Coenzyme Q10 depletion in medical and neuropsychiatric disorders: potential repercussions and therapeutic implications.

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Abstract.

Coenzyme Q10 (CoQ10) is an antioxidant, a membrane stabilizer, and a vital cofactor in the mitochondrial electron transport chain, enabling the generation of adenosine triphosphate. It additionally regulates gene expression and apoptosis, is an essential cofactor of uncoupling proteins and has anti-inflammatory, redox modulatory and neuroprotective effects.

This paper reviews the known physiological role of CoQ10 in cellular metabolism, cell death, differentiation and gene regulation and examines the potential repercussions of CoQ10 depletion including its role in illnesses such as Parkinson's disease, depression, Myalgic Encephalomyelitis / chronic fatigue syndrome and fibromyalgia. CoQ10 depletion may play a role in the pathophysiology of these disorders by modulating cellular processes, including hydrogen peroxide formation, gene regulation, cytoprotection, bioenergetic performance and regulation of cellular metabolism. CoQ10 treatment improves quality of life in patients with Parkinson's disease and may play a role in delaying the progression of that disorder. Administration of CoQ10 has antidepressive effects. CoQ10 treatment significantly reduces fatigue and improves ergonomic performance during exercise and thus may have potential in alleviating the exercise intolerance and exhaustion displayed by people with ME/CFS. Administration of CoQ10 improves hyperalgesia and quality of life in patients with Fibromyalgia. The evidence base for the effectiveness of treatment with CoQ10 may be explained via its ability to ameliorate oxidative stress and protect mitochondria.

Key words: Coenzyme Q10, oxidative and nitrosative stress, inflammation, cytokines, mitochondria

Coenzyme Q10: CoQ10

Adenosine triphosphate: ATP

reactive oxygen species: ROS

reactive nitrogen species: RNS

oxidative and nitrosative stress: O&NS

nuclear factor- κ B: NF- κ B

malondialdehyde: MDA

superoxide dismutase: SOD

Myalgic Encephalomyelitis / chronic fatigue syndrome: ME/CFS

Parkinson's Disease: PD

nitric oxide: NO

tetrahydrobiopterin: BH₄

poly-unsaturated fatty acids: PUFAs

endoplasmic reticulum: ER

N-methyl-D-aspartate: NMDA

ubiquitin-proteasome system: UPS

low-density lipoprotein-cholesterol: LDL-C

4-hydroxynonenal: 4HNE

peroxisome proliferator-activated receptor (PPAR) gamma co-activator-1 alpha: PGC-1 α

uncoupler protein: UCP

nuclear factor (erythroid-derived 2)-like 2: Nrf2

antioxidant response element: ARE

mitochondrial DNA: mtDNA

mitochondrial transcription factor A: Tfam

nuclear respiratory factor 1/2: NRF1/2

tumor necrosis factor (TNF) α

chemokine (C-X-C-motif)

C-X-C-motif ligand 2 (CXCL2)

Chemokine (C-C-motif) ligand 3 (CCL3)

Regulated upon activation, normal T cell expressed and secreted: RANTES

nuclear factor of activated T cells: NFATc1

interleukin: IL

neutral-sphingomyelinase: n-SMase

cardio-vascular disorder: CVD

forward rate constant: kfor

Unified Parkinson Disease Rating Scale: UPDRS

1. Introduction

Coenzyme Q10 (CoQ10), also named ubiquinone, is found in all cells. It is a redox modulator, a membrane stabilizer, and a vital cofactor in the electron transport chain, enabling the generation of adenosine triphosphate (ATP) [1-3]. CoQ10 is also required for the optimum performance of many essential cellular functions. As an antioxidant, it shields cells and tissues from damage mediated by the corrosive effects of reactive oxygen species (ROS) and nitrogen species (RNS), or oxidative and nitrosative stress (O&NS).

CoQ10 exists in the body as both the reduced form, i.e. ubiquinol, and the oxidized form, i.e. ubiquinone [4, 5]. Ubiquinol can be recycled from ubiquinone by CoQ10 reductases, such as NAD(P)H: quinone reductase and NADH: cytochrome b5 reductase [6-8]. CoQ10 located in the mitochondria and other plasma membranes exerts antioxidant effects directly or indirectly either by regenerating oxidized tocopherol and ascorbate or increasing brain mitochondrial effects and as a consequence CoQ10 has putative neuroprotective effects [9,10].

CoQ10 has numerous biological roles. For example CoQ10 promotes cellular membrane repair [11], modulates the transcription of genes governing the proinflammatory JAK/STAT signaling pathways and regulates inflammatory response by suppressing the activation of nuclear factor- κ B (NF- κ B) [12]. CoQ10 has an essential role in pyrimidine biosynthesis and is an essential cofactor of uncoupling proteins [13]. CoQ10 also regulates gene expression [14-16], particularly those governing cell metabolism [14,17]. CoQ10 also regulates inflammatory processes [18-20] and apoptosis [21,22].

Free radical levels are significantly increased in cells with depleted CoQ10 levels. Studies reveal that CoQ10 supplementation reduces plasma levels of oxidative stress biomarkers, including malondialdehyde (MDA) [23] and increases the antioxidant capabilities of antioxidant

enzymes, such as superoxide dismutase (SOD) and glutathione reductase [24]. The fact that ROS levels and oxidative stress biomarkers may be normalized by addition of exogenous CoQ10 provides further evidence of the role that CoQ10 plays in the management of O&NS in cells [25].

Diminished CoQ10 levels frequently lead to deficits in mitochondrial energy production combined with an increased amount of free radical damage because of diminished scavenging capability of CoQ10 [26]. Human CoQ10 deficiencies are characterized by infantile encephalomyopathy, renal failure, cerebellar ataxia and myopathy [27-30]. Different authors have reported that administration of CoQ10 improves both biochemically and clinically patients suffering from mitochondrial dysfunction or disease [31-33].

Decreased levels of CoQ10 have been reported in medical disorders such as Myalgic Encephalomyelitis / chronic fatigue syndrome (ME/CFS) and Fibromyalgia, and neuropsychiatric disorders, such as depression [34-40]. Patients with neurodegenerative disorders often display abnormal levels of ubiquinone or ubiquinol, pointing to a probable role in the pathophysiology underpinning these illnesses [41-43]. An accumulating body of evidence now points to abnormal mitochondrial function coupled with excessive O&NS damage in the pathophysiology of neurodegenerative diseases, including Parkinson's (PD) and Alzheimer's disorder, stroke, Friedreich's ataxia, Huntington's disease, bipolar disorders and schizophrenia [44-48]. Recent clinical trials in these diseases report that supplementation with CoQ10 can impede the functional decline seen in some of these diseases particularly PD [49-52].

