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Peer Review

# Review of: "The Adaptive Compromise Hypothesis: Host Accommodation to Pathogen Exploitation of Neutrophil Defenses in Tuberculosis"

**Elías Barquero-Calvo**[1]

1. Universidad Nacional, Costa Rica

**Overall Evaluation**

This manuscript presents an original and intellectually stimulating hypothesis: that host defense against *Mycobacterium tuberculosis* has evolved through an adaptive compromise, in which intermediate neutrophil abundance and NOX2-derived reactive oxygen species (ROS) provide greater protection than maximal neutrophil responses. The integration of human genetics, neutrophil biology, host-pathogen coevolution, and tuberculosis immunopathogenesis yields a coherent conceptual framework that is both novel and potentially impactful. The manuscript is generally well written and logically organized, and it proposes several experimentally testable predictions, which considerably strengthen its value as a hypothesis article.

Overall, I found the hypothesis scientifically interesting and worthy of publication. However, several key aspects should be revised to distinguish established evidence from interpretation and speculation better. Most of my concerns do not question the originality of the hypothesis itself, but rather the strength with which some conclusions are presented.

**Major Comments**

**1. Clearly distinguish hypothesis from established evidence**

My primary concern is that, throughout the manuscript, speculative interpretations are sometimes presented with a level of certainty that exceeds the available evidence. For example, the proposed U-shaped relationship between neutrophil activity and tuberculosis susceptibility is presented as the central biological model of the manuscript. Although this is an attractive and plausible hypothesis, it has

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not yet been directly demonstrated experimentally. Rather, it represents a conceptual synthesis of evidence obtained from different genetic studies, animal models, and clinical observations. I recommend that the authors consistently distinguish between:

- observations directly supported by experimental evidence,
- interpretations derived from multiple independent studies,
- and predictions generated by the proposed hypothesis.

Using more cautious language ("may", "could", "is consistent with", "supports the possibility that") in appropriate sections would substantially strengthen the scientific rigor of the manuscript without reducing its impact.

**2. Expand the discussion regarding the limitations of the NCF1 genetic evidence**

The manuscript is largely built around the protective association of the NCF1 rs201802880 (p.Arg90His) variant with tuberculosis susceptibility. Although this finding is highly interesting, the current hypothesis depends heavily on a relatively limited body of evidence. I recommend expanding the discussion of several limitations, including:

- the need for replication in additional ethnic populations;
- the possibility that the observed association may be population-specific;
- uncertainty regarding the magnitude of the protective effect;
- potential confounding factors inherent to case-control genetic association studies.

Although these limitations are briefly acknowledged near the end of the manuscript, they deserve greater emphasis because they represent the principal foundation of the proposed hypothesis.

**3. Moderate the evolutionary conclusions**

The evolutionary interpretation is one of the most attractive aspects of the review. However, several statements imply that the increased frequency of the NCF1-His90 allele in East Asian populations is the result of positive selection driven by historical tuberculosis burden. While this explanation is certainly plausible, the manuscript does not present direct population-genetic evidence to support this conclusion. I recommend presenting this interpretation more cautiously and explicitly acknowledging that alternative evolutionary explanations remain possible unless formal analyses of positive selection are available.

**4. Present alternative interpretations in greater depth**

The review mainly focuses on evidence supporting the proposed hypothesis. A stronger and more balanced review would also discuss observations that could support alternative interpretations, including:

- studies emphasizing the protective role of robust neutrophil responses during early tuberculosis infection;
- the possibility that neutrophilia reflects disease severity rather than being a direct driver of pathology;
- additional mechanisms by which reduced NOX2 activity may influence tuberculosis susceptibility independently of neutrophil-mediated bacterial dissemination.

Including a broader discussion of conflicting evidence would increase the manuscript's credibility and demonstrate that the hypothesis has been evaluated against competing explanations rather than resting solely on supportive observations.

**5. Moderate the therapeutic implications**

The discussion regarding host-directed therapy is interesting and provides a logical extension of the proposed hypothesis. However, the therapeutic implications currently appear somewhat premature. Before suggesting pharmacological modulation of NOX2 activity as a therapeutic strategy, the authors should acknowledge that:

- the proposed "optimal immune window" has not yet been experimentally defined;
- no validated biomarkers currently exist to identify patients within this theoretical window;
- selective pharmacological modulation of neutrophil activity remains largely experimental.

A more cautious discussion would better reflect the current state of the evidence.

**Minor Comments**

- Figure 1 effectively summarizes the proposed hypothesis but should be explicitly described as a conceptual model, rather than an experimentally validated relationship.
- Table 1 includes estimated percentages of NOX2 activity, presented as approximate values derived from the available literature rather than experimentally established thresholds.
- Some concepts, particularly the description of the Adaptive Compromise Hypothesis, are repeated throughout the Introduction and could be condensed to improve readability.

- The manuscript would benefit from a summary table distinguishing observations supported by experimental evidence from the authors' proposed mechanistic interpretations. Such a table would help readers identify which aspects of the model are evidence-based and which remain hypothetical.

**Recommendation**

This manuscript proposes a novel, potentially influential conceptual framework for understanding host-pathogen interactions in tuberculosis. The hypothesis is scientifically interesting, logically developed, and likely to stimulate future research. Nevertheless, several conclusions are currently presented with greater certainty than they warrant given the available evidence.

I therefore recommend Major Revision. The requested revisions primarily involve improving the balance of the discussion, clearly separating evidence from speculation, expanding the discussion of limitations, and moderating conclusions that currently extend beyond the available experimental support.

## Declarations

**Potential competing interests:** No potential competing interests to declare.