The Immune System and Bodily Defence

4.How Does the Immune System Recognize Everything Under the Sun?

Vineeta Bal and Satyajit Rath

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 mechanisms of antigen processing, T cell activation and tolerance, T-B cell interactions and B cell maturation [SR].

How does the immune system make sure that it has a key for every lock in the world?

What are the Constraints on Creating a 'Repertoire'?

We have argued earlier that the clonally diverse model of immune target recognition or the adaptive immune system forms the mainstay of the defence mechanisms in a vertebrate host and that there is much to be said about it. But such a system design also creates some fairly major problems. One problem is that the developing immune system does not know what it is going to meet out there in the big bad world. For all it knows, it may even have to deal with green Martian bugs. Since it is supposed to be ready for any possible target, so-called evolutionary experience does not help either, since it will simply indicate what has been met in the past, but does not guarantee that nothing new will be met in the future. So the sky is the limit on the potential diversity of targets. There is also no way the immune system, or the organism for that matter, can limit its exposure to new enemies, since the external environment is pretty much beyond the control of the organism. A major exception to this is, of course, the fairly recent innovation in biology called *Homo sapiens* that does control its environment radically, but it is a natural experiment of fairly short duration and may turn out to be self-limiting.

In any event, if the number of potential targets is unlimited, naturally, the potential diversity of antigen recognition structures, or receptors, needed in every individual is also unlimited. But the genome cannot carry unlimited numbers

of prefabricated genes. So how can this diverse array, this 'repertoire', of receptors be generated? The only way of generating such an infinity of receptors is to take a gene for a basic receptor shape and chop and change it at random to generate new genes for new shapes, and do this each time afresh in each individual. This explains the last peculiarity of the immune system mentioned at the beginning, - wherein the component cells rearrange their DNA during their development.

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.

How is Genome Tailoring to be Done for Making Receptors?

Subjecting the entire receptor gene to such tailoring would frequently cause a change, not in the bit of the receptor molecule that actually binds to its target, but in the bits that do other things, such as anchoring it to the membrane of the cell, for example. So it would be nice to restrict the alteration process to a very small portion of the receptor molecule. Also, this 'changing' would involve either adding, removing, or altering the sequence of the stretch of DNA concerned, at random. Such random DNA change is a very risky business for the cell to indulge in. So it would be better if the cell relies on such changes to a lesser extent. It would, therefore, also be better and safer to generate a fair-sized repertoire without having recourse to mutations if we can.

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To do all this, first it is necessary to break the receptor down to its basic functional elements, so that the rearranging machinery only has to tinker with small well-defined bits in the receptor rather than play with the whole receptor. Obviously what we need, for each B cell and each T cell, is a receptor that recognizes a different target antigen. But having once recognized its own unique target, each receptor must be embedded in the surface membrane of the cell in the usual way. It must carry a signal into the B or the T cell it belongs to so as to stimulate it in exactly the same fashion as

any of its cousins on other B or T cells would. In other words, while the recognition function of each receptor must be unique, the anchoring and signalling functions must be common to all cells of a particular lineage, and therefore to all receptors in the repertoire of that lineage. In fact, the anchoring-signalling functions would be expected to differ only if the cell type and lineage is different, so that all B cells should share a common structure, while all T cells would share a common structure different from that of the B cells (see *Figure 1*).

So to begin, we can divide the receptor molecule itself into two, a recognition portion which must vary between individual cells, and an anchoring-signalling portion that must be common to all the cells of that particular lineage, either B or T as the case may be. The anchoring-signalling portion is the basic structural framework for the receptors which is shared by many receptors and is therefore the 'constant region', while the recognition

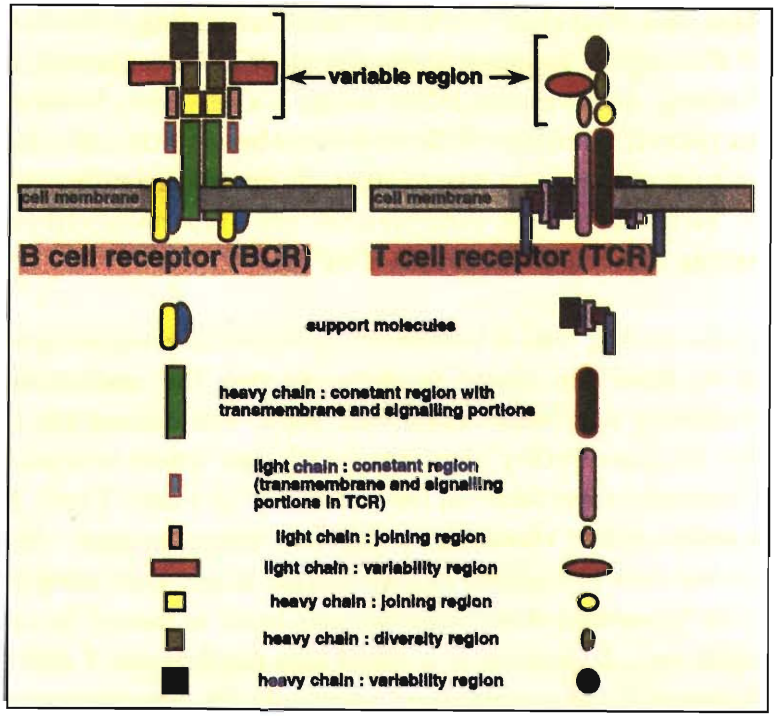

Figure 1

portion is 'variable' between receptors (see *Figure 1*). So one can now get the constant region coded for by one *exon* [1] of the receptor gene and leave that untouched by the process of generation of diversity which would create the 'variable' exon.

