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A virus invading the host must first breach natural barriers at the portal of entry. These may include (1) the physical barrier of the skin or the epithelial lining of the respiratory, gastrointestinal, or urogenital tract, (2) secretions at mucosal surfaces, for example, the surfactant and mucociliary functions of the respiratory tract, or the mucus, acid and detergent (bile) environment of the gastrointestinal tract.

Two major forms of immune defense then operate after an incoming virus has penetrated these physiological and anatomical barriers (Table 5.1). The first, innate immunity, is a mechanism that is continually present and operates immediately to limit tissue injury and prevent the spread of virus to adjacent, healthy cells, the so-called bystander effect. This innate response is of broad specificity, modulated largely by the secretion of an extensive array of signaling molecules (lymphokines, cytokines, etc.), and forms the basis of any immediate localized inflammatory response. In contrast, the adaptive immune response is pathogen-specific and requires more time to develop; it also generates long-term pathogen-specific memory that is the basis for a more rapid immune response and enhanced protection should the same pathogen be encountered again at a later date.

Although it is convenient to consider innate and adaptive responses as distinct responses to virus infection, many aspects of the initial innate response play a continuing role in later immune processes and thus the distinction between responses based on broad, non-specific recognition of viruses and specific recognition by immune cells is becoming increasingly blurred as more becomes known, especially in regard to cell signaling pathways. In short, the development of a robust adaptive immune response to an invading virus is intimately linked to the early innate response to infection.

Since the last edition of this book, it has become apparent that most, if not all, viruses of humans have evolved ways to circumvent the innate immune response. Some viruses can block or modify various stages in the intracellular pathways for expression of signaling molecules induced by infection. These effects may be exerted in a temporal manner during the different stages of virus replication (see below).

**INNATE RESPONSES**

The host responds rapidly in a matter of a few hours following virus invasion. The innate defense includes (1) phagocytic cells (macrophages, dendritic cells, and neutrophils) that engulf invading viruses, (2) natural killer (NK) cells that lyse infected cells, (3) activation of pattern recognition receptors (PRRs) that induce inflammatory mediators to stimulate the maturation of innate immune cells and their recruitment to the site of infection. This also induces the interferon response with direct antiviral activity and contributes significantly to the development of an adaptive immune response several days later, (4) small interfering RNA molecules (RNAi) that interfere with virus replication, and (5) induction of apoptosis (programmed cell death) that leads to elimination of infected cells.

**MONOCYTES, MACROPHAGES, AND DENDRITIC CELLS**

These cells are very much at the front line in the early host response to virus infection. Monocytes display considerable mobility and a homing capacity for sites of infection, infiltrating tissue, and thence differentiating into macrophages. Macrophages and dendritic cells occupy key locations in various tissues, for example, alveolar macrophages in the lung, Kupffer cells in the liver, and Langerhans dendritic cells in the skin. Both monocytes and macrophages are important initiators of the immune response against viral invasion. Macrophages often become the predominant cell within a focus of infection by 24 hours. Activated macrophages have increased chemotactic activity, phagocytic activity, and digestive powers. Dendritic cells carry out afferent immune functions at all body surfaces by promoting the transfer of immune signals and cells into the regional lymph nodes where together with the liver and spleen most phagocytic removal of foreign particles occurs. All three cell types bear immunoglobulin Fc and C3b receptors on their cell surface to promote the phagocytosis of immune complexes (consisting of virions coated with antibody). By serving as “professional” antigen-presenting cells these cells exercise a controlling influence over the
rapidity, magnitude, and dynamics of the immune response. Macrophages then also contribute to the efferent limb of the immune response: cytokines secreted by activated T cells bring more monocytes into the infection focus that then become differentiated into macrophages.

Viruses have developed a number of ways to circumvent the extreme degradative environment of the macrophage cytoplasm. Dendritic cells infected with viruses lose endocytic capacity, allowing the virus the opportunity to migrate into distant organs and tissues, for example, HIV and Ebola virus. The Ebola virus VP35 protein (see Chapter 28: Filoviruses) blocks dendritic cell activation and effectively breaks the link between innate and adaptive immunity. A few viruses, for example, poxviruses and herpesviruses, trigger dendritic cell apoptosis, with the result of a reduced capacity of the system to present viral antigens to the adaptive immune system.

