

Peer Review

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

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Thank you for the invitation to assess this review by Edwards *et al.* The proposals behind the review involving Fc-gamma receptors, cytokines (particularly IFN-gamma), and the implications for T-cell : B-cell : Macrophage interactions (and interplay) are thought-provoking and useful for further understanding the enigma of ME/CFS. I particularly enjoyed the discussion on antibody affinity variation - this makes sense in the context of auto-immunity (maybe T-receptor variation too?).

My only comments are to encourage clarification on the comment, *"Furthermore, the symptoms of ME/CFS overlap with those of viral infection. As a result, there is not the stereotyped history of post-infective illness seen, for instance, in Reiter's syndrome, in which new symptoms appear several days after the acquisition of infection"*, under the "Relation to Intracellular Infection" sub-heading. I am not sure that I agree with this position and would quote recent Long COVID examples where 12 weeks are needed to see the appearance of idiopathic, long-term fatigue, PEM, and associated symptoms (not including the immediate post-infection period where the impacts of acute inflammation may be observed via cardiac, lung, or other organ sequelae).

Another comment to consider is the view, under the section "Evidence for Nervous System Involvement", that, *"No consistent macroscopic or microscopic structural changes have been found in the brain,..."*. I do not think that this is correct and would recommend reviewing the primary MRI, fMRI, etc. studies and systematic/scoping reviews on the topic (for example, Nelson T, Zhang LX, Guo H, Nacul L, Song X. Brainstem Abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Scoping Review and Evaluation of Magnetic Resonance Imaging Findings. *Front Neurol.* 2021 Dec 17;12:769511. doi: 10.3389/fneur.2021.769511).

Congratulations on this review. Thank you for the opportunity to review this contribution.

Declarations

Potential competing interests: No potential competing interests to declare.