The Biology of HIV

HIV is the virus which causes the fatal disease of the immune system, AIDS. At least 28 million people worldwide have died from Aids – their bodies' defence systems deteriorated by the HIV virus to the point where everyday infections become life-threatening.

AIDS was first recognized as a disease in 1981. The discovery of HIV as the cause of AIDS happened in 1983. More than 20 years later, there remains no vaccine against HIV and no cure for Aids, although a new generation of drugs has dramatically extended the life expectancy of those who contract HIV.

The human immunodeficiency virus (HIV) is now known to have originated from a simian source. Transmission to humans probably occurred while animals were butchered for food in sub-Saharan Africa, with animal blood contaminating wounds of humans. The transmission likely passed unnoticed for a long period of time, but in the last half of the 20th century, accompanied social upheavals led to the outbreak of AIDS.

The conditions in Africa that favored transmission first and foremost is that the virus first spread in Africa, but also includes factors such as: massive migration from rural areas to urban areas, the breakup of family units due to the human migrations, conflict, and gender inequalities. New data suggest that the virus in chimpanzees resulted from a recombination between two simian immunodeficiency viruses, SIV_{rcm} from red-capped mangabeys and SIV_{gsn} from greater spot-nosed monkeys. Both of these primate species are preyed on by chimpanzees.

. The Immune System

HIV is a particular kind of virus – a retrovirus. While simpler than ordinary viruses, retroviruses tend to be harder to defeat. They embed their genes into the DNA of the cells they target, so that any new cells that the host cell produces also contain the virus genes.

Retroviruses also copy their genes into the target cell with a high level of error. In combination with HIV's high replication rate, this means the virus mutates at speed as it spreads.

Furthermore, the "envelope" the HIV virus particle is contained inside is made of the same material as some human cells, making it difficult for the immune system to distinguish between virus particles and healthy cells.

First of all, learning about the dynamic of the immune system is fundamental to have an understanding of the action and complexities of the HIV in human body. The immune system protects the body from invading disease-causing organisms, or pathogens. Pathogens and other non-self molecules are antigens – foreign molecules recognized by the immune system, stimulating an immune response. Both non-specific and specific lines of defense help thwart the invasion of pathogens. Non-specific defenses act quickly and indiscriminately to exclude microbes from the body or actively kill intruders. Mechanical barriers - such as the mucus, hairs, and cilia in the respiratory tract, and the flow of urine through the urinary tract - are among these non-specific defenses. The majority of infections by pathogens occurs in mucous membranes of our body.

Skin oils and chemicals in perspiration and gastric juices also serve as non-specific barriers. Tears, nasal secretions and saliva contain bacteria-destroying enzymes. Mechanisms involving complex chemical signals, such as fever and inflammation, also act against a wide variety of pathogens. One non-specific defense involves phagocytes, a particular type of leukocyte (white blood cell), which engulfs and digests microbes or other irritants, like dust and pollen.

Phagocytes (*"phago-"=eating, "cyte"=cell*) migrate to affected areas and engulf pathogens. This migration of white blood cells causes the redness and inflammation associated with infection. Some cells of innate immunity are of special importance for regulating our immune response. These cells called dendritic cells or Langerhans cells can move through out our body, and are particularly rich in our skin and mucus membranes of our body that are exposed to foreign material, including our disgestive systems, airways, and sexual apparatuses. When dendritic cells encounter foreign material, they also are phagocytic (eat the material), but have special receptors that allow them to distinguish harmless and pathogenic (disease causing) organisms. However, these cells carry fragments of pathogen to lymph nodes where they either prevent or stimulate an adaptive immune response. The decision about which response to cause depends on the foreign material (dangerous pathogens cause a dramatic response) and whether cells of your own body are sending out "danger" or distress signals. The significance of the dendritic cells is that they can prevent you from reacting against your own tissues, against food that you ingest or harmless materials from your environment, or they can tell the rest of your immune system to make an adaptive immune response.

