Evasion of Host Defenses

Viruses have several ways by which they evade our host defenses. These processes are often called *immune evasion*.

1- Some viruses encode proteins for various mediators of immunity such as interleukin-1 (IL-1) and tumor necrosis factor (TNF).

   For example, vaccinia virus encodes a protein that binds to IL-1 and fibroma virus encodes a protein that binds to TNF. *When released from virus-infected cells, these proteins bind to the immune mediators and block their ability to interact with receptors on their intended targets, our immune cells that mediate host defenses against the viral infection.*

   By reducing our host defenses, the virulence of the virus is enhanced. These virus-encoded proteins that block host immune mediators are often called *cytokine decoys*.

2- In addition, some viruses (e.g., HIV, cytomegalovirus) can reduce the expression of class I MHC proteins, thereby reducing the ability of cytotoxic T cells to kill the virus-infected cells, and others (e.g., herpes simplex virus) inhibit complement.

3- Several viruses (HIV, Epstein-Barr virus, and adenovirus) synthesize RNAs that block the phosphorylation of an initiation factor (eIF-2), which reduces the ability of interferon to block viral replication.

4- Cytomegalovirus (CMV) encodes a micro RNA that binds to the mRNA of a cell surface ligand for natural killer cells. Binding of the micro RNA prevents synthesis of the ligand which prevents killing of the CMV infected cells by the NK cells.
5- Measles virus blocks synthesis of IL-12, thereby reducing an effective Th-1 response. Ebola virus synthesizes two proteins, one of which blocks the induction of interferon, while the other blocks its action. Collectively, these viral virulence factors are called virokines.

6- Another important way by which viruses evade our host defenses is by having multiple antigenic types (also known as multiple serotypes). The clinical importance of a virus having multiple serotypes is that a patient can be infected with one serotype, recover, and have antibodies that protect from infection by that serotype in the future; however, that person can be infected by another serotype of that virus.

The classic example of a virus with multiple serotypes is rhinovirus, which has more than 100 serotypes. This is the reason why the "common cold" caused by rhinoviruses is so common.

Influenza virus also has multiple serotypes, and the severe worldwide epidemics of influenza are attributed to the emergence of new antigenic types. HIV and hepatitis C virus have multiple serotypes, which contributes to the difficulty in obtaining a vaccine against these viruses. Note that only some viruses have multiple serotypes.

Many important human pathogens (such as measles virus, rubella virus, varicella-zoster virus, and rabies virus) have only one serotype, and some have only a few serotypes (e.g., poliovirus has three serotypes).
Persistent Viral Infections

In most viral infections, the virus does not remain in the body for a significant period after clinical recovery. However, in certain instances, the virus persists for long periods either intact or in the form of a subviral component, e.g., the genome.

The mechanisms that may play a role in the persistence of viruses include:

1. Integration of a DNA provirus into host cell DNA, as occurs with retroviruses.
2. Immune tolerance, because neutralizing antibodies are not formed.
3. Formation of virus–antibody complexes, which remain infectious.
4. Location within an immunologically sheltered "sanctuary," e.g., the brain.
5. Rapid antigenic variation.
6. Spread from cell to cell without an extracellular phase, so that virus is not exposed to antibody.
7. Immunosuppression, as in AIDS.

There are three types of persistent viral infections of clinical importance. They are distinguished primarily by whether virus is usually produced by the infected cells and by the timing of the appearance both of the virus and of the symptoms of disease.

1- Chronic-Carrier Infections

Some patients who have been infected with certain viruses continue to produce significant amounts of the virus for long periods. This carrier state can follow an asymptomatic infection as well as the actual disease and can itself either be asymptomatic or result in chronic illness.
Important clinical examples are chronic hepatitis, which occurs in hepatitis B and hepatitis C virus carriers, and neonatal rubella virus and cytomegalovirus infections, in which carriers can produce virus for years.

2- **Latent Infections**

In these infections, best illustrated by the herpesvirus group, the patient recovers from the initial infection and virus production stops. Subsequently, the symptoms may recur, accompanied by the production of virus. In herpes simplex virus infections, the virus enters the latent state in the cells of the sensory ganglia. The molecular nature of the latent state is unknown.

Herpes simplex virus type 1, which causes infections primarily of the eyes and face, is latent in the trigeminal ganglion, whereas herpes simplex virus type 2, which causes infections primarily of the genitals, is latent in the lumbar and sacral ganglia.

Varicella-zoster virus, another member of the herpesvirus family, causes varicella (chickenpox) as its initial manifestation and then remains latent, primarily in the trigeminal or thoracic ganglion cells. It can recur in the form of the painful vesicles of zoster (shingles), usually on the face or trunk.

3- **Slow Virus Infections**

The term "slow" refers to the prolonged period between the initial infection and the onset of disease, which is usually measured in years. In instances in which the cause has been identified, the virus has been shown to have a normal, not prolonged, growth cycle.

It is not, therefore, that virus growth is slow; rather, the incubation period and the progression of the disease are prolonged. Two of these diseases are caused by conventional viruses, namely, subacute sclerosing panencephalitis, which follows
several years after measles virus infections, and progressive multifocal leukoencephalopathy (PML), which is caused by JC virus, a papovavirus.

**Atypical Virus-like Agents**

There are four exceptions to the typical virus as described above:

1. **Defective** viruses are composed of viral nucleic acid and proteins but cannot replicate without a "helper" virus, which provides the missing function. Defective viruses usually have a mutation or a deletion of part of their genetic material.

   During the growth of most human viruses, many more defective than infectious virus particles are produced. The ratio of defective to infectious particles can be as high as 100:1. Because these defective particles can interfere with the growth of the infectious particles, it has been hypothesized that the defective viruses may aid in recovery from an infection by limiting the ability of the infectious particles to grow.

2. **Pseudovirions** contain host cell DNA instead of viral DNA within the capsid. They are formed during infection with certain viruses when the host cell DNA is fragmented and pieces of it are incorporated within the capsid protein. Pseudovirions can infect cells, but they do not replicate.

3. **Viroids** consist solely of a single molecule of circular RNA without a protein coat or envelope. There is extensive homology between bases in the viroid RNA, leading to large double-stranded regions. The RNA is quite small (MW $1 \times 10^5$) and apparently
does not code for any protein. Nevertheless, viroids replicate but the mechanism is uncertain. They cause several plant diseases but are not implicated in any human disease.

4. Prions are infectious particles that are composed *solely of protein*; i.e., they contain no detectable nucleic acid. They are implicated as the cause of certain "slow" diseases called *transmissible spongiform encephalopathies*, which include such diseases as Creutzfeldt-Jakob disease in humans and scrapie in sheep.