Journal of Zhejiang University SCIENCE B
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.zju.edu.cn/jzus; www.springerlink.com
E-mail: jzus@zju.edu.cn

Review:

Interactions between mycoplasma lipid-associated membrane proteins and the host cells*

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Received Dec. 5, 2005; revision accepted Mar. 10, 2006

Abstract: Mycoplamas are a group of wall-less prokaryotes widely distributed in nature, some of which are pathogenic for humans and animals. There are many lipoproteins anchored on the outer face of the plasma membrane, called lipid-associated membrane proteins (LAMPs). LAMPs are highly antigenic and could undergo phase and size variation, and are recognized by the innate immune system through Toll-like receptors (TLR) 2 and 6. LAMPs can modulate the immune system, and could induce immune cells apoptosis or death. In addition, they may associate with malignant transformation of host cells and are also considered to be cofactors in the progression of AIDS.

Key words: Mycoplasma, Lipid-associated membrane proteins (LAMPs), Toll-like receptor (TLR), Immunomodulin
doi:10.1631/jzus.2006.B0342 **Document code:** A **CLC number:** R37

INTRODUCTION

Mycoplasmas are a heterogeneous group of the smallest and simplest self-replicating prokaryotes. These organisms are different from other eubacteria in many aspects, such as lack of a cell wall, possessing an unusually small genome (580~2200 kb) having high A+T content (67% to 76%), requiring cholesterol for survival, using universal stop codon UGA for tryptophan, etc. Most mycoplasmas are non-pathogenic when they enter an appropriate host, in which they multiply and survive for extended periods of time. However, several species are real pathogens for humans and animals, and cause a wide variety of diseases, including acute respiratory illness, genitourinary tract or joint infections, autoimmune disorders, and act as possible cofactors in AIDS pathogenesis. In addition, some mycoplasmas are also troublesome contaminants of tissue cultures.

Mycoplasmas are extracellular surface parasites of host cells and tissues, although some species have been reported to occupy additional intracellular niches (Baseman *et al*., 1995). Yet they possess only a limiting plasma membrane without the additional protective outer membrane system or cell wall matrix characteristic of other eubacteria. Interestingly, this wall-less organism possesses a large number of lipoproteins, termed lipid-associated membrane proteins (LAMPs). LAMPs have attracted much attention in recent years, since their abundance in mycoplasmas membranes in contrast to the limited number of lipoproteins in the membranes of other eubacteria.

In the past decade, much progress has been made in elucidating the pathogenicity and pathogenesis of the mycoplasma LAMPs although questions still far outnumber answers. The aim of this review is to collate present knowledge on the LAMPs and to help us get better understanding on the interactions between the lipoproteins on the cell surface and the host cells.

STRUCTURAL-FUNCTIONAL RELATIONSHIP OF LAMPS

Unlike all other prokaryotes, mycoplasmas have

* Project (No. 30570093) supported by the National Natural Science Foundation of China

no cell wall, and their bilipid membrane is the only structure that regulates the interaction with the external environment. The mycoplasma membrane classically consists of two bilipid sheets and membrane proteins. The latter can be classified into two main categories. The first category includes the integral membrane proteins and the second the peripheral proteins. Integral proteins are embedded with varying degrees in the lipid bilayer and are closely associated with the membrane, from which their extraction requires detergents or protein denaturants. In contrast, peripheral proteins are linked to the membrane mainly by electrostatic interactions and therefore can be released easily. These outer peripheral proteins, namely, LAMPs as aforementioned, are also named membrane lipoproteins in some documents or TXLP (Triton X-114 extracted lipoproteins because of their hydrophobic characteristic in Triton X-114 extraction) (Shibata *et al*., 2000).

