The Immune System and Bodily Defence

1. Why Do We Need an Immune System?

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How does the human body defend itself, and why does it choose the paths it does choose?

How is the Immune System Peculiar?

The immune system is unusual among physiological systems in many respects. Each individual peculiarity may be shared, perhaps, with others, but together, these characteristics make the immune system distinctly different from its fellow systems. One, it is not an anatomically well-localized and circumscribed set of organs. Two, it is resting in the ideal state and must be called upon before it becomes active. Three, even after being triggered to function, it has to undergo cellular maturation before it can be effective. Four, apart from the reproductive organs, it is perhaps the only system in which component cells rearrange their DNA and even lose large portions as a necessary step during development and maturation.

Why does the immune system behave so peculiarly in so many ways? Like good Darwinians, let us try to derive all these peculiarities from requirements imposed by the functional demands on the immune system. So the first question that arises is - why is the immune system necessary ?

Why is the Immune System Necessary?

To answer this, consider what an organism that has chosen true multicellularity has to do. It has to keep its component cells together, and it has to get different groups of them to perform different functions. This commitment to division of labour means that every cell of the body cannot do everything. Some

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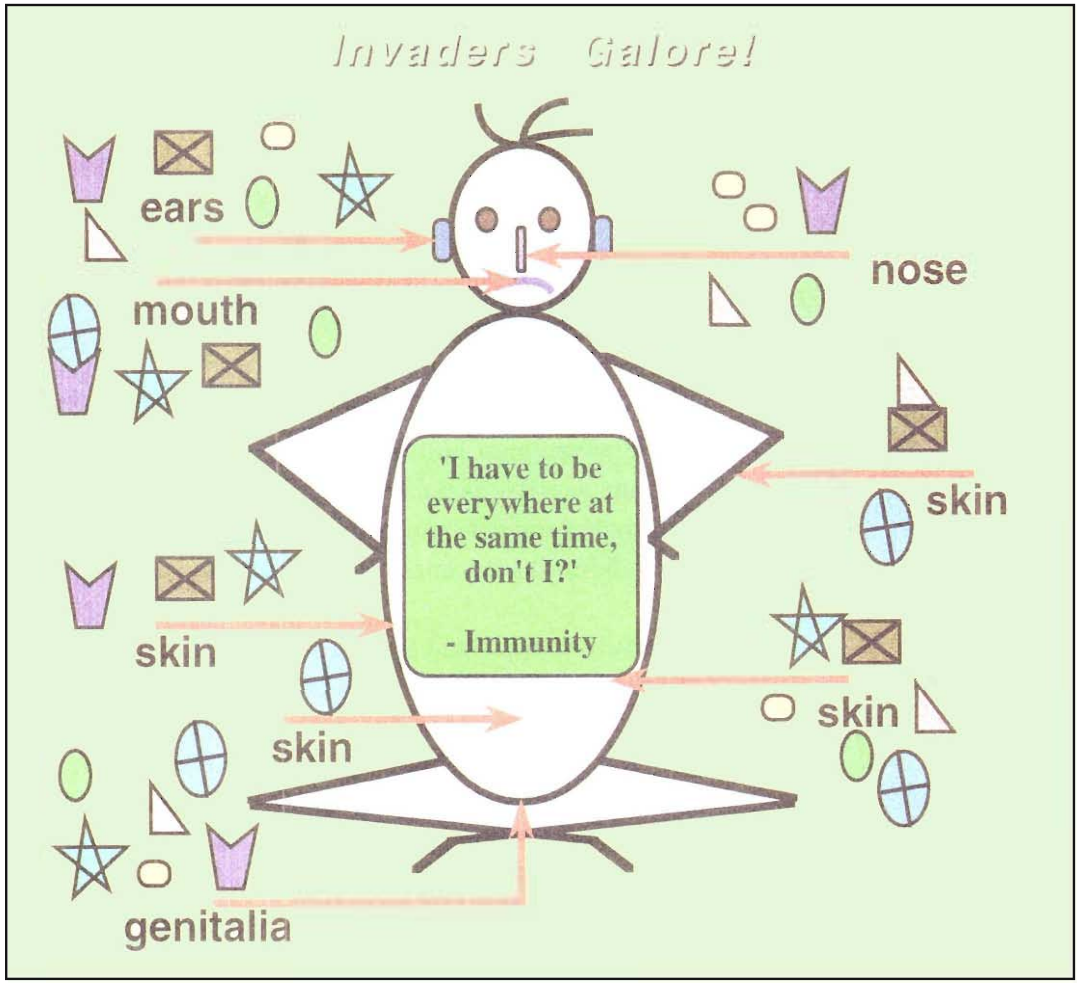
cells may become so specialized that they cannot survive as free-living entities. Many such cell types will therefore have to be provided with readymade essentials of life. For this, the body has to maintain a rigidly controlled internal environment that is rich in nutrients. This is an invitation to all sorts of creatures from outside to come in and feed off the bonanza. If the host organism is to maintain its integrity, it must be able to get rid of these freeloading invaders.

