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MINIREVIEW

Lectinophagocytosis: a Molecular Mechanism of Recognition between Cell Surface Sugars and Lectins in the Phagocytosis of Bacteria

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INTRODUCTION

Since the turn of the century (96), it has been known that serum factors enhance the rate of uptake of microorganisms by phagocytes. The serum factors were named opsonins (from opsonos, to eat, in Greek), and the process became known as opsonophagocytosis. Over the years it has been established that the primary role of the opsonins is to provide a means of recognition between the phagocytes and their targets, e.g., bacteria (26, 38). The opsonins function by binding specifically in a lock-and-key manner to integral surface membrane molecules on the phagocytes on the one hand and to the bacteria on the other.

Two types of opsonin have been described: one is represented by the C3b and C3bi fragments of the third component of complement (C3), and the other is represented by antimicrobial antibodies (usually immunoglobulin G molecules). Opsonophagocytosis can occur in three modes. In the first, only antibodies participate by reacting via their $(Fab)_2$ combining sites with the appropriate antigenic determinants on the bacterial surface. The Fc portion of the coating immunoglobulin G molecule binds the microorganisms to the corresponding Fc receptors on the surfaces of the phagocytes. In the second mode, only the C3b or C3bi fragment of complement participates. The C3b and C3bi fragments are generated from C3 as a result of its activation by contact with certain microbial surface constituents, a process known as the alternative pathway of activation. C3b or C3bi attaches to the microbial surface covalently via thiol ester or amide bonds and to the phagocyte surface via specific receptors known as CR1 or CR3, respectively. In the third mode, both antibody and C3b (or C3bi) participate. The antibody binds to microbial surface antigens, and the antigen-antibody complexes thus formed activate the complement, either by the classical pathway or the alternative pathway, followed by deposition of C3b or C3bi onto the microbial surface. The microorganisms, which are now coated with both antibody and complement fragments, bind to the phagocytes via the receptors for both ligands. This binding is much stronger than that with either immunoglobulin G or the fragments of C3 alone.

The second mode of opsonophagocytosis has been a subject of much interest, since it can occur in a nonimmune host and, therefore, serves as an early defense mechanism against microbial infections (19). It depends on the availability of complement at the site of infection, on the ability of bacteria to activate complement by the alternative pathway and to deposit fragments of C3 on their surfaces, and on the proper orientation of the cell-bound fragments to react with the appropriate receptors on the phagocytes. These conditions are not always met. Certain sites, such as the lungs (25, 40) or renal medullae (83, 84), have low local serum opsonin concentrations which may not be sufficient to effectively opsonize many bacterial species; not all organisms activate the alternative pathway efficiently (19, 34, 64), and complement-deficient states have been reported during, e.g., the neonatal period (1, 16). Moreover, patients deficient in C3 can frequently cope with a variety of bacterial infections, irrespective of the ability of the bacteria to activate the alternative pathway.

The inescapable question is, therefore, whether phagocytosis occurs without opsonins, and if so, how. There is little doubt that the answer to the first question is yes. This is evident from in vitro studies that demonstrate phagocytosis of bacteria in opsonin-free media (17, 26, 35, 44, 70, 71, 92) and from in vivo studies that show clearance of bacteria from the lungs by alveolar macrophages (25, 40) or from the blood by the reticuloendothelial system of animals depleted of complement (13). However, the molecular basis underlying the nonopsonic recognition between bacteria and phagocytes has, for a long time, remained an enigma (30).

Several investigators have postulated that the net surface charge or the hydrophobicity of particles or bacteria determines whether they can be bound by phagocytes (88, 93), but no direct evidence for these assumptions has been obtained. It is still possible that nonspecific or ill-defined surface properties may account for the recognition by phagocytes of some particles (e.g., polystyrene latex beads). However, as pointed out by Griffin (26), recognition of most physiologically relevant particles must involve more specific mechanisms.

During the last decade, considerable evidence has accumulated showing that specific recognition between phagocytes and their targets may be accomplished by the interaction of carbohydrate-binding proteins, e.g., lectins on the surface of one type of cell that combine with complementary sugars on the surface of another in a lock-and-key manner (78, 79). This type of recognition, which also leads to phagocytosis, has been termed by us lectinophagocytosis. In the present review, we summarize the evidence for lectinophagocytosis and discuss its possible significance in defense against bacterial infections.

