Editorial

How do microbes (viruses, bacteria, and protozoa) attach to cells for adhesion, colonization, or entry? How does this association influence infection and pathogenesis? Studies of the mechanism of attachment and the molecules involved are beginning to provide new insights into the critical early steps in microbial infection.

Cell surface glycosaminoglycans (GAGs) such as heparan sulfate (HS), dermatan sulfate (DS), and chondroitin sulfate (CS) are long repeating sulfated glycoconjugates that are found on many cells and tissues of animal hosts (1). They are usually linked to a core protein to form proteoglycans and have been shown to be important for cell association of several microbes (2, 3). These include initial binding of herpes simplex virus (HSV), pseudorabies virus (PRV), human cytomegalovirus (HCMV), varicella zoster virus, bovine herpesvirus types 1 and 4, and possibly human immunodeficiency virus; adhesion of protozoa such as trypanosomes; and colonization by several bacteria (*Chlamydia trachomatis* and *Bordetella pertussis*). Now the Lyme disease spirochete, *Borrelia burgdorferi,* also seems to bind proteoglycans, as described in this issue of *The Journal* by Issacs (2).

Association with cell surface GAGs offers notable advantages for microbes. GAGs provide many binding options since they are easily accessible, ubiquitous, and abundant on eucaryotic cells (1). Versatility in fine structure of GAGs provides specificity to the microbe for cell association. Initial interaction with the glycan offers the advantage during infection of facilitating subsequent association with a target protein or lipid moiety on the same or a different molecule in close proximity. Important to long-term survival, a variety of glycoconjugates provide alternative attachment sites that would require only small changes in binding ligands of the microbe.

Issacs (2) shows that the Lyme disease spirochete binds to HS, and possibly DS and CS, proteoglycans on cultured epithelial cells. This association appears similar to that recently described for herpesviruses (3). Consistent with possible attachments to other cellular components, competitors of HS binding also only partially block attachment of *B. burgdorferi* (greatest inhibition was 68%). Multiple attachments to HS and non-HS receptors are indicated for HSV, PRV, and HCMV (4–8), and for other viruses (9) and bacteria (10). In vivo, multiple independent or sequential attachments (3, 5, 6) likely play a critical role in tissue and organ tropism and in establishing the different phases of the microbial life cycle. Variation in valency or affinity provide the microbe with a mechanism to respond to changes in the cell environment (9, 10). For example, with HSV, initial binding to HS as an easily accessible cell surface molecules may concentrate the microbe at the cell surface so it can more easily find a second non-HS receptor. Alternatively, binding to HS may be required to induce changes in the microbe that facilitate subsequent events such as fusion of viruses with cellular membranes or altered gene expression for bacteria.

Issacs also identifies a 39-kD *B. burgdorferi* protein as a prime ligand candidate. Relevance to spirochete infection of binding of the 39-kD protein to heparin, and possibly to HS, remains to be determined. With herpes viruses, several viral envelope proteins that appear not to have identical functions can bind to HS (3–7).

Cellular glycoconjugates clearly perform many functions for eucaryotic cells (1). That microbes have taken advantage of their presence is not surprising. Understanding the similarities and subtle variations of this mode of microbial–cell association will be the subject of continued intense investigation. Some important questions are: What part of HS is bound? What other cell receptors do these microbes bind? What are the microbial attachment proteins (ligands), and what roles do they play in infection? How does interaction with the proteoglycans affect pathogenesis, and does it influence cell, tissue, and species tropism? Is attachment to HS required, and is there cooperativity between different types of attachment? Finally, can this or subsequent microbial–cell interactions during colonization or entry be effectively and safely circumvented to prevent or treat clinical infection? Interaction of the Lyme disease spirochete with HS proteoglycans is an important development toward understanding and controling infection by this common human pathogen.

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