

The Immune System and Bodily Defence

2. How Do Parasites and the Immune System Choose Their Dances?

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Parasites use different strategies for successful invasion. So what are the responses that the immune system must tailor-make for these strategies?

Are There Easy Pigeonholes Into Which Parasites Fit?

When we were discussing the need to separate ways to recognize targets from ways of deciding what to do after recognizing them, we said in the first part of this series that the immune system must use appropriately tailored responses in order to deal effectively with the wide range of strategies parasites use for invasion. So, are there any broad categories that parasite strategies fit into, since that would make it easier to appreciate the pathways of corresponding immune responses available?

The Extracellular Niche

The answer, mercifully, is yes (*Box 1*). Consider the rich food environment we talked about last time, that metazoans have created for efficient division of labour among their specialized cell types. How many possible ecological niches can one imagine in such a milieu for freebooters? One, obviously, is the actual nutrient bath itself, all around the cells of the body (*Figure 1*). A parasite can simply sit in this jacuzzi, all expenses paid, and live it up. Many bacterial infections due to bugs such as, say, the pneumococcus causing pneumonia, or the staphylococcus causing acne, fall into this 'extracellular' category. They starve the cells around them, and produce waste products that poison the 'atmosphere' for these body cells.



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The previous article of this series was:

1. Why do we need an immune system? January 1997.

Box 1

Parasites invade cells using either of two strategies:

1. Occupy the extra-cellular niche.
2. Occupy the intra-cellular niche. Either the cytoplasm or an organelle

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The Intracellular Niches

The second ecological niche for pirates in the vertebrate body is, logically, inside the cells instead of between them (*Figure 1*). There are two major variants possible on this theme, given the structure of metazoan cells. Parasites may either sit in the walled-off organs of the cell, or 'organelles', or they may penetrate straight through these last membrane barriers to the cytoplasmic fluid of the cell.

Organelle Bubbles as Niches

The easiest way for parasites to get into these bag-like cellular organelles is to take advantage of the fact that all cells regularly replace their cell membrane as part of normal maintenance. So bits of old membrane are pinched off from the surface as bubbles into the cell, fresh membrane is inserted, and the old stuff is carted off for disposal. During this process, the cell will have to take a certain amount of the fluid from the outside into this bubble. This is the process of *pinocytosis*. All a parasite has to do is to be around when such a bubble is formed, and it can get into the bubble, or the pinosome [the 'drunk body'], from the outside and let itself be carried to the waste disposal organelles of the body (*Figure 1*). The organelles affected are those of the endosomal compartment through which pinosome traffic is guided. If a particle, such as a bug, gets into the pinosome, the bubble is too large to be called a pinosome and is called a *phagosome* instead [the 'eaten body']. Both kinds of sac-like bodies are part of the general category of *endosomes*, or internalized bodies. Bugs can even induce the formation of phagosomes by molecular 'scratching' of the cell membrane.

So getting into the endosomes of the cell is, relatively, a piece of cake for bugs. The trouble is, these endosomes are destined for disposal, meaning that they go and fuse with the lysosomes which are full of active enzymes. This is not a bright future for any self-respecting parasite to look forward to. So parasites

