

Review of: "Proposal to Explain the Cause of Long COVID Based on the Concept of Host Factor Variants"

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Potential competing interests: No potential competing interests to declare.

Major Comments:

Clarity and Structure of Hypothesis:

- The **central hypothesis** regarding the role of host factors, including MHC polymorphisms and antigen-presenting cells (APCs), in long COVID is compelling but lacks clear progression and structure in the manuscript. The hypothesis could benefit from a **more concise summary in the introduction** to guide readers through the rest of the paper.
 - **Recommendation:** Revise the introduction to better articulate the main hypothesis, perhaps providing a brief outline of the specific mechanisms proposed (e.g., MHC variability and its implications for viral persistence).

Lack of Direct Evidence for Long COVID Mechanism

- Although the paper provides a solid theoretical framework linking MHC polymorphism and APC function to long COVID, there is a **lack of direct experimental evidence or references** supporting this explanation in the specific context of long COVID. Most of the data presented are based on general viral infections.
 - **Recommendation:** Either conduct or reference specific studies on long COVID pathogenesis in relation to MHC polymorphisms or clearly state this as a proposed model/theory rather than a proven explanation.

Mechanistic Ambiguity Regarding APCs and Viral Persistence

- The manuscript presents macrophages and dendritic cells as potential long-term reservoirs of viral particles, leading to persistent symptoms. However, the paper is unclear on whether this viral persistence in APCs is a recognized mechanism in long COVID.
 - **Recommendation:** Clarify the **current evidence** supporting viral persistence in APCs specifically in the context of long COVID. If speculative, clearly differentiate between what is known and what is hypothesized.

Overuse of Hypothetical Terminology:

- There is a recurring use of terms such as "might," "could," and "possibly," which weakens the scientific rigor of the arguments presented.

- **Recommendation:** Strengthen claims by providing **more definitive language** where supported by evidence, or clearly label speculative sections.

Confusing Terminology: Viral Invasion vs. Infection:

- The differentiation between "viral invasion" and "viral infection" is not widely accepted terminology in the scientific community and may confuse readers. This distinction is made in several sections without clear operational definitions.
- **Recommendation:** Either align the terminology with more widely accepted terms or **provide clear definitions** early in the manuscript.

Lack of Exploration of Alternative Explanations

- The manuscript focuses heavily on the role of MHC polymorphisms and APCs but does not consider **other mechanisms** for long COVID symptoms, such as autoimmunity, endothelial dysfunction, or viral reactivation.
- **Recommendation:** Include a section that explores other **leading hypotheses** of long COVID to present a balanced discussion.

Minor Comments:

Introduction - Citation Inconsistencies:

- Inconsistent citation format for various references (e.g., Donald et al., 2024; Chen et al., 2022).
- **Recommendation:** Standardize the **citation style** and ensure all references are correctly formatted.

Typographical Errors:

- There are several minor typographical and grammatical errors throughout the manuscript.
- **Recommendation:** A thorough **proofreading** is required to correct these issues.

Table 1 Clarification:

- Table 1, which classifies individuals based on MHC compatibility and susceptibility to long COVID, is informative but may be confusing to readers unfamiliar with MHC biology.
- **Recommendation:** Consider adding a **legend** to Table 1 that explains terms like "MHC I allele" and "MHC II allele" for a broader audience.

Ambiguity in 'Blood or White Blood Cells as Diagnostic Samples':

- The statement suggesting that **blood or white blood cells** could be the proper diagnostic samples for long COVID patients is vague.

- **Recommendation:** Elaborate on why these samples would be more suitable and provide evidence or references to support this claim.

Further Explanation of Trojan Horse Mechanism:

- The mention of APCs potentially using the **Trojan horse mechanism** to cross the blood-brain barrier and cause CNS infection is briefly discussed but lacks depth.
 - **Recommendation:** Provide **more detail** about this mechanism, particularly in the context of long COVID, and include relevant citations.

Redundancy in the Discussion Section:

- Some sections, particularly those explaining **MHC polymorphisms** and their impact on immune responses, are repetitive.
 - **Recommendation:** Revise to avoid redundancy and ensure that each paragraph adds unique insights.

Figures and Diagrams:

- The manuscript would benefit from **visual aids** or diagrams to clarify complex immunological processes, particularly the role of MHC molecules and APCs in long COVID.
 - **Recommendation:** Consider adding **figures** or **schematics** to illustrate key points.

Overall Recommendation:

While the paper introduces an interesting hypothesis regarding the role of MHC polymorphisms and APCs in long COVID, it requires **significant revisions** to clarify the hypothesis, strengthen the scientific claims, and integrate existing evidence.