In fact, it is even possible that a cell of the host organism may escape the control of the organism and take off on its own on an autonomous lifestyle, using the controlled internal environment and the nutrients available in it to make hay. This is what we commonly call a *malignant* or *cancerous* cell. Such aberrant cells also have to be dealt with. In other words, metazoan life necessitates some form of defence against many kinds of invasion.

Experimentally, one can ask the question what is the immune system good for ? by looking at animals that do not have immune systems, either through spontaneous defects such as genetic immunodeficiencies, or engineered defects such as in mice which have had some gene critical for immune function deleted. In most respects, such 'immunodeficient' animals may appear to be quite normal, healthy and happy insofar as can be determined. They do not suffer particularly from any increased frequency of cancers either, which suggests that the evolution of the immune system is unlikely to be driven strongly by the occurrence of cancerous transformations, and estimates of the low frequency of normal spontaneous rates of mutation during DNA replication, which are of the order of one in ten million, would help explain why mutation-derived cancers are not a major evolutionary pressure for the immune system.

The major function of the immune system is to defend the body against infections, and therefore its evolution would be shaped by the nature and form of these infections.

However, such immune-deficient animals do fall ill very readily with a variety of infections, and in fact, they tend to die very quickly if exposed to even so-called normal external environments which are, of course, teeming with potential freeloaders.



This experimental finding, too, would thus argue that the major function of the immune system is to defend the body against infections, and therefore its evolution would be shaped by the nature and form of these infections.

How does all this explain the peculiarities of the immune system we started with? One, since the invasion is going to come from the outside, the body cannot know, in the nature of things, at which points its defences are going to be breached. So components of the defence system must be available everywhere in the body to detect invasions right at the point of entry (*Figure 1*). This means that the

Figure 1 Necessity for the omnipresence of the immune system. The human body is vulnerable to parasite attack through a variety of routes, and these invaders come in wide varieties themselves; hence the need for the anatomically spread-out nature of the immune system.

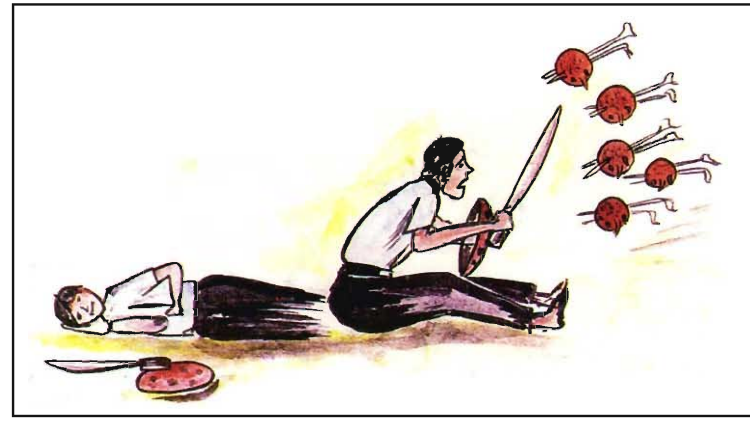


Figure 2 The immune system sits back and rests, but watches out for freeloaders.

immune system must infiltrate the entire body in order to be useful, and then it is no wonder that it is not restricted to a well-circumscribed and self-contained set of organs, although it does use specific organs for certain activities such as development.