THE ROLE OF NATURAL KILLER (NK) CELLS AND THE LINK WITH ADAPTIVE IMMUNITY

NK cells are another important component of the early defense system, with the activity of these cells greatly enhanced within one to two days of viral infection. Resting NK cells are found in large quantities in the spleen, uterus, liver, and blood, but can be rapidly recruited to any site in the body in response to chemokine signaling from damaged tissue, tumor cells, and cells infected with a pathogen. The NK cell surface markers include the neural cell adhesion molecule (NCAM: CD56) or the low affinity IgG receptor CD16, or both. These large, non-phagocytic cells of the lymphoid system share the same lineage as mature T cells of the adaptive immune system, but differ in a number of important regards. The first is that NK cells lack T cell receptors (TCRs) but are activated by recognizing infected or tumor cells on which the density of molecules of the major histocompatibility complex (MHC: see Chapter 6: Adaptive Immune Responses to Infection) has been reduced. Viruses downregulate surface MHC class I molecules, in order to escape recognition by CD8$^+$ T cells. However, cells lacking class I MHC molecules are susceptible to NK cells: the so-called missing self hypothesis. This reduced MHC density on the target cell disturbs the balance between activator and inhibitory receptor signaling at the surface of the NK cell, as the inhibitory receptors recognize class I MHC molecules on the surface of healthy cells. Second, NK cells are activated by several non-antigen-specific mechanisms to produce preformed pore-inducing (perforin) and granzyme molecules that induce apoptosis in the target cell: this is in contrast to cytotoxic, CD8$^+$ T cells of the adaptive immune response that only produce these effector molecules once activated via recognition of class I MHC molecules in association with viral peptides. The third, and most important, difference is that NK cells do not need to proliferate and differentiate into viral-specific cells before activation. Overall, NK cells, while not displaying any immunological specificity for particular viral antigens, play an essential role in defense by mediating the death of infected cells by apoptosis, and by priming the adaptive response through secretion of several cytokines including interferon $\gamma$, tumor necrosis factor $\alpha$ (TNF-$\alpha$), IL-4, and IL-13 (Fig. 5.1).

Several families of viruses have developed mechanisms for evading NK responses, most notably members of the

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### TABLE 5.1 Characteristics of Two Types of Immune Response

| Property       | Innate Immunity                                      | Adaptive Immunity                                      |
|----------------|------------------------------------------------------|--------------------------------------------------------|
| Speed of response | Minutes/hours                                        | Days—response is accelerated when the same antigen is met on subsequent occasions |
| Antigen specificity | No                                                   | Yes                                                   |
| Duration$^a$      | Days                                                 | Weeks                                                  |
| Memory            | No                                                   | Yes                                                   |
| Effector mechanisms | (1) Complement, other serum proteins                | (1) Humoral response—different classes of antibodies produced by plasma cells which are derived from B lymphocytes |
|                 | (2) Natural antibodies, prod. by B1 lymphocytes     | (2) Cell-mediated response—mediated by cytotoxic T lymphocytes (CTLs), usually CD8$^+$ |
|                 | (3) Phagocytic cells (neutrophils, macrophages, dendritic cells) | (3) Macrophages, esp. following activation by cytokines, e.g., IFN-$\gamma$ released by antigen-specific T cells and NK cells |
|                 | (4) Natural killer (NK) cells                        |                                                        |
|                 | (5) Local cells (many types) that respond to PAMPs and produce cytokines including interferons |                                                        |
|                 | (6) Apoptosis to remove infected cells               |                                                        |
|                 | (7) Small RNA molecules (RNAi) that interfere with virus replication |                                                        |

