MINIREVIEW

Recognition of Bacterial Surface Polysaccharides by Lectins of the Innate Immune System and Its Contribution to Defense against Infection: the Case of Pulmonary Pathogens[▽]

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Many pathogenic bacterial species are classified into serological types, distinguished by their carbohydrate-rich surface antigens. These antigens are referred to as serotypic epitopes or glycoepitopes. Glycoepitopes are most commonly associated with capsular polysaccharides (CPS) or the O-antigen domains of bacterial lipopolysaccharides (LPS).

The association of specific bacterial serotypes of a given genus with defined clinical infections is a common phenomenon that applies to a variety of gram-negative bacteria and gram-positive bacteria. As discussed below, of the 77 distinct capsular serotypes in the species *Klebsiella pneumoniae*, only 25 account for most pulmonary and blood infections (12). Likewise, of the more than 90 capsular serotypes of *Streptococcus pneumoniae*, only 23 account for most infections, and these are included in the current capsular vaccine (25).

The surfaces of the pulmonary pathogens *Klebsiella pneumoniae* and *Streptococcus pneumoniae* are coated with a variety of glycoconjugates that confer specific properties. For example, the polysaccharide capsules enable these pathogens to resist phagocytosis. In a few cases, it has been argued that serotype-associated differences in capsular size contribute to virulence and the high frequency of isolation. However, there is no satisfactory explanation why only a limited number of capsular serotypes are responsible for most infections (12, 25).

Because lectins are important components of the lung's innate immune system, it is reasonable to hypothesize that differences in the frequencies of isolation of specific serotypes in the setting of pneumonia are in part determined by the recognition, or the lack of recognition, of their corresponding glycoepitopes by lectins. We propose that the lack of recognition of glycoconjugates by one or more lectins of the lung contributes to the high frequency of isolation from pneumonia patients of the pulmonary pathogens bearing reactive glycoepitopes. Conversely, lectins that recognize serotype-specific

glycoepitopes contribute to the eradication of these serotypes, resulting in a lower frequency of their isolation from clinical samples.

In this review, we first correlate the sugar specificities of several types of lung lectins with the glycoconjugates on the surfaces of selected pulmonary pathogens. We then briefly describe in vitro data that suggest mechanisms through which the lung C-type lectins contribute to the elimination of specific glycoepitope-bearing serotypes. Finally, we review available evidence supporting our hypothesis that the high frequency of isolation of serotypes bearing a specific glycoepitope results from the ability of these serotypes to evade recognition by lectins of the innate immune system.

PULMONARY LECTINS OF THE INNATE IMMUNE SYSTEM

During the last 3 decades, there has been intensive research on animal lectins (59, 90). Although lung lectins play a variety of homeostatic roles (38, 89), considerable research has focused on the contributions of several lectins to the innate, natural defense system of the lung against pulmonary pathogens (6, 9, 11, 59, 67, 95, 97).

Host defense lectins can be conveniently categorized as cell associated or secreted. The pulmonary cell-associated lectins are expressed primarily by macrophages and/or dendritic cells and include the mannose/N-acetylglucosamine (GlcNAc)/fucose receptor (MR), DC-SIGN, and Dectin-1 (18, 58, 59, 87, 88). All of these proteins are members of the C-type lectin family and show calcium-dependent interactions with a variety of carbohydrate ligands. Dectin-1, which binds to β -glucan, primarily contributes to the defense against fungi and is not discussed further (88). The secreted lung lectins include at least two distinct families of proteins with collagenous domains: the collectins, which include surfactant proteins A and D (SP-A and SP-D), and ficolins (42, 49, 69). Both are synthesized by respiratory epithelial cells and secreted into the distal airways and air spaces of the lung. SP-D, in particular, is also expressed more proximally in the respiratory tract.

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MR. The macrophage MR (also known as MMR or CD220) has been studied extensively with respect to its role in host defense (14, 45, 53, 58, 59, 68, 89, 94). It is expressed as a transmembrane glycoprotein with eight sequential, C-type, carbohydrate binding domains that can mediate the binding and uptake of glycoconjugates (87). Based on competitive-inhibition studies, the MR shows a preference for mannose, *N*-acetylglucosamine, and fucose (87). At least in vitro, the MR can mediate nonopsonic (lectino-)phagocytosis of bacteria by recognizing corresponding sugar residues on the bacterial surface (69).

DC-SIGN. DC-SIGN is a C-type lectin that is expressed on the membranes of macrophages and dendritic cells. It binds carbohydrates found on pathogenic viruses, bacteria, and fungi (1, 59), but it also recognizes carbohydrates expressed on host cells. Although it can bind to a variety of carbohydrate structures, mannose-rich glycans and other mannose-rich carbohydrates are well-recognized microbial targets with which DC-SIGN interacts. The multimerization of DC-SIGN at the cell surface is probably required for high-affinity ligand binding (3, 62).

Lung collectins. SP-A and SP-D are assembled as oligomers of trimeric subunits stabilized by amino-terminal disulfide cross-links. SP-A most commonly occurs as a hexamer of trimers (octadecamer), and SP-D often occurs as a tetramer of trimers (dodecamer). These lectins interact with a wide variety of microorganisms, as well as with phagocytic cells (9, 10, 82, 90, 97). In addition, the levels of lung collectins often increase following microbial challenge (76). Mice lacking the SP-A gene show increased bacterial proliferation, more-intense lung inflammation, and increased dissemination following challenge with a variety of bacteria (21, 28, 39, 49–51). SP-D-deficient mice exhibit a more complex phenotype (4, 40). However, they also show a decreased uptake of bacteria by macrophages and an altered inflammatory response to bacterial challenge (21, 51). Although SP-A and SP-D are synthesized by type II and bronchiolar epithelial cells, SP-D is found in many other tissues, including salivary glands, where it could interact with potential pulmonary pathogens that initially colonize the upper respiratory tract (55).