Similarly, if its major, and perhaps the only function is to deal with infections, in an anthropomorphically idealized world where there are no parasites, the immune system would have nothing to do. In fact, even in the real world, it will not have continuous functions; it is called upon only when invasion does occur. So 'normally', the immune system would do nothing, although it would watch and wait (*Figure 2*). It all sounds like a job in the defence services, and that is not a bad analogy, although it is probably better extended to all the forces that maintain law and order in society.

The defence system must be available everywhere in the body to detect invasion right at the point of entry. This means that the immune system must infiltrate the entire body in order to be useful.

How Does the Immune System Deal with Infections?

So how does the immune system deal with infections? In the first place, 'dealing with' infections must have two components – detection and action. One has to recognize foreign invaders, and then do something about them. The easiest way to accomplish this is to have a special receptor on the surface of an immune system cell that would recognize all invaders and stimulate the cell to carry out the necessary protective function. Unfortu-

nately, neither the recognition nor the protective function can be this single-minded if they are to be useful. Pathogenic or disease-causing parasites come in great variety and flexibility, so that one cannot imagine any one receptor recognizing a molecular 'tag' that all pathogens carry. So one needs an array of receptors. Similarly, parasites use a wide range of strategies for invasion, and the immune system must use appropriately tailored responses in order to deal with each of these. So a single response after recognition will not work either. Finally, there is no guarantee that a given 'tag' will necessarily be associated with only one kind of parasite and that one specific response will definitely be useful. So recognition of targets, and the decision of what to do in the way of an effective immune response have to be delinked, separate decisions.

Let us now look at these constraints one by one. First, the immune system has to generate an array of receptors that recognize, together, all pathogenic parasites. How can this be done? There are two possible models of recognition that can be used: one based on clonal uniformity and one on clonal diversity.

Models of Immune Target Recognition

Before we look at these models, the terms need some explanation. *Clonally uniform* cell populations are all identical copies of each other, and every cell would bear exactly the same receptors. This is the normal state of affairs in the body, so that all liver cells, for example, look exactly like each other. On the other hand, *clonally diverse* cell populations would have descended from the same parent cell, would perform the same functions, and yet have one receptor species unique to each cell in the collection so that it does not share it with any of its sisters.

Clonally uniform receptors identify 'foreign' targets by recognizing molecules that are 'foreign' by classification categories, whose basis is quite unrelated to the issue of immediate 'foreignness'. One can extend the analogy that we used earlier of the

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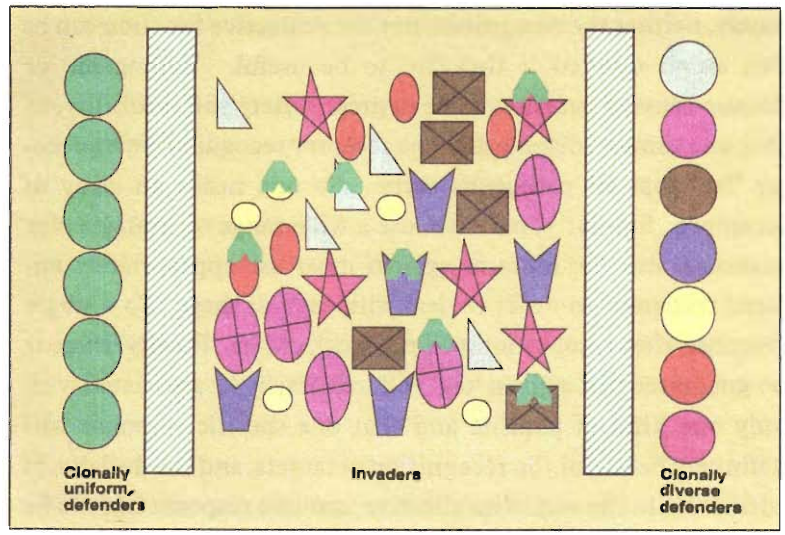

