The Immune System and Bodily Defence

6. How Does the Immune System Live With a Randomly Generated Repertoire?

Vineeta Bal and Satyajit Rath

How does the immune system make sure that the assorted recognition keys it cuts for itself do not open the wrong doors and cause self-inflicted disease?

How Does the Immune System Weed the Developing Repertoire?

Clearly, if the immune system is geared to 'deal' in fairly drastic fashion with targets it recognizes, one does not want anything one needs, such as one's own liver cell, to be a 'target'. But the developing immune repertoire is essentially random, as we have argued for a while now, and is therefore as likely to generate receptors recognizing 'normal' body components, or 'self', as targets, as it is to generate those recognizing potential invading parasites. Since we do not want to lose the randomness of the receptor generating system, we are stuck with the occurrence of these B and T cells carrying self-recognizing receptors. If one cannot prevent them from coming up, one can only hope to turn them off after they come up. This entails first finding cells which have a receptor that recognizes some body component, and then turning it off in some fashion. The much-acclaimed 'fundamental paradigm' of immunology, that the immune system distinguishes between 'self' and 'non-self', is thus so mundane a task as weeding, although immunologists tend to refer to the process somewhat pompously as 'negative selection'.

This inevitably means that the immunological distinction between 'self' and 'non-self' is not done by any general rules of structure; there are no preset criteria in the immune system that would suggest to it that a given molecule was 'normally' made in

The authors are scientists at the National Institute of Immunology, New Delhi, and have been working on various aspects of cellular and molecular immunology for the past six years or so. In addition to teaching post-graduate immunology, their research interests and ongoing projects address the differential commitment of effector T cell pathways and signal requirements for such activation of T cells [VB], and the mechanism of antigen processing, T cell activation and tolerance, T-B cell interactions and B cell maturation [SR].

The previous articles of this series were:
1. Why do we need an immune system? January 1997.
2. How do parasites and the immune system choose their dances? February 1997.
3. How does the immune system organize itself so as to connect target recognition to expected functions? June 1997.
4. How does the immune system recognize everything under the Sun? September 1997.
5. How does the immune system generate a truly infinite repertoire capability? November 1997.

the body itself. The definition is purely empirical; if something is constantly around, ubiquitous, and not associated with the functional hallmarks of an invader (what these are is a general problem we will come to in a bit), it is likely to be a 'self' molecule, otherwise it is probably a foreign one.

How Does the Immune System Identify 'Self'?

How does the system make such empirical judgements? One way is to say that if a given molecule is constantly present, then it is likely to be encountered almost immediately by an appropriate 'new' B or T cell that has just been born. So one rule of thumb for B and T cells becomes: if you encounter a target when you are very very young, you (i.e. T or B cell) are harmful, and should shut up (see *Figure 1*), while if you encounter it after you have become 'adult' [the individual B or T cell, not the organism], it is likely to be a foreign molecule and you should respond with all your might and main, so to say. In other words, there is a window during the development of B and T cells immediately after the expression of their receptors on the cell surface, when encountering an antigen turns them off rather than on.

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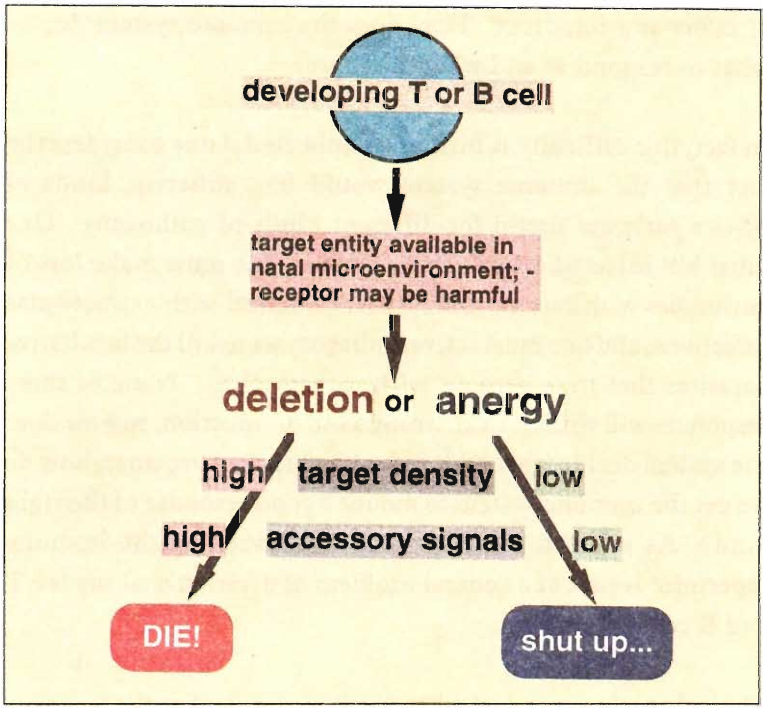
This creates problems, obviously, of both commission and omission. If there is an ongoing infection whose molecules are seen by developing immune cells, they would be weeded of those reactivities instead of becoming responsive to them, as happens, for example, in the immune system of a baby in the uterus if it catches an infection, say, hepatitis B virus, from its mother. This means that the baby cannot now make an immune response against hepatitis B virus to eliminate it, and such babies become chronic carriers of the virus in real life. Secondly, all molecules of the body cannot parade in and out of the bone marrow, say, or the thymus, all the time: there are many bodily molecules that are expressed as intracellular proteins, or that are only expressed in specialized tissues. So B or T cells may not meet these while in the bone marrow or the thymus, but would meet them once

