Colloquium

Strategies and mechanisms for host and pathogen survival in acute and persistent viral infections

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Persistent viral infections causing serious diseases derive, primarily, from altered function of the immune system. Knowledge of the very complex composition and function of the innate and adaptive branches of the immune system is essential to understanding persistent infection. The best solution to the problem of persistent infection is by prevention using prophylactic vaccines. Hit and run viruses evade immune destruction by infecting new hosts and rarely persist. Hit and stay viruses evade immune control by sequestration, blockade of antigen presentation, cytokine escape, evasion of natural killer cell activities, escape from apoptosis, and antigenic change. Twelve prophylactic vaccines against hit and run agents exist, and there are only three vaccines against hit and stay viruses, all of which are of DNA composition. Several new vaccines against hit and stay viruses are feasible, but protective vaccines against RNA HIV and hepatitis C agents are highly unlikely, short of a major breakthrough. Therapeutic vaccines are very improbable without a magnitude of favorable new discoveries. In the meantime, antiviral chemotherapy, chemotherapy/prophylactic vaccination, and short interfering RNA silencing are worthy of intense investigation.

virus immunology | viral strategies

It may seem strange to devote an entire colloquium to therapeutic vaccines for which there is no example other than, perhaps, that against rabies. However, therapeutic vaccinology remains a ''Holy Grail'' for future conquest of yet to be conquered diseases.

There is a credible but uncertain basis for hope that effective therapeutic vaccines may be developed eventually, because the healthy immune system can and does cure most infections in the normal recovery processes, mainly through cell-mediated immune mechanisms. Although it is true that the most effective resolution of viral infections must start early after infection, it is well known that spontaneous elimination of some infectious agents, such as that for hepatitis B, can occur at any time, even late in the disease process.

Viewed simply, the inappropriate or inadequate interface between host and invader or between host and its own immune system brings together an array of diseases of individual diversity that are the topics for this colloquium. For infectious agents, the means for host recovery is one of detection, apprehension, and destruction of the parasite by the immune system. The strategy of the pathogen is to evade, escape, and survive. This paper is dedicated to discussions of the pathogenesis and the means for evasion used by viruses in their battle with the immune system.

Quest for Survival

The mechanisms for infection, proliferation, and persistence of viruses in cells of the permissive host are the means by which these genetic entities preserve their specificity and identity in perpetuity. Irrespective of their wishes, viruses have no choice because they are programmed genetically to survive and to propagate, and those viruses that exist today are the ones that have been successful. Others, which have not been successful, have disappeared or may have evolved into new entities that are not readily identifiable with their more primordial ancestors.

Strategies for Survival

Two different strategies for survival are assumed by viruses. One is hit and run infection whereby there is successive propagation in a series of hosts. The other is hit and stay with viral persistence in the same host. Hit and run viruses are mainly cytolytic and destroy the cells of the host in which they multiply. They are highly infective, readily transmit to susceptible new hosts, and include viruses such as influenza, rhinoviruses of the common cold, and measles. The most common resolution of viral infection is by an effective cell-mediated immune response, requiring the virus to escape to new hosts before immunological resolution or before death of the host itself. Some viruses, such as the pox agents, may be able to survive in the environment for a period in dried form, and enteroviruses and rotaviruses may remain viable in water. Rabies and yellow fever viruses have reservoirs in alternative animal hosts, such as in feral species. Influenza viruses travel rapidly and induce herd immunity, requiring the virus to mutate and change its antigenic specificity to continue to infect. It is aided also by alternate seasonal high communicability in epidemics in the Northern and Southern geographic hemispheres.

In the hit and stay strategy, the virus achieves long term residence in the individual host, from whom there may be frequent or infrequent transmission to successive hosts. Latency, with rare vegetative proliferation, is a very favorable means for viral preservation. It is not in the best interest of any parasite to destroy its own host or the host population on which it depends for its existence. Also, it is rarely in the best interest of the host to support a virus. Optimal accommodation between host and virus is with inapparent clinical infection in what may be a commensal state, or one in which the host immune control achieves a tolerable disease state. In persistent infections, such as with hepatitis B virus, an excessive and inappropriate host immune response can turn an otherwise inapparent nonlytic infection into a severe disease, and the consequence may be fulminant or chronic–active hepatitis leading to death by cirrhosis and/or cancer of the liver.

Understanding the game of viral persistence or elimination requires a working knowledge of the structure, dynamics, and strategies of the host immune system and of the virus in their collective engagements, as are discussed below.