Lectinophagocytosis of bacteria can occur in two major modes (Fig. 1). In the first mode, bacteria which carry

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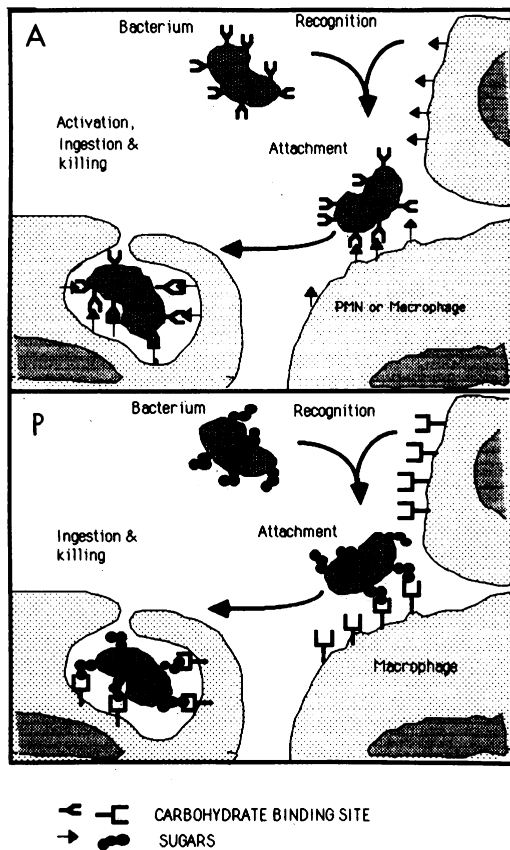

FIG. 1. Diagrammatic representation of lectinophagocytosis mediated by bacterial surface lectins which recognize corresponding sugar residues on the surfaces of phagocytes (A) and by phagocyte surface lectins which recognize corresponding sugar residues on the surfaces of bacteria (B). The lectin-sugar-mediated recognition between bacteria and phagocytic cells leads to attachment, ingestion, and killing of the bacteria by the phagocytes. PMN = human PMNL.

surface lectins bind to complementary carbohydrates on the surfaces of the phagocytic cells. In the second mode, lectins that are integral components of the phagocytic cell membrane bind to carbohydrates on the bacterial surfaces. Although other modes of lectinophagocytosis are possible, e.g., when a lectin forms a bridge between bacteria and phagocytes by binding to surfaces on both types of cells (7, 23, 31), these will not be discussed here.

METHODOLOGY

The methodology used to ascertain the involvement of lectin-carbohydrate interactions in the recognition step of phagocytosis includes procedures commonly used in studies of ligand-animal cell receptor interactions in general and of lectin-mediated adherence of bacteria to animal cells in particular (56, 80). As a first step, it requires testing the effect of a panel of sugars (usually mono- and oligosaccharides) on bacterial binding to or agglutination of the phagocytes. This step is based on the well-known hapten inhibition technique used in the study of the specificity of antibodies and lectins. Since the recognition phase of bacterial phagocytosis is followed by a series of events, such as stimulation of antimicrobial systems (e.g., oxygen burst and degranulation), engulfment, and killing of the bacteria, collectively termed phagocytosis, specific agents which prevent recognition are expected to inhibit these events, too. Control experiments should include bacteria coated with a specific antibody to examine the effect of the inhibitory sugars on opsonophagocytosis as well as isogenic mutants which lack the lectin and show no activity in the phagocytic assay. While isogenic mutants of bacteria lacking surface lectins or sugars are relatively easy to obtain, this is not the case for phagocytes deficient in a specific cell surface carbohydrate or lectin.

The finding that a sugar or a family of structurally related sugars inhibits the bacterium-phagocyte interaction at low concentrations (<0.1 mM) does not distinguish whether the lectin is on the bacteria or on the phagocytes. Such information may be obtained from inhibition experiments in which each cell type is separately pretreated with either defined polysaccharides (e.g., mannans in the case of interactions inhibited by mannose) or multivalent glycoconjugates containing the inhibitory sugar (e.g., neoglycoproteins), which should bind specifically and avidly to the cell surface lectin. In addition, important information may be obtained by examining the effect on the bacterium-phagocyte interaction of treatment of the participating cells with lectins, enzymes, or other agents which modify surface carbohydrates. In all assays, the possibility that more than one type of surface lectin is involved should be considered. In such cases, a combination of sugars should be more inhibiting than the individual ones. Recognition mediated by more than one type of lectin may be the result either of coexpression on the cell surface of multiple types of lectin or of the presence of heterogeneous populations of cells, each bearing a different lectin.

Lectinophagocytosis involves integral lectins and sugars which may not always be expressed on the surfaces of bacteria or phagocytes. Variations in the surface expression of bacterial lectins or sugars are well known and may occur among strains within the same species or within the same strain under different growth conditions (54). Likewise, the source and type of phagocytic cells may give rise to a heterogeneous population with regard to the expression of surface receptors or lectins (14). It is therefore necessary to perform independent assays to establish the percentage of the total test population of bacteria or phagocytes which expresses certain lectins or sugars. This may be done by performing binding assays with glycoconjugates of known structure and plant lectins of defined sugar specificity.

