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Review
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Anti-Immunology: Evasion of the Host Immune System by Bacterial and Viral Pathogens

B. Brett Finlay[1,*] and Grant McFadden[2,*]
[1] Michael Smith Laboratories, University of British Columbia, Vancouver, B.C. V6T 1Z4 Canada
[2] Robarts Research Institute and University of Western Ontario, London, Ontario, N6G 2V4 Canada
*Contact: bfinlay@interchange.ubc.ca (B.B.F.); mcfadden@robarts.ca (G.M.)
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Multicellular organisms possess very sophisticated defense mechanisms that are designed to effectively counter the continual microbial insult of the environment within the vertebrate host. However, successful microbial pathogens have in turn evolved complex and efficient methods to overcome innate and adaptive immune mechanisms, which can result in disease or chronic infections. Although the various virulence strategies used by viral and bacterial pathogens are numerous, there are several general mechanisms that are used to subvert and exploit immune systems that are shared between these diverse microbial pathogens. The success of each pathogen is directly dependant on its ability to mount an effective anti-immune response within the infected host, which can ultimately result in acute disease, chronic infection, or pathogen clearance. In this review, we highlight and compare some of the many molecular mechanisms that bacterial and viral pathogens use to evade host immune defenses.

Introduction

The three biggest global infectious disease threats to humans are HIV, tuberculosis, and malaria, each killing one to two million people worldwide each year (Morens et al., 2004; Fauci, 2005). Each of these three causative agents (which represent a virus, a bacterium, and a parasite) have developed highly effective mechanisms to subvert the human immune system, which explains why developing vaccines and controlling these pathogens have been so difficult. Successful pathogens have evolved a range of anti-immune strategies to overcome both innate and acquired immunity (Table 1), which play critical roles in their abilities to cause disease. In this short review, we can highlight only a few of the myriad of molecular mechanisms that bacterial and viral pathogens use to effectively overcome host immune defenses. Although at first glance the immunomodulatory mechanisms used by viruses and bacteria might appear quite different, there are a surprising number of similarities and shared mechanistic concepts. Both types of pathogens have to overcome the same host immune mechanisms, and it is illustrative to see how they have developed parallel strategies to neutralize host immunity. Moreover, viral and bacterial diseases are often linked, exploiting weaknesses in host defenses that are caused by another pathogen. For example, influenza infections predispose humans for subsequent pneumococcal pneumonia, and HIV infections are often associated with an increased incidence of tuberculosis and salmonellosis.

The field of microbial "anti-immunology" is rapidly expanding. To comprehensively review the entire field of viral and bacterial mechanisms would require a very large review, and the reader is referred to other more comprehensive and specific reviews (Hornef et al., 2002; Rosenberger and Finlay, 2003; Bieniasz, 2004; Coombes et al., 2004; Hilleman, 2004).

Instead, we have chosen to highlight some key concepts that viral and bacterial pathogens use to ensure their success. These concepts are then followed by a small number of illustrative examples. We have also chosen to focus more on pathogens that cause human disease or mimic these diseases in animal models.

Surface Expression and Secretion of Immune Modulators

The external surface of viral and bacterial pathogens is the central interface between host and pathogen, and recognition of the exposed surface by immune systems provides the host a key signature to initiate microbial clearance. It also affords the pathogen significant opportunity to present mimics of host immune modulators, to alter host immune responses (or avoid them), to express adhesins or receptor ligands to anchor the pathogen to host surfaces, and to present invasins or fusion proteins to mediate uptake into host cells. Other surface molecules, such as protective capsules or even captured host proteins, can enhance survival within the host.

Table 1. Anti-Immune Strategies of Viruses and Bacteria

Strategy	Viral Examples	Bacterial Examples
(1) Secreted modulators or toxins	- ligand mimics (virokines) - receptor mimics (viroceptors)	- many toxins - proteases
(2) Modulators on the pathogen surface	- complement inhibitors - coagulation regulators - immune receptors - adhesion molecules	- Lipid A of LPS - carbohydrates such as capsules - outer membrane proteins - adhesins and invasins
(3) Hide from immune surveillance	- latency - infect immunopriviledged tissues	- avoid phagolysosomal fusion - inhibit phagocytosis
(4) Antigenic hypervariability	- express error-prone replicase - escape from antibody recognition - "outrun" T cell recognition	- vary many surface structures - pili, outer membrane proteins, LPS - strain to strain variation
(5) Subvert or kill immune cells/phagocytes	- infect and kill immune cells (DCs, APCs, lymphocytes, macrophage, etc.) - inhibit CTL/NK cell killing pathways - alter immune cell signaling, effector functions, or differentiation - express superantigens	- superantigens - avoid phagolysosomal fusion - block inflammatory pathways by injecting effectors - replicate within and overrun immune cells
(6) Block acquired immunity	- downregulate MHC-I or –II - block antigen presentation/proteosome - prevent induction of immune response genes	- IgA proteases - block antigen presentation
(7) Inhibit complement	- soluble inhibitors of complement cascade - viral Fc receptors	- proteases to degrade complement - produce capsules and long chain LPS to avoid complement deposition and MAC attack
(8) Inhibit cytokines/ interferon/chemokines	- inhibit ligand gene expression - ligand/receptor signaling inhibitors - block secondary antiviral gene induction - interfere with effector proteins	- block inflammatory pathways - activate alternate pathways - secrete proteases to degrade
(9) Modulate apoptosis/autophagy	- inhibit or accelerate cell death - block death signaling pathways - scavenge free radicals - downregulate death receptors or ligands - inactivate death sensor pathways	- inhibit apoptosis - activate death signaling pathways - alter apoptotic sigaling pathways
(10) Interfere with TLRs	- block or hijack TLR signaling - prevent TLR recognition	- alter TLR ligands to decrease recognition - bind to TLR to dampen inflammation - inject effectors to inhibit downstream inflammation signaling
(11) Block antimicrobial small molecules	- prevent iNOS induction - inhibit antiviral RNA silencing	- secrete proteases to degrade - alter cell surface to avoid peptide insertion - use pumps to transport peptide - directly sense small molecules to trigger defense mechanisms
(12) Block intrinsic cellular pathways	- inhibit RNA editing - regulate ubiquitin/ISGylation pathways	- alter ubiquitin pathway - alter transcriptional programs

Modulators on Virion Surfaces

One of the first ways that an infecting virus can impinge on the immune system prior to infecting susceptible cells is via molecules that decorate the virion external surface. Virus particle surfaces not only can be studded with potentially immunomodulatory viral proteins but, particularly in the case of enveloped viruses, can also display a wide diversity of host-derived proteins (Cantin et al., 2005). These virion-embedded host proteins can be immunoregulators, CD-family receptors, complement inhibitors, signaling ligands, or adhesion molecules, any of which can transform the extracellular virus particle into a "macro-ligand" that

can stimulate immunomodulatory responses even in nonpermissive host cells. The most extensively studied immune modulators located on virions are virus encoded, and one of the best studied examples of this is the gp120 env glycoprotein of HIV, which in addition to mediating virus binding and entry is a potent signaling ligand in its own right (Ahr et al., 2004; Badr et al., 2005; Perfetti et al., 2005). Env is the only viral protein that protrudes through the HIV virion membrane, forming the characteristic virion spikes, and it is thought to play a significant role in the bystander killing of uninfected T lymphocytes during late-stage AIDS progression (Gougeon, 2005; Petrovas et al., 2005). Although much is now known about the role of the major conformational shift that gp120 undergoes when it binds to the cellular receptors (Chen et al., 2005), less is known about how the virion bound gp120 mediates its effects as a signaling ligand. There are some clues, however, that gp120 bioactivity can be affected by host proteins on the virion because virus particles with higher levels of captured MHC-II and B7-2 are more efficient at killing uninfected $CD4^+$ T cells (Holm and Gabuzda, 2005). Consequently, the immunomodulatory properties of virion particles from other virus families may also depend on the precise synergism between host and viral proteins.

