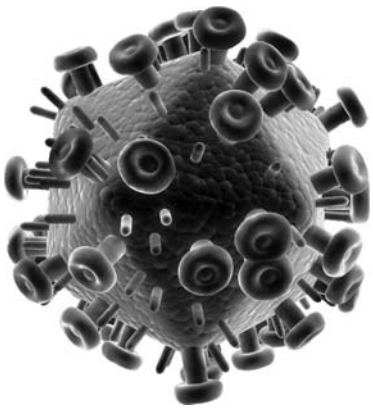
Resistance Is Futile ... or Is It? The Immunity System and HIV Infection



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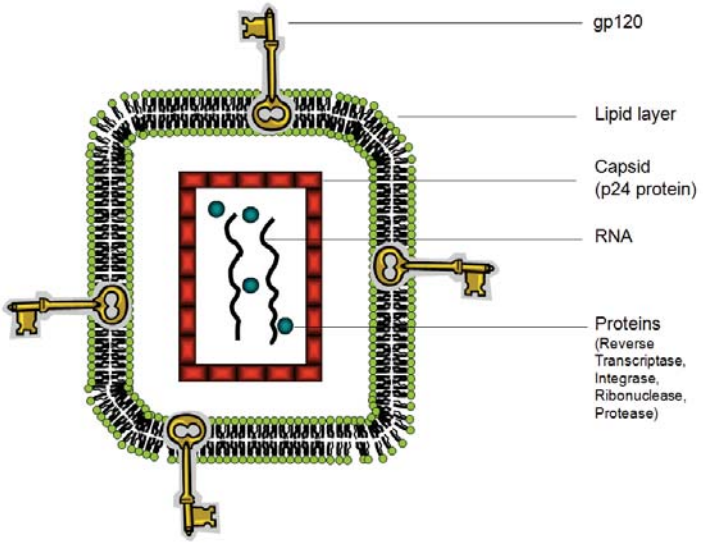
Part I – HIV and the Immune System

The vast majority of people are susceptible to HIV infection. However, in the 1990s, several individuals noticed that despite repeated exposure to the HIV virus they remained HIV negative. This could be due to the fact that these individuals were extremely lucky, or perhaps there was something different about them that made HIV infection less likely.

William Paxton and his colleagues at the Aaron Diamond AIDS Research Center in New York became interested in this phenomenon of HIV protection. In this case study, you will retrace the steps and experiments that these researchers performed to understand the mechanism underlying the protection against HIV (Paxton et al., 1996).

To this end, you must first review a few facts about the HIV virus, the immune system, and HIV infection.

