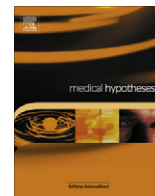


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journal homepage: www.elsevier.com/locate/mehyIncreased nuclear factor- κ B and loss of p53 are key mechanisms in Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS)Gerwyn Morris^a, Michael Maes^{b,*}^a Tir Na Nog, Pembrey, Llanelli, UK^b Maes Clinics @ TRIA, Bangkok, Thailand

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ABSTRACT

Fukuda's criteria are adequate to make a distinction between Myalgic Encephalomyelitis/chronic fatigue syndrome (ME/CFS) and chronic fatigue (CF), but ME/CFS patients should be subdivided into those with (termed ME) and without (termed CFS) post exertional malaise [Maes et al. 2012]. ME/CFS is considered to be a neuro-immune disease. ME/CFS is characterized by activated immuno-inflammatory pathways, including increased levels of pro-inflammatory cytokines, nuclear factor κ B (NF- κ B) and aberrations in mitochondrial functions, including lowered ATP. These processes may explain typical symptoms of ME/CFS, e.g. fatigue, malaise, hyperalgesia, and neurologic and autonomic symptoms. Here we hypothesize that increased NF- κ B together with a loss of p53 are key phenomena in ME/CFS that further explain ME/CFS symptoms, such as fatigue and neurocognitive dysfunction, and explain ME symptoms, such as post-exertional malaise following mental and physical activities. Inactivation of p53 impairs aerobic mitochondrial functions and causes greater dependence on anaerobic glycolysis, elevates lactate levels, reduces mitochondrial density in skeletal muscle and reduces endurance during physical exercise. Lowered p53 and increased NF- κ B are associated with elevated reactive oxygen species. Increased NF- κ B induces the production of pro-inflammatory cytokines, which increase glycolysis and further compromise mitochondrial functions. All these factors together may contribute to mitochondrial exhaustion and indicate that the demand for extra ATP upon the commencement of increased activity cannot be met. In conditions of chronic inflammation and oxidative stress, high NF- κ B and low p53 may conspire to promote neuron and glial cell survival at a price of severely compromised metabolic brain function. Future research should examine p53 signaling in ME/CFS.

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Introduction

Fukuda et al. [1] suggest that the label “chronic fatigue syndrome” (CFS) is applied to people who present with chronic fatigue and at least four self reported symptoms, which are not explained by routine blood testing. Other more liberal criteria require the presence of idiopathic chronic fatigue [2,3]. Maes et al. [4] found that Fukuda's criteria may be adequate to differentiate people with CFS from those with idiopathic chronic fatigue. However, the terms CFS and even chronic fatigue have been used to describe people with Myalgic Encephalomyelitis (ME). The diagnosis of CFS according to Fukuda's criteria [1] defines a heterogeneous population of individuals with chronic fatigue, of whom individuals with ME are a subset [4,5]. In fact, patients with ME/CFS according to Fukuda's criteria should be divided into those with post-exertional

malaise (PEM; termed ME) and without PEM (termed CFS) [4]. Thus, the use of the much wider criteria created by Sharpe et al. [3] and Reeves et al. [2], coupled with the mandatory exclusion of neurological signs and symptoms, produce heterogeneous study cohorts or cohorts where only few if any patients actually suffer from ME [6]. These inclusion and exclusion criteria have caused biased study results and wasted research funds [7].

ME/CFS patients suffer from a disease, which has at its core the inability to make energy on demand [8,9]. The World Health Organization considers ME to be a nervous system disease. ME/CFS is an acquired neuro-immune disease [4,8,9] involving malfunctioning of the central nervous (CNS) [10–12] and immune system [4,13–16]; pathologically dysfunctional impairments in cellular energy metabolism and ion transport mechanisms [17–19]; and abnormalities of the autonomic nervous and cardiovascular system [20–22]. Other findings indicate that ME may share basic immune pathophysiology with CFS but with additional PEM and significantly more immune disorders [4]. Marked cognitive and or physical fatigability following mental and physical activities are symptoms that typically occur in ME [8,9]. Post-exertional exacerbations of key symptoms, such as fatigue, hyperalgesia, malaise

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and neurocognitive disorders, may occur immediately after mental and physical activities or be delayed by days [23]. Moreover, these symptoms may range from minimal to a full clinical relapse that can last days or weeks [9].

