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MINIREVIEW

Consequences of Microbial Attachment: Directing Host Cell Functions with Adhesins

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ADHESINS SERVE NOT ONLY TO RECOGNIZE ADDRESSES BUT ALSO AS BIOLOGICAL EFFECTORS

During the course of infectious diseases, bacteria colonize body sites by sequentially engaging their surface-bound adhesins with cognate receptors available on epithelial cells, endothelial cells, leukocytes, or the extracellular matrix. It is generally accepted that this recognition process is required to establish bacteria at a given site. Although less rigorously proven, address recognition by adhesins is also thought to determine which tissue and which host is targeted by each pathogen. For example, adhesins of *Bordetella pertussis* appear to carry sufficient information to discriminate between cilia and macrophages and distinguish human from other mammalian cells (31).

Aside from the ability to recognize a eukaryotic address, adhesins play a substantial role in determining the outcome of a prokaryotic-eukaryotic interaction. They may initiate invasion by the pathogen, either by themselves or by engaging a cascade of secondary molecules. They have inherent abilities to incite, subvert, or co-opt host defense systems. The more complex the adhesin, the wider the array of possible outcomes. Adhesins can even be toxins. For instance, the ability to interact with a repertoire of glycoproteins and glycolipids on many types of eukaryotic cells confers on pertussis toxin (36) and other toxins (29) the capability on the one hand to act as an adherence bridge for the whole bacterium and on the other hand to mediate cellular intoxication by presentation of the enzymatically active toxic subunit. Thus, in the current view, it appears fair to say that simple address recognition is the tip of the iceberg of biologically significant attributes of adhesins. This review will focus on those studies which expand our view of adhesins to include their potential as biological effector molecules.

A great deal of information is available on the structures and sequences of bacterial adhesins. Most bacteria can display a number of adhesins; for instance, at least nine have been described for *Escherichia coli*: colonization factor antigen I, K88, K99, X, O75X, PapG-P fimbriae, PrsG-P fimbriae, type 1 fimbriae, and S fimbriae. Adhesive proteins come in fimbrial and nonfimbrial forms and usually recognize carbohydrates on eukaryotic cells, although strict protein-protein interactions also occur. Pathogens have been divided into classes based on the ability to recognize galactose, mannose, or sialic acid on eukaryotic glycoconjugates (10, 11). Elegant studies using libraries of glycoconjugates have deciphered the critical structural requirements of the cognate carbohydrates for many known adhesins. Taken together, it can be said that we currently understand adhesins as whole molecules, knowing their sequences but relatively little of the domains which enter into receptor recognition. Conversely, we know in exquisite detail the arrangement of carbohydrates preferred as receptors but relatively little about the native molecules that such receptors may be found on. It can be predicted that as the functional domains of adhesins are discerned, relationships will become apparent between prokaryotic adhesins and other systems of cell-cell recognition in the plant and animal worlds. Similarly, as the identity of receptors becomes known, the cell biology attendant with those receptors will be linked to adhesin biology. This process is certain to open the field of adhesins to study as biological effector molecules.

EXPANDED BIOLOGY OF ADHESINS: EXAMPLE OF *B. PERTUSSIS*

B. pertussis displays at least seven potential adhesins: four types of fimbriae and three nonfimbrial adhesins, filamentous hemagglutinin (FHA), pertussis toxin, and pertactin. Studies of FHA and pertussis toxin illustrate how the decoding of the fine structure of an adhesin and the identification of a receptor can lead to an expanded view of the biological activities of adhesins. The carbohydrate recognition domains of pertussis toxin have been localized to the otherwise homologous subunits S2 and S3 (31). Examination of the sequences of prokaryotic carbohydrate-binding proteins reveals a kinship between toxin subunits S2 and S3 and the PapG fimbriae. A similar kinship between sialic acid-binding fimbriae and toxins has also recently been reported (15). If prokaryotic molecules as different as toxins and fimbriae can be demonstrated to have related lectinlike properties, what about possible relationships between prokaryotic and eukaryotic lectins? The pertussis toxin S2 and S3 carbohydrate recognition domains have structural features in common with eukaryotic C-type lectin domains (and not with lectins from plants) (31), indicating that toxin and fimbrial recognition units are related to the broader family of C-type lectins of eukaryotes. This structural relationship can be extended to a functional homology between S2 and S3 and the subset of C-type lectins termed the selectins (36a). Endothelia express selectins (e.g., ELAM and GMP-140) to promote leukocyte adhesion, and recent work in our laboratory suggests that S2 and S3 are active in assays of selectin activity. Thus, identification of the precise binding domains in two adhesins of *B. pertussis* revealed striking parallels in structure and function between eukaryotic and prokaryotic

