1. ABSTRACT

Mycoplasmas are unique cell wall deficient, cholesterol requiring, highly pleomorphic bacteria that possess a very small genome. M. pneumoniae is an important human pathogen that possesses specialized tip organelle to mediate cytaadherence. It is a complex multifactorial process requiring a group of mycoplasma proteins such as P1, P30, P116 and HMW1-3. Expression of major mycoplasma adhesin proteins in heterologous expression systems provides an opportunity to study the role(s) of these proteins in pathogenicity and helps to develop diagnostic reagents. In this review we highlight the role(s) of various cytaadhesin proteins of M. pneumoniae.

2. INTRODUCTION

The bacterial class Mollicutes represents the six genera Asteroleplasma, Anaeroplasma, Acholeplasma, Spiroplasma, Ureaplasma and Mycoplasma. Mycoplasmas are the smallest, spherical to filamentous in shape, self-replicating, cell wall deficient organisms. Over 190 species are known, widely distributed among human, animals, insects and plants. These are presumably evolved by degenerative evolution from gram-positive bacteria and are phylogenetically closely related to some Clostridia. M. pneumoniae is the commonest pathogen among mycoplasmas in humans and a leading cause of pneumonia in children as well as in young adults (102). M. pneumoniae infection depends upon adherence to host epithelial cells, which is accomplished by ciliostasis and progressive destruction of epithelia. A variety of chemical, genetic, immunological and ultrastructure study has identified a group of mycoplasma proteins that act interdependently to achieve cytaadherence (adhesion to epithelial cells). Present review focuses mainly on cytaadherence related proteins, which are primarily responsible for the pathogenesis.

3. GENOME ORGANIZATION

Mycoplasmas have an extremely small genome (0.58-2.20Mb). The entire genome of M. pneumoniae has been sequenced. The complete M. pneumoniae genome has a size of 816,394 bp that codes for 677 ORFs and has a G+C content of 40 mol%. One of the unique features of the genome of M. pneumoniae is the presence of UGA codons that codes for tryptophan instead of acting as universal stop codons. Of the predicted ORF’s, 75.9% showed significant homology to genes/proteins of other organisms while 9.9% did not reveal any significant similarity to gene sequences in the data base (37). Comparative genome sequencing of M. pneumoniae and closely related species M. genitalium...
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(size 580,070 bp with 470 ORFs) (26) showed an identity of approximately 66.1% at nucleotide level, 67.4% at amino acid level and 98% at 16S and 23S ribosomal RNAs level (36). Both these organisms share similar morphology and show serological cross reactivity (102). However, they differ in many features including G+C content (by 8 mol%), genome size (by 236 kb), DNA:DNA hybridizations, tissue specificity and human pathogenicity. The additional 236 kb in hybridizations, tissue specificity and human pathogenicity.

M. pneumoniae code for an additional 209 proposed ORFs which are not identified in M. genitalium, in which 110 ORFs were significantly distinct from M. genitalium (38).

4. PATHOGENESIS

M. pneumoniae infections are associated with community acquired pneumonia (28,29,88), asthma (75,110), lower and upper respiratory illnesses (63,71,81,82), heart diseases (74,90), leukemia (13), Steven-Johnson syndrome (89,108), polyarthritis or septic arthritis, CNS disorders and diseases (96), Crohn’s and irritable bowel syndrome, Guillain-Barre syndrome (61), polyarthritis (78), encephalitis (9), septic meningitis (113), and autoimmune diseases (24). Between 10-20% of X-ray proven pneumonia cases that occur in endemic period, and up to 50% of all cases that occur in epidemic period, are caused by M. pneumoniae (72). It is estimated that M. pneumoniae accounts for as many as 20% of all cases of community acquired pneumonia in general population and for as many as 50% in closed populations such as students and military recruits living in dormitories (10).

In India and developing countries, the exact incidence of M. pneumoniae infections in patients with pneumonia is still unknown because of lack of awareness and non-availability of rapid diagnostic techniques. A number of studies based on gelatin particle agglutination (GPA) and ELISA has estimated 10-35% incidence of M. pneumoniae infection (11,17).