This paper aims to focus on the roles of CoQ10 in the management of cellular metabolism, cell death, differentiation and gene regulation and will examine the potential repercussions of CoQ10 depletion in illnesses classified as neuropsychiatric by the WHO namely unipolar and

bipolar depression and illnesses classified as neurological disorders by the WHO, i.e. PD and ME/CFS. The role of CoQ10 depletion in Fibromyalgia will also be considered. This illness is currently categorized as a soft tissue disease but tends to co-occur with ME/CFS. The evidence base for the effectiveness of treatment with CoQ10 in a wide range of medical conditions, via its ability to ameliorate O&NS and protect mitochondria is reviewed.

2. Causes and consequences of O&NS

O&NS may be conceptualized as an excessive production and / or insufficient clearance of reactive free radicals, including ROS and RNS [53]. Examples of ROS are: superoxide (O_2^-), hydroxyl ($\text{OH}^\bullet$), peroxy ($\text{RO}_2^\bullet$), hydroperoxyl ($\text{HRO}_2^\bullet$) and nonradical members, such as hydrogen peroxide (H_2O_2) and hydrochlorous acid (HOCl) [54]. The RNS family includes nitric oxide ($\text{NO}^\bullet$), nitrogen dioxide ($\text{NO}_2^\bullet$), peroxyxynitrite (ONOO^-), nitrous oxide (HNO_2) and alkyl peroxyxynitrates ($\text{RONOO}^\bullet$) [53,54]. ROS such as O_2^- and H_2O_2 activate intracellular signaling networks, including NF- κ B, p38-MAPK and STAT-JAK. $\text{NO}^\bullet$ readily engages in a chemical reaction with superoxide, leading to the formation of the excessively reactive molecule ONOO^- , producing a wide array of deleterious consequences, including lipid peroxidation, single-stranded DNA breakage and oxidation of tetrahydrobiopterin (BH_4) [53,55].

ROS have a number of biological targets including proteins and poly-unsaturated fatty acids (PUFAs) in cell membranes as well as DNA [56]. The consequences of ROS attacks on proteins involve the creation of cross linkages and leads to the removal of double bonds in PUFAs. This depletion of PUFAs results in reduced membrane fluidity and consequently reduced activity of membranes bound to the plasma membrane together with dysfunctional

receptors and ion channels [57]. ROS also damage DNA via ring opening, the induction of hydroxylation and fragmentation [58] leading to the production of 8-hydroxy-2'-deoxyguanosine [59]. ROS can also damage and distort the backbone of the DNA strand [60] and shorten the telomere [61]. The abovementioned processes may cause endoplasmic reticulum (ER) stress, damage to mitochondria and proteasome inhibition [62,63]. NO and peroxynitrite cause damage to cellular processes not only by decreasing glutathione but also by S-nitrosylating numerous proteins. Excessive nitrosative stress is a major contributor to chronic stimulation of the N-methyl-D-aspartate (NMDA)-type glutamate receptor, and impaired mitochondrial function [63].

Excessive ROS and RNS may generate abnormal mitochondrial dynamics, misfolded proteins and activate neuronal apoptotic pathways [63,64]. Protein misfolding and degradation, caused by the modifying effects of O&NS, play a major role in the pathophysiology of many if not all neurodegenerative diseases. Oxidized proteins are degraded by two major pathways: a) the ubiquitin-proteasome system (UPS) [65]; and b) the autophagy-lysosome pathway [66-68]. The UPS is the prime mechanism governing the lysis of short-lived and misfolded proteins located in the endoplasmic reticulum [67]. The other mechanism involves several different modes of autophagy which transfers proteins to the lysosomes where they are degraded. The UPS, macroautophagy, microautophagy and chaperone mediated autophagy take part in the disposal of oxidized proteins. However, excessive O&NS impairs the degradation of oxidized proteins [69-71]. Oxidative modifications in the UPS system may impair the normal unfolding needed to enable substrates to migrate through the proteasome for lysis, rendering these molecules highly resistant to hydrolysis and at least potentially reducing the overall activity of the proteasome [72-76]. Moreover, oxidatively modified proteins adversely affect the cellular processes underpinning autophagic degradation [72,77]. The lysosomal membrane may

additionally be damaged by ROS/RNS causing leakage of hydrolases into the cytosol [72,78-80]. Some oxidatively modified aggregates are highly resistant to lysis and therefore accumulate in the lysosome, which in turn may become a new source of ROS/RNS that further damage the lysosomal membrane [72,81].

3. Repercussion of lowered CoQ10 for the pathophysiology of medical and neuropsychiatric disorders.

CoQ10 plays an orchestral role in many cellular processes, including hydrogen peroxide formation, gene regulation, cytoprotection, bioenergetic performance, cellular redox state modulation and regulation of cellular metabolism. The existence of ubiquinone and ubiquinol are well recognized but the existence of the partially reduced semi-quinone form which allows CoQ10 to also function as a prooxidant is less well known [82]. We now consider these functions in more detail.

3.1. CoQ10 and mitochondrial functions

CoQ10 is a vital player in the mitochondrial respiratory chain, acting as an electron carrier from complexes I and II of the electron transport chain to complex III and hence essential for ATP synthesis [83,84]. Dysregulation of this system can jeopardize the oxidative capacity of the mitochondria resulting in diminished levels of energy production [85]. Apart from its role in energy generation, CoQ10 is also a component of redox chains in cellular membranes [86], designed to remove excess reducing power generated by the adoption of glycolysis at times of reduced mitochondrial respiration [87,88]. CoQ10 plays also a role in the two main regions within the respiratory chain which act as a source of ROS [89], the first being Complex I (NADH Coenzyme Q reductase) [90-92] and the second being complex III (ubiquinol cytochrome c

reductase; [93]). The stability of complex III in the mitochondrial membrane is partly determined by CoQ10 [94,95].

