Review Article

The Role of T-Cell Exhaustion as a Driver in the Development of Post-Acute Infection Syndromes: A Literature Review

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This literature review summarizes recent studies on T cell exhaustion and its role in post-acute infection syndromes (PAIS), including Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID. It synthesizes the current evidence on how persistent immune dysfunction contributes to the chronic symptoms seen in these conditions. T cell exhaustion, marked by continuous antigen exposure, diminished effector function, and increased expression of inhibitory receptors such as PD-1, CTLA-4, TIM-3, and TIGIT, is increasingly recognized as a key factor in the pathogenesis of PAIS. Clinical and molecular studies have revealed altered T cell populations, impaired proliferative responses, and metabolic dysregulation in affected patients. Persistent viral antigens are implicated in maintaining this exhausted state, whereas neuroimmune interactions and autoimmune processes may further sustain symptomatology. Although this review did not employ a formal systematic methodology, it integrated findings from multiple studies to provide a comprehensive overview of the field. Challenges remain regarding standardized diagnostic criteria and biomarkers; however, advances in immune exhaustion markers present the potential for improved diagnosis and targeted treatments. Emerging therapeutic approaches include immune checkpoint modulation, metabolic interventions, antiviral therapy, and immunomodulation. Further research is needed to clarify the mechanisms, validate the biomarkers, and develop effective clinical interventions. Recognizing T cell exhaustion as a central mechanism offers a foundation for advancing our understanding and management of PAIS.

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 doi.org/10.32388/YDRIR2

Introduction

Post-Acute Infection Syndromes (PAIS) are a group of conditions characterized by persistent, often disabling symptoms following the resolution of an acute infection [1][2]. Historically, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) has served as a prototypical example of PAIS, with documented outbreaks and patient clusters described over several decades [3]. ME/CFS is characterized by chronic fatigue, post-exertional malaise, cognitive impairment, sleep disturbances, and autonomic dysfunction, often following a viral illness [2][4][5].

The COVID-19 pandemic has brought unprecedented attention to this class of disorders through the recognition of Long COVID, which shares many clinical features with ME/CFS but occurs following SARS-CoV-2 infection [1][2]. The global scale of Long COVID has highlighted the public health impact of PAIS and accelerated research into its underlying mechanisms [4].

Recent advances in immunology have identified immune dysregulation as a central feature of PAIS, with particular attention focused on T cell exhaustion, a dysfunctional state resulting from chronic antigen exposure, as a possible unifying mechanism underlying symptom persistence and multisystem involvement [5][6][7][8]. This review synthesizes the current evidence implicating T cell exhaustion in PAIS pathogenesis, with an emphasis on ME/CFS and Long COVID.

Methods

This literature review was conducted by searching major biomedical databases, including PubMed, Google Scholar, and Scopus, to identify relevant studies on T cell exhaustion in post-acute infection syndromes (PAIS), with a specific focus on ME/CFS and Long COVID. Searches were performed using combinations of keywords such as “T cell exhaustion,” “post-acute infection syndrome,” “ME/CFS,” “Long COVID,” and “immune dysfunction.” The search included peer-reviewed articles published up to June 2025.

Studies were selected based on their relevance to the role of T cell exhaustion in PAIS, emphasizing clinical, molecular, and immunological findings. Inclusion criteria encompassed original research articles, review papers, and clinical studies addressing immune mechanisms or therapeutic approaches related to T cell exhaustion in PAIS. Exclusion criteria included non-peer-reviewed articles, studies not available in English, and publications focusing on unrelated conditions or acute infections only.

Data extraction involved manually screening titles and abstracts for relevance, followed by a full-text review of selected articles. Key information regarding study design, patient populations, immune

parameters, and main findings was summarized narratively. Owing to the heterogeneity of the available literature and the scope of this review, no formal risk of bias assessment or protocol registration was conducted.

Given the emerging and heterogeneous nature of research on T cell exhaustion in PAIS, this literature review aims to provide an accessible synthesis of the current findings without performing a full systematic review. The objective of this study was to synthesize the current understanding and highlight emerging themes in the immunopathology of PAIS related to T cell exhaustion.

Immunopathological Mechanisms in PAIS

Overview of Immune Dysfunction

The fundamental immunological abnormalities in PAIS involve complex dysregulation of multiple immune components. Evidence has consistently pointed to chronic immune activation, inflammation, autoimmunity, and impaired cellular immune function [9][10]. Specifically, alterations in cytokine profiles, reduced natural killer (NK) cell cytotoxicity, and T cell abnormalities have been documented in both ME/CFS and Long COVID [5][11].

Persistent antigen exposure after an acute infection drives T cell exhaustion, leading to immune dysfunction and the core symptoms of PAIS (Figure 1).

