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REVIEW

Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Physical Fatigue Through the Perspective of Immunosenescence

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ABSTRACT

Background: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating illness marked by persistent fatigue, yet its mechanisms remain unclear. Growing evidence implicates immunosenescence—the age-related decline in immune function—in the onset and persistence of fatigue.

Methods: This review synthesizes clinical and experimental data to examine how immunosenescence contributes to ME/CFS. We focus on chronic inflammation, senescent immune phenotypes, mitochondrial dysfunction, and neuroendocrine imbalance, with emphasis on maladaptive crosstalk among immune, muscular, neuroendocrine, and vascular systems.

Results: Aging immune cells drive chronic inflammation that impairs mitochondrial ATP production and promotes muscle catabolism. Concurrently, HPA-axis suppression and β_2-adrenergic dysfunction amplify immune dysregulation and energy imbalance. Together, these processes illustrate how immunosenescence sustains pathological cross-organ signaling underlying systemic fatigue.

Conclusion: Immunosenescence provides a unifying framework linking immune, metabolic, and neuroendocrine dysfunction in ME/CFS. Recognizing cross-organ communication highlights its clinical relevance, suggesting biomarkers such as cytokines and exhaustion markers, and supports integrated therapeutic strategies targeting immune and metabolic networks.

1 | Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic illness characterized by persistent fatigue and exercise intolerance, with a global prevalence of approximately 0.68%, affecting more than 17 million individuals worldwide (Lim et al. 2020). Patients often experience a marked worsening of symptoms following physical or cognitive exertion—a phenomenon known as post-exertional malaise (PEM)—which can last for several days and severely impair daily functioning. A substantial proportion of patients become bedridden or unable to work, resulting in a significant socioeconomic burden (Bonk and Khedkar 2022).

The most prominent symptom of ME/CFS is persistent intolerance to exercise and routine physical activities, manifested as profound fatigue and malaise triggered even by mild physical or cognitive exertion—termed PEM. PEM is typically delayed

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in onset (often 12–48 h after the trigger) and recovery is prolonged, lasting days or even weeks; immediate onset can also occur in some patients (National Institute for Health and Care Excellence 2021; Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue S, Board on the Health of Select P Institute of M 2015). Patients frequently report an "energy-depletion–type" exhaustion: Even minor actions are difficult to sustain, often accompanied by muscle soreness, cognitive slowing, sleep disturbances, and mood abnormalities such as anxiety and depression (Carruthers 2007). Muscle fatigue (MF) is one of the core manifestations of the disease. It may arise during or after physical exertion, and its underlying mechanisms involve dysregulated energy supply within skeletal muscle, mitochondrial dysfunction, and reduced muscle fiber contractility (Jammes and Retornaz 2019).

In ME/CFS, MF appears as the combined outcome of both central fatigue and peripheral fatigue. Central fatigue refers to a reduced capacity for motor neuron recruitment, which leads to insufficient muscle activation. Peripheral fatigue involves impaired muscle contraction due to dysfunctions in calcium (Ca^{2+}) and potassium (K^{+}) ion channels, as well as disturbances in oxidative metabolism (Jammes and Retornaz 2019). Research has demonstrated that individuals with ME/CFS exhibit significant functional decline and prolonged recovery in repeated-exercise testing. Specifically, reductions in handgrip strength (HGS) and quadriceps strength are observed, and peak oxygen uptake (VO_2 peak) values are notably lower on the second day of cardiopulmonary exercise testing, indicating systemic intolerance to routine physical exertion (Meeus et al. 2016; Nacul et al. 2018).

Recent theoretical models further suggest that fatigue in ME/CFS does not stem from a dysfunction in a single system, but rather arises from aberrant communication between the central nervous system (CNS) and skeletal muscle—a complex, integrated response (Cordeiro et al. 2017). Skeletal muscle not only functions in movement but also secretes myokines—bioactive cytokines produced by contracting muscles—that modulate immune responses and inflammation (Afzali et al. 2018). Conversely, systemic inflammation can exacerbate skeletal muscle atrophy and metabolic dysregulation.

Although debate persists over whether ME and CFS represent the same disease or distinct conditions, most groups and studies use ME/CFS as an umbrella term that encompasses both conditions (Populations BotHoS and Syndrome CotDCfMECF 2015). In this review we adopt that convention and do not argue that ME and CFS are separate diseases. In 2015, the U.S. National Academy of Medicine (formerly Institute of Medicine) proposed renaming the condition "Systemic Exertion Intolerance Disease (SEID)" to underscore the centrality of post-exertional symptom exacerbation rather than to advocate a change in nomenclature or case definition (Clayton 2015). We reference SEID solely to highlight this clinical hallmark. Within this umbrella usage, skeletal muscle dysfunction remains a highly specific and underappreciated component of the illness, and its connection to persistent physical debilitation cannot be ignored (Wirth and Scheibenbogen 2021).

In summary, ME/CFS is a profoundly debilitating disorder in which persistent somatic fatigue is closely linked to multisystem dysfunction (Clayton 2015). The pathophysiological mechanisms remain unresolved, particularly the fundamental origin of fatigue. In recent years, immunosenescence—a cross-system, chronically progressive pathological state—has gained increasing recognition as a potential key contributor to fatigue formation in ME/CFS (Van Campenhout et al. 2025). Current evidence suggests that several inter-organ crosstalk pathways are particularly relevant: (i) immune–muscle interactions, whereby pro-inflammatory cytokines and senescent immune cells impair mitochondrial bioenergetics and promote proteolysis, leading to muscle fatigue and atrophy (Van Campenhout et al. 2025; Syed et al. 2025); (ii) immune–neuroendocrine crosstalk, where chronic inflammation suppresses the HPA axis while sustaining sympathetic overactivation, amplifying energy imbalance (Silverman et al. 2010; Yang et al. 2019); and (iii) immune–vascular–brain interactions, in which inflammatory mediators and β_2-adrenergic receptor dysfunction disrupt cerebrovascular regulation and neurovascular coupling, contributing to cognitive and physical fatigue (Hartwig et al. 2020; Wirth et al. 2021). Despite these insights, a critical gap remains: most studies investigate these pathways in isolation, without integrating them into a unifying framework centered on immunosenescence. This review explores how immunosenescence may mediate the development and persistence of somatic fatigue in ME/CFS by altering immune function, skeletal muscle metabolism, and neural regulation, and seeks to provide a theoretical foundation for future research and interventions. Beyond an intrinsic immune alteration, immunosenescence acts as a driver of maladaptive crosstalk among the immune, muscular, neuroendocrine, and vascular systems, thereby sustaining the cycle of physical fatigue.

2 | Immunosenescence and Immune Dysregulation in ME/CFS

2.1 | What Is Immunosenescence

Immunosenescence refers to the gradual decline of immune system function due to aging or prolonged stress, involving phenotypic and functional changes across multiple immune cell subsets (Coppé et al. 2010). A key underlying mechanism is cellular senescence, characterized by irreversible cell-cycle arrest triggered by stresses such as oxidative injury, DNA damage, oncogene activation, and age-related telomere shortening (Campisi 2013). While cellular senescence plays physiological roles—such as in tissue repair and tumor suppression—chronic or aberrant senescence can lead to persistent tissue damage and inflammation (Campisi 2013).

Senescent cells typically exhibit telomere shortening, resistance to apoptosis, extensive epigenetic remodeling, and a hallmark feature known as the senescence-associated secretory phenotype (SASP) (Campisi 2013). SASP is one of the core mechanisms of immunosenescence, driving cells to secrete a diverse array of pro-inflammatory cytokines and chemokines—such as IL6 and IFNγ—which contribute to persistent local and systemic inflammation (Wang et al. 2024).

In the adaptive immune system, T and B lymphocytes are the most susceptible to immunosenescence (Akbar and

Henson 2011). T cell senescence is typically accompanied by the downregulation of co-stimulatory molecules such as CD27 and CD28, concurrent with upregulation of inhibitory receptors including CD57, KLRG1, and TIM3 (Akbar and Henson 2011; Choi et al. 2023). Additionally, a subset of T cells may aberrantly express natural killer (NK) cell–associated markers, such as KIR and NKG2A (Akbar and Henson 2011; Choi et al. 2023). Functionally, senescent T cells often transition from a naive phenotype into terminally differentiated effector-memory (TEMRA) cells and exhibit enhanced secretion of pro-inflammatory cytokines, including TNFα, IFNγ, and IL6, which increases the risk of tissue damage in an inflammatory environment (Zanni et al. 2003).

In the adaptive immune system, B cells are significantly affected by immunosenescence. Aging is marked by a decline in naive B cells and a relative increase in memory B cells, which impairs the capacity to respond to novel antigens (Huang et al. 2022). This phenotypic shift is closely associated with upregulation of pro-inflammatory cytokines (Ratliff et al. 2013). Although CD27 is widely used to identify memory B cells, its specific role in the aging process remains to be fully elucidated (Bulati et al. 2011).

Contrary to T and B cells, NK cells typically do not decline in number during aging; in fact, their circulating frequency—especially of the cytotoxic $CD56^{dim}$ subset—may even increase. However, their immune function undergoes notable changes (Gounder et al. 2018). Aging is associated with receptor repertoire remodeling, including upregulation of KLRG1, NKG2A, and CD57, which collectively indicate diminished cytotoxic capacity and proliferative potential (Björkström et al. 2010). Despite these phenotypic shifts, there is no single, universally accepted biomarker of NK cell senescence.

Overall, immunosenescence impairs the responsiveness of multiple immune cell types—including T cells, B cells, and NK cells—manifesting in reduced responses to novel antigens, compromised memory cell function, enhanced chronic low-grade inflammation (inflammaging), and increased susceptibility to autoimmunity (Goronzy and Weyand 2013). Notably, factors such as chronic stress and sleep disturbances—both prevalent clinical features among ME/CFS patients—have been shown to accelerate immunosenescence (Carroll et al. 2017; Cortes Rivera et al. 2019). This convergence offers a valuable angle from which to investigate the immunological underpinnings of somatic fatigue in ME/CFS.