CoQ10 deficiency may result in reduced activities of the mitochondrial complexes I, II and IV of the electron transport chain together with diminished expression of proteins within mitochondria connected with oxidative phosphorylation and a reduced mitochondrial membrane potential [96]. Furthermore CoQ10 deficiency leads to elevated synthesis of ROS, leading to the activation of mitochondrial permeability transition pores and ultimately mitophagy [96]. These abnormalities were partially restored by CoQ10 supplementation [96].

In humans there is accumulating evidence of relationships between impaired mitochondrial function, O&NS and fatigue levels [97,98]. In similar vein mitochondrial mutations can lead to severe muscle fatigue [97]. Impaired mitochondrial complex I activity is also associated with severe fatigue [99]. A number of authors have suggested the beneficial effect of CoQ10 supplementation on complex 1 function [100-102]. Werbach [103] suggested that improvement of mitochondrial functions with CoQ10 supplementation could be an important treatment for the reduction of fatigue [103].

3.2. CoQ10 as antioxidant

The role of ubiquinone within ROS production is biphasic displaying both pro-oxidant [89,90,104] and antioxidant activities [17,87,83,88,105]. CoQ10 is the only lipid soluble antioxidant which may be synthesized endogenously and is unique being the only one mostly present in reduced form. Two mechanisms for the antioxidant activities of the reduced form of CoQ10 have been illuminated [106-108]. In one mechanism, CoQ10 quenches lipid peroxyl radicals directly [109,110], and in the other, CoQ10 has an indirect antioxidant function by being

a key player in regenerating other antioxidants such as α -tocopherol from α -tocopheroxyl radicals [107,108]. The protective effect conferred upon lipids, proteins and DNA largely results from its close proximity to the events causing O&NS and its ubiquitous and continual regeneration by reduction [111,112]. CoQ10 is a membrane protective antioxidant that protects unsaturated lipids in cell membranes, mitochondrial membrane proteins and low-density lipoprotein-cholesterol (LDL-C) in blood from damage mediated by free radical species [113-116]. CoQ10 plays a crucial role in maintaining the fluidity of membranes and shielding phospholipids located in cell membranes from peroxidation and oxidative damage [43,83]. Dietary supplementation with CoQ10 protects LDL lipoproteins from peroxidation processes [4, 83,117,118]. CoQ10 administered to 22 human volunteers led to higher plasma CoQ10 levels and a significant depletion of H₂O₂ coupled with reduced signs of lipid peroxidation [119]. CoQ10 supplementation dose-dependently attenuated increased levels of 8-hydroxy-2'-deoxyguanosine (8OHdG) and nitrosative stress and inflammatory markers [120]. A study by Ahmadvand et al. [121] demonstrated that CoQ10 markedly reduced MDA levels in serum and increased serum glutathione and catalase and superoxide dismutase activity. Via its inhibition of lipid peroxidation and 4-hydroxynonenal (4HNE) production, CoQ10 will impact on the 4HNE mediated sirtuin-3 conformational change, which decreases sirtuin-3 function [122]. Sirtuin-3 is mitochondria localized and important to mitochondrial function. Lipid peroxidation, in damaging DNA, increases levels of PARP1, leading to decreased NAD⁺, in turn decreasing sirtuin-1 and peroxisome proliferator-activated receptor gamma co-activator-1 alpha (PGC-1 α), classically seen a master mitochondria regulator [123], and elaborated on below. Impacts on levels of sirtuins are another means by which CoQ10 modulates mitochondrial function via the regulation of lipid peroxidation.

Oxidized CoQ10 has also a role when acting as a prooxidant in the genesis of H₂O₂ and superoxide. Continuous formation of these molecular entities are vital for normal cell function and redox state regulation [124-126]. H₂O₂ can activate phosphatase cascades, which generate a pattern of altered nuclear gene transcription [127]. The redox state of CoQ10 varies according to the redox potential of the cell and mitochondrial membrane potential and hence acts as a surrogate marker of the energetic and metabolic needs of the cell. H₂O₂ functions as intracellular second messenger communicating cellular needs with the mitochondrial and nuclear genomes in real time [125]. Minute alterations in the intracellular redox state can produce strikingly different outcomes from a metabolic and cell differentiation perspective. Cumulative data also highlights the fact that large numbers of biomembrane systems are powered by redox processes which form temporary and highly localized biological-capacitors. This energy is used, apart from ATP synthesis, to power other activities such as nerve conduction and the translocation of metabolites [124].

3.3. CoQ10 and uncoupler proteins

CoQ10 is a vital molecule needed by the uncoupler protein (UCP) family to perform normally [128]. In essence these UCP proteins, located on the inner membranes of mitochondria, carry protons across membranes in the reverse direction as that needed for the production of energy. Therefore they have the capability to modulate the membrane potential. UCP1, UCP2 and UCP3 are known to modulate cellular fuel metabolism and inhibit ROS generation (in particular UCP2 and UCP3). Activation of UCP1 increases respiration and the uncoupling mechanism leads to a futile cycle resulting in metabolic oxidation and energy being lost as heat [129-135]. Accumulating evidence highlights the pivotal role of UCP2 in processes, such as

cytoprotection [136-139], immune modulation [140,141] and the modulation of glucose sensing by brain and pancreas cells [142,143]. There is also some evidence that UCP2 in cells is a key player in regulating the changeover from aerobic to anaerobic respiration [144,145]. UCP2 also governs immune cell activation by regulating MAPK pathways, the production of cytokines and nitric oxide as well as migration of antigen presenting cells. The weight of evidence indicates that UCP2 modulates innate immunity, during an acute infection, via its capacity to regulate ROS, cytokine and chemokine production and consequently the recruitment of phagocytes [141]. UCP3 can be activated by superoxide [146,147] and lipid peroxidation products [148]. The protein extinguishes protein oxidation in skeletal muscle [149] and seems to attenuate production of ROS during exercise [150]. UCP3 may also play a role in fatty acid metabolism by increasing transport and oxidation of fatty acids [151-153]. The role of UCP4 and UCP5 is less delineated but these proteins are thought to be cytoprotective. Studies indicate that UCP5 which is more specific to the brain plays an important role in apoptosis [154,155].