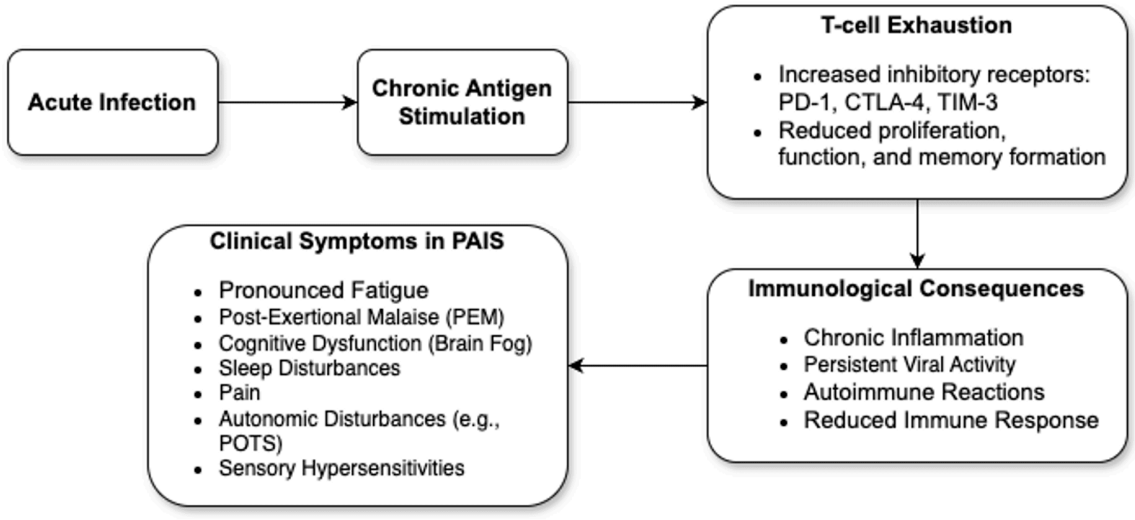

Figure 1. Persistent antigen exposure after an acute infection drives T cell exhaustion, leading to immune dysfunction and core symptoms of PAIS.

T cell Exhaustion: Definition and Significance

T cell exhaustion is a progressive dysfunction arising from persistent antigen stimulation and chronic inflammation, originally described in chronic viral infections [8][12][3]. This adaptive mechanism limits T cell activity to prevent immunopathology but impairs pathogen and tumor clearance when sustained [3][13] [14][15]. Exhausted T cells show diminished proliferation despite antigen exposure, elevated expression of inhibitory receptors (e.g., PD-1, CTLA-4, LAG-3, TIM-3, and TIGIT), and markedly reduced cytokine production, notably IFN-γ, TNF-α, and IL-2 [8][9][14][15]. At the molecular level, transcription factors, such as TOX, drive distinct transcriptional and epigenetic programs that stabilize exhaustion and hinder functional restoration [15][16][16][17][18]. Metabolic dysfunction, including impaired mitochondrial activity and altered glucose and fatty acid metabolism, further compromises T cell responses [14]. Importantly, exhausted T cells fail to develop into effective memory cells, contributing to persistent immune impairment [8][3]. These integrated phenotypic, molecular, and metabolic alterations underpin the immune dysfunction observed in chronic infections and conditions like Post-Acute Infection Syndromes (PAIS)[5][7] [17].

Molecular Characteristics of T cell Exhaustion

Exhausted T cells display distinct transcriptional and epigenetic programs compared to effector and memory T cells [3]. The transcription factor TOX plays a central role in initiating and maintaining exhaustion, with contributions from Eomes, T-bet, and NFAT [13][16]. This altered transcriptional landscape drives the increased expression of inhibitory receptors such as PD-1, CTLA-4, LAG-3, TIM-3, and TIGIT [15] [18].

Epigenetically, exhausted T cells develop a unique chromatin accessibility profile that becomes increasingly fixed over time, limiting the potential for functional restoration, even with checkpoint blockade therapy [3][13]. Metabolically, these T cells exhibit impaired mitochondrial function, reduced glucose metabolism, and diminished fatty acid oxidation capacity, all of which contribute to their decreased immune responsiveness [14]. Such metabolic dysfunction may be particularly relevant in PAIS, where systemic metabolic alterations have been observed.

Evidence for T cell Exhaustion in PAIS

Emerging evidence supports the central role of T cell exhaustion in the pathogenesis of PAIS, including ME/CFS and Long COVID. Alterations in T cell subsets have been consistently observed. Early-stage ME/CFS patients often exhibit reduced CD8+ T cell counts, whereas chronic cases show decreased CD4+ T cells and lower CD4:CD8 ratios, accompanied by impaired proliferative capacity and effector function [7][13]. These immune changes are characteristic of the exhausted T-cell phenotype.

