 23.

Do nutritional supplements have a role in age macular degeneration prevention?

Pinazo-Durán MD[1], Gómez-Ulla F[2], Arias L[3], Araiz J[4], Casaroli-Marano R[5], Gallego-Pinazo R[6], García-Medina JJ[7], López-Gálvez MI[8], Manzanas L[9], Salas A[10], Zapata M[11], Diaz-Llopis M[12], García-Layana A[13].

Author information

Abstract

Purpose. To review the proposed pathogenic mechanisms of age macular degeneration (AMD), as well as the role of antioxidants (AOX) and omega-3 fatty acids (ω -3) supplements in AMD prevention. Materials and Methods. Current knowledge on the cellular/molecular mechanisms of AMD and the epidemiologic/experimental studies on the effects of AOX and ω -3 were addressed all together with the scientific evidence and the personal opinion of professionals involved in the Retina Group of the OFTARED (Spain). Results. High dietary intakes of ω -3 and macular pigments lutein/zeaxanthin are associated with lower risk of prevalence and incidence in AMD. The Age-Related Eye Disease study (AREDS) showed a beneficial effect of high doses of vitamins C, E, beta-carotene, and zinc/copper in reducing the rate of progression to advanced AMD in patients with intermediate AMD or with one-sided late AMD. The AREDS-2 study has shown that lutein and zeaxanthin may substitute beta-carotene because of its potential relationship with increased lung cancer incidence. Conclusion. Research has proved that elder people with poor diets, especially with low AOX and ω -3 micronutrients intake and subsequently having low plasmatic levels, are more prone to developing AMD. Micronutrient supplementation enhances antioxidant

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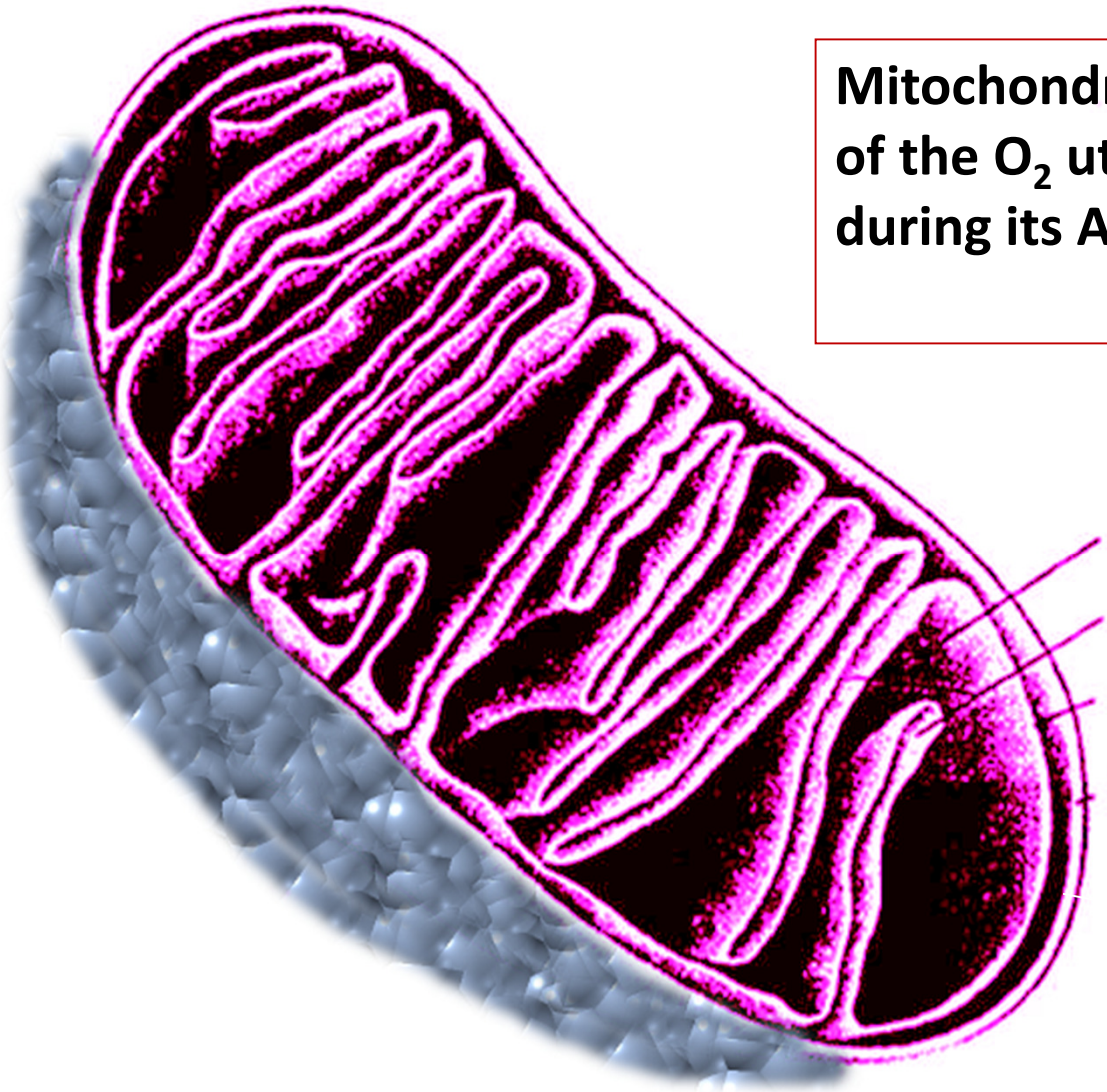