LECTINOPHAGOCYTOSIS MEDIATED BY BACTERIAL SURFACE LECTINS

During the past decade many bacterial species have been found to express on their surfaces a hemagglutinin(s) or lectin(s) through which the organisms can bind to animal cells (49, 78, 79). Most of these hemagglutinins and lectins are in the form of fimbriae or pili and are specific for either simple or complex sugars. A minor fimbrial subunit distinct from the major fimbrial subunit is usually responsible for sugar binding (45, 47, 53, 91). In some cases the minor subunit is at the tip of a fimbria (51). Although purified fimbriae also bind to different cells in a sugar-specific manner, in most cases they do not act as agglutinins unless they have been cross-linked, presumably because they are monovalent (51; C. C. Brinton, *Proceedings of the IVth International Symposium on Pyelonephritis*, in press). Many of the hemagglutinins serve as adhesins which bind the bacteria to animal cells, in particular, to epithelial cells of mucosal

TABLE 1. Lectinophagocytosis mediated by bacterial cell surface lectins

Type and location of lectin	Sugar specificity	Bacterium	Phagocytic activity assayed	Reference(s)
Type 1 fimbriae	Mannose	*Escherichia coli*	Attachment	8, 9, 11, 12
			Ingestion	59, 60, 63
			Stimulation	72, 82, 86, 90
		Klebsiella pneumoniae	Attachment	6
			Ingestion	6
		Salmonella typhimurium	Association	8
Type 2 fimbriae	Lactose	*Actinomyces* spp.	Killing	73
Type P fimbriae	Galα4Gal	*Escherichia coli*	Stimulation of Galα4Gal-coated beads	90
Outer membrane	Glucosamine	*Neisseria gonorrhoeae*	Stimulation	68

surfaces (49). In a number of cases it was found that bacterial surface lectins recognize a particular sugar on the phagocytic cell surface and mediate phagocytosis of the bacteria (Table 1). The cells with which bacteria interact via their surface lectins include different classes of phagocytes, such as human polymorphonuclear leukocytes (PMN) (11, 44, 59, 60, 63, 68, 72, 73, 83, 84, 86, 90) and peritoneal macrophages from mice (8, 9), rats (12), and humans (G. Boner, M. Rodriguez-Ortega, and N. Sharon, Abstr. IVth Congr. Int. Soc. Peritoneal Dialysis, 1987, p. S-7). Frequently, lectin-mediated binding to phagocytes leads to stimulation, ingestion, and killing of the bacteria. Whenever tested, specific sugars inhibit these activities induced by nonopsonized but not opsonized bacteria, reemphasizing that the biological activities are the consequence of the lectin-mediated adherence. When bacteria bind poorly to phagocytes because the latter lack the appropriate receptor sugar, lectinophagocytosis can be induced by precoating the phagocytes with suitable carbohydrates. This has been demonstrated for type P-fimbriated *Escherichia coli*, which binds poorly to human PMNL since the latter are deficient in Galα4Gal-containing glycolipids, which the type P lectin recognizes. (The abbreviations for monosaccharides are as follows: Gal, D-galactose; GalNAc, *N*-acetyl-D-galactosamine; Glc, D-glucose; GlcNAc, *N*-acetyl-D-glucosamine; Man, D-mannose.) However, after the human PMN were coated by globotetraosylceramide (GalNAcβ3Galα4Galβ4Glcβ-CerCer, ceramide]), there was increased binding of the bacteria to the phagocytes, followed by their activation, as evidenced by the induction of chemiluminescence (90).

Lectinophagocytosis of *E. coli* mediated by the mannose-specific lectin associated with type 1 fimbriae has been most thoroughly investigated (78, 81). Based mainly on inhibition studies of yeast (*Saccharomyces cerevisiae*) and erythrocyte agglutination, it has been shown that this lectin is specific for oligomannose and hybrid oligosaccharides of the type commonly found in N-linked carbohydrate units of membrane and soluble glycoproteins (21, 52). The evidence that the recognition of type 1-fimbriated *E. coli* by phagocytes is mediated by interaction of the fimbrial lectin with mannose-containing glycoproteins on the surfaces of the phagocytes has several bases: (i) the specific pattern of inhibition observed for the bacterium-cell interaction by various oligosaccharides was the same for phagocytic and nonphagocytic (20, 21) target cells; (ii) mannose or its derivatives did not inhibit the phagocytosis of opsonized bacteria (9, 83); (iii) a very good correlation was found between the mannan-binding activity of the bacteria and the extent of their attachment to mouse peritoneal macrophages (8); (iv) pretreatment of type 1-fimbriated bacteria with yeast mannan inhibited their attachment to mouse and human phagocytes, whereas pretreatment of the phagocytes did not have such an effect (9), indicating that the receptor for the bacterial lectin is on the surface of the phagocytes; and (v) latex particles coated with purified type 1 fimbriae stimulated human PMN, and this activity was inhibited by mannose (24). Since the only mannose-containing compounds in animal membranes are glycoproteins (67), the receptor for mannose-specific bacteria must belong to this class.

