What is the basis of the immune system's specificity?

Uri Hershberg[1], Sorin Solomon[2], and Irun Cohen[3]

[1] ICNC Hebrew University, Jerusalem, Israel.
[2] Racah Institute of Physics, Hebrew University, Jerusalem, Israel
[3] Department of Immunology, Weizmann Institute of Science, Rehovot Israel.

Abstract. In this paper, we present a model of T cell clonal repertoire dynamics and present a new view of the place of self reactivity in the maintenance of the T cell repertoire, and in the specificity of the immune reaction. Taking into consideration the cross reactivity and self affinity of T cell receptors, essential to their maintenance in the healthy immune system, we have built a simulation of T cell dynamics in the shape space[1] of T cell and antigen forms. This simulation replicates the time course of a response to a primary infection and the return to a steady state, without requiring receptor affinity exclusively to non self antigens. These results suggest that the self-affinity should be seen not as a confounding paradox but as part of the background physiology of immune reaction, and show the need for a reevaluation of several basic principles of immunology. In order to better understand the place of self-reactivity, the function of the immune system, and how the cross-reactivity of immune receptors enables this function, we suggest that future research should focus on immune reactivates in the healthy body, and not just in disease.

1 Introduction

Immune interactions can be divided into three basic components. Antigens, cells that sense them and effector mechanisms. In this model we wish to focus on the first two components and more specifically to suggest how it is possible to have an effective sensing mechanism built of highly cross-reactive receptors. We present a model of T cell repertoire dynamics in the immune response based on existing knowledge of these dynamics, which aims to illuminate the basis of immune specificity in primary reactions to pathogens.

The immune system is unique in having a highly diverse variety of receptors like no other system in the body. This great variance is used to identify a near infinite number of antigens. This sensitivity of different antigen receptors is however highly regimented allowing the immune system to react to one type of antigen in a given context while ignoring other antigens. It is as yet an open question how the immune system maintains the specificity of reaction. - The possible answers lie in two camps: Receptor specificity and

[1] Protein shape space is an analogy commonly used to describe a vector space in which every point describes a configuration of the protein (A. S. Perelson and G. Weisbuch 1997).

systemic response specificity. By receptor specificity we mean that antigen receptors themselves are each highly focused and specific. Thus the specificities of an immune response is based on a repertoire built only of certain kinds of receptors. By systemic specificity we mean a mechanism that does not rely on the specificity of the receptors, but rather on some specific global behavior of the system.

The fact that we can find receptors sensitive to practically any substance and the importance of negative selection in the building of the immune repertoire in the thymus have led to the wide acceptance of the clonal selection theory [2], which supports receptor specificity. However, a closer look at the way immune cells are selected in the bone marrow and the thymus indicates that this interpretation is problematic:

- Immune cells are not completely specific; they are degenerate and cross-reactive.
- A certain level of benign affinity to self-antigens exists in all receptors.

These points hold true for all cells of the adaptive immune system, both B cells and T cells, and weaken the claims that the immune system's specificity is based on either type of receptor specificity. As we wish to present a model of T cells we shall focus on the theoretical problems relevant to T cells, ignoring at present the existing parallel problems relevant to B cells.

The basic tenet of the clonal selection theory is that all receptors with affinity to self are destroyed leaving a repertoire which only reacts to foreign antigens. Most of the varying views on immune specificity, including those that have moved away from this severe view, hold that the cause of specificity is still in some way the result of receptor specificity. This is true whether it is the theory of B and T cell cooperation of Cohn and Lahngman [7], the danger theory of Matzinger [8] or Grossman's theory of changing receptor excitation [6]. All in the end insist that there must be a greater receptor affinity for foreign antigens among immune receptors. This receptor specificity is what brings about the system's specificity of reaction to the pathogen and not to the self. Such a view raises immediately the question of self-reactivity. How does the system deal with the self-reactive receptors that are known to exist in healthy immune systems? The answers to this question lead to various mechanisms, from regulatory T cells to anergy of cells, which lead to the cancellation of all self-reactive T cells and a functional blindness to all the information that could be gleaned form such cells. All such theories are incapable of reconciling several facts of immune physiology with the concept of blindness to self-antigens. Most importantly, T cells are highly cross-reactive, each T cell can react to as many as 3×10^7 different peptide - MAC complexes [1]. Furthermore, although T cells of a high affinity to self antigens are culled by negative selection, all T cells must have some level of affinity to self or they will not pass the positive selection phase and die of neglect [5]. Positive selection appears to be especially important as it is now found to be an essential factor in the maintenance of the T cell repertoire in the periphery. Low level

affinity to self is not only essential as a maintaining signal of T cells but is also causes them to proliferate [4]. We thus find a situation where the actual T cell repertoire is not, as is commonly suggested by clonal selection and the other immune theories, built of specific receptors reactive to foreign antigens. The repertoire is, in point of fact, built of highly cross-reactive receptors that all share some minimal common affinity to self antigens.

