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A Proposal for Explaining Progression from Light/Moderate to Severe Chronic Fatigue

Review Article

Anna Dorothea Höck*
Internal Medicine in Albertus-Magnus University in Cologne, Germany

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***Corresponding author:** Anna Dorothea Höck, Internal Medicine in Albertus-Magnus University in Cologne, Germany

Abstract

Background: Chronic mild to moderate fatigue is also called chronic idiopathic fatigue. Physicians at best consider about psychotherapy for treatment. But most physicians do not view this condition as a real disease. In contrast, debilitating chronic severe disease has been termed chronic fatigue syndrome (CFS), or if more severe, myalgic encephalopathy (CFS/ME). Meanwhile published metabolic aberrations in CFS/ME suggest estimating these diseases no longer as mere psychiatric diseases. The metabolic results inspire to further exploration of cell stress response mechanisms, which are summarized in this paper. Interestingly, cell stress responses were tightly linked to vitamin D_3-mediated effects, such as homeostatic regulation of metabolism, energy and redox balance, as well as defense against pathogens and toxins. Specific personality traits, prevalence of indoor activities, latitude and climate predispose to vitamin D_3 deficiency, which is supposed to represent a missing link for a comprehensive model of disease progression from mild chronic fatigue to most severe forms. By diagnosing vitamin D deficiency in early stages of chronic fatigue, the progression to severe and debilitating chronic fatigue may be prevented. In more severe stages of chronic fatigue, such as CFS/ME, resistance against mere vitamin D replenishment seems to be the rule. Some causal mechanisms for this resistance and potential treatment options are shown.

Conclusion: Scientific insight to the biomolecular mechanisms of cell homeostasis helps to understand and treat all clinically manifestations associated with different stages of chronic fatigue.

Keywords

Chronic idiopathic fatigue; Chronic fatigue syndrome/myalgic encephalopathy; Nrf2, vitamin D_3; Metabolic/energetic/redox balance; Cell stress defense mechanisms

Introduction

Meanwhile several recent and comprehensive papers about metabolic alterations in chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) have been published, serving as an important step to a better understanding. The patient-physician relation could take profit of these latest findings. However busy physicians do not have time to go in the depth of these results. They need a shorter overview in order to support the needs of their patients. The aim of this paper is to fill this gap.

The more recent metabolic findings have in common, that they report about a generalized metabolic reprogramming with alteration of carbohydrate, amino acid, lipid and nucleotide metabolism. The interdependence between metabolic, energy, redox and immune regulation and the role of chronic oxidative stress, going along with low-grade inflammation, altered mitochondrial function and metabolic reprogramming, are pointed out [1-11].

In particular, the studies of Fluge et al., and Naviaux et al., help to get a more comprehensive approach to metabolic alterations occurring in CFS/ME. Fluge et al., found increased messenger RNA expressions of the stress proteins "silent mating-type information regulator protein 4" (sirtuin-4 or SIRT4), pyruvate dehydrogenase kinases 1, 2, and 4 (PDK1, PDK2, PDK4), and peroxisome proliferator activator receptor 1 delta (PPARδ). SIRT4 and PPARδ gene up regulation correlated with disease duration and severity. They report also a functional inhibition of pyruvate dehydrogenase complex (PDHC) and glutamate dehydrogenase (GLDH) resulting in altered metabolic flux in the tricarboxylic (TCA) cycle and decreased serum levels of ketogenic and anaplerotic amino acids. The authors describe also increased coupling between respiration and ATP generation, and excessive lactate production under energetic stress. Naviaux et al. report about a metabolic reprogramming, termed "dauer" (german word for persistence) in CFS/ME patients. "Dauer" resembles in some manner the hibernation reaction and is viewed as a "unified hypometabolic cellular response, different from acute stress response". Similar to Fluge et al., the authors describe as well an inhibition of PDHC. They emphasize a shortage of "central gauges of energy metabolism", such as flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD). These metabolic studies stimulate to more extensive exploration about general principles of cellular stress responses.