Table 1. General characteristics of the immune systems

Activity	Innate	Adaptive
Origin	Primitive, ancient	More recent
Recognition	Chemical pattern	Specific epitopes
Development	Rapid, immediate	Slow (1–2 weeks)
Messengers	Cytokines	Cytokines (diverse)
Memory	None	Long, up to lifetime
Presentation	Direct recognition by toll, other receptors	Processing, synapse. Dual system: Humoral-antibody Cell-mediated Cytotoxic T helper
System	Very simple, direct recognition and response	Highly complex, recognition and response

Table 2. Cells and functions of the innate immune system

Cells and systems	Important functions
Macrohages/monocytes	Engulf, destroy invaders, secrete cytokines, signal cell proliferation
Dendritic cells	Pattern recognition, secrete cytokines, influence adaptive immune response
NK cells	Recognize the abnormal and kill
NK T cells	Recognize lipid antigens, activate T cells
Phagocytic, inflammatory	
Neutrophils	Phagocytic, inflammatory at site of tissue damage
Eosinophils	Recognize allergens, helminths, bring inflammation
Mast and basophils	Cytokine, important to inflammatory and allergic responses
Soluble factors	
Cytokines, chemokines	Chemical messengers; signal cellular responses
Complement	Complex proteolytic enzymes Opsonize, lyse cells, mediate inflammation

The mechanisms and systems for immune function and for immune evasion are extremely complex, and the numbers of published contributions by individual workers are far too large to cite in this brief review. Fortunately, the literature has been assembled in numerous excellent reviews. This report aims to provide an overview and intends to cite only a small number of pertinent references

The Immune System (1–8)

It is the purpose of the immune system to seek out and destroy both free viruses and somatic host cells that are infected. The mammalian immune system is highly complex and incompletely understood. The brief discussion of the immune system that is given here intends to provide a superficial overview of information that is critical to understanding immune evasion in persistent viral infection.

Comparison of Systems. Table 1 shows a separation of the immune system into two arms, known as the innate and the adaptive, that coexist, cofunction, and complement each other. Such separation has no lines of demarcation in a system in which the innate activities transition into the adaptive while retaining all functions of both as their mediators interact with each other. The principal difference between the two arms is that activation of the primitive innate system relies on predetermined molecular pattern recognition of microbial substances (danger signals) that are foreign and not of self. The adaptive system relies on specific recognition and response to antigens, which includes immunologic memory. Innate recognition may be by toll receptors on macrophages and dendritic cells and by special recognition receptors on natural killer cells (NK). The messengers that signal responses between the various collaborating cells of the immune system are called cytokines, which initiate signal transduction leading to genetic expression for production of proteins as well as for initiation of cell replication. The innate immune response to a signal is soon lost, and there is no mechanism for immunologic recall of previous experience or memory.

The adaptive immune system is of more recent phylogenetic origin, and its activation relies on recognition of specific determinants of antigens called epitopes. Activation or priming of the adaptive response is slow to develop, and the signaling messengers are cytokines, as in the innate system. Once activated, there usually is retained memory and capacity for rapid anamnestic recall by memory effector cells, which do not need to be reprimed. Such memory may last for a lifetime. Presentation of epitopes, and recognition by cells of the adaptive immune system, is very complex, involving collaboration between several participants in every individual immune response. Adaptive

immunity, itself, comprises a dual system consisting of humoral (antibody) and cell-mediated responses, which are aided by T helper cells. Simply stated, the outstanding feature of innate immunity is in its direct recognition of the abnormal. The adaptive response, by contrast, is highly complex, both in recognition of what is not self and in its specificity.

Innate Immunity. Principal members of the innate immune system (Table 2) include cells of the monocyte/macrophage lineage and the dendritic cells. The monocyte/macrophages engulf and destroy invaders, secrete cytokines, and signal for proliferation of cells of the immune system. The dendritic cells recognize patterns, engulf pathogens, and secrete cytokines that influence both the innate and the adaptive immune responses, especially in preparing the adaptive system to respond appropriately. The NK cells of the innate immune system recognize and kill host somatic cells that are coated with antibody or fail to express MHC proteins, and they secrete cytokines that affect the immune response. NK T cells recognize lipid antigens that are presented by CD1 molecules on dendritic cells, and they secrete cytokines that are biased toward cell-mediated immune responses. The neutrophils are phagocytic and engage in bringing acute inflammatory reactions to the site of infection. Eosinophils are granulocytes, which bear highly toxic proteins, are principally recruited in response to allergens and to generalized infection with parasitic helminths. Collectively, the granule-containing mast cells and basophils release histamines, tumor necrosis factor (TNF) α, and other proteins of importance in allergic and inflammatory responses. Soluble cytokines are chemical messengers that bind to cytokine receptors and provide signals for action between cells. Such signaling may also be achieved by surface contact. Chemoattractant chemokines control leukocyte trafficking and play major roles in acute and chronic inflammation as well as in other activities in immune function. Complement is comprised of a group of serum proteins that can act in an enzymatic cascade, providing molecules involved in inflammation, phagocytosis, and cell lysis. In general, inflammation is a process whereby tissues respond to injury and leukocytes and soluble mediators work to control and eliminate invaders. Massive autodestruction of tissues may occur when the inflammatory

