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mTORC1 syndrome (TorS): unifying paradigm for PASC, ME/CFS and PAIS

Jacob Bar-Tana[1*]

Abstract

Post-acute SarS-Cov2 (PASC), Myalgia encephalomyelitis/Chronic fatigue syndrome (ME/CFS) and Post-acute infection syndrome (PAIS) consist of chronic post–acute infectious syndromes, sharing exhaustive fatigue, post exertional malaise, intermittent pain, postural tachycardia and neuro-cognitive-psychiatric dysfunction. However, the concerned shared pathophysiology is still unresolved in terms of upstream drivers and transducers. Also, risk factors which may determine vulnerability/progression to the chronic phase still remain to be defined. In lack of drivers and a cohesive pathophysiology, the concerned syndromes still remain unmet therapeutic needs. 'mTORC1 Syndrome' (TorS) implies an exhaustive disease entity driven by sustained hyper-activation of the mammalian target of rapamycin C1 (mTORC1), and resulting in a variety of disease aspects of the Metabolic Syndrome (MetS), non-alcoholic fatty liver disease, chronic obstructive pulmonary disease, some cancers, neurodegeneration and other [Bar-Tana in Trends Endocrinol Metab 34:135–145, 2023]. TorS may offer a cohesive insight of PASC, ME/CFS and PAIS drivers, pathophysiology, vulnerability and treatment options.

Keywords Post-acute SarS-Cov2 (PASC), Myalgia encephalomyelitis/chronic fatigue syndrome (ME/CFS), Post-acute infection syndrome (PAIS), Mammalian target of rapamycin C1 (mTORC1), mTORC1 syndrome (TorS)

Main text

Post-acute sequelae of SARS-CoV-2 infection (PASC), Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and post-acute infection syndrome (PAIS) represent a spectrum of post-infectious conditions often triggered by viral infection, and characterized by persistent debilitating fatigue, unrefreshing sleep, post-exertional malaise and cognitive dysfunction that may last for months after the acute infection phase. These diseases were hypothesized to reflect long-lasting systemic inflammation due to persistent viral RNA and/or protein, on-going immune response, induction of autoimmunity, mitochondrial dysfunction and/or gut microbiome dysbiosis. However, the pathophysiology of the concerned diseases in terms of shared upstream driver(s) and transduction pathway(s) remain(s) unresolved. Also, predictive risk factors and/or background diseases which may determine vulnerability/progression of respective acute infections to the post-acute/chronic phase remain to be defined. Most importantly, in the absence of a driver and vulnerability profile, the concerned diseases present unmet therapeutic needs. This perspective may offer a cohesive insight of PASC, ME/CFS and PAIS pathophysiology, vulnerability and treatment options.

PASC, ME/CFS and PAIS: unresolved syndromes/unmet treatment needs

Post-acute SARS-Cov2 (PASC)/Long Covid consists of multi-system relapsing–remitting disease, including fatigue, post exertional malaise, intermittent pain, dyspnea, autonomic failure/postural tachycardia syndrome (PoTS) and neuro-psychiatric dysfunction (brain fog, anxiety, depression, peripheral neuropathy) [1]. PASC may follow an initial recovery from acute Covid-19, or the acute illness may persist for more than 12

*Correspondence:
Jacob Bar-Tana
jacobb@ekmd.huji.ac.il
[1] Hebrew University Medical School, 91120 Jerusalem, Israel

weeks [2]. PASC inflicts more than 10% of those who had Covid-19 (over 65 million patients worldwide) [3, 4], independently of prior anti-SARS-Cov2 vaccination [5; however see 6] or anti-viral treatment [7]. Females, in particular premenopausal, are twice as affected by PASC compared to males [8], pointing to sex hormones in promoting PASC [9]. PASC is hypothesized to be driven by long-lasting systemic inflammation due to persistent SARS-Cov2 viral RNA and/or protein, on-going immune response, induction of autoimmunity, reactivation of other latent viruses (e.g., EBV, HHV6), and/or gut microbiome dysbiosis [1, 10, 11]. PASC pathophysiology is still unresolved, resulting in unmet therapeutic need [1, 10, 11].

Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/CFS) consists of post-infectious (e.g., EBV, HHV6) multi-system disease that persists for more than 6-months, presenting profound fatigue, post-exertional malaise, unrefreshing sleep, PoTS, intermittent muscle/joint pain, and neuro-cognitive dysfunction (brain fog, depression, peripheral neuropathy) [12, 13]. ME/CFS inflicts nearly 0.9% of worldwide population [14]. Similarly to PASC, ME/CFS affects premenopausal females (3:1 preponderance compared to males) [15]. ME/CFS is hypothesized to be due to persistent pathogen-associated molecular patterns (PAMPs) (e.g., viral, bacterial, parasitic), long-lasting systemic inflammation, mitochondrial dysfunction, on-going immune response, induction of autoimmunity, and/or gut microbiome/virome/mycobiome dysbiosis [16, 17]. ME/CFS pathophysiology and biomarker-based tests are still unresolved, resulting in unmet therapeutic need [17–19].

PASC major symptoms, including fatigue, post exertional malaise, myalgia, PoTS and neuro-cognitive-psychiatric dysfunction, overlap with ME/CFS [16]. Also, the pathophysiology proposed for PASC overlaps with that proposed for ME/CFS, including PAMPS-induced long-lasting systemic inflammation, immune activation, autoimmune response against self-antigens, mitochondrial dysfunction, reactivation of latent viruses and gut dysbiosis. The PASC/ME/CFS overlap has been realized by many [16, 20, 21], resulting initially in viewing PASC as a particular case of ME/CFS [22]. Alternatively, PASC and ME/CFS were proposed to present two particular reflections of a Post active phase of infection syndromes (PAPIS) sharing the same pathophysiology [23]. Since the concerned symptoms and pathophysiology are shared as well by a variety of viral (e.g., SARS-CoV2, EBV, SARS, MERS, other) and some non-viral pathogens, the PAPIS view has been further advanced by proposing recently the disease category of Post-acute infection syndromes (PAIS) [24], implying an exhaustive unifying syndrome, including PASC and ME/CFS as particular examples.

The proposed PAIS paradigm still remains 'Unexplained' [24] with respect to the following:

a. Driver: The PAIS paradigm lacks an upstream driver which may transduce the complexed pathophysiology and multi-symptoms of PAIS. Specifically, while being central to the PAIS paradigm, mitochondrial stress and its systemic fatigue and neuro-cognitive-psychiatric outcomes, remain to be defined in terms of an upstream mechanistic driver [25, 26]. Similarly, the preponderance of premenopausal females' progression to PAIS remains to be defined in terms of respective driver(s).
b. Risks: The PAIS paradigm fails to define predictive risk factors/background diseases which may determine vulnerability/progression of respective acute infections to the post-acute PAIS phase.
c. Diagnosis/treatment: In lack of a cohesive pathophysiology, PAIS biomarker(s) remain(s) undefined, resulting in critical deficiency in diagnosing PAIS. Most importantly, in the absence of a driver, PAIS remains an unmet therapeutic need. The mTORC1 Syndrome (TorS) paradigm may offer a cohesive framework for the 'Unexplained' aspects of PAIS.

mTORC1 syndrome (TorS)

The mammalian target of rapamycin complex 1 (mTORC1) controls growth and metabolism by affecting a variety of its downstream targets (e.g., S6K1, 4EBP, CRTC2, lipin, ATF4, HIF1a, PPARg, PPARa, ULK1, TFEB and others) [27]. mTORC1 kinase controls G1/S transition and G2/M progression, activates ribosome biogenesis and CAP-dependent mRNA translation, drives purine and pyrimidine biosynthesis, promotes glycolysis and the pentose shunt, and suppresses fatty acid oxidation and ketogenesis [27]. Most importantly, mTORC1 blocks autophagy and mitophagy [28]. mTORC1 kinase activity may range between hyper- and less- active state, as function of genetic, epigenetic, tissue and/or context-dependent factors. These may determine mTORC1 sensitivity to growth factors, nutrients and stress. mTORC1 kinase activity may be hyper-activated by growth factors (e.g., insulin, IGF1), energy/nutrients excess (e.g., glucose, leucine, arginine) and inflammation (e.g., NFkB/IKK), while being suppressed by a variety of metabolic stresses (e.g., hypoxic, hyperosmotic, oxidative, acidic, DNA damage) [27, 29], including caloric restriction [30, 31], carbohydrate restriction [32–34], bariatric surgery [35], or sustained physical exercise [36, 37]. When applied, these suppression measures are effective in increasing health span and predicting an increase in life span [38].

