nature portfolio

Peer Review File

Quantifiable Blood TCR Repertoire Components Associated with Immune Aging

Editorial Note: This manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments and rebuttal letters for versions considered at *Nature Communications*.

REVIEWERS' COMMENTS

Reviewer #1 (Remarks to the Author):

The authors have provided several new analyses to substantiate their conclusions and have successfully addressed the points that I raised. I do not have any new comments, but all reviewers commented on the limitations of this type of study for our understanding of immune aging, and these limitations could be more explicitly discussed.

Reviewer #2 (Remarks to the Author):

This MS is a greatly improved version of the previous submission. The authors have addressed my major concerns, and specifically have toned down many of their more unsubstantiated claims. The study remains predominantly descriptive but it is an interesting application of TCR repertoire analysis, and has the potential to stimulate further study of an intruiging set of immune reperotire changes associated with aging.

Reviewer #3 (Remarks to the Author):

The revision is much improved, and the authors have addressed most of my questions. The use of TCR CDR3b sequences has yielded good results, partly due to the bias of many abailable TCRs relying more on TCRb. With the rapid expansion of paired TCR sequences from known antigens, it has been observed that some antigen-specific TCRs predominantly use TCRa (Choy et al. Nat Commun. DOI: 10.1038/s41467-023-42430-z). The authors could discuss this in the Discussion as current limitation and future improvements.

RESPONSE TO REVIEWERS

Reviewer #1 (Remarks to the Author):

The authors have provided several new analyses to substantiate their conclusions and have successfully addressed the points that I raised. I do not have any new comments, but all reviewers commented on the limitations of this type of study for our understanding of immune aging, and these limitations could be more explicitly discussed.

Thank you for your positive feedback and for acknowledging the new analyses we have provided. We appreciate your comments and agree that discussing the limitations of our study more explicitly is important. We have revised the manuscript to more clearly discuss the limitations of this study by stressing its descriptive nature.

Reviewer #2 (Remarks to the Author):

This MS is a greatly improved version of the previous submission. The authors have addressed my major concerns, and specifically have toned down many of their more unsubstantiated claims. The study remains predominantly descriptive but it is an interesting application of TCR repertoire analysis, and has the potential to stimulate further study of an intriguing set of immune repertoire changes associated with aging.

Thank you very much for your positive feedback. We appreciate your recognition of the improvements made in this version of the manuscript and are glad to hear that our revisions have addressed your major concerns. We are pleased that you find the study's application of TCR repertoire analysis interesting and that it holds potential for stimulating further research into immune repertoire subset changes associated with aging.

Reviewer #3 (Remarks to the Author):

The revision is much improved, and the authors have addressed most of my questions. The use of TCR CDR3b sequences has yielded good results, partly due to the bias of many available TCRs relying more on TCRb. With the rapid expansion of paired TCR sequences from known antigens, it has been observed that some antigen-specific TCRs predominantly use TCRa

(Choy et al. Nat Commun. DOI: 10.1038/s41467-023-42430-z). The authors could discuss this in the Discussion as current limitation and future improvements.

Thank you for your constructive feedback and for acknowledging the improvements in our revised manuscript. We appreciate your point regarding the reliance on TCRβ sequences and the observation that some antigen-specific TCRs predominantly use TCRα, as highlighted by Choy et al.. We included this reference and revised the Discussion section of our manuscript to further acknowledge the importance of TCRα sequences and their inclusion for future improvements.