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Possible role of mycoplasmas in pathogenesis of gastrointestinal diseases.

Revisión

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SUMMARY.

Although the ability of internalized mycoplasmas to multiply within the host cell remains to be convincingly demonstrated, reports of invasive mycoplasmas offer new insights into the potential virulence strategies employed by mycoplasmas. Several factors are suspected to play a role in gastrointestinal diseases, including exogenous chemical, genetic factors, pathological conditions and infectious agents in the gastrointestinal tract. This review describes the role of mycoplasmas in the pathogenesis of gastrointestinal diseases.
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Key words: mycoplasmas, gastrointestinal diseases.

RESUMEN.

Posible participación de micoplasmas en la patogénesis de enfermedades gastrointestinales.

Debido a la capacidad que presentan diversas especies de micoplasmas para multiplicarse intracelularmente en sus respectivas células hospederas, los reportes de micoplasmas intracelulares permiten conocer factores de virulencia que utilizan estos microorganismos. Diversos factores juegan un papel importante en la etiología de padecimientos gastrointestinales, incluyendo los compuestos químicos exogenos, factores genéticos, condiciones patológicas y agentes infecciosos principalmente. Esta revisión presenta el papel de los micoplasmas en la patogenicidad de enfermedades gastrointestinales.
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Palabras clave: micoplasmas, enfermedades gastrointestinales.

INTRODUCTION.

Mycoplasmas are the smallest and simplest self-replicating bacteria. These microorganisms lack a rigid cell wall and are bound by a single membrane. The lack of a cell wall is used to distinguish these microorganisms from ordinary bacteria and to include them in a separate class

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named Mollicutes. Because mycoplasmas have an extremely small genome (580-1380 kbp), these organisms have limited metabolic options for replication and survival (1). Comparative genomic studies suggest that the genome of this organism still carries almost double the number of genes included in the minimal gene set essential for cellular function (2,3).

These microorganisms have evolved the molecular mechanisms needed to deal with the host immune response and transfer and colonization in a new host. These mechanisms include mimicry of host antigens, survival within phagocytic and nonphagocytic cells, and generation of phenotypic plasticity (4).

Although mycoplasmas are generally commensal parasites in humans, some species are real pathogens and are capable of causing a wide variety of diseases. Mycoplasmas present in the human oropharynx included *Mycoplasma orale, M. salivarium, M. faucium*, which produce ammonia and cause tissue damage, and *M. fermentans*, which induces inflammatory cytokines from macrophages and epithelial cells (5-9). The major question is whether mycoplasmas cause damage to the host cells and to what extent the damage is clinically apparent. Mycoplasmas have long resisted detailed analysis because of complex nutritional requirements, poor growth yields, and a paucity of useful genetic tools. Although questions still far outnumber answers, significant progress has been made in identifying the mechanisms by which mycoplasmas interact and damage eukaryotic host cells (4).

The presence of mycoplasmas in gastritis and gastrointestinal tumors has been reported. These reports provoked concern about the epidemiological role of mycoplasmas in gastric cancer, though the fact the identified species was of porcine origin, *M. hyorhinis*, was unexpected (10-12). Pathobiological similarities between mycoplasmas and *H. pylori*, and questions about additional risk factors in the tumorigenesis of Korean gastric cancer encouraged us to further investigate the detection and identification of mycoplasmas in chronic gastritis (13). The purpose of the present review is to provide an updated, comprehensive summary of the role of mycoplasmas in the pathogenesis of gastrointestinal diseases.

MECHANISMS OF DAMAGE TO HOST CELLS.

Many animal mycoplasmas depend on adhesion to host tissues for colonization and infection. In these mycoplasmas adherence is the major virulence factor, and adherence-deficient mutants are avirulent (1,5). The best studies on adherence systems are those of *M. pneumoniae*, the causative agent of primary atypical pneumonia in humans, which inhabits the respiratory tract, and *M. genitalium*, which preferentially colonizes the urogenital tract. These organisms exhibit the typical polymorphism of mycoplasmas, with the most common flask and filamentous shape. Cytadherence of these organisms to cells in the respiratory or urogenital epithelium is an initial and essential step in tissue colonization and subsequent disease pathogenesis (14,15).

Current theory holds that mycoplasmas remain attached to the surface of epithelial cells, although some mycoplasmas have evolved mechanisms for entering host cells that are not naturally phagocytic. The intracellular location is obviously a privileged niche, well protected from the immune system and from the action of many antibiotics. The ability of *M. pneumoniae* isolated from the urogenital tract of acquired immunodeficiency syndrome (AIDS) patients, to invade and survive within host cells has been intensely studied (16,17). This microorganism has invasive properties and localizes in the cytoplasm and perinuclear regions (18-20). Other mycoplasmas known to be surface parasites such as *M. fermentans* (21,22), *M. pneumoniae* (4), *M. genitalium*, and *M.* gallisepticum (23), under certain circumstances, reside within nonphagocytic cells.