Persistent viral antigen stimulation is a key driver of this exhaustion. Chronic infections with viruses such as Epstein-Barr Virus (EBV) and enteroviruses (notably Coxsackie B) have been implicated in sustaining antigenic pressure on T cells, promoting their dysfunction [19][20][21][22]. The chronic presence of viral antigens provides a continuous stimulus that can lock T cells into a hyporesponsive state, impeding effective immune clearance and perpetuating symptoms.

Study	Patient Group	Markers/Features Assessed	Main Findings
Cliff et al., 2019 [18]	ME/CFS	PD-1, CTLA-4, TIM-3 (flow cytometry)	Increased inhibitory receptor expression; impaired function
Saito et al., 2024 [7]	Long COVID w/ CFS	CD4+, CD8+ counts; cytokine profile	Decreased T cell counts, chronic inflammation
Eaton-Fitch et al., 2024 [6]	ME/CFS, Long COVID	PD-1, TIGIT levels; proliferation	Elevated exhaustion markers; reduced T cell proliferation
Loretelli et al., 2021 [11]	Post-COVID	PD-1 expression; cytokine secretion	Persistent high PD-1 after infection, reduced IFN-γ
Wiech et al., 2022 [23]	Long COVID	T cell subsets; exhaustion markers	Remodeling toward exhaustion proportional to severity
Iu et al., 2024 [24]	ME/CFS	TOX, Eomes (transcriptional)	Transcriptional priming for exhaustion phenotype

Table 1. Summary of Evidence for T Cell Exhaustion in ME/CFS and Long COVID

Supporting this, recent studies have demonstrated elevated expression of multiple inhibitory receptors—

such as PD-1, CTLA-4, TIM-3, and TIGIT—on circulating T cells from both ME/CFS and Long COVID patients relative to recovered controls [5][6][17][10][11]. This upregulation of inhibitory receptors is a hallmark of T-cell exhaustion and correlates with impaired immune responsiveness. Together, these findings provide compelling immunological evidence that T cell exhaustion driven by persistent viral stimuli is the fundamental mechanism underlying PAIS.

Neuroimmune Interactions in PAIS

Neuroimmune communication plays an important role in sustaining T cell exhaustion and symptom persistence in patients with PAIS. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, commonly observed in ME/CFS and Long COVID, can alter immune responses by affecting cortisol levels, which in turn influence T cell function and may reinforce exhaustion [5][23].

Autonomic nervous system dysfunction, including increased sympathetic activity, affects immune regulation. Adrenergic signaling can modulate T cell activity and contribute to the exhausted phenotype, creating a feedback loop between the nervous and immune systems [5][25]. Neuroinflammation, characterized by microglial activation, further exacerbates this crosstalk by releasing proinflammatory cytokines that affect both central and peripheral immune cells, potentially sustaining T cell dysfunction [26][27].

Molecular Mimicry and Autoimmunity

Molecular mimicry, in which pathogen-derived antigens resemble host tissues, may trigger autoimmune responses in patients with PAIS. This mechanism can promote autoreactive immune activity when exhausted T cells fail to maintain proper immune regulation. Chronic inflammation driven by T cell exhaustion may facilitate epitope spreading, worsening the autoimmune phenomena observed in some patients with PAIS [28][29][30].

Clinical Manifestations of PAIS

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long COVID exhibit remarkably similar clinical features, indicating shared underlying biological mechanisms. Recent research has implicated T cell exhaustion as a central driver of these syndromes, contributing to the multisystem symptoms observed in affected individuals [31][32].

Profound fatigue, which is a persistent and disabling tiredness that is not alleviated by rest, is a hallmark of both ME/CFS and Long COVID. This symptom is thought to reflect chronic systemic inflammation and impaired cellular energy homeostasis, both of which may be consequences of sustained immune activation and mitochondrial dysfunction [33].

Another defining feature is post-exertional malaise (PEM), characterized by a marked exacerbation of symptoms after physical or cognitive exertion. Patients often experience worsening fatigue, pain, and cognitive impairment after minimal activity. This phenomenon is hypothesized to arise from dysfunctional energy metabolism within exhausted immune cells, resulting in an inability to meet the increased energy demands during exertion [34].

Cognitive dysfunction, frequently described as “brain fog,” is highly prevalent among individuals with ME/CFS and those with Long COVID. Patients reported difficulties in memory, attention, and processing speeds. Neuroinflammation, driven by immune dysregulation and aberrant cytokine signaling, has been proposed as the underlying mechanism of these cognitive impairments [35].

Sleep disturbances are also commonly reported, with patients experiencing unrefreshed sleep and disrupted sleep architecture. Altered cytokine profiles, particularly those involved in sleep regulation, such as interleukin-6 and tumor necrosis factor-alpha, may contribute to these abnormalities[32].

In addition to these core symptoms, patients often report widespread musculoskeletal pain, autonomic dysfunction (including orthostatic intolerance and postural orthostatic tachycardia syndrome), and immune-related symptoms such as flu-like feelings, lymph node tenderness, and increased sensory sensitivity. The breadth of these manifestations suggests persistent neuroimmune interactions and inflammatory signaling associated with T cell exhaustion and broader immune dysregulation[32][34].