4.1. Factors involved in the pathogenesis of M. pneumoniae

In M. pneumoniae infections, adherence is the major virulence factor for the pathogenesis, and adherence deficient mutants are avirulent (86). Cytadherence of mycoplasma to respiratory epithelium is an essential and crucial step in tissue colonization and subsequent disease pathogenesis. A number of in vitro models have been used to study the mycoplasma infections (and delete) that increase our understanding regarding the nature of the receptors (27,49,114). Hamsters infected with hemadsorption negative mutants of M. pneumoniae neither survive nor produce pneumonia (32,59,80). Through the use of human lung fibroblasts monolayers, it has been shown that M. pneumoniae attaches to sialoglycoprotein on the surface of host cells. Purified sialic acid at a level of 0.1 to 0.5%, pronase as well as neuraminidase significantly reduces mycoplasma attachment (27). These experiments (also- delete) provide valuable insight not only into the process of mycoplasma attachment but also the subsequent metabolic alterations that cause cytotoxicity via disrupting de novo purine synthesis within hrs after infection (27). M. pneumoniae has a polar, tapered cell extension at one of the poles containing an electron dense core in the cytoplasm, called the tip organelle (92). This specialized tip organelle consist of a network of several interactive proteins and accessory proteins present on the attachment organelle, which attaches to sialoglycoproteins receptors of the tracheal epithelium via protein adhesion on the attachment organelle that permits highly oriented surface parasitism of the host target cells. It was assumed that hydrogen peroxide and free radical O₂⁻ ions secreted from the M. pneumoniae tip at the time of adherence cause the pathogenicity (1). However, evidence for the existence of enzymes dealing with oxidative stress factors like catalase, superoxide dismutase or peroxidase was not found on sequencing of M. pneumoniae genome (37). D.allo et al 2002 have shown that elongation factor TU and pyruvate dehydrogenase E1 β which express on mycoplasma cell surface, are also involved in binding M. pneumoniae to fibronectin (15). Various other factors including motility, adaptation to the host environment, secretion of toxic substances damaging host cells, possession of mechanisms for evading phagocytosis, and the induction of pathologic immune response are also involved in the pathogenesis of M. pneumoniae (46).

5. CYTADHERENCE

M. pneumoniae cytadherence is a complex multifactorial process requiring a group of mycoplasma proteins which act independently or dependently to achieve cytadherence (7). Protease treatment of M. pneumoniae markedly reduces surface parasitism, suggesting that specific mycoplasma proteins function as mediators of cytadherence (39). Using a chimpanzee model, a number of protein bands could be identified as immunogenic components of M. pneumoniae in immunoblot analysis of their sera after infection with M. pneumoniae. Similar findings were observed in immunoblot analysis of patients sera infected with M. pneumoniae showing protein bands of approximate masses of 169, 148, 130, 117, 86, 56, 35, 32, 30 and 29kDa (25). However, the major proteins that have been experimentally shown to participate in cytadherence are P1 (170 kDa), P30 (30 kDa), P116 and proteins HMW1 (High molecular Weight) to HMW3, as well as proteins A, B and C (Figure 1) (30,39,100,101). These proteins cooperate structurally and functionally so that M. pneumoniae major surface adhesins display polar clustering at the organelle tip assisted by HMW proteins. P1 and P30 (and perhaps P65 and P116) appear to be directly involved in receptor binding, although the receptor specificity of each is not known (54). The HMW proteins and proteins A, B, and C are accessory proteins since they are not adhesins but are required for proper functioning. The cytadherence-deficient mutants have also shown light on the role of some of these proteins in cytadherence. Mutants either lacking or deficient in high molecular weight proteins could not colonize and cause infection (59). In a study it has been shown that the HA’ revertants reacquire these specific proteins which are absent in their homologous mutants. Cytadsorption capabilities and virulence also gets activated in revertants (58).
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FIGURE 1. Schematic representation of M. pneumoniae cytadherence and accessory proteins.

