In: **A Concise Review of Veterinary Virology**, Carter G.R., Wise D.J. and Flores E.F. (Eds.). International Veterinary Information Service, Ithaca NY (www.ivis.org), 3-Mar-2005; A3405.0305

Host Defenses to Viruses

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Just as viruses, by their ability to infect host cells and initiate host-mediated viral replication, are able to cause disease, the host and the host cells have some mechanisms to prevent, minimize, or contain viral infections. This chapter discusses these defenses, from the innate responses and protective barriers to the specific immune responses. The outcome of the interaction between the host and the virus can be reflected in the character of the disease. Table 5.1 lists the mechanisms of the host immune response and the aspects of the viral replication cycle they are designed to target.

Table 5.1. Host Defense- Virus Infection Interactions

Defense Type	Defense Effector	Effector Target
Nonspecific Immune Responses	Fever	Virus replication
	Inflammation	Virus replication
	Interferons	Virus replication
	NK* Cells	Virus-infected cells
	Phagocytosis	Virus particles
Nonspecific Immune Responses	Antibody	Virus particle, virus-infected cells
	Classical Complement Pathway	Virus particle, virus-infected cells
Cell-Mediated Immune Responses	Cytotoxic T cells	Virus-infected cells
	Macrophages (activated)	Virus particle, virus-infected cells
	ADCC**	Virus-infected cells

* NK= natural killer
**ADCC= antibody-dependent cell-mediated cytotoxicity

Host Defenses

Physical / Chemical Barriers

Physical /chemical barriers are part of the innate immune system, those features each host has at birth. These barriers either prevent or limit infection. Any compromise to the integrity of one of these barriers affords a virus access to the cells of the host. In contrast, because of their replication cycle, some viruses are able to bypass these barriers readily.

- Skin. The skin is an effective barrier to most infections, including those of viruses. This is because the skin is

composed in part of dead, keratinized cells, which cannot support viral replication. To circumvent this barrier, viruses need to penetrate deeper into the epithelium via cuts, burns, or insect bites.

- Mucous Membranes. These act as a physical barrier, preventing direct access to host cells. Alternatively, mucus interferes with virus attachment to target cells by providing virus receptors within the mucus. For example, paramyxoviruses bind to sialic acid receptors associated with host cells. The presence of sialic acid-glycoproteins in mucus interferes with attachment at these sites.
- Ciliated Epithelium. The combined action of cilia with mucus of the epithelium facilitates the physical movement of trapped viruses out of the body, thus diminishing their infectivity. The following are associated with penetration of this barrier: inoculum size, droplet size, air current, humidity, and temperature.
- Acidic pH. The acidic pH of the gastrointestinal (pH 2) tract readily denatures the proteins associated with many viruses. However, enteric viruses can either withstand this pH or use exposure to this pH to facilitate uncoating and thus be infective within the gut.
- Tears. These provide constant washing to minimize the amount of virus particles available to infect conjunctival cells.
- Lack of Receptors. This involves host range or a specific tissue receptor. If the receptor necessary for attachment of the virus is not present, then infection cannot occur.

Nonspecific Immune Responses

The nonspecific immune responses occur with any viral infection. These responses serve largely to limit viral dissemination from the site of infection, impede virus replication, and aid the specific immune response in a targeted attack by the infecting virus.