$^a$Duration is prolonged if there is continuing antigenic stimulus.
families *Herpesviridae*, *Papillomaviridae*, *Poxviridae*, *Retroviridae*, and *Flaviviridae*. These fall into five broad strategies (Table 5.2). Four of these strategies are designed to interfere with the stimulation of NK cells by the presence of infected cells, either by enhancing inhibitory signals or blocking stimulatory signals to NK cells. For example the herpesvirus protein UL18 mimics host cell class I MHC molecules, such that, when bound with NK inhibitory cellular receptors, cell activation is suppressed. Viruses can also have a direct effect on NK cells. Both HIV and herpes simplex virus can infect NK cells *in vitro*, and the E2 protein of hepatitis C virus binds directly to the CD81 protein on the surface of NK cells leading to inhibition of activation signals.

**THE IMPORTANCE OF MOLECULAR RECOGNITION**

As mentioned above, an early important line of defense is the recognition of viral components by germline-encoded pattern recognition receptors (PRRs) capable of distinguishing viral products from those of the host. PRRs are expressed in many cell types likely to be present at portals of virus entry, including macrophages, dendritic cells, neutrophils, NK cells, endothelial cells, and mucosal epithelial cells. These cellular receptor molecules recognize different classes of pathogen-associated molecular patterns (PAMPs). There are a number of classes of PRRs that are present on the majority of mammalian cells. These include the C-type lectin receptors, NOD-like receptors, the transmembrane Toll like Receptor (TLR) receptors, and the cytosolic RIG-I like receptors (RLR) such as RIG-I and MDA5. TLRs consist of amino-terminal leucine-rich repeat domains responsible for PAMP recognition and a cytoplasmic carboxyl-terminal domain that recognizes interleukin-1 and leads to downstream signal transduction. In contrast, the RLRs recognize associated PAMP via caspase activation and recruitment (CARD) domains. Common to both classes of PRR, the PRR–PAMP complex then triggers a series of signaling cascades, culminating in the production of pro-inflammatory cytokines and other

![FIGURE 5.1 Activating and inhibitory receptors of NK cells. (A) Healthy cells express self class I MHC molecules which are recognized by inhibitory receptors, thus ensuring NK cells do not attack normal cells. Healthy cells may express ligands for activating receptors (not shown) or they may not express such ligands (as shown), but they do not activate NK cells because they engage the inhibitory receptors. (B) In virus-infected cells, class I MHC expression is reduced so that the inhibitory receptors are not engaged and ligands for activating receptors are expressed. The result is that NK cells are activated and the infected cells are killed. Reproduced from MacLachlan, N.J., Dubovi, E.J., 2011. Veterinary Virology, fourth ed. Academic Press, London (Figure 4.1), with permission.]

| TABLE 5.2 Viral Mechanisms for the Evasion of Natural Killer (NK) Cells |
|-----------------------------|-----------------------------|
| **Mechanism of Action**     | **Examples**                | **Outcome**                      |
| (1) Homologues of class 1 MHC | Herpesviruses               | Bind to NK cell inhibitory receptor, Inhibit NK cytotoxicity |
| (2) Regulation of class 1 MHC expression on target cell | Herpesviruses, SIV | Inhibition of NK cytotoxicity |
| (3) Virus-coded protein interfering with NK cell-activating receptor/ligand interactions | Herpesviruses, HIV, HTLV | Inhibition of NK cytotoxicity and IFN-γ production |
| (4) Inhibition of NK cell-activating cytokine by binding cytokine or producing chemokine antagonist | Herpesviruses, papillomaviruses, | Inhibition of IFN-γ production, trafficking |
| (5) Direct effects of virions; e.g., block an inhibitory receptor, or directly infect NK cells; HCV E2 protein binds directly to CD81 on NK cell | Herpesviruses, HIV | Reduces NK cell activity |
Table 5.4

| Ligand                                      | Endosomes | Cell surface | Toxoplasma gondii (TLR11,12) bacterial ribosomal RNA (TLR13) |
|---------------------------------------------|-----------|--------------|---------------------------------------------------------------|
| Microbial cell walls (lipopolysaccharides)  |           |              |                                                               |
| dsRNA (TLR7,8), unmethylated CpG DNA (TLR9) |           |              |                                                               |
| Bacterial lipopolysaccharides               |           |              |                                                               |
| ssRNA (TLR7,8), unmethylated CpG DNA (TLR9) |           |              |                                                               |
| Bacterial lipopolysaccharides               |           |              |                                                               |
| dsRNA                                        |           |              |                                                               |
| Bacterial lipopolysaccharides               |           |              |                                                               |