2.2 | Immunological Abnormalities in ME/CFS

Studies indicate that ME/CFS patients exhibit complex immune dysregulation, including disturbed cytokine networks, aberrant lymphocyte phenotypes and function, metabolic reprogramming, and autophagy dysregulation (Blundell et al. 2015; Straus et al. 1993; Masson et al. 2024). Numerous investigations have detected altered levels of both pro-inflammatory and regulatory cytokines in plasma or peripheral blood—implying a state of coexisting immune activation and suppression (Khaiboullina et al. 2015; Clarke et al. 2025). However, cohort-to-cohort variability is high. For example, IL8 has been reported as both elevated and reduced (Hornig et al. 2015), and cytokines such as IL4, IL10, IL17, TNFα, and IFNγ show inconsistent expression across different studies (Peterson et al. 2015). A particularly contradictory case is IL10, where most serum studies report elevated IL10—suggesting a counter-regulatory, immunosuppressive response to chronic inflammation—yet cerebrospinal fluid (CSF) analyses report significantly decreased IL10 (Khaiboullina et al. 2015; Hornig et al. 2015). This discrepancy underscores the impact of sample source (serum vs. CSF) and disease stage on cytokine profiling outcomes.

At the cellular level, abnormalities in T cells and NK cells are particularly pronounced in ME/CFS. Patients often exhibit T cell functional impairment and an exhaustion phenotype, evidenced by upregulation of inhibitory receptors such as PD1 and TIM3 on peripheral $CD4^+$ and $CD8^+$ T cells (Iu et al. 2024). However, in some subpopulations, KLRG1 expression is paradoxically decreased, possibly reflecting regulatory imbalance under persistent antigen exposure (Hardcastle et al. 2015c). NK cell effector function is also persistently reduced, with multiple studies consistently reporting significantly lower cytotoxic activity in ME/CFS patients compared to healthy controls (Eaton-Fitch et al. 2024; Mandarano et al. 2020). Concurrently, T cells show metabolic alterations: increased expression of the glucose transporter GLUT1 suggests an attempt to boost glucose uptake in response to energy deficit, yet downstream glycolytic enzymes (e.g., hexokinase I [HK1]) are downregulated, indicating persistent glycolytic constraints (Iu et al. 2024). Collectively, these immune phenotypes align with features of T cell exhaustion and senescence driven by chronic antigen stimulation, suggesting that ME/CFS patients may experience immune system functional aging.

Metabolic reprogramming of immune cells is also a crucial facet of immune dysfunction in ME/CFS. Studies have shown that peripheral T cells in ME/CFS patients exhibit reduced metabolic activity, with $CD8^+$ T cells showing decreased mitochondrial membrane potential and both $CD4^+$ and $CD8^+$ T cells displaying lower basal glycolysis, which persists even upon activation in $CD8^+$ T cells (Mandarano et al. 2020). Integrating metabolomic and proteomic analyses, researchers found upregulated expression of enzymes involved in fatty acid oxidation (FAO) and ketone metabolism within PBMCs, suggesting a shift under chronic stress from glycolysis-dependent energy production to FAO dependence (Maya et al. 2023). This metabolic adaptation closely mirrors patterns seen in T cell exhaustion during chronic infections or cancer, characterized by a "low-energy, high-exhaustion" cellular state (Maya et al. 2023). Additionally, NK cells exhibit reduced glycolytic reserve and mitochondrial dysfunction, further supporting the notion of immunometabolic deterioration in ME/CFS (Maya et al. 2023).

Preliminary evidence also points to abnormalities in autophagy. In one cohort, serum levels of the autophagy-related protein ATG13 were reported to be elevated, consistent with dysregulated autophagic signaling; however, circulating measures cannot distinguish enhanced initiation from impaired autophagic flux (Gottschalk et al. 2022). Conceptually, disturbed autophagy may aggravate oxidative stress, mitochondrial injury, and proteostasis burden, thereby compounding immune-cell dysfunction, but this requires replication with flux-sensitive assays and longitudinal designs.

Importantly, significant variability persists across ME/CFS studies, influenced by differences in sample selection criteria, disease duration, comorbidities, and other factors that complicate data interpretation (Peterson et al. 2015; Iu et al. 2024). Some cohorts—particularly those following viral infection onset—report elevated acute inflammatory markers, while others fail to identify consistent inflammation profiles (Lyall et al. 2003; Hardcastle et al. 2015a). Such inconsistencies highlight the high heterogeneity of immune abnormalities in ME/CFS, suggesting that the disease may not arise from a single mechanism but rather from a complex interplay of multiple drivers (Lyall et al. 2003). Moreover, most existing studies are cross-sectional with limited sample sizes and rely on coarse immune-phenotyping methods, which are inadequate to capture the dynamic evolution of immune changes over time (Eaton-Fitch et al. 2024; Maya et al. 2023). Against this heterogeneous background, autophagy-related signals have also been described: as noted above, elevated serum ATG13 has been observed in one cohort and, in exploratory analyses, linked to markers of oxidative stress—plausibly via RAGE-dependent pathways (Gottschalk et al. 2022). While intriguing, these findings remain preliminary and should be validated in larger, well-phenotyped cohorts using intracellular autophagy–flux readouts and longitudinal sampling.

Accumulating evidence demonstrates that ME/CFS patients exhibit hallmark features of immunosenescence across multiple dimensions of the immune system—namely, impaired cytotoxic function, chronic low-grade inflammation (inflammaging), diminished metabolic capacity, and reduced efficiency in antigen clearance—which closely mirror the immune aging profile observed in older adults (Arron et al. 2024; Maya 2023). This striking alignment suggests that ME/CFS may involve a premature or accelerated form of immune aging, rather than being driven by a singular pathogenetic mechanism. Importantly, this immunosenescent state is not merely a reflection of immune dysfunction but likely serves as a primary underpinning of persistent fatigue- in ME/CFS. The subsequent sections will explore how immunosenescence may drive physical fatigue via three interconnected pathways: chronic inflammation–induced metabolic dysregulation, inflammatory muscle damage and atrophy, and disruption of the neuroendocrineimmune axis.

3 | How Immunosenescence Leads to Physical Fatigue in ME/CFS

3.1 | Chronic Inflammation–Induced Metabolic Impairment

Skeletal muscle contraction and sustained exercise capability depend on efficient ATP resynthesis, primarily via three energy-generation pathways: glycolysis, mitochondrial oxidative phosphorylation (OXPHOS), and fatty acid β-oxidation (Sun et al. 2025). Glycolysis occurs in the cytosol, rapidly converting glucose to pyruvate to produce limited ATP; during hypoxia or high-intensity activity, pyruvate is reduced to lactate for short-term energy support (Sun et al. 2025). Within mitochondria, pyruvate is further oxidized through the tricarboxylic acid (TCA) cycle to generate NADH and $FADH_2$, which fuel the electron transport chain and generate substantial ATP (Sun et al. 2025). Additionally, beta-oxidation of fatty acids within the mitochondrial matrix yields acetyl-CoA and reducing equivalents, which also enter oxidative phosphorylation—though this pathway depends on oxygen and predominates in resting and endurance states (Sun et al. 2025). Muscle fiber types exhibit distinct metabolic preferences: Type I (slow-twitch) fibers are rich in mitochondria, favor oxidative metabolism, and resist fatigue, whereas Type II (fast-twitch) fibers—especially IIb/IIx—have fewer mitochondria, rely on glycolysis, contract rapidly, but fatigue quickly (Bourdeau et al. 2018). Mitochondria serve as the central site for TCA cycle activity, β-oxidation, and OXPHOS; thus, any impairment in mitochondrial integrity undermines muscular ATP generation, compromising exercise tolerance (Sun et al. 2025).

In ME/CFS, an increasing body of research confirms the presence of a low-grade, persistent inflammatory state, characterized by elevated levels of multiple pro-inflammatory cytokines in peripheral blood—such as IL1β, IL6, TNFα, IFNγ, IL17, and the damage-associated molecular pattern HMGB1 (Mandarano et al. 2020; Sun et al. 2025). These elevated cytokine levels not only serve as immunological markers of disease activity but also positively correlate with fatigue severity, reduced exercise tolerance, and muscle pain, which are hallmark symptoms of ME/CFS (Montoya et al. 2017). Additionally, evidence shows that ME/CFS patients experience abnormal cytokine surges post-exercise, particularly with IL1β and TNFα, exacerbating PEM (Rutherford et al. 2016). Furthermore, even at rest, ME/CFS patients may exhibit lactate accumulation, suggesting a basal reliance on anaerobic glycolysis for energy generation (Sun et al. 2025). Integrative investigations—including in vivo 31P-MRS of skeletal muscle and metabolomic profiling—indicate reduced oxidative phosphorylation capacity with a relative shift toward glycolytic ATP generation in ME/CFS, consistent with early intracellular acidosis and impaired phosphocreatine recovery reported across cohorts (Rutherford et al. 2016; Wong et al. 1992; Hollingsworth et al. 2010). Notably, these metabolic abnormalities are closely associated with the long-term effects of pro-inflammatory cytokines. Chronic inflammation can damage mitochondria at the molecular level, trigger a cascade of reactions, impair ATP production, reduce oxidative substrate utilization efficiency, and ultimately manifest as energy deficiency and exercise intolerance.