Ficolins and other lectins. The family of ficolins consists of three members, namely, L-, H-, and M-ficolins (17, 54). H- and M-ficolins are produced in the liver and secreted into serum but are also secreted by bronchial epithelial and type II alveolar cells (17). Like the collectins, ficolins contain collagen-like, N-terminal sequences and assemble into oligomeric structures. Carbohydrate binding is mediated by the C-terminal, fibrinogen-like domains. Ficolins bind to acetylated molecules, including *N*-acetylgalactosamine and *N*-acetylglucosamine. Although H-ficolin bound to a strain of *Aerococcus viridans*, there was no binding to the strains of *S. pneumoniae*, *Staphylococcus aureus*, or *Escherichia coli* tested (42). The role of ficolins in host defense is attributed primarily to their ability to activate complement via the lectin pathway (17). There are other lectins expressed in the lung, including members of the galectin family of S-type lectins, which show a preference for β -galactosides. Although some microbial interactions have been described, their role in innate immunity is still unclear. Because little is known about the interactions of ficolins and galectins

with specific bacterial serotypes, our discussion of secreted lectins emphasizes the lung collectins SP-D and SP-A.

INTERACTIONS OF C-TYPE LECTINS WITH BACTERIA

Lung C-type lectins can interact with a wide variety of extracellular and intracellular bacterial pathogens (Table 1). The current review will focus on interactions with extracellular bacteria.

The interaction of lung lectins with bacterial surface glycoepitopes can protect the host from microbial infections in a number of ways (Table 2). Bacterial binding or agglutination can inhibit epithelial adhesion and colonization. Enhanced killing can occur by enhancing phagocytosis, either directly via cell-associated lectins (MR or DC-SIGN) or indirectly via collectins. The collectins can also opsonize certain bacteria with resultant enhanced killing. In some cases, the enhancement of uptake by SP-D has been attributed to bacterial aggregation. The binding of SP-A and SP-D to bacteria can also mediate the killing of some organisms via permeabilization of the bacterial membrane. In addition, opsonized bacteria can trigger macrophages to secrete cytokines and other mediators that signal the presence of the pathogen, resulting in the rapid recruitment of inflammatory cells to the site of infection and the activation of other antimicrobial defenses (23). For example, neutrophils and monocytes that are recruited to the site of infection may secrete reactive oxygen radicals, antimicrobial peptides, and nitrogen radicals. While these activities can enhance the eradication of the pathogen, an overly intense or prolonged response can lead to an acute or chronic inflammatory-disease state.

KLEBSIELLA GLYCOEPITOPES

Whereas most of the extracellular pathogens listed in Table 1 were studied with only one or two of the C-type lectins, *Klebsiella pneumoniae* has been extensively characterized with respect to its interactions with the MR, SP-A, and SP-D. Moreover, those studies employed strains belonging to various serotypes previously shown to be isolated with high or low frequencies from clinical specimens. Thus, *Klebsiella* provides a unique opportunity to examine our hypothesis.

Most *Klebsiella* infections are nosocomial (73, 80). As an opportunistic pathogen, *Klebsiella* attacks primarily immunocompromised individuals who are hospitalized and have severe underlying diseases. Depending on the type of infection and study, their prevalence ranges from 3% to 17% of all such infections. This places them among the eight most important pathogens in hospitals, second only to *E. coli* as the most common cause of gram-negative sepsis, often associated with pneumonia (7, 22, 75, 86, 93, 99). In humans, the intestinal tract and the nasopharynx are the most common *Klebsiella* habitats. The carriage rates in stool samples range from 5% to 38% and in the nasopharynx from 1% to 6% (63). However, in hospitalized patients undergoing ventilation, colonization of the upper respiratory tract may reach up to 80%.

Because only a few of the capsular and O serotypes of *Klebsiella* are responsible for most pulmonary and blood infections, serotype-dependent mechanisms must contribute to the innate immune defense against *Klebsiella*. For these reasons,

TABLE 1. Interactions of C-type lectins with bacterial ligands^a

Pathogen	Lectin	Microbial ligand(s)	Reference(s)
Extracellular pathogens			
Gram-negative bacteria			
<i>Escherichia coli</i>	SP-D	LPS core	43
<i>Haemophilus influenzae</i>	SP-A	OMP P2	60, 61
<i>Helicobacter pylori</i>	DC-SIGN	Unknown	1
<i>Klebsiella pneumoniae</i>	SP-A	CPS	32
	SP-D	LPS core, mannose-rich O antigen	70, 79
	MR	CPS	31, 35, 70
	DC-SIGN	CPS, O antigen	100
<i>Pseudomonas aeruginosa</i>	SP-A	LPS	5, 56
	SP-D	LPS	5
Gram-positive bacteria			
<i>Bacillus subtilis</i>	SP-D	LTA	91
Group B streptococcus	SP-A	Unknown	48
<i>Staphylococcus aureus</i>	SP-D	Peptidoglycan	91
	SP-A	Unknown	61
<i>Streptococcus pneumoniae</i>	SP-A	Unknown	61
	DC-SIGN	Unknown	34
Intracellular pathogens			
<i>Mycobacterium tuberculosis</i>	SP-D	LAM	20
	SP-A	LAM	85
	MR	LAM	66
	DC-SIGN	LAM	1
<i>Mycobacterium avium</i>	SP-D	LAM	44
	SP-A	LM	44
<i>Mycoplasma pneumoniae</i>	SP-D	Membrane glycolipid	8

^a OMP, outer membrane protein; LAM, lipoarabinomannan; LM, lipomannan; LTA, lipoteichoic acid.

we believe that *Klebsiella*, a hospital-acquired pathogen, can be used as a paradigm for the interactions of lung pathogens with pulmonary innate immunity.

K. pneumoniae strains possess two types of glycoconjugate surface structures that show distinct affinities for C-type lectins: outer membrane LPS and CPS. The former are predominantly recognized by SP-D, while the latter are recognized by SP-A and the MR. Relevant data regarding the roles of these glycoconjugates as virulence factors and their roles in evading C-type-lectin-mediated innate immunity are summarized.