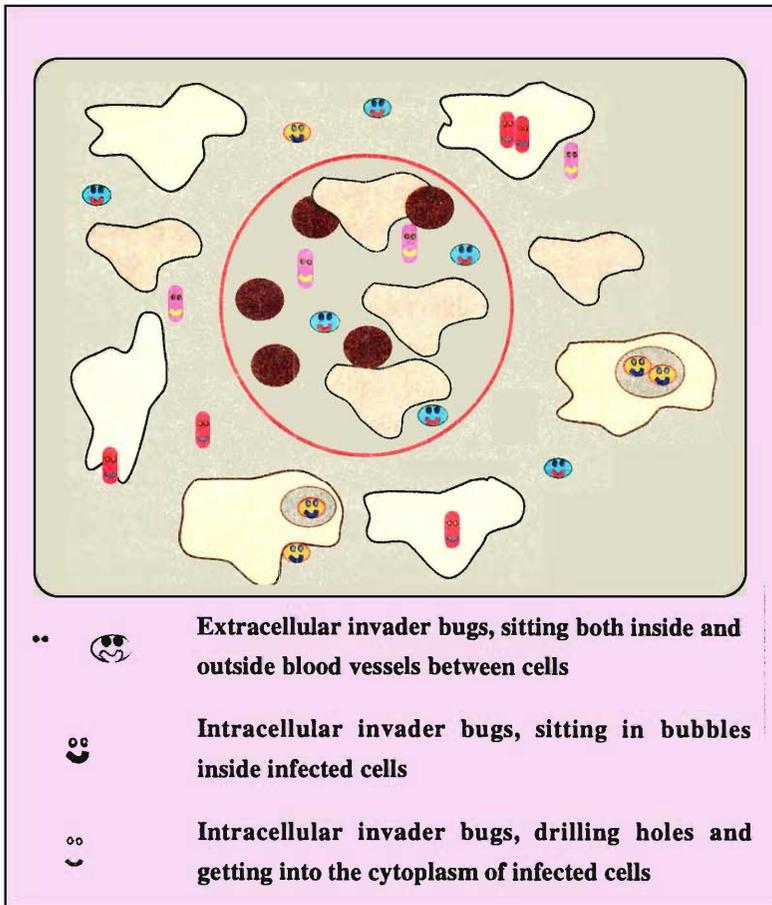


Figure 1 Parasite strategies for invasion.

Invader bugs are floating around in the blood vessel amongst many cells [red and white], as well as between body cells. Some bugs have waved good-bye to other pals around in the extracellular space as they get inside host cells, either by scratching the surface to form a bubble, or by drilling their way across cellular membranes to reach the cytoplasm. All successful parasites sport victory smiles as they feed off the bonanza!

which adopt this niche successfully have to work out ways to evade such a tragic end. They do this in a variety of fashions. Some of them, like the tuberculosis bug, put on coats so thick and fatty that enzymes simply cannot get a grip on them, and they can then happily get on with their lives like elephants, ignoring the dogs yapping at their heels. Others, like the typhoid bug, take over the bubble in which they are travelling, and redirect its route or change its composition such that it does not fuse with lysosomes any longer, and they can then continue to thrive in a rogue phagosome inside the host cell. A third way out for parasites in this scene, like one of the dysentery bugs, is to bore a hole through the wall of the phagosome and escape into the cytoplasm of the cell.

Foreign organisms can enter a cell through the endosomes.

Facultative intracellular parasites do not need to live inside cells in order to survive. They can be grown quite well, for example, in cell-free nutrient broths.

Which cells are most affected by these phagosomal Trojan horses? Obviously, cells which are very efficient at phagocytosis, meaning cells which love to eat, would be most at risk. Such cells fall into the general category called phagocytes, and in a logical paradox, they are the cells entrusted with surveillance duties to look for invaders and eat them. Most invaders get eaten and digested quite submissively, but the evasive strategies we talked about allow some parasites to turn the tables on these cells and infect them instead. Although the list of phagocytic cell types includes the polymorphonuclear neutrophilic and the eosinophilic granulocytes in the blood, these cells are very short-lived, and therefore infecting them is no great help to the parasite looking for shelter. The major cell type infected in this fashion is thus the monocyte-macrophage group, and we will see as we go along that the host has dreamt up strategies to allow the macrophage to fight back even against these Trojan horses.

