145e Molecular Mechanisms of Microbial Pathogenesis

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Over the past four decades, molecular studies of the pathogenesis of microorganisms have yielded an explosion of information about the various microbial and host molecules that contribute to the processes of infection and disease. These processes can be classified into several stages: microbial encounter with and entry into the host; microbial growth after entry; avoidance of innate host defenses; tissue invasion and tropism; tissue damage; and transmission to new hosts. *Virulence* is the measure of an organism's capacity to cause disease and is a function of the pathogenic factors elaborated by microbes. These factors promote *colonization* (the simple presence of potentially pathogenic microbes in or on a host), *infection* (attachment and growth of pathogens and avoidance of host defenses), and *disease* (often, but not always, the result of activities of secreted toxins or toxic metabolites). In addition, the host's inflammatory response to infection greatly contributes to disease and its attendant clinical signs and symptoms. The recent surge of interest in the role of the microbiota and its associated *microbiome*—the collection of microbial genomes residing in or on mammalian organisms—in the physiology of, susceptibility to, and response to infection and in immune system development has had an enormous impact on our understanding of host-pathogen interaction.

THE MICROBIOME

(See also Chap. 86e) We now understand that the indigenous microbial organisms living in close association with almost all animals are organized into complex communities that strongly modulate the ability of pathogenic microbes to become established in or on host surfaces. The sheer numbers of these microbes and their genomic variability vastly exceed the numbers of host cells and genes in a typical animal. Changes and differences in microbiomes within and between individuals, currently characterized by high-throughput DNA sequencing techniques and bioinformatic analysis, affect the development and control of the immune system as well as such diverse conditions as obesity, type 1 diabetes, cognition, neurologic states, autoimmune diseases, and infectious diseases of the skin, gastrointestinal tract, respiratory tract, and vagina. It has been more difficult to directly associate specific types of microbiomes with pathophysiologic states and to assess how conserved or variable microbial species within human and animal microbiomes are evolving. Defining clusters of organisms associated with diseases may become more feasible as more data are obtained. Complicating this task are the results from the Human Microbiome Project suggesting a high level of variability among individuals in the components of the microbiome, although many individuals appear to maintain a fairly conserved microbiome throughout their lives. In the context of infectious diseases, clear changes and disruptions of the indigenous microbiome have a strong and often fundamental impact on the progression of infection. Such alterations can be associated with the effects of antibiotic and immunosuppressive drug use on the normal flora, with environmental changes, and with the impact of microbial virulence factors that displace the indigenous microbial flora to facilitate pathogen colonization. As the available technology for defining the microbiome expands, there is no doubt that the resulting data will markedly affect our concepts of and approaches to microbial pathogenesis and infectious disease treatment.

MICROBIAL ENTRY AND ADHERENCE

Entry Sites A microbial pathogen can potentially enter any part of a host organism. In general, the type of disease produced by a particular microbe is often a direct consequence of its route of entry into the body. The most common sites of entry are mucosal surfaces (the respiratory, alimentary, and urogenital tracts) and the skin. Ingestion, inhalation, and sexual contact are typical routes of microbial entry. Other portals of entry include sites of skin injury (cuts, bites, burns, trauma) along with injection via natural (i.e., vector-borne) or artificial (i.e., needle-stick injury) routes. A few pathogens, such as *Schistosoma* species, can penetrate unbroken skin. The conjunctiva can serve as an entry point for pathogens of the eye, which occasionally spread systemically from that site.

Microbial entry usually relies on the presence of specific factors needed for persistence and growth in a tissue. Fecal-oral spread via the alimentary tract requires a biologic profile consistent with survival in the varied environments of the gastrointestinal tract (including the low pH of the stomach and the high bile content of the intestine) as well as in contaminated food or water outside the host. Organisms that gain entry via the respiratory tract survive well in small moist droplets produced during sneezing and coughing. Pathogens that enter by venereal routes often survive best in the warm moist environment of the urogenital mucosa and have restricted host ranges (e.g., *Neisseria gonorrhoeae*, *Treponema pallidum*, and HIV).

The biology of microbes entering through the skin is highly varied. Some of these organisms can survive in a broad range of environments, such as the salivary glands or alimentary tracts of arthropod vectors, the mouths of larger animals, soil, and water. A complex biology allows protozoan parasites such as *Plasmodium*, *Leishmania*, and *Trypanosoma* species to undergo morphogenic changes that permit transmission to mammalian hosts during insect feeding for blood meals. Plasmodia are injected as infective sporozoites from the salivary glands during mosquito feeding. *Leishmania* parasites are regurgitated as promastigotes from the alimentary tract of sandflies and injected by bite into a susceptible host. Trypanosomes are first ingested from infected hosts by reduviid bugs; the pathogens then multiply in the gastrointestinal tract of the insects and are released in feces onto the host's skin during subsequent feedings. Most microbes that land directly on intact skin are destined to die, as survival on the skin or in hair follicles requires resistance to fatty acids, low pH, and other antimicrobial factors on the skin. Once it is damaged (and particularly if it becomes necrotic), the skin can be a major portal of entry and growth for pathogens and elaboration of their toxic products. Burn wound infections and tetanus are clear examples. After animal bites, pathogens resident in the animal's saliva gain access to the victim's tissues through the damaged skin. Rabies is the paradigm for this pathogenic process; rabies virus grows in striated muscle cells at the site of inoculation.

Microbial Adherence Once in or on a host, most microbes must anchor themselves to a tissue or tissue factor; the possible exceptions are organisms that directly enter the bloodstream and multiply there. Specific ligands or adhesins for host receptors constitute a major area of study in the field of microbial pathogenesis. *Adhesins* comprise a wide range of surface structures, not only anchoring the microbe to a tissue and promoting cellular entry where appropriate but also eliciting host responses critical to the pathogenic process (Table 145e-1). Most microbes produce multiple adhesins specific for multiple host receptors. These adhesins are often redundant, are serologically variable, and act additively or synergistically with other microbial factors to promote microbial sticking to host tissues. In addition, some microbes adsorb host proteins onto their surface and utilize the natural host protein receptor for microbial binding and entry into target cells.

VIRAL ADHESINS All viral pathogens must bind to host cells, enter them, and replicate within them. Viral coat proteins serve as the ligands for cellular entry, and more than one ligand-receptor interaction may be needed; for example, HIV utilizes its envelope glycoprotein (gp) 120 to enter host cells by binding both to CD4 and to one of two receptors for chemokines (designated CCR5 and CXCR4). Similarly, the measles virus H glycoprotein binds to both CD46 and the membrane-organizing protein moesin on host cells. The gB and gC proteins on herpes simplex virus bind to heparan sulfate, although this adherence is not essential for entry but rather serves to concentrate virions close to the cell surface; this step is followed by attachment to mammalian cells mediated by the viral gD protein, with subsequent formation of a homotrimer of viral gB protein or a heterodimer of viral gH and gL proteins that permits fusion of the viral envelope with the host cell membrane. Herpes simplex virus can use a number of eukaryotic cell