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Mitochondria are consumers of 85% of the O_2 utilized by the cell during its ATP production.

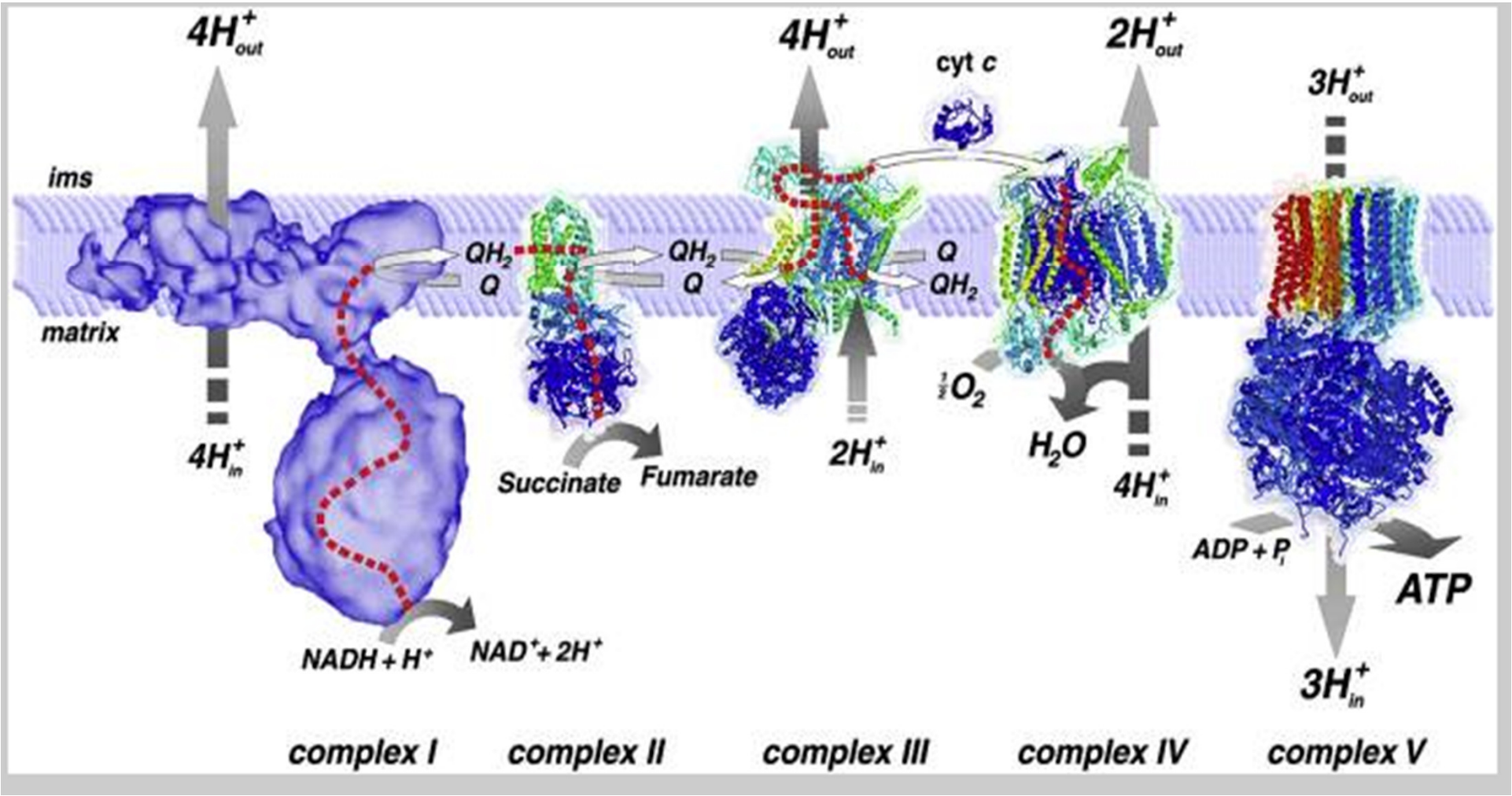
Matrix

Cristae

Inner Mitochondrial Membrane

Outer Mitochondrial Membrane

Intermembrane Space

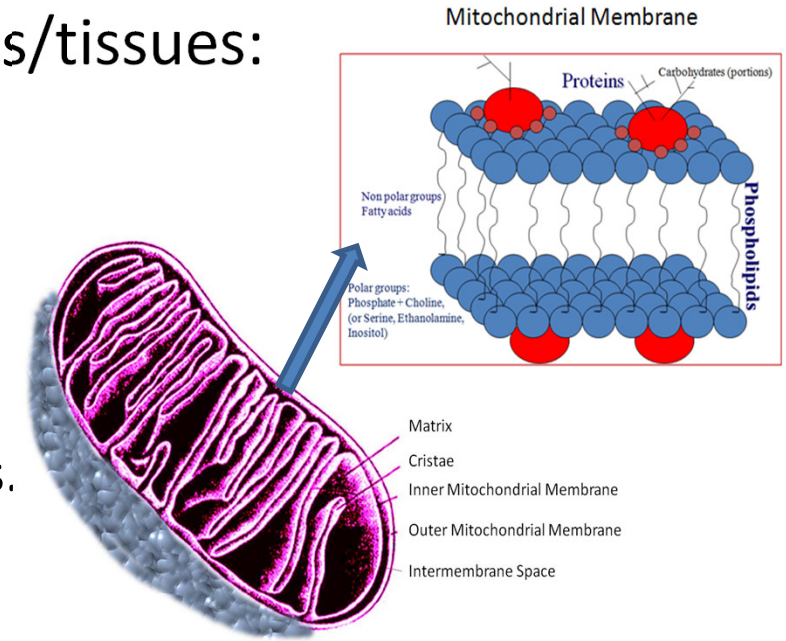


Oxidative phosphorylation is the metabolic pathway in which the mitochondria use their structure, enzymes and energy (released by the oxidation of nutrients) to reform ATP.

In the ETC electrons are transferred from electron donors to electron acceptors in REDOX reactions which are carried out by the enzymes of the sequential complexes.

Mt control pivotal functions in the cells/tissues:

- Cell cycle
- Apoptosis
- Iron/Sulfur cluster assembly
- Generation of ROS
- Ca^{2+} homeostasis
- Biosynthesis of many cellular metabolites.