Table 3. Cells, factors, and functions in adaptive immunity

Cells and systems	Important functions
APCs	Detect, engulf antigens, present fragments
Dendritic cells	Prime lymphocytes, secrete cytokines
Macrophages	Phagocytose, present, secrete cytokines
B cells	Engulf antigens, process, present fragments, differentiate, produce antibody
T cells	
CD8+ cytotoxic killer	Recognize, kill, secrete cytokines
Natural killer T cells	Recognize lipid antigens
CD4+ Helper*	
T helper 1	Secrete cytokines, aid humoral responses
T helper 2	Secrete cytokines, aid cytotoxic T cells
Suppressor T cells	Suppress T or B cell responses

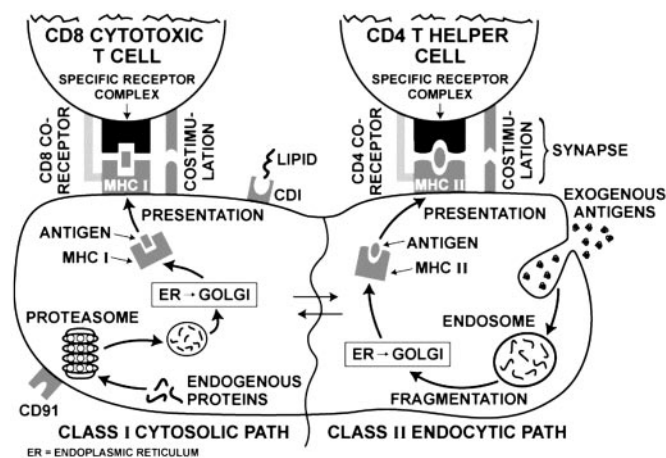T helper 1 and 2 cytokines are mutually antagonistic.

Fig. 1. Antigen presentation and T cell priming.

process is poorly controlled. Especially important in the early innate immune response is its recognition of double-stranded RNA as abnormal, and its elicitation of α, β, and γ interferons. The IFN cytokines are highly effective in early suppression of viral replication at the transcription–translation level, and they also activate certain immune responses. IFN-γ serves as a regulator of immune response.

Adaptive Immunity. Cells of the adaptive system (Table 3) consist mainly of phagocytic professional antigen-presenting cells (APCs) (dendritic cells and macrophages), B lymphocytes that produce antibodies, and T lymphocytes, of which there are two kinds, the CD8-positive cytotoxic killer T cells (Tc) and CD4-positive T helper cells. The T helper cells are divided further into two kinds: CD4-positive T helper 2 cells facilitate proliferation and differentiation of B lymphocytes to plasma cells, which secrete their receptors as antibodies. By contrast, CD8-positive T helper 1 cells facilitate proliferation and differentiation of killer cytotoxic T cells. Suppressor T cells also exist and may depress or alter CD4 and CD8 T cell activation by processes in an antigen-specific manner that is poorly understood.

Newly minted precursor T and B lymphocytes derived from the bone marrow undergo genetic rearrangement, creating individual cells with receptors of widely different antigenic specificities. Antigen epitopes (ligands) of diverse specificity that match the specificity of the lymphocyte receptor are said to be complementary. Antigens and receptors that are complementary bind together, and those that are not complementary do not bind. Binding brings about activation of T and B cells described below.

Primordial T lymphocytes, in their maturation, must pass through the thymus gland, where they differentiate into CD8- and CD4-positive T cells. T cells that have receptor specificities that are complementary to self antigens of the body are destroyed by a process called apoptosis. Apoptosis is a normal activity by which the body rids itself of cells that are defective or no longer needed. This includes cells of the immune system. In apoptosis, the cells are dissolved by proteases (caspases) in which there is no toxicity to adjoining cells.

B cells, like T cells, also originate in the bone marrow but are not selected in the thymus. Instead, they must be helped to differentiate and to mature by reacting with T helper cells that, themselves, have been selected in the thymus not to react with self antigens. B cells that are not helped die. By these mechanisms of elimination, the host prevents self-destruction by both humoral and cell-mediated autoimmune reactions and is usually, but not always, successful.