Some of the properties of the mannose-specific lectinophagocytosis of *E. coli* are shown in Fig. 2 to 4. This lectinophagocytosis is quantitatively comparable to opsonophagocytosis in the attachment and stimulation phases. The rate of ingestion, however, varies among different strains or conditions (59, 60). Ingestion of *E. coli* attached to human PMNL via mannose-specific lectins was observed by electron microscopy: bacteria were found within typical intracellular vacuoles (72, 83). Furthermore, ingestion of mannose-specific *E. coli* and *Klebsiella pneumoniae* was confirmed by assays with agents (e.g., dyes or antibodies) which distinguish between externally attached and ingested bacteria (6, 59, 60). The specific inhibition of both attachment and ingestion by methyl α-mannoside strongly suggests that receptors for the type 1 fimbrial lectin are involved in the

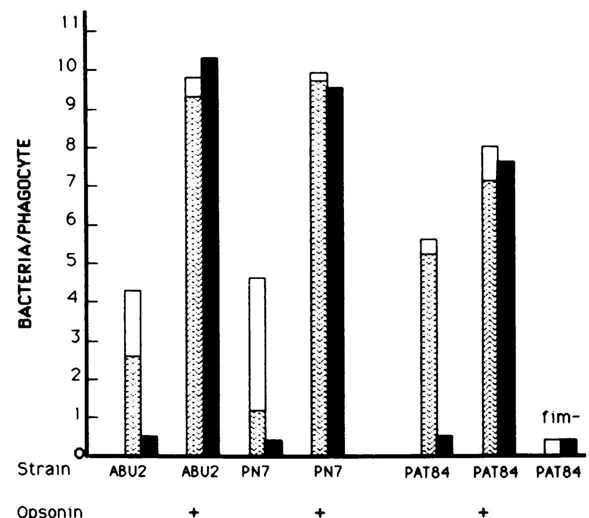

FIG. 2. Lectinophagocytosis and opsonophagocytosis of mannose-specific type 1-fimbriated and nonfimbriated (fim⁻) *E. coli* strains. Phagocytosis is expressed as the number of bacteria per phagocyte. Symbols: open bars, association of opsonized (antibody-coated) or nonopsonized bacteria; hatched bars, ingested bacteria; solid bars, effect of methyl α-D-mannoside on association. Data were adapted from studies which used (i) human PMNL and the ABU2 and PN7 strains of *E. coli* (59, 60) and (ii) mouse peritoneal macrophages and the PAT84 strain of *E. coli* (11).

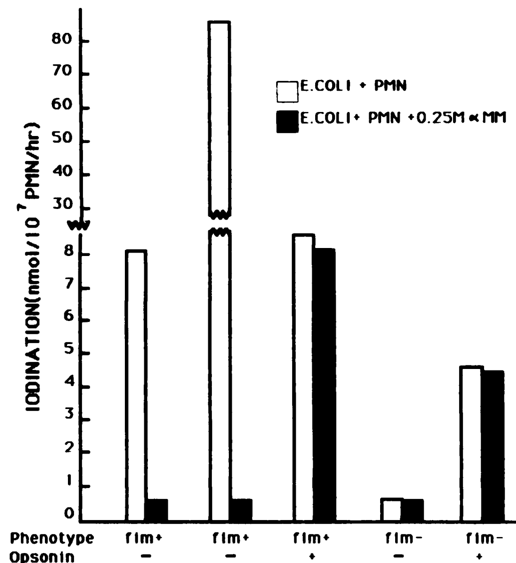

FIG. 3. Protein iodination by type 1-fimbriated (fim^+) and nonfimbriated (fim^-) *E. coli* in human PMNL (PMN). Cross-linking of fimbriae was done with $F(ab)_2$ antifimbrial antibodies or glutaraldehyde, and opsonization was performed by coating the bacteria with antisomatic antibodies. Broken bar represents results with cross-linked fimbriae. Data were adapted from Perry et al. (63). αMM, Methyl α-D-mannoside.