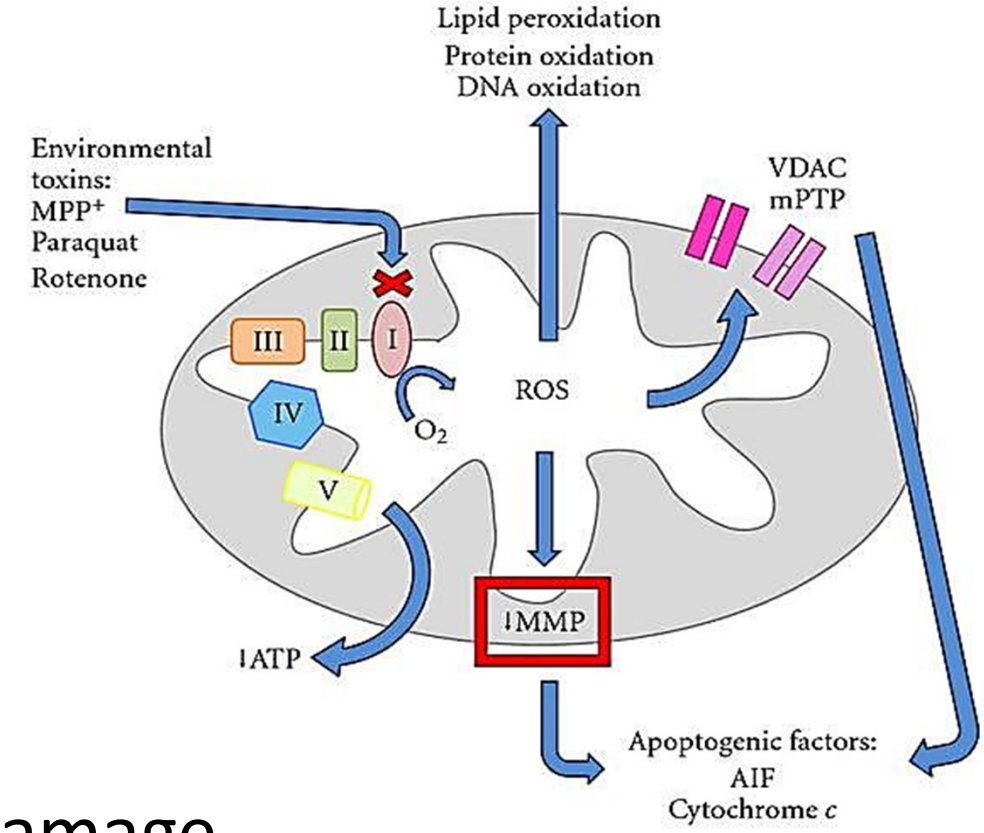


Mt changes may induce, in turns, a wide range of pathological situations, leading to senescence-associated disorders:

- Loss of membrane potential
- Increase in ROS formation/Elevations in oxidized proteins
- Loss of mitochondrial DNA
- Programmed cell death

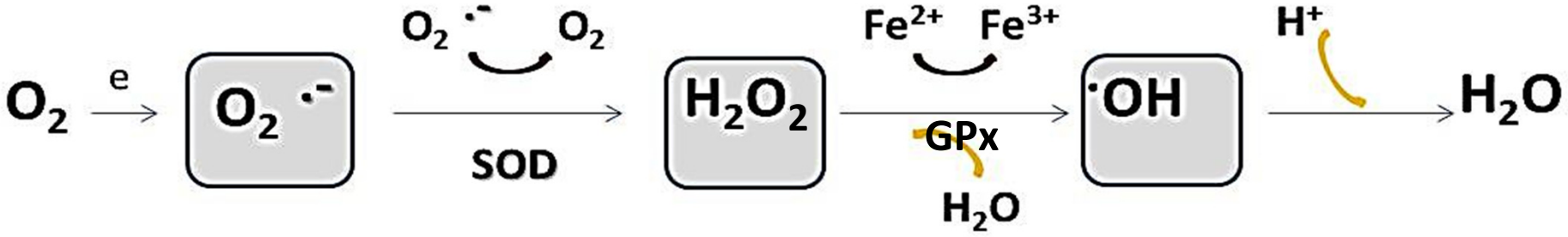
- **Damage to Mt** is caused primarily by ROS that in turns are generated by the mt themselves

  Murphy MP. 2013



- ROS can inflict oxidative damage on biomolecules (proteins, lipids, n. acids), resulting in **loss of catalytic and/or structural integrity**.
- **With ageing, ROS-damaged proteins accumulate and OX-PHOS activity declines**.

- In normal conditions during the OX-PHOS all **O_2** consumed is converted to **O_2•** in the mt.
- The **O_2•** is transformed to **H_2O_2** (by the *superoxide dismutase: SOD*) and water (by the *glutathione peroxidase: GPx*).
- When these two enzymes did not work appropriately, ROS accumulates and the cell undergoes **oxydative stress.**



ROS-MEDIATED APOPTOSIS / The Mitogen-Activated Protein Kinase

Am J Med Genet A. 2010 Jan;152A(1):4-24. doi: 10.1002/ajmg.a.33183.