INTERACTION OF *KLEBSIELLA* CPS WITH THE MR

K. pneumoniae strains are capable of producing a prominent capsule composed of complex acidic polysaccharides made of repeating oligosaccharides that consist of four to six sugars, including negatively charged uronic acids. Based on the serological variability of their CPS, *K. pneumoniae* strains have been classified into 77 serotypes (72). It is generally accepted that the *Klebsiella* capsule is a major determinant of virulence, even though only a limited num-

TABLE 2. Examples of mechanisms involved in antibacterial host defense against extracellular pulmonary pathogens recognized by lung C-type lectins

Host defense	Mechanism	C-type lectin	Bacterium(a)	Reference(s)
Prevention of mucosal colonization	Antiadhesion	SP-D	<i>P. aeruginosa</i>	65
	Aggregation	SP-D	<i>K. pneumoniae</i>	79
		SP-A	<i>B. bronchiseptica</i>	15
Killing	Phagocytosis	MR	<i>K. pneumoniae</i>	2, 41
			<i>E. coli</i>	101
	Opsonization	SP-A, SP-D	<i>K. pneumoniae</i>	32, 71
		SP-A	<i>S. pneumoniae</i>	61
	Permeabilization	SP-A, SP-D	<i>E. coli</i> and others	98
Inflammation	Mediator release			
	Direct	MR	<i>K. pneumoniae</i>	36
	Opsonization	SP-D	<i>K. pneumoniae</i>	36, 71

TABLE 3. Binding of *Klebsiella pneumoniae* serotypes and their corresponding CPS to macrophages and the MR^a

Serotype	Repeating unit of CPS	Binding to:	
		MR	AM
K1	-4)-[2,3-(S)-pyruvate]βD-GlcA-(1-4)αL-Fuc-(1-3)βD-Glc-(1-	—	—
K2	-4)β-Glc-(1-4)β[GlcA-(1-3)α]-Man-(1-4)βD-Glc-(1-	NT	—
K3	-2)-[(4,6-(S)-pyruvate)αD-Man-(1-4)]αD-GalA-(1-3)αD- Man-(1-2)αD-Man-(1-3) βD-Gal-(1-	+	+
K7	-3)βD-GlcA-(1-2)β[Gal-1-3]αD- Man-(1-2)αD-Man-(1-3) βD-Glc-(1-3)-[(4,6-(S)-pyruvate)αD-Glc-(1-	NT	—
K11	-3)βD-Glc-(1-3)-[(4,6-(S)-pyruvate)αD-Gal-(1-4)]βD-GlcA-(1-3)αD-Gal-(1-	—	NT
K12	-3)αD-Glc-(1-3)Rha-(1-3)βD-Gal-(1-2)[1-3]β-GlcA-(1-4)βD-Galf-(4,6-(S)-pyruvate)]βD-Galf-(1-	NT	—
K17	-3)βL-Rha-(1-4)βD-Glc-(1-2)-[αL-Rha-(1-3)]αL-Rha-(1-4)αD-GlcA-(1-	—	NT
K21a	-3)-[(4,6-(S)-pyruvate)αD-Gal-(1-4)]α-GlcA-(1-3)αD- Man-(1-2)αD-Man-(1-3) αD-Gal-(1-	NT	+
K21b	-3)-[(4,6-(S)-pyruvate)αD-Gal-(1-4)]α-GlcA-(1-3)αD- Rha-(1-3)αD-Rha-(1-3) βD-Gal-(1-	NT	+
K22	-4)βD-Glc-(1-3)-[(4-O-lactate)βD-GlcA-(1-6)αD-Glc-(1-4)]βD-Gal-(1-6-OAC	—	NT
K24	-3-[Man-(1-4)]α-GlcA-(1-3)D- Man-(1-2)αD-Man-(1-3) D-Glc-(1-	NT	-
K26	-3)βD-Gal-(1-2)-[(4,6-(S)-pyruvate)]βD-Gal-(1-4)]βD-Glc-(1-6)αD-Glc-(1-4)]αD-GlcA-(1-3)αD- Man-(1-2)αD-Man-(1-	—	+
K27	-3)βD-Glc-(1-3)-?Gal-(1-3)-]βD-Glc-(1-4)-?Gal-(1-6) βD-Glc-(1- (6-1) βD-GlcA	—	NT
K31	-3βD-Gal-(1-3)βD-Glc-(1-3)-[4,6-(S)-pyruvate-βD-Glc-(1-2)αD-Man-(1-4)]αD-GlcA-(1-	—	NT
K32	-3αD-Rha-(1-3)-Rha-β(1-4)-D-Rha-α(1-3)α-Gal-(1-	NT	—
K36	-2αL-Rha-(1-3)βD-Gal-(1-3)-[(4,6-(S)-pyruvate)βD-Glc-(1-4)βD-GlcA-(1-2)]αL- Rha-(1-3)αL-Rha-(1-	—	+
K40	-3)αL-Rha-(1-2)αL-Rha-(1-4)αD-GlcA-(1-2)αD- Man-(1-2)αD-Man-(1-3) αD-Gal-(1-	—	NT
K46	-3)-αD-Gal-(1-3)βD-Glc-(1-3)-βD-Glc-(1-3)-(4,6-(S)-pyruvate)-?Man-(1-4)]αD-GlcA-(1-3)αD-Man-(1-	+	NT
K52	-3)-[αD-Gal-(1-2)]αD-Gal-(1-4)αL-Rha-(1-3)βD-Gal-(1-2)αL-Rha-(1-4)βD-GlcA-(1-	—	NT
K53	-2)βD-GlcA[αD-Rha-(1-3)]αD- Man-(1-2)αD-Man-(1-3) D-Galβ(1-2)-Rha-(1-	NT	+
K55	-3)βD-Glc-(1-4)-αD-GlcA-(1-3)αD-Gal-(1-3)]αL-Rha-(1-2-OAC	—	—
K60	-3)αD-Glc-(1-4)βD-GlcA-(1-3)-βD-Glc-(1-2)]αD-Gal-(1-3)-βD-Glc-(1-2)]αD-Man-(1-3)βD-Glc-(1-	—	NT
K62	-4)βD-GlcA-(1-2)[αD- Man-(1-3)-D-Man β(1-3)Gal-(1-4)α-D-Glc-(1-	NT	+
K64	-4)αD-GlcA-(1-3)αD-Man-(1-3)βD-Glc-(1-4)-[(4,6-(S)-pyruvate)βD-Glc-(1-2)]αD-Man-(1-(3-1) αL-Rha	+	NT
K67	-3)αD-Rha-(1-3)-[βD-Rha-(1-4)-[βD-GlcA-D-(1-3)Gal]-D-(1-2)]αD- Man-(1-3)αD-Man- βD-Glc-(1-	NT	+
K70	-2)αD-GlcA-(1-4)βD- Rha-(1-2)αD-Rha-(1-2) α-D-Glc-(1-3)βD-Gal-[(3,4-(S)-pyruvate)]βD-Rha(1-	NT	+