'mTORC1 Syndrome' (TorS) implies an exhaustive cohesive disease entity driven by sustained hyper-activation of mTORC1 [39]. Hyperactive mTORC1 may drive the glycemic context/beta-cell failure of type 2 diabetes (T2D) as well as a variety of non-glycemic disease aspects of the Metabolic Syndrome (MetS), including obesity, dyslipidemia, hypertension, atherosclerotic cardiovascular disease (ASCVD), MetS/T2D cardiomyopathy, nephropathy and peripheral neuropathy, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH), chronic obstructive pulmonary disease (COPD), some cancers, neurodegeneration, polycystic ovary syndrome (PCOS), psoriasis and other [39]. The TorS paradigm may offer a unifying view for T2D/MetS pathophysiology and treatment, while solving the apparent disconcordance between response and resistance to insulin in shaping the exhaustive phenotype of T2D/MetS [39, 40]. Also, mutual interactions between TorS and viral effectors/non-viral pathogens are proposed here to predispose/drive PASC, ME/CFS or PAIS (Fig. 1).

Of note, TorS has been previously proposed to drive the acute COVID-19 disease through interplay of the host innate stress response, plethora of viral measures aimed at subverting the innate stress response, mTORC1-enabled viral proliferation, mTORC1-suppressed autophagy/mitophagy and the impact of the TorS-driven host diseases [41, 42]. Hence, TorS is proposed to predispose/drive both, the acute viral disease as well as the chronic PASC phase of SARS-Cov2 infection.

TorS/PASC

PASC is reported to be predisposed by background diseases, including obesity, T2D, dyslipidemia, hypertension, ischemic cardiovascular disease, cardiomyopathy, chronic kidney disease, restrictive lung disease, thromboembolic disorders, NAFLD, cerebrovascular disease and polyneuropathy [43–47]. These background diseases may all be considered as TorS diseases driven by hyperactive mTORC1 [39, 40]. In line with that, the predisposition of PASC in premenopausal females may be accounted for by mTORC1 activation through estrogen signaling [48, 49]. Of note, in addition to PASC being driven by background TorS diseases, SARS-CoV2 infection may drive new-onset TorS diseases, including T2D, insulin resistance, cardiovascular disease, hypertension, chronic kidney disease, dyslipidemia, autoimmune diseases, systemic inflammation, and neurological and cognitive impairments [50, 51; however see 52]. Hence, hyperactive mTORC1/TorS may act both, as upstream driver of PASC (Fig. 1) as well as downstream target of SARS-CoV2 infection.

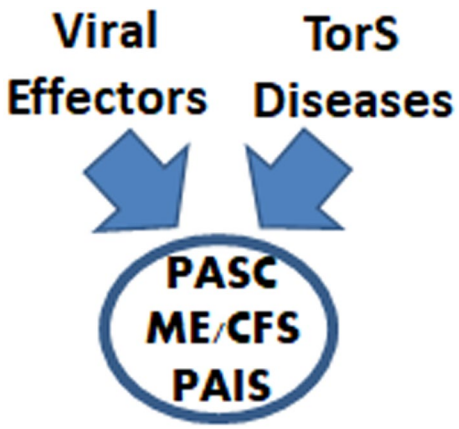

Fig. 1 TorS/Viral synergism. Background TorS diseases driven by hyperactive mTORC1 are proposed to synergize with a variety of respective viral effectors (and/or non-viral pathogens) to predispose/drive post-infectious PASC, ME/CFS or PAIS

In addition to PASC being predisposed by background TorS diseases, hyperactive mTORC1 may further drive the multi disease aspects of PASC. Thus, the most experienced symptoms of PASC include chronic fatigue, post-exertion malaise and brain fog, being presented by more than half of Covid-19 survivors [1, 53], and ascribed to 'mitochondrial dysfunction' [54, 55]. Indeed, PASC results in disrupted mitochondrial integrity and mtDNA, decrease in mitochondria membrane potential, oxygen uptake, oxidative phosphorylation and ATP production, with increased mitochondrial ROS production and disrupted ER-mito Ca++ dynamics in heart, liver, kidney and brain [1, 56, 57]. Mitochondrial stress has been primarily ascribed to direct binding and/or transcriptional disruption of mitochondrial components by viral proteins [56, 57]. Alternatively, in line with the TorS paradigm, PASC mitochondrial dysfunction/stress is proposed here to be due to inhibition of mitophagy by hyperactive mTORC1 [28], resulting in disrupted mitochondrial integrity and cell death [58, 59]. Hence, PASC may be predisposed by TorS diseases, while being further driven by disruption of mitophagy due to hyperactive mTORC1. The TorS paradigm may also account for the concomitant increase in glycolysis in PASC patients [60, 61], being driven by mTORC1-driven HIF1alpha [62].