Multiple human and animal studies have confirmed that pro-inflammatory cytokines such as IL-6 and TNFα induce mitochondrial damage through oxidative stress pathways (Rutherford et al. 2016). Specifically, IL-6 and TNFα stimulate the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which directly injure mitochondrial structure and function (Rutherford et al. 2016). Clinically, ME/CFS patients exhibit elevated serum markers of lipid peroxidation (e.g., isoprostanes) and protein carbonyls, indicating sustained oxidative damage affecting mitochondria and other subcellular components (Rutherford et al. 2016). In animal models, elevated IL-6 suppresses mitochondrial biogenesis and the antioxidant regulator PGC1α, whereas IL-6 deficiency reduces mitochondrial ROS in muscle and mitigates inflammation-induced atrophy (Chen et al. 2023) (Figure 1). TNFα further exacerbates mitochondrial dysfunction by upregulating NADPH oxidase, accelerating ROS generation, damaging mtDNA, lowering membrane potential, and triggering failure of the electron transport

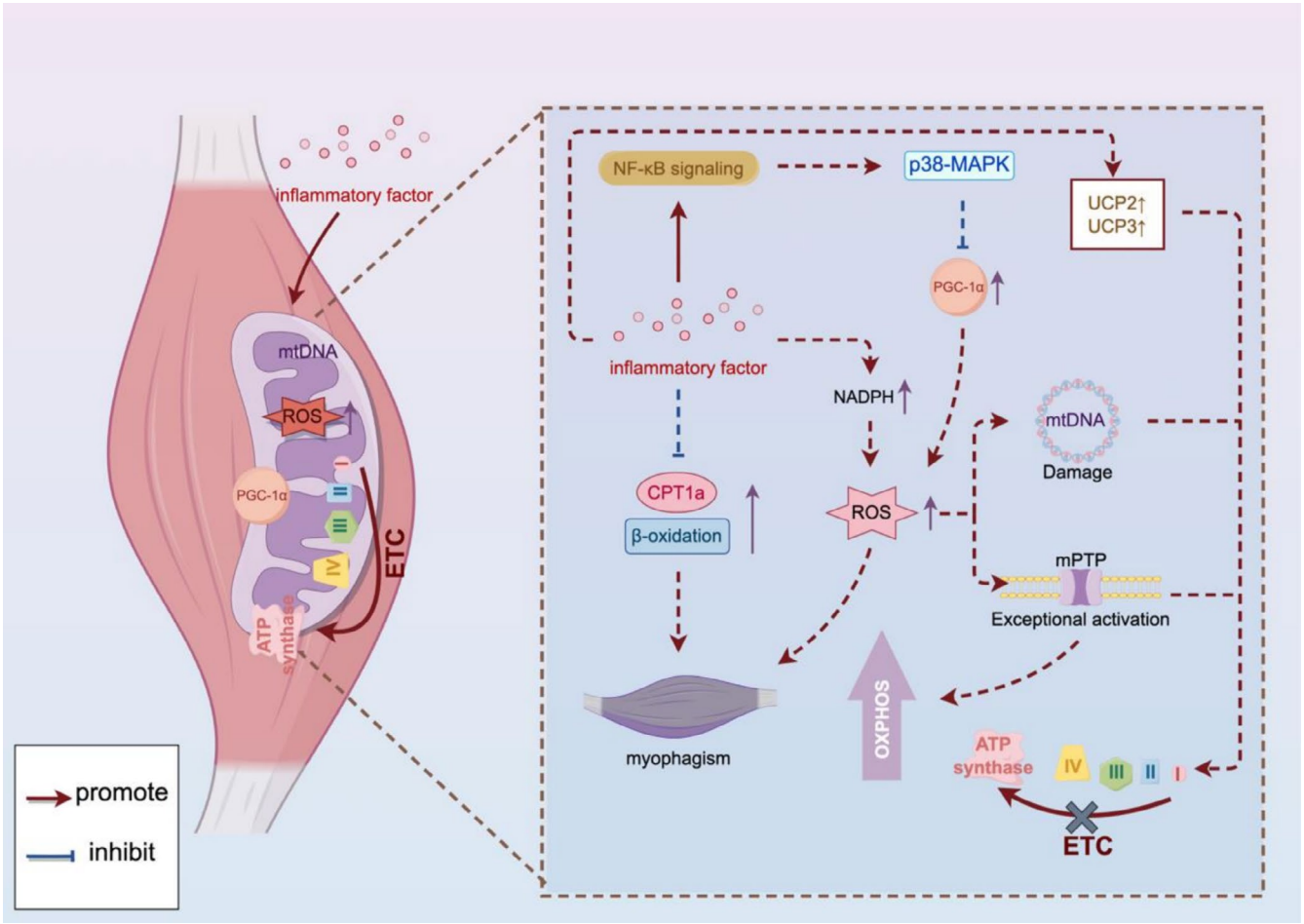

FIGURE 1 | Inflammation-linked bioenergetic impairment in ME/CFS skeletal muscle—patient observations, canonical pathways, and testable hypotheses. Patient observations. ME/CFS cohorts demonstrate elevated inflammatory cytokines and exertional bioenergetic limitations consistent with impaired oxidative phosphorylation. Canonical pathways (mechanistic context). Inflammatory cytokines can activate the NF-κB and p38-MAPK signaling axes, leading to repression of PGC-1α and increased mitochondrial ROS, processes that are known to favor myofibre catabolism. Experimental evidence also shows cytokine-driven upregulation of NADPH oxidases with consequent ROS accumulation, mitochondrial DNA injury, and loss of membrane potential, thereby compromising electron-transport-chain function. Excess ROS can trigger mitochondrial permeability-transition-pore opening, collapsing membrane potential and inhibiting oxidative phosphorylation. Inflammatory signaling additionally down-modulates CPT1 and β-oxidation enzymes, shifting substrate use away from fatty-acid oxidation, and pro-inflammatory stimuli can induce UCP2 and UCP3, increasing proton leak and lowering ATP yield per substrate. Working model (testable in ME/CFS). Integrating patient observations with these well-characterized pathways, we propose that chronic cytokine signaling sustains a state of bioenergetic constraint—via PDH/PGC-1α–centred suppression of oxidative metabolism and ROS-driven mitochondrial dysfunction—while concurrently engaging proteolytic programmes, together contributing to fatigue, reduced muscle performance, and atrophy in ME/CFS skeletal muscle.

chain (ETC) (Suematsu et al. 2003) (Figure 1). Excess ROS can open the mitochondrial permeability transition pore (mPTP), collapsing membrane potential and impairing oxidative phosphorylation, ultimately causing mitochondrial inactivation (Suematsu et al. 2003) (Figure 1). Moreover, mitochondrial membrane potential was found to be significantly reduced in immune cells from ME/CFS patients, further supporting systemic energy-supply dysfunction driven by chronic inflammation (Mandarano et al. 2020).

Persistent inflammation in ME/CFS can also impair mitochondrial function through the action of nitric oxide (NO) and its reactive derivatives (such as peroxynitrite), which inhibit key ETC complexes (Brown and Borutaite 2007). Pro-inflammatory cytokines such as TNFα and IL1β upregulate inducible nitric oxide synthase (iNOS). iNOS can react with metal centers in Complex I and Complex IV, significantly reducing their electron transfer efficiency and markedly lowering ATP production (Pall 2000). Consistently, studies in ME/CFS patients report decreased enzymatic activity of skeletal muscle citrate synthase, Complex II (succinate dehydrogenase), and Complex IV (cytochrome c oxidase), confirming impaired ETC function (Rutherford et al. 2016). Another key finding is reduced mitochondrial coenzyme Q10 (CoQ10) levels in ME/CFS, which correlate inversely with fatigue severity and underscore mitochondrial dysfunction as a biological basis for clinical fatigue (Rutherford et al. 2016).

In the context of mitochondrial dysfunction, muscle energy metabolism undergoes compensatory reprogramming, shifting from reliance on fatty acid oxidation and oxidative phosphorylation to anaerobic glycolysis—a rapid yet inefficient ATP-generating pathway that leads to lactate accumulation, acidosis,

and impaired muscle contraction and recovery (Sun et al. 2025). This pattern is consistent with CFS patient data showing abnormally early lactate accumulation on repeat CPET and metabolic signatures compatible with impaired pyruvate dehydrogenase (PDH) function (Fluge et al. 2016; Lien et al. 2019). Inflammatory states contribute to this metabolic shift by suppressing the expression of mitochondrial fatty-acid transport enzymes (like CPT1) and β-oxidation enzymes, decreasing muscle lipid utilization while enhancing glucose dependence (Batista-Gonzalez et al. 2019) (Figure 1). In endotoxemia/sepsis, inflammatory signaling suppresses the PPAR-α/PGC-1 axis and downstream fatty-acid oxidation genes (e.g., CPT1, MCAD), thereby attenuating mitochondrial biogenesis and β-oxidation; in parallel, stabilization of HIF-1α and induction of PDK inhibit PDH, while increased GLUT1 expression enhances glucose uptake—together shifting energy supply toward glycolysis (Vandewalle et al. 2022; Shimada et al. 2022; Zeng et al. 2021). This coordinated switch (↓FAO/OXPHOS; ↑glycolysis) is a conserved response to acute inflammation and provides a mechanistic analogue and testable hypothesis for how chronic low-grade inflammation could act in ME/CFS. Moreover, TNFα upregulates mitochondrial uncoupling proteins UCP2 and UCP3, as demonstrated in mice models where TNFα injections significantly increased UCP2/UCP3 mRNA in skeletal muscle (Rial et al. 2010) (Figure 1). This induces proton leak, dissipating the electrochemical gradient as heat and further reducing ATP synthesis efficiency (Rial et al. 2010) (Figure 1). This inflammation-driven uncoupling–energetic-waste axis has been documented in cachexia and other chronic inflammatory/infectious states, characterized by reduced mitochondrial coupling efficiency (increased uncoupling), lower ATP yield per unit substrate, and concomitant losses in muscle strength and endurance (Busquets et al. 1998; Dolly et al. 2020). These features parallel the energy-inefficient metabolic adaptation described here, supporting a shared inflammation-induced mechanism of energetic wastage underlying chronic fatigue conditions (Busquets et al. 1998; Li et al. 2024). Consequently, chronic inflammation weakens aerobic ATP pathways, reinforces anaerobic glycolysis, and promotes UCP-mediated uncoupling, creating a vicious cycle of energy deficit that impairs muscle function and reduces endurance (Sun et al. 2025; Rutherford et al. 2016).