*Toll-Like Receptor (TLR) Family  Other TLR Members  Location  Ligand
1 2,6,10  Cell surface  Microbial cell walls (lipopolysaccharides)
3  Endosomes  dsRNA
4  Cell surface  Bacterial lipopolysaccharides
5  Cell surface  Bacterial lipopolysaccharides
7  8,9  Endosomes  ssRNA (TLR7,8), unmethylated CpG DNA (TLR9)
11  12, 13  Endosomes  Toxoplasma gondii (TLR11,12) bacterial ribosomal RNA (TLR13)

Interferons are thus a response to the infection of any one cell, and the secreted interferon molecules induce the expression of interferon stimulatory genes (ISGs) by the surrounding cells leading to an antiviral response. The numbers of ISGs induced in the surrounding cells can number in excess of 100 (Fig. 5.2).

Interferons (IFNs) are classified into three types according to receptor usage (Table 5.4). Type I interferons (IFN-α, IFN-β, and others) are produced by a majority of cells and play a major role in limiting the spread of virus infections; type II interferon (IFN-γ) activates macrophages, recruits leukocytes to the sites of infection, and potentiates type I interferons; while type III (IFN-λ) interferons are particularly prominent in the control of infections at mucosal surfaces, for example the gastrointestinal and respiratory tracts.

All interferons bind to specific cell surface receptor complexes consisting of multiple polypeptide chains. Among the type I interferons, IFN-α and IFN-β have received much attention as potential therapeutics although other interferons are present in humans (IFN-ε, IFN-κ, and IFN-ω). IFN-α is used for the treatment of hepatitis B and hepatitis C as well as for the treatment of some cancers. IFN-β has been recommended for the treatment of multiple sclerosis.

The IFN-λ cytokine family is composed of IFN-λ1 (previously known as IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28B), and IFN-λ4, all of which are coded on human chromosome 19. In contrast to IFN-α and IFN-β signaling, IFN-λ receptors are specific to melanocytes, liver cells, and epithelial cells. Indeed, IFN-λ appears to have evolved specifically to protect the epithelium from virus infection. Since the induction of ISGs in surrounding cells by IFN-λ is perhaps more prolonged than with IFN-α, it is receiving considerable attention as a potential therapeutic agent. The density of receptor molecules on hepatocytes for IFN-λ3 varies according to genotype; a link has been established between IFN-λ3 genotype and the degree of responsiveness of hepatitis C patients to treatment with commercial IFN-α.
**FIGURE 5.2** Pathways of action of interferons. Type I IFNs interact with IFN- (α, β, and ω) receptor 1 (IFNAR1) and IFNAR2; type II IFN interacts with IFN-γ receptor 1 (IFNGR1) and IFNGR2; type III IFNs interact with IFN-λ receptor 1 (IFNLR1; also known as IL28RA) and IL-10 receptor 2 (IL10R2; also known as IL10RB). Type II IFN-γ is an antiparallel homodimer exhibiting a twofold axis of symmetry. It binds two IFNGR1 receptor chains, assembling a complex that is stabilized by two IFNGR2 chains. These receptors are associated with two kinases from the JAK family: Janus (JAK)1 and tyrosine (TYK2) for types I and III IFNs; JAK1 and JAK2 for type II IFN. All IFN receptor chains belong to the class 2 helical cytokine receptor family, with the 200 amino acid extracellular domains usually contain the ligand binding site. IFNAR2, IFNLR1, IL10R2, IFNGR1, and IFNGR2 are classical representatives of this family, whereas IFNAR1 is atypical, as its extracellular domain is duplicated. GAS, IFN-γ-activated site; IRF9, IFN regulatory factor 9; ISGF3, IFN-stimulated gene factor 3 (refers to the STAT1–STAT2–IRF9 complex); ISRE, IFN-stimulated response element; P, phosphate; STAT1/2, signal transducers and activators of transcription 1/2. Adapted from Borden, E.C., et al., 2007. Nat. Rev. Drug Discov. 6, 975–990 and MacLachlan, N.J., Dubovi, E.J., 2011. Veterinary Virology, fourth ed., Academic Press Fig. 4.2, with permission.