PASC pathophysiology may further be ascribed to mTORC1/STAT3 interplay. Indeed, mTORC1 kinase activates the transcriptional activity of STAT3 [63], while STAT3 may activate mTORC1 kinase activity by suppressing REDD1 [64, 65]. Indeed, STAT3 is reported to drive both, the acute Covid-19 [66, 67] and PASC [68], implying that mTORC1 and STAT3 may synergize each other in promoting the acute and PASC phases of SARS-CoV2 infection (Fig. 2). Indeed, the mTORC1/STAT3 synergism may account for the immune profile of PASC (M1-macrophages activation with decrease in CD4 + and

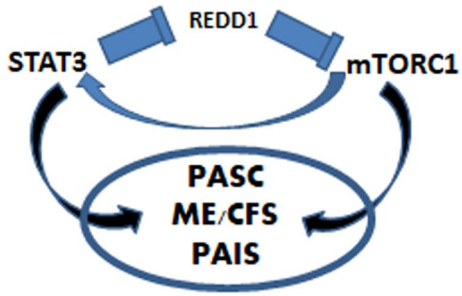

Fig. 2 mTORC1/STAT3 synergism. Hyperactive mTORC1 and STAT3 may each drive respective patho aspects of PASC, ME/CFS or PAIS. Moreover, hyperactive mTORC1 and STAT3 are proposed to synergize each other: mTORC1 kinase activates the transcriptional activity of STAT3, while STAT3 may activate mTORC1 kinase activity by suppressing REDD1

CD8 + effector memory cells [1]) [69–71], increase in IL6, CCL11, fibrinogen and D-dimer [1, 72–75], complement dysregulation [76, 77], NLRP3 inflammasome activation [78, 79], HPA axis dysfunction/decrease in plasma cortisol and serotonin [80, 81], increase in autoimmune antibodies (e.g., anti-ACE2, anti-GPCR) [1, 82], heart failure [83, 84], deep vein thrombosis/pulmonary emboli [85, 86], angiogenesis markers [87, 88], restrictive lung failure/pulmonary fibrosis [89–91], autonomic dysfunction/PoTS [92, 93], endothelial dysfunction [94, 95], erectile dysfunction [96, 97], neurocognitive decline, fatigue/post-exertional malaise [1, 28, 53], systemic inflammation, neuro-inflammation/glia activation [98–102] and small nerve fiber loss [103–105]. Hence, mTORC1 and IL6/STAT3 may synergize in driving PASC (Fig. 2).

TorS/ME/CFS

Similarly to PASC, ME/CFS is reported to be predisposed/driven by background MetS diseases, including obesity, hyperglycemia/T2D, dyslipidemia and hypertension [106–109]. In line with that, the ME/CFS fatigue score is reported to be linearly correlated with the number of MetS diseases, implying a putative causal linkage [106–109]. Of note, the concerned MetS diseases may all be considered as diseases driven by hyperactive mTORC1, namely, disease aspects of TorS [39]. Hence, background TorS is proposed to predispose/drive post-infectious ME/CFS (Fig. 1). In line with that, mTORC1 activation through estrogen signaling [48, 49] may account for the increased ME/CFS morbidity of pre-menopausal females. Moreover, TorS has been previously proposed to predispose/drive the acute disease phase of viral infections, due to mTORC1-enabled viral proliferation [41, 42, 110]. Hence, TorS is proposed to predispose/drive both, the acute viral proliferation phase that precedes ME/CFS, as well as the chronic ME/CFS disease (Fig. 1).