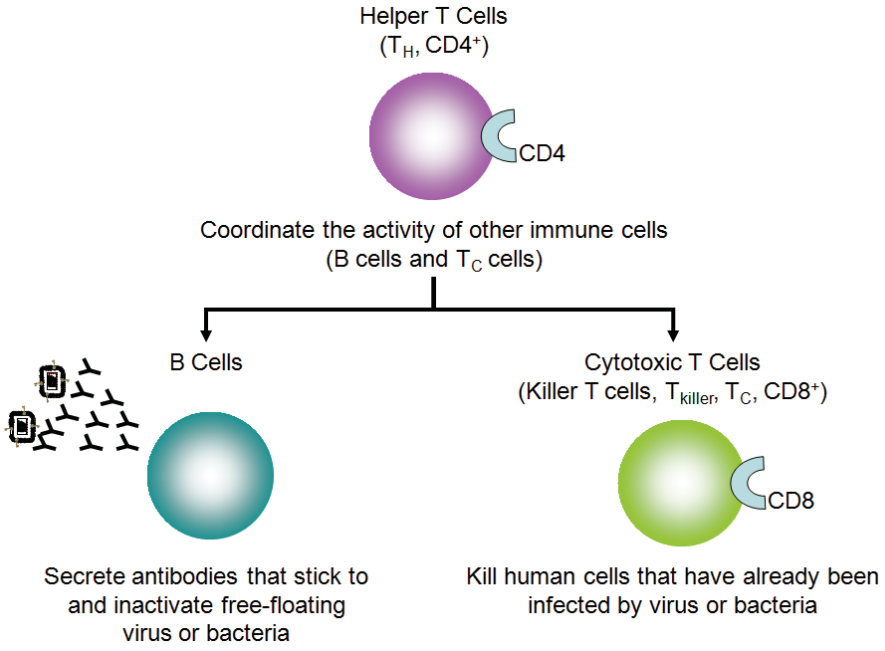
The HIV Virus



The virus particle is spherical in shape. Its structure consists of multiple enclosed layers, like the skin of an onion. It is considerably smaller than human cells. At the center of a virus particle are two copies of its genetic material. HIV encodes its 9 genes using the nucleic acid molecule RNA (by comparison, our cells use DNA for this capacity). At the core of the virus particle are also proteins important for the replication of the virus (reverse transcriptase, integrase, protease, ribonuclease). The RNAs and proteins are wrapped in a protein coat (called the capsid) made of the protein p24. The capsid in turn is wrapped in a double layer of phospholipids. Finally, there are proteins that stick out of the lipid layer, such as gp120 (sometimes called Env). This latter protein gives HIV its specificity: gp120 interacts with specific proteins found only on certain human cells (like a lock and key mechanism), allowing the HIV virus to infect specific cell types.

The Immune System

The immune system is a very complex system. Here, we review only those aspects that are relevant to this case.



B cells (sometimes called B lymphocytes, plasma cells, plasma B cells, plasmocytes, or effector B cells) are white blood cells involved in neutralizing a virus or bacteria that have not yet infected a cell and are "free floating" in the body (this is called the humoral immune response). B cells secrete a protein called an antibody into the circulatory system. Each antibody binds to a particular virus or bacteria very specifically and strongly. When antibodies bind to a virus or to bacteria, the foreign object is inactivated. Therefore, when B cells secrete antibodies, they "take out" free-floating foreign invaders.

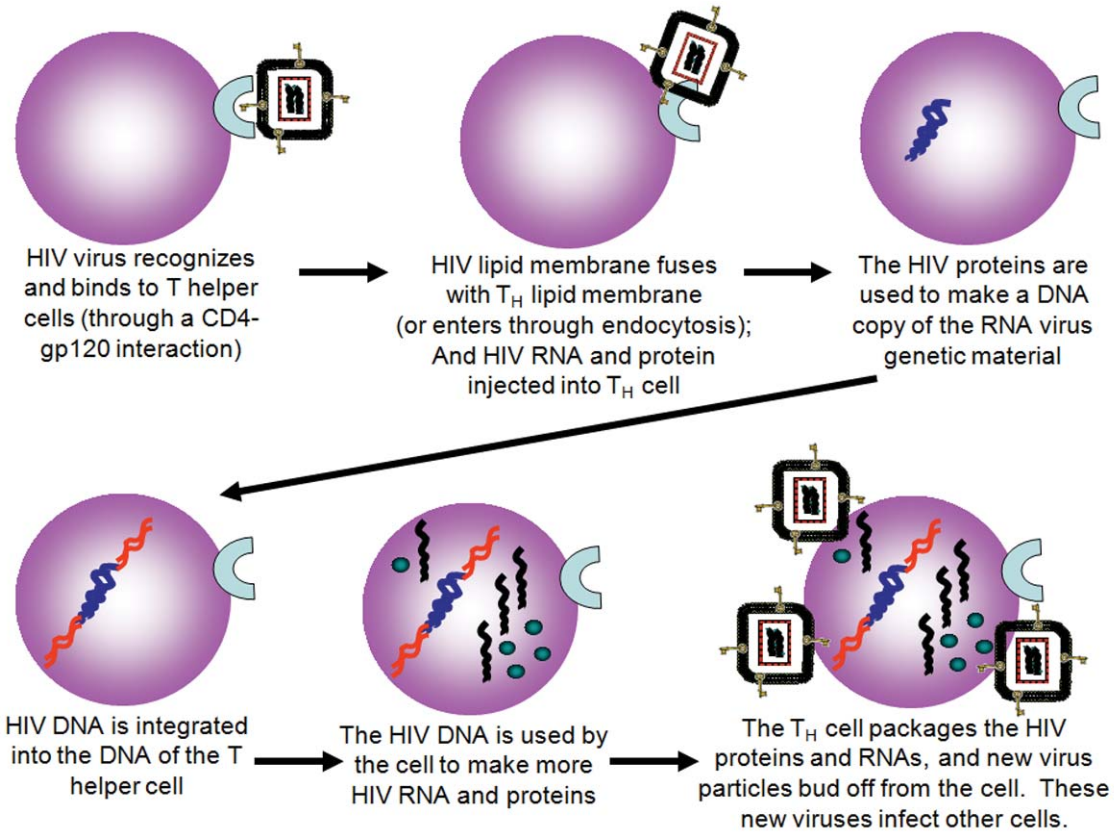
Cytotoxic T cells (sometimes called killer T cells, or T_C or T_{killer} or cytotoxic T lymphocytes [CTL] or $CD8^+$) recognize human cells that have already been infected by a foreign virus or bacteria (this is called the cellular immune response). Their job is to kill these infected cells. So while B cells remove free floating virus particles, T_C cells remove virus particles that have already made their way inside human cells by killing the infected cells. On their cell surface is a protein called CD8, which is why they are sometimes called $CD8^+$ cells.