^a Structures of CPS are from Kenne and Lindberg (37) and Zamze et al. (100). Data on the binding of the MR to isolated, immobilized CPS are from Zamze et al. (100). Data on the binding of intact bacteria to AMs are from Athamna et al. (2). Boldface characters are the sequences of residues recognized by the MR. —, no binding; +, binding; NT, not tested.

ber of capsular serotypes account for most blood and pulmonary isolates (13, 16, 27, 73).

A number of different serotypes isolated at high and low frequencies were tested for their ability to bind to rat alveolar macrophages (AMs) in a serum-free system (2). Serotypes that express a CPS containing Man-α2-3-Man or L-Rha-α2-3-L-Rha (di-Man/Rha) sequences bound with high affinity to AMs (Table 3) (2, 31, 35, 70). The binding resulted in the ingestion and killing of the organisms. In contrast, serotypes that lack such sequences (e.g., K2) did not bind to the AMs and were not internalized. Consistent with these observations, purified CPS containing di-Man/Rha bound to AMs, while CPS lacking these disaccharide units did not. The serotype binding specificity of the macrophage lectin was confirmed by interserotype switching of the CPS genes. Such reciprocal recombination enabled the use of the capsule-switched recombinant strains K2(K21a) and K21a(K2). The latter strains retained their respective recipient K2 and K21 strain backgrounds but inherited genes encoding CPS of the parental donor strain (30, 69). As a result, the capsule-switched derivative K2(K21a) was bound effectively by the macrophages, whereas the K21a(K2) derivative bound poorly to the macrophages. To ascertain that the binding is mediated by the MR, binding of the *Klebsiella* strains to tissue culture cells transfected with MR-encoding DNA was examined (31). All of the *Klebsiella* strains tested bound poorly to nontransfected tissue culture cells. Strains and recombinant strains expressing di-Man/Rha in their CPS bound significantly to the MR-transfected cells, whereas *Klebsiella* strains lacking

these sequences in their CPS bound poorly to the transfected cells.

The MR is not expressed by blood monocytes, but the maturation to macrophages is accompanied by MR expression (84). Strains expressing appropriate CPS (e.g., K21a) bound specifically to the mature-monocyte-derived macrophages in a calcium-dependent manner but not to monocytes (36). Consistently with the suggested binding specificity of the macrophage MR, whenever it was tested, the binding was inhibited by mannan.

Earlier studies suggested that the MR binds only terminal mannose/GlcNAc/fucose residues (47, 96). More-recent studies, however, that examined the binding of purified recombinant MR to purified CPS isolated from *K. pneumoniae* and *S. pneumoniae* immobilized on microtiter plates also suggested binding to internal residues (Table 3) (100). These studies employed 10 *Klebsiella* capsular serotypes that lack the di-Man/Rha sequences in their CPS and 5 serotypes which contain these sequences in their CPS. The results showed that the MR bound to only three CPS serotypes, one of which contains the di-Man/Rha sequences (CPS of K3), one of which contains the Man-α1-3-Rha sequence (K64), and one of which lacks these sequences (K46). Among the immobilized 10 CPS that did not bind the MR, 4 contain the di-Man/Rha sequences (K17, K26, K36, and K40). Earlier studies found that whole bacteria belonging to K26 and K36 capsular serotypes bound avidly and specifically to intact AMs (2). These differences may reflect a difference in the presentations of the CPS to the MR in the two

systems. Even with whole bacteria, it was found that 2 out of 16 strains tested did not bind to intact macrophages even though they contained the di-Man/Rha sequences in their CPS (2). It is possible that *Klebsiella* strains expressing certain CPS that contain internal di-Man/Rha sequences can bind to DC-SIGN on the surfaces of the macrophages. It is also possible that some are recognized only by DC-SIGN. The latter also has an extended site with secondary sites of interaction. The MR has been suggested to prefer terminal mannose residues. DC-SIGN, however, can also bind internal mannosyl residues, and multimerization increases its affinity to such ligands (59).

Table 3 presents a summary of data on the binding of the soluble recombinant MR to immobilized *Klebsiella* CPS of various serotypes. It also shows the binding of bacteria of various serotypes to monolayers of rat AMs. Fifteen CPS were tested for binding to the recombinant MR, and 16 *Klebsiella* capsular serotypes were tested for binding to the macrophages. Only five CPS and corresponding serotypes were examined in both types of assays; the results for two of these (K26 and K36) were discordant and excluded from analysis. Therefore, correlations between structure and binding could be made for the remaining 24 CPS and corresponding capsular serotypes. The analysis showed that there was a significant correlation between the presence of the di-Man/Rha glycoepitope in the CPS and binding, as determined by either type of assay ($P < 0.02$). Out of the 10 CPS and corresponding capsular serotypes tested and containing di-Man/Rha sequences, 7 were positive for binding to macrophages and/or the MR, while 3 were negative. Out of the 14 CPS and corresponding capsular serotypes tested and lacking di-Man/Rha sequences, 3 were positive for binding to macrophages and/or the MR and 11 were negative. Altogether, nine CPS were tested for binding to the MR, and 12 capsular serotypes were tested for binding to the macrophages. In three cases, binding data for both the bacterial serotype and the corresponding CPS were in agreement and included in the analysis. If it is assumed that the assays of the interactions between the bacteria and the macrophages are more relevant, results for K26 and K36 could be included in the analysis, resulting in an even stronger correlation ($P < 0.006$).