In response to mitochondrial dysfunction, cells typically activate key transcription factors such as PGC1α to stimulate mitochondrial biogenesis and restore energy homeostasis (Abu Shelbayeh et al. 2023). However, inflammatory mediators that converge on NF-κB/p38 signaling can impair this compensatory mechanism. In this context, we discuss three prototypical signals—IL-6, TNF-α, and TWEAK (TNFSF12). We include TWEAK here not because it is routinely reported as elevated in ME/CFS cohorts, but because it is a TNF-superfamily cytokine that signals through the Fn14 receptor, activates canonical NF-κB and p38-MAPK, and has been shown to repress PGC-1α and oxidative gene programs in skeletal muscle and kidney, reduce mitochondrial content, and worsen exercise tolerance—thus mechanistically paralleling the effects of IL-6/TNF-α on the PGC-1α node (Tajrishi et al. 2014; Sato et al. 2013). These cytokines activate NFκB and p38-MAPK signaling pathways, which in turn downregulate PGC1α expression and activity, thereby weakening mitochondrial biogenesis (Palomer et al. 2008; Ruiz-Andres et al. 2016) (Figure 1). A study using a cardiomyocyte model found that TNF-α suppresses the expression of PGC-1α via this pathway, thereby shifting cellular metabolism toward anaerobic glycolysis (Palomer et al. 2008). Similarly, in a mouse kidney injury model, TWEAK also inhibits PGC1α and its downstream targets via NFκB activation and histone deacetylation; this suppression is reversed by NFκB or HDAC inhibitors (Ruiz-Andres et al. 2016). Reviews further demonstrate that reduced PGC1α under inflammatory conditions diminishes antioxidant gene expression, exacerbating ROS and reinforcing NFκB activation in a bidirectional negative feedback loop, thereby eroding mitochondrial quantity and quality (Abu Shelbayeh et al. 2023). By analogy to these non-ME/CFS inflammatory models—and given reports of low-grade inflammation and bioenergetic impairment in ME/CFS—we therefore consider TWEAK alongside IL-6/TNF-α as a mechanistic exemplar of cytokine-driven repression of PGC-1α, which could plausibly reinforce a bidirectional ROS–NF-κB/p38 loop that chronically limits ATP availability and aggravates fatigue.

This mechanism has also been prominently observed in other diseases, further supporting its relevance in ME/CFS. Patients with long COVID frequently experience muscle weakness and exercise intolerance, symptoms that are linked to a persistent low-grade inflammatory state even after viral clearance (Chen et al. 2025). Studies have shown sustained mitochondrial dysfunction in skeletal muscle following COVID-19 infection, along with elevated levels of IL6 and TNFα, closely resembling the pathophysiological features observed in ME/CFS (Chen et al. 2025). Cancer-related fatigue exhibits similar characteristics. In patients with advanced-stage cancer, increased IL6 and TNFα levels strongly correlate with subjective fatigue scores (Inagaki et al. 2008). In autoimmune conditions such as rheumatoid arthritis and multiple sclerosis, the use of IL6 receptor blockers or TNFα antagonists not only reduces inflammatory activity but also significantly alleviates fatigue symptoms (Jiao and Guo 2022). Taken together, findings from adjacent conditions (long COVID, cancer-related fatigue, autoimmune disease) support the plausibility that inflammation can drive mitochondrial dysfunction; by analogy, this suggests testable ME/CFS hypotheses—namely that low-grade cytokine activity will co-occur with impaired mitochondrial coupling and worse fatigue, especially after exertion—without implying disease equivalence. Of particular interest are non-classical inflammatory mediators such as HMGB1, which have also been associated with fatigue severity in multiple chronic conditions. By activating pathways such as TLR4, HMGB1 may sustain sterile inflammation, potentially playing a similar pathogenic role in ME/CFS (Yang et al. 2010).

In summary, pro-inflammatory cytokines such as IL6, TNFα, and HMGB1 inflict synergistic damage on skeletal muscle mitochondria via multiple mechanisms. Upon activation of NADPH oxidase and iNOS, these cytokines generate excessive ROS and nitrogen species (RNS), which cause lipid peroxidation of mitochondrial membranes, protein nitration, DNA damage, and collapse of membrane potential, thereby suppressing the activity of key electron transport chain complexes (I/III/IV) (Rutherford et al. 2016). The "TLR radical cycle" (or Harm Redox cycle) model posits that this chronic oxidative–nitrosative stress perpetually inhibits mitochondrial ATP production while amplifying inflammatory signaling in a self-sustaining,

energy-depleting, and inflammation-maintaining vicious cycle (Morris et al. 2015). Indeed, ME/CFS patients exhibit reduced mitochondrial membrane potential and impaired oxidative phosphorylation capacity in both skeletal muscle and immune cells, indicative of persistent energy deficiency (Mandarano et al. 2020; Castro-Marrero et al. 2021). Additionally, these cytokines downregulate fatty acid transporters and β-oxidation enzymes, forcing a metabolic shift to anaerobic glycolysis and leading to lactate accumulation, acidosis, and increased muscle fatigue (Batista-Gonzalez et al. 2019). Moreover, TNFα upregulates mitochondrial uncoupling proteins (UCP2/UCP3), promoting proton leak and dispersing the proton gradient as heat—further diminishing ATP synthesis efficiency (Rial et al. 2010; Busquets et al. 1998). Similar mechanisms have been observed in cachexia, chronic infections, and multiple sclerosis, and are closely associated with fatigue symptoms (Busquets et al. 1998; Li et al. 2024; Morris et al. 2015).

Based on these mechanisms, mitochondria have emerged as a critical target in addressing somatic fatigue in ME/CFS. Multiple clinical studies demonstrate that interventions aimed at improving mitochondrial function—such as supplementation with the antioxidant CoQ10 and mitochondrial substrates—can significantly alleviate fatigue and enhance quality of life in ME/CFS patients (Castro-Marrero et al. 2021; Tsai et al. 2022). In a randomized, double-blind placebo-controlled trial involving 207 ME/CFS patients, daily supplementation with 200 mg CoQ10 and 20 mg NADH for 12 weeks led to significant improvements in fatigue perception (measured by FIS-40), sleep quality, and health-related quality of life (Castro-Marrero et al. 2021). Meta-analyses have confirmed CoQ10's efficacy in reducing fatigue across chronic fatigue and related conditions, showing a moderate effect size and dose-duration dependence (Tsai et al. 2022). Additionally, mitoquinone mesylate (MitoQ), a mitochondria-targeted ubiquinone derivative, has been shown to attenuate mitochondrial oxidative damage in humans during exercise and in preclinical disease models (Williamson et al. 2020). The positive effects of these interventions reinforce the central pathogenic role of mitochondria in ME/CFS and support an integrated therapeutic approach—combining anti-inflammatory, antioxidant, and mitochondrial-support strategies—as a promising direction for treating physical fatigue.

3.2 | Inflammatory Damage and Atrophy of the Muscle System

In skeletal muscle, protein homeostasis is maintained by a delicate equilibrium between synthesis and degradation (Sato et al. 2014). The PI3K/Akt/mTOR signaling pathway promotes anabolic activity by enhancing mRNA translation and inhibiting proteolysis (Sato et al. 2014). Conversely, catabolic stimuli such as fasting, disuse, or stress activate kinases and transcription factors, including ERK, JNK, p38 MAPK, AMPK, NFκB, AP1, p53, and FoxO. This triggers both the ubiquitin–proteasome system (UPS) and the autophagy–lysosome system (ALS), which serve as the main mediators of muscle protein breakdown (Sato et al. 2014). These events converge on FoxO nuclear translocation, which upregulates "atrogenes"—including the E3 ubiquitin ligases MuRF1 (TRIM63) and Atrogin-1/MAFbx—thereby accelerating the degradation of myofibrillar proteins and inducing muscle fiber atrophy (Sandri et al. 2004). Experimental evidence from cultured myotubes and animal models demonstrates that persistent FoxO3 activation robustly increases Atrogin1 expression and causes significant muscle wasting, whereas FoxO inhibition mitigates atrophy even under catabolic conditions (Sandri et al. 2004). Thus, muscle mass and function depend on the antagonistic balance between the anabolic PI3K/Akt/mTOR axis and the catabolic FoxO/UPS/ALS pathways (Kaiser et al. 2022).

In ME/CFS patients, this protein homeostasis becomes disrupted, and signs of muscle atrophy and functional decline are frequently reported. Patients often experience marked exercise intolerance and excessive muscle fatigue (Rutherford et al. 2016; Bizjak et al. 2024). Recent human skeletal-muscle studies led by Wüst have reported post-exertional myopathic changes in cohorts with exertional intolerance (e.g., long COVID), including myofiber structural abnormalities, reduced oxidative capacity, and microvascular alterations, which co-occur with exercise intolerance and symptom exacerbation within those cohorts (Appelman et al. 2024). These tissue-level observations provide a rigorous pre–/post-exertion template—paired muscle sampling with multimodal readouts (capillary density/rarefaction, fiber-type distribution, high-resolution bioenergetic indices)—that can be deployed in ME/CFS to resolve the time course of PEM-linked bioenergetic impairment. Muscle-specific studies reveal bioenergetic impairments, with a shift toward anaerobic glycolysis during mild exercise, evidenced by excessive lactate production and slowed post-exercise lactate clearance (Rutherford et al. 2016). This metabolic preference leads to rapid accumulation of acidic metabolites during muscle work, which may explain why ME/CFS patients feel extreme fatigue and pain after minimal activity (Rutherford et al. 2016). Additionally, the metabolomic signature in ME/CFS indicates impaired oxidative energy production and increased protein catabolism. In a cohort of 200 ME/CFS patients, serum 3-methylhistidine—a marker of muscle protein breakdown—was significantly elevated, along with increased expression of PDK1, PDK2, and PDK4 in peripheral blood mononuclear cells, suggesting inhibition of the pyruvate dehydrogenase complex and a reliance on glycolytic and ketone-based metabolism (Fluge et al. 2016) (Figure 2). Ultrastructural analyses have also shown mitochondrial damage, particularly in subsarcolemmal regions of skeletal muscle, indicating compromised oxidative "powerhouses" (Scheibenbogen and Wirth 2025). Moreover, analogous patterns have emerged in post-viral fatigue syndromes (e.g., long COVID), where focal muscle fiber necrosis alongside satellite cell–mediated regeneration has been observed post-exercise—consistent with repeated micro-damage and PEM, mirroring ME/CFS muscle pathology (Scheibenbogen and Wirth 2025). Collectively, these findings suggest that even though ME/CFS is not primarily a muscular disease, the muscle system in these patients experiences low-grade inflammatory injury, mitochondrial dysfunction, and catabolic stress, placing them at heightened risk of muscle atrophy and reduced strength.