Immunofluorescent staining of internalized bacteria and of those remaining on the cell surface, combined with confocal laser scanning microscopy, has demonstrated that *M. penetrans* penetrates eukaryotic cells. This nondestructive, high-resolution method allowed infected host cells to be optically sectioned after fixation and immunofluorescent labeling. Imaging single infected HeLa cells revealed that invasion is both time and temperature dependent. Penetration of HeLa cells has been observed as early as 20 min after infection, whereas invasion of cultured Hep-2 cells by *M. penetrans* has been shown to begin after 2 h of infection (5,19).

Genomic analyses of mycoplasmas have revealed the limited biosynthetic capabilities of these microorganisms (24-26). Mycoplasmas apparently lost almost all the genes involved in the biosynthesis of amino acids, fatty acids, cofactors, and vitamins and therefore depend on the host microenvironment to supply the spectrum of biochemical precursors required for the biosynthesis of macromolecules (26,27). Competition for these biosynthetic precursors by mycoplasmas may disrupt host cell integrity and alter host cells function. Nonfermenting *Mycoplasma spp*. utilize the arginina dihydrolase pathway for generating ATP and rapidly deplete the host's arginina reserves affecting protein synthesis, host cell division, and growth (26-28). Certain strains of arginina-utilizing *Mycoplasma spp*. have been shown to induce chromosomal aberrations in host cells, most commonly chromosomal breakage, multiple translocations, a reduction in chromosome number, and the appearance of new and/or additional chromosome varieties (15, 29). Because histones are rich in arginina, it has been suggested that arginina utilization by mycoplasmas inhibits histone synthesis and causes chromosomal damage (15,28,29). *M. fermentans* infection of rat astrocytes has been shown recently to result in a choline-deficient environment and in the induction of apoptosis (30). Choline is an essential dietary component that ensures the structural integrity and signaling function of the cell membranes, it is the major source of methyl groups in the diet, and it directly affects cholinergic, neurotransmission, transmembrane signaling, and lipid transport and metabolism (31).

The attachment of mycoplasmas to the surface of host cells may interfere with membrane receptors or alter transport mechanisms of the host cells. The disruption of the K^+ channels of ciliated bronchial epithelial cells by *Mycoplasma hyopneumoniae* that resulted in ciliostasis has been described (32). The host cell membrane is also vulnerable to toxic materials released by the adhering mycoplasmas, the production of cytotoxic metabolites and the activity of cytolytic enzymes is well established. Oxidative damage to the host cell membrane by peroxide and superoxide radicals excreted by the adhering mycoplasmas appears to be experimentally well-substantiated (33). The intimate contact of the mycoplasma with the host cell membrane may also result in the hydrolysis of host cell phospholipids catalyzed by the potent membrane-bound phospholipases present in many mycoplasma species (34). This could trigger specific signal cascades or release cytolytic lysophospholipids capable of disrupting the integrity of the host cell membrane (35,36).

During the fusion process, mycoplasma components are delivered into the host cells and affect the normal functions of the cell. A whole array of potent hydrolytic enzymes have been identified in mycoplasmas (27,35,36). Most remarkable are the mycoplasmal nucleases that may degrade host DNA (27,37,38). It has recently been shown that *M. fermentans* contains a potent phosphoprotein phosphatase (39). Phosphorylation of cellular constituents by interacting cascades of serine-threonine and tyrosine protein kinases and phosphatases is a major means by which a eukaryotic cell responds to exogenous stimuli (40). The delivery of an active phosphoprotein phosphatase into the eukaryotic cell upon fusion may interfere with the normal signal transduction cascade of the host cell. In addition to delivery

of the mycoplasmal cell content into the host cell, fusion also allows insertion of mycoplasma membrane components into the membrane of the eukaryotic host cell. This could alter receptor recognition sites as well as affect the induction and expression of cytokines and alter the cross-talk between the various cells in an infected tissue (4).

PRESENCE OF MYCOPLASMAS IN GASTROINTESTINAL BIOPSIES.

Intestinal mycoplasmas, either in the small bowel or colon, were found in rats (41), dogs (42), horses, pigs (43), cattle (44), primates (45) and humans (46,47). However, only those in dogs have been associated with colitis, although many of these older investigations are not as comprehensive or precise as could now be undertaken with newer experimental techniques. Two studies in humans have detected mycoplasmas in the rectum and anal canal in cases without Crohn´s disease(46,47).