Together, these findings underscore the complex interplay between immune dysfunction, neuroinflammation, and metabolic disturbances in the pathogenesis of ME/CFS and Long COVID. Ongoing investigations into the specific immunological pathways involved may provide new insights into therapeutic targets for these debilitating conditions.

Conventional Clinical Approach

Diagnostic Evaluation

Currently, PAIS diagnosis relies mainly on clinical assessment and the exclusion of other conditions, as specific biomarkers are lacking [36][37]. Symptom-based criteria guide diagnosis; however, objective tests

reflecting immune exhaustion or the underlying pathophysiology have not yet been established.

Therapeutic Approaches

Treatment is primarily supportive and symptom-focused [36][38]. Common strategies include pacing activities, cognitive behavioral therapy (CBT), and graded exercise therapy (GET). However, the effectiveness of CBT and GET is debated, especially because they do not address the underlying immune dysfunction and may worsen symptoms in some patients [39][40]. No approved therapies specifically target T cell exhaustion or other immune abnormalities in patients with PAIS. Care aims to improve the quality of life, while research continues to explore targeted interventions.

Diagnostic Approaches and Biomarkers

Potential T cell Exhaustion Biomarkers

Research on diagnostic markers for PAIS has focused on identifying the signatures of T cell exhaustion. Elevated expression of inhibitory receptors such as PD-1, CTLA-4, TIM-3, and TIGIT on peripheral T cells serves as accessible markers of immune dysfunction [5][6][17]. Transcriptional profiling of exhaustion-associated genes like TOX and Eomes provides detailed molecular insights [3][13][41]. Functional assays that measure T cell proliferation, cytokine production, and metabolic capacity further characterize immune competence and exhaustion [14][17]. Integrative multi-omics approaches combining transcriptomics, epigenetics, and metabolomics are emerging to develop comprehensive biomarker panels that enable accurate diagnosis, patient stratification, and longitudinal monitoring [3][13][14].

Challenges in Biomarker Development

T cell exhaustion exists along a spectrum, with marker expression influenced by disease stage, infection, and individual variability, complicating the establishment of diagnostic criteria. The clinical heterogeneity of PAIS implies that no single biomarker can reliably capture all cases. Therefore, robust diagnosis and monitoring will likely require multiparameter panels that combine inhibitory receptor levels, transcriptional signatures, functional assays, and metabolic indicators. Ongoing research aims to validate these panels across diverse patient populations to ensure clinical applicability [5][6][3].

Therapeutic Implications of T cell Exhaustion in PAIS

Several therapeutic strategies targeting T cell exhaustion in PAIS have been explored previously. Checkpoint inhibition, which involves blocking inhibitory receptors such as PD-1 and CTLA-4, has the potential to restore the function of exhausted T cells; however, this approach requires careful dosing and monitoring to avoid autoimmune side effects [6][24]. Metabolic support strategies focus on improving mitochondrial function and glucose metabolism and providing alternative energy sources to aid T cell recovery. Nutritional supplements such as coenzyme Q10, L-carnitine, and B vitamins have shown promise but require further investigation [5][14]. Antiviral therapies targeting persistent infections, such as those caused by Epstein-Barr virus (EBV), enteroviruses, and SARS-CoV-2, may reduce chronic antigen stimulation, thus alleviating immune exhaustion [20][42]. Additionally, immunomodulatory treatments, including low-dose naltrexone (LDN), aim to rebalance the immune environment without causing broad immunosuppression; other immunomodulators are also under study [6][42][43]. Given the complexity of PAIS, the combination of checkpoint inhibitors with metabolic support, antivirals, and immunomodulators may provide synergistic benefits and improve patient outcomes [6][24].

Challenges and Future Directions

Understanding and effectively treating T cell exhaustion in PAIS remains a significant challenge owing to several critical knowledge gaps. A key question is whether T cell exhaustion acts as a primary driver of symptom persistence or emerges as a consequence of ongoing disease processes. Clarifying this causal relationship requires carefully designed longitudinal studies that track exhaustion markers over time, from acute infection through PAIS development and progression [6][7][12].

Moreover, the interplay between T cell exhaustion and other systemic dysfunctions, such as autonomic nervous system abnormalities frequently observed in PAIS, remains poorly understood. Exploring how these systems influence each other could reveal important mechanistic connections and therapeutic targets [5][19][25]. Another unresolved issue is whether distinct infectious triggers induce unique exhaustion phenotypes, which would have implications for personalized treatment strategies [19][20].