**TABLE 5.4** Three Types of Interferons

| Type I | Type II | Type III |
|--------|---------|----------|
| Examples | IFN-α: Different species-specific examples | IFN-γ | IFN-λ-1, IFN-λ-2, IFN-λ-3, IFN-λ-4, |
| IFN-β: 1 type | IFN-β: 1 type | | |
| IFN-δ, IFN-ε, IFN-κ, IFN-ω, IFN-τ | IFN-δ, IFN-ε, IFN-κ, IFN-ω, IFN-τ | | |
| Produced by | Most nucleated cell types | T cells and NK cells | Many cell types |
| Receptor | IFNAR, a heterodimer of INFAR-1 and INFAR-2 | IFNGR, a tetramer of 2 heterodimers of IFNGR-1 and IFNGR-2 | IFNLR1, present on melanocytes, liver cells, epithelial cells |
| Effects of binding to receptor | Activates cascade including TYK, JAK, STAT, and IRF9 to induce IFN-stimulated response elements (ISREs) | Activates pathway involving JAK and STAT to induce IFN-γ-activated site (GAS) | Activates pathway involving JAK and STAT leading to expression of IFN-stimulated genes |

The induction of innate responses results in the activation of intracellular pathways that often involve overlapping signaling mechanisms. For example, transcription of IFN mRNAs is controlled by several IFN regulatory factors (IRFs), which are activated by signaling pathways that themselves become activated following interaction between different PAMPs and PRRs, particularly the TLRs 3, 7, 8, and 9 in the endosome but also RLRs in the cytoplasm. The role of the transcription factor NF-κB is also critical for both IFN and inflammatory
responses. Normally sequestered in the cytoplasm through attachment to an inhibitory protein, the latter is degraded once virus infection has activated the relevant pathway, allowing NF-κB to translocate into the nucleus and there activate a myriad of cytokine genes, including IFN-β.

Together, the IRF systems in conjunction with NF-κB are major regulatory elements controlling inflammatory gene expression and IFN production (Fig. 5.3).

It is thought that the major site of TLR recognition occurs within endosomes, where internalized viruses are detected. This endosomal location provides some specificity for recognition of viral RNA/DNA, as cellular derived nucleic acids are not normally present within endosomes. The role of each TLR may also differ between cell types. Intracellular TLR3 is particularly important as a cytoplasmic sensor of viral nucleic acid, especially dsRNA, a replicative intermediate present in many virus-infected cells. Activation of TLR3 leads to the production of both IFN types I and III and inflammatory cytokines via the TRIF-dependent pathway (Fig. 5.3): TLR3 agonists provide protection against many different viruses, for example HIV, coronaviruses, and hepatitis B virus.

Another example of endosomal recognition is the interaction between ssRNA and TLR7 and TLR8. TLR7 signaling is particularly prominent in peripheral dendritic cells, leading to the expression of type I IFNs. Viruses entering by direct membrane fusion at the cell surface may undergo autophagy, and viral ssRNA molecules are transported to endo-lysosomes where contact can be made with TLR7. A third mechanism has been uncovered whereby exosomes containing viral RNA are transferred by cell-to-cell contact to peripheral dendritic cells. DNA viruses such as herpesviruses and poxviruses activate IFN-α production via a TLR9-dependent pathway: cooperation is required between TLR9 and TLR2 for a response to EBV and adenoviruses. The role of TLR9 in recognizing the ssDNA of parvoviruses is less clear. Also little is known regarding the role of other TLRs in responding to viral infection: although TLR2 and TLR4 sense primarily bacterial components, there is some evidence for either or both playing a role in controlling virus infection.