Figure 3 Recognition through clonally 'uniform' versus 'diverse' identification. The clonally uniform immunocytes will recognise all invaders, no matter what their differences are, if they are wearing red caps, but not otherwise. The clonally diverse immunocytes will recognise their colour targets on invaders individually.

immune system being like a police force, and it then becomes obvious that the clonally uniform target recognition model is analogous to a religion or community based foreigner identification model in society. As an example, lipopolysaccharide is a 'foreign' molecule in this fashion, because, by and large, the mammalian body itself does not make anything that looks very much like *lipopolysaccharide* [1]. Clonally uniform effector cells like macrophages and polymorphonuclear leukocytes bear such receptors. Such a repertoire of receptors will have only a limited and fixed range, since it is meant to recognize a few frequently occurring *ligands* (*Figure 3*).

[1] A substance composed of lipid and carbohydrate moieties.

Why is Clonally Uniform Recognition Not Enough?

Dependence on such a limited repertoire of frequent, conserved targets that can be used to*tag* invaders carries major risks, similar to the risk of using a religion or community based foreigner identification model in society. First, if pathogenic parasites simply stop making this marker 'tag' molecule, or change it sufficiently so that it is no longer recognized by the receptor, the immune system will become blind to these modified invaders

and be of no use against them. These will thus be 'false negative' slip-ups by the immune system. On the other hand, there are many bacteria, for example, that live in perfectly happy collaboration with the mammalian body on or in it, especially in the gut or on the skin. All of these would also express, say, lipopolysaccharide, and the immune system would recognize them and make a great to-do about beating them over the head; wasted effort, since they were doing no harm, and quite frequently, were doing good (by making vitamins, or providing enzymes), in the first place. These would then be 'false positive' identification and action by the immune system against non-dangerous 'commensal' entities.

If the chances of parasites coming in are few, a small number of immune system cells bearing such receptors can be expected to function well. This will be particularly true if the host is going to know fairly well in advance what parasites are likely to try and get in. If sedentary organisms which live in the same place, have a relatively constant environment, deal with a restricted range of invaders, and have a hard shell around them to make any kind of entry very difficult for parasites, their immune system needs may be fairly simple. One can imagine arthropods or molluscs, for example, which are hard-shelled and stationary or sedentary, and would thus need only a rudimentary immune system based on the *clonally uniform recognition model*. In fact, that is what most of them have, with cells capable of engulfing particles such as bacteria as the main effectors. For mobile, soft and sensitive-skinned mammals, however, the possibilities of exposure to parasites are likely to be much greater both in quantity and in range, and the limitations of the clonally uniform model would become overwhelming for them.

The clonally uniform recognition model may work well for some organisms but its limitations would overwhelm others.

So how does the mammalian immune system deal with such problems? A highly variable target recognition system would deal well with the problem of a flexible pathogen. The only way

to make such a system reliable is to provide a separate, specific receptor for each unique molecular shape that one may come across, and provide each cell with only one of these receptors so that each cell can now recognize a unique target- *the clonally diverse model* of target recognition (*Figure 3*). Obviously, it has major similarities with an individual recognition-based foreigner identification model in society, the *voter card* model, so to say.

Implications of Clonally Diverse Recognition

This model has a number of advantages for the immune system. One, each target will trigger only a small subset of cells of the immune system, since each cell will be specific for a unique target (*Figure 4*) This means that one can mount a focussed response with a small number of cells and waste less energy. However, if only one cell out of a million, say, is going to respond to a given target, it is unlikely that it can make a difference all by itself. It will have to recruit more cells like itself before it can make a dent in the infection, and for this it cannot recruit other cells standing around, since they have receptors quite different from its own. It must therefore divide itself into many cells in order to generate a high frequency of cells specific for that particular target (*Figure 4*). This makes cell proliferation a fundamentally necessary response for the immune system.