Modulators on Bacterial Surfaces

Bacterial surfaces are complex structures which, from the host's viewpoint, present many diverse antigenic targets. A major difficulty for bacterial pathogens is hiding this complex surface of proteins and carbohydrates from immune surveillance and TLR recognition yet exposing key molecules such as adhesins and invasins. A common mechanism of masking bacterial surfaces is to express a carbohydrate capsule. This mechanism is used by most extracellular bacterial pathogens that circulate systemically within the body. For example, the pneumococcus (*Streptococcus pneumoniae*) relies extensively on its capsule to prevent antibody and complement deposition on its surface, thereby avoiding opsonization and phagocytic clearance. Similarly, bacteria that cause meningitis (*Haemophilus influenzae*, *Escherchia coli* K1, and *Neisseria meningitidis*) rely extensively on capsules to promote their extracellular lifestyle within the host by preventing antibody and complement deposition and insertion. Pathogens expressing surface capsules also often have filamentous adhesins (fimbriae and pili) that protrude through the capsular surface, enabling the adhesins to bind to host receptors yet keeping the bacterial surface hidden.

Lipopolysaccharide (LPS) is a major surface-exposed component of the Gram negative bacteria. LPS is a key molecule from both the pathogens' and hosts' points of view. The essential core component of LPS, lipid A, is highly conserved among most Gram negative organisms and thus plays a central role in activation of TLRs such as TLR4. However, the outer part of LPS is made of highly variable carbohydrates, giving each strain their particular serotype (O antigen). Thus different strains of the same species can often reinfect the same host due solely to differences in O antigen. LPS is surface exposed, and a target of complement, but since it protrudes from the surface, membrane insertion by the membrane attack complex does not occur in the cellular membrane.

Bacterial pathogens, especially Gram negatives, have developed secretion systems to export virulence factors across the bacterial membranes and either into the supernatant or even directly into host cells. In Gram negative organisms, these are named according to the type, and there are at least seven secretion systems in addition to the general secretion system. Secretion of virulence factors such as toxins and immune modulators is a major use of these secretion systems, as well as conjugal DNA transfer. In Gram negative pathogens, both type III secretion systems (T3SS) and type IV secretion systems (T4SS) can insert various molecules directly into host cells (Christie et al., 2005; Mota and Cornelis, 2005). These two types of systems are not genetically related, although they both have a very diverse repertoire of secreted molecules (called effectors) that can be delivered into host cells. These include toxins (to kill host cells), molecules that mediate bacterial uptake (invasion), effectors that reprogram vesicular transport to enhance intracellular parasitism, mechanisms to paralyze phagocytosis, molecules that form receptors for bacteria to adhere to, and many diverse effectors that alter immune functions to enhance immune evasion.

Although Gram positive surfaces are more simple (one membrane surrounded by peptidoglycan), there are suggestions that even Gram positive organisms can form localized pores in host cells to deliver bacterial molecules into host cells. For example, *Streptococcus pyogenes* has a cholesterol-dependent cytolysin (making it host specific) that is needed to deliver a NAD-glycohydrolase into host cells to trigger cytotoxicity (Madden et al., 2001). Similarly, *Mycobacterium tuberculosis* has a specialized secretion system that is needed to deliver major T cell antigens (ESAT-6 and CFP-10) and presumably other proteins that are needed for bacterial replication inside macrophages and virulence (Stanley et al., 2003). The ability to drive bacterial molecules directly into host cells is a major strategy used by diverse bacterial pathogens to subvert and overcome host defenses.

Avoiding Immune Surveillance

The ability to avoid detection by either the innate or acquired immune system is a central feature for both viral and bacterial pathogens. One strategy is to camouflage the surface of the microbe or the infected cell such that it is not recognized by host surveillance systems, while another is to dampen immune responses such that a complete immune response is avoided.

Viral Modulators that Are Secreted or at the Infected Cell Surface

Unlike bacteria, which have their own secretory and protein trafficking pathways, viruses must rely on the infected host cell to provide the machinery for protein transport to

the cell surface, and for secretion of virus-encoded immunomodulators into the extracellular environment. In general, viral proteins that interact directly with the immune system tend to be expressed at the infected cell membrane, the virion surface, or are secreted into the extracellular environment where they can act either locally or systemically. In the case of viral immunomodulators that are secreted and released from the infected cell, the literature is vast and includes host targets that range from cytokines, chemokines, interferons, complement, leukocytes, inflammatory cascades, and immune recognition pathways. For details, the reader is referred to some of the many specialty reviews for specific examples (Alcami, 2003; Seet et al., 2003; Nicholas, 2005). One recent development of this field is that some of these secreted viral immunomodulatory proteins, which tend to exhibit potent anti-inflammatory or anti-immune properties, have been used as biopharmaceuticals to treat diseases of exacerbated inflammation or hyperacute inflammation (Lucas and McFadden, 2004).

The spectrum of viral proteins that traffic to the cell surface of the infected cell, and exhibit immunomodulatory properties, is remarkably diverse and includes superantigens, immune cell ligands, receptor mimics, CD-homologs, complement inhibitors, binding proteins that sequester cytokines, and regulators of leukocyte activation. Among the various classes of leukocytes that can be regulated by viral proteins, particular attention has been paid recently to NK cells, T cells, dendritic cells, and macrophage (Ambagala et al., 2005; Andrews et al., 2005; Lodoen and Lanier, 2005; Pollara et al., 2005). Some of these viral cell-surface proteins mimic the structure or function of host receptors but alter their biologic properties to better suit the virus agenda. For example, herpesviruses and poxviruses are known to collectively encode over 40 viral members of the seven transmembrane-spanning G protein-coupled chemokine receptor (vGPCR) superfamily (Sodhi et al., 2004; Couty and Gershengorn, 2005; Nicholas, 2005; Rosenkilde, 2005). Dissecting how these viral vGPCRs contribute to the biology of the viruses that express them has only begun, but some exhibit properties, such as ligand-independent signaling, that allow the constitutive activation of intracellular pathways that are normally only inducible for uninfected cells. The spectrum of immunomodulatory viral membrane proteins is simply too broad to be covered here, but it is worth noting that many of these proteins are not just transiently en route to being incorporated into virions that bud from the surface but rather function as true anti-immune receptors at the infected cell surface.