Inflammatory responses are believed to link immune dysregulation in ME/CFS with muscle atrophy. In chronic inflammation, pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IFN-γ, IL-17) induce skeletal muscle protein degradation via specific signaling pathways (Ji et al. 2022). IL-6, elevated in wasting states, impairs muscle protein homeostasis through the gp130/

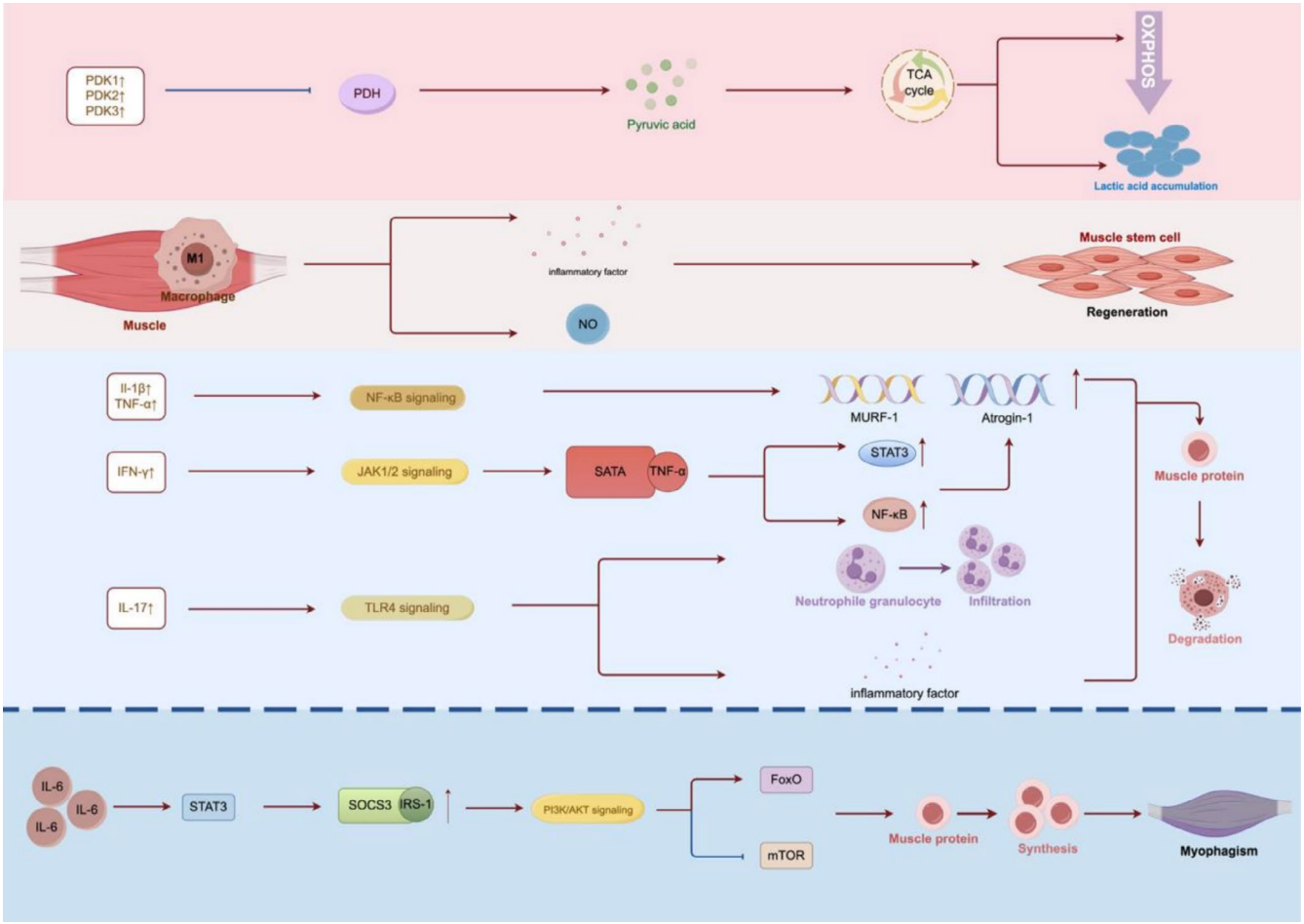

FIGURE 2 | Inflammation-linked bioenergetic and proteostatic disturbance in ME/CFS skeletal muscle: ME/CFS observations and model-derived hypotheses. *ME/CFS observations*. In ME/CFS, upregulation of *PDK1, PDK2, and PDK4* has been reported in circulating cells, consistent with *pyruvate dehydrogenase (PDH) constraint* and reduced entry of pyruvate into the TCA cycle. Clinically and physiologically, patients show *reduced oxidative phosphorylation capacity* and *excess lactate accumulation* during repeat exertion. Mechanistic synthesis (model-derived). Building on established inflammatory pathways, IL-6 activates STAT3, inducing SOCS3, which interacts with and promotes degradation of IRS-1. This attenuates PI3K/Akt signaling—removing restraint on FoxO and reducing mTOR-dependent protein synthesis—thereby shifting the balance toward protein breakdown and muscle wasting. TNF-α and IL-1β activate NF-κB, increasing transcription of the atrogenes MuRF1 and Atrogin-1 and facilitating degradation of structural myofibrillar proteins. IFN-γ engages JAK1/2–STAT signaling and, in combination with TNF-α, further augments STAT3 phosphorylation and NF-κB activity, synergistically amplifying atrogene expression and accelerating proteolysis. IL-17 can drive TLR4-dependent cascades that recruit neutrophils and secondary mediators, reinforcing local inflammatory stress. With aging, senescence-biased (M1-like) macrophages accumulate in muscle, produce nitric oxide and pro-inflammatory cytokines, damage adjacent tissue, and suppress satellite-cell regenerative capacity. Working model. Integrating these ME/CFS observations with well-characterized inflammatory pathways, we propose a testable framework in which chronic cytokine signaling sustains bioenergetic constraint (via PDH inhibition and downstream oxidative deficits) and catabolic remodeling (via NF-κB/FoxO-centred atrogene programmes), thereby contributing to fatigue, diminished strength, and atrophy in ME/CFS skeletal muscle.

JAK2/STAT3–SOCS3 axis. STAT3 activation upregulates SOCS3, which interacts with IRS1 promoting its degradation and thereby blocking the PI3K/Akt pathway's downstream suppression of FoxO and activation of mTOR—resulting in reduced protein synthesis, increased breakdown, and muscle wasting (Ji et al. 2022) (Figure 2). TNFα and IL1β act as catabolic factors by activating the NFκB pathway to drive transcription of atrogenes such as MuRF1 and Atrogin1. NFκB binding to the MuRF1 promoter enhances structural protein ubiquitination via the UPS (Ji et al. 2022) (Figure 2). IFNγ synergizes with TNFα via JAK1/2–STAT signaling and NF-κB, collectively amplifying atrogene expression and initiating a cachexia-like gene program (Ma et al. 2017) (Figure 2). IL-17, produced by Th17 cells, also contributes to muscle atrophy. Overexpression in animal models induces TLR4-dependent atrophy, marked by neutrophil infiltration and amplification of local inflammation (Tang et al. 2010) (Figure 2). Together, these cytokines suppress protein synthesis (such as via IL-6/SOCS3 inhibiting Akt) while promoting degradation (via NF-κB/FoxO-driven UPS and autophagy), and also trigger oxidative stress and mitochondrial dysfunction—further weakening muscle fibers and enhancing fatigue and damage (Ji et al. 2022; Ma et al. 2017). Notably, chronic activation of the FoxO transcription factors emerges as a central hub. In chronic inflammatory models, FoxO-driven autophagy and UPS hyperactivation are key drivers of atrophy (Milan et al. 2015). Muscle-specific FoxO knockout mitigates atrophy under inflammatory or nutritional stress, indicating the pathway's critical role (Milan et al. 2015).

In addition to soluble cytokines, immune cells themselves may directly contribute to localized inflammatory damage in muscle. In ME/CFS patients, substantial evidence indicates a state of chronic immune activation and dysregulation, which may enable immune cell–mediated muscle injury (Eaton-Fitch et al. 2024; Sun et al. 2024). Specifically, abnormalities in peripheral blood immune cells have been reported: the proportion of "effector" T lymphocytes is often elevated, while NK cells are reduced in both frequency and cytotoxic activity (Sun et al. 2024). Numerous studies have documented impaired NK cytotoxic function and altered T cell phenotypes—such as shifts in memory subsets and signs of overactivation (Rivas et al. 2018). These changes resemble immune alterations seen in chronic infections and aging, but they are not equivalent: in chronic infections, persistent antigen load and a sustained pro-inflammatory set point drive terminal $CD8^+$ T-cell exhaustion and NK dysfunction, often with tissue inflammatory infiltration (Saeidi et al. 2018; Utzschneider et al. 2020); in physiologic aging, thymic involution, homeostatic proliferation, and inflammaging lead to telomere attrition and accumulation of $CD28^-CD57^+/PD\text{-}1^+$ phenotypes (Liu et al. 2023; Huang et al. 2024). By contrast, in ME/CFS, similar exhaustion/senescence-like signatures are detected under low-grade, often fluctuating inflammation rather than overt myositis—suggesting accelerated immune biological aging as a plausible framework for ME/CFS (Montoya et al. 2017; Rajeevan et al. 2018; Iu et al. 2024). Consistent with this framework, a large study measuring leukocyte telomere length in ME/CFS reported significantly shorter telomeres—equivalent to ~10–20 years of additional aging—relative to age-matched controls, supporting an immunosenescent phenotype and reduced proliferative reserve (Rajeevan et al. 2018; Bellon and Nicot 2017). Consistent with this, $CD8^+$ T cells in ME/CFS exhibit an exhausted phenotype—including increased expression of inhibitory receptors and loss of proliferative potential—comparable to end-stage or senescent T cells seen in chronic infection or aging (Iu et al. 2024). These exhausted $CD8^+$ T cells, often $CD28^-$, $CD57^+$, and $PD1^+$, show weakened cytotoxicity yet may continue producing inflammatory mediators such as IFNγ and TNFα, and fail to clear latent infections, thereby perpetuating a chronic low-grade inflammatory environment (Van Campenhout et al. 2025; McLane et al. 2019).