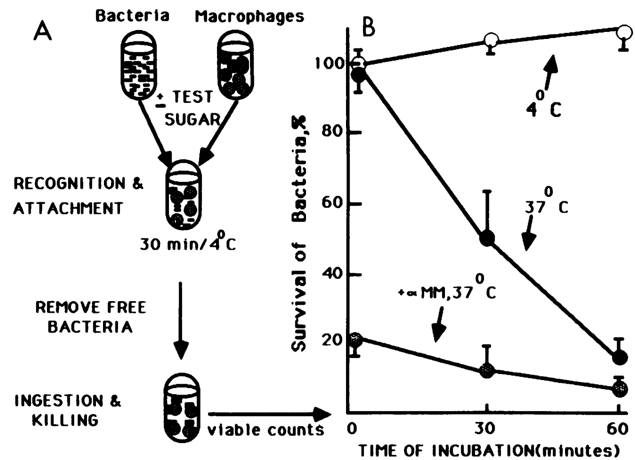

FIG. 4. Schematic diagram (A) of an assay of intracellular killing of mannose-specific type 1-fimbriated *E. coli* by mouse peritoneal macrophages. A suspension of washed mouse peritoneal macrophages was mixed with a bacterial suspension containing 2.5% methyl α-D-mannoside (αMM) at a ratio of 1:100. After incubation at 4°C for 30 min, the mixture was washed free of nonattached bacteria by differential centrifugation, suspended in buffer, and shifted to either 37 or 4°C. Aliquots were withdrawn at various times, diluted in distilled water to disrupt the macrophages, and cultured on agar plates for CFU. The results (B) are expressed as percent survival. Control assays were performed without methyl α-D-mannoside. The results show that the number of bacteria associated with macrophages at zero time was markedly inhibited by the sugar, suggesting that a significant number of bacteria were bound to the macrophages via the mannose-specific lectin. Killing was temperature dependent and was insignificant at 4°C, suggesting that the ingestion and killing of the bacteria were mediated by the mannose-containing receptor on the surfaces of the phagocytes. Data were from M. Pocino, I. Ofek, and N. Sharon (unpublished observations) and are similar to those obtained elsewhere (83, 84).

ingestion process. There is evidence to suggest that constituents other than the type 1 fimbriae which modify the physicochemical surface properties of the bacteria may interfere with ingestion. Thus, ingestion of type 1-fimbriated *E. coli* expressing negatively charged K antigen was much slower than that of type 1-fimbriated *E. coli* expressing a hydrophobic surface and a weak negative charge, although the extent of mannose-specific attachment to phagocytic cells of both strains was the same (59, 60). Mannose-specific attachment of *E. coli* to mouse peritoneal phagocytes with diminished ingestion can be induced by growing the bacteria in sublethal concentrations of β-lactam antibiotics (8), which cause the formation of filaments and affect the expression of type 1 fimbriae (55). Some results for association and ingestion are shown in Fig. 2.

Stimulation of antimicrobial systems in phagocytes interacting with the surfaces of type 1-fimbriated *E. coli* was described by several investigators. An increase in chemiluminescence (11, 12, 42, 86), protein iodination (63), and lysozyme release (42) were among the activities observed with human PMN and rat macrophages. Whenever tested, mannose or its derivatives inhibited these activities, and mutants or strains which lacked the fimbrial lectin failed to induce an increase in these activities. Examples of typical results showing stimulation are shown in Fig. 3. Maximum stimulation of antimicrobial systems in phagocytes appears to require cross-linking of type 1 fimbriae. Such cross-linking of the fimbrial lectin on the bacterial surface potentiates the stimulation of antimicrobial systems in phagocytes, probably by causing aggregation of the corresponding receptors on the phagocytic cells (63, 86). Aggregation of surface receptors by lectins is believed to be important for other membrane-initiated intracellular events of leukocytes (10, 33, 65). However, enhanced stimulation, which depends on clustering of receptors, may not necessarily be followed by increased internalization of the organisms.

Subsequent to internalization via mannose-containing receptors, bacteria are often killed by phagocytes (59, 83). Hence, the rate of ingestion is the limiting factor which affects the rate of killing (59). Nevertheless, attached mannose-specific *E. coli* are able to trigger the release of antimicrobial agents, resulting in extracellular bacterial killing (59). A typical rate of killing of *E. coli* attached to mouse peritoneal macrophages via a mannose-specific lectin is shown in Fig. 4.

The mannose-specific lectins are not always associated with type 1 fimbriae; in certain strains they may be associated with the cell wall (18). Such nonfimbriated strains may undergo mannose-specific lectinophagocytosis to a similar extent as do fimbriated strains (12, 60).

Three surface glycoproteins designated as gp150, gp100, and gp70/80 have recently been isolated from membranes of human PMN by affinity chromatography on a column of immobilized type 1 fimbriae of *E. coli* (69). These glycoproteins may be the receptors mediating lectinophagocytosis of type 1-fimbriated *E. coli*. Two of the receptors, gp150 and gp100, may be identical with the α and β subunits of Mac-1, which is the receptor for C3bi (3, 87). Although more data are required, it is tempting to speculate that mannose-specific lectinophagocytosis is mediated by the same receptor that functions in opsonophagocytosis. If this is so, the type 1 fimbriae bind to the mannose-containing carbohydrate moieties of the C3bi receptor while C3bi binds to the peptide backbone of the receptor.In this regard it is worthwhile to mention that phagocytosis of erythrocytes induced by wheat germ agglutinin is mediated by the carbohydrate moiety of

TABLE 2. Survival of fim$^+$ and fim$^-$ strains or isogens in phagocyte-rich and -poor sites following infection with mixed strains