Bacterial Surface Modulators

Camouflaging a complex bacterial surface is a major problem. Capsules are effective at hiding many bacterial surfaces and preventing opsonization. However, there are predominant molecules on bacterial surfaces that the host's immune system uses as key signatures. These are often TLR agonists such as lipid A of LPS, flagella, and peptidogycan. Bacterial pathogens have evolved ways of altering these molecules such that they are less well recognized by immune surveillance systems. Many Gram negative pathogens modify lipid A to alter TLR4 responses (Portnoy, 2005). For example, *Salmonella* has a two-component sensor (PhoP/PhoQ) that senses host environments, regulating many virulence genes. Some of these genes are enzymes involved in lipid A modification, including a 3-O-deacylase (PagL) and a lipid A palmitoyltransferase (PagP) (Kawasaki et al., 2004). These modified forms of lipid A are up to 100-fold less active for TLR4 activation and NFκB production. Although lipid A is fairly well conserved, some organisms produce lipid A structures that are not efficient TLR2 and 4 activators. For example, *Porphyromonas gingivalis*, a major dental pathogen, contains multiple lipid A species which function as both agonists and antagonists of TLR2 and 4 (Darveau et al., 2004), selectively moderating the inflammatory response.

Another major signature of bacterial pathogens is peptidoglycan. Nod1 and Nod2 are leucine rich repeat (LRR) intracellular proteins that function analogously to TLRs to detect peptidoglycan inside host cells (Philpott and Girardin, 2004; Inohara et al., 2005). Human Nod1 detects N-acetylglucosamine-N-acetylmuramic acid, a tripeptide motif characteristic of Gram negative organisms (Girardin et al., 2003a), while Nod2 detects a N-acetylglucosamine-N-acetylmuramic acid dipeptide (Girardin et al., 2003b). Activation of either Nod leads to NFκB activation and inflammatory responses. Bacterial pathogens have developed ways to avoid peptidoglycan processing and recognition by Nods (Boneca, 2005). Genes involved in peptidoglycan synthesis, turnover, and recycling have been identified as virulence factors. For example, *Listeria monocytogenes* resides in the cytosol of macrophages and other host cells. Surface-located and -secreted peptidoglycan hydrolases have been identified that are also virulence factors (Lenz et al., 2003; Cabanes et al., 2004). This work suggests that cleavage of peptidoglycan promotes a virulence mechanism involving exploitation of Nod2 and the innate inflammatory response to promote *Listeria* pathogenesis (Lenz et al., 2003).

Antigenic Variation in Bacteria

Another classic mechanism viral, bacterial, and parasitic pathogens use to avoid immune responses is to vary immunodominant molecules (known as antigenic variation). Acquired immunity relies on memory of previous exposure to antigens, and thus antigenic variation is especially appropriate for circumventing humoral and cellular responses. There are few, if any, examples of antigenic variation being used to escape innate immunity. Although strain to strain variation in antigenic molecules is common, antigenic variation refers to a single strain specifically changing a subset of its antigens, either to sustain an ongoing infection or reinfect hosts even though the first infection was successfully cleared.

The molecular mechanisms used by bacterial pathogens to cause antigenic variation are diverse but very well studied (Finlay and Falkow, 1997). These mechanisms usually involve one of three mechanisms: (1) having

multiple but different copies of a molecule, each of which is under an independent on/off switch; (2) having one expression locus plus many silent copies of the gene, and constantly changing which gene is expressed; or (3) having a highly variable region in a molecule that is constantly changing. *Neisseria* species (which cause meningitis and gonorrhea) are perhaps the best bacterial models of antigenic variation, using all three of these concepts and emphasizing why a vaccine to these organisms has not been successful. The gonococcus contains 10–11 outer membrane Opa proteins, each of which is antigenically different. Each gene is under a genetic switch that independently controls expression of each Opa. During infection, multiple Opas are expressed in various combinations. The *Neisseria* pilus is expressed at the *pilE* locus. However, these organisms have many silent copies of partial pilin genes stored in "silent" (*pilS*) loci. By genetically recombining various *pil* alleles into the expression locus, a constantly shifting pilus is made. Because these organisms are naturally competent, they acquire additional pilin gene sequences and incorporate them into *pilS* loci. *N. menigitidis* also varies its lipooligosaccharide (LOS, similar to LPS) structure in a phase variation mechanism. It can express up to 13 different immunotypes by switching various terminal sugar structures. This is achieved by varying expression of various carbohydrate biosynthesis genes. For example, glycosultransferase activity is regulated by slipped strand mispairing, resulting in incorporation of different sugars in LOS (Kahler and Stephens, 1998). There are several other examples of antigenic variation of surface molecules with *Neisseria* species, enabling it to survive and replicate within normally sterile sites within the host such as the CNS.

Antigenic Variation in Viruses

Antigenic hypervariation has been more effectively adopted by RNA viruses than DNA viruses, most likely because of the higher mutational frequency of RNA replicases compared to most viral DNA polymerases (Elena and Sanjuan, 2005). In some cases, such as Hepatitis C and HIV, the antigenic drift rate is so rapid that it effectively outpaces not only development of an effective immune response in the individual infected host but also confounds our attempts to develop prophylactic vaccines (Bowen and Walker, 2005; Derdeyn and Silvestri, 2005; Letvin, 2005; Wieland and Chisari, 2005). In general, viral RNA replicases lack proofreading capacity and generate swarms of genetic variants of progeny viruses that become subject to selection pressure for fitness, particularly in the form of immune bypass variants. However, even DNA viruses can undergo significant levels of mutational drift and thus become subject to immune selection. For example, single-stranded DNA viruses can exhibit mutational frequencies that rival the RNA viruses (Shackelton et al., 2005), and even double-stranded DNA viruses with high-fidelity polymerases like cytomegalovirus can still spin off a sufficiently diverse set of progeny to permit selective escape from host elements of innate immunity, such as NK cell clearance (French et al., 2004).

Subversion of Immune Response Pathways

A central component of the innate response is the deployment of specialized cells such as phagocytes to counter infectious agents that may have breached the initial physical barriers. Phagocytic cells have the ability to internalize microbes and kill them, as well as to recruit additional immune cells and amplify the innate response if needed. Successful pathogens have developed a variety of ways of counteracting phagocytic cells.