The UCPs are vital for protection against free radicals and are essential regulators of ATP-dependent processes [156]. There is evidence that elevated levels of superoxide [146,147] and lipid peroxidation products [157-159] can trigger uncoupling by all UCPs. This may occur via the binding of superoxide with membrane phospholipids generating a proximal activator, hydroxynonenal [148,158]. For example, elevated reactive oxygen species and their metabolites are thought to result in increased UCP2 activity producing a negative feedback loop that reduces production of ROS [160-162]. This mechanism explains that UCP2 acts as a physiological dampener of ROS signaling. The downregulation of UCP2 is essential to enable the elevation of mitochondrial ROS generation required to amplify MAPK activation and foster the immune

response. Macrophages deficient in UCP2 demonstrate an increased inflammatory state evidenced by elevated production of nitric oxide and increased ability to migrate.

CoQ10 has a double role in this uncoupler protein system: it functions as a proton carrier molecule and activates the UCPs, and it may be a player in superoxide generation [124]. CoQ10 is an obligatory factor for proton transport by UCP1 [128]. Also UCP2 and UCP3 are activated by CoQ10 and require CoQ10 as cofactor for proton transport [163]. CoQ10 supplementation has been reported to induce mitochondrial uncoupling mediated by UCP-2 in the substantia nigra [164].

3.4. Coenzyme Q10 and gene regulation

The regulatory mechanisms involved in mitochondrial biogenesis are complex and there are a number of excellent reviews which explore this area in considerable depth [165-168]. Mitochondrial biogenesis involves a complex matrix of transcription factors that stimulate the activation of genes responsible for encoding enzymes of fatty acid oxidation, cellular antioxidant defenses and oxidative phosphorylation.

Schmelzer et al. [18] provided evidence that CoQ10 modulates the transcription of hundreds of human genes. CoQ10 increased the expression of 694 genes connected to cell signaling, metabolism, transport control of transcription and oxidative phosphorylation [14]. More specifically, CoQ10 supplementation alone or in combination with lipoic acid stimulates the transcription of PGC-1 α and nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and antioxidant response element (ARE) gene activation, involving regulation of bioenergetics performance, cellular redox state and mitochondrial biogenesis [169,170]. PGC-1 α , a transcriptional co-activator, regulates mitochondrial functions in mammalian tissues. PGC-1 α

regulates gene expression and couples external, environmental cues to mitochondrial functions and biogenesis [52,171]. PGC-1 α enhances mitochondrial functions by increasing the expression of numerous nuclear transcription factors in turn connected to expression of genes in the nuclear or mitochondrial genome needed for mitochondrial proliferation [172-174]. PGC-1 α constitutes one of the most transparent examples whereby biological pathways are mostly regulated by a transcriptional coactivator whose activity changes in response to qualitative and quantitative changes in environmental stimuli [175,176]. PGC-1 α activates and coordinates gene expression which stimulates oxidative metabolism in mitochondria and modulates biological programs linked to energy homeostasis [175-177]. The cofactor encourages the development of muscle fiber-type which is metabolically more reliant on oxidative phosphorylation and less reliant on glycolysis. PGC-1 α is also involved in the regulation of both carbohydrate and lipid metabolism [178-180]. PGC-1 α also acts indirectly to regulate mtDNA transcription via its capacity to increase the expression of mitochondrial transcription factor A (TFAM), which in turn is coactivated by NRF-1 [181,182]. PGC-1 α controls a number of genes connected with mitochondrial respiration and biogenesis via its capacity to modulate the transcription and activity of several transcription factors which include nuclear respiratory factor 1/2 (NRF-1/2) [181,183].

Nrf2 binds with ARE to facilitate gene transcription either constitutively or as a result of oxidative stress signals. Nrf2 regulates a wide array of ARE-driven genes in a wide range of cell types, hence the Nrf2-ARE pathway is a vital component in the cellular antioxidant defense system. ARE induces the transactivation of genes responsible for encoding Phase II detoxification and antioxidative enzymes [184]. The cytoprotective effects of Nrf2 stem from the unified expression of genes with, anti-oxidant and detoxifying capabilities [185]. In particular

Nrf2 activates and coordinates the expression of two enzyme systems the heme oxygenase system [186,187] and a group of enzymes involved in glutathione superoxide, dismutase and glutathione peroxidase synthesis [188,189].

3.5. CoQ10 and anti-inflammatory effects.

Other CoQ10-sensitive genes are implicated in the control of cell termination and cell differentiation and inflammatory compounds, e.g. tumor necrosis factor (TNF) α , chemokine (C-X-C-motif) ligand 2 (CXCL2) and Chemokine (C-C-motif) ligand 3 (CCL3). CoQ10 also exerts anti-inflammatory properties via attenuating nuclear factor NF- κ B dependent gene expression; the expression of LPS-induced release of chemokines, e.g. macrophage inflammatory protein-1 α and RANTES (Regulated upon activation, normal T cell expressed and secreted); and LPS-sensitive genes, which are known to regulate signal transduction, cell proliferation pathways and transcriptional regulation [12,18,190]. CoQ10 has been shown to suppress the nuclear factor of activated T cells (NFATc1) and NF- κ B signaling [191].

In mice, administration of ubiquinol induces the expression of genes connected to peroxisome proliferator-activated receptor- α (PPAR α) and regulating fatty acid metabolism and inflammation [190]. In rats, CoQ10 administration not only decreased O&NS, but also the release of pro-inflammatory cytokines, e.g. TNF α and interleukin (IL)-1 β [192].

Perhaps unsurprisingly given the information above, CoQ10 supplementation has been shown to have profound effects on immunoglobulins (Igs) and T cell populations. CoQ10 stimulates increases the production of antibody levels, e.g. IgG, and increases the numbers and/or function of macrophages and T lymphocytes, e.g. the CD4 to CD8 T-cell ratio [193-197]. These effects may explain the increased resistance to infection [198-200].

3.6. CoQ10 and the control of apoptosis

When considered together the weight of evidence indicates that CoQ10 and its reductases constitute an antioxidant system, which spans the plasma membrane [201]. Cells with elevated levels of CoQ10 in their plasma membranes display an increased resistance to oxidative stress-mediated apoptosis [94,202]. CoQ10 controls the permeability transition pore opening [203] and assists in stabilizing the plasma membrane, not only by regenerating antioxidants such as α -tocopherol and ascorbate, but also by modulating Mg^{2+} -dependent neutral-sphingomyelinase (n-SMase) located within the plasma membrane. Activation of the latter pathway which is dependent on ceramide levels is an early event of the apoptotic process through catalyzing ceramide ultimately inducing cell death by activating caspases [94,202,204]. CoQ10 interferes with this early phase of apoptosis by inhibiting Mg^{2+} -dependent n-SMase [94,202].