[1] Exon is a protein-coding region of a gene that is represented in the mature RNA. Most protein-coding genes in eukaryotes consist of a series of exons interrupted by introns.

Can the Repertoire be Maximized Without Recourse to Mutation?

Next, are there any ways of generating a fair degree of diversity without having recourse to actual changes in the gene sequence, that is, by simply 'recombining' available genes rather than 'mutating' them? One way, of course, is to take small pools of building blocks for variable regions, and make a diverse repertoire by shuffled permutations and combinations of these. To maximize the results of such a shuffling exercise, it is useful to have multiple components to the variable region.

First, B cells can recognize any specific target shape, while T cells recognize target only as a peptide bound to an MHC molecule. Also, these are two different lineages of cells, which respond to different types of signals given to them by the receptor. So the constant regions also have to be different (see *Figure 1*). It is thus useful to have separate sets of receptor genes from which to generate the receptors for B cells versus T cells.

Second, it would be useful to have receptors made of two protein chains rather than just one, so that chain-1 A plus chain-2 B make one receptor, but chain-1 A plus chain-2 C make a receptor with a different specificity. Many biological systems use two-chain receptors, so this is not a great practical problem either. Both B and T cell receptors thus have two chains, the smaller one called *alpha* or light chain and the larger one *beta* or heavy chain (see *Figure 1*).

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Third, rather than simply using one small pool of variable regions for each chain from which to draw a lottery at random in

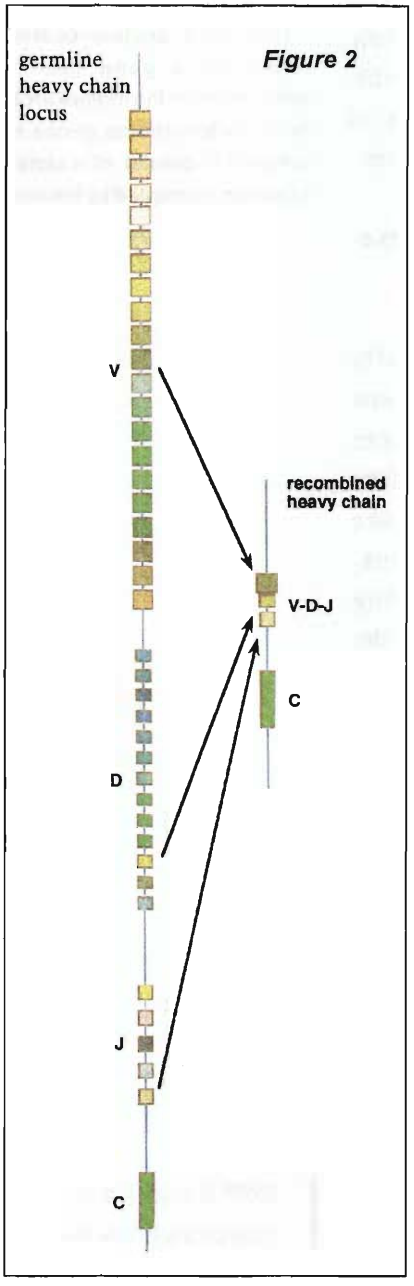

Figure 2

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

each B or T cell, it would be nice to have this variable region itself broken up into smaller portions, and then to have a lottery from each pool for these smaller bits. The larger chain genes have three such *minigene pools*, the 'V group', the 'D group' and the 'J group' (see *Figure 2*), while the smaller receptor chain genes have only two of these, the 'V group' and the 'J group'.

Thus, each of these minigenes contributes a brick resulting in the final composite structure of the variable region of one protein chain of the receptor. In each minigene pool, there are many alternative bricks available and each one, selected randomly from each group in each cell, joins with its counter parts from the other groups to form a variable region (see *Figure 2*). Each of these bricks has a sequence 'tag' at its end, so that one from the heavy chain V group, for example, cannot join with one from the heavy chain J group without a D group member in the middle. This 'recombination' process thus generates a significantly diverse repertoire in a fairly orderly fashion. However, this is still not an infinite repertoire, since all the information comes from the genome, which is finite after all. So how is real 'open-endedness' injected into this process of repertoire generation, and what are the problems of opening the bottle for the genie of real randomness of repertoire? In the next article, we will try to look at the mechanisms that generate such randomness.

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 in immunology]**