The cells of both the innate and adaptive immune complexes communicate with each other via the particular cytokines that they secrete or receive, or by direct contact between them. Cytokines bind to receptors on cells and activate them through signal transduction of their genes, eliciting production of the cytokines needed for selective immune cell multiplication referred to as clonal expansion. The cytokines of the T helper 1 and 2 kinds usually are mutually antagonistic to each other. Sometimes there may be excessive production of the cadre of either type 1 or type 2 cytokines, which polarizes the immune response and upsets the homeostatic balance needed to maintain an appropriate mix of activities of humoral and cell-mediated immunity. Specific antibodies neutralize or impair infectious agents, reducing the parasite load and preventing reinfection of the host after recovery. Cytotoxic T cells are the killers that detect and destroy cells that are infected with pathogenic agents. Alternatively, they secrete cytokines such as IFN-γ and TNFα, which interfere with viral proliferation without cell death. T helper cells secrete cytokines that are needed to bring about differentiation and clonal expansion of primed cytotoxic T and B cells.

Priming and Activating Effector Lymphocytes. The activation or priming of naïve cytotoxic T and T helper cells is achieved by a complex of interactions (Fig. 1) between the APCs and the lymphocytes. Professional APCs, i.e., dendritic cells and macrophages, may be considered to have two compartments. These are the enclosed endosome and the cytoplasm or cytosol. The APCs sample antigens from two sources. Exogenous proteins that are endocytosed from the outside are broken down enzymatically, by endosomal organelles, into small peptide fragments of 13–15 amino acid residues that bear antigenic specificities (epitopes). Normal intracellular proteins, abnormal proteins deriving from infection in the APCs, and antigens that enter by fusion with the cell membrane are transported into enzymatic structures called proteasomes, where they are fragmented to small peptides $\approx$9 amino acid residues in length.

Once fragmented, the short segments of antigens of exogenous and endogenous origin must be bound to MHC molecules within the endoplasmic reticulum for transport and display on the surface of the APC via the Golgi secretory system. MHC molecules are of two kinds, called MHC I and MHC II, based on the gene sites from which they are encoded. The MHC molecules are somewhat diverse with respect to the pattern of binding sites in the groove to which the antigen fragments become attached. Binding to a particular allelic MHC molecule is restricted to fragments with sufficient affinity for the binding sites in the MHC groove. A collection of allelic MHC molecules of mod-
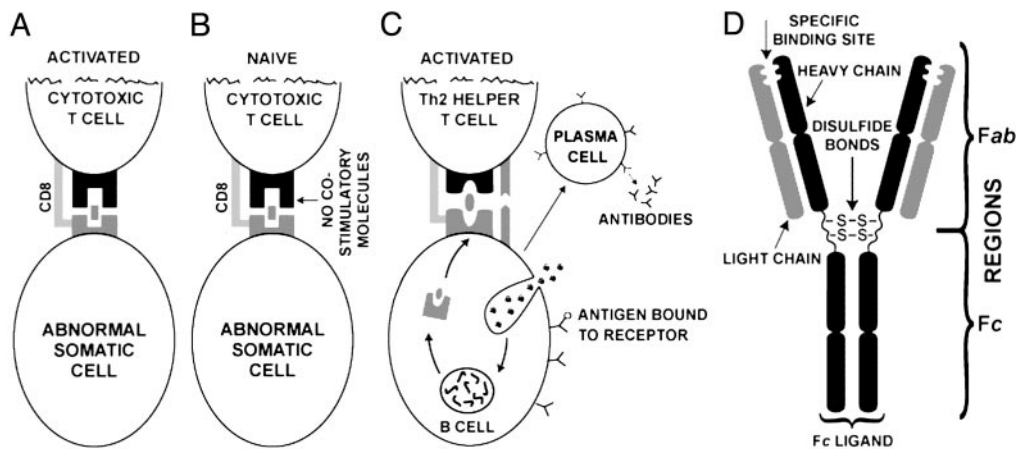
Fig. 2. T cell priming and antibody structure.

erate diversity are an attribute of every person, and are the basis for what is called allelic restriction imposed by the mix of particular MHC proteins made in the individual being.

Fragments of exogenous peptides, which bind to MHC II proteins, follow the endocytic class 2 pathway to presentation on the cell surface. Endogenous peptides that bind to MHC I molecules are transported by the class 1 or cytosolic pathway. Mechanically, the fragments of class 1 peptides that exit from the proteasome are bound to a transporter protein (TAP) and are carried to the lumen of the tubular complex of the endoplasmic reticulum, where they are bound to the MHC I protein and carried to the surface membrane via the Golgi secretory system. Class 2 peptide fragments enter the lumen of the endoplasmic reticulum (without a TAP protein), where they are bound to MHC II proteins and exported to the surface of the APC in the same way as class 1. The TAP serves to distinguish between class 1 and class 2 peptides and assures that only the peptides of exogenous origin are bound to MHC II proteins.

