A second process that breaches nonimmune host defenses results from infection by respiratory viruses. Influenza virus may damage upper and lower respiratory host defenses by destroying the respiratory epithelium, inhibiting ciliary action and mucus production. Bacterial pathogens, most commonly *S. pneumoniae*, that colonize the respiratory tract in normal hosts may then colonize and invade the lower respiratory tract, leading to pneumonia. Organisms such as *M. tuberculosis,* an intracellular pathogen, may evade upper respiratory and lower respiratory defenses and lodge in alveolar macrophages in the lung, where they can survive and multiply. Interference with alveolar macrophage function (e.g., silica exposure) may increase susceptibility to tuberculosis.

The innate immune system is critical during the early phases of infection. The response is rapid, although nonspecific, and eliminates the pathogen or holds the infection in check until the more powerful, highly specific adaptive immune system has time to respond. Phagocytes such as tissue macrophages patrol the periphery and detect pathogens through receptors such as TLRs. This activates the phagocyte, induces phagocytosis and killing, and stimulates the phagocyte to produce cytokines and chemokines that initiate the inflammatory response.

Complement may be activated through the alternative pathway and produce products to attract neutrophils, opsonize pathogens, and lyse pathogens. Vasodilation results from histamine release, and circulating neutrophils are localized to the vascular endothelium nearest the site of invasion by integrins, pass through the vascular wall, and move down a chemokine gradient to the site of infection. Opsonization helps neutrophils and other immune cells ingest and kill the pathogen. These immediate inflammatory and innate immune responses are initiated immediately and increase over hours to days. Although they are effective, these responses are temporizing measures while more specific and more effective host responses of the adaptive immune system are developing.

Immature dendritic cells in peripheral tissues are watchman for foreign molecules. Through pinocytosis and phagocytosis initiated by TLRs and other receptors, they detect pathogens; when identified, dendritic cells migrate to regional lymph nodes. There the dendritic cells mature, stop phagocytosis, and process antigen for presentation to T cells, initiating the specific adoptive immune response. The type of response depends on the type of pathogen. Intracellular pathogens such as *M. tuberculosis* stimulate a T cell–mediated response, whereas *S. pneumoniae* stimulates primarily a B-cell, antibody-mediated (humoral) response. Most infections produce components of cellular and humoral host responses in various degrees that often act in concert. For example, influenza virus induces a B-cell and T-cell response.

Humoral Response

Early in infection, complement and preexisting circulating or tissue antibodies react to pathogens directly and can initiate direct lysis, opsonization, and neutralization of pathogens. B cells may be activated by T cell–independent antigens or through interaction with $CD4^+$ T cells and T cell–dependent antigens. B-cell populations proliferate and produce IgM antibodies initially and then with isotype switching produce other types of antibodies, including IgG and IgA. Antibodies acting in the extracellular space bind to pathogens or their products, potentially leading to neutralization, opsonization, complement fixation, and ADCC.

Cell-Mediated Response

Naïve T cells with specificity for the invading pathogen are activated, proliferate, and produce cytokines. $CD4^+$ T cells produce cytokines that stimulate other T cells, enhance the overall inflammatory response, activate phagocytes for killing, and stimulate antibody production. Previously sensitized T cells may react rapidly with activation and proliferation on exposure to a previously recognized intracellular pathogen.

SUGGESTED READINGS

Bennett JE, Dolin R, Blaser M, editors: Mandell, Douglas, and Bennett's principles and practice of infectious diseases, ed 8, Philadelphia, 2015, Saunders.

Medzhitov R, Shevach EM, Trinchieri G, et al: Highlights of 10 years of immunology in Nature Reviews Immunology, Nat Rev Immunol 11:693–702, 2011.