The Cytoplasm as Niche

Most of the users of the two niches that we have talked about so far are free-living creatures like bacteria, protozoa or fungi. They are only taking shelter and finding a food niche even when they live inside cells. Therefore, they are *facultative* intracellular parasites, in that they do not need to live inside cells in order to survive. They can be grown quite well, for example, in cell-free nutrient broths. However, there is one category of parasites that have taken the art of freebooting to such heights of decadence that they are only 'alive' when they have a cell to live off. These are the viruses, the *obligate* intracellular parasites, which sit as almost inert particles with no signs of life till they get into a cell. But once they get in, they take over the life processes of the host cell to make more viruses which are then set free to infect other cells, damaging the host cell in the process. So whether they get in through the cell membrane directly, or through the phagosome, viruses bore through membrane barriers to enter the cytoplasmic fluid of the cell (*Figure 1*), where they can wrest control of the



protein-making machinery of the cell. Some viruses make lots of new viral particles and then break the host cell open to release them. Others will prolong the agony of the host cell by continuing to make new virus particles and releasing them by budding off the cell surface, so that the host cell dies slowly and bit by bit as it is irrecoverably damaged internally.

Those are the major strategies that invaders use to pick out niches for themselves. How can the immune system deal with these?

Protection of the Extracellular Space

Let us take the strategies one by one. For bugs which sit in the nutrient bath of the body, making molecules that will float around in the blood circulation, and recognize and wound the bugs mortally is an excellent notion that works even for invertebrates, which have far simpler immune systems. The molecules in mammals include acute-phase proteins, complement, antibodies and other such curious beasts that we will come back to as we go along. They all work by recognizing something on the surface of a bug, binding to it and either causing damage to the bug by themselves, or by recruiting other molecules or even cells like phagocytes to come and help chew up the bug (*Figure 2*).

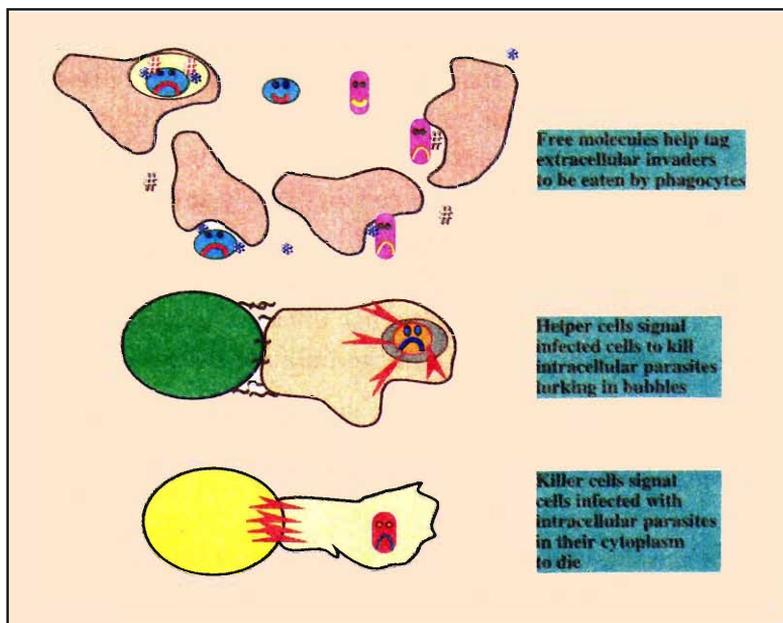
Junking Infected Organelle Bubbles or Cells

The trouble is, these molecules in extracellular circulation cannot get inside cells, since cells maintain a fairly tight control over what comes in and goes out. So intracellular parasites can sit safely in their havens and cock a snook at these circulatory effector molecules. What does the body do about these hidden menaces? Well, if they are sitting in the endosomes of macrophages, the body can use their footprints on the infected cell to identify it for 'helper' cells which would instruct the macrophage to increase its endosome trafficking and its enzymatic



Figure 2 Host strategies for defence.

The host makes floating molecules that catch and destroy bugs floating in the blood or outside the cells. Signals from a helper cell prick the placid macrophage to get converted into an 'angry' macrophage that kills the bugs in their internal bubbles. Other cells, infected with viruses in their cytoplasm, get the 'killer' signal from an immunocyte and shrink and die as a result.



arsenal such that bugs which are normally safe suddenly discover that an angry 'activated' macrophage makes nonsense of their plans (Figure 2).

