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Peer Review

Review of: "A Proposed Mechanism for ME/CFS Invoking Macrophage FcγRI and Interferon Gamma"

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Title: A Proposed Mechanism for ME/CFS Invoking Macrophage FcγRI and Interferon Gamma

In this paper, evidence for possible mechanisms of the clinical syndrome of ME/CFS is reviewed. The authors propose a novel mechanism that focuses primarily on T-cell-macrophage interaction, but is influenced by the binding of IgG antibodies to the interferon-gamma-inducible high-affinity immunoglobulin receptor Fc γ RI. The authors conclude that this proposed mechanism may explain why the disease resembles T-cell-mediated post-infectious autoinflammatory syndromes in age of onset and time course, but has a female preponderance similar to autoantibody-mediated disease.

This paper seems good to me; however, I have some concerns.

The paper should clarify whether the authors' hypotheses are supported by their scientific data.

mTOR (mechanistic Target of Rapamycin) plays a key role in cellular energy balance, autophagy, and inflammation—and emerging evidence suggests it's significantly implicated in the pathogenesis of ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome). Studies show chronically elevated activity of mTORC1 in lymphoblasts (immune precursor cells) from ME/CFS patients, evidenced by increased phosphorylation of 4E-BP1, a hallmark of mTORC1 activation.

In light of these concepts, to make this paper more interesting for the readers of this important journal, the authors should expand the discussion (or introduction) a bit. Below, I report an interesting article that should be studied, incorporated in meaning, and reported briefly in the discussion and in the list of references.

Avivar-Valderas A. Inhibition of PI3Kβ and mTOR influence the immune response and the defense mechanism against pathogens. *International Journal of Infection.* 2023;7(2):46-49. (www.biolife-

 doi.org/10.32388/724UCE

publisher.it).

Interleukin-37 (IL-37) is an anti-inflammatory cytokine that broadly suppresses innate immune responses—especially by inhibiting IL-1β, IFN-γ, IL-6, and TNF, etc. ME/CFS patients exhibit elevated pro-inflammatory cytokines, and preclinical evidence suggests that IL-37 reduces inflammation and restores energy metabolism in mice—directly targeting fatigue mechanisms.

Again, in this context, to make this paper more interesting, the authors should expand the discussion (or introduction) a bit. Below, I report an interesting article that should be studied, incorporated in meaning, and reported in the list of references.

Toniato E. IL-37 is an inhibitory cytokine that could be useful for treating infections . *International Journal of Infection.* 2024;8(1):1-2. (**www.biolife-publisher.it**).

I don't see any figures or tables. For better presentation, a figure and a table should be added.

I believe these suggestions are important for improving this paper. Without these corrections, the paper cannot be published. So, I recommend **minor revision**.

Declarations

Potential competing interests: No potential competing interests to declare.