Previously, we have explained that activation of immuno-inflammatory pathways, including increased levels of pro-inflammatory cytokines and cyclo-oxygenase 2, oxidative and nitrosative stress (O&NS) pathways and mitochondrial aberrations may explain ME/CFS symptoms, such as fatigue, malaise, sleep disorders, hyperalgesia and neurocognitive disorders [4,8,24]. Here we hypothesize that the symptoms of ME/CFS, such as fatigue and fatigability, and ME, such as PEM following mental and physical activities, may be caused by an interplay between intracellular signal molecules and mitochondrial dysfunction.

P53 and nuclear factor kappa B

Elevated levels of NF- κ B [25,26] and accompanying O&NS [27–30] have been observed in ME/CFS. Upregulated IgM responses directed against NO-adducts in ME/CFS are consistent with chronic elevations in nitric oxide (NO) [28]. Considering this environment it comes as no surprise that mitochondrial damage has been reported and, indeed, shortfalls in supplies of ATP have been reported in people with ME/CFS [17,31]. Consistent with the existence of low levels of ATP, elevated levels of adenosine have also been demonstrated [32].

O&NS rapidly elevates both the signal transducer and activator of transcription 3 (STAT3) and NF- κ B [33,34]. Activated STAT3 and NF- κ B mediate the expression of pro-proliferative, anti-apoptotic and immune genes. STAT3 and NF- κ B both interact via a feedback loops [35]. Thus, activated STAT3 constitutively activates NF- κ B [36]. STAT3 activation results in downregulation of FOXP3 and loss of functionality of T regulatory cells [37,38]. This leads to profound impairments in the homeostatic control of immune activity discussed in more detail elsewhere. Moreover, there exists a functional antagonism between NF- κ B and p53. When the transcription of NF- κ B is initiated in a cell the transcription of p53 is terminated [39]. STAT3 also inhibits the transcription and function of p53 [40,41].

This paper hypothesizes that elevated NF- κ B and/or loss of p53 explain symptoms of ME/CFS, such as muscle pain, fatigue, fatigability and neurocognitive disorders, and typical symptoms of ME, such as PEM following mental and physical activities. These pathways entail mitochondrial dysfunctions and reduced levels of ATP in the periphery and the brain.

P53, glycolysis, mitochondrial respiration and NF- κ B

P53 regulates glycolysis and mitochondrial respiration as well. P53 reduces the activity of the glycolytic pathway and stimulates mitochondrial oxygen utilization by activating protein SCO2 homolog and the cytochrome c oxidase complex (COX), which is a site with very high oxygen utilization [42]. As such, p53 regulates the balance between the glycolytic and respiratory pathways [42]. Loss of p53 promotes a switch to anaerobic glycolysis and results in reduced oxygen consumption and aerobic respiration in the mitochondria. This bears testimony to the role of p53 in regulating two different ATP generating pathways [43].

Fig. 1 summarizes the effects of p53 on mitochondrial respiration and anaerobic glycolysis and other functions as well. Moreover, p53 regulates energy metabolism by effects on the expression of glutaminase 2, the glucose transporter (GLUT) and fatty acid synthase [44]. P53 additionally modulates the transcription of TP53-induced glycolysis regulator (TIGAR) and fructose-2,6-bisphosphatase. TIGAR is a p53-inducible gene that lowers the