However, the structures of LAMPs were not fully understood for a period of time because of lack of sufficient starting material and/or difficulties in purification of the lipophilic substances although many lipoproteins had been identified in many bacteria. In the early 1990s, Mühlradt and Schade (1991) extracted a high-molecular-weight material (MDHM) from *Mycoplasma fermentans* (*M. fermentans*) and found that this material can inducing interleukin (IL) 6 production in cultures of both murine macrophages and human monocytes. Initial partial biochemical characterization of MDHM suggested that it should be a mixture of lipoproteins, but the key molecule in this mixture remained unknown, and the biological contribution of the various molecules could not be defined. Further studies (Mühlradt *et al*., 1997) led to the identification of a 2 kDa *M. fermentans* lipopeptide, named MALP-2 (for macrophage-activating lipopeptide). It is a truncated lipopeptide which represents the N-terminal of the MALP-404 lipoprotein by proteolysis, and the lipopeptide has the following structure: S-(2,3-bisacyloxypropyl)-cysteine-Gly-Asn-Asn-Asp-Glu-Ser-Asn-Ile-Ser-Phe-Lys-Glu-Lys with one mole palmitic (C16:0), and a further mole of a mixture of stearic (C18:0) and oleic fatty acid (C18:1) per lipopeptide molecule. Based on the structure of the MALP-2 and chemical analysis, we can speculate the LAMPs contain two ester-linked fatty acids bound to glyceryl cysteine and by the N-terminal lipid moiety, the lipoproteins anchored into the membrane. It was previously believed that the amino group of the cysteine residue was not acylated in LAMPs (diacylated lipoproteins), which was different from the lipoprotein in many Gram-positive or Gram-negative bacteria and that in these bacteria, the amino group was often acylated (triacylated lipoproteins). But recently, more and more evidences showed that triacylated lipoproteins may also exist in mycoplasmas (Shimizu *et al*., 2004). Nevertheless, most of the LAMPs are not N-acylated, which may have important implications for the interactions of mycoplasmas with the environment. Mühlradt *et al*.(1997) showed that diacylated lipoproteins are much more active than triacylated lipoproteins as stimulators of some immune responses.

The structure-functional relationship of LAMPs has been fully studied mainly based on MALP-2 (a special example of LAMPs as described above) in the monocytes/macrophages-stimulating activity. LAMPs derived from most of the mycoplasmas have been reported to be capable of stimulating the release of proinflammatory cytokines such as IL-1β, IL-6, and forming tumor necrosis factor (TNF-α) from human peripheral blood monocytes in a dose-dependent manner (Mühlradt and Frisch, 1994). Comparison of the effects of intact LAMPs with those of proteinase K treated LAMPs reveals that the lipopeptide is responsible for the immunostimulating properties. A number of studies showed that the lipopeptide carrying 2~5 amino acids or containing two ester-bounded palmitoyl residues exhibit stronger biological activity compared with the native lipoproteins and the lipopeptide containing only 1 amino acid or the lipoproteins/lipopeptides carrying ester-bounded palmitoyl residues, respectively. Lipopeptides containing two ester-bounded palmitoyl residues and a free NH_2-terminus exhibit more potent activity toward murine splenocytes than NH_2-terminally elongated lipopeptides whereas the macrophage-stimulating activity of natural MALP-2 carrying heterogeneous fatty acids (C16:0, C18:0 and C18:1) and the synthetic substance (C16:0 only) showed that the two compounds were equally active (Mühlradt *et al*., 1997). Nonlipidated MALP-2 and S-(2,3-bispalmitoyloxypropyl)-N-palmitoyl-Cys (Pam3-cysteine) fail to activate monocytes/macrophages (Mühlradt *et al*., 1997). In addition, the lipid moiety of MALP-2 has an asymmetric C atom at the 2 position. Takeuchi *et*

al.(2000) showed that different configuration of the MALP-2 had different macrophage stimulating activity. These findings suggest that both peptide and fatty acid portions of lipopeptides are indispensable for the expression of their biological activities.