Epitopes presented via MHC I molecules on APCs are recognized and bound to naïve CD8 cytotoxic T cells of complementary receptor specificity. In this process, there is also binding of the CD8 molecule of the cytotoxic T cell receptor to the MHC I protein. In addition, one or more sets of complementary costimulatory molecules of the APC and cytotoxic T cell, e.g., B7:CD28, bring stability to the union. Such costimulatory binding is needed in order for priming to take place. In its absence, the T cell becomes anergic and incapable of further response. Successful binding between the MHC epitope and its complementary receptor complex brings about lymphocyte activation referred to as priming. CD4$^+$ T helper cells are essential to support differentiation and clonal expansion of B cells and cytotoxic T cells. Naïve T helper lymphocytes are activated by a similar process to that described for cytotoxic T cells. They recognize epitopes that are presented with MHC II proteins.

As noted above, the T helper lymphocytes are of two kinds, T helper 1 and 2. Activated T helper 1 cells secrete cytokines that favor maturation and clonal expansion of cytotoxic T cells (e.g., IL2, -12, and -15 and IFN-α, -β, and -γ). T helper 2 lymphocytes secrete cytokines that favor a B cell humoral response (e.g., IL4, -5, -6, -13, and -16,). Just how T helper CD4 cells achieve such preferred activities is not well understood, but the particular kinds of pathogens found in the cell environment may themselves signal a need for a cell-mediated or an antibody response. T helper 1 and 2 lymphocytes, in reality, may represent only the extreme ends for the secretory cytokine patterns, with all sorts of mixtures in between. The cytokines secreted by T helper 1 and 2 cells do antagonize each other, and a preponderance of the T helper 1 or 2 cytokines may polarize the immune response in favorable or unfavorable ways.

With the aid of T helper 1 lymphocytes, the primed cytotoxic T cells are activated to differentiate and to expand clonally into mature activated effector cells. They are then transported from the lymphoid organs (lymph nodes and spleen) into the circulation and the intercellular fluids, where they seek out and destroy altered somatic cells that present epitopes of complementary specificity. B cells are primed and activated by a different means, which is discussed below (see Table 3 and Fig. 2C).

Functions and Fates of T and B Cells. Fig. 2 illustrates the functions of effector cells of the immune system in three different situations. Essentially, all of the somatic cells of the body continuously process and present epitopes on their cell surfaces, which reveals their internal composition, both normal and abnormal. In Fig. 2A, an epitope of the abnormal somatic cell has been recognized by an activated complementary cytotoxic T cell. Such engagement brings about destruction of abnormal body cells through lysis or by apoptosis by binding of Fas ligand to Fas receptors on somatic cell surfaces. Alternatively, cytotoxic T cells may elaborate cytokines including TNFα and IFN-γ, which interrupt replication of a virus within the infected somatic cell and may eliminate the infection without damage to the cell.

In the situation shown in Fig. 2B, a naïve (not primed) cytotoxic T cell has engaged an abnormal somatic cell. Somatic cells do not produce costimulatory molecules. Here, the lack of costimulation renders the T cell anergic and incapable of further immunologic activity. This may be a mechanism for induction of peripheral tolerance by which T cells that have escaped detection during passage through the thymus are eliminated. Peripheral tolerance may also be brought about by overload in presentation by abnormal cells that causes a clonal exhaustion or deletion of the corresponding T lymphocytes.

In the situation shown in Fig. 2C, a (primed) B cell has endocytosed an antigen that was attached to a surface antibody-like receptor. Much like APCs, the B cell processes the antigen and presents an epitope on its cell surface bound to an MHC molecule. The epitope is recognized by an activated complementary T helper 2 cell together with a costimulatory molecule. This brings about close contact between the B cell and the helper cell from which it receives cytokines that facilitate its differentiation and multiplication into antibody-producing plasma cells. Plasma cells produce and shed their specific surface receptors as antibodies having the structure shown in Fig. 2D. This binding process is not required by the cytotoxic T cell to receive cytokine