5.1. P1 Protein

Hu et al (39) identified a 169 kDa designated as P1 protein on the M. pneumoniae surface which are functional in receptor recognition, as the probable adhesin protein (23). M. pneumoniae cytadherence is inhibited if protein P1 is enzymatically cleaved or coated with monospecific or monoclonal anti P1 antibodies. Mutants of M. pneumoniae which lack P1 are unable to mobilize and anchor protein P1 at the tip of attachment organelle and are avirulent (5,50,59). P1 protein has also been shown to be involved in gliding motility of M. pneumoniae (93).

The P1 gene has been sequenced and contains an open reading frame of 4,881 nucleotides coding for a protein of 1,627 amino acids, with a molecular mass of 176,288 Da (100) and 21 UGA codons, that codes for tryptophan (100). The G+C content is 53.5 mol%, considerably higher than 40% of entire M. pneumoniae genome (30). This protein has some interesting characteristics. It has a high percentage of hydroxy amino acids and no cysteine, so that the protein cannot be stabilized by intra or extracellular disulphide bridges. Also, the TGA codon for tryptophan is slightly preferred over the TGG codon (21:16) and the high proline content at carboxy terminal region plays a role in regulating the topological organization of the cytadhesin on the membrane (59). Subsequent studies have described the direct role of P1 gene in cytadherence (87). Two stretches of sequence divergence were found in multiple copy regions of the P1 gene that resulted in considerable amino acid changes (99). Kenri et al identified few new stretches of variable sequences in the P1 cytadhesin gene of M. pneumoniae that were shown to be in the antigenic determinant region (52). Based on these findings, these authors postulated that the repetitive sequences of the M. pneumoniae serve as a reservoir to generate antigenic variation of the cytadhesin gene.

The variable regions of the predicted amino acid sequences have been suggested to modulate the interaction of M. pneumoniae with the host immune system. Several potential antigenic sites at amino acid positions 240-260, 280-304, 314-333, 450-479, 680-690, 746-767, 898-913, 1244-1260 and 1476-1485, have been suggested in the P1 protein sequence on the basis of hydrophilicity plots. Topological mapping of P1 gene using cytadherence-inhibiting mAbs showed that the three regions of the protein viz. N-terminal region, D-1 region and D-2 region in C-terminus were shown to be immunoreactive (16,45). The epitope mapping experiments suggested a stronger adherence capacity and close relationship of the N-terminal region, D-1 domain and D-2 domain to form a functionally active three-dimensional arrangement of different protein loops rather than a linear amino acid sequence. Jacobs et al identified an immunodominant region at the N-terminal of P1 gene using a chemically synthesized peptide library (44). Dallo et al identified an immunodominant region of P1 gene spanning 4067-4185 bp while screening a JG11 library with patient sera (16). Later Swentrup and coworker expressed 3 domains of P1 protein spanning N-terminal, middle and C-terminal parts in an E. coli. They raised monoclonal antibodies against these three fragments and showed that a monoclonal corresponding to C-terminal fragment of P1 block attachment to the respiratory epithelial cells (101). Our group also expressed two recombinant truncated fragments of P1 protein (P1-N1 and P1-C1) and corroborated the findings of Swentrup et al. Though initial findings suggest a role for all regions of P1, recent data seems to indicate that C-terminal of P1 protein represents the immunodominant region and can be exploited for understanding pathophysiology and specific diagnosis of infection (12).

In vitro test has confirmed that anti-P1 adhesin antibodies inhibit the adherence of M. pneumoniae to host cells and protect against the infection. Immunization with purified P1 protein in guinea pigs induced strong immunological responses, thereby suggesting that P1 is an effective vaccine candidate antigen (43,47). In vitro binding assays have indicated that trypsin sensitive surface protein P1 is highly capable of binding avidly to the host cells (56). FACS analysis also revealed a high proportion of mature lymphocytes (94-95%) in M. pneumoniae-immunized mice or P1 protein immunized mice compared to control animals. Both M. pneumoniae and P1 protein activate T helper cells and increase Mac 1 receptor-bearing cells (macrophages) as compared to controls (77). Antibodies directed against P1 markedly reduced M. pneumoniae adherence to the respiratory epithelium which could be either due to steric interference of the interaction between adhesin and receptor or by inhibition of metabolic activity. However, anti-P1 immunoglobulin did not affect growth and metabolic activity of the organism. These findings suggests that the inhibition in attachment is due to steric interference of adhesin- receptor interactions. Inhibition (upto 80%) of M. pneumoniae attachment to tracheal rings by anti-P1 immunoglobulin further indicated that P1 is a primary mediator of adherence to the respiratory epithelium (57).