INTERACTION OF *KLEBSIELLA* CPS WITH SP-A

The interaction of SP-A with *Klebsiella* was examined employing the K21a and K2 serotypes and their capsule-switched derivatives (32). SP-A specifically agglutinated the K21a serotype, which expresses the Man- α 2-Man sequence in its CPS. SP-A also bound to the immobilized parent K21a strain and to a recombinant strain of K2 that expresses the K21a capsule. In contrast, there was no significant binding of SP-A to the K2 strain, which lacks Man- α 2-Man sequences. Furthermore, the isolated CPS of K21a bound to immobilized SP-A, and the binding was inhibited by mannan (32). Taken together, the data suggest that SP-A recognizes the same capsular structure as recognized by the macrophage MR. SP-A did not agglutinate a noncapsulated phase variant of K21a, suggesting that, as for the MR, structures underneath the capsule are not recognized by SP-A (unpublished data).

Macrophages express at least one SP-A receptor (82). Because SP-A binds to the *Klebsiella* capsule and to macrophages (92), its ability to opsonize the K21a serotype was tested. Pre-

treatment of the bacteria with SP-A followed by washing to remove unbound SP-A caused a significant increase in the number of bacteria associated with AMs. Other experiments showed that the increase of *Klebsiella* association with macrophages was followed by the ingestion and killing of the bacteria, suggesting that SP-A acts as an opsonin in bridging between the capsulated K21a and the AMs (32). The SP-A-induced association of K21a with AMs was inhibited by mannan, but no association occurred with K2 or the capsule-switched derivative K21a(K2), which expresses the K2 CPS.

CAPSULAR GLYCOEPIOTOPE-DEPENDENT CLEARANCE OF *KLEBSIELLA* IN MURINE MODELS

The contribution of di-Man/Rha glycoepitopes to the virulence of *K. pneumoniae* was examined in mice using serotypes K2 and K21a and their respective capsule-switched derivatives (31). The results suggest that the switching of the *cps* genes in *K. pneumoniae* serotypes affects the interactions of the bacteria with the macrophages, as well as the blood clearance of the bacteria, and thus their virulence. *Klebsiella* serotypes that express a CPS with di-Man/Rha glycoepitopes were significantly less virulent than serotypes that do not. Moreover, the lung clearance of di-Man/Rha-bearing *Klebsiella* strains was significantly enhanced compared to that of *Klebsiella* strains lacking such glycoepitopes in their CPS (41). Thus, the chemical structure of the capsule partially determines the virulence of *K. pneumoniae* in mice, consistent with the roles of the MR and SP-A and possibly of DC-SIGN too. The results also showed that the switching of the *cps* genes in *K. pneumoniae* serotypes affects the interactions of the bacteria with macrophages, as well as the blood clearance of the bacteria, and thus their virulence. This selective recognition of serotypes will be further discussed in the context of the virulence of the organisms in humans.

INTERACTION OF *KLEBSIELLA* O ANTIGEN OF LPS WITH C-TYPE LECTINS

Early studies identified the core region of gram-negative LPS as the glycoepitope that is preferentially recognized by SP-D (43, 52). This interaction was subsequently shown to be mediated by the carbohydrate recognition domain of the collectin which bound to the LPS of *K. pneumoniae* and other gram-negative bacteria (51). SP-D does not recognize the *Klebsiella* CPS. Thus, it interacts with noncapsulated strains of *Klebsiella* but not with the capsulated variants, suggesting that LPS is masked by the capsule (71). Binding to SP-D results in bacterial agglutination as well as enhanced internalization and killing by macrophages (71). Notably, SP-D was more effective in the agglutination of a noncapsulated phase variant of the O3 serotype than in that of a noncapsulated phase variant of the O1 serotype. The minimal SP-D concentration needed to induce the agglutination of the O1 serotype was approximately 10-fold higher than that needed for the O3 serotype (71). These findings indicate that the structure of the O antigen of LPS influences the binding of SP-D to *Klebsiella* and the SP-D-dependent killing of the organism in vitro.

Klebsiella LPS consists of a mixture of molecules that vary in their numbers of oligosaccharide repeating units, all of which

TABLE 4. Structures of *Klebsiella pneumoniae* O-antigen serotypes and the interactions of their LPS with the MR^a and SP-D

Serotype	Repeating unit of O antigen	Binding of LPS to:	
		MR	SP-D
O3	-3)αD-Man-(1-3)αD-Man-(1-2)αD-Man-(1-2)-αD-Man-(1-2)αD-Man-(1-	+	+
O5	-3)αD-Man-(1-2)αD-Man-(1-3)αD-Man-(1-2)-αD-Man-(1-2)αD-Man-(1-	NT	+
O1	-3)αD-Galp-(1-	NT	—
O4	-2)βRibf-(1-4)-D-Galp-(1-	—	—

^a +, binding; -, no binding; NT, not tested. Data for the MR are from Zamze et al. (100). Data for SP-D are from Sahly et al. (79). Boldface sequences of the O-antigen side chain of LPS are those that are recognized by the MR and that facilitate the binding of SP-D to the core regions of LPS.

contain identical core and lipid A regions, which bind to SP-D (43). In experiments in which LPS was extracted from O1, O3, O4, and O5 serotypes, resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis, blotted, and overlaid with SP-D, it was found that the collectin bound to the low-molecular-weight LPS molecules of all serotypes (79). These LPS molecules lacked an O antigen or contained only small numbers of oligosaccharide repeating subunits. In contrast, SP-D binding to the high-molecular-weight LPS molecules, which contain longer oligosaccharide chains (e.g., with higher numbers of repeating units, ranging from 20 to 100), was limited to those molecules belonging to the O3 and O5 serotypes. The glycoepitope of the O antigen of these SP-D-reactive serotypes contains alternating linear linkages, including Man- α 2-Man units (O-polyMan) (72), which seem to facilitate SP-D binding (Table 4). Because SP-D can bind to mannose and mannose-rich carbohydrates, interactions with LPS are probably mediated by the core and/or appropriate polymannose-containing O antigens.