Cell stress activates cell-protective metabolic-energy-redox cascades

Cell stress response is mediated by a group of sensor and simultaneously effector proteins which interact in a highly cooperative manner [12-29]. The important protein family of sirtuins (SIRTs) senses elevations of the oxidized/ reduced nicotinamide adenine dinucleotide (NAD^+/ NADH) ratio, which signals energy deficit and redox change [12]. Sirtuins contribute substantially to cell protection against all sorts of cell challenge. Decreased sirtuin expression is believed to be responsible for aging conditions and tumorigenesis [12-15]. Up to now, seven sirtuins are known. SIRT1, SIRT6 and SIRT7 are primarily located in the nucleus, SIRT2 in the cytoplasm, and SIRT3, SIRT4 and SIRT5 in mitochondria [13,16].

Sirtuins elicit changes of epigenetic, metabolic, energetic and redox functions by removing inhibitory post-translational proteome modifications (PTMs), such as acetyl, or acyl, or other moieties from histone proteins, transcription factors and cofactors, and further enzymes [12-17].

The best-studied stress response is that of SIRT1 activation [12,20,21]. SIRT 1 is a predominantly nuclear stress protein, but acting also in cytoplasm. Starvation, exercise, cold adaptation, and all sorts of cell stress, such as pathogens, xenobiotics, and reactive oxygen species (ROS) generation trigger a coordinated and interacting metabolic, energy and redox response by activating SIRT1 and further members of the stress response pathway, such as 5' adenosine monophosphate-activated kinase (AMPK) [18,19], a transcription factor termed nuclear factor erythroid 2-related factor 2 (Nrf2) [21,24-27], peroxisome proliferator activator receptor gamma co-receptor 1 α(PGC-1α) [12, 22, 23] and forkhead box proteins (FoxO) [12,18]. All these proteins are most important for cellular adaptation to an actual challenge and metabolic flexibility.

AMPK senses energy depletion in particular by a low ATP/AMP ratio. It redirects metabolism to energy saving and metabolic optimization, but in addition, mediates a strong anti-oxidant response by augmenting activity of the highly redox-sensitive transcription factor, called Nrf2 [18,19,21]. Also Nrf2/PGC-1α co-expression is mediated by AMPK [22]. PCG-1α enhances energy expenditure, mitochondrial biogenesis, antioxidant defense, and mitochondrial unfolded protein response (UPR_{mt}) [12,23]. The transcription factors forkhead box proteins, class O (FoxOs) are involved in both a potent anti-oxidation and metabolic reprogramming, including promotion of glucose supply for energy generation [18].

In particular, Nrf2 initiates a broad antioxidant and also detoxifying response through induction of target genes, such as the antioxidant machinery of glutathione/ thioredoxin systems, reductases, perioxidases, superoxide dismutases 1 and 2, NAD (P) H:quinone oxidoreductase-1, aldo-keto-reductases, drug metabolizing isoenzymes of phase I and II, and multi-drug effusion pumps of phase III

[18,21,24-27]. Nrf2 is also involved in wound healing [25]. This Nrf2-related stress response contributes substantially to a metabolic switch resulting in enhancement of glucose flow to the pentose phosphate pathway which promotes cytosolic NADPH generation, used for anti-oxidative or oxidative defense, depending on cellular needs. Nrf2 promotes also serine and purine synthesis and metabolic flux through the TCA cycle in order to provide energy and metabolic intermediates [21, 26,27]. Serine is not only used for glycine and nucleotide synthesis, but also for synthesis of sphingolipid and phosphatidylserine head groups in cell membranes [26]. On the other hand, Nrf2 regulates negatively pyruvate kinase and ATP-citrate lyase, thus suppressing synthesis and storage of lipids [21]. Importantly, Nrf2 supports removal of defective cell organelles and toxic proteins by enhancing cellular autophagy/mitophagy and mitochondrial regeneration [21,26]. In addition, Nrf2 enhances gene expression of all ferritin subunits and the iron-exporting protein ferroportin, whereas suppressing gene expression of the iron transport-inhibitor hepcidin. Binding of hepcidin to ferroportin induces ferroportin decay. Thus Nrf2 protects potential toxic iron effects by supporting iron uptake, cellular exit and safe storage for use in erythropoiesis or iron-dependent enzymes (24). Since Nrf2 activation and stabilization requires carbon monoxide (CO) and biliverdin production through heme-oxygenase-1 (HO1), and activated HO1 releases free iron, the iron-regulatory function of Nrf2 seems to be most useful [24].