If invaders have breached the non-specific defenses, the immune system will use a variety of leukocytes to mount directed defenses against specific invaders. Lymphocytes bind and respond to specific foreign molecules (antigens). One subset of lymphocytes, the B cells, matures into antibody-secreting cells. Another subset of lymphocytes, the T cells, includes immune cells that directly kill cancerous or virally infected cells. Some subtypes of T cells serve a regulatory function, releasing chemical signals that can stimulate or suppress a variety of immune functions. Because HIV preferentially infects one of these regulatory T cells, the so-called helper T (TH) cell, it can subvert and decimate the immune system, leading to AIDS.

In resume, if innate immune cells (dendritic cells) decide that the material is dangerous (part of a virus or bacteria), then they stimulate a specialized group of white blood cells causes $CD4^+$ helper T cells to become activated. $CD4^+$ refers to a surface protein on this class of T cells. Helper T cells can stimulate another group of cells, the B cells, to produce antibodies that bind that specific antigen and immobilize it, preventing it from causing infection. B cells must interact with Helper T cells to initiate antibody production. Chemical signals from helper T cells stimulate the production of B cells specific to an infecting pathogen, and then stimulate the B cells to differentiate into plasma cells. The plasma cells are factories for the production of antibodies, which are specific to given pathogens circulating in blood or lymph. Antibodies are specific for only one antigen. Antibodies work by blocking the receptors that allow pathogens to attach to target cells, or by creating clumps of bacteria. Clumping makes the job of phagocytes easier, as they will more readily engulf bacteria in clumps. Bound antibodies sometimes serve as tags, called opsonins, enhancing phagocytosis. Antibody binding can also initiate a cascade of biochemical reactions, activating a set of chemicals known as complement. Activated complement components can form holes in bacterial membranes and enhance inflammation.

An important concept is that once activated, memory cells are produced that insure that a more rapid and stronger immune response can be made upon re-exposure to the same pathogen. This is why vaccinations provide lasting protection against disease.

Helper T (T_H) cells are critical to coordinating the activity of the immune response. The chemical messages they secrete (cytokines) stimulate the non-specific immune response to continue, and strengthen appropriate specific responses. In fact, helper T cells are the "conductors" of the immune system.

Pathogens (viruses or bacteria) that escape antibody detection can enter and infect cells. The surface of infected cells changes, and this change is recognized by T cells. Cytotoxic T cells kill infected cells, preventing these cells from producing more pathogen. Cytotoxic T cells must interact with Helper T cells to regulate destruction of infected cells. Remember that the dendritic cells must activate CD4+ helper T cells before our bodies can produce B cells secreting pathogen specific antibodies or cytotoxic T cells to destroy infected cells.

. HIV Transmission

HIV is stopped by innate defenses; it cannot penetrate unbroken skin. HIV is transmitted through direct exchange of body fluids. HIV is **not** spread by the fecal-oral route; aerosols; insects; or casual contact, such as sharing household items or hugging. HIV is transmitted principally in three ways: by sexual contact, by blood (through transfusion, blood products, or contaminated needles), or by passage from mother to child. Sexual intercourse is the most common mode of transmission.

Thirteen to thirty-five percent of pregnant women infected with HIV will pass the infection on to their babies; transmission occurs in utero, as well as during birth. Breast milk from infected mothers has been shown to contain high levels of the virus also. The risk to health care workers is primarily from direct inoculation by needle sticks. Although saliva can contain small quantities of the virus, the virus cannot be spread by kissing.

HIV transmitted through sexual activity enters the bloodstream via mucous membranes lining the vagina, rectum and mouth. Macrophages and dendritic cells on the surface of mucous membranes bind virus and shuttle it into the lymph nodes, wich contain high concentrations of helper T cells (CD4+ cells).

. HIV's Action

Once HIV has entered the body, the immune system initiates anti-HIV antibody and cytotoxic T cell production. However, it can take one to six months for an individual exposed to HIV to produce measurable quantities of antibody. The immune response is weakened as memory T cells ($CD4^+$ $CCR5^+$) are destroyed. HIV enters the body and binds to dendritic cells which carry the virus to CD4+ T cells in lymphoid tissue establishing the infection.

The virus attacks the CD4+ cell like this: it hijacks the cell, inserts its own genes into the cell's DNA and uses it to manufacture more virus particles. These go on to infect other cells. The CD4+ host cells eventually die, although scientists do not know exactly how. The body's ability to fight diseases decreases as the number of CD4+ cells drops, until it reaches a critical point at which the patient is said to have AIDS - Acquired Immune Deficiency Syndrome.