Genetic and host factors likely modulate individual susceptibility to T cell exhaustion and PAIS development. Identifying relevant genetic variants may help stratify patients and effectively tailor interventions [41]. To address these complexities, future research should emphasize longitudinal immune profiling that integrates immunological, metabolic, and neurological parameters using a systems biology

approach. Developing animal models that accurately recapitulate PAIS features is crucial for mechanistic studies and preclinical therapeutic testing [13][14].

Finally, clinical trials targeting exhaustion pathways are urgently needed to translate mechanistic insights into effective treatments. Parallel efforts must focus on validating robust biomarker panels capable of diagnosing PAIS and monitoring treatment response across diverse patient populations to enable precision medicine approaches [5][6][41].

This multifaceted research agenda offers the best path to unraveling the complexities of T cell exhaustion in PAIS and improving outcomes for affected individuals.

Discussion

This literature review highlights the emerging role of T cell exhaustion as a central immunological mechanism potentially driving Post-Acute Infection Syndromes (PAIS), including ME/CFS and Long COVID. Multiple studies have reported consistent alterations in T cell populations, characterized by increased expression of inhibitory receptors such as PD-1, CTLA-4, and TIM-3, alongside impaired proliferative responses and cytokine production [6][17][10]. These findings align with earlier studies describing T cell dysfunction in chronic viral infections and immune-mediated conditions [8][12].

Persistent antigen exposure, for example from Epstein-Barr virus or SARS-CoV-2, has been proposed as a unifying driver of sustained immune exhaustion that underlies key PAIS symptoms, including profound fatigue, cognitive impairment, and autonomic dysfunction [1][20][31]. Neuroimmune interactions further complicate this pathophysiology, where dysregulation of the hypothalamic-pituitary-adrenal axis and autonomic nervous system may contribute to the maintenance of T cell exhaustion and symptom persistence [23][25].

While this literature synthesis provides valuable insights into the complex immunopathology of PAIS, several limitations must be acknowledged. The heterogeneity of study designs, patient populations, and immunological assays limits direct cross-study comparisons [7][11]. Moreover, as this is a literature review without a formal systematic methodology or risk-of-bias assessment, definitive conclusions regarding causality or treatment efficacy cannot be drawn from the results.

Future research should prioritize prospective longitudinal studies using standardized immune phenotyping and functional assays to clarify the temporal dynamics and specific mechanisms of T cell exhaustion in PAIS [6][41]. Additionally, clinical trials targeting exhaustion pathways, such as immune

checkpoint inhibitors or metabolic modulators, are essential to translate these immunological findings into effective therapies [24][42].

Limitations

This literature review did not include a formal risk-of-bias assessment or prospective protocol registration. Therefore, relevant studies may have been missed, and selection bias could not be excluded. Readers should interpret the findings considering these limitations of the study.

Conclusion

T cell exhaustion presents a promising target for understanding and potentially treating the persistent immune dysfunction characteristic of PAIS. Integrating clinical and molecular evidence underscores the critical need for rigorous, systematic investigations to validate biomarkers and develop targeted immunotherapies aimed at the underlying immune impairment.

Abbreviations and Definitions

Abbreviation	Full Term	Explanation
CBT	Cognitive Behavioral Therapy	A psychological intervention aiming to change patterns of thinking or behavior that contribute to a patient's symptoms.
CD4+	Cluster of Differentiation 4 positive T cell	A subset of T lymphocytes (helper T cells) involved in immune system regulation and activation.
CD8+	Cluster of Differentiation 8 positive T cell	A subset of T lymphocytes (cytotoxic T cells) that directly kill infected or cancerous cells.
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4	An inhibitory receptor on T cells that downregulates immune responses to prevent excessive activation.
EBV	Epstein-Barr Virus	A herpesvirus associated with infectious mononucleosis and implicated in various chronic illnesses, including ME/CFS.
GET	Graded Exercise Therapy	A structured physical activity program where exercise is gradually increased, sometimes used in ME/CFS and Long COVID management.
HPA axis	Hypothalamic-Pituitary-Adrenal axis	A complex set of interactions among the hypothalamus, pituitary gland, and adrenal glands regulating stress response and immunity.
IFN-γ	Interferon gamma	A cytokine critical for innate and adaptive immunity against viral and intracellular bacterial infections.
IL-2	Interleukin 2	A cytokine that plays a central role in the activation and proliferation of T cells.
LAG-3	Lymphocyte Activation Gene-3	An inhibitory receptor on T cells associated with regulation and exhaustion.
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome	A chronic, debilitating illness characterized by fatigue, post-exertional malaise, cognitive dysfunction, and other symptoms.