Though most actions of Nrf2 are highly cell protective, excessive Nrf2 upregulation is reported to result in cancer and other unwanted side effects, on the other hand [21,24-27]. Of interest, many nutritional compounds are known to induce Nrf2 activation by generating mild oxidative stress [24].

In summary, the cooperative gene expression and mutual activation of several stress-activated proteins promote a most protective response which includes anti-inflammation, anti-fibrosis, proteome, metabolic, energetic and redox homeostatic flexibility, survival and longevity. Nrf2 and SIRT1 are key components of this regulatory network.

Cellular regulation depends on NAD^+/NADH ratio, and cellular NAD pools

The amount of synthesis of the pyridine-nucleotide containing molecules NAD^+/NADH, and the phosphorylated counterparts $NADP^+$/NADPH are of paramount importance for orchestrating cellular functions according to cellular needs [16,28-32]. They are not only universal cofactors for metabolic enzymes, but also cooperate with gene transcription and coordinate cellular metabolism, energy and redox regulation. A high ratio of NAD+/NADH signals decrease of energy and redox balance, followed by activation of nuclear SIRT1 and mitochondrial SIRT3, directing metabolism either to energy-saving and stress defense or to processes linked with more energy expenditure. In contrast, a sufficiently high NADPH/NADP+ ratio are necessary for adequate anti-oxidation, detoxification, pathogen defense and biosynthesis.

However, not only the ratios of NAD $(P)^+$/NAD(P)H are important for cellular functions, but also the amount of NAD pool in different cell compartments [12-15,28]. This pool decreases through sirtuin-dependent deac(ety)lations, since the hydrolytic cleavage of NAD produces O-ac(et)yl-ADP ribose and nicotinamide [16]. Nicotinamide inhibits SIRT1 and SIRT3, but can become rebuilt to NAD through the so-called salvage pathway which is an ATP-consuming process. A more severe NAD consumption occurs through activation of the enzyme termed poly (ADP-ribose) polymerase transferase 1 protein (PARP1), acting either as DNA-repair enzyme, but also as inhibitory poly-ADP-ribosylating enzyme in energy-regulation pathways [12,14,16,33,34]. Also enzymes called ADP-ribosylcyclases (CD38/CD157) contribute to NAD consumption [35, 36]. They produce ADP-ribose derivatives which enhance the activity of calcium transporting ion channels [16,30,37]. Of importance, decline of NAD-pools are reported to induce SIRT4 up regulation [38], which is able to function as ADP-ribosyl transferase, thus consuming NAD by its own, and to compromise mitochondrial functions [33]. Nuclear NAD decline has been found to disrupt nuclear-mitochondrial communication [39].

