Review of: "SARS-CoV-2-specific T cells in unexposed adults display broad trafficking potential and cross-react with commensal antigens"

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In this paper, the authors present data to support that individuals who have never been exposed to SARS-CoV-2, carry pre-existing immunity in the form of SARS-CoV-2-antigen specific CD4 T-cells. The concept of pre-existing immunity against SARS-CoV-2 in non-exposed individuals has been demonstrated in multiple studies, including ours (Mahajan et al. Sci Rep. 2021 Jun 23;11(1):13164).

The paper has taken a more direct approach than the other studies - of enriching antigen-specific CD4 T-cells using tetramers. The choice of SARS-CoV-2 peptides from published studies covering the SARS-CoV-2 proteome was a good approach. They have characterized antigen-specific T-cells by their phenotype and activation state and by their expression of gut trafficking receptors. In the final section they demonstrate that T-cell clones isolated from a tetramer-enriched population of T-cells recognized pure microbial peptides or peptides extracted from fecal matter.

Overall, the work is in line with other studies showing that pre-existing immunity arises as a result of cross-reactive CD4 and CD8 T-cells, primed by a variety of different antigens that may or may not be related to SARS-CoV. Our study showed that pre-existing immunity is contributed by CD8 T-cells that recognize immunodominant epitopes in Inf-M antigen. The study is well conducted with appropriate controls and will get published in a peer reviewed journal.

Few questions to understand the broader implications of this study.

1. The authors selected antigens from published papers which induced strong CD4 activation in SARS-CoV-2 infected patients. Is there a link between strength of activation and expression of gut trafficking receptors? For example if the authors activate naive CD4 T-cells from healthy donors using an immunodominant epitope say HA or flu, will the T-cells coexpress CCR9 and integrin-beta-7. The authors should show that this is not the case and the T-cells they have enriched using tetramers do arise microbial antigens they have seen in the gut.
2. The authors should compare the magnitude of CD4 T-cell activation in their assay and compare it with the published papers to see if they T-cells are more responsive to gut microbial peptide compared to the cognate antigen.

3. Finally, COVID-19 infection causes severe diarrhea in many indviduals. Could there be a link with gut microbial peptide primed T-cells getting inappropriately activated by SARS-CoV-2 antigen?