Virus replication accelerates producing massive viremia and wide dissemination of virus throughout the body's lymphoid tissues. An immune response against virus causes some protection but a chronic persistent infection is established. The production of cytokines and cell divisions that regulate the immune response for protection also cause HIV replication. There is a rapid turnover of CD4+ T cells that ultimately leads to their destruction and to a change in lymphoid tissues that prevent immune responses.

An HIV infection can progress for eight to ten years before the clinical syndrome occurs. The long latent period of the virus has contributed to many of the problems relating to diagnosis and control. On the other hand, not all cases exhibit

the long latent period, and abrupt progression to AIDS occurs. Many factors, including genetics, determine the speed at which the disease will progress in a given individual.

The stages of a typical HIV infection: In the first stage, Category A, it can be difficult to determine whether an individual is infected without performing a blood test. While at least half of infected individuals will develop a mononucleosis-like illness (headache, muscle ache, sore throat, fever, and swollen lymph nodes) within three weeks of exposure, some individuals are asymptomatic. Moreover, the symptoms themselves can be the result of many different infections. The presence of a rash may help differentiate an HIV infection from other infections, but not all HIV-infected individuals get a rash. Most of these signs and symptoms subside, but swollen lymph glands and malaise can persist for years through Category A HIV.

The number of virus particles circulating in the bloodstream is usually highest soon after exposure. At this point the CD4 cell population plunges (helper T cells are among the immune cells that express the CD4 receptor, which can be used as a marker for counting cell types). As antibodies to HIV appear the numbers of CD4 cells rise; however, CD4 cell levels drop again as the infection progresses. This lowering of CD4 cell levels typically happens slowly, over the course of years. Category C HIV (clinical AIDS) occurs once CD4 numbers have fallen substantially (to 200/mm^3 from the normal level of 800-1200 cells/ mm^3).

In the Category B stage indications of immune system failure begin. Persistent infections - such as yeast infections, shingles, diarrhea, and certain cancerous conditions of the cervix - are apparent.

Category C is synonymous with AIDS. In this stage the opportunistic infections associated with AIDS appear. According to the CDC, twenty-six known clinical conditions affect people with AIDS; most are infections that do not usually affect healthy individuals. These include yeast infections of the esophagus, bronchi, and lungs; Pneumocystis pneumonia (a fungal infection); toxoplasmosis (caused by a protozoan that is spread by cats); Kaposi's sarcoma (a rare cancer of the skin caused by a virus); cytomegalovirus (CMV) infections; and tuberculosis. In addition, individuals who have been affected by HIV are more likely to become seriously ill or die than other members of the population during outbreaks of infections such as cryptosporidium (a water-borne parasite) and coccidiomycosis (a dust-borne fungus).

Despite repeated exposure, some individuals never become infected with HIV. These individuals often have unusual helper T cells with a less-efficient variant of the coreceptor CCR5, which is necessary for viral entry into helper T cells. There are also individuals who become infected, but do not progress to AIDS. These long-term survivors, or long-term non-progressors, include individuals who have been AIDS-free as long as eighteen years after infection. A variety of factors may be responsible; for example, infection with less-virulent viruses. Some long-term non-progressors seem to have CD8 cells, which are particularly adept at curtailing HIV infection. (In most AIDS patients CD8 cells become less active).

There are five major subtypes of HIV; each of one predominates in different geographical areas. For example, subtype B is more common in North America. In contrast, subtype C predominates in sub-Saharan Africa. Considerable variation within a given subtype also exists. In fact, any given individual infected with HIV will harbor multiple variants of the virus. HIV makes many mistakes as is copies its viral RNA to the DNA that integrates into the host's chromosome. Because of its sloppy copying of reverse transcriptase, HIV's mutation rate is high, causing great variability. This large number of variants makes the virus more difficult to treat and hinders vaccine development. In addition, because of its rapid rate of evolution, even within a single individual, HIV can quickly evolve resistance to the drugs the individual is taking to combat the virus.