The difference between SIRT1/SIRT3 against SIRT4 cell response

Nuclear SIRT1 and also the mitochondrial equivalent, SIRT3, function mainly as deacetylases and activate the acute stress response cascade of AMPK, Nrf2, PGC-1α, and FoxO proteins [12,14,40,41]. Activity-induced glycolysis in muscle cells, mitochondrial electron transport, nucleotide synthesis, overall cell defense, and flexibility of metabolic-energy-redox regulation are promoted [12-15]. Furthermore, SIRT1 prevents

adiposity and insulin resistance by inducing homeostasis of fatty acid, lipid and cholesterol metabolism through activation of liver X receptor (LXR) [42]. Additionally, SIRT1 interacts with the circadian regulatory machinery [43,44]. Interestingly, a link between circadian and memory dysregulation has been reported [45]. Most importantly, SIRT1 antagonizes NAD-consuming PARP 1 activity through deacetylation [14,16]. In turn, PARP1 protein antagonizes SIRT1, since the PARP-dependent decline of NAD pools inhibits SIRT1 activity [14]. Also free radicals and high fat diet inhibit SIRT1 activation [46,47].

SIRT4 effects are less well studied than those of SIRT1. SIRT4 regulates metabolism in a total different mode compared to SIRT1 [36]. SIRT4 is highly expressed in muscle, kidney, testis and liver cells. SIRT1 and SIRT4 share some cell-protective effects, such as enhancement of NAD synthesis [17], suppression of the activation of pro-inflammatory nuclear factor kappa-light-chain-enhancer of activated B-cells (NFkB) [14,35], and prevention of DNA damage [36]. Of note, SIRT4 becomes antagonized through high activity of SIRT1 and of mechanistic target of rapamycin (mTORC1), and also through abundant leucine availability [36]. In contrast to SIRT1, SIRT4 acts not predominately as histone deacetylase, but mostly as deacylase, de-lipoamidase and ADP-ribosyltransferase [36]. The activation of SIRT4 is promoted through the fed state, while inhibited in the fasting state [36,48]. SIRT4 represses mostly metabolic enzymes, instead of enhancing them like the other sirtuins [49]. Unlike SIRT1, SIRT4 neither augments glucose uptake and oxidation, nor promotes β-oxidation of fatty acids [36,50]. Instead, lipid synthesis is enhanced [48]. SIRT4 mediates reduced electron flow through the TCA cycle through inhibitory de-lipoamidation of PDHC and also through inhibitory ADP-ribosylation of GLDH [36,51]. As a result, pyruvate and glutamine entry into the TCA cycle is inhibited, followed by diminished α-ketoglutaric acid generation, thus inhibiting cell proliferation and tumor growth [36]. SIRT4 also controls insulin secretion by enhancing the insulin-degrading enzyme and decreasing leucine availability [15,36,48,50].

As the multiprotein enzyme complexes of PDHC, α-ketoglutaric acid dehydrogenase (αKDGH) and branched chain amino acid dehydrogenase (BCKDH) share the same dihydrolipoyl-containing E2 and E3 subunits, the de-lipoamidase activity of SIRT4 might affect all three of these mitochondrial dehydrogenases [51]. These dehydrogenases generate high amounts of ROS, but are in turn ROS-sensitive, showing functional activation by low, but auto-inhibition through high amounts of ROS [52]. Of note, ROS-dependent activation of PDK1, PDK2, and PDK4 results in an additional inhibition of PDH through PDHC phosphorylation, which is supposed to contribute as well to TCA cycle obstruction [53].

On the one hand, SIRT4-dependent deacylation of adenine nucleotide translocator 2 (ANT2) abolishes the uncoupling ability of ANT2, thus enhancing transport of ADP/ATP across the inner mitochondrial membrane, resulting in facilitated ATP generation [36,54]. On the other hand and in contrast to all other known sirtuins, SIRT4 mediates increase in ROS generation, and not decrease [46,54]. ROS levels become elevated through SIRT4-dependent repression of SOD2 and GLDH [54], and through enhanced angiotensin II activity [17]. The augmented ROS-generation is thought to cause the observed exercise intolerance and neuro-immunologic dysregulation in case of SIRT4 overexpression [48,54].

