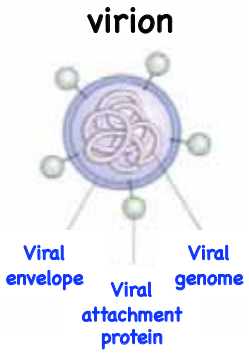
Workshop 2009 Virus Fact Sheet

The Virus



• viruses consist of a ball of genetic material (DNA or RNA) surrounded by a protein coat

• the protein coat is made up of attachment proteins that are usually specific for a particular cell type—different viruses infect different cell types like a lock and key mechanism

• viruses are "obligate intracellular parasites" meaning they must hijack the host cell's replication machinery in order to reproduce

• viruses that are prevalent today have evolved because they have solved 3 main problems:

1) how to reproduce inside the host cell
2) how to spread from one host to another
3) how to evade the host's defenses or escape the immune system

The Immune "Army"

• the immune system consists of 2 interacting groups, or armies: the innate response and the adaptive response

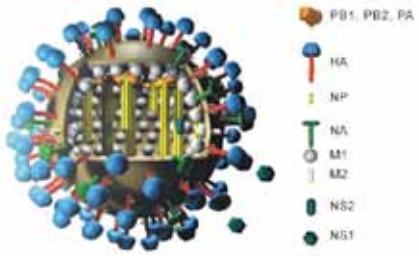
• innate immune cells carry receptors that sense danger signals sent out by the virus and they in turn raise the alarm to activate the adaptive response. Some innate cells called macrophages and dendritic cells can engulf and chew up virus particles (phagocytosis) and interact with T cells. These Mϕ and DC are also known as antigen presenting cells.

• adaptive immune cells are specific for proteins in each virus and are comprised of 2 main groups: T cells and B cells.

• B cells make antibodies that can bind to the virus and prevent re-infection with the same virus—vaccines usually target B cells to make antibodies

• T cells are subdivided based on how they "see" or recognize virus bits (peptides). CD8 cells see virus peptides within surface proteins called MHC Class I. CD8 cells can kill virally infected cells. CD4 cells see virus peptides within surface proteins called MHC Class II. CD4 cells interact with B cells to help B cells make specific antibodies.

Influenza



• influenza is a single stranded RNA virus and enters the cells lining the respiratory tract by binding of hemagglutinin (HA) to specific proteins on the surface of lung epithelial cells.

• influenza infection is responsible for about 30,000 deaths per year in the US, and is more prevalent during the winter months.

• influenza is subtyped based on the hemagglutinin (HA) and neuraminidase (NA) outer proteins—there have been 16 HA and 9 NA proteins identified in flu viruses that infect birds, but H1N1 and H3N2 are most prevalent in people.

• there is concern that a pandemic may occur in which avian influenza viruses are able to infect people, or viruses mutate within other hosts (pigs) and acquire the ability to infect people—latest news stories on "swine" flu.

Evading the "Army"

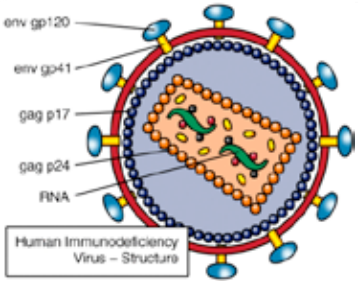
• B cells and antibodies recognize the outer flu coat proteins (HA and NA) of the virus, antibodies are very good at "neutralizing" the virus by binding to the HA so that the virus can't enter the host cell.

• Vaccines activate the antibody response and are made up of the most prevalent influenza strains during the previous winter (usually an H1N1, an H2N3 and an influenza B)

• BUT, flu is a "bait and switch" virus and can mutate it's outer proteins very quickly so the antibodies generated by the vaccine strain no longer bind to the new virus—the vaccine must be changed every year and distributed

• Highly pathogenic flu strains (those that cause death and possible pandemics) also escape the immune response by inducing an overproduction of inflammatory proteins. This "cytokine storm" is responsible for damage to the lung.

HIV



• HIV can be transmitted through blood, sexual contact and from mother-to-child. Currently, over 30 million people worldwide are infected

• Sub-Saharan Africa has a high rate of infection with 15-30% of women in Zambia infected. Mother to child transmission in Zambia is estimated at 30-39%

• the HIV env glycoproteins are specific for binding to immune cell surface markers called CD4 as well as co-receptors such as CCR5 and CXCR4. HIV specifically infects CD4 T cells and macrophages.

