unable to produce the type IVa pili were actually better able to colonize the gastrointestinal mucosa, although the basis for this observation was not identified. *V. cholerae* cells appear to use two different types of pili for intestinal colonization. Whereas interference with this stage of colonization would appear to be an effective antibacterial strategy, attempts to develop pilus-based vaccines for human diseases have not been highly successful to date.

Flagella are long appendages attached at either one or both ends of the bacterial cell (polar flagella) or distributed over the entire cell surface (peritrichous flagella). Flagella, like pili, are composed of a polymerized or aggregated basic protein. In flagella, the protein subunits form a tight helical structure and vary serologically with the species. Spirochetes such as *T. pallidum* and *Borrelia burgdorferi* have axial filaments similar to flagella running down the long axis of the center of the cell, and they "swim" by rotation around these filaments. Some bacteria can glide over a surface in the absence of obvious motility structures.

Other bacterial structures involved in adherence to host tissues include specific staphylococcal and streptococcal proteins that bind to human extracellular matrix proteins such as fibrin, fibronectin, fibrinogen, laminin, and collagen. Fibronectin appears to be a commonly used receptor for various pathogens; a particular amino acid sequence in fibronectin, Arg-Gly-Asp or RGD, is a critical target used by bacteria to bind to host tissues. Binding of a highly conserved *Staphylococcus aureus* surface protein, clumping factor A (ClfA), to fibrinogen has been implicated in many aspects of pathogenesis. Attempts to interrupt this interaction and prevent *S. aureus* sepsis in low-birth-weight infants by administering an intravenous IgG preparation derived from the plasma of individuals with high titers of antibody to ClfA failed to show efficacy in a clinical trial; however, this approach is being pursued in some vaccine formulations targeting this organism. The conserved outer-core portion of the lipopolysaccharide (LPS) of *P. aeruginosa* mediates binding to the cystic fibrosis transmembrane conductance regulator (CFTR) on airway epithelial cells—an event that appears to play a critical role in normal host resistance to infection by initiating recruitment of polymorphonuclear neutrophils (PMNs) to the lung mucosa to kill the cells via opsonophagocytosis. A large number of microbial pathogens encompassing major gram-positive bacteria (staphylococci and streptococci), gram-negative bacteria (major enteric species and coccobacilli), fungi (*Candida*, *Fusobacterium*, *Aspergillus*), and even eukaryotes (*Trichomonas vaginalis* and *Plasmodium falciparum*) express a surface polysaccharide composed of β-1-6-linked-poly-*N*-acetyl-D-glucosamine (PNAG). One of the functions of PNAG for some of these organisms is to promote binding to materials used in catheters and other types of implanted devices. This polysaccharide may be a critical factor in the establishment of device-related infections by pathogens such as staphylococci and *E. coli*. High-powered imaging techniques (e.g., atomic force microscopy) have revealed that bacterial cells have a nonhomogeneous surface that is probably attributable to different concentrations of cell surface molecules, including microbial adhesins, at specific places on the cell surface **(Figs. 120-1*C* and 120-1*D*)**.

FUNGAL ADHESINS Several fungal adhesins have been described that mediate colonization of epithelial surfaces, particularly adherence to structures like fibronectin, laminin, and collagen. The product of the *Candida albicans INT1* gene, Int1p, bears similarity to mammalian integrins that bind to extracellular matrix proteins. The agglutinin-like sequence (ALS) adhesins are large cell-surface glycoproteins mediating adherence of pathogenic *Candida* to host tissues. These adhesins possess a conserved three-domain structure composed of an N-terminal domain that mediates adherence to host tissue receptors, a central motif consisting of a number of repeats of a conserved sequence of 36 amino acids, and a C-terminal domain that varies in length and sequence and contains a glycosylphosphatidylinositol (GPI) anchor addition site that allows binding of the adhesin to the fungal cell wall. Variability in the number of central domains in different ALS proteins characterizes different adhesins with specificity for different host receptors. The ALS adhesins are expressed under certain environmental conditions and are crucial for pathogenesis of fungal infections.