Taken together, the knowledge that metabolic, energetic and redox regulation is interrelated through several central and universal sensing and signaling tools, such as NAD(P)+/NAD(P)H ratio, NAD pools, ROS and free calcium levels, provides a comprehensive approach to diseases going along with chronic fatigue. NAD consumption is supposed to be an important missing link to explain metabolic reprogramming towards a SIRT4-dependent pattern. Whereas SIRT4 appears to maintain life and basal functions, the elevated basal ROS level and decreased metabolic flexibility are supposed to explain the striking exertional incapacity of CFS/ME patients. The SIRT1-dependent cascade of stress defense and adaptation appears to be suppressed due to low NAD pools. According to Naviaux et al., "harsh conditions" induce the metabolic switch to SIRT4-associated condition of "dauer".

What "harsh conditions" may act on CFS/ME patients?

Listening to the reports of CFS/ME patients about preceding life events, indeed stressful conditions can be found most frequently before disease outbreak, such as infection, high workload, accidents, in particular if followed by immobilization, operations, xenobiotic contact, or loss of a beloved person, besides other sorts of possible triggers. However, such events belong more or less to common life course. So why recover many individuals and others not? Difficult interpersonal problems, which would

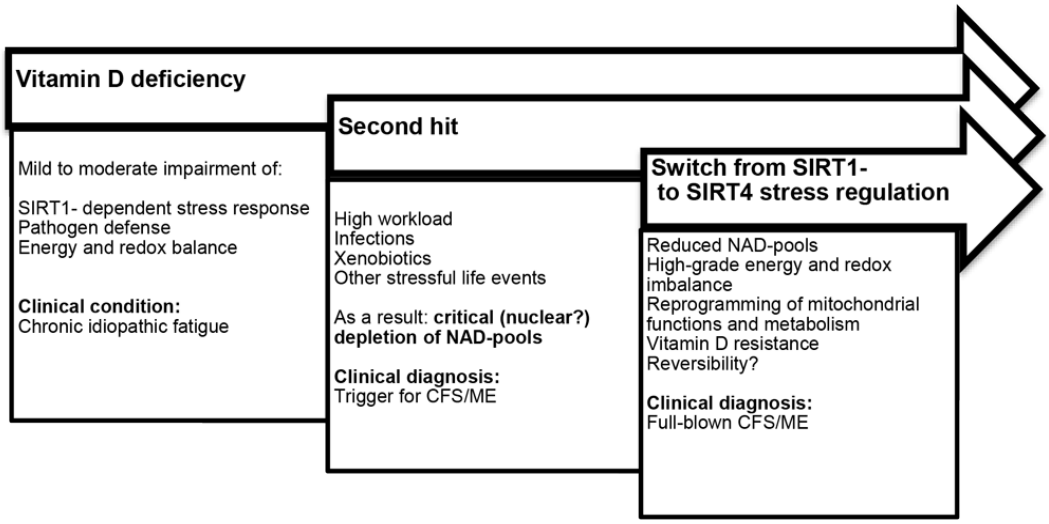

Figure 1: Proposed model for transition from idiopathic chronic fatigue to CFS/ME

CFS: Chronic Fatigue Syndrome; ME: Myalgic Encephalitis; NAD: Nicotinamide Adenine Dinucleotide; SIRT: silent mating-type information regulator protein

explain persistent mental stress, are usually very rare in life histories of CFS/ME patients, according to the author's own clinical experiences. Yet, there can be found a high prevalence of highly motivated and engaged personalities, with high self-demands, and high-grade premorbid functional capabilities. This might result in insidious NAD consumption, which at first induces chronic idiopathic fatigue. Their high motivation disposes these individuals to neglect this condition mostly. Only after the second hit, which is conceived as disease trigger, they realize that they are no longer able to cope with demands of their usual life (Figure 1). Of note, the fact that most patients report premorbid high physical and mental performance, contradict the hypothesis, that inherited genetic conditions might be responsible for disease development. However, the existence of vitamin D_3 deficiency, preceding and accompanying these life stresses, would explain why exactly these personalities progress to CFS/ME.

