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Pathogenic Mycoplasma Infections in Chronic Illnesses: General Considerations in Selecting Conventional and Integrative Treatments

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Abstract

The presence of pathogenic mycoplasmas in various chronic illnesses and their successful suppression using conventional and integrative medicine approaches are reviewed. Evidence gathered over the last three decades has demonstrated the presence of pathogenic mycoplasma species in the blood, body fluids and tissues from patients with a variety of chronic clinical conditions: atypical pneumonia, asthma and other respiratory conditions; oral cavity infections; urogenital conditions; neurodegenerative and neurobehavioral diseases; autoimmune diseases; immunosuppressive diseases; inflammatory diseases; and illnesses and syndromes of unknown origin, such as fatiguing illnesses. Only recently have these small intracellular bacteria received attention as possible causative agents, cofactors or opportunistic infections or co-infections in these and other conditions. Their clinical management is often inadequate, primarily because of missed diagnosis, under- and inadequate treatment and the presence of persister or dormant microorganisms due to biofilm, resistence and other mechanisms. Pathogenic *Mycoplasma* species infections have been suppressed slowly by anti-microbial and integrative treatments, resulting in gradual reductions in morbidity, but not in every patient. Even if mycoplasmas are not a cause or an initial trigger for many chronic illnesses, they appear to play important roles in the inception, progression, morbidity and relapse of chronic illnesses in rather large patient subsets. Ignoring such infections can result in failure to achieve eventual patient recovery, even with application of potentially curative treatments.

Keywords

Chronic Diseases, Infections, Antibiotics, Herbel Therapy, Immune Enhancement, Membrane Lipid Replacement, Mycoplasma, Natural Supplements, Integrative Medicine

1. Introduction

Mycoplasmas belong to the class *Mollicutes*, and they are considered the smallest free-living prokaryocytes capable of self-replication [1] [2]. There are more than 200 bacterial microorganisms that belong to the genus of Mycoplasma, and the more than two dozen pathogenic species found in humans are typified by: 1) lack of an external cell wall; 2) obligate parasitic behavior; 3) intracellular growth; and 4) the loss of many of their genes due to reductive evolution [2] [3] [4]. Mycoplasmas are widely distributed in nature, where they are often found attached to the external surfaces of cells or residing and replicating inside host cells [1] [2].

It has been only fairly recently that mycoplasmas have been identified as important pathogens in humans, animals, plants and insects [1] [3] [5] [6]. There is evidence in humans that pathogenic mycoplasmas are associated with certain chronic diseases where they could function as causative agents, cofactors or opportunistic infections that cause patient morbidity [5] [6] [7]. For example, pathogenic mycoplasmas in humans are often associated with respiratory infections, urogenital infections, fatiguing illnesses, autoimmune diseases, neurodegenerative and neurobehavioral diseases and complications affecting the central nervous system, cardiac infections, oral infections, peridontal diseases, sexually transmitted diseases and systemic infections found in various solid cancers and leukemias and immunosuppressive diseases, such as HIV-AIDS [5] [6] [7].

Although various mycoplasmas are commonly found as commensals in the oral cavity and at other superficial sites [3], certain pathogenic species appear to cause morbidity when they penetrate into the blood and spread to and colonize various tissues [2] [5] [6] [7]. For example, *Mycoplasma hominis* and *Ureaplasma urealyticum* are common inhabitants of the human genital tract, but they can play an etiologic role in pyelonephritis, pelvic inflammatory disease as well as in post-abortion and post-partum fevers [3] [7] [8] [9] [10]. Furthermore, there are reports of mycoplasmas causing serious acute infections, such as septicemia, septic arthritis, neonatal meningitis and encephalitis [2] [6] [7] [11]. As an example of their pathogenic potential in mammals, it was shown that *M. fermentans* can cause severe neurological signs and symptoms after injection into the cerebral fluid of rats [12] [13]. Although still a subject of intense discussion, several pathogenic mycoplasma species have been proposed to be etiologic agents or cofactors in various chronic diseases of man [1] [2] [3] [5] [6] [7]. This will be discussed briefly in the next sections.

Mycoplasmas contain the smallest known self-replicating genomes, and they have an unusually low G + C content (25% - 33%) [1] [4]. With their limited genomes mycoplasmas have provided researchers with a simple model for the identification of the minimal gene set required for the survival and growth of a free-living bacterium [14] [15]. The small genomes of *M. genitalium* and *M. pneumoniae* encode approximately 400 - 600 proteins, compared to about 4000 in *E. coli* [16]. Furthermore, mycoplasmas still maintain all of the essential genes

for replication, transcription, and translation as well as the minimal number of energy metabolism genes needed for their parasitic modes of life. They can do this with a core number of slightly less than 400 essential genes [17].