The most experienced symptoms of ME/CFS include extreme chronic fatigue, post-exertion malaise and brain fog, being ascribed to mitochondrial energy stress [111, 112; however see 113]. Indeed, ME/CFS results in disrupted mitochondrial integrity, basal respiration, aerobic respiratory capacity, mito membrane potential, coupling efficiency and ATP production, combined with increased mito ROS production in muscle, brain, immune cells, PBMC and other [25, 26, 114–117]. However, in contrast to classical mitochondrial diseases which present pronounced fatigue [118], no mtDNA mutations or differences in individual mito complexes activity have been reported in ME/CFS patients [119], pointing to an upstream driver in causing mitochondrial stress [115, 120]. Also, ME/CFS mitochondrial stress is accompanied by increased glycolysis [121–123]; however see 124], with concomitant decrease in PDH/TCA cycle activity [125], implying an upstream driver(s) which control(s) non-oxidative metabolism. In line with the TorS/ME/CFS paradigm, ME/CFS mitochondrial stress is proposed to be driven by inhibition of mitophagy/autophagy due to hyperactive mTORC1 [25, 28, 59, 126], resulting in disrupted mitochondrial integrity and cell death. Hyperactive mTORC1 may also account for HIF1alpha activation, resulting in driving glycolysis [62], while suppressing PDH/TCA activity [127]. The TorS/mitochondrial stress paradigm may further account for the immune exhaustion of CD8 + T cells in ME/CFS [25, 128–133], meta-inflammation [117, 134–136], cardiovascular, endothelial dysfunction, platelet hyper-activation and coagulopathy [21] profiles of ME/CFS. Meta-inflammation and immune exhaustion of ME/CFS may further be driven by mTORC1-activated IL6/STAT3 [132, 133] (Fig. 2). Hence, mTORC1 and STAT3 may synergize in driving ME/CFS.

TorS: unified paradigm for PASC, ME/CFS, PAIS

Viewing PAIS (including PASC and ME/CFS as particular examples) in the context of TorS may answer some of the 'Unexplained' [24] aspects of PAIS:

a. Driver: PAIS is proposed to be driven by hyperactive mTORC1/TorS. Hyperactive mTORC1 enables virus proliferation during the acute infectious disease preceding PAIS [41, 42], and further persists throughout the post-acute PAIS phase, being sustained by background TorS diseases. The two concerned effectors of hyperactive mTORC1, namely the acute viral infection and background TorS are proposed to be both required for driving PAIS, while synergizing each other (Fig. 1). Of note, viewing PAIS in the context of hyperactive mTORC1/TorS may account for PAIS

mito dysfunction due to suppression of mitophagy [28].

b. Risks: Viewing PAIS in the context of TorS implies that TorS diseases may serve as risk factors in transforming respective acute viral diseases into persistent PAIS, being driven by the mTORC1/STAT3 synergism [63–65] (Fig. 2). Also, mTORC1 activation by estrogens may account for the female preponderance in progression to PAIS. Indeed, estrogens may activate mTORC1 through multiple pathways, including the PKC-ERK1/2 pathway, the PI3K/AKT pathway, and/or direct interactions with ERα thereby initiating a signaling cascade involving c-Src and/or PI3K/AKT (48, 49). Activated ERK1, or AKT phosphorylate and inhibit TSC1,2, a negative regulator of mTORC1, thereby promoting mTORC1 activation.
c. Treatment: Prior to the vaccination era, Covid-19 treatments have aimed at inhibiting viral proliferation and/or acute inflammation, using antiviral drugs [137], STAT3 inhibitors [138] and/or glucocorticoids [139]. These treatments became mostly redundant due to the efficacy of Covid-19 vaccinations to prevent and antagonize the acute Covid-19 infection and disease. However, PASC still remains an unmet need, in spite of Covid-19 vaccinations or anti-viral measures [140, 141]. Similarly, ME/CFS still remains a treatment deadlock, resulting in human suffering and major health expenditures [142].