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TABLE 1. Pathogens which recognize integrins

Target cell and strategy	Microorganism	Ligand	RGD	Integrin	Reference
Macrophage					
Mimicry	*Bordetella pertussis*	FHA	Yes	CR3	24
Ancillary ligand recognition	*Leishmania mexicana*	gp63	No	CR3	28
	Leishmania donovani	?	No	CR3	39
	Histoplasma capsulatum	?	No	CD18	1
	Escherichia coli	Type 1 fimbriae	No	CD18	33
Masking	*Legionella pneumophila*	Adsorbed C3bi	Yes	CR3	22
	Mycobacterium tuberculosis	Adsorbed C3bi	Yes	CR3	32
	Leishmania major	Adsorbed C3bi	Yes	CR3	16
Tissue culture cell					
Mimicry	Foot-and-mouth disease virus	VP1	Yes	Fibronectin receptor	4
	Coxsackie virus A9	VP1	Yes	?	26
Ancillary ligand recognition?	*Yersinia* spp.	Invasin	No	β1	8
	Shigella spp.	?	?	Possibly β1	30
Masking	*Trypanosoma cruzi*	Adsorbed fibronectin	Yes	Fibronectin receptor	19
	Treponema pallidum	Adsorbed fibronectin	Yes	Fibronectin receptor	34

adhesive proteins. Such relationships will likely become more prevalent as more functional domains of adhesins are identified, a process which will not only enrich our understanding of pathophysiology in disease but also provide insight into the normal physiology of intercellular recognition systems.

INTEGRINS AS RECEPTORS FOR PATHOGENS

Although the cognate oligosaccharides for bacterial adhesins are known, the molecules bearing these determinants are virtually uncharacterized, with the notable exception of glycophorins A and B, which serve as a receptors for some falciparum malaria parasites (7) and reovirus (21). One reason for this is the fact that many glycoproteins or glycolipids on the eukaryotic cell surface carry similar carbohydrate decorations. Only a few laboratories have the extensive libraries of natural glycoconjugates needed to discriminate subtleties of three-dimensional structure of seemingly similar carbohydrate moieties. The current state of the art has been extensively reviewed (10), and research is being directed to three areas: the charting of precise adhesin-receptor pairs, the determination of the domains of each partner which make contact, and the physical forces between partners which add up to sticking.

In distinct contrast to the anonymity of carbohydrate-bearing receptors, one group of receptors has recently received much attention: the large family of eukaryotic adhesion molecules, the integrins. This family of glycoproteins mediates cell-cell and cell-extracellular matrix recognition between eukaryotic counterparts. Characteristically, the integrin binds to a protein containing an Arg-Gly-Asp triplet (27). A surprising number of pathogens have co-opted the existing integrin-based system of addresses and ligands (Table 1). Three strategies appear to be used to gain entry into the system. The first can be termed masking, whereby adsorption of the natural ligand for the integrin onto the bacterial surface (for example, C3bi, as shown in Table 1) smuggles the pathogen along natural reaction pathways. The second is most easily called ancillary ligand recognition, whereby the pathogen binds to carbohydrates on glycosylated integrins rather than to the Arg-Gly-Asp recognition site. The third process, true mimicry, is the rarest but perhaps the most sophisticated strategy, in which the pathogen takes one of two routes: (i) expression of an integrin analog to promote interactions with endothelia (shown for *Candida albicans* [6]) or (ii) expression of proteins containing the Arg-Gly-Asp binding motif (shown for FHA of *B. pertussis* [24]).

Knowing the communication between integrins and the internal cytoskeleton, it has recently become possible to explain and appreciate the vivid descriptions by Sansonetti (30) and later by Tilney and Portnoy (35), Falkow (3), and Isberg (8) of intracellular rearrangements, particularly the coalescing of actin filaments, under the point of contact of a pathogen with the external surface of a cell. Such cytoskeletal rearrangement is a response which may become characteristic of intracellular pathogens as they engineer their own uptake, often beginning with recognition of integrins.