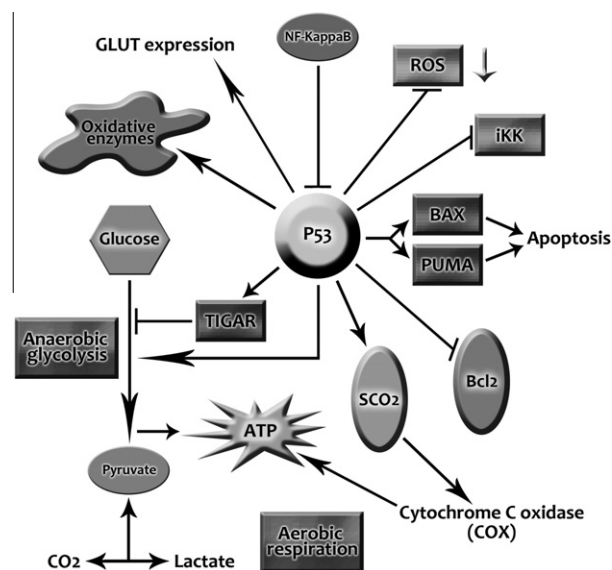


Fig. 1. Effects of p53 on mitochondrial respiration and anaerobic glycolysis and other functions as well. ROS: reactive oxygen species; iKK: I κ B kinase; BAX: Bcl-2 associated X protein PUMA: p53 upregulated modulator of apoptosis; Bcl2: B cell lymphoma 2; TIGAR: TP53-induced glycolysis regulator; GLUT: glucose transporter.

levels of fructose-2,6-bisphosphate. This mechanism inhibits anaerobic glycolysis and lowers production of reactive oxygen species (ROS). As such p53 plays a role in ROS production and protection against damage by O&NS. P53 also modulates many genes with antioxidant functions [45,46]. For example, p53 regulates aldehyde dehydrogenase 4 ALDH12 [47], glutathione peroxidase, superoxide dismutase [48,49], catalase [50], TIGAR [51], two members of the sestrin family [52,53], glutaminase 2 [54], as well as p53-induced nuclear protein 1 [55].

Decreased p53, on the other hand, results in significant increases in intracellular ROS [45]. P53-knockout mice show increased ROS levels and lowered expression of p53-regulated antioxidant genes. The consequent increases in ROS may cause O&NS-mediated damage to mitochondria and mitochondrial DNA (mtDNA) and may affect the rate of mutagenesis. Moreover, decreased p53 activity impairs mitochondrial biogenesis, reduces oxygen consumption and increases lactate production [42,56].

There is also a link between NF- κ B, p53 and glycolysis. P53 deficiency is associated with an activation of NF- κ B through IKK α and IKK β kinase activities [57]. Activation of NF- κ B by decreased p53 activity induces aerobic glycolysis (the Warburg effect) leading to increased uptake of glucose to compensate for the reduced ATP production [57,58]. Thus, NF- κ B contributes to the shift towards glycolytic ATP production [58] or aerobic glycolysis (the Warburg effect) [59]. P53 inhibits the translocation of RelA, a NF- κ B family member, to mitochondria, whereas a loss of p53 allows RelA to be transported into the mitochondria where it suppresses oxygen consumption and cellular ATP production [60,61].

P53 in skeletal muscles

Skeletal muscle mitochondria are major determinants of aerobic exercise capacity and are therefore major sources of aerobic respiration [62,63]. P53 may initiate the biogenesis of skeletal mitochondria in response to muscle contractile activity [63]. P53 enhances transcription and maintenance of mtDNA and mitochondrial biogenesis through binding with the mitochondrial transcription factor A, Tfam [64]. By increasing skeletal muscle mtDNA

contents, p53 also improves aerobic metabolism and exercise capacity [65]. While p53 increases aerobic exercise capacity, loss of p53 markedly decreases exercise capacity [65]. For example, p53 knockout mice have significantly lowered mitochondrial contents in muscles and show decreased endurance and increased fatigability [63]. Loss of p53 is associated not only with reduced respiration, but also with elevated production of ROS in mitochondria [63].