• HIV is an RNA virus (retrovirus) and must first copy the RNA into a complementary DNA molecule. This process of "reverse transcription" is prone to errors and results in mutations that make the new HIV strain drug resistant or better able to evade the host immune response

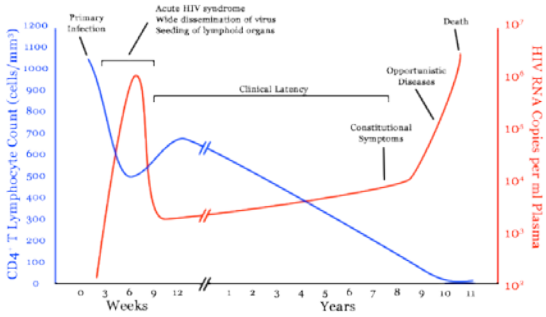
Evading the "Army"

• HIV replicates slowly in non-dividing and dividing cells causing life long, chronic infection. HIV can infect non dividing T cells and remain dormant (latent) until the T cell starts dividing

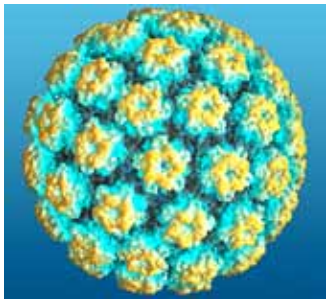
• Special immune cells called dendritic cells (DC) can trap HIV on their surface. DC are important for activating CD4 T cells so the virus "catches a ride" with the DC right into the lymph node where all the CD4 cells hang out.

• HIV infects and eventually kills off CD4 T cells, those cells needed to mount an effective immune response

• HIV causes a chronic viral infection and is constantly infecting and killing CD4 T cells, eventually the host becomes "immunosuppressed" and open to other infections that would normally be cleared by a healthy adult.



Human Papilloma Virus



• HPV infects the epidermis and is responsible for plantar and genital warts. About 30-40 different HPV subtypes can be transmitted through sexual contact and HPV 16 and 18 have been shown to cause cervical and anogenital cancers.

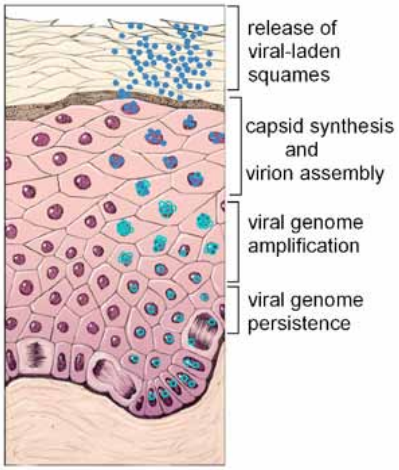
• The HPV E6 and E7 genes can act as “oncogenes”. Oncogenes can promote tumor growth and help change a normal cell into a cancerous cell.

• HPV is considered a non-cytolytic virus, that means it does not kill the cell that it infects (unlike influenza or HIV).

• Recently a vaccine has been developed (Gardasil) that can protect women against the “high risk” HPV subtypes 16 and 18.

Evading the “Army”

• HPV replicates in epithelial cells in different layers of the skin and genital tract. HPV first infects the lower layer, or basal cells and “integrates” its genome into the cells.



• As the basal cells proliferate and copy their DNA, the viral DNA is copied along with it, but no virus is made. Here the virus can hide and remain undetected. As the epithelial cells mature and move up to the last layer of the skin, more viral proteins are produced and an infectious viral particle is then released.

• When HPV is hiding in the basal cells, it doesn’t induce an activator of the innate immune system called “interferon”. The adaptive immune response, in turn, is not activated enough.

• However, once there is an active infection, the immune system can respond.

Herpes Virus

• Herpes viruses belong to a large family of DNA viruses that include herpes simplex virus 1 (cold sores) and 2, (genital herpes) varicella zoster virus (chicken pox), cytomegalovirus and Epstein Barr Virus (mononucleosis).

• Herpes viruses infect a large proportion of the population with about 60% of people infected with HSV-1 and approximately 25% infected with HSV-2. 90-95% of people are infected with EBV, and most remain asymptomatic,

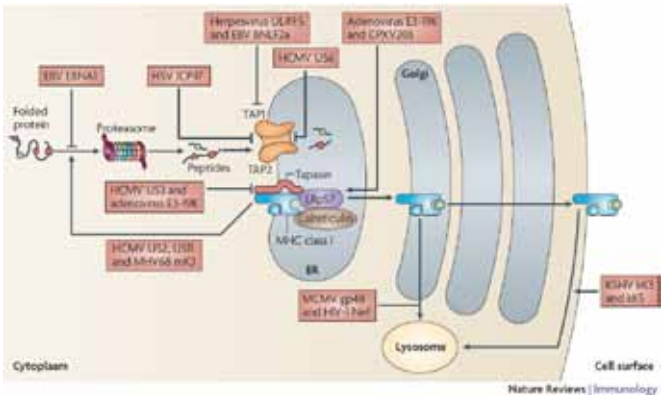
• Herpes viruses undergo a period of lytic infection in which the virus kills epithelial cells that it infects initially and then a period of latent infection in which the virus hides out inside nerve cells and goes undetected for months or years.

• The virus then reactivates in response to fever, stress, or injury and can be spread from host to host at this time.

Evading the "Army"

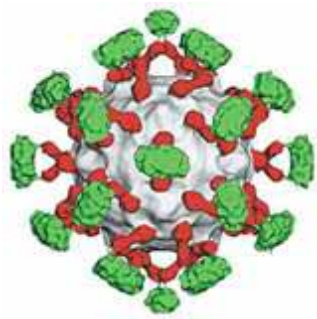
• HSV glycoproteins can bind to IgG and inhibit the complement cascade, an innate immune defense mechanism that can recognize and lyse virally infected cells.