4. O&NS and related pathways in selected medical and neuropsychiatric disorders

4.1. O&NS in ME/CFS and fibromyalgia

A number of teams using peripheral blood measurements have reported elevated O&NS in ME/CFS patients. O&NS related abnormalities include elevated levels of isoprostane, MDA, 8-OH-deoxyguanosine, 2,3 diphosphoglyceric acid, thiobutyric acid, and protein carbonyls [34-36,44,205-216]. The synthesis of inducible NOS is significantly increased in patients with ME/CFS compared to healthy controls [217]. There is also data demonstrating chronic hyperproduction of NO [205,218].

Prolonged elevated O&NS develops in patients with ME/CFS during and following exercise [219-221] potentially explaining one of the mechanisms underpinning the development

of post-exertional flu like malaise. Increased physical activity induces striking changes in the muscle membrane activity in this patient group [219] and oxidative imbalance within muscle fibres is associated with increased muscle fatiguability [222]. O&NS measures correlate positively with the severity of symptoms [35,36,44,205,207,212,214,223].

Patients with ME/CFS also display diminished levels of antioxidants, such as zinc and glutathione [36,205,223,224]. Changes in the redox state of glutathione correlates with diminished methylation activity and B vitamin together with folate supplementation has been demonstrated to improve glutathione redox in patients [225]. Decreased cortical glutathione concentration inversely correlated with lactate levels have been reported in the brain in ME/CFS patients [223]. Miwa and Fujita [216] reported that patients entering remission displayed a marked drop in O&NS levels.

The evidence indicating that mitochondrial dysfunction, diminished oxidative phosphorylation and abnormally high lactate levels play a major part in the etiology of ME/CFS is robust [review: 226,227]. Vermeulen et al. [228] reported an increase in lactate production and decrease in ATP production relative to controls in two identical exercise programs held on successive days. Patients with ME/CFS reached their anaerobic threshold and maximum exercise capacity at a significantly lower oxygen consumption than healthy controls. This difference was even more pronounced in the subsequent test. Kennedy et al. [212] found that the magnitude of elevated O&NS in patients with ME/CFS correlated positively and significantly with the degree of symptom exacerbation which followed gentle exercise. Paul et al. [229] reported a decrease in voluntary muscle contractions during and immediately following exercise. Interestingly this abnormality became more pronounced in the immediate aftermath of exercise than while actually engaging in the exercise program, again indicating mitochondrial dysfunction. Arnold et al.

[230], utilizing ^{31}P nuclear magnetic resonance spectroscopy, reported an abnormal increase in the level of intracellular lactic acid, proportional to corresponding changes in high-energy phosphates, in the exercised forearm of a ME/CFS patient. Behan [231] detected structural abnormalities in the skeletal muscle mitochondria of ME/CFS patients. ME/CFS patients display a significant increase in intracellular lactate levels and a significantly lower ATP resynthesis rate following exercise compared to controls as a result of diminished oxidative phosphorylation [232]. ME/CFS patients display a grossly abnormal rise in lactate levels with even trivial exercise and an excessively slow return to baseline levels [228,229,232-234]. Fatigue can emanate from an accumulation of ROS and concomitant diminished availability of ATP in muscle cells [235]. Prolonged exposure to elevated ROS produced in mitochondria damages the DNA within the organelle [236]. This in turn leads to a decrease in activity of the electron transfer chain and a further increase in generation of ROS, producing a vicious spiral of increasing O&NS levels and energetic decline [237].

Total antioxidant capacity or antioxidant enzymes such as SOD and catalase are decreased in the plasma of patients with Fibromyalgia [238-240]. There is also evidence that fibromyalgia is accompanied by increased ROS and O&NS, including lipid peroxidation [38,241,242]. H_2O_2 is increased in neutrophils of patients with fibromyalgia [241], while superoxide of mitochondrial origin is observed in the peripheral blood mononuclear cells of Fibromyalgia patients [241]. Measurements of lipid peroxidation and carbonylated proteins, end products of membrane damage induced by ROS, are increased in the plasma of patients with fibromyalgia [238,239]. Space precludes a detailed consideration of the biological abnormalities reported in people with Fibromyalgia but suffice to say that there is considerable evidence of mitochondrial dysfunction [37,38,243,244].

4.2. O&NS in depression

Recently, we have reviewed that depression is accompanied by increased signs of O&NS, including damage to lipids, proteins and DNA as well as IgG and IgM-mediated autoimmune responses directed against neoepitopes generated by damage to endogenous epitopes which subsequent to O&NS had become immunogenic [44,245,246]. These autoimmune responses are directed against multiple neoepitopes, such as membrane fatty acids, anchorage molecules, neurotransmitters and NO-adducts. We refer the reader to the abovementioned papers for in depth reviews on activated O&NS pathways in clinical depression and different animal models of depression. Recently, activated O&NS pathways were also detected in diverse neuropsychiatric disorders, including autism, schizophrenia and bipolar disorder [45,46]. In addition to abundant evidence of O&NS in these neuropsychiatric disorders, these disorders are linked to lowered concentrations of a number of endogenous redox modulators including vitamin E, zinc and glutathione, and enzymes, such as glutathione peroxidase, as well as reduced total antioxidant status [45,46,247,248].

4.3. O&NS in neurodegenerative disorders: focus on PD

O&NS in PD is evidenced by the existence of oxidatively damaged lipids and protein molecules in the brains of PD patients. This damage results from lipid peroxidation [249] and protein oxidation and nitration [250,251] and oxidative damage to DNA [249,252]. In PD, lipid peroxidation is present in the substantia nigra as evidenced by increased levels of 4HNE and MDA [253,254]. Moreover an increase in carbonyl groups has been detected in several regions

of the brain in PD patients [250]. Nitrotyrosine residues are present in Lewy bodies indicating that protein nitration may partly underpin the pathophysiology of PD [251]. Increased lipid peroxidation detected in PD patients is a cause of neuronal cell death in nigral cells [252,255]. Observed pathologic DNA rearrangements are not considered to be the prime drivers of the disease but result from O&NS arising from mitochondrial dysfunction [256].