Abbreviation	Full Term	Explanation
NK cell	Natural Killer cell	A type of cytotoxic lymphocyte critical to the innate immune system, involved in controlling viral infections and tumor growth.
PAIS	Post-Acute Infection Syndrome	Disorders with persistent symptoms following the resolution of an acute infection, including ME/CFS and Long COVID.
PD-1	Programmed Death-1	An inhibitory receptor on T cells, upregulated during chronic antigen exposure, leading to reduced immune function (exhaustion).
PEM	Post-Exertional Malaise	Worsening of symptoms following physical or mental exertion, a hallmark of ME/CFS and Long COVID.
POTS	Postural Orthostatic Tachycardia Syndrome	A form of autonomic dysfunction characterized by an increased heart rate upon standing and associated symptoms.
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2	The virus responsible for COVID-19, implicated in Long COVID.
TIGIT	T cell immunoreceptor with Ig and ITIM domains	An inhibitory receptor on T cells involved in the regulation of immune responses and exhaustion.
TIM-3	T cell immunoglobulin and mucin-domain containing-3	Another inhibitory receptor associated with T cell exhaustion and immune regulation.
TNF-α	Tumor Necrosis Factor alpha	A pro-inflammatory cytokine involved in systemic inflammation and immune regulation.
TOX	Thymocyte selection-associated high mobility group box protein	A transcription factor critical for establishing and maintaining T cell exhaustion programs.

Note:

- *Some abbreviations refer to protein markers (e.g., PD-1, CTLA-4), others to syndromes (e.g., ME/CFS, PAIS), therapies (CBT, GET), or physiological systems (HPA axis).*
- *All abbreviations above are explained as used in the context of the article.*

Statements and Declarations

Conflicts of Interest

The authors declare no conflicts of interest.

Funding

This research received no external funding.

Author Contributions

WG and MG conducted the literature review and drafted the manuscript. NMC contributed immunological input and critically revised the manuscript. PDCL supervised the project and provided clinical expertise. All authors approved the final version of the manuscript.

Data Availability

No new data were generated in this literature review. All data analyzed are available in the referenced publications.

Ethics

This article is a literature review of published literature and does not contain any studies with human participants or animals performed by any of the authors.

Originality

This manuscript has not been published previously and is not under consideration elsewhere.

References

1. a, b, c *Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. (2021). "Post-Acute COVID-19 Syndrome." Nat Med. **27**(4):601–15. https://www.nature.com/articles/s41591-021-01283-z.*
2. a, b, c *Choutka J, Jansari V, Hornig M, Iwasaki A (2022). "Unexplained Post-Acute Infection Syndromes." Nat Med. **28**(5):911–23. https://www.nature.com/articles/s41591-022-01810-6.*
3. a, b, c, d, e, f, g, h, i *Belk JA, Daniel B, Satpathy AT (2022). "Epigenetic Regulation of T Cell Exhaustion." Nat Immunol. **23**(6):848–60. doi:10.1038/s41590-022-01224-z.*

4. a, b Mirin AA (2022). "A Preliminary Estimate of the Economic Impact of Long COVID in the United States." Fatigue Biomed Health Behav. 190–9. https://www.tandfonline.com/doi/abs/10.1080/21641846.2022.2124064.
5. a, b, c, d, e, f, g, h, i, j, k, l Maya J (2023). "Surveying the Metabolic and Dysfunctional Profiles of T Cells and NK Cells in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." Int J Mol Sci. **24**(15):11937. https://www.mdpi.com/1422-0067/24/15/11937.
6. a, b, c, d, e, f, g, h, i, j, k, l Eaton-Fitch N, Rudd P, Er T, Hool L, Herrero L, Marshall-Gradisnik S (2024). "Immune Exhaustion in ME/CFS and Long COVID." JCI Insight. **9**(20):e183810. https://pmc.ncbi.nlm.nih.gov/articles/PMC11529985/.
7. a, b, c, d, e, f Saito S, Shahbaz S, Osman M, Redmond D, Bozorgmehr N, Rosychuk RJ, et al. (2024). "Diverse Immunological Dysregulation, Chronic Inflammation, and Impaired Erythropoiesis in Long COVID Patients with Chronic Fatigue Syndrome." J Autoimmun. **147**:103267. doi:10.1016/j.jaut.2024.103267.
8. a, b, c, d, e Yi JS, Cox MA, Zajac AJ (2010). "T-Cell Exhaustion: Characteristics, Causes and Conversion." Immunology. **129**(4):474–81. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-2567.2010.03255.x.
9. a, b Kahan SM, Wherry EJ, Zajac AJ (2015). "T Cell Exhaustion During Persistent Viral Infections." Virology. **479-480**:180–93. doi:10.1016/j.virol.2014.12.033.
10. a, b, c Loretelli C, Abdelsalam A, D'Addio F, Ben Nasr M, Assi E, Usuelli V, et al. (2021). "PD-1 Blockade Counteracts Post–COVID-19 Immune Abnormalities and Stimulates the Anti–SARS-CoV-2 Immune Response." JCI Insight. **6**(24). doi:10.1172/jci.insight.146701.
11. a, b, c, d Wiech M, Chroscicki P, Swatler J, Stepnik D, De Biasi S, Hampel M, et al. (2022). "Remodeling of T Cell Dynamics During Long COVID Is Dependent on Severity of SARS-CoV-2 Infection." Front Immunol. **13**:886431. doi:10.3389/fimmu.2022.886431.
12. a, b, c Wherry E (2011). "T Cell Exhaustion." Nat Immunol. **12**:492–9. doi:10.1038/ni.2035.
13. a, b, c, d, e, f, g Zu H, Chen X (2024). "Epigenetics Behind CD8+ T Cell Activation and Exhaustion." Genes Immun. **25**(6):525–40. doi:10.1038/s41435-024-00307-1.
14. a, b, c, d, e, f, g, h Zheng K, Zheng X, Yang W (2022). "The Role of Metabolic Dysfunction in T-Cell Exhaustion During Chronic Viral Infection." Front Immunol. **13**:843242. doi:10.3389/fimmu.2022.843242.
15. a, b, c, d Jin S, Shang Z, Wang W, Gu C, Wei Y, Zhu Y, et al. (2023). "Immune Co-Inhibitory Receptors CTLA-4, PD-1, TIGIT, LAG-3, and TIM-3 in Upper Tract Urothelial Carcinomas: A Large Cohort Study." J Immunother. **46**(4):154–9. doi:10.1097/CJI.0000000000000466.
16. a, b, c Balkhi MY (2020). "Receptor Signaling, Transcriptional, and Metabolic Regulation of T Cell Exhaustion." Oncoimmunology. **9**(1):1747349. doi:10.1080/2162402x.2020.1747349.