Vitamin D_3 supports SIRT1-driven pro-survival and life-span extension

Western world life style, prevalent indoor activities, reduced outdoor leisure and diligent use of highly protective sunscreen are usual factors promoting vitamin D deficiency. Later-on after transition from idiopathic fatigue to CFS/ME, the muscular weakness and light hypersensitivity are the most potentiating factors for lack of sunlight. All this diminishes the synthesis of 25-hydroxyvitamin D_3 ($25OHD_3$), which is the precursor molecule of the active 1α,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] [55,56]. Therefore vitamin D deficiency/ insufficiency is indeed a very common and mostly overlooked condition in populations. As a rule, very busy people are affected, but also all those who are disabled through chronic health problems, including those suffering already from CFS/ME/fibromyalgia. $1,25(OH)_2D_3$ binds to and activates the dimeric protein complex vitamin D receptor protein/retinoid X receptor α (VDR/RXRα), then acting as a transcription factor which modifies the expression of up to 500 target genes [56-60]. Some plant ingredients such as curcumin, polyunsaturated fatty acids, anthocyanidins, and in particular resveratrol, initiate and augment VDR signaling [56]. On the contrary, xenobiotics and drugs, such as cortisone, anti-epileptics and antiretroviral drugs can induce vitamin D3 deficiency, by binding to the xenobiotic dimer receptor protein pregnane X receptor/retinoic X receptor-α (PXR/RXR) [61]. As this dimer and the VDR/RXR dimer share the same DNA-binding protein RXR, and additionally PXR and VDR share about 60% structural homology in their ligand-binding domain, the mentioned drugs can bind aberrantly to VDR/RXR and induce gene expression of the vitamin D-degrading enzyme cytochrome oxidase enzyme 24 (CYP24), which promotes vitamin D_3 deficiency

[61]. As vitamin D_3 is reported to ensure genomic and phenotypic stability, as well as metabolic, energetic and redox homeostasis and "anti-aging", this form of induced vitamin D deficiency might play a substantial role for health problems in our population [55,56,62].

A bewildering multitude of $1,25(OH)_2D_3$-mediated modulatory effects on genomic, non-genomic, epigenetic and transcriptome functions are described meanwhile [57-59]. Beyond the well-known regulation of extracellular calcium (Ca^{2+}_{ec}) and its effects on bone health, $1,25(OH)_2D_3$ also regulates cellular calcium-signaling through diverse mechanisms [55,56,60,62,63]. Vitamin D_3-dependent responses are often characterized by direct and indirect induction of rather opposing effects. This seems counter-intuitive at first sight, but is indeed most important for mediating effective functional balance. The cellular functions of all organ systems are favorably modulated and orchestrated [55,56,58]. However, this homeostasis depends on sufficient amounts of the precursor metabolite $25OHD_3$.

In order to understand the role of vitamin D_3 in metabolic, energetic, and redox regulation, it is helpful considering that VDR expression and vitamin D_3 activation is elicited in many cells through cell stress [55,56, 62]. In particular, gene expression of two most important homeostatic proteins is enhanced by $1,25(OH)_2D_3$. The first is the already discussed key transcription factor Nrf2, which senses reactive species and mediates a most effective stress response. The second is a multi-functional protein, called α-klotho [55,56]. It is primarily a transmembrane protein which is highly expressed in kidney and choroid plexus, but also in epithelia and neurons [56,64]. The transmembrane klotho protein is cleaved by two metalloproteases, termed "a disintegrin and metalloprotease" 10 and 17 (ADAM10/17), thus generating two truncated proteins, called soluble and secreted α-klotho protein. These proteins act as humoral co-factors on far distant cells and organs, and modulate a wide array of signaling pathways and cellular processes. Most importantly, α-klotho prevents vitamin D-dependent potential calcium and phosphate toxicity [56,64]. Klotho mediates calcium homeostasis through binding of α-klotho to Na+/K+ ATPase, phosphate homeostasis through binding to the fibroblast growth factor 23 receptor, and overall mineral homeostasis through binding to ion channels, such as the "transient receptor potential protein 5" (TRP5), and "renal outer medullary potassium channel" (ROMK1) [56,64]. Anti-oxidation is promoted through klotho-dependent upregulation of anti-oxidant enzymes, such as superoxide dismutase 2 (SOD2), catalases, peroxiredoxins, and thioredoxin reductase [55,56,64]. Of note, α-klotho expression becomes inhibited by ROS, NFkB, angiotensin II, and by aging, and gene deletion of *α-klotho* reduces life span through defective anti-oxidant reserve [55,64].

