Microbiology 204
Discussion Session #3 October 26, 2018
1-2:30PM CL220/223
Faculty leader: Julie Zikherman

Burnett, et al. Germinal center antibody mutation trajectories are determined by rapid self/foreign discrimination. Science 360:223 (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:

STUDENT ASSIGNMENTS
1. Discussion leader (see instruction page for advice on leading the discussion)

2. The introduction to this paper is very brief, but one disease is mentioned: Guillain-Barré syndrome. Look this up in Wikipedia and tell the group about what it is and what the relationship is between it and *C. jejuni* infection.

3. Explain Fig. 1, describing how the mixed chimeric mice are made, so that they generate animals with a tiny fraction of self-reactive B-cells. What happens when the SW_{HEL} cells are present in a HEL^{3X} mouse that expressed self-Ag? Describe how the authors prove these anergic cells can still respond to high density antigen. It is stated that the SW_{HEL} B-cells have about a 1×10^{-7} affinity for antigen. What is normal affinity ($1/K_D$) of a "high" affinity antibody?

4. Explain Fig 2, showing the difference between HEL^{3X} and DEL (from Fig S6A). What happens to the SW_{HEL} B cells when the mice are immunized with DEL? Why do you think they need to immunize with SRBC at day -11, then boost with SRBC-DEL antigen? Try to describe the binding curves shown in Fig. S7A for the new S52R and S52N mutant SW_{HEL} B-cells that come out (how are the percentages of mutants counted? What is the method). This is done with SRBC that are densely coated with DEL antigen. What would happen if the SRBCs were lightly coated?

5. Fig. 3 is the heart of the paper. It shows that new mutant clones of SW_{HEL} B-cells emerge as the immune response continues. Try to describe the order and the affinity of mutant B-cells that appear at day 4 versus 7 versus 11. Show an example of the affinity curves for the triple mutant SW_{HEL} antibodies (I29F-S52T-Y53F mutants). Try to talk only about the case when the mice are immunized with SRBC-DEL (ie the right hand "self-reactive" panels in Fig 3A

6. Compare the timing of mutations that appear when the mice are immunized with SRBC alone (ie the "not self-reactive" blue panels in Fig. 3A). Why are there similarities with mutations that arise with SRBC-DEL immunized mice?

7. The crystal structures explain the affinity differences for the mutant antibodies. Briefly review Fig. 4, but no need to go in depth.

8. Explain the experiment in Fig S13. How is this different than the experiments in Fig. 3?

9. Summarize the main finding from this paper. We all have auto-reactive B-cells in our bodies, yet we keep them in check. Why don't we just get rid of them? Sometimes, people say that autoimmune diseases can be triggered by infection with various viruses or bacteria. Through antigen mimicry, self reactive B-cell clones are selected out, which results in production of pathogenic self-reactive Abs. Does this paper support this old idea?

Student assignment #s

1. Darwin Kwok
2. Suraj Makhija
3. Nick Mroz
4. Jennifer Umhoefer
5. Adam Wade-Vallance
6. Benjamin Wheeler
7. Brian J Woo
8. Iowis Zhu
9. Marissa Chou
10. Cody Mowery
11. Julie Cole
12. Rachel DeBarge
13. Ki Hyun Kim
14.

(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).