DETERMINANTS OF THE OUTCOME OF AN INTERACTION BETWEEN AN ADHESIN AND A HOST CELL

The outcome of an interaction between a pathogen and a mammalian cell is determined at first by which receptor is bound. This is illustrated by the studies of Joiner (9) on *Toxoplasma gondii*, which have elegantly shown that the route of entry determines the fusion potential of the vacuole and therefore the survival of the protozoa. Although it has been stated that, in general, adherence to host cell carbohydrates results in a surface-bound pathogen (8), diversity of fates can also be documented for particles bound to carbohydrate receptors. For instance, *Histoplasma capsulatum* readily enters cells even though bound only to carbohydrates (1). The process of lectinophagocytosis also dictates internalization in response to binding of ligands to eukaryotic cell surface carbohydrates (e.g., type 1 fimbrial recognition of oligomannose) (18). Thus, no class of receptor can be said to always lead a pathogen down a given response pathway, but conversely, each receptor has a limited repertoire of responses.

Although the receptor chosen necessarily restricts the possible fates of the bound pathogen, virtually every pathogen has more than one adhesin, thereby conferring the capability to interact with more than one receptor and their attendant signal transduction systems. Thus, the outcome of an adherence interaction of a particle as complex as a pathogen is more realistically dependent not only on the identity of the receptor involved but also on the sequence in

which receptors are bound, the communication between receptors, and the state of the receptors on a target cell. This can be illustrated by the diversity of fates seen when leukocytes encounter ligand-coated particles which bind to the integrin CR3 (CD11b/CD18) (Table 1). CR3 binds to endothelia when leukocytes transmigrate from blood into tissues. Such movement necessarily means that CR3 in the front of the moving leukocyte is functioning differently from that at the back of the cell; i.e., CR3 in the front of the cell is actively holding on and CR3 in the back of the cell is letting go. Seen from this point of view, CR3 exists in at least two different states and the fate of the pathogen bound to CR3 seems to differ depending on which "activation state" CR3 is in at the time of binding. For example, particles coated with the *Leishmania mexicana* adhesin gp63 bind to CR3 but remain on the surface of the macrophage unless the cell is activated, in which case engulfment occurs (28). Another example, the *Yersinia* invasin protein, has recently been reviewed by Isberg (8). Invasin and fibronectin apparently bind to the same site on the same β1 integrins (although only fibronectin contains an Arg-Gly-Asp triplet). Despite such similarities in recognition, invasin triggers internalization, while fibronectin does not. One explanation suggests that invasin confers higher affinity binding than fibronectin and therefore more effectively promotes engulfment by lamellipods (8). While this would be sufficient to explain differential engulfment in a cell which continuously produces pseudopods, it doesn't explain why ligation of the integrin in one case induces the rearrangement of the cytoskeleton needed to produce lamellipods in a naturally nonphagocytic cell and in the other case it does not. To explain this difference, one might invoke differential abilities of the ligands to induce signal transduction from the integrin to the cytoskeleton either alone or in conjunction with other adhesins on the surface of the pathogen. Such a cascade for uptake has been described for the IpaB and IpaC proteins of *Shigella flexneri* (30).

It is particularly fascinating that pathogens recognize that receptors exist in inactive and active forms and exploit these properties. In the case of *B. pertussis*, activation of an integrin is accomplished by a cascade coordinated by two adhesins. In this system, the binding of the B oligomer of pertussis toxin to macrophage carbohydrates first up-regulates the integrin CR3. The activated CR3 then in turn binds the adhesin FHA, leading to bacterial uptake into the macrophage (37). Binding by the toxin or FHA alone leads to significantly less ingestion than in cells "primed" by preligation to the toxin. This cooperative process is analogous to the interactions between selectins and integrins in the process of leukocyte transmigration across endothelia. The binding of selectins to leukocyte glycoconjugates upregulates integrins which in turn mediate the actual transmigration of the leukocyte across the endothelium (13). Since pertussis toxin subunits have properties of selectins and FHA binds to the integrin CR3, it appears that *B. pertussis* has co-opted existing communication pathways between eukaryotic surface molecules which govern leukocyte mobility to promote its own entry into macrophages.

