

Microbiology 204  
Discussion Session #2  
1-2:30PM CL220/223  
Faculty leader: Jeroen Roose

October 17, 2018

Sanchez-Blanco et al. Protein tyrosine phosphatase PTPN22 regulates LFA-1 dependent Th1 responses. *J Autoimmunity*, *in press*, 2018

Review article: Vang et al Autoimmune variants of PTPN22. *Science Signaling* [eaato936](#), 2018

Everyone should read these papers before coming to class. You do not need to read the supplemental materials and supplemental figures, although the Discussion Leader may choose to have the class discuss one or a few supplemental figures.

See below if you have an assignment, in which case you have some additional preparation for class. Assignments rotate among the students.

#### LEARNING OBJECTIVES:

To appreciate that altered T-cell signaling thresholds, whether increased or decreased, can lead to autoimmune disease in patients. Also to learn about PTPN22, which is one of the most common genes implicated in human autoimmune disease

#### STUDENT ASSIGNMENTS

1. Discussion leader (see instruction page for advice on leading the discussion)
2. Show Fig. 1 from the review article and discuss the association of PTPN22 in various autoimmune diseases. Look up which autoimmune diseases are implicated. Describe how PTPN22 could work to regulate T-cell receptor signaling. Describe the PTPN22 R620W allele. There is controversy about whether this is a gain-of-function or loss-of-function mutation, since it seems to have different effects in B-cells versus T-cells. There are also human/mouse differences. Review these issues for the group.
3. The primary paper implicates PTPN22 as a regulator of LFA-1 signaling. Describe the role of LFA1 in forming the immunological synapse. You may need to look up review #10 from the paper. Show a cartoon image of the immunological synapse.
4. Describe Fig. 1. Both the PTPN22<sup>-/-</sup> and the PTPN22<sup>619W</sup> mice show elevated IFN $\gamma$  and IL17 T cells with age, with the difference between WT versus the KO mice being in IFN $\gamma$ . But why does the IL-17 T cells also go up? Note this does not occur in the CIA model (panel C).
5. Describe Fig. 2, which is mainly negative (but important) data. What is the take home message from this figure? Look at reference #13; why are the results different in this paper compared to reference #13?
6. Go over Figure 3, outlining what addition of ICAM-Fc should be doing. Pay careful attention to the Y axis in these plots and compare them to Fig. 2 as well, to make sure that logical results are occurring. What is the difference between panel E and F. Panels G-J imply that more ICAM-1 is bound at the immunological synapse and that PTPN22<sup>-/-</sup> T-cells bind better to DCs.

The authors argue this is the result of increased LFA1 affinity. What could also explain this (how about expression levels of LFA1?).

7. Figure 4 argues that PTPN22<sup>-/-</sup> DCs can present Ova antigen better to OTII transgenic T-cells, driving more differentiation towards IFN $\gamma$  producing cells. But the PTPN22<sup>-/-</sup> DCs express the same level of CD86, CD40 and MHCII, so how do you think PTPN22 is regulating this DC function? Figure 5 rules out one mechanism, which you can briefly review.

8. Discuss Fig. 6 of the paper. These data support the idea that the increased ability of PTPN22<sup>-/-</sup> DCs to driven Th1 differentiation is at least LFA1 dependent. But the mutation here is in the DCs, and LFA-1 is on the T-cell. What signaling pathway is PTPN22 regulating in the DC? Does ICAM1 signal in DCs?

9. Discuss the model Figure (Fig S4). The data for the T-cell intrinsic effect make sense, but what is lacking is an understanding of what PTPN22 is doing in the DC. Do you agree? How would you address this (the relative role of PTPN22 in T-cells versus DCs) *in vivo*? Nevertheless, this paper is important because it argues that PTPN22 is regulating LFA1 signaling in T-cells more than it is regulating TCR signaling, which is a new idea.

#### Student assignment #s

- |    |                    |     |               |
|----|--------------------|-----|---------------|
| 1. | Nick Mroz          | 10. | Ki Hyun Kim   |
| 2. | Jennifer Umhoefer  | 11. | Darwin Kwok   |
| 3. | Adam Wade-Vallance | 12. | Suraj Makhija |
| 4. | Benjamin Wheeler   | 13, | Cody Mowery   |
| 5. | Brian J Woo        |     |               |
| 6. | Lowis Zhu          |     |               |
| 7. | Marissa Chou       |     |               |
| 8. | Julie Cole         |     |               |
| 9. | Rachel DeBarge     |     |               |

(NOTE : if you will miss a discussion session, inform Dr. Lowell in advance; if assignments have already been made, you should additionally make a trade with one of your classmates who does not have an assignment that week so that your assignment is covered).