So Nrf2 and α-klotho are key gene products which contribute extensively to $1,25(OH)_2D_3$-mediated homeostasis. Furthermore, $1,25(OH)_2D_3$ enhances substantially the cell-protective SIRT1-driven stress response [55,56,65-67]. A cooperative stress-induced interplay exists between SIRT1 and $1,25(OH)_2D_3$. SIRT1 deacetylation and hence activates VDR, Nrf2, FoxOs, and PCG1α [55,65-67]. The deacetylation of VDR enhances gene expression of vitamin D-dependent targets, and deacetylation of Nrf2 and FoxO proteins promotes a more reducing nuclear environment which favors also VDR-dependent gene expressions [68,69]. Of note, besides the deacetylation of PCGα, a successful cooperation between VDR/PCGα, important for mitochondrial fate, is also dependent on sufficient amounts of methyl donors, such as folate and vitamin B12 [70]. Similar to Nrf2, $1,25(OH)_2D_3$ enhances also the oxidative part of the pentose phosphate pathway (PPP) [71]. Similar to SIRT4 it restricts glutamine entry in the TCA cycle, though by a different mechanism which favors glutamate export from the cell [72]. Therefore cytosolic NADPH generation and context-dependent antioxidant or oxidant actions are favored, yet preventing excessive use of NADPH for biosynthesis and malignant cell proliferation, thus opposing malignancy. It is noteworthy that key metabolic pathways, inhibited by SIRT4, are enhanced by $1,25(OH)_2D_3$, such as PDHC activity, fatty acid oxidation and TCA cycle flux [73,74]. In summary, vitamin D_3 is a most important and context-driven enhancer of stress adaptation which is important for homeostasis and longevity. Vitamin D-deficiency diminishes this adaptation. Then even minor or "normal stress" is presumed to be turned into critical NAD pool decline, resulting in SIRT1 inhibition and increased ROS generation, followed by decreased PARP inhibition and further NAD-consumption.

Discussion

Considering vitamin D3 deficiency as a substantial causal factor for disturbed stress tolerance allows a more comprehensive approach to CFS/ME patients. The here presented data tell, that cell stress effects become