The possibility that interactions with bacteria can stimulate the release of cytokines and other mediators has also been examined. The coating of noncapsulated phase variants of *Klebsiella* strains with SP-D markedly increased their ability to stimulate cytokine mRNA accumulation in both macrophages and peripheral blood monocytes. SP-D-coated O3 strains, which express the polymannose epitope, induced significant cytokine release by human-monocyte-derived macrophages, while SP-D-treated O1 bacteria, which express the galactose epitope, were without effect (36). Likewise, noncapsulated mannose-containing O3 serotypes triggered higher interleukin-1 β and interleukin-6 production than other serotypes and were more efficiently cleared from the lungs of mice. In contrast, O1 serotypes showed a lower cytokine response and were inefficiently cleared in vivo. This did not occur in macrophage-depleted mice (41).

SP-D-coated noncapsulated variants of polymannose-expressing O3 *K. pneumoniae* also stimulated NO production in AMs (71). This suggests that complexes of *Klebsiella* strains with SP-D interact efficiently with macrophage surface receptors involved in the triggering of NO production. In order to better understand how the binding of SP-D affects interactions with macrophage receptors, a bacterium-free model system was used. Latex particles were coated either with SP-D, with

Klebsiella LPS, or sequentially with LPS and SP-D and delivered to macrophage monolayers. Significantly, increases in NO production were observed only when the beads were coated sequentially with LPS and SP-D (71). Solution-phase LPS or SP-D, even at amounts 100-fold greater than that adsorbed onto the beads, did not induce detectable stimulation of NO production. These effects were calcium dependent, consistent with the involvement of the lectin domain; they were not inhibited by polymyxin B, a known inhibitor of LPS-mediated stimulation, and did not require ingestion of the beads (M. Kalina, E. Crouch, and I. Ofek, unpublished observations). The data suggest that the engagement of SP-D with its LPS ligand on bacteria or the latex particles enables the collectin to bind more efficiently to its cognate receptors on macrophages to stimulate the cells.

Various studies have shown that noncapsulated phase variants of *K. pneumoniae* preferentially attach to and invade epithelial cell lines, presumably because the adhesins of the noncapsulated variants are not masked or better expressed than those of capsulated variants (19, 81, 83). The epithelial attachment of the bacteria was inhibited by SP-D in a dose-dependent manner in vitro (79). However, the minimal concentration of SP-D needed to inhibit the adhesion of the noncapsulated variants of *Klebsiella* to the epithelial cells was four times lower for the O3 serotype, which expresses the polymannose epitope, than that required for the O1 serotype, which lacks this epitope. These studies suggest that the polymannose epitope of the bacterial O3 and O5 antigens facilitates the clearance of the bacteria by enabling SP-D to better inhibit the adhesion of *Klebsiella* to epithelial cells. Such SP-D-mediated innate immunity is not limited to *Klebsiella*. A recent study showed that SP-D inhibits the adherence of *Pseudomonas aeruginosa* to corneal epithelial cells (65).

It should be emphasized that interactions with the mannose-rich O antigens are not confined to SP-D. Immobilized O3-containing LPS, but not O1-containing LPS, was found to bind avidly to purified MR (Table 4) (100). These findings suggest that the Man- α 2-3-Man of the O antigen of *Klebsiella* LPS (O-polyMan) may mediate binding of the bacteria to macrophages via the MR.

RELATIONSHIP BETWEEN VIRULENCE AND GLYCOEPITOPES

Hypotheses regarding the relationship between virulence and innate immune recognition of specific glycoepitopes might be tested using experimental infections in murine models of lectin deficiency or overexpression. However, there are significant potential limitations. First, humans are the sole host of most pulmonary pathogens, including *K. pneumoniae*. Second, there is considerable potential redundancy in host defense. For example, MR^{-/-} mice do not show increased susceptibility to infection by *Candida albicans*, despite interactions with the MR in vitro (46); on the other hand, Dectin-1 can efficiently mediate the clearance of yeast (26). Third, most of these lectins are known to play other important homeostatic roles, which might influence microbial clearance. Fourth, there is now considerable evidence for species divergence in specific lectin expression, as well as for functional differences among homologous proteins, as best exemplified by DC-SIGN and its

TABLE 5. Distribution of *Klebsiella pneumoniae* and *Streptococcus pneumoniae* serotypes by their levels of the frequency of isolation^a

Bacterium	Serotypes isolated at:	
	High frequency	Low frequency
<i>Klebsiella pneumoniae</i> ^b	K1, K2, K3 , K5, K7 , K8, K9 , K16, K17 , K18, K20, K21b , K22, K25, K27, K28 , K30, K33, K38, K39, K41, K43, K46, K48, K52, K53 , K54, K55, K60, K61, K62 , K63, K64, K68	K4, K5, K6, K11, K12, K13, K14, K19, K21a , K23, K24 , K26 , K31, K32, K34 , K35, K36 , K37, K40 , K44 , K45 , K47, K49, K50 , K51, K56, K58, K59 , K67 , K69, K70 , K71 , K72, K74 , K79 , K80 , K81 , K82
<i>Streptococcus pneumoniae</i> ^c	1, 2, 3, 4, 5, 6B, 7F , 8, 9N , 9V, 10A, 11A, 12F , 14 , 15B , 17F, 18C, 19F, 19A, 20, 22F , 23F, 0	6A, 7A, 7B , 9A, 9L , 10F, 11F , 11B , 11C , 12A , 13 , 15F , 15A , 15C , 17A , 18F, 18A , 18B , 19B, 19C , 27, 29, 31, 32F, 32A, 33B, 34, 35A, 35B, 37 , 45

^a This table includes only those serotypes whose CPS structure has been elucidated. See Table 6 for a quantitative analysis.