17. ^a, ^b, ^c, ^d, ^e, ^fCliff JM, King EC, Lee JS, Sepúlveda N, Wolf AS, Kingdon C, et al. (2019). "Cellular Immune Function in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)." Front Immunol. **10**:796. doi:10.3389/fimmu.2019.00796.

18. ^a, ^b, ^cAnderson AC, Joller N, Kuchroo VK (2016). "Lag-3, Tim-3, and TIGIT: Co-Inhibitory Receptors with Specialized Functions in Immune Regulation." Immunity. **44**(5):989–1004. doi:10.1016/j.immuni.2016.05.001.

19. ^a, ^b, ^cBarathan M, Mohamed R, Yong Y, Kannan M, Vadivelu J, Saeidi A, et al. (2018). "Viral Persistence and Chronicity in Hepatitis C Virus Infection: Role of T-Cell Apoptosis, Senescence and Exhaustion." Cells. **7**(10):165. doi:10.3390/cells7100165.

20. ^a, ^b, ^c, ^dRuiz-Pablos M, Paiva B, Montero-Mateo R, Garcia N, Zabaleta A (2021). "Epstein-Barr Virus and the Origin of Myalgic Encephalomyelitis or Chronic Fatigue Syndrome." Front Immunol. **12**:656797. doi:10.3389/fimmu.2021.656797.

21. ^Ariza M (2021). "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Human Herpesviruses Are Back!" Biomolecules. **11**(2):185. doi:10.3390/biom11020185.

22. ^Hwang JH, Lee JS, Oh HM, Lee EJ, Lim EJ, Son CG (2023). "Evaluation of Viral Infection as an Etiology of ME/CFS: A Systematic Review and Meta-Analysis." J Transl Med. **21**(1):763. doi:10.1186/s12967-023-04635-0.

23. ^a, ^b, ^cMorris G, Anderson G, Maes M (2017). "Hypothalamic-Pituitary-Adrenal Hypofunction in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) as a Consequence of Activated Immune-Inflammatory and Oxidative and Nitrosative Pathways." Mol Neurobiol. **54**(9):6806–19. doi:10.1007/s12035-016-0170-2.

24. ^a, ^b, ^c, ^dAlmawash S (2025). "Revolutionary Cancer Therapy for Personalization and Improved Efficacy: Strategies to Overcome Resistance to Immune Checkpoint Inhibitor Therapy." Cancers (Basel). **17**(5):880. doi:10.3390/cancers17050880.

25. ^a, ^b, ^cGlobig AM, Zhao S, Roginsky J, Maltez VI, Guiza J, Avina-Ochoa N, et al. (2023). "The β1-Adrenergic Receptor Links Sympathetic Nerves to T Cell Exhaustion." Nature. **622**(7982):383–92. doi:10.1038/s41586-023-06568-6.

26. ^Tate W, Walker M, Sweetman E, Helliwell A, Peppercorn K, Edgar C, et al. (2022). "Molecular Mechanisms of Neuroinflammation in ME/CFS and Long COVID to Sustain Disease and Promote Relapses." Front Neurol. **13**:877772. doi:10.3389/fneur.2022.877772.

27. ^Huang X, Hussain B, Chang J (2021). "Peripheral Inflammation and Blood-Brain Barrier Disruption: Effects and Mechanisms." CNS Neurosci Ther. **27**(1):36–47. doi:10.1111/cns.13569.