The protein portion of LAMPs is not involved in the macrophage-stimulating activity since protease K treated LAMPs retained most of the stimulating activity. Nevertheless, the protein moiety is relevant to antigenicity and cytotoxicity, etc. (Into *et al*., 2002a). Previous studies showed that the specificity for the recognition of LAMPs ligands by Toll-like receptor 2 (TLR2)-TLR6 was determined by the lipid part only. But recent researches show that both the lipid and the peptide/protein parts contribute to the specificity of signaling through TLRs (Shimizu *et al*., 2005). MALP-2 for example, addition of a positively charged end-group Ser-Lys-Lys-Lys-Lys (-SK4) enables this derivative to induce TLR6-independent signaling (Buwitt-Beckmann *et al*., 2005). The exact biological activity of the protein moiety needs further investigation.

RECEPTORS

The innate immune responses against infectious pathogens precede the cell-mediated immunity. The cells of the innate immune system recognize constituents of microbes by specific receptors, which transmit signals into the cells. Recent work has demonstrated that the human Toll-like receptors are the macrophage cell-surface receptors for LAMPs (Rawadi, 2000). The Toll protein of *Drosophila melanogaster* is a transmembrane protein with an intracellular domain similar to that of the IL-1 receptors (IL-1R) which trigger cell-signaling pathways. Toll is highly conserved among vertebrates and invertebrates, and human homologues have been discovered (Rock *et al*., 1998). To date, at least ten human TLRs have been identified and shown to be critical for signaling by pathogen associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), peptidoglycans, and LAMPs (Akira *et al*., 2001; Takeda and Akira, 2001), etc.

Although numerous lines of evidence have been accumulated that LAMPs are recognized by TLR2 and TLR6, it remains unclear how TLRs recognize their ligands. Recently Fujita *et al*.(2003) have showed leucine residues at positions 107, 112, and 115 in a leucine-rich repeat motif of TLR2 are involved in the recognition of LAMPs. In addition, previous studies showed that LAMPs interacted with TLRs to cause cytokine induction, and that the stimulatory pathway was independent of CD14 and LPS binding protein (LBP) (Chambaud *et al*., 1999). But Schroder *et al*.(2004) demonstrated that CD14 and LBP are also involved in recognition of diacylated lipopeptides such as MALP-2, a feature that previously demonstrated for triacylated lipopeptides only.

Studies have already demonstrated that both TLR2 and TLR4 are implicated in LPS signal transducers, and that TLR1 apparently forms heterodimers with TLR2 to recognize triacylated lipopeptide structures corresponding to, e.g. *Borrelia burgdorferi* lipoproteins (Takeuchi *et al*., 2002). In contrast, the signaling pathways, induced by mycoplasma LAMPs are mediated by TLR2, and require TLR6 (such as form heterodimers) as a coreceptor for recognition. This is not absolute, however. Whether or not TLR6 participates in recognition of LAMPs is partly determined by the structure of the N-terminal peptides just as Buwitt-Beckmann *et al*.(2005) showed. TLR6 per se does not mediate the activity.

SIGNALING PATHWAYS TRIGGERED BY MYCOPLASMA LAMPS

One of the well-documented effects of mycoplasma LAMPs is their capacity to interact with immune competent cell leading to proinflammatory cytokine production or in particular cases, to cell death (Into *et al*., 2004). The intracellular signaling pathways triggered by LAMPs have been extensively studied in previous years (Garcia *et al*., 1998; Into *et al*., 2004; Zeng *et al*., 2004).

The monocyte surface molecule CD14 is part of the receptor complex for several microbial products implicated in the response to peptidoglycan and other bacterial cell wall components. Previous studies showed that cytokine induction by *M. fermentans* LAMPs did not proceed through CD14 (Rawadi *et al*., 1999) since anti-CD14 monoclonal antibodies failed to block cytokine induction. However, opposite re-

sults were obtained by Schroder *et al*.(2004). To a lesser extent, cellular response to LAMPs and tricylated lipopeptides is facilitated by CD14. Additionally, LBP also mediates cytokine induction caused by LAMPs. The possible mechanism is that LAMPs, are bound by LBP and transferred to CD14, the LAMPs-LBP-CD14 complex facilitates the recognition of these ligands by TLR2 in synergy with TLR6.