5.2. P30 Adhesin

P30 is the second important protein that has been shown to be involved in cytadherence and virulence of M. pneumoniae. Anti-30 kDa adhesin monoclonal antibodies blocked cytadherence and this protein elicited a strong immunological response in convalescent phase sera from humans and infected hamsters (6,68). It is a transmembrane protein with an intracytoplasmic N-terminal domain and a C-terminal domain on the mycoplasma cell surface. The extracellular portion of P30 is dominated by multiple
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Figure 2. Schematic representation of organization of genetic loci associated with Cytadherence of Mycoplasma pneumoniae genome.

P30 gene of M. pneumoniae is required for cytadherence and is associated with proper cell development (91). Layh-Schmitt et al isolated and characterized a mutant (M7), which had lost the ability to adsorb erythrocytes and to bind to epithelial cells. This mutant exhibited a truncated adhesin related 30-kDa protein of 25kDa, because of a loss of 12 out of 13 repeated sequences in its 3’end. The deletion of 12 repeated sequences in the 30-kDa protein gene in the hemadsorption negative mutant M7 was the only detectable defect, indicated that the region comprising the proline rich repeated sequences was essential for (the- delete) adhesion related functions (67). It is present in the cluster on the tip of attachment organelle and thought to be directly involved in receptor recognition, although evidence of P30 is not clear (14).

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The G+C content of 54.4% in P30 is similar to the P1 adhesin gene (14). It is present in the cluster on the tip of attachment organelle and thought to be directly involved in receptor recognition, although evidence of P30 is not clear (14).

5.3. P116 Protein

A 116 kDa surface protein of M. pneumoniae has also been found to be a major immunoreactive protein which is encoded in an operon (21). Nucleotide sequencing (which contained the gene- delete) of the 3093 bp gene revealed two ORFs encoding a 16 kDa protein and 116 kDa protein in the order 5’-16 kDa ORF – 116 kDa ORF-3’ (Figure 2). It is a trypsin sensitive, surface antigen involved in cytadherence of M. pneumoniae to respiratory epithelium. This protein gene of M. pneumoniae strain FH Liu has been recognized as (the- delete) equivalent to gene G07_orf1030 of M. pneumoniae strain M-129 (37). According to hydropathy plot, the 26 amino acids of amino-terminal of 116 kDa protein constituted the most hydrophobic region (62). The genomic locations of the M. pneumoniae genes G07_orf1030 and G07_orf135 showed homology with M. genitalium MG074 and MG075 genes that are in the same order and in the same transcriptional orientation (26,37). The recombinant protein(s) derived from p116 have been shown to be antigenic based on ELISA and immunoblot analysis using (the- delete) patient
5.4. P65 Protein

A cytoskeletal protein characterized by an acidic and proline-rich (APR) domain near the N-terminus, which revealed an ORF with a molecular weight of 47,034 Da (83). The gene encoding P65 immediately precedes and is co-transcribed with the gene for HMW2. It requires a functional core for efficient transport from the cytoplasmic pool to the cell surface. P65 is co-localizing with P30 gene. Immunofluorescence microscopy and immunoadsorption experiments indicated P65 have surface-exposed regions (84). Co-expression of the P65 protein labeled with enhanced cyan fluorescent protein clearly showed that the P65 did not overlap with the sites of localization of P41 and P24 (51). P65 also exhibits size polymorphism in Mycoplasma pneumoniae M129 and FH which is caused by an intragenic duplication of a 54-bp sequence within the FH orf P65 (84). P65 exhibited a polar localization like that in wild type M. pneumoniae and in all mutants having normal levels of HMW1 and HMW2. Partial or complete loss of these proteins, however, correlated with severe reduction in the P65 level and the inability to localize P65 properly (48).