Immunosenescence is typically accompanied by the development of a SASP, in which senescent or exhausted immune cells—without overt acute infection—secrete high levels of pro-inflammatory cytokines, matrix-degrading proteases, growth factors, and other bioactive substances, resulting in chronic sterile inflammation (inflammaging) (He et al. 2021). Within skeletal muscle, this process parallels age-related sarcopenia, as senescent cells—including immune cells—accumulate with age, secreting IL-6, IL-1β, and TNFα that promote a chronically catabolic microenvironment (He et al. 2021). While transient SASP can aid in tissue repair by recruiting inflammatory cells and activating satellite cell regeneration, sustained high-level SASP is deleterious. Studies found that senescent M1-like macrophages in aged muscle continuously release NO and inflammatory mediators that damage adjacent tissue and impair satellite cell regenerative capacity (He et al. 2021) (Figure 2). In animal models, removal of these senescent immune cells—such as via senolytic agents—attenuates inflammation-induced muscle atrophy and restores muscle function, directly demonstrating that SASP from senescent immune cells drives chronic muscle degeneration (Liu et al. 2022). Extrapolating to ME/CFS, if immune cells exhibit a premature senescent phenotype, their SASP-driven inflammatory milieu within muscle may similarly disrupt protein balance, promote atrophy, and contribute to fatigue.

Although direct histological proof of extensive immune-cell infiltration in ME/CFS muscle tissue is limited (muscle biopsy is not routine), mechanistic insights can be inferred from other inflammatory myopathies and relevant models. In idiopathic inflammatory myopathies (IIM)—such as polymyositis (PM) and dermatomyositis (DM)—muscle biopsies frequently reveal dense infiltration of lymphocytes and macrophages. In PM, cytotoxic $CD8^+$ T cells invade and destroy muscle fibers, often clustering around non-necrotic fibers, indicating antigen-driven immune attack (Danielsson et al. 2020). Activated M1-like macrophages surround damaged fibers, releasing proteases and ROS that exacerbate tissue injury (Tu and Li 2023). In inclusion body myositis (IBM)—a chronic, age-associated IIM—the infiltrating $CD8^+$ T cells are often terminally differentiated and senescent ($CD28^-$, $CD57^+$), clonally expand in muscle, and persistently target fibers (Greenberg et al. 2016). The degree of their infiltration correlates with blood levels of similar large granular lymphocytes. Beyond autoimmune myopathies, severe infections—such as COVID-19—can also result in immune-cell–mediated muscle damage. Post-mortem and biopsy studies of severe COVID-19 patients report type II fiber atrophy and T-cell/macrophage infiltrates with muscle fiber necrosis, demonstrating that immune activation can drive muscle pathology in those conditions (Suh et al. 2021). By comparison, post-exertional muscle changes documented in long-COVID cohorts emphasize non-destructive yet functionally significant alterations—microvascular constraints and impaired oxidative phosphorylation—observed within those cohorts and methodologically pertinent to hypothesis-driven testing in ME/CFS (Appelman et al. 2024). Taken together, within these diseases, activated or senescent immune cells are capable of causing inflammatory muscle injury and atrophy. In ME/CFS, relevance is addressed by testing whether subclinical perimuscular immune signaling with comparable effector features is present and tracks with fatigue and PEM-related bioenergetic deficits.

Although there is no direct histological evidence confirming substantial immune-cell infiltration in the skeletal muscle of ME/CFS patients—since muscle biopsy is not routine—evidence from other inflammatory myopathies and disease models helps build a plausible inference chain. ME/CFS is likely to involve low-grade, chronic antigen-driven immune activation, such as from latent viruses (e.g., EBV, HHV6), which the immune system fails to clear due to regulatory defects, potentially resulting in subclinical muscle inflammation (Sokolovska et al. 2024). Even limited immune cell trafficking into muscle could expose the local microenvironment to cytokines (IL6, TNFα, etc.) and chemoattractants, driving persistent proteolytic signaling (Muñoz-Cánoves et al. 2013). Furthermore, chronic fatigue and reduced activity lead to disuse atrophy, triggering FoxO-mediated upregulation of atrogenes, which synergizes with inflammatory catabolism (Milan et al. 2015). From an immunosenescence perspective, ME/CFS patients exhibit early aging of immune cells—such as T-cell exhaustion, NK-cell dysfunction, and pro-inflammatory

macrophage accumulation—that creates a persistent inflammatory damage in muscle tissue. These mediators activate pathways including NFκB, JAK/STAT3, and FoxO to upregulate MuRF1 and Atrogin1, activating ubiquitin-proteasome and autophagy–lysosome systems, inhibiting protein synthesis, and promoting muscle protein degradation and atrophy (Ji et al. 2022; Peris-Moreno et al. 2020). Although ME/CFS research has largely focused on immune and neuroendocrine dysregulation, emerging data highlight that peripheral tissue pathology—including skeletal muscle dysfunction—plays a crucial role in chronic fatigue (Rutherford et al. 2016; Fluge et al. 2016). Therefore, investigating the causal relationship between immune-mediated muscle damage and fatigue, and whether targeting immunosenescence or inflammatory pathways can ameliorate muscle pathology and fatigue in ME/CFS, represents a vital direction for future research.

4 | Neuro–Endocrine–Immune Axis Dysfunction

4.1 | Blunted HPA Axis Response and Sustained Sympathetic Activation

Following our discussion on how chronic inflammation and muscle disuse disrupt muscle metabolism and proteostasis, it is essential to examine how peripheral tissue damage feeds back through the neuro–endocrine–immune axis, particularly via dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis. Under normal physiology, hypothalamic CRH stimulates pituitary ACTH, which in turn triggers adrenal cortisol (CORT) release, forming the CRH → ACTH → cortisol axis (Sheng et al. 2020). Cortisol exhibits a robust circadian rhythm—low at midnight, peaking upon awakening, and declining through the day under control of the suprachiasmatic nucleus (SCN)—with negative feedback onto CRH and ACTH to maintain homeostasis (Sheng et al. 2020). In ME/CFS patients, however, this axis becomes hypofunctional, featuring mild hypocortisolism, blunted diurnal variation, and attenuated cortisol responses to stressors such as social stress tests or low-dose ACTH/insulin, alongside exaggerated negative feedback sensitivity in dexamethasone suppression tests (Zhang and Wang 2024). As a result, cortisol insufficiently restrains inflammation, while a persistently activated sympathetic nervous system and reduced vagal tone promote chronic low-grade inflammation, pain sensitization, and disrupted sleep–wake cycles (Zhang and Wang 2024). This hormonal imbalance creates a state akin to adrenal insufficiency, marked by fatigue, orthostatic intolerance, and malaise—symptoms mirrored in Addison's disease and observed in post-viral syndromes like Long COVID, where low cortisol predicts persistent fatigue (Klein et al. 2023; Lee et al. 2025; Munir et al. 2017). Although small trials of low-dose glucocorticoid supplementation have yielded temporary fatigue relief, long-term benefits are limited and side effects notable (Nijhof et al. 2014). These findings suggest a vicious feedback loop: chronic inflammation suppresses the HPA axis, weakening anti-inflammatory control, which in turn sustains immune dysregulation and peripheral tissue damage—further potentiating fatigue via neuroendocrine–immune axis disruption.

Meanwhile, sustained sympathetic nervous system (SNS) activation plays a crucial role in ME/CFS. Many patients exhibit signs of autonomic dysfunction, such as orthostatic intolerance (e.g., orthostatic hypotension or tachycardia), thermoregulatory abnormalities, and peripheral vascular dysregulation—indicative of heightened sympathetic tone (Garner and Baraniuk 2019). Objective measures show that ME/CFS patients have elevated plasma norepinephrine and epinephrine levels at rest, with exaggerated or dysregulated catecholamine responsiveness during exercise and postural changes (Lim and Torpy 2000; Hendrix et al. 2025). A recent meta-analysis confirmed significantly higher baseline adrenaline and adrenergic receptor expression, alongside atypical catecholaminergic responses (Hendrix et al. 2025). This chronic adrenergic overactivation likely arises as a compensatory mechanism for HPA axis hypofunction, stepping in to maintain cardiovascular homeostasis when cortisol output is insufficient (Lim and Torpy 2000). However, prolonged SNS hyperactivity is itself pathological—leading to raised heart rate, redistribution of blood flow away from the gut, and a "wired but tired" state (Brinth et al. 2019). Importantly, SNS and immune systems are tightly interconnected. Acute catecholamine release can transiently mobilize NK cells and neutrophils, but chronic exposure can lead to adrenergic receptor desensitization, loss of immunomodulatory control, and immune dysregulation (Jürgens et al. 2024). Indeed, repeated β-adrenoceptor stimulation is linked to catecholamine resistance, dampened immune responses, and imbalances in pro- and anti-inflammatory signaling (Jürgens et al. 2024). Thus, in ME/CFS, the co-occurrence of HPA axis suppression and SNS activation constitutes an "inappropriate stress-response syndrome"—characterized by low cortisol, high catecholamines, persistent inflammation, and systemic dysregulation (Lim and Torpy 2000; Jameson 2016). This dual-axis malfunction undermines stress reactivity and inflammation control, fueling a vicious cycle of inflammation, energy inefficiency, and chronic fatigue (Jameson 2016).

4.2 | Neuroinflammation and Cerebrovascular Dysregulation

Converging evidence indicates CNS structural and functional abnormalities in ME/CFS (Nelson et al. 2021; Lange et al. 2005; Caseras et al. 2006; Shan et al. 2018). MRI studies frequently describe alterations in white and gray matter together with aberrant brainstem-centric connectivity, both within the brainstem and between the brainstem and distributed cortical networks (Nelson et al. 2021). Given the brainstem's pivotal role in autonomic integration, recurrent reports of brainstem structural/functional abnormalities in ME/CFS are mechanistically salient (Nelson et al. 2021; Shan et al. 2020). Functional imaging aligns with this picture: relative to controls, patients recruit additional task-related regions yet exhibit attenuated or delayed BOLD responses, consistent with impaired neurovascular coupling (NVC) (Lange et al. 2005; Caseras et al. 2006; Shan et al. 2018). Mechanistically, these central alterations are compatible with glial dysregulation and chronic neuroinflammatory signaling (Nelson et al. 2021). In support ^{11}C-(R)-PK11195 TSPO-PET demonstrates elevated binding across multiple regions in ME/CFS, with regional signal tracking the severity of cognitive impairment and pain, consistent with a glia-associated neuroinflammatory signal; importantly, because TSPO is not cell-type specific, PET cannot apportion microglial versus astrocytic

contributions (Nakatomi et al. 2014). Cohort and methodological heterogeneity further motivate standardized, multicenter acquisition/analysis pipelines to enhance reproducibility. Taken together, these imaging findings relate to symptom burden: task-evoked BOLD abnormalities and regional TSPO signal track cognitive complaints and pain, supporting a central contribution to fatigue beyond peripheral muscle metabolism (Shan et al. 2020; Nakatomi et al. 2014).