The role of mitochondrial dysfunction in the etiology of PD is well documented [257,258]. A dramatic fall in glutathione levels in the substantia nigra accompanies the onset of PD. This fall results in a decreased activity of mitochondrial functions and in particular in aberrations in mitochondrial complex I [259]. Diminished mitochondrial performance is a prominent characteristic of the disease with diminished activity in OXPHOS complexes associated with oxidative phosphorylation and increased deletions in neuronal mtDNA [258]. Further evidence of mitochondrial dysfunction is revealed by impoverished levels and misassembly of complex I subunits [260-264]. Deficiencies in mitochondrial complex I have been detected not only in the brain but also in other tissues of PD patients, including platelets and muscles [265-267]. Moreover, neurons from preclinical PD patients demonstrate a diminished mitochondrial biogenesis capability [268].

Impaired autophagy is held to be a major mechanism in PD [269,270]. NO through the induction of NO synthase may impair the initiation of autophagy [271]. Impaired autophagy could in turn impair clearance of damaged mitochondria and the clearance of α Synuclein. Evidence suggests that O&NS can modify α Synuclein at critical residues thereby altering its native configuration and the way it oligomerises [272-274]. Autophagy is of great importance since neurons do not replicate and therefore impaired basal autophagy almost invariably results in neuronal death [275-277]. Autophagy is differently regulated in neuronal and non-neuronal

cells [278,279].

Possible mechanisms explaining the pathology of PD involve direct impairment of mitochondrial functions by α Synuclein or mitochondrial dysfunctions, which exacerbate the toxicity of α Synuclein, or a self-amplifying and self-sustaining cycle between both phenomena [274]. Normal functioning of parkin activates the autophagy of damaged mitochondria. Nitrosative modification of parkin results in aborted mitophagy, leading to a buildup of dysfunctional mitochondria with a concomitant increase in ROS production, further amplifying the O&NS experienced by neurons [280-282].

5. Lowered CoQ10 levels in the abovementioned disorders.

Lowered plasma levels of CoQ10 have been reported in ME/CFS [36,223]. The lowered plasma CoQ10 levels in ME/CFS are significantly associated with fatigue, neurocognitive symptoms, including concentration and memory disturbances, and autonomic symptoms [35]. Many ME/CFS patients had concentrations beneath 490 μ g/L, which is the lowest CoQ10 concentration measured in normal controls. Lowered plasma COQ10 is also a risk factor for cardiovascular disorder, chronic heart failure and due mortality and therefore lowered CoQ10 may play a role in the comorbidity between ME/CFS and cardiovascular disorder and the early mortality in ME/CFS due to cardio-vascular disorder (CVD) [36,283]. Cordero et al. [284] reported diminished CoQ10 in blood mononuclear cells from Fibromyalgia patients. Plasma levels of CoQ10, as indicated by ubiquinone-10, ubiquinol-10, are decreased in juvenile Fibromyalgia, negatively correlating with measures of O&NS and hypercholesterolemia [285], potentially contributing to CVD.

Interestingly, treatment with statins may cause some typical symptoms of ME/CFS and Fibromyalgia, such as fatigue, neurocognitive disturbances and myalgia through significant reductions in plasma CoQ10 concentrations [286,287]. Statin treatment diminishes CoQ10 levels in serum and striated muscles [288,289]. Statins are indeed known to inhibit the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A to the cholesterol precursor mevalonate and the side chain of CoQ10 [290,291]. Patients with diseases characterized by lowered plasma CoQ10 levels also display increased fatigue and exercise intolerance, e.g. cardiac and skeletal muscle dysfunctions, autosomal recessive CoQ10 deficiency, Steinert's myotonic dystrophy, Prader-Willi syndrome and Friedrich's ataxia [292-294].

Lowered plasma CoQ10 concentrations are also detected in major depression [295]. Lowered CoQ10 was associated with resistance to treatment with antidepressants and with the presence of chronic fatigue symptoms. Moreover, a high percentage of depressed patients (51.4%) show plasma CoQ10 levels that were lower than the lowest value in healthy volunteers. In depression, compared to controls, CoQ10, ATP levels and mitochondrial mass were reduced, whereas lipid peroxidation was elevated [296]. The lowered CoQ10 levels in this study appear to be aggravated by the antidepressant amitriptyline, leading the authors to speculate about the putative remedial role of CoQ10.

Significantly lower CoQ10 levels were detected in mitochondria from PD patients as compared with matched controls [40]. Diminished plasma CoQ10 concentrations were also decreased in these patients [297]. There is also evidence suggesting that CoQ10 supplementation slows the functional decline in PD [51,52].

6. Effects of CoQ10 administration.

6.1. Effects of CoQ10 treatment on fatigue, hyperalgesia and Fibromyalgia.

Mizuno et al. [298] reported that CoQ10 supplementation at 300 mg per day improved fatigue and physical performance. Performance-enhancing effects were also reported by Gokbel et al. [299] in subjects engaging in repeated bouts of supramaximal exercises given 100 mg a day of CoQ10 8 days and the authors suggested that CoQ10 could be utilized as an ergogenic aid. Cooke et al. [300] examined the results of acute and chronic CoQ10 administration on exercise parameters in untrained and trained individuals and reported that there was a significant positive correlation between the plasma concentration of CoQ10 and treadmill time to exhaustion and maximal oxygen consumption. The authors also reported a trend towards improved exercise performance following two weeks of supplementation with CoQ10 [300]. Another study involving CoQ10 supplementation appears to be particularly relevant for patients with ME/CFS given the exercise intolerance and activated O&NS pathways evident in these patients [219,226]. Díaz-Castro et al. [301] examined the effects of exercise on surrogate oxidative stress markers in exercising muscle and found that aerobic exercise resulted in a significant elevation of TNF α , IL-6, 8-hydroxy-2'-deoxyguanosine and isoprostane levels, which were all decreased when CoQ10 was taken during exercise. CoQ10 administration also prevented the overexpression of TNF α which otherwise occurred following exercise and increased catalase expression and decreased creatine levels [301].

CoQ10 is often used successfully to treat the fatigue, myalgias and neurocognitive disorders associated with low CoQ10 syndrome due to statin use or diseases such as cardiac and skeletal muscle dysfunctions, autosomal recessive CoQ10 deficiency, Steinert's myotonic dystrophy, Prader-Willi syndrome and Friedrich's ataxia [293,302,303]. Patients taking very high doses of statins experienced relief of the statin-induced musculoskeletal pain following

treatment with CoQ10 [304-306]. As well as decreasing pain in statin users, CoQ10 also attenuates statin induced muscle weakness and cramps, as well as improving general tiredness [307].

