lies downstream of IFN receptors. Other viruses produce proteins that inactivate or inhibit double-stranded RNA–dependent protein kinase (PKR), an important mediator of the antiviral effects of IFN, or produce proteins that block complement activation.

- *Evasion of recognition by CD4+ helper T cells and CD8+ cytotoxic T cells*. This is also an important mode of immune evasion by viruses, which involves several different mechanisms. Several DNA viruses (e.g., HSV, CMV, and EBV) bind to or alter localization of major histocompatibility complex (MHC) class I proteins, impairing peptide presentation to CD8+ T cells. Downregulation of MHC class I molecules could lead to targeting by NK cells, but herpesviruses also express MHC class I homologues that inhibit NK cells by engaging NK cell inhibitory receptors (Chapter 6). Herpesviruses also can target MHC class II molecules for degradation, impairing antigen presentation to CD4+ T helper cells.
- Another strategy exploits *immunoregulatory mechanisms to downregulate anti-microbial T cell responses*. During chronic viral infections, antigen-specific T cells initially acquire effector functions but gradually lose their potency as infection progresses. This loss of function, termed T cell exhaustion, is a feature of chronic infections by HIV, hepatitis C virus, and hepatitis B virus. A major mechanism regulating T cell exhaustion is upregulation of immunoinhibitory T cell pathways. The PD-1 pathway, which normally functions to maintain T cell tolerance to self-antigens, is an important mediator of T cell exhaustion during chronic viral infection.
- The ultimate means of avoiding the immune system is to "lie low" by establishing a state of *latent infection* in which few if any viral genes are expressed. Examples include latent infections of neurons by *herpes simplex* and *Varicella* and of B lymphocytes by Epstein-Barr virus. These latent infections persist in an asymptomatic state throughout life, but may produce disease if the viruses are "awakened" from their latent state and enter a phase of viral replication. Other pathogens infect leukocytes, and in doing so interfere with their function, leading to persistent infection. A classic example is HIV, which infects CD4+ T cells and by doing so sets the stage for T cell dysfunction and persistent, progressive disease.

KEY CONCEPTS

Immune evasion by microbes

After bypassing host tissue barriers, infectious microorganisms must also evade host innate and adaptive immunity to successfully proliferate and be transmitted to the next host. Strategies include:

- Antigenic variation
- Inactivating antibodies or complement
- Resisting phagocytosis, e.g. by producing a capsule
- Suppressing the host adaptive immune response, e.g. by interfering with cytokines or inhibiting MHC expression and antigen presentation.
- Establishing latency, during which viruses survive in a silent state in infected cells.

Injurious Effects of Host Immunity

As mentioned earlier, while generally beneficial, the host immune response to microbes can sometimes be the major cause of tissue injury. The granulomatous inflammatory reaction to *M. tuberculosis* sequesters the bacilli and prevents their spread, but it also can produce tissue damage and fibrosis. Similarly, damage to hepatocytes following hepatitis B virus and hepatitis C virus infection is mainly due to the effects of the immune response on infected liver cells rather than cytopathic effects of the virus. Humoral immune responses to microbes also can have pathologic consequences. Following infection with *S. pyogenes*, antibodies produced against the streptococcal M protein can cross-react with cardiac proteins and damage the heart, leading to rheumatic heart disease. Similarly, poststreptococcal glomerulonephritis is caused by immune complexes formed between antistreptococcal antibodies and circulating streptococcal antigens; these complexes deposit in the renal glomeruli, producing inflammation in the kidney.

Inflammation elicited by microbes also underlies a wide variety of chronic inflammatory disorders as well as some forms of cancer. A cycle of inflammation and epithelial injury is involved in the pathogenesis of inflammatory bowel disease, with microbes playing at least a peripheral role (Chapter 17). Viruses (hepatitis B virus, hepatitis C virus) and bacteria (*H. pylori*) that are not known to carry or activate oncogenes are associated with cancers, presumably because these microbes trigger chronic inflammation, which provides fertile ground for the development of cancer (Chapter 7).

Infections in People with Immunodeficiencies

Inherited or acquired defects in innate and adaptive immunity (Chapter 6) often impair only part of the immune system, rendering the affected individual susceptible to specific types of infections. These rare disorders have served to illuminate important aspects of specific components of host defense, as well as the unique vulnerabilities of certain pathogens. The following are some specific examples:

- *Antibody deficiencies*, as seen in patients with X-linked agammaglobulinemia, lead to increased susceptibility to infections by extracellular bacteria, including *S. pneumoniae, H. influenzae*, and *S. aureus*, as well as a few viruses (rotavirus and enteroviruses).
- *Complement defects* in early components of the complement cascade lead to susceptibility to infections by encapsulated bacteria, such as *S. pneumoniae,* whereas deficiencies of the late membrane attack complex components (C5-C9) are associated with *Neisseria* infections.
- *Defects in neutrophil function* lead to increased susceptibility to infections with *S. aureus*, some gram-negative bacteria, and fungi.
- *Defects in Toll-like receptor (TLR) signaling pathways* have varied effects. Mutations in MyD88 or IRAK4, which are downstream of several TLRs, predispose to pyogenic bacterial infections, particularly invasive infections with *S. pneumoniae*, while impaired TLR3 responses are associated with childhood herpes simplex virus encephalitis.