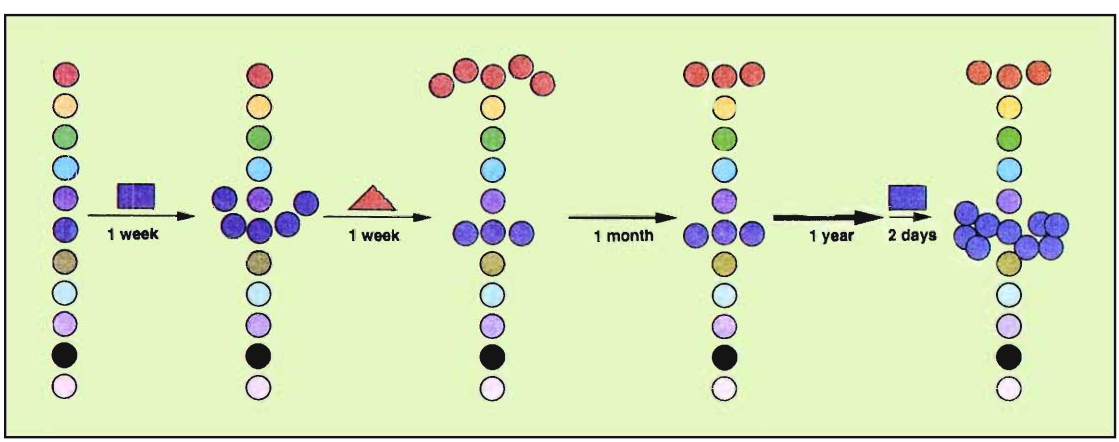

Figure 4 Focussed immune response and memory with clonally diverse receptors. Immunocytes with separate specificities are shown by differences in their colours. When they see invader A, only the relevant immunocytes respond and proliferate. This expanded group dies down, but its response to a re-exposure to the same invader is much faster.

An advantage of this dependence on cell proliferation is that effector cells do not have to be ready all the time, since they can be matured into *fighting fit* effectors even as proliferation takes place. This is yet another of those unique characteristics that we referred to at the beginning, that cells of the immune system need further maturation after seeing a target or before they can be effective. This property allows the system to remember past contact in a target-specific fashion, so that a slightly expanded and more sensitive group of cells recognizing a given target can be stored once the system sees the target for the first time. This allows an accelerated response to the target the second time it is seen, which is a great adaptive advantage, since the chances of the same parasite trying its tricks again and again are pretty high.

So a difference between the functions of clonally uniform and clonally diverse immune cells is that the former have to be *on* all the time, while the latter can be *resting* until called upon by their specific target. Another difference is that every clonally uniform cell will participate in any ongoing action, while only a few of the clonally diverse cells will do so. This means that the clonally uniform cells cannot usefully *remember* past contact, since it makes no difference to what they would do, while the clonally diverse immune cells would stay in *alert-but-resting* mode after first contact so that an accelerated response can be mounted upon re-exposure. Thus, the clonally uniform target recognition system is used for so called innate, or natural immunity, which has no potential for *immune memory*. The effector responses based on clonally diverse recognition, on the other hand, are referred to as *adaptive immunity*, and they are the component that can maintain immune memory and make vaccines possible.

Of course, the complications of the clonally diverse system of immune target recognition leads to a variety of practical problems in implementing it, and these will be the next issue of conversation.

Suggested Reading

- **G Bck and G S Habicht, Immunity and the invertebrates in *Scientific American*. Vol.275(5). p60.1996.**
- **G W Litman. Sharks and the origins of vertebrate immunity in *Scientific American*. Vol.275(5), p67.1996**
- **C A Janeway Jr and P Travers. *Immunobiology: the immune system in health and disease.* Blackwell Scientific Publications. (A concise and useful text book for serious readers in immunology)**

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