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Peer Review

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

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Overall, I think this is an interesting hypothesis paper, but in its current form, I **would recommend Major Revision** before publication. The central idea that host evolution may favor an intermediate level of neutrophil/ROS activity because *M. tuberculosis* exploits excessive neutrophil responses is thought-provoking and potentially valuable. However, many of the conclusions are presented with a level of certainty that exceeds the available evidence, and several key immunological concepts require a more balanced discussion. The manuscript introduces the "Adaptive Compromise Hypothesis," proposing a U-shaped relationship between neutrophil/ROS activity and TB susceptibility, centered on the NCF1-His90 variant.

Overall assessment

The manuscript presents a novel evolutionary hypothesis that attempts to integrate human genetics, neutrophil biology, ROS signaling, and tuberculosis immunopathology into a unified framework. The hypothesis is intellectually stimulating and testable. However, the current manuscript often presents speculative concepts as established mechanisms. The evidence supporting the proposed U-shaped model remains indirect, and several alternative explanations are insufficiently discussed.

Major Comments

- My biggest concern is that the manuscript overstates causality. Throughout the manuscript, the authors frequently write statements such as "The host has evolved to strategically moderate defense investment." Or "Positive selection occurred because of TB." These are evolutionary claims that require far stronger evidence than is currently presented.

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- The manuscript mostly provides one protective genetic association, mechanistic studies, and literature supporting neutrophil pathology. These do not demonstrate evolutionary selection driven specifically by tuberculosis.
- The authors should consistently distinguish hypothesis, interpretation, and demonstrated facts throughout the manuscript.
- The proposed U-shaped model is attractive but lacks direct evidence. The central figure is elegant. However, no experimental dataset currently demonstrates host defense investment, continuous ROS level, and continuous TB susceptibility forming a U-shaped curve. Instead, the paper assembles different studies performed under completely different conditions. The authors should explicitly acknowledge that the U-shaped relationship remains conceptual rather than experimentally demonstrated.
- Neutrophils are only one component of TB immunity. The review focuses almost exclusively on neutrophils. However, TB immunity depends heavily on alveolar macrophages, monocyte-derived macrophages, dendritic cells, Th1 immunity, CD4 T cells, CD8 T cells, IFN-γ, TNF, IL-12, and granuloma organization. Readers unfamiliar with TB immunology may incorrectly conclude that neutrophils are the dominant determinant of disease outcome.
- The review should include a section discussing how the proposed hypothesis integrates with established adaptive immune mechanisms.
- The manuscript assumes that reduced ROS is protective because it limits bacterial exploitation. Other explanations should also be considered. Examples: altered cytokine production, altered macrophage activation, altered antigen presentation, altered granuloma structure, altered recruitment of inflammatory monocytes. These possibilities deserve discussion.
- The manuscript repeatedly argues that NCF1 His90 reached high frequencies because of TB selection. However, high allele frequency, proof of positive selection, and population genetic analyses would be needed. The manuscript should tone down these statements or provide stronger evolutionary evidence.
- The paper mentions stronger protection in women. However, the mechanistic explanation remains speculative. Potential roles of estrogen, androgen signaling, sex hormones, and X-linked immune regulation should be discussed more comprehensively.
- The manuscript recommends partial NOX2 inhibition as host-directed therapy. This recommendation seems premature because no preclinical therapeutic studies exist, the timing of intervention remains

unknown, and balancing bacterial burden versus immunopathology is difficult. The therapeutic section should emphasize uncertainty.

- Many studies suggest that ROS is beneficial in controlling TB. Others show neutrophils contribute to pathology. The manuscript emphasizes literature supporting the hypothesis while giving less attention to conflicting findings. A balanced review should discuss both sides equally.
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Minor Comments

- Figure 1 is clear but oversimplifies TB immunity. Adding macrophages and adaptive immunity would improve the conceptual model.
- Table 1 presents estimated NOX2 activity values. Please clarify whether these values are experimentally measured or inferred.
- Several statements use definitive language: Proves, demonstrates, establishes. Consider replacing with suggests, supports, is consistent with
- The Introduction could briefly summarize the current understanding of neutrophils in TB before introducing the hypothesis.
- Some paragraphs are very long. Breaking them into smaller sections would improve readability.
- The Prediction section is one of the strengths of the paper. However, prediction 4 requires more justification regarding why maximal ROS should increase bacterial survival.
- The manuscript occasionally repeats similar concepts. For example, examples include ROS-dependent dissemination, pathogen exploitation, adaptive compromise. These sections could be shortened.
- The conclusion is slightly repetitive. It could end with a stronger statement emphasizing future experimental validation rather than restating the hypothesis.

Additional literature that should be discussed: The review would benefit from discussion of recent work on

- granuloma heterogeneity
- ROS differences in different populations of mycobacteria (normal cells and short cells)
- Multinucleated cells under antibiotic or ROS stress

These areas have expanded considerably in the last five years and would place the hypothesis in a broader context.

Overall recommendation to the editor

Recommendation: Major Revision

This manuscript presents an interesting and potentially impactful conceptual framework linking neutrophil biology, host genetics, and tuberculosis pathogenesis. The hypothesis is novel and generates several experimentally testable predictions. However, many conclusions currently extend beyond the available evidence. The manuscript would be substantially strengthened by tempering causal claims, providing a more balanced discussion of conflicting literature, integrating adaptive immune mechanisms more thoroughly, and clearly distinguishing speculative aspects of the model from experimentally established findings.

One additional point that I consider particularly important: The manuscript is framed as a **review article**, but much of it functions as a **hypothesis/perspective**. More than half of the text is devoted to introducing and defending a new conceptual model rather than comprehensively reviewing the field. I would encourage the authors either to (1) explicitly position the article as a **Hypothesis or Perspective**, or (2) substantially broaden the review of the existing literature before presenting their model. This distinction will help set appropriate expectations for readers.

Attachments: available at https://doi.org/10.32388/RS46QM

Declarations

Potential competing interests: No potential competing interests to declare.