Leading Edge
Review

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

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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