Organism	Animal	Route of infection	Site of infection	Level of phagocytes at infection site	Predominant phenotype	Reference(s)
Escherichia coli	Mouse	Intravesicular	Kidney	Rich	fim$^-$	28, 74
			Bladder	Poor	fim$^+$	28, 74
		Oral	Blood	Rich	fim$^-$	27
			Oral cavity	Poor	fim$^+$	27
		Peritoneal	Peritoneum	Rich	fim$^-$	2
	Rat	Intravesicular	Kidney	Rich	fim$^-$	43
Klebsiella pneumoniae	Mouse	Intravesicular	Kidney	Rich	fim$^-$	41
			Bladder	Poor	fim$^+$	41

the Fc receptor (50). In contrast, coating encapsulated *E. coli* with concanavalin A promotes attachment to phagocytes but is not sufficient to trigger ingestion of the coated bacteria (31). These findings are consistent with the notion that the triggering of ingestion requires the organization and coordination of contractile elements, leading to movement of the phagocytic membrane toward engulfment of the bacteria (30). The nature of the receptors on the phagocytic surface and the presentation of the lectins on the bacterial surface determine whether attachment to phagocytic cells will lead to the internalization and killing of the attached bacteria. The possibility, however, that putative constituents other than the receptors for mannose-specific lectins on the surfaces of the phagocytes play a role in the internalization of the bacteria cannot be excluded. At this stage, we may conclude that mannose-specific lectinophagocytosis is dependent on the interaction between the fimbrial lectin and its receptor, as much as opsonophagocytosis is dependent on the interaction between C3b (or C3bi) or Fc and its respective receptor on the phagocytic surface.

Lectinophagocytosis has recently been demonstrated to occur with type 2-fimbriated *Actinomyces* species (73). The fimbrial lectin of these bacteria is specific for β-galactosides such as lactose, Galβ4GlcNAc, and Galβ3GalNAc. Attachment, internalization, and killing of *Actinomyces viscosus* TIV4 and *Actinomyces naeslundii* WVU45, both carrying type 2 fimbriae, by human PMN was blocked by methyl β-galactoside and lactose, whereas cellobiose and methyl α-galactoside were ineffective. Phagocytosis was markedly enhanced (to over 95%) by pretreating the human PMN with sialidase, which unmasks galactose residues on oligosaccharide units of glycoproteins and glycolipids. Only bacteria expressing the galactose-specific lectin were phagocytosed in the absence of serum; phagocytosis of mutants of *A. viscosus* TIV4 and *A. naeslundii* WU45 deficient in type 2 fimbriae was minimal or absent.

DOES LECTINOPHAGOCYTOSIS BY BACTERIAL SURFACE LECTINS OCCUR IN VIVO?

Whereas the occurrence of lectinophagocytosis mediated by bacterial surface lectins has been established unequivocally in vitro, little is known about its occurrence in vivo, and most of the available evidence is circumstantial.

Indirect evidence that mannose-specific lectinophagocytosis may take place in vivo was obtained in experimental infections with mixed bacterial strains (or isogens), one of which is fimbriated and expresses mannose-specific lectin activity (designated fim$^+$) and the other of which is not fimbriated and does not express this activity (designated MS fim$^-$). Such experiments revealed that whenever the organisms reached phagocyte-rich sites, the MS fim$^-$ phenotype survived, while at phagocyte-poor sites, the MS fim$^+$ phenotype survived, irrespective of the bacterial species, experimental animals used, or the route or site of the infection (Table 2). The results were interpreted as being due to the selective survival of the fim$^+$ phenotype on mucosal surfaces, since it is capable of binding to epithelial cells, and the selective survival of the fim$^-$ phenotype in deep tissues (e.g., kidneys or the peritoneal cavity), in which the fim$^+$ phenotype is eliminated by the macrophages and/or human PMN present in these tissues. It was suggested that phase variation, a random on-off switching process that allows the cells to alternate between fimbriated and nonfimbriated states, is a virulence trait of type 1-fimbriated *E. coli* (54, 57) and other fimbriated species (54, 83, 85) important for the survival of the organisms in tissues.

If mannose-specific lectinophagocytosis can occur in vivo, it may be inhibited by soluble mannose-containing glycoconjugates. One line of evidence comes from studies of the effect on such lectinophagocytosis of Tamm-Horsfall urinary glycoprotein (39), which is the most abundant glycoprotein in normal human urine and which contains N-linked oligomannose units (77). It is not surprising, therefore, that it binds to type 1 fimbriae and that this binding can be inhibited by methyl α-mannoside. Bacteria coated with Tamm-Horsfall glycoprotein were less susceptible to mannose-specific lectinophagocytosis than were uncoated bacteria. The glycoprotein did not affect phagocytosis in the presence of serum. It was suggested that these observations may account for the virulence of *E. coli* in the upper urinary tract (e.g., renal medulla) of susceptible hosts, in whom cleansing mechanisms are ineffective in eradicating the bacteria while local serum activity is low and Tamm-Horsfall glycoprotein reaches high concentrations (39).