The downstream signaling events that follow the TLR-mediate activation by LAMPs and lead to cytokine synthesis seem to be similar to the intracellular events induced by LPS. The TLR6 has a cytoplasmic domain homologous to the IL-1 receptor. Triggering of the TLR/IL-1R family signaling cascade requires the recruitment of the myeloid differentiation protein MyD88 to the receptor complex, which then activates nuclear factor-κB (NF-κB) and c-jun amino-terminal kinase (JNK), via interleukin-1 receptor-associated kinase (IRAK). Indeed, *M. fermentans* or the MALP-2 activate NF-κB and activator protein (AP)-1, the two transcription factors play a central role in the induction of proinflammatory cytokines, and induce cell apoptosis, as well as the mitogen-activated protein kinase family members including extracellular signal-regulated kinase 1 and 2, JNK, and p38 (Garcia *et al*., 1998; Rawadi *et al*., 1999), etc.

IMMUNOMODULINS

The term modulin has been proposed to describe components and products of bacteria that can stimulate cytokine synthesis with pathological consequences (Henderson *et al*., 1996). The first and most widely studied modulin was the LPS of Gram-negative bacteria. During the past decade it has been shown that in addition to LPS, other bacteria components, mainly those associated with the cell wall, such as peptidoglycan fragment, lipoteichoic acid and murein lipoproteins can stimulate mammalian cells to produce cytokines. Recent attempts to identify mycoplasmal cytokine-inducing moieties have targeted on superantigens, choline-containing phosphoglycolipids and LAMPs (Chambaud *et al*., 1999).

Modulatory effects on monocytes and macrophages

It has been suggested that during mycoplamal infection, the damage to host cells is not by direct lesion but is caused by immunopathogenesis. It is also recognized that LAMPs, like many other modulins, are capable of stimulating monocytes, macrophages, and brain astrocytes and inducing the secretion of the proinflammatory cytokines such as TNF-α, IL-1 and IL-6, chemokines, such as IL-8, monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein 1 (MIP-1α), granulocyte-monocyte colony stimulating factors (GM-CSFs), as well as prostaglandins and nitric oxide (Razin *et al*., 1998). The potent molecules and mediators released by cells responding to mycoplasma LAMPs enhance expression of major histocompatilbility complex (MHC) Class I and Class II antigen and of costimulatory end cell adhesion molecules in leukocytes and endothelial cells, and induce recruitment and extravasation of leukocyte to the site of infection and cause local tissue damage (Razin *et al*., 1998). Additionally, Into *et al*.(2002b) found that extracellular ATP (ATPe) had synergic effects with mycoplasma lipopeptides in activation of macrophage and induced lymphocytes and macrophages death. The effects are P2X purinergic receptor mediated. It has been suggested that under acute inflammatory or mechanical stress, various types of cells induce release of ATP. In this sense we can speculate on the sequence of events that may occur during mycoplama-associated urinary inflammation, joint disease and AIDS.

Downregulation of inflammation

As described above, mycoplasma LAMPs are potent stimulants of the host immune response, but mycoplasma infections are not necessarily associated with a strong inflammatory response and most infections do not present apparent clinical symptoms. It is therefore temping to speculate that in addition to triggering the production of proinflammatory cytokines, LAMPs may have the capacity to downregulate the synthesis of proinflammatory cytokines. As postulated, LAMPs derived from *M. fermentans* can also induce IL-10 production in freshly isolated human monocytes (Rawadi *et al*., 1996). IL-10 is a cytokine which could downregulate inflammatory response. Other cytokines such as IL-4, IL-13 or transforming growth factor-β, induced by certain mycoplasmas or LAMPs, contribute to the complex network of synergistic and antagonistic influence (Rottem, 2003).