Bacterial Subversion of Phagocytes

Because of their size (1–3 microns), bacteria make particularly appropriate phagocytic targets. Several bacterial pathogens have developed ways of avoiding phagocytosis (Celli and Finlay, 2002). For example, *Yersinia* species, including the causative agent of plague (*Y. pestis*), use their type III secretion system to inject several T3SS effectors that effectively neutralize phagocytic activity (Mota and Cornelis, 2005; Viboud and Bliska, 2005) Because actin is central to phagocytosis, many of these effectors target this part of the cytoskeleton. These include YopH, which is a tyrosine phosphatase that dephosphorylates key actin cytoskeletal proteins such as FAK, paxillin, and p130cas; YopE, which is a Rho GTPase-activating protein (GAP), thereby inactivating this key actin regulator; YopO, which is a serine/threonine kinase; and YopT, which is a cysteine protease that cleaves Rho GTPases. For organisms that use insect bites to introduce organisms directly in the blood (such as *Y. pestis*, transmitted by flea bites), the first host immune cells that would be encountered are patrolling phagocytes. The ability to avoid internalization and killing plays a central role in their virulence strategy.

For organisms that are internalized, they generally choose three strategies to avoid intracellular killing—escape from the phagosome (moderately common), blockage of phagosome-lysosome fusion (most common), or utilization of mechanisms to allow survival in phagolysosomes (rare) (Rosenberger and Finlay, 2003). Species of *Shigella* and *Listeria monocytogenes* and some *Rickettsia* species secrete lysins that are highly effective at lysing the vacuolar membrane that engulfs internalized organisms (Sansonetti, 2004). Lysteriolysin O is a key virulence factor for *L. monocytogenes*. Many intracellular pathogens reside within an intracellular vacuole that differs in composition from normally microbicidal phagolysosomes. However, the mechanisms by which these pathogens subvert and alter normal vesicle transport are not well understood. It is thought that intracellular bacterial pathogens secrete effectors via type III and type IV secretion systems into the host cytosol where they disrupt normal vesicular trafficking. *Legionella pnumophila* uses its type IV secretion system (Dot/ICM) to target the organism to a privileged intracellular niche. The effector, RalF, is a GTPase exchange factor (GEF) that targets ARF-1, a small GTPase that is then activated on *Legionella* phagosomes (Nagai et al., 2002). Similarly, *Salmonella* species use their Spi-2 type III secretion system to secrete effectors such as *SifA* into the host cytosol and membranes, which alter the composition of the *Salmonella*-containing vacuole

(Rosenberger and Finlay, 2003). *M. tuberculosis*, which is probably the most successful intracellular human pathogen, has many surface glycolipids and carbohydrates that prevent phagosome acidification and alter phagosomes (Russell, 2001).

The ability to alter inflammatory responses within phagocytic cells provides significant advantages to pathogens. Although blockage of inflammatory responses is the predominant (and most obvious) survival strategy, ironically some pathogens actually activate inflammatory pathways. Recruitment of inflammatory cells may provide replicative niches for pathogens that cause serious inflammatory diseases (Portnoy, 2005). For example, species of *Shigella* and *Salmonella* which cause severe intestinal inflammation use their T3SS to secrete effectors (IpaB and SipB, respectively) that bind to and activate caspase-1, which cleaves and activates IL-1β and IL-18, and the downstream proinflammatory pathway, which provides additional host cells to promote the infection (Navarre and Zychlinsky, 2000). This also activates rapid apoptosis of macrophages (see later), thereby neutralizing these key defense cells.

There are increasing numbers of examples of pathogens that produce and secrete molecules that dampen inflammation. A common target of many of these pathways is to target the MAP kinase and NFκB signaling pathways. For example, *Yersinia* species have a type III effector, YopJ(YopP), which is a ubiqutin-like cysteine protease that targets and downregulates both of these pathways (Navarro et al., 2005). YopJ binds multiple members of the MAPK kinase superfamily, including MKKs and IκB kinase β. Cleavage of ubiquitin and ubiqutin-like proteins from these substrates blocks their ability to activate these inflammatory pathways. Similarly, *Bacillus anthracis* lethal factor (a key component of anthrax toxin) cleaves MKKs that activate p38 MAPKs, also blocking activation of NFκB target genes (Park et al., 2002).

Viral Subversion of Phagocytes

Many viruses have evolved protective mechanisms to counter the antimicrobial functions of nitric oxide and reactive oxygen radicals generated by activated phagocytes, particularly macrophage. In some cases, virus infection induces the synthesis of inducible nitric oxide synthase (iNOS), which generates nitric oxide by the oxidation of L-arginine, whereas other viruses have evolved strategies to prevent iNOS induction. The iNOS gene is under the control of NFκB and STAT-1, which many viruses directly modulate as a component of their anti-interferon strategies (Bowie et al., 2004; Weber et al., 2004). Thus, viruses that block the induction of type I interferon also frequently repress iNOS gene expression, whereas viruses that induce iNOS generally exploit the immunoregulatory or proinflammatory properties of NO to augment their pathogenesis or dissemination strategies. In some cases, viruses have been shown to express modulatory proteins that directly affect phagocyte activation. For example, herpesviruses and poxviruses express surface proteins that mimic CD200 (Foster-Cuevas et al., 2004; Cameron et al., 2005), a host regulator of immune tolerance that delivers inhibitory signals to macrophage.

TLRs: Viral Subversion Strategies

The discovery that TLRs recognize pathogen-associated molecular patterns (PAMPs) has stimulated a barrage of research into the various ways that microbes can be recognized by TLR-expressing sentinel cells, particularly macrophage and dendritic cells. At present, 10 TLRs are expressed in man and 12 in the mouse, and many have been assigned viral PAMPs that can be recognized as ligands (Bowie and Haga, 2005; Kawai and Akira, 2005). Cell-surface TLRs like TLR2 and 4 are thought to recognize virion components, while intracellular TLRs like TLR3, 7, 8, and 9 are thought to detect viral nucleic acids or nucleoprotein complexes. There is growing evidence that TLRs transduce the earliest signals of the innate immune responses to microbial infections and that anti-TLR strategies are likely common amongst all successful pathogens. For viruses, a major focus of current research has been to characterize the viral strategies to neutralize either recognition or the downstream TLR signaling pathways that alert cells to viral infection (Boehme and Compton, 2004; Finberg and Kurt-Jones, 2004; Netea et al., 2004; Bowie and Haga, 2005). Intriguingly, the precise roles that the various specific TLR family members play during viral pathogenesis in vivo has sometimes been difficult to pin down, for example by infecting knockout mice, likely because of overlapping TLR redundancies and complex cellular expression profiles. For example, TLR3-minus mice infected with a variety of RNA viruses undergo normal pathogenesis and immune responses (Edelmann et al., 2004; Schroder and Bowie, 2005), whereas TLR3 is critical for responses to at least one DNA virus, murine cytomegalovirus (Tabeta et al., 2004). In some cases, TLR3 can actually exacerbate viral pathogenesis (Wang et al., 2004). In all likelihood, TLRs crosscover for each other, and the role of specific TLRs may vary widely according to the specifics of such parameters as entry route, tissue tropism, and viral replication specifics for any given virus infection.