• Many herpes virus proteins can interfere with antigen processing and presentation. In order for killer T cells to recognize and lyse virally infected cells, a molecule called MHC class I must present viral peptides to a CD8 T cell so the CD8 cell knows which cells are virally infected and marked for elimination.



• Herpes virus proteins block the association of class I with the viral peptides or decrease the amount of class I being made in the cell. The end result is that killer CD8 T cells no longer recognize the virally infected cells and cannot eliminate them.

Coxsackie Virus



• Coxsackie virus belongs to the picornavirus family and enterovirus genus that also includes polio virus. Coxsackie A virus can cause hand foot and mouth disease in young children and the Coxsackie B viruses can cause myocarditis or pericarditis (inflammation of the heart).

• Coxsackie B virus has been linked to diabetes

Evading the "Army"

For more information:

http://www.cancer.gov/cancertopics/factsheet/risk/HPV

http://en.wikipedia.org/wiki/HIV

http://en.wikipedia.org/wiki/Influenza

http://en.wikipedia.org/wiki/Herpes_simplex_virus

http://www.soundprint.org/radio/display_show/ID/774/name/HPV+-+the+Shy+Virus

http://www.itmonline.org/arts/coxsackie.htm

For more information:

MHC class I antigen presentation: learning from viral evasion strategies. Ted H. Hansen & Marlene Bouvier
Nature Reviews Immunology 9, 503-513 (July 2009)

Coxsackie refers to a collection of closely related viruses classified among the enteroviruses, namely those that cause infection after being taken in orally with contaminated food or water and then multiply in the intestines (entero = intestinal). The coxsackie viruses were named after the town Coxsackie, New York. A strain of this virus was discovered there during the investigation of an epidemic that occurred in 1948 alongside a polio epidemic (polio being another enterovirus). The coxsackie viruses are divided into two major subgroups, labeled A and B. There are 23 known coxsackie A viruses that usually cause only enteric diseases, and 6 known coxsackie B viruses, which are the ones of greatest concern because of their ability to cause serious diseases beyond the intestinal tract. Coxsackie B3 has been found to be one of the main causes of certain debilitating or life-threatening diseases, such as viral myocarditis.

The coxsackie virus apparently produces few or no symptoms in most instances, but it can cause a commonly occurring intestinal disease, with abdominal distress and diarrhea. Even when symptomatic, the resulting disease is usually a relatively mild one, which might be referred to as "intestinal flu." It most often occurs in late summer or early autumn and is consistent with what the Chinese call "summer heat syndrome," which usually manifests as an intestinal disorder accompanied by muscle aches and/or headaches, and fever. Rarely, the coxsackie virus can cause a more severe disease.

It has been suggested that most people experience coxsackie infections at some time, and they are particularly prevalent in infants and young children, and, to a lesser extent, adolescents, with first onset related largely to the hygienic conditions (lack thereof) in which the child lives. The disease symptoms appear between 2 and 10 days after exposure, and are gone within a few days, similar to the experience of the common cold or influenza, but with intestinal symptoms. It is thought that a partial immunity to coxsackie viruses develops in most children exposed to it, so that symptomatic disease is rare or even milder for adults.

In some cases, however, the virus escapes the intestinal tract to cause serious disease. In children, coxsackie may go on to produce viral meningitis and it has been proposed, on the basis of epidemiological evidence, that coxsackie and other enteroviruses (such as ECHO) may be among the causes of childhood insulin-dependent diabetes. In adults, viral myocarditis and dilated cardiomyopathy can occur if the virus infects the heart muscle. Coxsackie B viruses are estimated to be responsible for at least 50% of the cases of infection-caused heart diseases. For reasons yet unknown, the cardiac disease caused by this virus mainly occurs in middle-aged men, with onset occurring, on average, around age 42. The cardiac disease becomes apparent about two weeks after exposure to the virus.

The early symptoms of the coxsackie-induced cardiac myopathy include some generalized viral symptoms-fever, fatigue, malaise-with the addition of chest pains. As the virus enters the heart cells, the immune system attacks and damages both infected and normal heart cells; the affected individual feels severe fatigue when there is significant impairment of heart function. In most cases, the disease is resolved spontaneously without any treatment, though some permanent heart damage may have occurred. But, in about 20% of the cases, there can be progressive disease or recurrence of symptoms; the heart damage can be extensive, causing arrhythmias, weakened left ventricular functions, and, in the worst cases, heart failure requiring heart transplantation. In these severe cases, cardiac disease progression persists after the virus is long gone: the immune system continues to damage the heart.

Effective medical therapies have yet to be worked out for viral myocarditis; one approach is to administer anti-inflammatory or immunosuppressive drugs during the early stage of the disease to impair the immune attack and resulting inflammatory response that damages the heart. Patients are usually told to rest, as the damaged heart does not withstand the demands for vigorous activity.