The TorS paradigm, proposed here as driver of PASC/ME/CFS/PAIS pathophysiology, implies that suppression of hyperactive mTORC1, and in particular rescue of mTORC1-suppressed mitophagy, may offer a disease-modifying treatment for PASC, ME/CFS or PAIS (Fig. 3). Indeed, anecdotal reports have indicated prospective efficacy of rapalogs in the treatment of PASC [143] or ME/CFS [144, 145]. In line with that, induction of mitophagy is reported to mitigate meta-inflammation [146–148], immune activation [149], and neurological/cognitive dysfunction [150], namely the core presentations of PASC/ME/CFS/PAIS. However, sustained inhibition of mTORC1 activity by rapalogs may result in inhibition of mTORC2 as well, resulting in diabetes [151]. Also, treatment with rapalogs may result in severe side-effects, while trials to bypass side-effects by intermittent treatments still remain to be accomplished. Moreover, suppression of mTORC1 kinase activity by rapalogs results in suppressing some (e.g., S6K1), but not all downstream targets of mTORC1 (e.g., 4EBP) [152], implying a potential resistance to rapalogs in the treatment of TorS-driven PASC, ME/CFS or PAIS.

Alternatively, hyperactive mTORC1 may be indirectly suppressed by a variety of metabolic effectors,

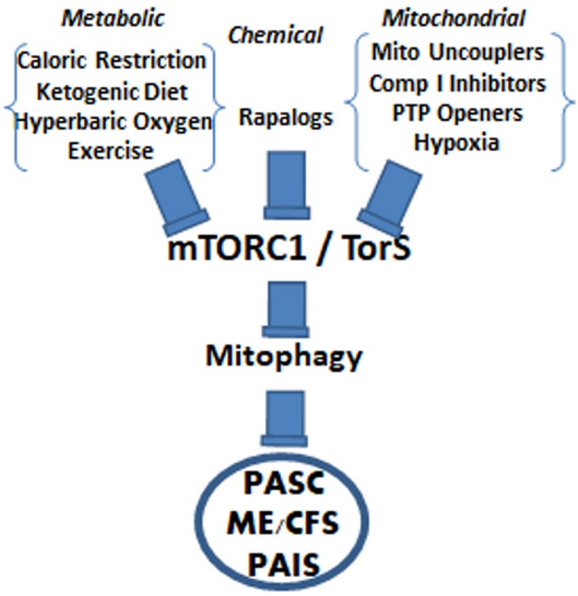

Fig. 3 Disease-modifying treatments for PASC, ME/CFS or PAIS. Suppression of mTORC1/TorS with concomitant rescue of mitophagy may result in disease-modifying treatment for PASC, ME/CFS or PAIS. mTORC1/TorS diseases may be suppressed by respective metabolic, chemical or mitochondrial inhibitors

including caloric restriction, carbohydrate restriction/ketogenic diets, hyperbaric oxygen or sustained physical exercise [39] (Fig. 3). When applied, these measures are effective in alleviating some of the pleiotropic diseases of TorS [40], including disease aspects of PASC/ME/CFS [44, 153–155]. However, the compliance to the concerned dietary and exercise behavioral measures is poor, in particular in PASC/ME/CFS/PAIS patients suffering from gastrointestinal dysbiosis and/or post-exertion malaise. Hence, treatment of TorS-driven PASC, ME/CFS and PAIS calls for alternative measures that may suppress hyperactive mTORC1 while inducing mitophagy.

Indeed, suppression of hyperactive mTORC1, with concomitant rescue of mitophagy, may be effected by mitochondrial energy stress, being transduced to mTORC1 through the integrated stress response (ISR), activated HRI, ATF4 and REDD1 [156, 157]. Mitochondrial energy stress resulting in rescuing mitophagy may be effected by mild uncoupling of mitochondrial oxidative phosphorylation (e.g., DNP, TPP-cations, long-chain fatty acids) [158–162], or mild inhibition of mito complex I (e.g., metformin, phenformin) [163–165], or opening of the mito permeability transition pore (PTP) [166], or mild hypoxia [167, 168] (Fig. 3). Of note, long-chain fatty acyl analogs of the MEDICA family are reported to inhibit mito complex I, to open mito PTP, to suppress mTORC1 kinase activity and to suppress STAT3 transcriptional

activity [169–171], implying prospective double-headed efficacy in the treatment of PAIS (Fig. 4).

Of note, suppression of mitochondrial oxidative phosphorylation by mild uncouplers, complex I inhibitors, PTP openers, hypoxia or MEDICA may apparently sound counterproductive when aiming to rescue 'mitochondrial dysfunction' inflicted by hyperactive mTORC1 and suppressed mitophagy. This apparent ambiguity implies that suppression of mitophagy in the PASC, ME/CFS or PAIS context is far more destructive than mitochondrial energy stress due to limited oxidative phosphorylation. Moreover, the concerned ambiguity implies that 'dysfunction' due to suppression of mitophagy may be rescued by limited mitochondrial energy stress.