5.5. Accessory Proteins

A number of accessory proteins have been described. These accessory proteins have been shown to play a role in the lateral movement and concentration of the adhesion molecule (P1) at the tip organelle. Therefore adhesin proteins like P1 and P30 alone (is-delete) are not sufficient for mycoplasma adherence to host cells. A number of mutants have been isolated which possess P1, fails to localize to the attachment organelle, but it is widely scattered elsewhere on the mycoplasma surface (5,31,91). Baseman et al. (has been delete) have shown that cytadherence accessory proteins are also required for proper functioning of adhesins. However, these are not directly involved with receptor binding but might be structural elements of the attachment organelle (5). Furthermore, dramatic changes in cell morphology, loss of adherence and motility have been found by analysis of mutants in some cytadherence-associated proteins by immunofluorescence microscopy (55,94).

5.5.1. HMW 1

(One such protein is - delete) HMW1 is one of the accessory cytoskeletal protein of molecular weight 112 kDa which contains an unusual domain dominated by repeating acidic and proline rich motifs (18). This protein (is shared the delete) shares structural features with cytadherence associated HMW3 and P65, as well as P200 (Figure 2) (83,85). The C-terminal region of HMW1 has been shown to be essential for protein function (79), including proper development of the terminal organelle and localization of P1 to this structure (111). Pulse-chase analysis showed that HMW1 becomes stabilized in the cytoskeletal fraction and (functions as the association delete) is associated with the cell surface in wild-type M. pneumoniae (4).

5.5.2. HMW 2

HMW2 is a large protein of 213 kDa characterized by (their delete) its potential to form an α-helical coiled-coil structure which is typical of filamentous domains of cytoskeletal proteins (60). It is primarily composed of heptad repeats consisting of hydrophobic and hydrophilic residues. Loss of HMW2 resulted in failure to localize to the attachment organelle, altered cell morphology (5,94), reduced cytadherence (59) and decreased steady-state levels of HMW1, HMW3, P65, and P30 (48,79). A reciprocal dependency between HMW1 and HMW2 indicated the requirement for HMW1 in localization of HMW2 to the attachment organelle (111).

5.5.3. HMW 3

Another cytadherence associated protein of 74 kDa, known as HMW3 appears to be associated with the cytoplasmic surface of the cell membrane of the cytadherence organelle, with no exposure on the mycoplasma cell exterior and no direct role in the attachment (54). The hmw1 and hmw3 genes are closely linked and located in a single operon (18) but separated from the hmw2 gene by approximately 160 kbp (37). No difference in transcript levels for hmw1 and hmw3 between wild-type and class I or crl mutant M. pneumoniae was shown by RNA slot blot hybridization, establishing that control of HMW1 and HMW3 levels occurred post-transcriptionally (79).

Subtle changes in morphology, inability to cluster the adhesin P1 consistently at the terminal organelle, reduced cytadherence and, in some cells, an atypical electron-dense core in the attachment organelle have been reported with the loss of HMW3. This suggested the role of HMW3 in the architecture and stability of the attachment organelle (112).

5.5.4. Proteins B and C

P1 attachment protein gene is flanked by two open reading frames with a coding capacity for two proteins of 28 kDa (ORF4) and 130 kDa (ORF6), respectively and proposed in an operon-like organization in the order ORF4-P1-ORF6 (40,41,100). Two proteins of molecular mass 40 kDa (protein C) and 90 kDa (protein B) were identified as the gene product of ORF6 which might arise from cotranslational cleavage (97). Biochemical and immunological studies provided the strong evidence that both 40 and 90kDa proteins are membrane-associated, demonstrating surface-exposed regions, since reduced attachment to host cells was found in a wild-type mutant lacking these proteins (64). The ORF6 gene product and 30 kDa protein were linked to each other and located at a maximal distance of 12Å on the tip structure of M. pneumoniae (65). Virulence specific proteins P90 and p40 are encoded by MPN142 (orf 6 gene). A mutation in gene MPN142 in mutant III-4 leads to (the-delete) a cytadherence defect (107).