CIRCUMVENTION OF THE HOST IMMUNE SYSTEM

As parasitic bacteria, mycoplasmas can continue to colonize the host even in the presence of a specific immune response. This property of mycoplasma may explain the slowly progressive chronic manifestations of mycoplasma-associated diseases. Circumvention of the host immune system is of utmost important to the survival of a mycoplasma with its host. The major mechanisms that have been studied at length are molecular mimicry and phenotypic plasticity (Rottem, 2003), which ensure that the mycoplasmas are not fully or efficiently recognized by the host's immune system. Molecular mimicry refers to antigenic epitopes that have been shown to be shared by different mycoplasmas and host cells and were proposed as putative factors involved in evasion of host defense mechanisms and/or induction of autoantibodies observed during infections with certain mycoplasmas. Mycoplasmas are also endowed with a sophisticated mechanism for varying the antigenic repertoire of their cell surface. In spite of the very limited genetic information that mycoplasmas contain, the number of mycoplasma genes involved in diversifying the antigenic nature of their cell surface is unexpectedly large. Most of the variable surface components are mature, processed LAMPs. These lipoproteins, depending upon the species are encoded by single or multiple gene(s) and undergo frequent phase and size variation during mycoplasmas growth (Horino *et al*., 2003; Roske *et al*., 2001). A variety of mechanisms are involved in the LAMPs variation, including: (1) a high frequency of ON/OFF switching of genes expression, resulting in differences in the expression of suface LAMPs, termed phase variation (Roske *et al*., 2001); (2) varying the number of tandem repeats at the carboxy terminus (Simmons and Dybvig, 2003; Tu *et al*., 2005), thereby varying the lipoprotein size, namely, size variation; (3) differential masking of selective lipoprotein regions by other surface antigen (Zhang and Wise, 2001); (4) posttranslational processing, such as Davis and Wise (2002) suggested, site-specific proteolysis of MALP-404, a *M. fermentans* lipoprotein, result in the MALP-2 and a soluble released fragment (RF) products, which contribute to the different ratios of MALP-404 and MALP-2 on the mycoplasma surface among isolates of *M. fermentans*, thereby altering the surface phenotype of this organism.

Variation of LAMPs have profound effects on the organism virulence, such as elongated surface lipoproteins protecting mycoplasmas from growth inhibiting antibodies, variable surface antigens (Vsa) of *Mycoplasma pulmonis* modulate susceptibility of mycoplasmas to complement killing, hemadsorption, etc. In this sense, the variation of LAMPs is a means for evading the host immune response, and this is true at least for some mycoplamsa species. However, a long-term study of *Mycoplasma hominis* (*M. hominis*)-infected patients indicated that serial isolates of this mycoplasma showed no antigenic variation with time, but isolates obtained from different patients showed a high degree of antigenic variation. Thus, the antigenic variation in *M. hominis* seems to be a means of adaptation to a specific host, rather than a reaction to the development of an immune response.

CYTOTOXICITY

Other than their modulatory effects on the immune system, LAMPs are also cytotoxic to host cells. Studies have demonstrated that LAMPs derived from *M. fermentans* and *Mycoplasma salivarium* (*M. salivarium*) possess cytocidal activity towards lympholytic cells and monocytic cells (Into *et al*., 2002b), thus inducing their death. Cell death is classified into two forms by morphological and biochemical features: apoptosis (or programmed cell death, characteristic of cell shrinkage, cytoplasmic vacuolization, apoptotic bodies and deletion of microvilli, surface protrusion) and necrosis (such as dissolution of the cytoplasm and absence of recognizable organelles).