These discrepancies between the theoretical and actual characteristics of T cell repertoires lead us to suggest a new role for self affinity which better captures the highly cross reactive nature of T cell receptors and their affinity to self. We do this using the basic components of the known dynamics of T cell repertoire maintenance [5]. These are:

- The maturation of T cells in the thymus, at a steady rate regardless of immune activity.
- The proliferation of peripheral T cells in the presence of antigens (self or non-self) occurs at a rate proportional to their affinity and concentrations.
- The Global competition of T cells among themselves reaches a homeostatic level.

The T cells and the antigens they react to are modeled as points in an abstract shape space. The closer a T cell and an antigen are in shape space, the higher the affinity between them. To model the high cross-reactivity of the T cells, we allow them to react not only to antigens at the same point in shape space but also to neighboring antigens. We further emphasize cross-reactivity by making the points in this shape space highly interconnected. This makes every point a close neighbor of much of the shape space.

2 The model

In this model, we focus on the relationship between similar antigens (be they foreign or self) and the T cells that react to them. To do so, we ignore the physical space of immune interaction and look at the shape space of T cell receptors and antigens. Every point in shape space represents the various similar antigen shapes that a single clone of T cell is reactive to with high affinity; high affinity is that affinity which leads to negative selection in the thymus. First neighbors in shape space are those antigens and T cells that have a high enough affinity to be affected by the positive selection of protein antigens. [2]

We present a generic scenario that models the immune reaction in terms of the following observed mechanisms:

- The continuous feeding of T cells from the thymus takes place at a steady rate regardless of immune activity. These T cells are positively selected

[2] This supposes the existence of a relatively permanent group of self-antigens, similar in the thymus and the periphery.

in the shape space 'around' certain self-antigens. We represent this by a probability rate (λ) for an immune cell to randomly appear on a specific lattice site.

- The local (in shape space) proliferation of peripheral T cells is triggered in the presence of antigens of more than minimal affinity. The rate of proliferation is proportional to their affinity and concentration, ($\tau_T \times ([Ai] + \sum_{Neighbors}[Aj] \times affinity)$) i.e. proportional to the number of antigens in its environs in shape space.
- The global down-regulation of the level of T cells represents the fact that the total population of T cell clones maintains a homeostatic level. We represent this by a death rate for T cells that is proportional to the average population of T cells in points in the shape space. ($\tau_D \times T_a vg$).

These three forces by themselves in synchrony with a steady level of self antigens brings about a steady population of T cell clones of various types with common levels of affinity to the self antigens that maintain them.

To show the feasibility of this model of T cell repertoire maintenance and behavior, we model the reaction to a primary infection by a pathogen. We therefore add a specific effector mechanism to these three basic forces of the T- cell repertoire maintenance. This mechanism is activated at high levels of T cell reactivity and acts to return the antigen pattern to its resting state. As in Grossman's model [6] this means that the T cells, during an infection, are not reacting to a specific antigen but to a change in antigen concentration. Although it is quite feasible that both a rise and a decrease in concentration could have biological relevance to the immune system our model uses an increase in antigen concentration as a signal for the T cells.

In the present instance of this model, the actual effector arm is not modeled. It is simply something that, at a rate proportional to the population of T cells, annihilates the antigens that caused the T cells to be activated.

The addition of an effector mechanism does not disturb the 'resting' state of the immune system, nor does it cause spurious activation. To cause an immune reaction we add an infection to the simulation. Infection is represented by an auto-catalytic antigen which starts proliferating in an hitherto 'uninhabited' point in the shape space. We emphasize again the lack of a need for T cells that are more highly reactive to foreign antigens. Therefore, the proliferating foreign antigen is placed in a spot in shape space that is no nearer (i.e. not of a higher affinity) to surrounding T cells than to their maintaining self-antigens.

3 Results

The simulation results in a repertoire of varied T cell clones that maintain a steady state without inimical reactivity as long as no pathogen is evident. Figure 1 shows the effect of a primary infection on the T cell repertoire. In these "snapshots"' of the T cell repertoire, the system turns it attention

and resources towards a change in the pattern of antigens in shape space progressing in the following stages: (a) Pre-infection day 0 - all the antigens