Concluding remarks

PASC, ME/CFS and PAIS consist of chronic post–infectious multi-system syndromes, sharing exhaustive fatigue, post exertional malaise, intermittent pain and neuro-cognitive-psychiatric dysfunction. In lack of a cohesive pathophysiology these syndromes still remain unmet therapeutic needs. TorS may offer an insight of PASC, ME/CFS and PAIS pathophysiology and patient vulnerability. Suppression of hyperactive mTORC1/STAT3 by mitochondrial energy stress may result in disease-modifying treatment for the concerned syndromes. 'That Which Does Not Kill Us Makes Us Stronger'.

The TorS/PASC/ME/CFS/PAIS paradigm leaves open the following questions:

(a) The proposed paradigm still has to account for the extreme variability of clinical presentations of concerned patients. The phenotypic variability could reflect the featured activity of respective infective agents and/or the multi genetic, epigenetic, and tissue/context-dependent factors that may modulate the mTORC1/STAT3 activity of infected patients. (b) The proposed paradigm still has to define accessible biomarker(s) (e.g., phospho-S6K1, phospho-4EBP1, phospho-STAT3(Y705) [172, 173]) that may point to mTORC1/STAT3 activity over time in candidate patients. (c) The reported anecdotal role of rapamycin in alleviating PAIS [143–145] remains to be confirmed in controlled clinical study. d. Mitochondrial energy stress, affected by mild uncoupling of mitochondrial oxidative phosphorylation, or mild inhibition of mitochondrial complex I, or opening of the mitochondrial permeability transition pore, or mild hypoxia may offer a disease-modifying treatment for PASC/ME/CFS/PAIS patients. However, the balance between therapeutic stress and pathological damage might be challenging. e. It still remains to be investigated whether suppression of mTORC1/STAT3 during the preceding acute infectious disease may prevent the chronic disease phase. Animal models may provide early disease correlates and molecular signatures associated with advanced disease development over time, including countermeasure performance before and during the acute infection [174, 175]. f. In view of the similar clinical profile shared by PASC/ME/CFS/PAIS and Fibromyalgia [176–178], Fibromyalgia may fit into the proposed TorS paradigm.

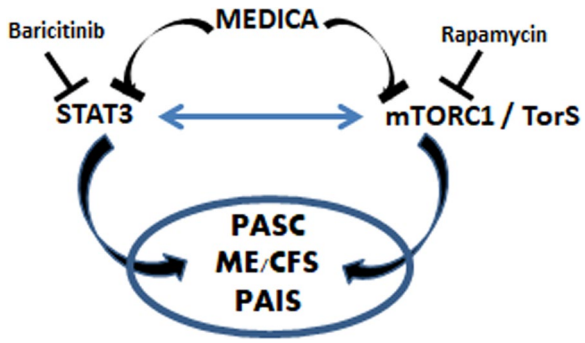

Fig. 4 Double-headed MEDICA. Long-chain fatty acyl analogs of the MEDICA family suppress mTORC1 kinase activity and STAT3 transcriptional activity, implying prospective double-headed disease-modifying treatment for PASC, ME/CFS or PAIS

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
COPD	Chronic obstructive pulmonary disease
ME/CFS	Myalgia encephalomyelitis/Chronic fatigue syndrome
MetS	Metabolic syndrome
mTORC1	Mammalian target of rapamycin C1
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PAIS	Post-acute infection syndrome
PAMPs	Pathogen-associated molecular patterns
PAPIS	Post active phase of infection syndromes
PASC	Post-acute SarS-Cov2
PBMC	Peripheral blood mononuclear cells
PCOS	Polycystic ovary syndrome
PDH	Pyruvate dehydrogenase
PoTS	Postural tachycardia syndrome
PTP	Permeability transition pore
SARS-CoV2	**S**evere acute respiratory syndrome Coronavirus 2
STAT 3	Signal transducer and activator of transcription 3
T2D	Type 2 diabetes
TCA	Tricarboxylic acid cycle
TorS	MTORC1 syndrome

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The authors declare that they have no competing interests.

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