Figure 1.



they leave their birthplaces and go out into the wide-open internal spaces of the body. If this happens, these molecules, despite actually being self from the body's point of view, would be thought foreign by the immune system and attacked, which is likely to be detrimental to health and happiness. So one needs some sort of a second level diagnostic mode in place. What can be used?

How Does the Immune System Decide What Needs to be Attacked and What Does Not?

We said a bit earlier that another way of identifying 'self' may be to say that 'self' is not normally associated with the functional hallmarks of an invader. This is connected to a more general problem we have noted in passing in earlier discussions of immune recognition models; that recognition of a 'tag' does not automatically mean that the entity associated with the tag is dangerous, so that responding to every tag is likely to be a waste

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of effort and resources. How does the immune system decide what to respond to and what to ignore?

In fact, this difficulty is further complicated if one considers the fact that the immune system would find different kinds of *effector pathways* useful for different kinds of pathogens. One must kill infected cells to stop viruses. One must make lots of antibodies with certain characteristics to deal with extracellular infections, and one must activate phagocytes to kill the facultative parasites that they harbour within themselves. None of these responses will work for the wrong kind of infection, so how does the system decide what to do? And, to bring in vaccines, how do we get the immune system to mount a good response of the right kind? As you can see, the problem of weeding the immune repertoire is part of a general problem of decision-making for T and B cells.

The only real way to deal with this is to decide that the 'context' of the target will have to be allowed to decide what the immune system should do after recognition of the target. This 'context' will thus consist of signals that do not say what the target is, but that spell 'danger' and invite immune cells to respond rather than sit quiet. Clearly, the easiest contextual signals that can be used are those that the so-called innate immune system such as phagocytes use in fighting parasites in their own fashion (see *Figure 2*). Cell surface molecules as well as secreted proteins whose levels are induced by infection are thus favorite contextual or 'co-stimulatory' signals for B and T cells, and if target recognition occurs in the absence of such signals, the B or T cell would mount no response but be turned off instead (see *Figure 2*), which would be a successful negative selection. None the less, all these modalities of negative selection are obviously approximate and one would expect them to be liable to having large holes in them, and in fact so-called 'autoreactive' immune cells are not particularly rare in normal individuals. Why such responsive cells do not cause 'autoimmune' disease more frequently than they seem to is a separate fairytale in itself, as is