LECTINOPHAGOCYTOSIS MEDIATED BY MACROPHAGE SURFACE LECTINS

Starting in the late 1960s with the work of Ashwell and co-workers on the blood clearance and endocytosis of glycoproteins mediated by receptors on the surfaces of liver cells (Kupffer cells and hepatocytes), at least three types of lectin expressed on the surfaces of tissue macrophages have been isolated and characterized (4, 5). All three are glycoproteins. The mannose-type lectin (or GlcNAc/Man lectin) in tissue macrophages (e.g., Kupffer cells and alveolar macrophages) has a molecular weight of 175,000 (95). It is specific for *N*-acetylglucosamine, mannose, glucose, and L-fucose. The galactose-type lectin is found in Kupffer cells,

TABLE 3. Inhibition of blood clearance and phagocytic attachment of bacteria by sugars and neoglycoproteins[a]

Inhibitor[b]	% Inhibition of blood clearance in mice of:			% Inhibition of phagocytic attachment[c] of type II group B streptococci
	E. coli 025[e]	Group B streptococci		
		Type 1b (desialylated)	Type II	
Me-Gal or Gal-BSA	<20	>70	<20	23
Me-Man or Man-BSA	>70	>20	<20	44
Me-Fuc or Fuc-BSA	>70 (<20)[d]	<20	<20	ND[e]
Me-Glc or Glc-BSA	>70	ND	ND	40
Gal-BSA and Glc-BSA	ND	ND	>70	71 (0.5)[d]

[a] Data were adapted from references 61 and 62. In these studies, the nature of the sugars exposed on the surfaces of the bacteria was established by agglutination experiments with three lectins. *E. coli* was agglutinated by concanavalin A (specific for mannose and glucose), desialylated streptococcus group B type 1b was agglutinated by *Ricinus communis* agglutinin and peanut agglutinin (specific for galactose), and streptococcus group B type II was agglutinated by all three lectins.

[b] Abbreviations used: Me-Gal, methyl α-galactoside; Me-Man, methyl α-mannoside; Me-Fuc, methyl α-fucoside;and Me-Glc, methyl α-glucoside. The inhibition of *E. coli* blood clearance was measured with the respective methyl α-glycosides, and that of streptococci was measured with the BSA neoglycoprotein derivatives.

[c] Thioglycolate-elicited mouse peritoneal macrophages were used.

[d] Values in parentheses were obtained with bacteria opsonized with a specific antibody. the degree of attachment of opsonized type II streptococci was seven times that of nonopsonized type II streptococci.

[e] ND, Not done.

hepatocytes, and a subpopulation of peritoneal macrophages. It has a molecular weight of 41,000 or 46,000 (76) and is specific for *N*-acetylgalactosamine and galactose. Although the galactose-type lectin has been studied mostly in rats, its expression on the surfaces of mouse macrophages may be inferred from studies on the blood clearance of neoglycoproteins in mice (66). The fucose-type lectin is found in liver cells and is specific for L-fucose (4).

The idea that the bacterial surface sugars are important for nonopsonic binding to macrophages was first suggested by Weir and colleagues (22, 58). The sugar specificity of the bacterium-macrophage interaction, however, was not defined, and the researchers did not refer to any of the macrophage lectins as being involved in the phagocytosis of particular strains of bacteria. Warr (94) was the first to implicate the mannose-type lectin of lung macrophages in the binding of mannan-containing yeasts.

Since bacteria are cleared from the circulation by liver phagocytes (46), Perry et al. (61) and Perry and Ofek (62) studied the blood clearance of gram-negative (nonfimbriated *E. coli*) and gram-positive (group B streptococci) bacteria in mice to establish whether macrophage lectins are involved in the sequestration of the bacteria by the liver. The bacteria resisted killing in the whole blood of mice in vitro and were sequestered in the liver after intravenous injection. Several lines of evidence were obtained to implicate the interaction between liver lectins and bacterial surface sugars as determinants of recognition in the blood clearance of the bacteria in mice (Table 3). First, the pattern of sugar derivatives and neoglycoproteins inhibiting the blood clearance of the bacteria corresponded to the sugar residues exposed on the surfaces of the organisms and to the sugar specificity of the liver lectins involved. Second, inhibitory sugars did not affect the blood clearance of *E. coli* cells precoated with antibodies. Third, in vitro studies in which *E. coli* was mixed with membranes of liver cells from mice resulted in a rapid coaggregation which was inhibited only by those sugars that had been shown to inhibit clearance of the bacteria from the blood (62). Lipopolysaccharide extracted from the test bacteria also inhibited coaggregation (62), suggesting that the sugars involved in the interaction reside in this amphipathic surface molecule.

To obtain more direct evidence that lectins on the surfaces of macrophages mediate the binding of bacteria, the attachment of type II group B streptococci expressing both galactose and mannose residues on their surfaces to a monolayer of thioglycolate-elicited macrophages was studied. As with the blood clearance of these organisms, only a combination of neoglycoproteins containing galactose and mannose (Gal-bovine serum albumin [BSA] and Man-BSA) strongly inhibited the attachment of the bacteria to the macrophage monolayer (Table 3). The specificity of the neoglycoproteins was further shown by their inability to inhibit the attachment to phagocytes of bacteria coated with antibodies (Table 3). Lectin-mediated attachment to thioglycolate-elicited peritoneal macrophages was considerably lower than attachment mediated by the Fc portion of the antibodies coating the bacteria (61). This result could be attributed to either a low proportion of cells expressing galactose- and mannose-type lectins (10 to 20%) as compared with those expressing Fc receptors or to the fact that the efficiency of attachment to elicited macrophages via the macrophage surface lectins is much lower than that via Fc receptors. It is also possible that in the elicited macrophage population there are macrophages expressing more than one type of surface lectin or subpopulations of macrophages each expressing a different type of surface lectin. It is now clear that resident macrophages are heterogeneous with respect to phagocytic ability (14) and that the expression of the macrophage lectins, especially the mannose type, is dependent on the degree of differentiation of the mononuclear phagocytes (36, 82). As far as the in vivo situation is concerned, it appears that the population of macrophages in the liver is sufficient to eliminate most of the nonopsonized type II group B streptococci from the blood via one type of lectin, since only a combination of two types of neoglycoprotein inhibited blood clearance (Table 3).