Crohn´s disease is an acute chronic inflammatory illness of the digestive tract characterized by pain, diarrhoea and fever, with thickening of the bowel wall, intestinal fistulae and fissures. It can affect almost any part of the gastrointestinal tract. Crohn´s disease is difficult to typecast for a single therapy due in part to the diversity of symptoms and the variability of the clinical course. Treatments vary and include the use of anti-inflammatory drugs and antibiotic therapies which are used without recourse to a causative organism while, in the most intractable cases, surgery may be the last resort (48,49). The cause of Crohn´s disease is unknown but dietary, environmental and genetic factors have all, at one time or another, been thought to be involved. Clinical observations suggest that luminal factors in the gut and microorganisms play an aetiological role in Crohn´s disease (50,51). However, those infective organisms that have been studied including the atypical mycobacteria, do not explain the manifestations of Crohn´s disease that occur throughout the gastrointestinal tract (52,53). Evidence can be mustered for the involvement of mycoplasmas in the pathogenesis of Crohn´s disease in the oral cavity, small bowel, colon and ano-rectum. The mycoplasmas did not appear to be pathogenic, but the distinction between non-pathogenic and pathogenic bacteria depends on a variety of host and environmental factors.

Intestinal microflora are believed to play an important role in the pathogenesis of inflammatory bowel disease. Mycoplasma have previously been suggested as organisms of ubiquitous distribution with the potential to cause inflammatory diseases, including inflammatory bowel disease in susceptible individuals. A total of 260 endoscopic biopsies (49 from 19 patients with Crohn´s disease, 76 from 27 patients with ulcerative colitis and 135 from 43 non inflammatory bowel disease controls) were used in the study. Overall, *M. pneumoniae* specific DNA was detected in 100 endoscopic biopsy samples (38.5%). Among them, the detection rate of *M. pneumoniae* DNA was significantly higher in biopsies from patients with Crohn´s disease (59.2%) than in those patients with ulcerative colitis (26.3%) or non inflammatory bowel disease controls (37.7%). The high prevalence of *M. pneumoniae* in both inflammatory bowel disease patients and controls suggest this organism is ubiquitous and may persist in the intestinal mucosa. Epidemiological studies in inflammatory bowel disease suggest acquisition of some agents early in life probably during epidemics in temperate latitudes. *M. pneumoniae* could be one the ubiquitous agents implicated in the pathogenesis of an inflammatory bowel disease (54).

Investigations by scanning microscopy into changes of surface morphology of small bowel mucosa in children with chronic nonspecific diarrhea are reported. The major findings were microorganisms on the mucosal surface; excessive extrusion of cells cytoplasm and of enterocytes (cell shedding); villous atrophy. All these changes are considered pathologic and, for the most part, are presumed to be due to the presence of antigens,

in particular, microorganisms. A depression of disaccharidase activities was encountered in 64% of the patients, but prevalence was without regard to age. Most common was a combined depression of lactase, sucrase and maltase, as well as an isolated depression of lactase. The possibility that enteroadherent microorganisms which are not usually considered pathogenic, and microorganisms such as mycoplasmas, may emerge as intestinal pathogens in susceptible children has to be considered. It is feasible that genetic traits of the host and environmental factors facilitate adherence and colonization of the small bowel mucosa which, in turn, produces chronic diarrhea (55).

Histological study using semiquantitative analysis and immunofluorescent microscopy of the intestine performed on 278 children of different ages who died of acute respiratory, viral and mycoplasma infections revealed intestinal changes in 168 cases. The incidence and degree of these changes depended on the duration of the disease and the type of intensive therapy used (12).

In another study twenty-three (41%) out of 56 chronic gastritis samples were positive for several human mycoplasmas (56). The presence of microorganisms other than *H. pylori* in gastric cancer and in the tissue of patients with other gastric disorders has been reported. *Streptococcus anginosus* and *M. hyorhinis* were identified in Japanese gastric cancer tissue by means of an in gel competitive DNA re-association method (57,58). *M. hyorhinis* as identified in more than 50% of gastric cancer tissue in a Chinese population by immunohistochemistry and PCR, and the positive rate in gastric cancer was found to be significantly higher than in other gastric disease (10,11). *M. hyorhinis* is a swine mycoplasma and is very commonly found in the nasal and tracheobronchial secretions of young swine (59). Human mycoplasmas are frequently detected on various mucous membranes, but to date *M. hyorhinis* has never been detected in other human tissue (60). Normally mycoplasma in the oral cavity can enter the stomach with food and saliva, and thus it is more likely that human mycoplasmas will be detected in gastric tissue than swine mycoplasmas (56).

Mycoplasmas present in tissue samples from patients resemble *H. pylori* with respect to the role that it plays in the tumorigenesis of gastric cancer. The non-fermentative mycoplasmas, *M. salivarium, M. orale, M. faucium* and *M. spermatophilum,* are known to produce ammonia from arginina, to cause tissue damage and to neutralize gastric acid (10).

CONCLUSION.

The mycoplasmas in gastric tissue could be regarded as simple contaminants of the oropharynx, but the fact that *M. faucium* is more frequent in chronic gastritis tissue than *M. salivarium* and *M. orale* does not support this possibility. Human mycoplasmas are present in the chronic gastritis tissue of patients and may exacerbate chronic inflammation status by recruiting neutrophils. The high prevalence of mycoplasmas in patients with gastrointestinal disease suggest a need for further study of the putative role of mycoplasmas in gastric tumorigenesis.

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