CoQ10 supplementation has been shown to produce significant improvement in quality of life of patients with Fibromyalgia [308]. For example, the intensity of severe fatigue, which is a common presentation of Fibromyalgia, is reduced by CoQ10 in both animal and human exercise-induced physical fatigue models [309, 298]. Cordero et al. [284] showed that oral CoQ10 supplementation normalized biochemical parameters and produced a significant improvement in the overall clinical picture particularly headache symptoms. At the cellular level, CoQ10 supplementation led to the restoration of mitochondrial function and the mitochondrial DNA copy number, diminished oxidative stress, and stimulated mitochondrial biogenesis. [38]. Recent work further supports this, with CoQ10 supplementation improving clinical measures in Fibromyalgia patients, suggested to be partly mediated by increased mitochondrial biogenesis [310].

CoQ10 administration also improves mitochondrial processes that play a role in the pathophysiology of ME/CFS and Fibromyalgia, e.g. lowered ATP and increased lactate production. CoQ10 administration may improve the clinical and biochemical characteristics of patients with mitochondrial disorders [e.g. 33,31]. In patients with mitochondrial disease, CoQ10 supplementation significantly improves ATP production in brain tissue and skeletal muscles [311]. Phosphorous magnetic resonance spectroscopy (31PMRS) has been used to examine the results of CoQ10 supplementation on mitochondrial function in the brain and skeletal muscle [311]. In one study examining the effects of CoQ10 treatment in mitochondrial cytopathies, the authors observed decreased lactate levels (25%) following exercise in approximately 33% of the

trial subjects studied [312]. Following 6 months of CoQ10 supplementation 50% of the trial participants showed a decrease in the ratio lactate / pyruvate in patients with mitochondrial encephalopathies during exercise and while at rest [313]. CoQ10 administration also increases concentrations of mitochondria in the brain [9,314,315].

CoQ10 administration has also significant effects on physical performance and muscle strength: CoQ10 improves muscle weakness [31,316,317]; exercise tolerance [318,319]; oxygen usage while engaging in exercise [320]; post-exercise recovery [321,322]; cardiac function and physical performance [323]; and muscle strength and neuromuscular function in mitochondrial encephalomyopathies [324,325]. In patients with CoQ10 deficiency, CoQ10 administration significantly improved muscle strength and walking distance and reduced muscle weakness [326]. Linnane et al. [126] examined the effect of CoQ10 supplementation on human vastus lateralis (quadriceps) muscle and found that CoQ10 changed the fibre type composition producing a fibre type profile commonly present in young people, i.e. a significantly lower amount of type 1 fibres and a higher concentration of type 2 fibres.

6.2. Effects of CoQ10 treatment in depression

In older adults with bipolar depression, high dose CoQ10 appeared to have antidepressant effects in an open label study. In this study, the forward rate constant (k_{for}) of creatine kinase (CK) was shown to be lower among older adults with bipolar disorder and CoQ10 increased the k_{for} in this cohort, suggesting a link between mitochondrial bioenergetic dysregulation in the disorder and remediation with CoQ10 [48].

In chronically stressed rats, CoQ10 appears to have antidepressant effects [327]. CoQ10 at different i.p. doses (25, 50, 100 and 150 mg/kg/day) was studied in the chronic restraint stress

model of depression in rats over 3 weeks. In this model, CoQ10 demonstrated antidepressant effects. It blocked chronic restraint stress-induced behavioral changes in the open field and forced swim tests. It also remediated hippocampal catalase, reduced glutathione and glutathione peroxidase levels as well as reducing markers of lipid and DNA oxidative damage including hippocampal nitric oxide, 8-hydroxy-2'-deoxyguanosine and MDA levels in a dose-dependent manner [327]. However, it should be noted that amitriptyline, an antidepressant, reduces CoQ10 levels in depressed patients [328]. Thus, these authors found that the levels of CoQ10 and ATP and mitochondrial mass were reduced while lipid peroxidation was increased in depressed patients as compared to normal controls. Treatment with amitriptyline, however, aggravated all those defects in the depressed patients. Such an effect may contribute to the association between lowered CoQ10 levels in depression and resistance to treatment with antidepressants [295].

6.3. Effects of CoQ10 treatment in Parkinson's disease.

In a multicenter and placebo-controlled study, treatment with CoQ10 significantly improved the Unified Parkinson Disease Rating Scale (UPDRS) from baseline to 16 months later, suggesting that CoQ10 slowed the progressive deterioration of Parkinson's disease [51]. A review of four randomized controlled trials showed that CoQ10 (1.2 g/day for 16 months) significantly improved the Schwab and England activities of daily living UPDRS subscale [52]. Chao et al. [329] concluded that nutraceuticals including CoQ10 target prominent risk factors of PD, including O&NS and mitochondrial dysfunctions and therefore may play a putative role in delaying the progression of the disorder. The beneficial effects of CoQ10 supplementation may be partly explained by its neuroprotective effects, which are associated with activated O&NS pathways and mitochondrial dysfunctions, and by increasing mitochondrial concentrations in the

brain [9,315,329-331]. Moreover, CoQ10 supplementation minimizes the depletion of dopaminergic neurons in PD [332,333].

Given data suggesting that statins may offset PD development [334], coupled to the intimate association of stress and depression in the etiology and course of PD [46], it is not uncommon for someone in the early stages of PD to be treated with statins and amitriptyline. All these factors may contribute to lowering CoQ10, potentially contributing to the course of PD. Given the beneficial effects of melatonin on mitochondrial function [335], melatonin has been proposed to have efficacy in PD and other mitochondrial disorders. Some of the benefits of melatonin may be partly mediated by CoQ10 maintenance [336].