P53 and NF- κ B in the brain

P53 plays an important role in the survival and activity of neuronal and glial cells. Elevated p53 transcription may cause death of neural and glial cells [66,67]. P53 production is enhanced in neuronal cells in response to insults, such as O&NS and cellular calcium overload. These insults may result in DNA damage, which is a common trigger for neuronal apoptosis. In the mature nervous system, p53 is an important component in apoptotic signaling cascades. Neural cell apoptosis may be mediated by physiological levels of p53 through elevations of the pro-apoptotic Bcl-2 associated X protein (BAX) family [68]. In neurons, p53 activates genes, which mediate p53-induced apoptosis, e.g. NOXA and p53-upregulated modulator of apoptosis [69]. P53 may trigger apoptosis by acting on mitochondria and inducing synaptic apoptosis in neurons, which is associated with neurodegenerative disorders [70]. For example, HIV-induced neurodegeneration requires p53 in microglia and neuronal glial cells [71]. Inhibition of p53 transcription and function, on the other hand, disables the apoptotic machinery and is neuroprotective [66,67,70].

The weight of evidence suggests that NF- κ B may be just as important in regulating neural function as it is in regulating the immune system [72]. In neuronal cells, NF- κ B may prevent cell death and promote survival by enhancing anti-apoptotic genes, including Bcl-2 and Mn-superoxide dismutase [73], and suppressing peroxynitrite formation and membrane lipid peroxidation [74]. Moreover, NF- κ B activation enables long term changes in the function and structure of neuronal circuits. For example, NF- κ B plays an important role in synaptogenesis and neurite outgrowth [75–77]. NF- κ B signaling alters the balance of excitatory and inhibitory synaptogenesis, leading to hyperexcitability [77].

Synaptic activity promotes NF- κ B, which plays a role in processes that are involved in learning and memory. Different subunits of NF- κ B target genes that regulate cognition. NF- κ B activation is required during induction of synaptic plasticity [78–81] and for long term memory formation [76,79,82,83]. NF- κ B/Rel transcription factors are key regulators of antagonistic excitatory and inhibitory neuronal functions regulating synaptic plasticity and long term memory formation [84].

On the other hand, increased NF- κ B production in astrocytes and microglia may cause neuronal degeneration through the elevated production of ROS and pro-inflammatory cytokines [25]. These and other detrimental effects may explain that increased NF- κ B production plays an important role in neurological disorders [85]. Increased NF- κ B production may thus be cell sparing or cause cellular death [86].

We have discussed that p53 modulates two ATP generating pathways and that loss of p53 causes reduced oxygen consumption and aerobic respiration in the mitochondria, while activation of NF- κ B may increase aerobic glycolysis. Therefore, in inflammatory and O&NS conditions, low p53 and high NF- κ B may conspire to promote neuron cell survival, but at a price of compromised cellular function in the brain. Moreover, increased NF- κ B, pro-inflammatory cytokines and O&NS may cause neuroprogression, that is neurodegenerative processes and reduced neuroplasticity and neurogenesis [87,88].

P53, ATP and mitochondrial dysfunction

Mitochondria have critical functions in the cell because, through β -oxidation, they produce ATP. β -oxidative processes continuously generate ROS, which may cause damage to mitochondria and mtDNA. Moreover, mitochondria play a key role in apoptosis and necrosis, homeostasis of intracellular calcium, excitotoxicity and neuronal excitability.

Skeletal muscle and brain cells have high metabolic rates and are, therefore, very sensitive to ATP deprivation and mitochondrial dysfunctions. The brain consumes around 20% of inhaled oxygen although it accounts for only 2% of body weight [89]. Neurons demand high amounts of ATP for synaptic remodeling, the transmembrane potential and signal transduction and therefore depend on mitochondria producing ATP by oxidative processes [90]. Skeletal muscle accounts for 40% of the body's oxygen consumption [91]. In the brain, the regulation of mitochondrial ATP production is triggered in response to daily activities [92]. ATP deprivation results in activation of alternative pathways that lead to lactate accumulation. P53 tightly regulates the balance between anaerobic glycolytic and mitochondrial energy metabolism [93]. While aerobic respiration is efficient in generating ATP, anaerobic glycolysis is preferred in short-lived, power-related activities. Moreover, p53 plays an important role in aligning metabolic processes with energy status and the condition of the cell [94–96]. Inactivation of p53 leads to greater dependence on anaerobic glycolysis and may greatly impair aerobic mitochondrial functions [56,97,98]. ATP depletion may cause “cellular energy depression” and consequent neuronal dysfunctions. By releasing cytochrome c, mitochondria may induce the apoptotic cell death program [99].