T Helper cells (sometimes called T_H, or $CD4^+$ cells) do not directly interact with foreign bodies. They are the "organizing centers" of the immune system, coordinating the action of cytotoxic T cells and B cells. Without them, T_C and B cells do not work effectively. On their cell surface is the protein CD4, which is why these cells are sometimes called $CD4^+$ cells.

HIV Infection

HIV targets and infects T_H cells. On the surface of the HIV particle is the protein gp120. This protein recognizes and binds (with a lock and key specificity) the CD4 protein on the surface of T helper cells. Once a virus particle has docked, its lipid membrane either fuses with the human cell's membrane, or the virus is brought in by endocytosis, and the contents of the virus are released inside the cell.

Recall that the HIV virus has an RNA genome. If the virus is to highjack the cell machinery, its genetic information must first be converted into the genetic information used by the cell (i.e., DNA). This is the job of the protein reverse transcriptase, which the virus brought into the cell. Reverse transcriptase makes DNA copies of the RNA virus. This newly made DNA is then integrated into the genome of the human cell. The human cell then uses the 9 genes as it would its own. It therefore produces all the proteins and RNA needed to make more virus particles. The newly-made virus particles bud off of the T helper cell, which is now a virus-producing factory.



Let's review this information and think of its implication for the study of individuals with an apparent resistance to HIV infection.

Questions

1. HIV is a retrovirus (a virus that uses reverse transcriptase).
   a. What is reverse transcriptase?
   b. How is a retrovirus different from other viruses?
   c. How does a retrovirus infect a cell and reproduce itself?
2. Review of the immune system.
   a. What is a T cell?
   b. What varieties of T cell exist? How are they functionally different?
   c. What are their roles in the human body?
   d. How is each T cell variety differentiated from the others (molecularly)?
3. Immune system and HIV
   a. Which type(s) of immune cells is/are targeted by HIV?
   b. Why are other cells not targeted by the virus?
   c. How should cytotoxic T cells respond to the initial phase of HIV infection (when some T helper cells are still functioning)? Explain your reasoning.

d. As time progresses, why do the cytotoxic T cells stop responding to the HIV infection? Propose an explanation.

e. What happens to the immune system after HIV infection? Why? Can this account for the symptoms of AIDS (i.e., immunodeficiency, or the inability to defend against any foreign invaders like viruses and bacteria)?

f. Why do you suppose that there is a delay between the time of HIV infection and the appearance of symptoms (and AIDS)?

g. How does HIV evade the immune system?

4. HIV protection
   a. Consider how HIV infects cells and reproduces. Also consider how the immune system fights off HIV infection. Humans differ by having mutations that result in slightly different proteins and immune function. Suggest as many hypotheses as possible to explain why some individuals might be protected against HIV infection. In other words, where and how might new viral infections be stopped? What could be different about the people who seem protected against HIV that caused viral replication to stop? Come up with at least three possibilities.