One area of particular interest relates to the signaling pathways that TLRs utilize to communicate PAMP engagement to the nucleus (Moynagh, 2005). In general, TLR engagement on immune effector cells, such as macrophage, NK cells, and neutrophils, induces proinflammatory pathways or cell activation, while dendritic cells and professional antigen-presenting cells upregulate IL-12, type I interferon, and costimulatory molecules such as CD80 and CD86 that kick-start the innate responses and harken the initiation of adaptive immune responses. The transcription factors activated by TLR signaling include NFκB and IRF3, both of which are key tranducers of the host antiviral responses (Kawai and Akira, 2005; Bowie and Haga, 2005). In some cases, the link between TLRs and the signaling molecules activated by viruses remains unclear. For example, several intracellular dsRNA sensors are now known, such as TLR3, PKR, and RIG-I. RIG-I in particular is believed to be an important cytoplasmic

sentinel for virus infection (Yoneyama et al., 2004) that signals via a mitochondrial checkpoint (Freundt and Lenardo, 2005; Seth et al., 2005; Xu et al., 2005), but the link between virus infection and TLR signaling is very cell specific and needs to be better defined in terms of the organism-wide responses (Kato et al., 2005). Our understanding of how viruses manipulate signaling by TLRs, or sensors like RIG-I, is also still in its infancy, and to date only a few examples of viral proteins that interrupt these pathways are documented for poxviruses (Harte et al., 2003; DiPerna et al., 2004; Stack et al., 2005) and Hepatitis A & C viruses (Breiman et al., 2005; Fensterl et al., 2005; Foy et al., 2005; Li et al., 2005a, 2005b; Sumpter et al., 2005), but likely many other examples remain to be uncovered.

The literature describing how viruses block interferon is now vast and is far beyond the scope of this commentary, but the reader is referred to a few of the many excellent reviews now available (Weber et al., 2004; Bonjardim, 2005; Hengel et al., 2005).

Bacterial Subversion of Innate Pathways

Evidence of bacterial pathogens that are capable of directly interfering with TLR signaling is limited. However, there are several examples of downstream modulation of TLR responses, altering many of the cytokines that are key to efficient innate responses (Underhill, 2004). *Yersinia* species secrete a virulence (V) antigen, LcrV. This molecule signals in a CD-14- and TLR2-dependent manner to, ironically, trigger IL-10 secretion and mediate immunosuppression (Sing et al., 2002). Emphasizing the contribution to virulence is the observation that TLR2-deficient mice are more resistant to infection with *Y. enterocolitica.* It has recently been shown that a particular residue in the N-terminal region of LcrV targets TLR2 and is required for altering IL-10 induction via TLR2 (Sing et al., 2005).

Small cationic peptides are a major component of the innate response in controlling diverse infections (Hancock, 2001). They have significant antimicrobial activity, which appears to be mediated by direct insertion of cationic and amphipathic peptides into negatively charged bacterial membranes, as well as many additional immunomodulatory activities central to innate responses (Hancock, 2001). Such peptides include defensins and cathelicidins. Resisting the antimicrobial activity of these peptides is critical to overcoming host innate defenses. Analogous to antibiotic resistance, pathogens will alter their surface structure to decrease insertion of peptide and resulting lysis, they can encode transport systems that remove the peptides, and they can secrete proteases that degrade these peptides. *Salmonella* species provide an excellent example of pathogens that utilize all three of these defense strategies. *Salmonella* species are intracellular pathogens, and macrophages and neutrophils produce several cationic antimicrobial peptides to control intracellular organisms. Intracellular *Salmonella* are capable of resisting these activities (Rosenberger et al., 2004). As discussed above, *Salmonella* modify lipid A by various mechanisms including deacylation, palmitylation, addition of aminoarabinose, and other modifications to its LPS. In addition to decreasing recognition by TLR2 and 4, this results in a net decrease in the membrane negative charge, which increases resistance to cationic peptide insertion (Ernst et al., 2001). *Salmonella* also express an outer membrane protease, PgtE, which promotes resistance to α-helical cationic antimicrobial peptides by cleaving these molecules. *Salmonella* also encode a locus (*sapA-F*) that mediates cationic peptide resistance. SapD and SapF exhibit homology to members of the ATP binding cassette (ABC) family of transporters and are thought to transport cationic peptides to the cytosol (Parra-Lopez et al., 1993). To fully coordinate these various resistance mechanisms, all of the above resistance mechanisms are all under the control of a global two-component regulator, PhoP/Q. It has recently been shown that PhoQ, the sensor domain, directly binds cationic peptides, which then activate the various transcriptional programs which mediate the variety of antimicrobial resistance mechanisms (Bader et al., 2005). Thus these pathogens actually sense innate immune molecules to promote their virulence in a highly programmed manner.

Another very efficient way of controlling intracellular pathogens by phagocytic cells is the production of reactive species such as oxygen species and nitiric oxide (NO). Inducible nitric oxide synthase (iNOS) plays a central role in inflammation and immune regulation, both in terms of producing NO for killing organisms and also using NO as a key signaling molecule. Pathogens have evolved several ways of avoiding NO-mediated killing (Chakravortty and Hensel, 2003). Intracellular *Salmonella*, which reside within a specialized membrane compartment called the *Salmonella*-containing vacuole (SCV) in macrophages, use a T3SS called *Salmonella* Pathogenicity Island 2 (Spi2) to mediate protection from reactive nitrogen intermediates. If the bacteria lack Spi2, iNOS efficiently colocalizes with the intracellular organisms in the SCV. The ability of Spi2 mutants to cause disease was partially restored in iNOS (−/−) mice. The ability to avoid colocalization with harmful host enzymes is a common theme for successful intracellular pathogens. Similarly, *Salmonella* Spi2 is also required to evade phagocyte NADPH oxidase-mediated killing (Vazquez-Torres et al., 2000). Intracellular organisms have also developed mechanisms to detoxify NO-mediated effects (Chakravortty and Hensel, 2003). These include the ability to repair damage caused by reactive nitrogen intermediates and methods to detoxify these molecules. Pathogens have evolved ways of not activating or inhibiting iNOS activity. For example, the murine intestinal mucosal pathogen *Citrobacter rodentium* causes a marked level in overall iNOS activity following infection. However, local iNOS activity in intestinal areas directly surrounding the adherent bacteria is very low, while in areas distant to the infection site iNOS activity is quite high (Vallance et al., 2002).

Complement Inhibition by Viruses

The complement system comprises several dozen proteins that circulate in serum, or are attached to cell surfaces, and which orchestrate three distinct cascades

(called the classic, alternative, and lectin pathways) into antimicrobial effector activities that range from the opsonization of foreign particles, the recruitment of phagocytes, to the lysis of infected cells. All three cascades converge by assembling a C3 convertase that can either initiate the opsonization of the foreign body or continue to activate C5 and thus propagate the cascade. Long considered to be a key arm of the innate immune system response to pathogens, there is growing evidence that the complement system also participates in the development of the acquired responses as well (Morgan et al., 2005). The complement cascade is under tight cellular control by host inhibitor proteins, and it is perhaps not surprising that viruses have either hijacked or co-opted some of these as an anticomplement defense system (Blom, 2004). Some viruses, for example human cytomegalovirus, induce the expression of cellular complement inhibitors like DAF and MCP at the surface of infected cells, whereas others like HIV, HTLV-I, and vaccinia incorporate host inhibitors into the virus envelop (Blom, 2004). Recently, this strategy has been exploited for the construction of lentivirus-based therapy vectors that can resist inactivation by human complement (Schauber-Plewa et al., 2005).