Recognition of LAMPs by the innate immune system can trigger the production of various proinflammatory cytokines from manifold cells; on the other hand, LAMPs can directly initiate apoptotic signaling by interaction with TLR2 and TLR6. Into *et al*.(2004) showed, after being stimulated by LAMPs, the human embryonic kidney cells (HEK293) present sequential bifurcate response: after 6 h of stimulation, LAMPs induced NF-κB activation in a dose-dependent manner, which is defined as the early event, and no cytocidal activity was shown. However after 24 h of stimulation, apoptosis occurred (later event). These

two events are TLR2 and TLR6 mediated, but the mechanisms are different: NF-κB activation is partially mediated by MyD88 and FADD (Fas-associated death domain), and apoptosis is regulated by p38 MAPK as well by MyD88 and FADD.

In addition to initiating apoptosis signals by TLRs, LAMPs also affect the permeability in lymphocytes and monocytes, which in turn induce the immune cells necrosis or apoptosis. Into *et al*.(2002a) suggested that mycoplasma LAMPs could increase the permeability of lymphocytes and monocytes, by which ATP was released from the cells. The released ATP interacts with the ATP-gated ionotropic receptors such as $P2X_1$ or $P2X_7$, by which necrosis or apoptosis occurred. These receptors are P2 purinergic receptors, which are known to recognize extracellular nucleotides, can be divided into two groups designated P2X, ligand-gated cation channels; and P2Y, G-protein coupled receptors, the P2X and P2Y receptor subtypes, include $P2X_1$, $P2X_7$, $P2Y_2$ and $P2Y_4$, which are sensitive to ATP. $P2X_1$, the non-selective intrinsic cation channel, is thought to be involved in ATP-mediated apoptosis. $P2X_7$, could form a pore allowing large molecule (<900 Da) to pass through. In this sense, the non-selective pore-forming properties of $P2X_7$, its activation by ATP is more likely to result in necrosis than apoptosis.

Although many bacteria pathogens induce apoptosis in host cells, the implication of this phenomenon remains elusive, like many other bacterial lipoproteins, LAMPs-induced apoptosis may be important for (1) the initiation of inflammation, (2) resolution of inflammation, (3) generating the proper signal necessary for adaptive immune response.

MALIGNANT TRANSFORMATION OF HOST CELLS

A linkage between mycoplasma and malignancy was mainly proposed in the 1960s when human-associated mycoplasmas were becoming of interest given the novel characterization of the human respiratory pathogen *Mycoplasma pneumoniae* (*M. penumoniae*). Because of their chronically colonizing our respiratory and urogenital tracts without apparent clinical significance, in this respect, wall-less mycoplasma can silently grow in close interaction with mammalian cells for a long period of time. However, the prolonged interaction with mycoplasmas with seeming low virulence could, through a gradual and progressive course, significantly affect many biological properties of mammalian cells.

Feng *et al*.(1999) found that 32D cells, a murine myeloid cell line, rapidly undergo apoptosis upon withdrawal of IL-3, if LAMPs or live mycoplasmas are added, they would live and continue to grow in IL-3-depleted cultures. Additionally, live *M. fermentans* or *Mycoplamsa penetrans* (*M. penetrans*) infection for 4 to 5 weeks induced malignant transformation of 32D cells, the transformed 32D cells quickly formed tumors when injected into nude mice. Another example are the effects of mycoplasma LAMPs on receptor response to steroid hormones in mammalian cells. As Iyama *et al*.(2001) suggested, LAMPs from several different species of human mycoplasmas had inhibitory effect on androgen receptor response to 5α-dihydrotestosterone in the E82 transfectants. The inhibitory effect of mycoplasma LAMPs appeared to be dose dependent. LAMPs from *M. penetrans*, *Mycoplasma genitalium* (*M. genitalium*), *M. salivarium*, *M. penumoniae* and *Mycoplasma oral* also had inhibitory effect on glucocorticoid receptor (GR) response to hormone dexamethasone (Dex) in TSU transfecants. In contrast, LAMPs from *M. fermentans* and *M. hominis* showed stimulatory effect on the GR response to Dex in these cells. It is well-known to us that steroid hormones, such as estrogen and androgen, promote cell proliferation in sexual organs and play an important role in the induction of cancer formation in these tissues. Although the effects of mycoplasma LAMPs on steroid receptor transactivities are not as strong as the effect of cAMP, the biological importance of the long-term effect on steroid receptor functions in human hosts with chronic mycoplasma infection or colonization could be significant.