Table 4. Precarious processing of antigenic peptides for presentation via APCs

Cytosolic class I (endogenous) pathway	Endocytic class II (exogenous) pathway
Bind and activate complementary cytotoxic T cells	Bind and activate complementary T helper cells
↑	↑
Presentation on cell surface together with costimulatory molecule(s)	Presentation on cell surface together with costimulatory molecules
↑	↑
Entry into intermediate compartment and Golgi-secretory system	Entry into intermediate compartment and Golgi-secretory system
↑	↑
Association of fragments with allelic polymorphic MHC I proteins	Association of fragments with allelic (polymorphic) MHC II proteins
↑	↑
Entry into endoplasmic reticulum	Fragment, entry into endoplasmic reticulum
↑	↑
Fragment attaches to transporter, TAP, protein	
↑	
Protease fragmentation in proteasome	Fragmentation in endosome
↑	↑
Endogenous proteins	Exdogenous (endocytosed) proteins

signals. Stimulation appears to be provided by its proximity to T helper 1 cells in the spleen–lymph node location.

Finally and importantly, it is emphasized that the dendritic cell is common to both the innate and adaptive immune systems and, hence, it serves as the central bridge between innate and adaptive immune responses. In effect, dendritic cells carry out both primitive and highly complex activities of the innate and adaptive immune systems.

Immune Evasion in Persistent Infection (General Reviews, Refs. 9–17; Other Reports, Refs. 18–30)

As discussed above, the battle between the host and an invading virus is one in which the host intent is to destroy the pathogen. The pathogen, which chooses to achieve persistent infection in the host, seeks to do so by evading host immune responses. It is not a viable strategy for the pathogen to destroy the host on which it depends for its existence and its ability to create a new virus that infects additional hosts in perpetuity.

It is of seminal importance that coevolution of the viruses and their hosts has taken place over millions of years. During this time, the host has evolved a highly specific immune system in which its myriad engagements can destroy the virus or limit its pathologic changes to a manageable level. During the same time period, the virus has evolved the means to exist with the hostile host by encoding and expressing a large arsenal of different proteins, which may restrict, modify, redirect, or ablate expression and function of cells of the host immune system. Gene sequences for these proteins may have been coopted from the host and expressed as native or homologs of host proteins. The viral proteins may act as ligands or receptors that are agonistic or antagonistic to host cell activities, bringing about changes at almost any level of immune function to the benefit of the invader. RNA viruses are aided in this endeavor by the infidelity of their polymerase genes, introducing many mutations in the course of replication. The virus, however, is restricted in the number and kinds of genes for evasion that it can include in its small genome. The existence of many different genetic quasispecies in a single host at any particular time attests to the variability of RNA viruses. DNA viruses, which usually have larger genomes, are able to encode more proteins, and there is greater fidelity in genomic replication than with most RNA viruses. Replication is a dangerous time for viruses because of their encoding of antigenic proteins, which may make them vulnerable to detection and control by host immune mechanisms.

There are many ways in which to separate and classify the means that viruses use to evade the immune system. For this discussion, the six categories that follow will be used.

Sequestration. Some viruses, as part of their strategies for survival, may infect nonpermissive or semipermissive host cells to store their genetic information without cytolytic consequences. These viruses may be retained in a latent state with little or no transcription until some event occurs to convert the latent nonpermissive state to permissive capability from which infectious virus can be replicated and released. DNA viruses, such as herpes simplex and varicella, and RNA viruses, such as HIV, may have this attribute for certain kinds of host cells. Similarly, virus may be stored in immunologically privileged sites such as the brain, which is protected by the blood–brain barrier and from which peripheral effectors may be excluded. Additionally, neural calls do not encode MHC-presenting molecules. Lack of capacity to detect and remove virus safely from sequestered cells may thwart the efforts of the host to achieve final viral sterilization.

Blockade of Antigen Presentation by APCs. Central to adaptive immune functions that detect and eliminate infected host cells is the process for antigen presentation by which antigenic proteins of endogenous or exogenous origin are processed and presented to bring about recognition and priming of cytotoxic T cells and T helper cells as described above.

Table 4 shows the steps in antigen processing and presentation of antigen by APCs to activate effector immune cells. Collectively, virus-encoded proteins of diverse variety may interfere with any, and probably all, steps in the pathway. For example, proteasomal fragmentation can be prevented and transport to the endoplasmic reticulum can be averted. Association of the fragments with MHC molecules can be prevented by blocking the synthesis of MHC molecules or by redirecting them to cytosolic proteolysis. Entry of the MHC–peptide complex into the intermediate compartment and the Golgi secretory systems may be averted. Presentation on the cell surface of the MHC complexes with peptides can be aborted by redirection of MHC to the cytosol for destruction. Costimulatory molecules may be excluded from APC presentation, and the CD8 or CD4 molecule may be destroyed.