Viral proteins that block the complement cascade segregate into those that are virus specific and unrelated to any know host regulators (i.e., orphan inhibitors) and those that appear to be host derived (i.e., complement control protein mimics). As an example of the former, the glycoprotein C-1 of HSV is a virion component that participates in virus binding to heparan sulfate on the surface of target cells and that also binds and inhibits C3b (Spear, 2004; Chang et al., 2005). Among the host-related viral complement control proteins, some are expressed at the cell surface, like the GPI-anchored vCD59 homolog of HVS, which blocks the formation of the complement membrane attack complex, and kaposica, the complement control protein of KSHV which inhibits both the classical and the alternative complement cascades (Mark et al., 2004; Mullick et al., 2005b). Additionally, several herpesviruses and poxviruses express secreted complement control proteins, such as the vaccinia complement control protein that also blocks both the classical and alternative pathways (Jha and Kotwal, 2003; Mullick et al., 2005a). Interestingly, the loss of the complement control gene of the West African strain on monkeypox, compared to the closely related strain from central Africa, may have contributed to the low mortality observed during the 2003 monkeypox outbreak in the midwest of the USA (Chen et al., 2005; Likos et al., 2005).

Bacteria can also inhibit complement activation. For example, a recently identified staphylococcal complement inhibitor acts directly on C3 convertases (C4b2a and C3bBb), thereby decreasing phagocytosis and killing of *Staphylococcus aureus* by neutrophils (Rooijakkers et al., 2005).

Inhibition of Cytokines and Chemokines by Viruses

Although any cytokine that plays a role in orchestrating immune responses during a virus infection could technically be called "antiviral," several (especially the interferons, TNFs, IL-1, and the chemokine superfamily) deserve special status in that they have been repeatedly targeted for manipulation by many viruses. As with the previously described examples of the various anti-interferon viral strategies, the range of anti-cytokine proteins expressed by viruses is remarkably broad and includes intracellular modulators of gene expression, immune ligand mimics, viral growth factors, secreted and membrane bound cytokine inhibitors, receptor homologs, and immune pathway regulators that influence the stability, trafficking, or signaling of infected cell receptors.

The examples of viral "anti-cytokinology" are too numerous to document here, but some anti-immune lessons taught by viruses in the chemokine field are particularly instructive. In addition to the previously mentioned examples of virus-encoded homologs of chemokine receptors, the large DNA viruses can also express secreted chemokine mimics that trigger host chemokine receptors inappropriately or chemokine binding proteins that interact with host chemokines and inhibit the ability of host chemokines to attract and activate leukocytes to the sites of virus infection (Lau et al., 2004; Boomker et al., 2005). Interestingly, there are two distinct binding mechanisms by which viral chemokine binding proteins interact with target chemokines. The first group (called type-1) interact with low affinity to the conserved glycosaminoglycan binding domains of chemokines and thus interfere with the generation of ligand gradients needed for directed chemotaxis, while the second group (called type-2) bind with high affinity to the receptor binding domain of chemokines and thus occlude the chemokine/receptor interface (Webb and Alcami, 2005). The fact that both classes of viral chemokine binding proteins can be effective at short circuiting diverse models of inflammation in vivo (Lucas and McFadden, 2004) re-enforces the growing appreciation that viruses are indeed well-versed in anti-chemokinology. In fact, in addition to the classic strategy of interrupting chemokine/receptor interactions, there is a recent upsurge in efforts to modulate chemokines by blocking their interactions with glycosaminoglycans for therapeutic purposes to treat diseases of inflammation (Rot and von Andrian, 2004; Handel et al., 2005; Johnson et al., 2005).

Inhibition of Cytokines by Bacteria

There are many reported examples of bacterial pathogens altering downstream inflammatory cytokines, although in most cases the molecular mechanisms by which this is achieved have not been elucidated (Tato and Hunter, 2002). Because of the complexity of bacteria and the diverse array of effectors and other immune modulators produced by these organisms, it has been difficult to identify which components are responsible for triggering cytokines versus those which selectively inhibit cytokine production. However, there are now examples of pathogens specifically targeting cytokine pathways to enhance pathogenesis. For example, *Staphylococcus aureus* protein A binds directly to the TNFα receptor, TNFR1, on respiratory epithelium, which then potentiates a chemokine and

cytokine cascade and subsequent disease (Gomez et al., 2004). *Shigella flexneri*, which causes severe diarrhea, has a type III effector, OspG, which is a protein kinase that targets ubiquitin-conjugated enzymes, thereby affecting phospho-IκBα degradation and subsequent NFκB activation. Infection of rabbit ileal loops with the OspG mutant results in increased inflammation due to the lack of OspG immune downregulation (Kim et al., 2005).

Blockade of Cellular Immunity by Viruses

Acquired cellular immune responses to viruses are thought to be critical for clearance and for quickly responding to re-infections. In terms of early cellular responses, the role of NK cells has assumed increasing prominence as more has been learned about how these cells discriminate host cells that are infected, or transformed, and those that are not (Hamerman et al., 2005; Lanier, 2005; Yokoyama, 2005). There is also increasing awareness that NK cells also modulate the functions of antigen-presenting dendritic cells, and vice versa, and thus significantly contribute to the development of acquired cellular immune responses (Andrews et al., 2005). Although NK cells lack specific antigen receptors, much has been published recently about the NK receptors that are either activating or inhibitory, and the viral strategies that have been discovered to counteract them (Lodoen and Lanier, 2005; Rajagopalan and Long, 2005). NK dysregulation by viruses has been better studied for viruses that cause chronic or persistent infections, like herpesviruses, but it is likely that even acute viral infections also modulate NK cell functions as part of their early anti-immune strategies. In general, viruses can interfere with either NK receptor-mediated recognition of the virus-infected cells, NK-activating cytokines, the intracellular activation pathways, or their effector cascades. The viral anti-NK strategies described to date include expressing homologs of MHC-I, modulating infected cell MHC expression, blockade of NK-activating cytokines like type I interferon, antagonism of NK receptor functions, or inhibition of NK effector pathways. Given the close similarities between the killing mechanisms of CTLs and NK cells, the viral strategies that target the granzyme/perforin or Fas pathways likely serve to protect viruses from attack by either class of activated lymphocyte. Activated NK cells also produce interferon-γ and chemokines (Dorner et al., 2004), and as already described, many viruses have evolved specific mechanisms to counter these cytokines as well.