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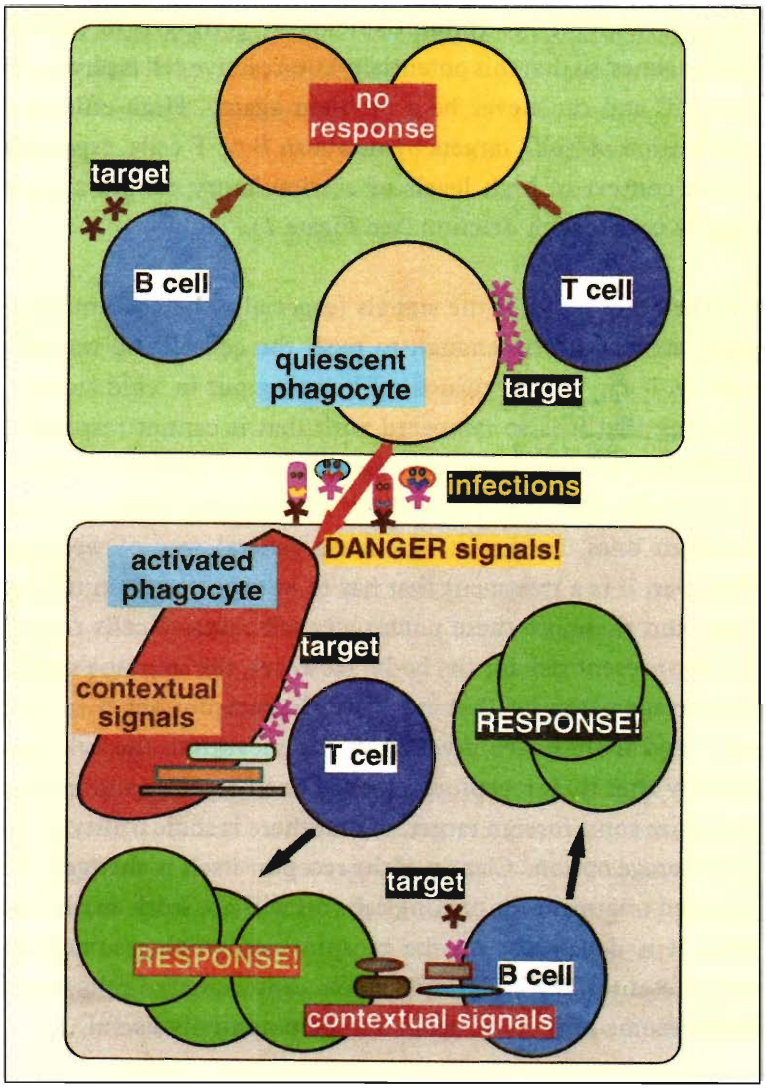

Figure 2. If a B cell sees its target as a circulating molecule but nothing else, or if a T cell sees its target as a peptide bound to phagocyte cell surface MHC molecules but receives no other signals, these cells will not respond and be turned off instead (upper panel). On the other hand, if phagocytes are 'activated' by infectious agents, they can now show both peptide-MHC target and contextual costimulatory signals to T cells and evoke a response from them (lower panel). One result of this process is that some of these activated T cells in turn can provide costimulation for any B cell that takes up its own target and converts it into a peptide-MHC target for the T cell to recognize. This combined stimulation then induces a B cell response (lower panel), which will result in antibody production.

the story of how contextual signals micromanage immune responses.

What Happens to the B and T Cells That are Turned Off?

Finally, it is all very well to say that you are going to turn a T or B cell 'off'. But what exactly does that mean? Broadly, there are two options for the immune system. One is to instigate the cell

Suggested Reading

- C A Janeway and P Travers. *Immunobiology: the immune system in health and disease.* Blackwell Scientific. [A concise and useful textbook for serious readers of immunology]

being turned 'off ' to commit suicide by getting it to turn on killing genes, so that this potentially autoreactive cell is physically 'deleted' and can never be a problem again. High-efficiency recognition of 'self ' targets by newborn B or T cells, especially in the context of high levels of costimulatory danger signals, usually causes such deletion (see *Figure 1*).

On the other hand, if the signals [especially the costimulatory ones] are not strong enough to push the cell all the way into suicide, it can still be turned off by being put in 'cold storage'; meaning that it is so tampered with that it cannot respond to anything at all for a long time (see *Figure 1*). This, of course, is a treatment that can be used on all B and T cells, not just newborn ones, so that it is a more general way of weeding. However, it is a treatment that has to be repeated from time to time, and therefore these potentially self-reactive cells remain an ever-present risk for the body. However, the immune system has salvage pathways that can 'edit' the receptor genes in such cells, and if those are invoked in the meantime the cell may actually alter their receptor, cease to be self-reactive and instead recognize some foreign target, so that there is some utility to the cold storage option. Clearly, if the receptor itself is changed, the repeated treatment for turning cells off will not work any longer since it is dependent on the receptor recognizing something ever-present in the body, and these receptor-altered cells would then become responsive again and be potentially useful.

Thus, borrowing cells and tricks from a variety of related systems, the immune system jerry-rigs for itself a tenuous set of working circuits and rules that allow it to function, in carefully targeted fashion, against any invader that the outside world can throw at it. Just what happens when this immovable object meets the irresistible force of parasitism is yet another long story that would need another series of articles.

Address for Correspondence
Vineeta Bal and Satyajit Rath
National Institute of Immunology
Aruna Asaf Ali Road
New Delhi 110 067, India.