Mitochondria produce ROS/RNS and are at the same time very susceptible to O&NS damage caused by ROS/RNS [100]. Lowered levels of key antioxidants in ME/CFS, e.g. coenzyme Q10, may cause an array of mitochondrial dysfunctions, such as increased O&NS, activation of mitochondrial permeability transition, and reduced functions of complexes II, III and IV [4,29]. Loss of ATP in the mitochondria is associated with the onset of neurodegenerative disorders [101].

There is evidence that immuno-inflammatory pathways and increased ROS production generated by oxidative processes in the mitochondria play synergistic roles in neurodegenerative disorders, including Alzheimer, Huntington and Parkinson disease and amyotrophic lateral sclerosis [102,103]. Moreover, the lowered levels of antioxidants in ME/CFS may contribute to dysfunctions in the mitochondria, which may eventually cause neuroprogression through necrosis and apoptosis [100,104]. However, even after years of neuro-inflammatory processes these patients do not become profoundly demented. This may indicate that neuroprotective processes, e.g. through increased NF- κ B, may be involved.

Physio-somatic symptoms in mitochondrial disorders

Physio-somatic symptoms are commonly encountered in mitochondrial disorders and quite often show a waxing and waning pattern [105–107]. Disorders in mitochondria may cause many different symptoms, from mild photophobia and muscle complaints to cerebellar ataxia and neonatal death [105,106,108–111]. Painful muscle stiffness and myoclonia may occur [112]. Cardiac manifestations include conduction abnormalities, dysrhythmias and even cardiomyopathy [111,113]. Mitochondrial dysfunctions may also cause decreased motility of the oesophagus, stomach and intestines. Episodic nausea and vomiting, gut dysmotility with chronic diarrhoea, or chronic constipation are common manifestations of mitochondrial disorders [109,110,114].

Cerebral symptoms may accompany mitochondrial disorders, e.g. migraine, stroke-like episodes, early strokes, cerebellar ataxia,

progressive encephalopathy with periodic exacerbations leading to seizures and dementia [106,109]. Peripheral neurologic symptoms may occur, such as neuropathy with loss of sensation, and severe neuropathic pain [106,109,110].

Other characteristic signs of mitochondrial disorders are the presence of air hunger in the absence of anoxia, and pulmonary or cardiac dysfunctions [110]. Audiological symptoms are quite common with tinnitus and sensorineural hearing loss [106,112,115,116]. Blurred vision, photophobia, nyctalopia, corneal edema, external ophthalmoplegia, visual impairment or even blindness due to cataracts or optic atrophy are some of the visual/ocular symptoms that are associated with mitochondrial aberrations [106,109,117–119].

Considering these observations, and that mitochondrial disorders are still unknown by many doctors, it is not surprising that such mitochondrial symptoms as fatigue, vertigo and photophobia are often dismissed as “psychosomatic” and “functional” [107,109,120]. Symptoms, such as fatigue, breathlessness and muscle weakness in depressed patients with mitochondrial disorders are often dismissed as being functional [109]. In fact, mitochondrial disorders should be suspected in any patient with a multisystem, and intermittent or progressive disorder [108]. It is important to note that all abovementioned mitochondrial symptoms mirror the physio-somatic symptom complex in ME/CFS [105,120,121].

Mechanistic explanations of ME/CFS and ME symptoms

There is evidence that ME/CFS symptoms may be caused by pro-inflammatory cytokines, including IL-1 and TNF α , and elevated levels of cyclo-oxygenase 2 (COX-2) [4,8]. Recently we have reviewed that administration of pro-inflammatory cytokines elicits behavioral changes, including fatigue, malaise, neuro-cognitive symptoms and sleep disorders [87]. There is additionally evidence that increased O&NS is associated with the onset of ME/CFS symptoms [8]. ATP depletion may explain why patients with ME/CFS suffer frequently from peripherally and centrally mediated fatigue and many physio-somatic symptoms, including muscle pain and cramps, autonomic and cardiac symptoms, gastro-intestinal symptoms, neurologic symptoms, etc. In fact, most mitochondrial symptoms are symptoms reported by people with ME/CFS. Gardner and Boles [105] found a clear relationship between physio-somatic symptoms and low levels of ATP production. Using SPECT scanning they found that in depressed patients mitochondrial dysfunctions may contribute to decreased metabolism in the brain.