In contrast to NK cells, which do not need to undergo receptor rearrangement and antigen recognition to be capable of antiviral effector functions, CTLs and helper T cells express selective antigen receptors that recognize non-self-epitopes presented in conjunction with MHC molecules. Thus, NK responses to virus infection tend to be rapid, whereas educated T cell responses can take days or even weeks to mature. Viruses can either undergo rapid infections associated with acute disease and rapid resolution or can induce persistent infections that may balance life-long accommodations with the immune system of the host (Klenerman and Hill, 2005). Thus, the extent to which any given virus manipulates acquired immunity varies dramatically according to the biology of the specific virus in question. Some viruses can inhibit MHC-I-restricted antigen presentation pathway of the infected cell, and collectively almost every step of the class I pathway can be blocked by at least one known virus (Ambagala et al., 2005; Lilley and Ploegh, 2005; Lybarger et al., 2005; Yewdell and Haeryfar, 2005). In contrast, much less is known about virus manipulation of MHC class II-restricted antigen presentation in part because APCs need not be infected to present acquired viral epitopes to $CD4^+$ T cells. Recently, it has been shown that MHC class II presentation can occur by processing viral antigens through the ubiquitin/proteosome-dependant pathway more usually associated with class I processing, rather than the classical endosome-mediated degradation pathway (Tewari et al., 2005), and it will be interesting to learn whether any virus can manipulate this aspect of $CD4^+$ T cell biology during virus infections. Autophagy is also known to promote processing of viral antigen into the MHC-II pathway (Paludan et al., 2005), and given the potential importance of autophagy in host responses to pathogens (Deretic, 2005; Levine, 2005), it would be expected that this pathway was also manipulated by viruses. Finally, it has been recently shown that several viruses can inhibit the presentation of lipids to CD1a-restricted T cells (Renukaradhya et al., 2005; Sanchez et al., 2005), suggesting that viruses can manipulate the full spectrum of T cell activation pathways in the host (Hegde and Johnson, 2005).

In terms of initiating cellular immune response to viruses, it is generally agreed that dendritic cells (DCs) are critical for both early innate responses as well as priming the slower MHC-restricted antigen-dependant T cell responses (Rossi and Young, 2005). Plasmacytoid DCs are particularly important as virus sentinels and for inducing type I interferon at peripheral sites of infection (Rinaldo and Piazza, 2004; Freigang et al., 2005; Liu, 2005). Viruses can interfere with DC functions in a variety of ways, but to date the anti-DC strategies usually fall into one of two major categories: either virus infection of DCs alters their differentiation or signaling pathways or else specific viral proteins modulate DC effector functions directly (Bautista et al., 2005; Flano et al., 2005; Majumder et al., 2005; Walzer et al., 2005).

Blockade of Acquired Immunity by Bacteria

Most bacterial pathogens avoid the acquired immune response by avoiding its activation (see above), and there are few examples of direct interference with acquired immunity. For example, *Helicobacter pylori* LPS binds to the C type lectin DC_SIGN on gastric dendritic cells to block Th1 development, thereby tilting the immune response from Th1 to a mixed Th1/Th2 response (Bergman et al., 2004). *Helicobacter pylori* also produces a vacuolating toxin, VacA, which blocks T cell proliferation by interfering with the T cell receptor/IL-2 signaling pathway, resulting in decrease in nuclear translocation of nuclear factor of

activated T cells (NFAT), a global regulator of immune response genes (Gebert et al., 2003). Despite triggering an inflammatory response, there is little specific immune response to *Neisseria gonorrhoeae*, and there are decreased T lymphocytes. The Opa proteins of this organism bind to CEACAM1, which is expressed on $CD4^+$ T cells, thereby suppressing their activation and proliferation (Boulton and Gray-Owen, 2002).

Superantigens certainly alter the T cell response by affecting their subset distribution, but the actual contribution this plays in infection and disease is not well understood. However, there is evidence that indicates superantigens may play a role in disease severity. For example, streptococcal disease severity is correlated to MHC haplotype, suggesting that the interaction between superantigens and MHC class II really influences the severity of disease through their ability to regulate cytokine responses triggered by streptococcal superantigens (Kotb et al., 2002).

Another strategy employed by several mucosal pathogens, including dental pathogens, is to secrete enzymes such as IgA proteases that degrade immunoglobulins. IgA is a secretory antibody that is found on mucosal surfaces and thought to play a key role in humoral defense of these surfaces. Bacterial examples include *Neisseria* species, *Haemophilus influenzae* (causes meningitis), and various Streptococci. For Gram negative pathogens, the IgA protease uses an autotransporter mechanism, including a self-cleavage reaction, to facilitate its secretion out of the bacterium.

Cell Death Manipulation by Viruses

When viruses infect somatic cells, the ability to control the cell death pathway can be crucial to the outcome of the infection, not only in terms of the ability of the virus to complete its replication cycle and disseminate within the host but also with respect to how the infected cell communicates to the immune system. For example, phagocytosis of infected apoptotic cells or subcellular fragments can cause viral antigens to enter the MHC-I-restricted cross-presentation pathway via uninfected macrophage or dendritic cells (Ackerman and Cresswell, 2004; Jutras and Desjardins, 2005). Crosspresentation is important for regulating the type of T cell response to a virus infection because it can trigger acquired immunity via crosspriming or induce T cell inactivation via crosstolerance. It is likely that viruses capable of preventing the maturation of antigen-presenting DCs would thereby favor the induction of crosstolerance to viral antigens. In some cases, viruses can hijack a costimulatory pathway of the T cell activation (Cheung et al., 2005; Watts and Gommerman, 2005), and it seems probable that this strategy is more common than generally appreciated.

In general, viruses either accelerate or inhibit the cell death pathways of the infected cell, depending on the biology of the specific virus. The subject of virus-encoded modulators of death pathways is beyond the scope of this commentary, but the diversity of these viral proteins is quite impressive (Bowie et al., 2004; Boya et al., 2004; D'Agostino et al., 2005).

Cell Death Manipulation by Bacteria

Many bacterial pathogens also alter apoptotic pathways as part of their virulence strategies. Like viruses, obligate intracellular bacteria generally suppress apoptotic death. Because apoptotic death is generally less inflammatory than cytotoxic death, many nonobligate intracellular pathogens choose this strategy to neutralize a variety of host cells. For example, *Salmonella enterica* utilize a variety of strategies to both promote and inhibit host cell apoptosis as part of their virulence strategy during enteric infections (Guiney, 2005).

Chlamydia are obligate intracellular bacteria that reside within a membrane bound inclusion in host cells. Not surprisingly, they have devised several strategies to avoid the host immune response, and to avoid triggering apoptosis in infected cells. These mechanisms include blocking mitochondrial cytochrome C release and inhibiting Bax, Bak, and caspase-3 activation (Fan et al., 1998). They also degrade proapoptotic factors such as BH3-only proteins Bim/Bod, Puma, and Bad, as well as several other reported mechanisms. Although the bacterial factors are not known, Chlamydia possess a type III secretion system that appears to be involved in modulating the intracellular environment and potentially apoptosis. Because of its obligate intracellular lifestyle, genetic experiments to further define the bacterial factors are impossible.