Essentially all mycoplasmas live as parasites or commensals in various species of animals and plants, where they are usually found attached to or inside host cells [3] [4] [5]. Thus a significant number of mycoplasmal genes are devoted to encoding cell adhesion and attachment structures as well as variable membrane surface antigens to maintain parasitism and evade host immune and non-immune surveillance systems [3] [4] [5]. The adherence of mycoplasmas to specific tissue cell surfaces is a crucial step in the establishment of infections, and pathogenic mycoplasmas possess specialized structures that permit targeted cell attachment to specific host cells. For example, *M. pneumoniae*, which is commonly found in cases of atypical childhood pneumonia, requires a network of interactive adhesion molecules and accessory proteins for its adherence to host epithelial cells [4] [5]. The adhesion molecules must cluster at specific mycoplasma organelles in close association with cytoadherence-related accessory proteins that appear to function together and comprise a primitive membrane adhesion structure [4] [5] [18] [19].

Mycoplasmas can adapt quickly to their microenvironments. This adaptation is an important element in mycoplasma pathogenicity, and it can be attributed to their rapidly varying genomic structures and abilities to quickly change [3]. When mycoplasmas evolved and adapted to parasitic modes of life, their transformation was likely made possible by devoting many of their genes to parasitic functions. Thus the genetic evolutions of mycoplasmas have ensured rapid alterations in cell membrane characteristics, such as membrane lipid phase variations and variable regulations of distinct membrane surface proteins involved in cell colonization and host immune system avoidance. Some examples include size and sequence variations in the structural domains of surface proteins, epitope masking and demasking, and changes in protein surface presentations [20].

Mycoplasmas are known to variably express structurally heterogeneous cell surface antigens and adhesion molecules. For example, variations in the genes encoding cell surface adherence molecules, such as the variable adherence-associated (Vaa) antigen, reveal distinct patterns of mutations capable of generating multiple changes in mycoplasma cell surface antigen molecules and their antigenic size and diversity [21]. In addition, mycoplasmas can scavenge host structures, such as host glycans, for decoration of their own surface glycolipids to avoid detection [22].

Variable surface antigenic structures and rapid changes in their expression are thought to play important roles in the pathogenesis of mycoplasmal infections by providing altered epitope structures for an escape from immune responses and changes in adhesion structures. This can influence cell and tissue colonization and penetration of mucosal barriers [21] [23].

Mycoplasmas have small and unique genomes that contain repetitive and other elements, and this contributes to the variability in antigenic structures. For

example, the genome of *M. genitalium* was recently sequenced and found to encode a number of identifiable membrane proteins as well as membrane glycolipo proteins whose sequences do not resemble previously sequenced genes [24]. For example, repeated fragments of a gene encoding a 140 kDa adhesion lipoprotein (MgPa) have been found, and interestingly, this lipoprotein has been localized to the tips of mycoplasma protrusions where it facilitates cell attachment and penetration [25]. Repetitive sequence elements are also variably present that do not appear to encode expressed proteins. However, recombination of these repetitive elements with other genes may explain the appearance of polymorphisms within the genes and their encoded surface proteins of different mycoplasma strains. These repetitive elements, for example in the *M. genitalium* genome, may provide a reservoir of sequences that could contribute to the variability of antigenic structures and adhesive properties found in pathogenic mycoplasmas [26].

2. Mycoplasmas and Host Response Systems

Pathogenic mycoplasmas can activate or suppress host response systems, and they apparently use these and other strategies to evade host immune surveillance [27]. For example, pathogenic mycoplasmas can act as immune cell suppressors/activators and inhibit or stimulate the proliferation of various lymphocyte subsets involved in memory, suppression and other activities. Pathogenic mycoplasmas can also induce B-cell differentiation and trigger the secretion of pro-inflammatory cytokines, including interleukin-1β (IL-1β), IL-2, IL-6, IL-8, among others, tumor necrosis factor-α (TNFα), various interferons, and granulocyte macrophage-colony stimulating factor (GM-CSF) from cells. This also occurs *in vivo* in patients with pathogenic mycoplasmal infections. In fact, the release of inflammatory cytokines *in vivo* is predictive of refractory mycoplasmal infections in children [28].

Mycoplasma-derived lipopeptides can directly stimulate host response cells, such as macrophages. Such lipoproteins have been found to be highly effective at immune stimulation similar to endotoxins derived from other bacteria [29]. Using nitric oxide release by macrophages as an indicator of immune stimulation a *M. fermentans*-derived lipopeptide was identified as a potent activator of macrophage function [30]. In addition, *M. fermentans*-derived lipoproteins can interfere with the interferon gamma-dependent (IFN-γ-dependent) expression of MHC class II molecules on macrophages [31].

Pathogenic mycoplasmas are also able to secret soluble factors that can activate and stimulate proliferation or inhibit the growth and differentiation of immune competent cells. For example, *M. penetrans* can induce significant proliferative responses in peripheral blood mononuclear cells, and this was found to be associated with the expression of surface markers of lymphocyte activation. The activation was observed in lymphocytes (both CD4+ and CD8+ T lymphocytes) from healthy donors as well as from HIV-infected subjects at different stages of disease progression [32]. Thus pathogenic mycoplasmas have evolved with the ability to modulate and interfere with host responses.