Cytokine Evasion. The cytokines of the immune system (Table 5) consist of secreted polypeptides that initiate, coordinate, and control the processes for immune cell activation, proliferation, chemotaxis, and inflammation. The hit and stay viruses encountered in persistent infections interrupt the synthesis of normal cellular cytokines and chemokines and their receptors and inhibit their functions. They encode mimics or homologs of normal cytokines (virokines) and their receptors, which bind to or replace the normal cell counterparts rendering them inactive

Table 5. Examples of interruption of cytokines by virus-encoded proteins

Interrupt cytokine production
Interfere with cytokine and chemokine synthesis
Halt maturation of cytokines
Interfere with cytokine signaling
Encode homologs of cellular cytokine and chemokine receptors
Viral encoded receptors give false signals, and interfere with chemokine trafficking
Viral molecules neutralize cytokines and inactivate cell receptors
Interfere with cytokine effector function
Inhibit or alter cytokine transduction pathways
Degrade messenger RNA, inhibit protein synthesis

Tolarella *et al.* (11) was the source for this information.

or dysfunctional. They interfere with normal cytokine signaling and leukocyte trafficking, and they may initiate spurious and inappropriate signals of their own that up- or down-regulate formation of cell receptors and coreceptors. They may inhibit cell cycle kinases and interfere with signal transduction pathways. They may inactivate viral RNAs and degrade messenger RNA, inhibiting protein synthesis.

Targets for viral subversion of cell cytokines and their receptors may include, among others, those of IFN-α, -β, and -γ; chemokines That bind to CC or CXC receptors; IL-1, -2, -4, -5, -6, -8, -10, -12, -16, and -18; colony stimulatory factors; TNF; and lymphotoxin. Thus, the collective means for viral evasion are overwhelmingly numerous and diverse, providing no simple or common approach to intervention.

Evasion of NK Cell Immunity. NK lymphocytes belong to the innate immune system, but they do not encode the conventional T cell receptors. Instead, they express receptors that recognize the Fc ligands of antibody molecules on antibody-coated virus-infected cells. They also express receptors that recognize the abnormal absence, by down-regulation, of MHC proteins on the surface of virus-infected cells. In both situations, the abnormal cells are destroyed by granular exocytosis with apoptosis initiated by NK cells. The process for recognizing and destroying antibody-coated cells by NK lymphocytes is called antibody-dependent cellular cytotoxicity.

At least one mechanism for viral evasion of NK immunity has been identified in infection with cytomegalovirus, which encodes a decoy analog of the MHC molecule that is called UL18 (30). Interaction of UL18 with the CD94 receptor on the NK cell vetoes the killing process through spurious recognition of a phony molecule as real. NK cells are a potent source of IFN-γ in early infection after activation by IL12 from phagocytic cells. IFNγ is very important in conditioning the subsequent adaptive immune response.

Inhibition of Apoptosis by Viral Proteins. Apoptosis, or programmed cell death, is a normal mechanism for silent noninflammatory imposition of cell death. It is engaged in the immune response to rid the host of virus-infected cells (Fig. 3). The central mechanism is that virus-infected cells alert and activate cytotoxic T cells and NK cells to deliver granzyme granules on contact with infected cells, or to deliver TNF and Fas ligands. Combinations of the latter with their receptors form death domains. The two paths engage proteolytic caspases, starting with caspase 9 or 8 individually, and then follow the common caspase cascade to apoptotic cell death. Bcl is a cell protein that inhibits apoptosis. Virus proteins may up-regulate Bcl production or may block its natural destruction. P53 is a proapoptotic antioncogene that can be blocked by viral proteins.

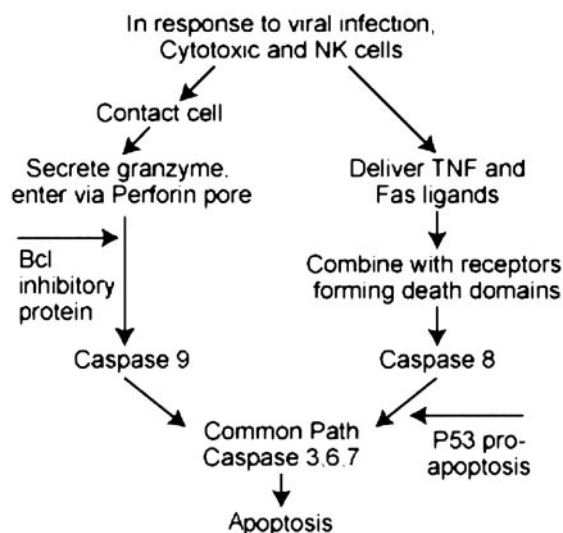Viruses of known wide variety encode inhibitory substances

Fig. 3. Blockade of apoptosis by altering cellular events.

that collectively are designed to block apoptosis at essentially every step in the ''save my cell'' antiapoptotic processes. It is of value to the virus to delay cell death until the viral progeny have been formed and are infectious. Blocking the apoptotic system must have been a positive strategy for virus survival, or else it would neither have been evolved nor retained.