The action of type I interferon involves its binding to interferon receptors (IFNAR1/2), which by activating further signaling cascades (JAK/Stat pathway) leads to expression...
of a large number of ISGs whose main function is control of viral replication and immune modulation. Those induced ISGs that contributes to the interferon-induced antiviral state are numerous. These continue to grow and include ISG15, a ubiquitin homologue that targets more than 150 proteins for degradation; MxGTPase, a hydrolyzing enzyme that affects vesicle formation and prevents virus maturation; the 2‘5‘ oligoadenylate synthetase pathway, which activates cellular RNAse that cleaves viral RNAs; and the protein kinase (PKR) pathway responsible for the phosphorylation of elongation initiation factor eIF-2α and which therefore inhibits protein synthesis.

**CELL DEATH AND APOPTOSIS**

Death of an infected cell may be viewed as beneficial to the host if it impedes the production of progeny viruses and thus prevents further dissemination in the body. Various derangements of cell function and metabolism due to virus infection have long been recognized as causes of cell necrosis, but it is also evident that the induction of apoptosis, or programmed cell death, is another mechanism whereby infected cells undergo active self-destruction. Apoptosis in the context of viral infection can be induced by one of two pathways: an intrinsic mitochondrial pathway whereby cell injury leads to increased mitochondrial permeability and leakage of mitochondrial proteins into the cytosol; or an extrinsic death domain pathway in which binding of TNF to, or interaction of cytotoxic T lymphocytes with, specific TNF cellular receptors triggers the apoptotic pathway. Once initiated by either route, the activation of host caspase enzymes degrades cellular DNA and proteins leading to cell death by apoptosis (known as the “executioner” phase) (Fig. 5.4).

As noted above, apoptosis of virus-infected target cells can also be initiated by cytotoxic T lymphocytes and NK cells using preformed mediators such as perforin and granzyme that directly activate caspases in the target cell.

**EVASION STRATEGIES**

Almost all viruses have developed elaborate, and often complex, strategies to circumvent host innate immunity highlighting the importance of the innate immune response; host cells have also evolved countermeasures to these evasion strategies, giving rise to a “genetic arms race” with both virus and host competing against the other. Viral evasion strategies include the degradation of TLR signaling components, interference with transcription factors, and mimicry of cellular proteins. Given its importance in dsRNA
recognition, the TLR3 pathway is frequently targeted, with TRIF, the adaptor for TLR3, being particularly targeted for degradation by viral proteases. This targeting of TRIF is particularly effective, as TRIF abrogation also inhibits both NF-κB and IRF3 production. Other points downstream in the pathways may also be blocked: the IKK complex, for example, a complex of cellular kinases pivotal in several activation pathways, is often inhibited, as is ubiquitination, a regulatory process controlling protein turnover and cellular location. The serine protease (NS3/4A) of hepatitis C virus and the 3C protease of several picornaviruses can all cleave TRIF leading to an attenuated antiviral response, but targeting TRIF is not confined to RNA viruses. For example, TRIF levels are significantly downregulated during gamma herpesvirus infections. Interestingly, the HCV serine protease also cleaves IPS-1, an adaptor molecule within the RIG-I pathway involved in sensing viral RNA, and thus HCV can modulate PRR sensing at multiple points.

For many viruses, preserving and expanding the endoplasmic reticulum of the infected cell is vital for the purpose of virus assembly and maturation while preventing stress-induced apoptosis that would otherwise be a natural consequence. Dengue viruses and other flaviviruses do this by careful control of the cellular unfolded protein response, or UPR, preventing the development of cytopathicity yet allowing for the rearrangement of cellular membrane components necessary for endoplasmic reticulum expansion. Autophagy, an important element of innate immunity, is also utilized by dengue viruses. Normally autophagosomes coalesce with lysosomes but dengue viruses inhibit this process, thus allowing these viruses to sequester within autophagosomes for the purpose of RNA replication. This complements the capacity of the virus non-structural protein NS4B to block synthesis of IFN-α and IFN-β through inhibition of the JAK/STAT pathway by blocking the phosphorylation of STAT1. The result is the inhibition of interferon-inducible transmembrane protein synthesis.