- Fever. This inhibits viral replication by stimulating other immune responses and decreasing viral replication. In addition, the increased temperature may mediate direct inactivation of virus particles. The importance of fever alone during viral infection is unclear.
- Inflammation. This refers to the local nonspecific immune response characterized by redness, swelling, heat, and pain. Neutrophils and macrophages are recruited to the area by cytokines. This recruitment aids in sequestering the infection. Continual production of cytokines and recruitment of immune cells continues until the antigen is effectively neutralized. Tissue repair then ensues. In some instances, the inflammatory response becomes chronic, leading to viral-induced immunopathology.
- Interferons (IFN). A group of host-specific, viral-induced glycoproteins that inhibit viral replication by inducing the degradation of viral RNA and blocking translation of viral proteins. Additionally, the interferons confer resistance to viral infection of neighboring cells. There are three types of interferons produced by the body, alpha, beta, and gamma. The alpha and beta are called Type 1 interferon and are involved in innate immunity. Gamma-IFN is involved with the specific immune response and will be considered there.
  Interferons alpha and beta work by specifically interfering with viral translation, while having little effect on cellular translation. This phenomenon is known as selective inhibition. Viral mRNAs are recognized by nucleotide sequences specific to the virus that are not found in the host cell. In addition, IFN stimulates the increased production of class I and class II major histocompatibility complexes (MHC) on the surface of host cells. This aids the recognition of viral antigens and the trigger of specific immune response in targeting virus-infected cells.
- Alpha-IFN. Stable at pH.2; production induced by products of viral replication (RNA viruses stimulate production greater than DNA viruses) and dsRNA. Also known as leukocyte-IFN.
- Beta-IFN. Stable at pH.2; production induced by products of viral replication (RNA viruses stimulate production greater than DNA viruses) and dsRNA. Also known as fibroblast-IFN.
- Natural Killer (NK) Cells. NK cells are white blood cells of lymphopoietic lineage. They are also called the third population of lymphocytes (T, B and NK), null cells or large granular lymphocytes. Some viruses, as part of their replication cycle, decrease the amount of MHC class I made by the host cell. NK cells recognize cells that lack or underexpress MHC class I and kill them by apoptosis. Thus, they target and destroy virus-infected cells. NK cells kill virus-infected cells in the same manner as described for cytotoxic T cells described below. NK cells are also important in tumor cells recognition and killing.
- Phagocytosis. The action of macrophages and neutrophils in engulfing and destroying virus particles. Macrophages become activated (more ready to engulf and destroy) in response to interferon-gamma and other cytokines.
- Complement Cascade. The majority of viruses are unable to fix complement by the alternative route. However, as the classical route employs specific antibody in the first step of the cascade, this mechanism can readily lyse virus or infected cells.

Specific Immune Responses

The specific immune responses are pathogen-tailored responses to an infection. These take several days to several weeks to develop. Therefore, the body is dependent upon the action of the nonspecific immune response to aid in localizing the infection until the specific immune response has been generated. Specific immune responses are either humoral (antibody production) or cell-mediated. In some instances, viral infection results in characteristic immunopathology or induces

immunosuppression.

Humoral Immune Response
The humoral immune response involves the production of antibodies against viral-specific antigen(s) by plasma cells, which are derived from B-lymphocytes. Stimulation of antibody production is the primary means involved in recovery from viral infections, in particular to cytolytic viral infections accompanied by viremia and viral infections of epithelial surfaces. The antibodies produced can be virus neutralizing or non-neutralizing, based upon their interaction with the virions and their effects on the replication cycle.

In most instances antibody production is the result of viral infections. This is active immunity. Alternatively, an individual can be given pre-formed antibodies from a recovered individual. This is an example of passive immunity. Pre-formed antibodies are given to individuals that may have been exposed to a particular virus, as with the rabies virus. Vaccines are discussed in Chapter 6.

- Neutralizing Antibodies. These are the antibodies that inhibit the ability of a virus to invade the cells and to replicate. They interfere with the viral attachment, penetration, and/or uncoating. Additionally, they are able to damage the viral envelope with the aid of complement (classical pathway). Neutralizing antibodies are most effective at the time of infection or during viremia.
- Non-neutralizing Antibodies. These are antibodies that have no direct virus neutralizing activity but may aid in controlling infection by other means, such as enhancing viral degradation. Additionally, they serve as opsonins to enhance phagocytosis of virions. Antiviral antibodies bound to the viral proteins in the surface of infected cells may also trigger the complement cascade and lead to complement-mediated cell killing.

Cell-Mediated Immune Response
Cell-mediated immunity (CMI) involves the action of cytotoxic T lymphocytes, antibody-dependent cell-mediated cytotoxicity (ADCC), the action of natural killer cells and activated macrophages. CMI is the defense mechanism most important in non-cytolytic infection in which the membrane of the virus-infected cell is altered by the virus.

- Cytotoxic T Lymphocytes. These are specific T cells that recognize viral antigen associated with MHC class I molecules on the cell surface of most cells. These T lymphocytes have a surface antigen called CD8. Interaction between the infected cell and the cytotoxic T cell results in the release of perforins by the cytotoxic T cell, which create pores in the membrane of the virus-infected cell. Also released by the cytotoxic T cell are granzymes, which are a group of serine proteases. The combined action of perforins and granzymes results in lysis of the cell. In addition, the cytotoxic T cells activate the Fas protein, which stimulates apoptosis in the virus-infected cell.
- Antibody-dependent Cell-mediated Cytotoxicity. ADCC refers to an immune response in which antibody-coated, virus-infected cells are targeted to attack by immune cells such as macrophages and NK cells.
- Helper T Lymphocytes. These T lymphocytes have a surface antigen called CD4. They are capable of recognizing protein antigens associated with MHC class II antigens, which are found on only a few cell types, such as macrophages, B-lymphocytes, and dendritic cells.
  Helper T lymphocytes orchestrate the immune response to antigen by either secreting cytokines that stimulate antibody production by specific B-lymphocytes or stimulate the production of specific cells for a CMI response.