Evasion of Antibody and Complement in Viral Infections. Although cell-mediated immune responses may be central to clearance of viral infections, antibody and complement are highly effective in reducing viral load and in preventing reinfection following previous experience. In their antiviral activities, antibodies bind to viruses, preventing their access to cell receptors and prohibiting entry into host cells, as stated above. Phagocytic cells remove antibody-bound virus from the circulation through recognition and engulfment via their Fc receptors, which they process for antigen presentation. NK lymphocytes kill host cells to which antibodies are bound. The complement system inactivates viruses that are bound to antibodies and kills infected cells that express complement receptors. As may be expected, viruses are able to subvert and evade antibody and complement activities through highly diverse and complex mechanisms too complicated to recount here. They are, however, reviewed in detail by Tortorella *et al.* (11). A second means for humoral evasion is by mutation and alteration of viral antigenic specificity during persistence. The best example is found with the lentiviruses, especially in HIV (see below), which shows hypervariability of its surface binding proteins and of certain of its core housekeeping activities that are not critical to viral replication and preservation of the species. Such antigenic variation allows for changes that evade host immune responses in its spread to newly minted susceptible cells. Viral quasispecies may coexist with parental wild-type virus. Hepatitis B virus (31) surface antigen is highly conserved, but may alter the specificity of its essential core antigens (e antigen/nucleocapsid) and escape from specific immune recognition by cell-mediated effectors.

Alternative Solutions to Viral Persistence

Prophylactic Vaccines. My published reviews on vaccines (31–39) reveal low-level probability and high-level uncertainty for development of therapeutic vaccines against persistent viral infections within the foreseeable future. Linkage of viral antigens with heat shock proteins induce humoral and cell-mediated immune responses in experimental studies (40), but are still

Table 6. Alternative solutions to acute and persistent viral infections

Vaccines				
Hit and run viruses		Hit and stay viruses		
Existing	Future	Existing	Future	Alternatives
Poliovirus	Respiratory syncytial virus	Hepatitis B	Cytomegalovirus	Chemotherapeutics
Measles	Parainfluenza	Varicella	Herpes simplex	Chemotherapy/vaccine
Mumps	Dengue	Adenovirus	Epstein–Barr virus	Gene silencing
Rubella	West Nile		Papillomavirus	
Influenza	Severe acute respiratory syndrome		Hepatitis C?	
Hepatitis A	Bioweapons		HIV?	
Yellow Fever				
Japanese encephalitis				
Rabies				
Rotavirus				
Smallpox				
Tick B encephalitis				

futuristic with respect to therapeusis. For these reasons, alternative solutions need to be sought. By far the simplest and most certain solution to persistent infection (Table 6) with viruses of the hit and stay variety lies with the development and use of prophylactic vaccines. Among the 15 approved vaccines of substantive current application, only three are against hit and stay viruses and 12 are against hit and run agents that have little or no importance in preventing persistent infections. Many new and improved preventive vaccines against hit and run agents will be developed in the near future because of feasibility, importance, and the need to protect against emerging infections and bioweapons (38). All three of the successful hit and stay vaccines are against DNA viruses. Four additional agents in this category are feasible (cytomegalovirus, Herpes simplex virus, Epstein–Barr virus, and papillomavirus) and are likely to be developed. The two persistent RNA viruses, HIV (41–43) and hepatitis C, present limited probability for development of prophylactic vaccines in the next decade, with even less likelihood for those that would be immunotherapeutic.

Chemotherapy. The alternative to vaccines against persistent viruses may lie in the area of antiviral chemotherapy, which has been aided by increasing knowledge that defines and separates specific host and from viral metabolism. Useful chemotherapeutic drugs against hepatitis B (31) and HIV (41–43) provide a hope that viral load may be brought to such low level as to permit restoration of immune function and capability for specific immune responses by prophylactic or therapeutic vaccines.

Gene Silencing. Perhaps the most exciting approach to removal or silencing of viral nucleic acid in infected host cells lies with the development of double-stranded short interfering RNA (siRNA) (refs. 44–46, see also ref. 31). A single strand of the siRNA, which is complexed with RNA (RISC), cuts viral messenger RNA at a position of complementary sequence specificity. Delivery of siRNA by viral vectors (46) provides a potential infective mechanism for easier and more specific target cell delivery.

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