Importantly, the presence of exercise intolerance may point toward a mitochondrial disorder [122]. For example, even trivial exercise may cause a sense of breathlessness and rapid heartbeat in patients with mitochondrial disorders without evidence of impaired heart conduction or cardiomyopathy [122]. Therefore, increased ventilatory and cardiovascular responses during exercise may indicate an underlying mitochondrial disorder [122]. After exercise, those patients may suffer from dyspnea and tachycardia [123] and lactic acidosis [124]. In some patients, diplopia and dysphagia may be present [125]. Muscle weakness with or without cramping in large and small muscles are sometimes the only sign of relatively minor mitochondrial dysfunction [110]. Very often no objective abnormalities can be found because fatigability is very difficult to quantify [110]. All in all, these data suggest that the mitochondrial disorders and depletion of ATP as established in ME/CFS may play a role in the onset of ME/CFS symptoms.

In addition, here we hypothesize that ME/CFS symptoms, such as exhaustion and neurocognitive dysfunctions, and characteristic ME symptoms, such as PEM following mental and physical activities, may be caused by an interplay between intracellular signal molecules, i.e. NF- κ B and p53, and mitochondrial dysfunctions.

Thus, decreased p53 levels in ME/CFS would lead to reduced exercise capacity and increased muscle fatigability due to the inability of mitochondria to elevate respiration rates coupled with a reduced switch from glycolysis to aerobic metabolism. Moreover, reduced p53 and aberrations in NF- κ B function may cause further metabolic disorders in mitochondria. Thus, decreased p53 is accompanied by an increased transport of RelA into the mitochondria and recruitment to mtDNA where it suppresses gene expression, oxygen consumption and cellular ATP [60,61]. The combination of reduced p53, elevated NF- κ B and mitochondrial damage indicates that the demand for extra ATP upon the commencement of increased activity cannot be met. This leads to exhaustion of available ATP leading to a global worsening of symptoms and profound disability, which may last hours, days or even months. The acidosis accompanying increased lactate levels and glycolysis may cause muscle fatigability and muscle damage. In addition, since lowered p53 and increased NF- κ B are both associated with elevated ROS production, increased O&NS may contribute to the mitochondrial exhaustion and consequent ME/CFS symptoms. The NF- κ B-induced production of pro-inflammatory cytokines will profoundly increase the rate of anaerobic glycolysis and further compromise mitochondrial functions. Since lowered p53 dramatically reduces endurance during physical exercise [127], this may explain why ME/CFS symptoms may worsen during graded exercise therapy [5].

It has been shown that reduced ATP levels lead to defects in learning and memory [128,129]. In inflammatory and O&NS conditions, the compromised brain energy metabolism as a consequence of low p53 and high NF- κ B may cause neuro-cognitive symptoms. In the brain, ATP formation is tightly coupled to changes in brain activity levels [130]. Mitochondrial dysfunction therefore may have a severely detrimental effect on energy homeostasis in the brain and thus may compromise brain function in people with ME/CFS. Neuroprogressive processes related to mitochondrial dysfunctions and increased O&NS and pro-inflammatory cytokines may further elicit neurocognitive dysfunctions [87].

In the absence of adequate ATP production two other systems may become dysfunctional. Firstly, ATP-dependent release of glutamate acts on presynaptic neuronal *N*-methyl-D-aspartate (NMDA) receptors, which in part determine synaptic signaling and learning and memory [131]. Secondly, ATP activates methionine's methyl group to form S-adenosylmethionine (SAM), which is a methyl donor. In the brain, SAM-dependent methylation is required for the production of neurotransmitters, and methylation of DNA and myelin sheath phospholipids [132–134]. Loss of methylation can lead to severe impairment of neurocognitive function. Low vitamin B12 and folate and high homocysteine adversely affect memory and abstract reasoning [135–137]. Transport of folate across the blood brain barrier by the folate receptor is an active transport mediated by ATP [138,139]. Uptake of cobalamin into the brain also requires active transport [140]. Hence mitochondrial dysfunctions and impairment in ATP production can lead to reduced levels of folate and B12 in the brain even though plasma levels are within normal levels.