In view of the apparent cooperativity which is possible between bacterial ligands, it is interesting that many fimbrial adhesins are difficult to purify away from endotoxin (15). If this reflects an association of the two in the natural setting, eukaryotic cells would be expected to experience the well-known biological effects of endotoxin in conjunction with presentation of adhesins. In fact, the effects of endotoxin and adhesins are additive in the induction of inflammation in the urinary tract (12). Such an opportunity for bacterial components to alter the state of readiness of a target cell may also occur when bacterial products are released and act at a distance from the bacterial surface itself. As discussed above, evidence suggests that this is true for the secreted adhesin pertussis toxin, which prepares the way for bacterial uptake by FHA. It is interesting that such an opportunity may also arise when fimbrial subunits are sheared from the surface of bacteria (23). Carrying a carbohydrate recognition domain on the soluble fimbrial fragment, the liberated adhesin could hypothetically bind to a target cell before the pathogen itself is engaged, an action not unlike that of a hormone. Viewed in this context, bacterial lectins may eventually be proven to be free-lance biological response modifiers which can play an active part in disease (see below). This idea also strengthens the functional relationship between fimbriae and the binding oligomers of toxins, both having cell recognition properties as well as inherent biological activities. It is not unreasonable to speculate that binding oligomers left behind on the surfaces of cells after delivery of the toxic subunits continue to have biological effects (e.g., T-cell mitogenicity of pertussis toxin).

ADHESINS AS PARTICIPANTS IN INFLAMMATION ON ENDOTHELIA AND EPITHELIA

In addition to the ability of adhesins to direct leukocyte mobility and phagocytosis, several adhesins are now recognized to induce or reduce inflammation in host tissues. Rhinovirus binds to ICAM-1 on the surface of eukaryotic cells (5) and thereby down-regulates the ability of leukocytes to eliminate virus-infected cells. Conversely, adherent pathogens serve to incite manifestations of vasculitis such as Rocky Mountain spotted fever, Osler's nodes in endocarditis, and ecthyma gangrenosum. It has recently been recognized that some *Salmonella* and *E. coli* fimbriae bind to the lysine-binding kringle domain of tissue plasminogen activator, inducing the formation of plasmin which degrades extracellular matrix proteins (20). In bacterium-bound form, plasmin activity has been suggested to promote bacterial penetration through or into basement membranes. When administered intravenously, purified O75X fimbriae of uropathogenic *E. coli* deposit on the basement membrane of the glomerulus via the type IV collagen-binding domain (38). Such fimbriae persist at this location for months, suggesting that they may serve to direct host defenses to the glomerular mesangium, thus precipitating glomerulonephritis. These examples demonstrate the ability of adhesins to recruit and derange host defenses and show expanded biological activities of these proteins.

The ability of adhesins per se to induce cytokine responses in epithelial cells has not as yet been demonstrated. However, de Man et al. have shown that adherence is a requirement for the induction of interleukin 6 on renal epithelium infected with *E. coli* (2). This suggests that adhesins may join two other widely distributed bacterial components, endotoxin (17) and cell walls (25), in promoting cytokine release from eukaryotic cells, with resultant enhanced endothelial permeability and leukocyte recruitment.

IMPLICATIONS OF BIOLOGICAL ACTIVITIES OF ADHESINS FOR VACCINE DESIGN

Antibodies to adhesins have been associated with protection from colonization, thus suggesting that these molecules

are desirable components of vaccines. Since colonization is probably eliminated only when such antibodies are induced, newer subcomponent vaccines for various pathogens are likely to contain adhesins. However, the new information indicating that adhesins are biologically active or serve as homologs of native cell-cell recognition proteins raises the possibility that adhesins may need to be "detoxified" prior to inclusion in vaccines. An example of the pathology induced by adhesins mimicking host proteins is seen in mycoplasma disease in which antibodies to the adhesin bind to the Ii blood group determinant, precipitating autoimmune manifestations of the illness (14). Antibodies to FHA of *B. pertussis* also appear to cross-react with a natural homolog, this time on cerebral capillary endothelial cells (36a). The biological significance of these cases of mistaken identity will have to be clarified as the effort to make defined subcomponent vaccines matures.

SUMMARY

We take the view that adherence is not just a static process of holding hands but rather elicits a response in the targeted cell. From this point of view, adherence is an active process with an outcome. This outcome or fate is predictable only when several parameters of the host cell-adhesin interaction are known: is the adhesin acting alone or in series with other products, is the receptor up- or down-regulated at the time of ligation, which domain of the receptor is bound, and finally, which intracellular response circuits are connected to the receptor in the cell type targeted? Variations in these parameters are the basis for the ability of the adhesins of pathogens to orchestrate outcomes as disparate as simple address recognition versus actin nucleation, cytokine induction, activation of plasmin, derangement of leukocyte migration, or deposition of antibody on host cell membranes. The recognition of the relatedness of some eukaryotic and prokaryotic adhesive domains and the shared use of existing eukaryotic cell-cell interaction systems between host and pathogen suggest that the cellular interactions of interest in eukaryotic cell biology can be revealed by taking clues from the pathogens, which have studied and adapted to them the longest.

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