But even this would only work for parasites which sit in organelle bubbles. The host cell can sacrifice the bubble along with the parasite; new organelles can always be made – *sar salamat to pagdee pachaas*.¹ However, if a parasite is going to sit in the cytoplasmic fluid of the host cell, there is no way for the host cell to chew it up without destroying its own cytoplasm, which means committing harakiri. So the principle of the greatest good of the greatest number is conveniently brought into play, and the infected cell which is identified, rather than being 'helped' to get 'angry', is told in no uncertain terms to die (Figure 2). In fact, most cells seem to carry a genetic 'software program' in them for suicide, *programmed cell death* or *apoptosis*.

Although killing your own cells sounds like a scarily drastic measure, it is frequently the only way to eliminate the last remnants of cytoplasmic infections. If multiplying viral particles in a host cell, for example, are going to burst it open to release



themselves so that they can infect other cells, it is possible that the circulating molecules we talked about, antibodies and suchlike, can indeed get a lock on them before the viruses reach new host cells and go to ground. But even here, we are talking about exponential increases in viral numbers, since one virus entering a host cell produces large numbers of new virus particles from that host cell, so that a single virus particle escaping these circulatory molecules will allow the cycle to start all over again. Also, viruses that simply bud new virus particles off the cell membrane of the host cell without killing it maintain a reservoir that cannot be gotten at by circulatory molecules. So getting to the root of the problem by cellular surgery or cautery, identifying and getting rid of infected cells, seems to be the only way to get over such infections fast. Even here, it would be a good idea to identify an infected cell long before any mature infectious virus particles have formed in it, so that when the cell dies, nothing infectious is released. We will discuss in the course of these conversations in immunology, strategies that the immune system uses to identify infected cells very early during infection.

In any event, the major 'effector' mechanisms or pathways that the immune system thus has to worry about generating are the production of fluid-phase 'terminator' molecules in circulation, the generation of 'helper' cells that will identify infected macrophages and 'activate' them, and the production of 'killer' cells that will identify infected cells and tell them to jump off a cliff. Both the clonally uniform and the clonally diverse modes of target recognition have evolved pathways for all three of these eventualities, and their ways of operation are quite strikingly similar although their target recognition strategies are radically distinct. Next time, therefore, we will come back to this vexing problem of recognition and figure out how on earth the immune system can recognize everything under the sun. The problem of how to decide which of these pathways to activate is even more complex. We will address these questions eventually in these perambulations in the logic of immunity.

Suggested Reading

- ◆ Scientific American . vol.269 (3), 1993 [special issue on origin development and functioning of the immune system].
- ◆ JERothman. Budding vesicles in living cells. *Scientific American*. Vol.274 (3). p70, 1996.
- ◆ C A Janeway Jr and P Travers. *Immunobiology: the immune system in health and disease*. Blackwell Scientific publication. [A concise and useful text book for serious readers of immunology]

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Table 1 . Examples of varied routes of entry of disease causing agents in humans.

Disease	Pathogen	Port of Entry
1. Tuberculosis	<i>Mycobacterium tuberculosis</i>	Respiratory tract (lung)
2. Leprosy	<i>Mycobacterium leprae</i>	Nasopharyngeal mucosa
3. Typhoid	<i>Salmonella typhimurium</i>	Gut
4. Louse borne typhus	<i>Rickettsia prowazekii</i>	Broken skin
5. Urogenital infection	<i>Chlamydia trachomatis</i>	Urogenital mucosa
6. Diphtheria	<i>Corneybacterium diphtheriae</i>	Respiratory tract
7. Plague	<i>Yersinia pestis</i>	Blood stream (flea bite)
8. Rabies	<i>Rabies Virus</i>	Skin, mucosa
9. Tetanus	<i>Clostridium tenani</i>	Skin or blood stream
10. Syphilis	<i>Treponema pallidum</i> (a spirochete)	Genital mucosa



Ayan Guha

And then someone told him that both coal and diamond are of same carbon