Qeios

Peer Review

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

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This manuscript introduces ´The Adaptive Compromise Hypothesis as a framework to address gaps in the knowledge of the evolutionary fight between pathogen and host. Specifically, the authors treat the case of TB and the paradoxical role of neutrophils in disease development. Neutrophils are needed to fight TB but are also used by the pathogen for dissemination. Throughout the manuscript, the authors discuss one of the most important questions in biology: how much is too much?

Overall Assessment

The authors present a deserving discussion idea in a well-written, logical, and nicely integrated manuscript. The sections described throughout the manuscript help to ensure smooth reading. The integration of human genetics, evolutionary medicine, neutrophil response/biology, and a pathogen offers an interesting proposal. However, during reading, several questions came to my mind, and by answering those questions, the authors may strengthen their manuscript.

Major comments:

1. The adaptive compromise hypothesis states that hosts evolve to moderate rather than maximize their defense investment. For the authors, is " maximize " only equal to more neutrophils? It is well-known that the immune system is highly regulated, and the response should be tuned to the level demanded by the cue. An exacerbated response is detrimental in several proven infectious models.

2. Dissemination of the pathogen occurs by evading the neutrophil response despite the number of neutrophils, and it seems more dependent on ROS production by NOX2 rather than neutrophil count in

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circulation. Are the authors giving the same weight to neutrophil count as to neutrophil effector function?

3. Here, the elevated numbers of neutrophils are associated with a major risk of dissemination and more damage, while the literature cited indicates that elevation in neutrophil number is detrimental due to exacerbated inflammation and tissue damage. According to your theory, do the NCF1 carriers control infection at the initial stages of infection? Do NCF1 carriers recruit the same levels of neutrophils upon damage?

4. The theory does not reflect the complexity of the disease. The role of macrophages and T cells is not taken into account by the theory. What is the status of these populations in the NCF1 carriers?

5. The hypothesis is supported mainly by one observational study that proves correlation but lacks solid experimental confirmation. Thus, the hypothesis seems to apply only to carriers of the NCF1-His90 polymorphism. Are there any other similar polymorphisms reported in TB-endemic regions?

6. The claim that NCF1 variant occurrence is due to an evolutionary race between host and Tb is feasible but lacks experimental evidence. The authors should clearly state that this is not a proven fact but an integral part of their theory.

Strengths

- Well-written manuscript.
- Section organization is clear and logical.
- Theoretical advancement.
- Proposed experiments to prove the theory are solid.
- Well-explained figure.

Minor comments:

- The strength of their claims needs experimental validation.
- The concept of evasion of the immune response is not even mentioned.
- Figure 1 should be clarified as a proposed model.
- Some statements are wrongly cited.
- In 2.4, you repeat the evidence from Mantegazza et al.
- The last statement of section 3, 1 is missing a reference.
- Inflammation is used as a synonym for neutrophilia.

- Several important statement citations come from a review instead of the original work.

Declarations

Potential competing interests: No potential competing interests to declare.