Cerebrovascular physiology is likewise perturbed. Orthostatic intolerance (OI)—present in over half of adults with ME/CFS and characterized by orthostatic dizziness, visual blurring, tachycardia, nausea, or syncope that improves supine (Christopoulos et al. 2025)—is recognized as a core domain in the IOM/NAM 2015 diagnostic framework (Populations BotHoS and Syndrome CotDCfMECF 2015). Quantitative head-up tilt studies consistently demonstrate substantial CBF reductions during orthostatic stress, with the magnitude of decline correlating with OI severity, implicating orthostatic cerebral hypoperfusion in symptom expression (van Campen, Verheugt, et al. 2020). Notably, CBF decrements occur both in classical autonomic phenotypes (POTS, delayed orthostatic hypotension) where HR/BP control is abnormal and in patients with ostensibly normal HR/BP responses, indicating broader autonomic/vascular dysregulation (van Campen, Verheugt, et al. 2020; van Campen et al. 2021; van Campen, Rowe, et al. 2020a). Declines in end-tidal CO2 (ETCO2) correlate with CBF reductions during tilt, identifying hypocapnia as a physiological amplifier of orthostatic hypoperfusion and underscoring the need to monitor ETCO2 alongside HR/BP (van Campen et al. 2023). Functionally, chronic or recurrent hypoperfusion plausibly contributes to "brain fog": cognition depends on adequate, stable CBF and intact NVC; sustained perfusion constraints degrade cognitive performance and task-evoked responses (van Campen, Verheugt, et al. 2020; van Campen, Rowe, et al. 2020b). In quantitative tilt cohorts, greater orthostatic CBF reductions parallel worse orthostatic symptom scores and cognitive decrement during/after tilt, reinforcing a central hypoperfusion pathway to fatigue ("brain fog") (van Campen, Verheugt, et al. 2020; van Campen et al. 2021; van Campen, Rowe, et al. 2020b). Importantly, lower resting CBF (global or regional) has been observed in subsets of ME/CFS even without formal OI, though resting perfusion and whole-brain morphometric findings remain heterogeneous across studies, reflecting cohort and methodological variability (Shan et al. 2020; Biswal et al. 2011). To resolve mechanistic timing, we recommend standardized tilt- or exertion-based paradigms that synchronously acquire BP, CBF, and $ETCO_2$ alongside fMRI/fNIRS, enabling quantitative assessment of dynamic cerebral autoregulation and neurovascular coupling and formal testing of the temporal sequence in which posture or exertional stress precedes perfusion/NVC impairments, which are then followed by changes in symptoms (Claassen 2016). Through impaired brainstem/autonomic integration and NVC, central deficits can down-regulate cerebrovascular support to working muscle and alter adrenergic signaling, thereby interfacing with the β-$_2$adrenergic receptor (β-$_2$AR) dysfunction detailed below (Barnden et al. 2016; Scheibenbogen et al. 2018). Collectively, central neuroinflammatory alterations and cerebrovascular dysregulation co-occur and interact in ME/CFS, restricting cerebral oxygen delivery and disrupting NVC, thereby intensifying cognitive dysfunction, fatigue, and autonomic complaints, and coupling with HPA axis hypofunction and SNS hyperactivation described earlier.

4.3 | β-$_2$AR Receptor Dysfunction

Chronic sympathetic overactivation in ME/CFS leads to β-$_2$AR dysfunction on peripheral target cells. Sustained high levels of norepinephrine/epinephrine cause β-$_2$AR downregulation and desensitization, significantly reducing signaling efficiency despite elevated catecholamines (Jürgens et al. 2024). Animal and human studies show chronic stress induces β-AR desensitization, disrupting downstream cAMP/PKA signaling (Jürgens et al. 2024). In the immune system, this undermines catecholamine-mediated regulation. Normally, β_2 activation suppresses pro-inflammatory cytokines (e.g., TNF-α, IL-12) and enhances IL-10, but desensitization blunts this anti-inflammatory control, fostering chronic low-grade inflammation (Dragan and Latek 2024). Moreover, β-$_2$AR dysfunction impairs immunometabolism and effector function (Jürgens et al. 2024). In T cells, weak β_2 signaling limits the metabolic shift toward glycolysis and mitochondrial activation needed for proliferation and cytokine production; blocking β_2-AR enhances T cell energy and function in vitro (Farooq et al. 2023). Thus, chronic catecholamine exposure in ME/CFS likely induces T cell metabolic suppression and exhaustion, with reduced proliferation and effector cytokines (such as IFNγ) (Zha et al. 2014). This phenotype bears resemblance to immunosenescence: individuals under chronic stress often exhibit reduced naïve T cell counts, increased numbers of terminally differentiated or exhausted T cells, and a disrupted $CD4^+/CD8^+$ ratio—hallmarks of "immunological aging" (Klopack et al. 2022). Such shifts in immune cell subsets may also occur in ME/CFS, causing the immune system to resemble that of elderly individuals or cancer patients—diminished in responsiveness to novel antigens yet sustaining a chronic inflammatory milieu due to accumulation of senescent effector cells (Curriu et al. 2013). Beyond T cells, NK cell function is also markedly affected by β_2-AR dysregulation. NK cells express high levels of β_2-ARs, and their activity is tightly modulated by sympathetic input. While acute stress enhances NK cell cytotoxicity via β_2-AR-mediated mobilization into circulation, chronic stimulation suppresses this function (Jürgens et al. 2024). Long-acting β_2-AR agonists have been reported to reduce NK cell adhesion molecule activation, impairing cytotoxic targeting, and prolonged stimulation leads to receptor desensitization, resulting in complete loss of downstream signaling (Jürgens et al. 2024). Thus, under chronic high-norepinephrine conditions, NK cells may exhibit an initial suppression of function followed by desensitization, culminating in reduced viral and tumor cell clearance. Importantly, both T cells and NK cells require robust energy support to maintain effector functions; for example, NK cell cytotoxicity depends on rapid glycolytic energy production (Wang et al. 2020).

β_2-AR dysfunction further impairs the body's capacity to mobilize and utilize glucose. Under normal stress, epinephrine promotes hepatic glycogenolysis and skeletal muscle glucose uptake via β_2-ARs to meet urgent energy demands. When receptor sensitivity is diminished, however, energy mobilization is compromised, and cellular access to glucose and oxidative substrates is reduced (Lim and Torpy 2000). This leads to a state of energy

production insufficiency (Lim and Torpy 2000). The combination of inadequate energy supply and chronic inflammation creates a vicious cycle: pro-inflammatory mediators impair mitochondrial function and muscle contractility, while cellular energy deficits trigger further stress and inflammatory signaling (Walsh et al. 2021). In summary, β_2-AR dysfunction exacerbates immune hypo-responsiveness and immunosenescence (manifested as suppressed T cell metabolism and exhaustion, reduced NK cell cytotoxicity), while simultaneously impairing systemic energy mobilization. These effects collectively contribute to chronic inflammation and energy deficiency—recognized as a key mechanism underlying the persistent physical fatigue seen in ME/CFS (Klopack et al. 2022; Walsh et al. 2021). Notably, similar patterns of immunometabolic dysfunction—such as blunted catecholamine responsiveness and increased systemic inflammation—have also been observed in the elderly, individuals with long COVID, and cancer-related fatigue (Klopack et al. 2022). These parallels suggest that β_2-AR-mediated mechanisms may represent a shared pathophysiological axis across diverse chronic fatigue conditions, providing valuable insight into the pathogenesis of ME/CFS.

4.4 | Integrated Intervention Strategies Targeting Immunometabolic Dysregulation in ME/CFS

Patients with ME/CFS often exhibit immune dysfunctions, suggesting that cellular senescence or exhaustion may contribute to its pathophysiology. Studies have shown that T lymphocytes and NK cells in ME/CFS patients display metabolic dysregulation, resembling features of chronic viral infection-induced cellular exhaustion (Van Campenhout et al. 2025; Maya 2023). In a study comparing 53 ME/CFS patients with 45 healthy controls, mitochondrial membrane potential was found to be reduced in $CD8^+$ T cells, and glycolytic activity was significantly impaired in both $CD4^+$ and $CD8^+$ T cells under resting conditions (Mandarano et al. 2020). These findings indicate compromised T cell metabolic capacity, consistent with a state of persistent immune activation. A growing body of literature supports $CD8^+$ T cell exhaustion as a possible immunopathological phenotype in ME/CFS (Maya 2023), and the need for further investigation into $CD4^+$ T cell and NK cell dysfunction has been emphasized (Eaton-Fitch et al. 2024; Maya 2023). Additional studies have reported an increased proportion of $CD4^+PD\text{-}1^+$ "exhausted" T cells in peripheral blood of ME/CFS patients, along with abnormal cytokine profiles and reduced NK cell cytotoxicity (Eaton-Fitch et al. 2024; Mandarano et al. 2020), suggesting that chronic stimulation may drive T/NK cell exhaustion during a prolonged disease course. Single-cell sequencing analyses have revealed decreased frequencies of NK cells and monocytes in ME/CFS patients, accompanied by disrupted cytokine and chemokine signaling pathways, indicating persistent immune activation and a shift toward a proinflammatory state (Sun et al. 2024; Vu et al. 2024). Interestingly, this single-cell study also identified upregulation of an estrogen receptor alpha (ESRRA)-associated signaling pathway in peripheral blood cells, proposing it as a potential biomarker for ME/CFS (Sun et al. 2024). Overall, ME/CFS patients may exhibit immunosenescence-related markers such as CD28 loss and elevated CD57 and KLRG1 expression in terminally differentiated T cell subsets (Rodriguez et al. 2020); dysregulated CD45RA/RO distribution in memory T cells; and increased secretion of proinflammatory cytokines such as IL-6 and TNF-α (Rodriguez et al. 2020). These features are characteristic of age-associated immune decline but occur in younger individuals with ME/CFS, suggesting a premature or aberrant immunosenescence process. To further elucidate these mechanisms, it is necessary to establish comprehensive assessment panels that integrate phenotypic markers (e.g., PD-1, KLRG1, CD57, CD28, CD45RA/RO), metabolic indicators (e.g., glycolytic flux, oxidative phosphorylation capacity, lipid metabolism), and cytokine profiles, which may help predict and monitor fatigue severity. As suggested by Hardcastle et al., longitudinal cohort studies tracking immune biomarkers over the disease course could provide essential evidence to validate potential biomarkers (Hardcastle et al. 2015b). Future research should incorporate multi-omics and single-cell technologies to investigate immune cell exhaustion, senescence, or energy deficiency in ME/CFS, and to assess their causal relationships and pathological relevance (Van Campenhout et al. 2025; Maya 2023).

