Quorum sensing allows T cells to discriminate between self and nonself
Thomas Charles Butler, Mehran Kardar, and Arup K. Chakraborty, Proceedings of the National Academy of Sciences USA **110**, 11833-11838 (2013).

Recommended with commentary by Alex Levine, UCLA.

The immune system has a problem. One of its main jobs is recognizing and then attacking alien proteins (nonself) in the body that are the sign of infections. Unfortunately, the set of distinct proteins made by the body (self) is both large and highly varied so distinguishing an ever changing set of foreign proteins from these heterogeneous and essential self proteins is complicated. The immune is constantly navigating between the Scylla and Charybdis of either being too permissive where immunodeficiency might allow infections to persist, or overly reactive, leading to it attacking healthy issue and resulting in a number of *auto-immune diseases* such as arthritis. Our understanding of how the immune system manages this balancing act remains in its infancy, but there has been progress and some of it comes from the sort of mathematical analysis of stochastic systems as performed in statistical mechanics.

Thomas Charles Butler and his collaborators, Professors Mehran Kardar and Arup Chakraborty at MIT have reported on such an analysis of the problem of distinguishing self from nonself in the Proceedings of the National Academy USA [1]. They conclude that a large number of independent actors (T-cells, more on them below) independently might be bad at making the correct decision in the problem of distinguishing self from nonself, but they can improve their discrimination through chemical interactions, which allow them to arrive collectively at the correct decision [1]. The article is accessible to the interested physicist, but to make things a bit easier, I introduce a few of the basic players in the immune system and sketch the basic problem below.

T-cells are the central players in the drama. They are a type of white blood cell that matures in the thymus [2] where the first part of the story plays out. Each T-cell comes with a receptor that can potentially bind to a short peptide string. A mature T-cell, which leaves the thymus and circulates in the blood, uses its T-Cell Receptor (TCR) to patrol for foreign proteins. In particular, infected cells put up a type of distress signal by putting fragments of the foreign proteins on their surface where they can interact with the TCR. Should the TCR bind strongly to the foreign protein fragments (antigens) on the Antigen Presenting Cells (APCs), the immune system swings into action attacking the diseased tissue.

[1] As election day approaches, the reader may wonder whether interacting voters may similarly arrive at wiser decisions.

[2] You might eat these glands as "sweetbreads."

Since the immune system cannot start at birth with a complete library of all potentially dangerous foreign proteins that one might face, the TCRs are built stochastically. The immune system continually shuffles a very large set of genetic cards to build a random set of TCRs. The molecular biologist, Prof. Susumu Tonegawa made fundamental contributions to our understanding of the underlying process of V(D)J or somatic recombination needed to keep reshuffling the deck [2].

But a random set of detectors alone is not sufficient. The mix and match process of making TCRs generates many receptors that bind strongly to self protein fragments that cells display as well. To try to prevent these bad actors from getting out and attacking the body, all maturing T-cells are presented an array of self-peptides. If the new T-cells bind too strongly to any of these, they are eliminated. But this negative selection in the thymus is imperfect: each T-cell is actually exposed to a small fraction of self-peptides. The failure of screening against self-peptide response is evident from experiments that show that many T-cells, even in healthy individuals, bind some self-peptides. The authors understand this as follows: If the probability of T-cell binding and activation is p, then thymic selection against M self-peptides out of a repertoire of $N \ll M$ self-peptides, puts the probability of a T-cell reacting inappropriately to the self peptides at $p\left(1-\frac{M}{N}\right) = px$. But there are $T \sim 10^6$ different T-cell receptors on the loose, making the probability of full avoidance of autoimmunity problems a minuscule

$$(1-px)^{TN} \simeq \exp\left(-xpTN\right) \sim 10^{-4}$$

for reasonable estimates of the various parameters. They may say at NASA that "Failure is not an option!" Here it seems to be inevitable.

How does this not lead to auto-immune disease? The answer appears to be quorum sensing. When activated, T-cells secrete a chemical (IL-2) that, when it reaches a threshold concentration, simulate other T-cells to act. By modulating the vigor with which T-cells respond to peptide binding and to this chemical, they can set a threshold number or quorum for mounting a full immune response to a particular peptide sequence. As described in the text, the combination of thymic selecting making it less likely for a T-cell to respond to self versus nonself and by setting the quorum necessary for collective action to the right size, the immune system may indeed sail safely between the dangers of immunodeficiency and auto-immune disease. They authors conclude with suggestions for testing this quorum rule by interfering in various ways with the chemical communication between the T-cells.

This is certainly not the end of the story. The immune system holds on to many of its secrets still, but, based on the work of Butler and collaborators, one imagines that at least some of these secrets are well explored using techniques pioneered in statistics and statistical physics.

References

[1] Thomas Charles Butler, Mehran Kardar, and Arup K. Chakraborty, PNAS **110**, 11833-11838 (2013).

[2] Prof. Tonegawa was awarded the Nobel Prize in Physiology or Medicine for this work. His Nobel lecture gives a nice introduction to the problem and can be found at the website at http://nobelprize.org.