The first cells encountered by *Salmonella* in the gut are thought to be intestinal epithelial cells, which the organisms enter into and replicate within. This is mediated mainly by the Spi1 T3SS and several injected effectors (see above). SopB/SigD is a phosphoinositide phosphatase that, following T3SS injection into the host cytosol, causes a sustained activation of host Akt/protein kinase B, which is a pro-survival kinase (Knodler et al., 2005). This results in decreased levels of apoptosis within epithelial cells, which presumably prolongs the life of the epithelial cells harboring intracellular *Salmonella*. These pathogens then normally escape intestinal epithelial cells and enter the underlying reticuloendothelial system. The interactions with macrophages are more complex than epithelial cells. The Spi1 T3SS delivers an effector (SipB), which activates caspase-1 and causes release of IL-1β and IL-18, which facilitates a rapid cell death that has features of both apoptosis and necrosis. Ironically, animals lacking caspase-1 are more resistant to *Salmonella* infection, and these pathogens cannot disseminate to systemic tissues in these mice (Monack et al., 2000). Thus this organism appears to drive apoptosis (and inflammation) as a mechanism to breach Peyer's patches and move to systemic sites.

However, at least in culture, these organisms mediate a delayed apoptosis via the Spi-2 type III secretion-mediated system. Initially in infection, the organisms trigger apoptosis and inflammation via the Spi-1 system to facilitate subsequent interactions with macrophages, which leads to systemic spread. Then the Spi-2 system facilitates intracellular survival and growth in these macrophages while delaying the onset of apoptosis in these host cells.

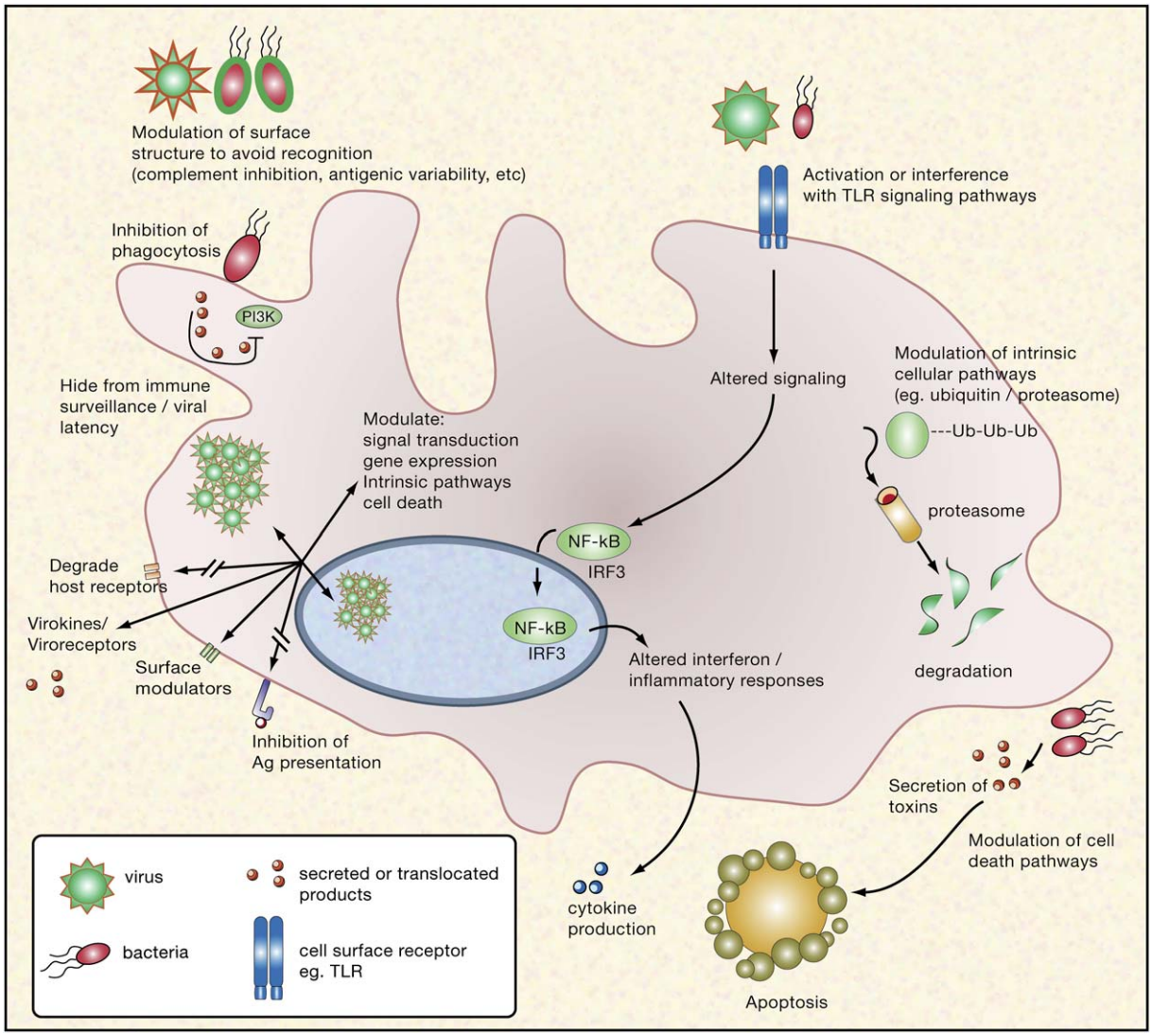

Figure 1. An overview of the Various Mechanisms Used by Bacterial and Viral Pathogens to Overcome Innate and Acquired Immune Systems

The major strategies used by both bacteria and viruses are discussed in more detail in the text.

A hallmark of apoptotic cells is their phagocytosis by other phagocytic cells. Thus, as a host cell becomes depleted by intracellular *Salmonella*, the delayed apoptosis then enables the infected macrophage (and intracellular bacteria) to be phagocytosed by other macrophages, providing a fresh host cell reservoir for these organisms. Alternatively, an attractive host defense mechanism would be to deplete potential host cells (such as macrophages) by promoting extensive apoptosis within infected organs, thereby depriving the pathogens from additional host cells.

Concluding Remarks

For a virus or a bacterium to be a successful vertebrate pathogen it must overcome or alter many normally very effective host defense mechanisms, including both innate and acquired immunity (Figure 1). Although the field of immunology is well established, pathogens serve as excellent tools to probe immune function further. The use of relevant animal infection models provides the necessarily more complete set of chemical and cellular interactions that occur during infections. Moreover, technological advances such as genomics, proteomics, in vivo gene expression, etc., now enable investigators to follow infections and the accompanying cell biology in real time. Because of the robustness and generic mechanisms of innate immunity, the ability to understand and exploit this highly effective system provides an attractive method to counter infectious agents (Finlay and Hancock, 2004). The need to develop alternative antimicrobial therapies

and preventatives are critical. By studying how pathogens insinuate their own anti-immune systems into a susceptible vertebrate host, we can better understand the various Achilles heels of host defense, and thereby more precisely deconstruct the fundamental properties of microbial pathogenesis. With new infectious diseases continually arising and classical infections ever present, this knowledge is critical to contemplating new preventatives and therapeutics.

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