For several fungal pathogens that initiate infections after inhalation of infectious material, the inoculum is ingested by alveolar macrophages, in which the fungal cells transform to pathogenic phenotypes. Like *C. albicans*, *Blastomyces dermatitidis* binds to CD11b/CD18 integrins as well as to CD14 on macrophages. *B. dermatitidis* produces a 120-kDa surface protein, designated WI-1, that mediates this adherence. An unidentified factor on *Histoplasma capsulatum* also mediates binding of this fungal pathogen to the integrin surface proteins.

EUKARYOTIC PATHOGEN ADHESINS Eukaryotic parasites use complicated surface glycoproteins as adhesins, some of which are lectins (proteins that bind to specific carbohydrates on host cells). For example, *Plasmodium vivax*, one of six *Plasmodium* species causing malaria, binds (via Duffy-binding protein) to the Duffy blood group carbohydrate antigen Fy on erythrocytes. *Entamoeba histolytica*, the third leading cause of death from parasitic diseases, expresses two proteins that bind to the disaccharide galactose/*N*-acetyl galactosamine. Reports indicate that children with mucosal IgA antibody to one of these lectins are resistant to reinfection with virulent *E. histolytica*. A major surface glycoprotein (gp63) of *Leishmania* promastigotes is needed for these parasites to enter human macrophages—the principal target cell of infection. This glycoprotein promotes complement binding but inhibits complement lytic activity, allowing the parasite to use complement receptors for entry into macrophages; gp63 also binds to fibronectin receptors on macrophages. In addition, the pathogen can express a carbohydrate that mediates binding to host cells. Evidence suggests that, as part of hepatic granuloma formation, *Schistosoma mansoni* expresses a carbohydrate epitope related to the Lewis X blood group antigen that promotes adherence of helminthic eggs to vascular endothelial cells under inflammatory conditions.

Host Receptors Host receptors are found both on target cells (such as epithelial cells lining mucosal surfaces) and within the mucus layer covering these cells. Microbial pathogens bind to a wide range of host receptors to establish infection (Table 145e-1). Selective loss of host receptors for a pathogen may confer natural resistance to an otherwise susceptible population. For example, 70% of individuals in West Africa lack Fy antigens and are resistant to *P. vivax* infection. *S. enterica* serovar Typhi, the etiologic agent of typhoid fever, produces a pilus protein that binds to CFTR to enter the gastrointestinal submucosa after being ingested by enterocytes. As homozygous mutations in *CFTR* are the cause of the life-shortening disease cystic fibrosis, heterozygote carriers (e.g., 4–5% of individuals of European ancestry) may have had a selective advantage due to decreased susceptibility to typhoid fever.

Numerous virus–target cell interactions have been described, and it is now clear that different viruses can use similar host cell receptors for entry. The list of certain and likely host receptors for viral pathogens is long. Among the host membrane components that can serve as receptors for viruses are sialic acids, gangliosides, glycosaminoglycans, integrins and other members of the immunoglobulin superfamily, histocompatibility antigens, and regulators and receptors for complement components. A notable example of the effect of host receptors on the pathogenesis of infection has emerged from studies comparing the binding of avian influenza A subtype H5N1 with that of influenza A strains expressing the H1 subtype of hemagglutinin. The H1 subtypes tend to be highly pathogenic and transmissible from human to human, and they bind to a receptor composed of two sugar molecules: sialic acid linked α-2-6 to galactose. This receptor is expressed at high levels in the airway epithelium; when virus is shed from this surface, its transmission via coughing and aerosol droplets is facilitated. In contrast, the H5N1 avian influenza virus binds to sialic acid linked α-2-3 to galactose, and this receptor is expressed at high levels in pneumocytes in the alveoli. Infection in the alveoli is thought to underlie the high mortality rate associated with avian influenza but also the low interhuman transmissibility of this strain, which is not readily transported to the airways from which it can be expelled by coughing. Nonetheless, it was recently shown that H5 hemagglutinins can acquire mutations that vastly increase their transmissibility while not affecting their high level of lethality.