Although there is no direct proof that the binding of bacteria to macrophage lectins is followed by ingestion and killing of the organisms, recent studies show clearly that both the galactose-type (37, 75) and the mannose-type (36, 89) lectins are capable of mediating the internalization of particles coated with sugars or glycoproteins. For example, promastigotes of *Leishmania* spp. bind and penetrate peritoneal macrophages in vitro via the interaction of sugars on the surfaces of the parasites with the mannose-type lectin on the surfaces of the phagocytes (15, 29). It has been suggested that the macrophage lectins are capable of functioning as receptors for lectinophagocytosis not only in vitro but also in vivo.

OTHER TYPES OF LECTINOPHAGOCYTOSIS

We have presented evidence to support the concept that cell-associated lectins or sugars on the surfaces of bacteria or phagocytes interact with each other, leading to phagocytosis of the microorganisms. It is possible, however, that lectin-sugar interactions between the surfaces of the two types of cells are mediated by soluble lectins or glycoconjugates which act as bridging molecules in a way similar to that which occurs in opsonophagocytosis. Such a possibility was indicated mainly with plant lectins that can "bridge" be-

tween the microorganisms and the phagocytes by interacting with sugar residues on the surfaces of both types of cell (7, 23, 30).

CONCLUDING REMARKS

The major conclusions arising from the evidence presented here are that lectin-carbohydrate interactions may act as a nonopsonic mechanism of phagocytosis and that this mechanism may function in vivo. Thus, there appear to be three principal receptor-mediated mechanisms that are responsible for the recognition, binding, and in vivo clearance of microorganisms (and perhaps also other foreign particles) by phagocytes: (i) lectin-carbohydrate interactions between integral constituents of the cell surfaces, (ii) bridging via immunoglobulin G molecules, and (iii) bridging via C3b or C3bi molecules.

The phagocytic process initiated by the first mechanism was termed lectinophagocytosis to distinguish it from the two other mechanisms that require serum opsonins as bridging molecules and that are known as opsonophagocytosis. It is possible, however, that other types of interactions are responsible for the binding of bacteria to phagocytes, as many bacterial species can undergo phagocytosis in the absence of opsonins. The term interactions of unknown mechanisms, rather than nonspecific, may be applied, therefore, to such nonopsonic phagocytosis until the surface molecules responsible for cell-cell interactions are identified.

Since amebae recognize and ingest bacteria via lectin-carbohydrate interactions (48), lectinophagocytosis of microorganisms by mammalian phagocytes may represent a conservation of a primitive system of host defense which acts against many saprophytic or opportunistic microorganisms encountered by humans and animals. Lectinophagocytosis may be of particular importance in the defense against bacteria which evade opsonophagocytosis. This may be the case for bacteria that do not activate the alternative pathway of complement or for bacteria that invade serum-poor sites or a complement-deficient host. However, bacteria may also possess the ability to escape lectinophagocytosis. This can occur, for example, by loss of the fimbrial lectin as a result of phase variation (32, 41, 54, 57). In addition, lectinophagocytosis may be inhibited by host factors, as indicated by the observation that phagocytosis of mannose-specific *E. coli* is inhibited by Tamm-Horsfall glycoprotein present in the urinary tract (39). Also, blood clearance of bacteria by the mannose-type lectin of liver macrophages may be blocked by high concentrations of glucose in the blood, such as those present in diabetes. In general, high local concentrations of soluble glycoconjugates bearing sugars specific for cell-associated lectin may render a host susceptible to infection by bacteria whose clearance by phagocytes is dependent on this lectin.

It is tempting to speculate that opsonophagocytosis may have developed in mammals as a potent defense against infections caused by bacteria which survived throughout evolution by evading lectinophagocytosis. Consequently, opsonophagocytosis and lectinophagocytosis seem to act as complementary processes in providing protection against invading microorganisms.

Further studies on the lectinophagocytosis process in vitro and in vivo should lead to the definition of conditions which render a host susceptible to certain bacterial infections on the one hand and to a better understanding of the mechanisms through which organisms evade lectinophagocytosis on the other hand. Such studies may lead to a more knowledgeable approach in preventing or treating bacterial and other microbial infections.

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