Immunological Effects of Viral Infection
These are the result of host immune system-viral replication interactions.

Viral-Induced Immunopathology
Viral-induced immunopathology is tissue damage resulting from the immune response to a virus. This immunopathology can result from various immunologic interactions, such as antibody-antigen complexes and tissue damage due to cytotoxic T cells, antibody or complement. The type and location of immunopathology can be characteristic of a particular viral infection.

Examples of viral-induced immunopathology are:

- Anterior Uveitis. Antigen-antibody complexes deposit in the eye, stimulating local inflammation, and result in anterior uveitis. Additionally, immune-complexes remaining in circulation deposit in the kidney, resulting in the immunopathology of glomerular nephritis. This is often seen during the recovery stage of infectious canine hepatitis infections.
- Lymphocytic Choroiomeningitis. Caused by an arenavirus infection in mice, which results in CNS damage from the destruction of virus infected cells by cytotoxic T lymphocytes. Old-dog encephalitis (canine distemper virus, a paramyxovirus) is similar in that the immunopathology is also the result of a cell-mediated immune response to persistent virus infection.
- Woodchuck Hepatitis and Duck Hepatitis B Infections. Most of the liver injury associated with these infections is thought to be due to the continuous action of $CD8^+$ T lymphocytes in killing infected hepatocytes rather than by the action of the virus itself.

Virus-Induced Immunosuppression
Some viruses, as result of their replication, suppress the host immune response and in doing so are able to establish infection. Virus-induced immunosuppression occurs with either cytolytic or noncytolytic infection. It is often observed as a consequence of viral infections involving lymphocyte infection, as with the human immunodeficiency virus (HIV) and feline immunodefiency virus.

Evasion of the Immune System
Some viruses because of the replication method used are able to evade the immune system of the host. There are various ways by which this is accomplished during viral replication. Some examples include infection of immunologically privileged sites, antigenic variability of virions, inhibition of INF-β, decrease in MHC class I expression, inhibition of peptide processing, and expression of immune system homologous structures.
Immunologically privileged sites are those regions of the body that do not come directly into contact with the circulation and are therefore normally segregated from the immune system. These include the brain, the testis and prostate, the retina of the eye, and hamster cheek pouches.

The production of immune system analogous structures by viruses includes:
- Cytomegaloviruses produce glycoproteins that are analogous to IgG-Fc receptors.
- Shope fibroma virus produces a TNF (tumor necrosis factor) receptor analog.
- Epstein-Barr virus produces an analog of interleukin (IL)-10.

The topics of antigenic variability (Chapter 3), the decrease in MHC class I expression (Chapter 4), and inhibition of interferon-β (see above section on interferons) have been previously discussed.
Latency (herpesviruses, retroviruses) is also a mechanism to evade the immune system.
Adenoviruses produce short segments of RNA that block activation of interferons.

Glossary
Alternative Complement Pathway: Pathway of complement activation by which complement component C3 is cleaved and C5-C9 formed without a requirement for C1, C2 or C4. It does not require antibody.
Antigen-antibody Complex: It is a macromolecular complex of antigen and antibody bound together specifically. Also called immune complex.
Classical Complement Pathway: This is a series of sequential enzyme-substrate interactions activated by antigen-antibody complexes and involving all of the C components.
Cytokines: Soluble molecules that mediate interactions between cells.
Fas Protein: A type 1 transmembrane protein of the TNFR (tumor necrosis factor receptor) superfamily. It is expressed on many cell types including those of the myeloid series.
Interleukin (IL)-10: Cytokine that can decrease immune response to viruses by inhibiting INF-γ production.
Opsonin: A substance that binds to particles including microorganisms and facilitates their phagocytosis.
Tumor Necrosis Factor: A cytokine produced by monocytes/macrophages (TNF-α) and some T cells (TNF-β). They are directly toxic to neoplastic cells and are also involved in inflammation.