To conclude, interplay of various proteins (HMW-1, HMW-2, HMW-3, P90, P65 and P30) is required (to participate- delete) in the establishment of a polar structure. (is established- delete). Once this polar structure
is established, an independently assembled complex of proteins B, C and P1 is drawn to the structure to complete formation of the functional terminal attachment organelle (3). Analysis of complete genome sequence of *M. pneumoniae* and (their- delete) its receptors will (through-delete) throw further light on the interaction with (the-delete) host cells and the process of cytadherence at the subcellular level, as described by Rottem (92).

6. DIAGNOSIS OF M. PNEUMONIAE INFECTION

The exact incidence of *M. pneumoniae* infections in patients with respiratory tract and other infections is still unknown because of lack of awareness and non-availability of specific diagnostic techniques especially in developing countries. Clinically, *M. pneumoniae* pneumonia cannot be differentiated (with- delete) from other bacterial and viral infections. Infected patients often present with symptoms that resemble with a persistent influenza like symptoms. The lack of a gold standard for diagnosis of these pathogens leads to misdiagnosis and inappropriate antibiotic treatment, that poses a threat to children and adults (105). The diagnosis is based principally on serology and culture. Diagnosis by culture is very tedious and take two to four weeks (to isolate- delete) (34) (and that's a time-cons uming process- delete). Complement fixation test is a more widely used method for *M. pneumoniae* antibody detection; however it lacks (the-delete) specificity due to cross reactivity of the antigen preparation (42,104) and (it- delete) also measures antibodies (deriving- delete) derived from earlier infections (95). While molecular diagnostic techniques, such as polymerase chain reaction (8,19,53,73) and real time PCR (2,33,70,103,106) offer improvements in sensitivity, specificity and rapidity over culture and serology, the need remains for a consistent and reproducible diagnostic technique, available to all microbiology laboratories. The commercially available micro-particle agglutination test (17,98) and ELISA (69,76,109) are more sensitive but less specific and also require paired sera for diagnosis.

Recombinant approaches offer opportunities to develop specific and sensitive test for the diagnosis of *M. pneumoniae* infection. P1, P30, and P116 adhesin proteins are major virulence factors of *M. pneumoniae* and allows the discrimination between colonization with less virulent and (colonization with- delete) highly virulent *M. pneumoniae* strains. Our research group has initiated studies to clone, express and identify the immunodominant regions of P1, P30 and P116 proteins. In this direction, we identified and expressed two domains of P1 gene, one in the N-terminal region and another in the C-terminal region. The C-terminal region was found to be immunogenic, since it showed strong reactivity on immunoblotting with *M. pneumoniae* IgG antibody-positive patient sera, whereas the region corresponding to N-terminal position showed no reactivity with these sera (12). Comparative evaluation of the reactivity of the patient sera with P1-C1, as well as with a Serion Classic ELISA kit, was carried out. At 0.5 absorbance, the cutoff points for the sensitivity and specificity of P1-C1 were determined to be 72.7% (24 of 33) and 100% (32 of 32), respectively (Figure 3). (The-delete) Attempts are (on- delete) being made to express and check the reactivity of different fragments of P30 and P116 recombinant protein in order to include all the three recombinant proteins in ELISA (to improve- delete) for improving the sensitivity and specificity. The use of these recombinant proteins and antisera raised against these proteins may provide an insight in understanding the mechanisms of cytadherence that may, in turn, help in the development of a drug/vaccine against the disease.

7. PERSPECTIVE

Knowledge obtained from complete genome sequence has been applied in epidemiological investigations (&- delete) and evaluation of diagnostic reagents and, as a result, understanding of this organism's cell biology, interaction with host cell and disease transmission (and contribution to newer clinical syndrome- delete) has improved. Due to the availability of rapid molecular diagnostic methods, it will be possible to attribute the causative role of mycoplasmas (in- delete) to new and emerging clinical syndromes. Despite these many advances, much remains to be explored about this tiny yet elusive pathogen.

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