It is worth commenting on the doses **and possible side effects** of CoQ10 which may produce beneficial results. Shults et al. [51] conducted a randomized mutually blinded controlled trial involving 80 patients comparing placebo and three dosages of CoQ10, i.e. 300, 600, and 1200 mg/day together with vitamin E at 1200 IU daily. The results of the lower doses were disappointing and no benefit was detected compared to placebo. The situation with the 1200 mg/day dose was quite different however with the improvements being highly significant. Interestingly the activity of complexes I-III in the mitochondria isolated from the highest dose group was significantly higher relative to the activity measured in the control group [337]. These authors [338] went on to investigate the tolerability and safety of very large coenzyme Q10 dosages in 17 patients diagnosed with PD. The participants received increasing doses of CoQ10, i.e 1200, 1800, 2400 and 3000 mg/day. The researchers reported that the plasma concentration of the CoQ10 peaked at 2400 mg/day and that this dose together with 1200 IU of Vitamin E daily should be the optimum dose in future studies [338]. **The dose required to convey the benefits in for example PD is very large however. On a more positive note there is no evidence of CoQ10**

induced mitotoxicity even at a dose of 3000 mg a day. It is not clear whether supplementation with CoQ10 has a benefit in patients suffering from other inflammatory and O&NS diseases in the absence of CoQ10 deficiency or mitochondrial dysfunction but the chance of side effects seem extremely low.

7. Conclusions.

Depleted levels of CoQ10 in cells lead to activation of intracellular signaling pathways including NF- κ B, MAPK and JAK-STAT and a chronic activation of immune-inflammatory and O&NS pathways. CoQ10 promotes the expression of several genes involved in suppressing inflammation and the inactivation of genes promoting inflammation and thus its depletion exacerbates inflammation. Increased ROS/RNS attack proteins and fatty acids in cell membranes producing chemical modifications of both ultimately reducing membrane fluidity and diminishing the performance of cell membrane receptors and ion channels disrupting intercellular and intracellular signaling processes. Elevated peroxynitrite produces chemical modification and degradation of lipids, proteins and DNA. Uncoupler proteins cannot function properly if CoQ10 levels are low and the latter leads to a loss of ability to regulate cellular fuel metabolism and other ATP dependent processes. CoQ10 is involved in upregulating genes involved in mitochondrial biogenesis and function in response to increasing energy demands. Hence, insufficient CoQ10 compromises the ability to stimulate oxidative metabolism in response to increased demands for energy. Prolonged O&NS additionally leads to mitochondrial dysfunction and inhibits processes responsible for protein degradation within cells. The breakdown of this clearance mechanism in neural and glial cells coupled by the exitotoxicity produced by chronically elevated O&NS can result in neuropathology. This explains why loss of

CoQ10 is implicated in the development of several neurological and neuropsychiatric diseases which involve elevated O&NS and dysfunction of the electron transport chain. In this paper we have described the role of defective CoQ10 in medical illnesses, including depression, CFS, fibromyalgia and PD. However, the cellular changes, which result from CoQ10 deficiency may be applicable to many medical conditions in which inflammation and O&NS play a part, suggesting that CoQ10 is a panacea for numerous physical and mental disorders.

A relationship exists between lowered COQ10 levels and elevated immune-inflammatory and O&NS pathways and mitochondrial dysfunction and the generation of specific symptoms/behaviors, including fatigue, hyperalgesia and depression, and the onset of neurodegenerative processes. Supplementation with CoQ10 has anti-inflammatory, antioxidant and neuroprotective effects and improves the performance of complex I of the electron transfer chain. CoQ10 treatment not only diminishes fatigue, depression and hyperalgesia, but decreases muscle weakness, improves exercise tolerance and creates objective improvements in exercise parameters such as increased walking distance and improved oxygen consumption. Treatment with CoQ10 shows promise in the treatment of fatigue, Fibromyalgia and Parkinson's disease and is a new drug candidate to treat depression.

Competing interests

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Authors' contributions

GM and MM participated in the design of this review, while GA and MB helped to draft the paper. All authors contributed equally to this paper. All authors read and approved the final version.

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Table 1. Functions of Coenzyme Q10 (CoQ10) and pathophysiological and symptomatic consequences of lowered CoQ10 levels

Function	Pathophysiology associated with CoQ10 deficiency	Resultant processes and symptoms
Mitochondrial - Electron transport chain - ATP synthesis - Complexes I, II, IV - Redox chains	↑ Loss of cellular energy ↑ ROS ↑ Mitophagy ↓ Bioenergetic performance	Mitochondrial disease Neurodegenerative diseases O&NS-related disorders Mental fatigue Physical fatigue Increased exercise intolerance Myalgia Neurocognitive symptoms
Antioxidant - modulator redox state - direct scavenger - induces antioxidant enzymes	↑ O&NS ↑ Damage by O&NS to fatty acids, proteins, DNA ↑ Lipid peroxidation including LDL-cholesterol ↓ Cellular membrane repair	Atherosclerosis O&NS-related disorders Neurodegenerative disorders Fatigue

<ul style="list-style-type: none"> - regeneration of vitamin E / A - membrane protectant 	<ul style="list-style-type: none"> ↓ Neuroprotection 	Hyperalgesia
Uncoupler protein function	<ul style="list-style-type: none"> ↑ ROS and RNS ↓ Cellular metabolism ↓ Cytoprotection ↑ MAPK and JAK-STAT ↓ Neuroprotection 	Neurodegenerative processes O&NS-related disorders Inflammatory disease
Gene regulation <ul style="list-style-type: none"> - cell signaling, metabolism - Nrf2 / ARE - PGC-1α - anti-inflammatory - LPS-sensitive genes - PPARα 	<ul style="list-style-type: none"> ↓ Bioenergetics ↓ Antioxidant defences ↓ Mitochondrial functions ↑ Inflammatory cytokines and chemokines 	Neurodegenerative disease O&NS-related disorders Inflammatory disease Fatigue
Anti-inflammatory <ul style="list-style-type: none"> - NF-κB - LPS-related mechanisms 	<ul style="list-style-type: none"> ↑ Inflammation ↑ NF-κB ↑ Pro-inflammatory cytokines and chemokines 	Inflammatory disorders

- RANTES		
Apoptosis	↓ Prevention against oxidative stress-induced apoptosis	Apoptosis

ROS: reactive oxygen species

RNS: reactive nitrogen species

O&NS: oxidative and nitrosative stress

LDL: low density lipoprotein

Nrf2: nuclear factor (erythroid-derived 2)-like 2

ARE: antioxidant response element

PGC-1: peroxisome proliferator-activated receptor gamma coactivator-1

LPS: lipopolysaccharides

PPAR α : peroxisome proliferator-activated receptor-alpha

NF- κ B: nuclear factor- κ B

RANTES: regulated upon activation, normal T cell expressed and secreted