Proceedings from the 2009 genetic syndromes of the Ras/MAPK pathway: From bedside to bench and back.

Rauen KA[1], Schoyer L, McCormick F, Lin AE, Allanson JE, Stevenson DA, Gripp KW, Neri G, Carey JC, Legius E, Tartaglia M, Schubbert S, Roberts AE, Gelb BD, Shannon K, Gutmann DH, McMahon M, Guerra C, Fagin JA, Yu B, Aoki Y, Neel BG, Balmain A, Drake RR, Nolan GP, Zenker M, Bollag G, Sebolt-Leopold J, Gibbs JB, Silva AJ, Patton EE, Viskochil DH, Kieran MW, Korf BR, Hagerman RJ, Packer RJ, Melese T.

Author information

Abstract

The RASopathies are a group of genetic syndromes caused by germline mutations in genes that encode components of the Ras/mitogen-activated protein kinase (MAPK) pathway. Some of these syndromes are neurofibromatosis type 1, Noonan syndrome, Costello syndrome, cardio-facio-cutaneous syndrome, LEOPARD syndrome and Legius syndrome. Their common underlying pathogenetic mechanism brings about significant overlap in phenotypic features and includes craniofacial dysmorphology, cardiac, cutaneous, musculoskeletal, GI and ocular abnormalities, and a predisposition to cancer. The proceedings from the symposium "Genetic Syndromes of the Ras/MAPK Pathway: From Bedside to Bench and Back" chronicle the timely and typical research symposium which brought together clinicians, basic scientists, physician-scientists, advocate leaders, trainees, students and individuals with Ras syndromes and their families. The goals, to discuss basic science and clinical issues, to set forth a solid framework for future research, to direct translational applications towards therapy and to set forth best practices for individuals with RASopathies were successfully meet with a commitment to begin to move towards clinical trials.

Molecular and Cellular Biology

MCB Article | Journal Info. | Authors | Reviewers | Permissions | Journals.ASM.org

Mol Cell Biol. 2011 Jul; 31(14): 2973–2983.

PMCID: PMC3133408

doi: 10.1128/MCB.05054-11

Loss of Shp2-Mediated Mitogen-Activated Protein Kinase Signaling in Müller Glial Cells Results in Retinal Degeneration▽†

Zhigang Cai,[1] David L. Simons,[2] Xin-Yuan Fu,[3] Gen-Sheng Feng,[4] Samuel M. Wu,[2] and Xin Zhang[1,*]

OCULAR CONDITIONS IN WHICH MITOCHONDRIAL DYSFUNCTION HAS BEEN INVOLVED		
Retinosis Pigmentosa	Duno et al., 2013	Griciuc et al., 2014
Retinal Vascular Occlusion	Finsterer and Mahjoub 2012	
Uveitis	Kaneko and Rao 2012	
Dry Eye Disorders	Messmer 2014	
Age-Related Macular Degeneration	Jarret et al., 2010	Terluk et al, 2015
Primary Open-Angle Glaucoma	Lee et al., 2011	Pinazo-Durán et al., 2015
Diabetic Retinopathy	Schrier and Falk 2011	Santos et al., 2014
Leber's hereditary optic neuropathy	Schrier and Falk 2011	Cwerman-Thibault et al. 2014
Aging and senescence	Brennan 2009	Gendron 2012

- **Thus, we assume that mt involvement is the rule rather than the exception in the aging eye and eye diseases.**
- **Improving mt function can be beneficial for aged eyes and can be used as an adjunctive therapy for certain ocular diseases.**

With the scientific evidence reviewed herein, it can be reached most accurate viewpoint as to how the oxidative stress and mitochondrial failure can interplay to build a solid pathogenic theory in **glaucoma, dry eyes, retinal vascular occlusion, diabetic retinopathy and age-related macular degeneration.**





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The Nobel Prize in Physiology or Medicine 1959 was awarded jointly to

Severo Ochoa

and

Arthur Kornberg

"for their discovery of the mechanisms in the biological synthesis of ribonucleic acid and deoxyribonucleic acid"

To "thank him" for his work and his commitment in this area


Muchas Gracias