substantially augmented through vitamin D- deficiency. This explains why patients often report about having not recovered from an infection, xenobiotic burden, an operation, or physical trauma which resulted in long-term immobilization. All these events, and of course also severe mental stressors, could explain the transition from the everyday-condition chronic idiopathic fatigue to CFS/ME which is then associated with a very high grade global stress intolerance. Vitamin D-resistance in the wake of elevated ROS burden, elicited by any specific cause, is presumed to impede recovery by fixing up a vicious cycle of metabolic, energetic and redox imbalance and chronic pro-inflammation. Vitamin D_3 resistance would explain the persistent downhill disease course observed in late stages of CFS/ME. The model would explain the multitude of CFS/ME symptoms, such as flu-like post-exertional malaise, protracted wound-healing, chronic widespread pains, the paradox of chronic fatigue and difficulty sleeping, and functional dysregulations in all organ systems. The often contradictory switches in distinct functional responses with unusually large amplitudes could become interpreted as compromised homeostasis. The decreased defense against pathogens, toxins, xenobiotics, and any sort of cell stress would potentiate NAD consumption up to a critical extent, thus fixing cellular regulation in a SIRT4-driven cell response, and resulting in decreased metabolic flexibility, higher ROS burden, and pro-inflammation. Another, at first sight enigmatic symptom in patients suffering from CFS/ME, is latent iron deficiency. Usually, patients show low normal ferritin levels, however without overt anemia. The trial of iron substitution reduces fatigue only minimally, and increases ferritin levels only very moderately. After termination of substitution, ferritin levels rapidly fall to base line. A possible explanation could be the reduction of Nrf2 expression, resulting in decreased production of ferritin and ferroportin, but augmented production of hepcidin. Of note, latent iron deficiency in CFS/ME should be protective against iron-induced oxidative stress. An unresolved puzzle, however, is the report of McGregor et al. about metabolic alterations during post-exertional exhaustion, going along with hyper-metabolism, hypo-acetylation and purine deregulation in CFS/ME [5]. Hypo-acetylation and hyper-metabolism appear to be inconsistent with the reported low deacetylation activity of SIRT4. It remains an open question, if exertion induces activation of SIRT3, which is the mitochondrial deacetylase equivalent of SIRT1. However in any case, any further SIRT-dependent deac(et)ylation and/or ADP-ribosylation will aggravate decrease of NAD pools in addition. Furthermore, decrease of methyl donors, such as folate and vitamin B12, in concert with NAD depletion and elevated ROS will compromise VDR/PGC1α interaction, resulting in diminished mitochondrial function and regeneration [70]. This also might contribute to post-exertional malaise.

According to own clinical experience, Vitamin D_3 supplementation cures idiopathic fatigue promptly. On the other hand, CFS/ME, diseases which are supposed to be accompanied by long-lasting vitamin D deficiency, proved to be less easily treatable, presumably due to vitamin D resistance. Often the $25OHD_3$ levels remained strikingly low in spite of a daily dosage of 10,000 IU (250µg) per day. Maybe the mechanism for drug- and xenobiotic-induced vitamin D deficiency, reported by Holick, plays a role [61]. As vitamin D deficiency goes along with deficiency and dysregulation of calcium and phosphate, this might also contribute to resistance. A presumably upregulated CD38/CD157 activity due to calcium deficiency might exacerbate NAD consumption in addition. Of interest, some more recent papers report about pain reduction through treatment with vitamin D_3 and calcium [75-78].

Conclusions

Vitamin D deficiency should be considered in all sorts of chronic fatiguing illnesses as a causal and aggravating factor. This would complete the actual model of homeostasis disruption, recently presented by Naviaux [79]. If physicians would be able to prevent the transition to higher grade chronic fatigue through colecalciferol substitution, it would be of great importance for world-wide health systems. Symptoms of CFS/ME and the burden of disease would be understood more easily, thus relieving the mutually strained and stressful relationships which still exist between patients and their physicians. Physicians could be stimulated to revise their treatment regimens by omitting all interventions which induce further redox stress and xenobiotic burden. The drug and chemical intolerances of CFS/ME patients call for only minor dosages of pain and psychoactive substances. Instead, restoration of effective VDR activity should be targeted. This is assumed to stabilize a SIRT1/Nrf2-driven stress response. This might be achieved by plant-based diets and/or supplementations, such as those recommended by Naviaux et al. [8], and Xiao W 2018 [31],

including all B vitamins, and by supplements of vitamin D_3 and minerals, which include calcium and magnesium, in particular. Phosphate deficiency through long-standing vitamin D deficiency should be considered as well. Due to presumed vitamin D_3 resistance and to distinct genomic and translational vitamin D_3 responses, personalized high doses such as 250 mcg cholecalciferol and up to 2400 mg calcium per day should be applied [57,58]. Careful clinical observations should clarify the potential reversibility of very severe and long-standing CFS/ME stages. In any case, any sort of stressful challenge, such as xenobiotics, drugs, nutrient additions, microwaves, and psychosocial stress, should be avoided as much as possible.

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