Building on the above mechanistic insights, therapeutic strategies targeting immunosenescence and physical fatigue in ME/CFS are receiving growing attention. Among pharmacological approaches, the Toll-like receptor 3 (TLR3) agonist rintatolimod (commercial name: Ampligen) has been employed as an immunomodulator in several clinical trials. A Phase III randomized controlled trial demonstrated that after six months of treatment, patients exhibited significant improvement in exercise tolerance (Seton et al. 2024). Rintatolimod has been approved in Argentina for the treatment of severe ME/CFS, though it remains experimental in other countries (Toogood et al. 2021). IL-2 analogs also represent a potential strategy. In vitro studies have shown that IL-2 can restore the cytotoxic function of NK cells in ME/CFS patients (Eaton-Fitch et al. 2021), suggesting that activating IL-2 signaling or related pathways may enhance innate immune function. In addition, anti-exhaustion strategies targeting immune checkpoints may offer translational relevance. For instance, blockade of the PD-1 pathway can reinvigorate T cells, and studies have shown that PD-1 inhibitors can restore the function of exhausted T cells in chronic infections and cancer (Lee et al. 2015). These findings point to the potential applicability of PD-1/PD-L1 inhibitors in ME/CFS, although this remains at the theoretical stage. By contrast, attempts to suppress proinflammatory cytokines—for example, using the IL-1 receptor antagonist anakinra—have not significantly alleviated fatigue symptoms (Roerink et al. 2017). This suggests that blocking a single inflammatory pathway may be insufficient to resolve the complex symptomatology of ME/CFS, highlighting the need for more refined and targeted therapeutic strategies.

Metabolic modulators represent another major category of intervention for ME/CFS. Clinical trials have shown that supplementation with energy metabolism substrates and antioxidants can improve fatigue and quality of life in patients. Supplementation with oxaloacetate—a tricarboxylic acid (TCA) cycle intermediate—was found to significantly reduce fatigue scores in a randomized controlled trial (Cash et al. 2024). Other supplements, including L-carnitine, NADH, CoQ10, and D-ribose, have been reported to improve physical stamina, cognitive function, and sleep quality (Seton et al. 2024). High-dose vitamin C and selenium, as antioxidant nutrients, appear to be safe and well-tolerated; appropriate supplementation may help counteract

oxidative stress and alleviate symptoms (Seton et al. 2024). Traditional therapies such as acupuncture and moxibustion have also demonstrated symptom-relieving effects in clinical studies. A systematic review concluded that acupuncture may offer an advantage over sham acupuncture or Chinese herbal medicine in improving overall symptom response, although heterogeneity in study quality limits the strength of these conclusions and warrants further validation through large, high-quality randomized controlled trials (Zhang et al. 2019). In addition, neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS), have shown promise. One study reported that rTMS significantly improved orthostatic hypotension and postural balance in ME/CFS patients (Miwa and Inoue 2023), suggesting that noninvasive neural modulation or electrical stimulation therapies may help restore neuroimmune function. Exercise rehabilitation remains contentious. A 2019 Cochrane review concluded that exercise therapy probably reduces fatigue in adults meeting older case definitions; however, most included trials employed criteria that did not require post-exertional malaise and provided limited characterization of harms (Larun et al. 2019). In view of these methodological constraints and the centrality of post-exertional symptom exacerbation to contemporary case definitions, the 2021 National Institute for Health and Care Excellence guideline (NG206) recommends against programmes based on fixed incremental increases in activity, and prioritizes symptom-contingent activity management and pacing under clinical supervision (Guideline NG206 N 2021). Consistent with this guidance, we do not endorse graded exercise therapy; any physical activity should be individualized, carefully titrated to avoid provoking post-exertional symptom exacerbation, and integrated within multidisciplinary care (Grach et al. 2023).

Interventions targeting the gut microbiome are receiving increasing attention in the context of ME/CFS. Preliminary studies suggest that probiotics may improve inflammatory markers and subjective symptoms in ME/CFS patients. However, the evidence supporting their efficacy remains limited (Stallmach et al. 2024). Fecal microbiota transplantation has also been proposed as a potential therapeutic approach. One report described substantial symptom relief in the majority of ME/CFS patients following FMT from multiple healthy donors—in a small-sample study, 17 out of 21 patients reported significant improvement ranging from 65% to 95% (Stallmach et al. 2024). While these results are encouraging, randomized controlled trials are needed to confirm the long-term safety and efficacy of this intervention. Overall, current research into interventions for ME/CFS-related fatigue linked to immunosenescence reflects a growing trend toward diversification. Strategies range from antiviral and immunomodulatory therapies (e.g., rintatolimod, IL-2), anti-exhaustion approaches (e.g., PD-1 blockade), to nutritional supplementation supporting metabolism and antioxidative defense. Non-pharmacological treatments—including acupuncture, neuromodulation, exercise therapy, and microbiome-targeted interventions—have also shown promise in early studies. However, most of these findings are based on preliminary or small-scale studies and require further validation through rigorously designed randomized controlled trials.

In light of current research gaps and controversies, future studies should further delineate how immune and metabolic dysfunction interact to drive physical fatigue and PEM in ME/CFS. Standardized pre−/post-exertion muscle-assessment protocols—paired tissue sampling aligned to symptom dynamics, with synchronized microvascular, mitochondrial, and performance readouts—are feasible in exertion-intolerant cohorts and are likely to reduce between-study heterogeneity in ME/CFS, aligning measurements with the 0–48 h PEM window (Appelman et al. 2024). First, the establishment of large-scale, longitudinal cohorts is essential, with regular assessments of immune cell phenotypes, metabolic function, and clinical symptoms. Such studies would enable dynamic analyses of the relationship between candidate biomarkers and fatigue severity, thereby validating potential predictive indicators (Sun et al. 2024; Hardcastle et al. 2015b). Second, combined immuno-metabolic intervention trials should be encouraged—for example, supplementing metabolic substrates alongside immunomodulatory agents, or pairing anti-exhaustion therapies with mitochondrial enhancers—to determine whether these combinations produce synergistic effects (Van Campenhout et al. 2025; Lee et al. 2015). Additionally, targeted investigations into specific signaling pathways warrant exploration. Interventions aimed at the PD-1/PD-L1 exhaustion axis or IL-2/STAT5 signaling, regulation of TRPM3 calcium channels and associated PIP_2 signaling, and modulation of metabolic sensors such as mTOR and AMPK may offer novel strategies for addressing physical fatigue in ME/CFS (Eaton-Fitch et al. 2021; Lee et al. 2015). Finally, given the complex etiology and marked heterogeneity among patients, multi-omics approaches—including genomics, transcriptomics, metabolomics, and epigenomics—should be integrated with systems biology to identify key drivers in specific patient subgroups. This would support the development of personalized therapeutic strategies. In summary, future research must advance both mechanistic understanding and clinical validation. Through rigorous study design and interdisciplinary collaboration, this integrated approach will help build a scientific foundation for biomarker development and multimodal interventions targeting fatigue in ME/CFS.

5 | Conclusion

In summary, this review elucidates how immunosenescence contributes to the pathophysiology of physical fatigue in ME/CFS through a multifaceted network of chronic inflammation, mitochondrial impairment, and immune-metabolic dysregulation. Pro-inflammatory cytokines damage mitochondrial bioenergetics and promote protein degradation, leading to skeletal muscle dysfunction and atrophy. Meanwhile, senescent immune cells infiltrate muscle tissues and perpetuate local inflammation, while dysregulation of the neuroendocrine–immune axis further amplifies immune aging and energy imbalance. These intertwined processes form a vicious cycle that underlies the persistent and debilitating fatigue experienced by ME/CFS patients. Recognizing immunosenescence as a core mechanism not only bridges disparate findings in inflammation, metabolism, and neuroendocrine function but also offers a promising paradigm for biomarker discovery and therapeutic development. Future research should aim to validate key immunosenescence signatures in longitudinal cohorts and test the efficacy of combined interventions targeting immune, metabolic, and neuroendocrine pathways. By reframing ME/CFS through the lens

of immune aging, we may uncover novel strategies to alleviate physical fatigue and improve quality of life for affected individuals. Beyond this, immunosenescence drives maladaptive crosstalk among organ systems, whereby immune aging perturbs skeletal muscle bioenergetics, neuroendocrine feedback loops, and cerebrovascular regulation, thereby underscoring the systemic nature of ME/CFS.

Taken together, these inter-tissue signals not only clarify mechanistic pathways—from immune-driven mitochondrial injury to neuroendocrine dysregulation and cerebrovascular hypoperfusion—but also suggest measurable biomarkers such as inhibitory receptor expression on T/NK cells, circulating SASP factors (IL-6, TNF-α, HMGB1), and metabolic readouts (lactate accumulation, reduced mitochondrial membrane potential) (Mandarano et al. 2020; Iu et al. 2024; Clarke et al. 2025). Clinically, this cross-organ perspective indicates that effective interventions will likely require multimodal strategies, for example, combining immunomodulators (e.g., IL-2 analogs, checkpoint inhibitors), mitochondrial support (e.g., CoQ10, NADH, MitoQ), and neuroendocrine regulation (e.g., HPA-axis or β_2-adrenergic modulators) (Castro-Marrero et al. 2021; Eaton-Fitch et al. 2021; Germain et al. 2025). By synthesizing mechanisms, biomarkers, and therapeutic avenues, our review highlights the translational potential of targeting inter-organ communication in ME/CFS.

Author Contributions

Yingzhe Luo: conceptualization, data curation, writing – original draft, writing – reviewing and editing. **Huimin Xu:** data curation, investigation, writing – original draft, writing – review and editing. **Shaoquan Xiong:** investigation, writing – review and editing. **Jianlong Ke:** supervision, funding acquisition, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No data was used for the research described in the article.

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