^b Data for the frequency of isolation of *K. pneumoniae* are from Cryz et al. (12), and all serotypes isolated at frequencies of $\geq 1\%$ and $< 1\%$ are included in the serotype groups of high frequency and low frequency, respectively. Serotypes shown in bold contain in their CPS the di-Man/Rha glycoepitope recognized by the MR according to the CPS structures from Kenne and Lindberg (37) and Zamze et al. (100).

^c The *S. pneumoniae* serotypes in the high-frequency-of-isolation group account for $> 90\%$ of symptomatic infections and are included in the 23-valent streptococcal vaccine (Pnu-Immune 23). All other serotypes are included in the low-frequency-of-isolation group. Serotypes shown in bold contain in their CPS *N*-acetylglucosamine, in which carbon 3 and/or carbon 4 is not substituted, and glucose, in which carbons 3 and 4 are not substituted, according to the CPS structures summarized by Kamerling (33).

related murine proteins (74). Lastly, lectins may contribute to different phases of the innate immune response. Even if a lectin does not contribute to the initial recognition and eradication of an organism following an acute challenge, interactions with the glycoepitope could contribute to the development of an ensuing acquired immune response.

Pathogens of the same genus and species are known to produce diverse surface glycoepitopes to give rise to large numbers of intraspecies glycoserotypes (72); these vary in their propensities to cause human disease. Thus, it should be possible to test the association of enhanced recognition by C-type lectins and diminished bacterial virulence by examining the correlation between the capacity of lectins to interact with specific glycoserotypes and the frequency of isolation of these same glycoserotypes in the context of pneumonia.

This type of analysis is now feasible for *Klebsiella* because the frequency of isolation of the various glycoserotypes has been determined, and as illustrated above, in vitro studies have correlated the interactions of specific glycoepitopes with one or more of the lung lectins. For example, the structures of 72 *K. pneumoniae* CPS have been sequenced, and the probable glycoepitope for C-type-lectin recognition is di-Man/Rha (Tables 5 and 6). The analysis of the distribution of serotypes bearing lectin-reactive glycoepitopes among isolates of the two species revealed a significant correlation between the presence

of capsular glycoepitopes recognized by one or more C-type lectins and a low frequency of isolation (Tables 5 and 6). In addition, the presence of capsular glycoepitopes that were not recognized by these lectins correlated with a high frequency of isolation.

Based on the structural variability of the O-antigen-specific polysaccharide, nine different O serotypes of *K. pneumoniae* have been described (24), among which the O1 serotype predominates among clinical isolates (24, 77, 78). It is also of interest that O1 serotypes were isolated at a significantly higher frequency from patients with *Klebsiella pneumoniae* than from patients with other *Klebsiella* infections (80). When the distribution of *Klebsiella* LPS serotypes bearing O antigens with a polymannose glycoepitope recognized by the MR and SP-D was analyzed, it was found that isolates expressing O antigens with these glycoepitopes (e.g., O3 and O5 serotypes) recognized by the MR and SP-D are isolated at significantly lower frequencies from the lung (Table 6). Conversely, serotypes bearing O-antigen-containing glycoepitopes (e.g., O1 and O2) not recognized by the lung lectins were more frequently associated with lung infections. The data and the analysis indicate a correlation between a specific glycoepitope in the surface glycoconjugates of *K. pneumoniae* and the frequency of isolation of the pathogens. This notion is also supported by murine models where O serotypes that contain a polymannose

TABLE 6. Relationship between the frequency of isolation of pulmonary pathogens and the structure of surface glycoepitopes recognized by C-type lectins^a

Bacterium	Glycoconjugate	C-type lectin(s)	Glycoepitope	% (No.) of glycoepitope-bearing serotypes or strains isolated at:		P value
				High frequency	Low frequency	
<i>K. pneumoniae</i>	CPS	MR, SP-A	di-Man/Rha	23.5 (34)	47.3 (38)	0.035
	O antigen	SP-D	Poly-D-Man	27.7 (83)	50.9 (55)	0.005
<i>S. pneumoniae</i>	CPS	MR?, SP-D?, DC-SIGN?	GlcNAc/Glc ^b	26 (23)	58 (31)	0.019

^a The data for the LPS O-antigen serotypes are from Sahly et al. (79) and represent 83 isolates from the lung (high frequency) and 55 isolates from other sites (low frequency). See Table 5 for details of capsular serotypes bearing the indicated capsular glycoepitopes.

^b GlcNAc in which carbon 3 and/or carbon 4 is not substituted, and Glc (terminal glucose) residues in which carbons 3 and 4 are not substituted.

glycoepitope are isolated at significantly lower frequencies than serotypes lacking such glycoepitopes in their O antigen (41).

INTEGRATIVE MODEL FOR *KLEBSIELLA*

Given the previous data and preceding analysis, we propose the following integrative model of pulmonary innate immunity against *Klebsiella pneumoniae*. Colonization of the upper respiratory tract by gram-negative bacteria precedes entry of the organisms into the lung. Because capsules can interfere with the expression or function of adhesins required for the colonization of epithelial cells by the organisms, it is likely that most of the bacteria colonizing the upper respiratory tract or other epithelial surfaces are in the noncapsulated phase (19, 57, 81, 83). Lung collectin SP-D, which reacts with a conserved region of the LPS core, may provide early protection against all strains of noncapsulated phenotypes either by opsonizing the bacteria to enhance their phagocytosis or by agglutinating the bacteria, which may inhibit their adhesion to the upper respiratory epithelium (71, 79). However, as discussed above, productive binding of SP-D to the LPS core region is influenced by the molecular structure of the O antigen. Polymannose-containing O serotypes can bind to SP-D, while those that lack such structures cannot. In vitro studies have shown that *Klebsiella* can undergo phase variation between capsulated and noncapsulated phenotypes (57). As a result, capsulated bacteria that emerge during the infection are prone to escape SP-D recognition. The macrophage MR in conjunction with SP-A, and possibly DC-SIGN, may provide additional protection by eliminating capsulated *Klebsiella* through recognition of the di-Man/Rha sequences in the CPS. SP-A, which opsonizes and agglutinates the di-Man/Rha-containing *Klebsiella*, may also augment the expression of the MR (32), which could in turn mediate the phagocytosis of the organisms.