Mimicry of key components of innate immunity is a strategy employed by many viruses. For example, the V protein of paramyxoviruses mimics IRF3 and acts as a non-functional substrate for IRF3 kinases, thereby inhibiting pathways initiated by TLR3 binding to viral RNA. Perhaps the best studied viruses in this respect are the poxviruses: protein A49 effectively blocks through mimicry the induction of type I IFN through abolishing NF-κB activation, a key molecule for the induction of IFN gene transcription (see above and Fig. 5.2).

Following initial infection of a host cell, many host restriction factors recognize viruses and directly inhibit their replication. HIV and simian immunodeficiency viruses (SIVs) are recognized by several host restriction factors in their respective human and non-human primate hosts. Tripartite motif-containing protein 5α (TRIM5α) is a species-specific host restriction factor that restricts the replication of HIV-1 in Old World monkeys such as rhesus and cynomolgus macaques. Rhesus TRIM5α restricts HIV-1 infection by interacting with the HIV-1 capsid at an early stage of infection, and is believed to be involved in the innate immune response to retroviral infection. Similarly, apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G (APOBEC3G) is a host protein; APOBEC3G restricts the replication of retroviruses including HIV and SIV, by converting deoxycytidine to deoxyuridine on the minus strand of viral DNA during reverse transcription, thereby introducing (often lethal) mutations into the genome. The retroviral protein viral infectivity factor (Vif) counteracts this by binding to, and assisting degradation of, APOBEC3G via a ubiquitin-dependent proteasomal pathway.

Recently, a study of four African green monkey subspecies, which can be infected with divergent strains of SIV, highlighted that there is ongoing evolution of simian APOBEC3G in the absence of ongoing disease even in a non-pathogenic infection. In response to these changes, both natural isolates from long-term infected individuals and viruses from experimentally infected individuals also adapt to retarget the host restriction factor. These factors may contribute to the narrow species specificity of closely related retroviruses, and highlight the ongoing conflict between virus and host.

In another example, the transmembrane protein tetherin inhibits the detachment of enveloped viruses from the cell membrane; in the case of HIV, the viral protein U (Vpu) counteracts this by degrading and downregulating tetherin, thereby enhancing virus release. This action of Vpu also helps to protect cells from elimination by antibody-dependent cell cytotoxicity. Vpu also acts to enhance the degradation of newly formed CD4 molecules.

**FURTHER READING**

Flint, S.J., Enquist, L.W., Racaniello, V.R., Rall, G.F., Skalka, A.-M., 2016. *Principles of Virology*, 4th ed. ASM Press, Washington, DC.

Green, A.M., Beatty, P.R., Hadjiio, A., Harris, E., 2013. Innate immunity to dengue virus infection and subversion of antiviral responses. J. Mol. Biol. Available from: [http://dx.doi.org/10.1016/j.jmb.2013.11.023](http://dx.doi.org/10.1016/j.jmb.2013.11.023).

Jost, S., Altfield, M., 2013. Control of human viral infections by natural killer cells. Annu. Rev. Immunol. 31, 163–194. Available from: [http://dx.doi.org/10.1146/annurev-immunol-032712-100001](http://dx.doi.org/10.1146/annurev-immunol-032712-100001).

Lester, S.N., Li, K., 2013. Toll-like receptors in antiviral innate immunity. J. Mol. Biol. Available from: [http://dx.doi.org/10.1016/j.jmb.2013.11.024](http://dx.doi.org/10.1016/j.jmb.2013.11.024).

Mercer, J., Greber, U.F., 2013. Virus interactions with endocytic pathways in macrophages and dendritic cells. Trends Microbiol. 21, 380–388. Available from: [http://dx.doi.org/10.1016/j.tim.2013.06.001](http://dx.doi.org/10.1016/j.tim.2013.06.001).