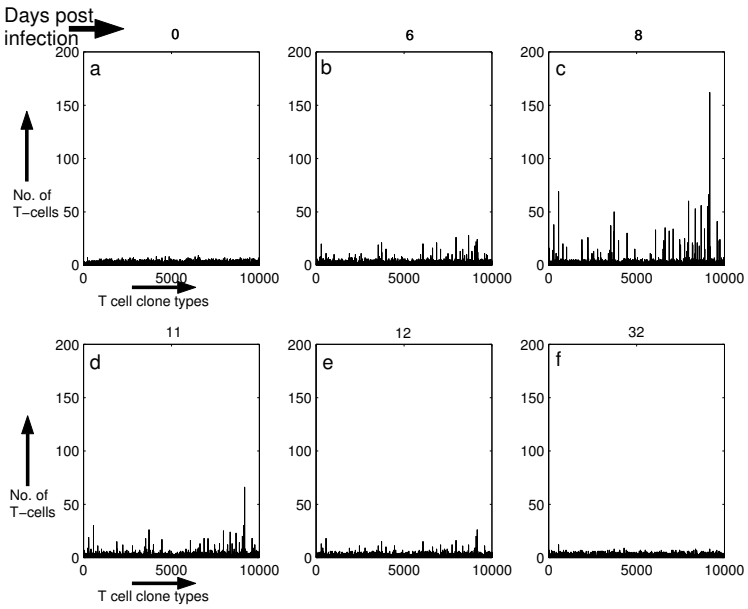

Fig. 1. Snapshots of the shape space showing the numbers of T cells of different clone types at various days after a primary infection.

are self-antigens and the repertoire is stable. (b) Six days after infection - the total level of T cells is only slightly higher, but it has become skewed towards those members of the repertoire that are reactive to the pathogen's antigens. (c) At 8 days, the immune system is completely committed to dealing with the pathogen. The high levels of T cells and pathogens trigger the specific reaction of the immune system that rapidly decimates the pathogen, causing a depletion of its antigens. (d) Day 11 - Without the driving force of the pathogen antigens, the homeostatic forces in the system quickly bring the total population back to pre-infection levels. (e) Even though at 12 days the levels of T cells relevant to the infection are still high, we can see that the rest of the repertoire is more or less at pre-infection levels.(f) As we can see from the last snapshot, the system has returned to its resting state three weeks after infection. The 'days' are calibrated according to the rate of T cell arrival from the thymus. T cells maturate from the thymus at a rate of $\sim 2\%$ of total T cell population (at rest) per day. The general time course of the reaction to the pathogen in silico fits in well with what occurs in vivo.

4 Conclusions

This simulation emphasizes several points that turn on its head the way we view self-reactivity in the immune repertoire and the nature of the immune system's function in general. Based on known dynamics of T cell behavior [5] - positive selection in the immune periphery and T cell homeostasis [4] - we change our view of self affinity. We have taken Grossman's theory or immune reaction to change in activity [6] to its logical extreme and done away with any kind of heightened receptor specificity to non self antigens. By showing, in our simulation, that this does not preclude a normal immune reaction, we have shown that affinity to self need no longer viewed as something to be avoided. Instead the ability to detect novel antigens and maintain a stable repertoire appears to be based on an affinity to self.

The immune system behaves like other perceptual systems [3]. It uses the self as a background signal, which it ignores, while reacting to the changes this background emphasizes. Affinity to self is the basis not the nemesis of immune reactivity.

This upward re-evaluation of the centrality of self-reactivity to immune capabilities, leads to important changes in our general view of immune dynamics. Primarily, it unifies the various functions of the immune system which deal with the self with those that deal with the foreign. Combating cancer and repairing tissue damage obviously requires some affinity to self. Here self-reactivity comes under one umbrella with combating infection. We can now view the immune system as a housekeeper rather than a gatekeeper.

The results using our model emphasize the need to study the dynamics and reactivities of the immune system in healthy states. We believe that further research of the clonal types and affinities found in the healthy body will further strengthen the view we have put forth in this paper. Immunology is unique among the life sciences that the basic state for most research is not the system active in a healthy body, but rather when the body is in distress. Realizing that there is meaningful immune activity when we are healthy should move the science of immunity to redress this basic prejudice.

References

1. Borras, E. and Martin, R. and Judkowski, V. and Shukaliak, J. and Zhao, Y., and Rubio-Godoy, V. and Valmori, D. and Wilson, D. and Simon, R. and Houghten, R. and Pinilla, C. (2002) Findings on T cell specificity revealed by synthetic combinatorial libraries, Journal of Immunological methods, **267**,79-97.
2. Burrnet, F.M. (1957) A Modification of Jerne's Theory of antibody Production Using the Concept of Clonal Selection, Aust J. Sci., **20**, 67-69.
3. Cohen, I.R. (2000) Tending Adam's Garden. San Diego, Calif., Academic Press.
4. Ernst, B. and Dong-Sup, Lee. and Chang, J.M. and Sprent, J. and Surh, C.D. (1999) The Peptide Ligands Mediating Positive Selection in the Thymus Con-

trol T Cell Survival and Homeostatic Proliferation in the Periphery. Immunity, **11**, 173-181.
5. Goldrath, A.W. and Bevan, M.J. (1999) Selecting and maintaining a diverse T cell repertoire. Nature, **402**, 255–262.
6. Grossman, Z. and Paul, W.E. (2001) Autoreactivity, dynamic tuning and selectivity. Current Opinion in Immunology, **13**, 687-698.
7. Lahngman, R.E. and Cohn, M. (2000) A minimal model for the self-nonself discrimination: a return to the basics. Seminars in Immunology, **12**, 3, 189-195.
8. Matzinger, P. (1998) An Innate Sense of Danger. Immunology, **10**, 399-415.