LAMPS AND AIDS

It has been suggested that some infectious agents such as *M. fermentans*, *M. penetrans* and *M. genitalium* are considered to be cofactors in the progression of AIDS, but the precise mechanisms have not been fully clarified. Shimizu *et al*.(2004) showed that

M. fermentans and *M. penetrans*-derived LAMPs can activate human immunodeficiency virus (HIV) long-terminal repeats and hence enhance the replication of HIV although the HIV long terminal repeat alone can serve as its own promoter. The activation is mediated by TLR1, TLR2 and TLR6 for *M. penetrans* and TLR1 and TLR2 for *M. fermentans*, respectively. The difference in TLRs may be due to the existence of tracylated lipoprotein in *M. penetrans* although no N-acyltransferase gene has been found in their genomes.

PERSPECTIVES

Great developments during the past decade helped us to understand the interactions between mycoplasma LAMPs and the host cells. However, most of the studies were carried out in vitro, the drawback of which is that it is not necessary the case reflecting the natural occurrence of the infection, and that most of these results are based on only a few parts of the pathogenic mycoplasmas, such as *M. penetrans* and *M. fermentans*. And other mycoplasmas, such as *M. genitalium*, the roles of this smallest organism-derived LAMPs are largely unknown. Most mycoplasmas chronically colonize our respiratory and urogenital tracts without apparent significant effect. The questions are: how do they cause damage to the host cells and to what extent is the damage clinically apparent?

It was believed that the diacylated lipoprotein was the feature of LAMPs and that triacylated lipoproteins belonged to other bacteria. However, more and more evidences demonstrated the possibility of the existence of triacylated lipoproteins in some mycoplasmas, such as the aforementioned *M. penetrans*. The mechanism of obtaining triacylated lipoproteins is still a riddle because no N-acyltransferase gene has been found in these genomes, and the presence of mycoplasma proteins with N-acyltransferase activity has not been reported either, so when do these species lose the lipoprotein N-acyltransferase genes and how does the extent of acylation alter the modulin activity of LAMPs? Although many mechanisms have been elucidated on the variation of LAMPs, what is the precise impact of LAMPs variation on the physical and chemical properties of the mycoplasma surface? As part of the normal microflora, why do mycoplasmas not induce inflammatory response? Do mycoplasmas really cause human cancer? If so, what is the mechanism? Evidently, these questions need our further investigation.

Based on the immunomodulation characteristic of LAMPs, new light has now been shed on the clinical therapy by this bioactivity. For example, Romero *et al*.(2004) showed that a low dose of MALP-2 could induce the production of granulocyte-monocyte colony stimulating factor without a significant reduction of peripheral blood leukocyte. This may open a way for the potential therapeutic use of this lipopeptide in neutropenic patients. Now that LAMPs can induce differentiation and apoptosis of mammalian cells just as Hall *et al*.(2000) showed, so some LAMPs may be potentially useful new agents for treating leukemia or as immunonodulatory agents in cancer and other diseases. Additionally, based on the structures of some LAMPs, such as M161Ag, an *M. fermentans* lipoprotein, we can synthesize a variety of TLR2 stimulants that facilitate dendritic cells activation without oncogenesis, and we may use these products as therapeutic immunepotentiators (Seya and Matsumoto, 2002).

ACKNOWLEDGEMENT

The authors wish to thank WAN Yan-ping and WANG Xin for their critical review of the manuscript, and thank Yi Chao-qun and WANG Ji-ping for their assistance with its preparation.

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