Conclusions

Fig. 2 summarizes the key functions of p53 in conditions, such as ME/CFS, which are characterized by activation of immuno-inflammatory and O&NS pathways. (A) Elevated inflammatory and O&NS pathways with increased NF- κ B are accompanied by suppressed p53 levels. P53 is a major regulatory gene and low levels can have dire consequences for the normal functioning of mitochondria. (B) In normal conditions, p53 enhances mitochondrial biogenesis, enables an increase in mitochondrial energy production

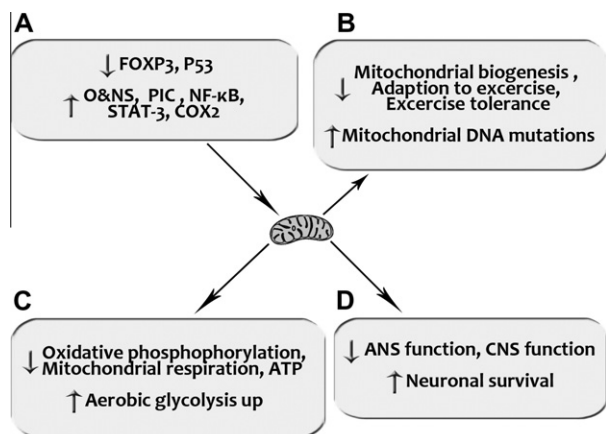


Fig. 2. This Figure shows the functions of p53 in conditions characterized by activation of immuno-inflammatory pathways. FOXP3: forkhead box P3; O&NS: oxidative & nitrosative stress; PIC: pro-inflammatory cytokines; NF-κB: nuclear factor κB; STAT-3: signal transducer and activator of transcription 3; COX2: cyclooxygenase 2; ANS: autonomic nervous system; CNS: central nervous system.

to fulfil the extra demand generated by exercise, and is a key molecule in maintaining cellular antioxidant defenses and repairing mitochondrial DNA mutations. Reduced p53 may impair mitochondrial biogenesis leading to a reduced mitochondrial density in skeletal muscle. In conditions of reduced p53 the increased energy output is not achieved and severe exercise intolerance may ensue. Mitochondrial DNA damage may accelerate in the absence of p53 leading to further dysfunction and propagation of mutated rather than healthy mitochondria. Loss of P53 leads to an inhibition of mitochondrial oxidative phosphorylation coupled with an increase in anaerobic glycolysis. This leads to a dramatic loss of available ATP which can lead to multiple system failure throughout the body. (D) ATP is crucial for normal functioning of the autonomic and central nervous system both in terms of supplying energy and by acting as a neurotransmitter. NF-κB is also vital for normal cognitive function. Low ATP coupled with high NF-κB can lead to profound loss of normal neurocognitive functions and autonomic dysregulation. P53 is needed to enable cell death or apoptosis. Hence, in conditions of chronic inflammation and O&NS, low p53 and high NF-κB conspire to promote neuron and glial cell survival at a price of compromised cellular functions in the brain. Thus, these mechanisms would avoid overt neuroprogression at the expense of impaired brain function, which may cause ME/CFS symptoms, including neurocognitive symptoms.

In conclusion, we hypothesize that (a) decreased p53 levels in patients with ME/CFS would lead to more neurocognitive symptoms, greater muscle fatigability and reduced exercise capacity due to the inability of mitochondria to increase respiration rates according to increases in demand; and (b) low p53 and high NF-κB together with low ATP and mitochondrial dysfunction may explain characteristic ME symptoms, such as PEM following mental and physical activities.

Competing interest

There was no financial support for this specific research. The authors declare that they have no competing interests.

Author contributions

G. M. and M. M. participated in the design of this review and drafted the paper.

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