28. ^Oldstone MB (1998). "Molecular Mimicry and Immune-Mediated Diseases." FASEB J. **12**(13):1255–65. doi:10.1096/fasebj.12.13.1255.

29. ^Vahabi M, Ghazanfari T, Sepehrnia S (2022). "Molecular Mimicry, Hyperactive Immune System, and SARS-COV-2 Are Three Prerequisites of the Autoimmune Disease Triangle Following COVID-19 Infection." Int Immunopharmacol. **112**:109183. doi:10.1016/j.intimp.2022.109183.

30. ^Suliman BA (2024). "Potential Clinical Implications of Molecular Mimicry-Induced Autoimmunity." Immun Inflamm Dis. **12**(2):e1178. doi:10.1002/iid3.1178.

31. a, bTate WP, Walker MOM, Peppercorn K, Blair ALH, Edgar CD (2023). "Towards a Better Understanding of the Complexities of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID." Int J Mol Sci. **24**(6):5124. doi:10.3390/ijms24065124.

32. a, b, cSeok JM, Yang KI (2024). "Sleep and Neuroimmunology: A Narrative Review." Encephalitis. **4**(3):55–61. doi:10.47936/encephalitis.2024.00024.

33. ^Ji RR, Nackley A, Huh Y, Terrando N, Maixner W (2018). "Neuroinflammation and Central Sensitization in Chronic and Widespread Pain." Anesthesiology. **129**(2):343–66. doi:10.1097/ALN.0000000000002130.

34. a, bJammoul M, Naddour J, Madi A, Reslan MA, Hatoum F, Zeineddine J, et al. (2023). "Investigating the Possible Mechanisms of Autonomic Dysfunction Post-COVID-19." Auton Neurosci. **245**:103071. doi:10.1016/j.autneu.2022.103071.

35. ^Gulyaeva NV (2024). "Brain Mechanisms Involved in Post COVID Syndrome: A Narrative Review." Neurochem J. **18**(3):397–405. doi:10.1134/S1819712424700156.

36. a, bRivera MC, Mastronardi C, Silva-Aldana CT, Arcos-Burgos M, Lidbury BA (2019). "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review." Diagnostics. **9**(3):91. https://pmc.ncbi.nlm.nih.gov/articles/PMC6787585/.

37. ^Murga I, Aranburu L, Gargiulo PA, Gómez Esteban JC, Lafuente JV (2021). "Clinical Heterogeneity in ME/CFS. A Way to Understand Long-COVID19 Fatigue." Front Psychiatry. **12**:735784. doi:10.3389/fpsyt.2021.735784.

38. ^Raj SR, Guzman JC, Harvey P, Richer L, Schondorf R, Seifer C, et al. (2020). "Canadian Cardiovascular Society Position Statement on Postural Orthostatic Tachycardia Syndrome (POTS) and Related Disorders of Chronic Orthostatic Intolerance." Can J Cardiol. **36**(3):357–72. doi:10.1016/j.cjca.2019.12.024.

39. ^Geraghty K, Jason L, Sunnquist M, Tuller D, Blease C, Adeniji C (2019). "The “Cognitive Behavioural Model” of Chronic Fatigue Syndrome: Critique of a Flawed Model." Health Psychol Open. **6**(1):2055102919838907. doi:10.1177/2055102919838907.

40. ^Twisk FNM, Maes M (2009). "A Review on Cognitive Behavorial Therapy (CBT) and Graded Exercise Therapy (GET) in Myalgic Encephalomyelitis (ME) / Chronic Fatigue Syndrome (CFS): CBT/GET Is Not Only Ineffecti

*ve and Not Evidence-Based, But Also Potentially Harmful for Many Patients with ME/CFS." Neuro Endocrinol Lett. **30**(3):284–99. https://pubmed.ncbi.nlm.nih.gov/19855350/.*

41. a, b, c, d *Iu DS, Maya J, Vu LT, Fogarty EA, McNairn AJ, Ahmed F, et al. (2024). "Transcriptional Reprogramming Primes CD8+ T Cells Toward Exhaustion in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." Proc Nat l Acad Sci U S A. **121**(50):e2415119121. doi:10.1073/pnas.2415119121.*

42. a, b, c *Apostolou E, Rosén A (2024). "Epigenetic Reprograming in Myalgic Encephalomyelitis/Chronic Fatigue S yndrome: A Narrative of Latent Viruses." J Intern Med. **296**(1):93–115. doi:10.1111/joim.13792.*

43. ^ *Kučić N, Rački V, Šverko R, Vidović T, Grahovac I, Mršić-Pelčić J (2021). "Immunometabolic Modulatory Role of Naltrexone in BV-2 Microglia Cells." Int J Mol Sci. **22**(16):8429. doi:10.3390/ijms22168429.*

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.