THE CASE OF *STREPTOCOCCUS PNEUMONIAE*

S. pneumoniae is a major cause of community-acquired pneumonia. It asymptomatically colonizes the upper respiratory tracts of a significant fraction of the population, reaching >50% of young children (64). The mechanisms through which asymptomatic infections turn into life-threatening diseases (e.g., pneumonia and/or sepsis) are obscure. We do know, however, that out of the 90 different capsular serotypes, only 23 account for most cases of pneumonia. The existing polyvalent vaccine composed of these 23 CPS efficiently protects adults against pneumonia. It follows that most of the capsular serotypes cannot escape the innate immune system, and the few that do have a CPS that is included in the polyvalent vaccine.

INTERACTION OF *S. PNEUMONIAE* POLYSACCHARIDES WITH C-TYPE LECTINS

Very few studies have examined the interaction of intact pneumococci with macrophages or C-type lectins, with respect to serotype recognition. The *S. pneumoniae* CPS contain repeating oligomeric units, some of which are characterized by glucuronic acid and/or galacturonic acid residues, which may be substituted with *O*-acetyl, pyruvate acetyl, and glycerol

phosphate groups (29, 33). It is generally accepted that the capsule enables the bacteria to escape recognition by phagocytic cells. In an attempt to identify a capsular glycoepitope specific for the MR, the binding of purified, recombinant MR to 12 immobilized, purified, pneumococcal CPS belonging to various serotypes was examined (100). A similar study was attempted for SP-D (30). Both studies failed to identify serologic determinants for binding. However, as for essentially all other studies of this type, all the CPS serotypes examined belong to serotypes isolated at a high frequency from clinical specimens. Thus, a correlation between the frequency of isolation of the *S. pneumoniae* serotypes and binding to lung lectins cannot be made.

PNEUMOCOCCAL GLYCOEPITOPES

As indicated above, there is limited in vitro data to implicate specific glycoepitopes in *S. pneumoniae*. However, given the insights obtained from studies with *K. pneumoniae*, we explored the possibility that specific glycoepitopes may be associated with known differences in frequency of isolation. Twenty-three out of more than 90 serotypes account for most *S. pneumoniae* infections, and the CPS of all these have been sequenced; only 30 of the CPS from organisms isolated at a low frequency are known (33). Notably, none of the available sequences contain mannose. An independent, computational analysis was performed to test whether any specific sugar residues within the known sequences were predictive of isolation frequency. This revealed that *N*-acetylglucosamine and glucose residues are found significantly more frequently in the CPS of serotypes isolated at low frequencies (in 18/31 serotypes, or 58%) (Tables 5 and 6) than in the CPS of serotypes isolated at high frequencies (in 6/23 serotypes, or 26%). This difference is statistically significant ($P = 0.019$). The analysis is consistent with the conclusion implicating glucose as a possible residue recognized by the MR (100). It should be noted that *N*-acetylglucosamine residues in some of the CPS have free hydroxyl groups, usually implicated in the coordination of calcium in C-type lectins (94). Although the findings generally support our hypothesis, additional studies will be needed to more precisely define the contributions of specific glucose and *N*-acetylglucosamine residues or sequences to the capsular glycoepitopes of *S. pneumoniae*. Interestingly, *N*-acetylglucosamine residues have also been implicated in ligand recognition by DC-SIGN (101), while terminal glucose is a preferred monosaccharide ligand for SP-D (11). Thus, the simple calculations are consistent with our general hypothesis regarding contributions of lectins to the innate immune response to *S. pneumoniae*.

PERSPECTIVES AND FUTURE DIRECTIONS

Despite the significant correlations between the frequency of isolation and expression of glycoepitopes recognized by one or more lung C-type lectins, there are obvious exceptions. As indicated in the introduction, there are other lung lectins, such as the ficolins and galectins, which have not yet been examined with respect to their interactions with specific bacterial serotypes. In addition, the field of innate immunity is rapidly evolving; new molecules with lectin activity continue to be identified, and glycol array studies promise to identify additional

bacterial ligands for endogenous lectins. Furthermore, lectin activity can be influenced by ligand presentation and secondary interactions of sugars with the carbohydrate recognition domain, as well as higher-order oligomerization of the lectin. Thus, caution must be exercised when attempting to extrapolate from the solution-phase inhibitory activities of carbohydrates to interactions with glycoconjugates displayed at bacterial surfaces.

Nevertheless, the studies reviewed above indicate important interactions between the glycoepitopes of specific serotypes of one gram-negative and one gram-positive species and at least three innate immune effectors of the C-type lectin family. Future studies should focus on those serotypes that escape recognition by the innate immune system. Efforts aimed at defining the glycoepitope(s) that escapes recognition could lead to the design of a vaccine that generally targets such an epitope(s). For *K. pneumoniae*, studies should focus on strains bearing glycoepitopes that are not recognized by the C-type lectins and strains isolated at high frequencies from hospitalized patients (e.g., the K2/O1 serotype [Table 5]) but cleared by otherwise healthy individuals. A proof of principle has already been provided by the high efficacy of the 23-valent vaccine for *S. pneumoniae* (Table 5), which includes the CPS of most serotypes not recognized by the lung C-type lectins.

In summary, the available data strongly support the notion that the innate immune system is responsible for recognizing and eradicating many emerging serotypes throughout the evolution of a pathogenic species. Those serotypes that escape innate immune recognition become pathogens with a high potential for causing disease. Additional analyses of the type described here could assist with the development of new preventive and therapeutic strategies to manage community- and hospital-acquired pneumonias in both healthy and immunocompromised patients.

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