Links and interactions between mycoplasmas and viruses: past confusions and present realities

Brief Review

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Summary. Links between mycoplasmas and viruses are ancient, multiple and complex, from past confusions during the first decades of the virus era to present realities illustrated by the possible implication of mycoplasms as co-factors in natural infections of AIDS. Mycoplasma viruses (phages) may also be responsible for modifying the pathogenic power of mycoplasmas, at least for plants and insects. In addition, several mycoplasmas are able to act as undesirable cell culture contaminants that induce erroneous results in both applied and general virology. These problems are examined within a historical context.

Introduction

Links between mycoplasmas and viruses are ancient, multiple and complex, and have been sometimes at the origin of unfortunate and persistent confusions. This follows from a fundamental property shared by these two types of infectious agents. i.e., the ability to pass through the pores of bacteriological filters, a character which has led to the definition of "filterable viruses" at the end of the nineteenth century [4, 47].

When, some years later, the bacterial nature of mycoplasmas (as "PPLO") was established [88] and the very peculiar characteristics of viruses recognized [62], the two types of agents were studied in separate ways and different laboratories. However, their frequent association continued to raise a number of problems for both virologists and mycoplasmologists. The most recent example of such problems is illustrated by mycoplasma studies performed in Europe and the U.S.A. which attempt to clarify the possible role of these organisms in the pathogenesis of AIDS.

From a historical point of view at least four types of definite links between mycoplasmas and viruses have occurred.

Mycoplasmas and viruses: a historical perspective

"At the beginning were the filterable viruses". This biblical-like sentence could eventually serve as an introduction to the historical record of mycoplasmas and viruses as well. Indeed, during the 1890's, the first "true" virus, the Tobacco mosaic virus, was discovered and isolated [4, 47] from a diseased plant whereas the first mycoplasma, the "bovine pleuropneumonia agent" (*Mycoplasma mycöides*), was cultured from sick cattle at the Pasteur Institute in Paris by Nocard et al. [72]. These two agents, although quite different in their biological properties, have been then included in the new, emerging group of "filterable viruses" [86] together with foot-and-mouth disease [61] and yellow fever viruses [79]. This was also the case for the "contagious agalactia agent" of sheep and goats (*M. agalactiae*) isolated some years later [8]. However, both the pleuropneumonia and the agalactia agents were visible under the microscope and were readily cultured in serum-enriched media unlike the other filterable viruses. This led to a durable confusion concerning the actual nature of "viruses". Many microbiologists spent unsuccessful and time-consuming efforts in order to find artificial media able to support the development of the filterable agents they were working on, and known today as true viruses.

During the 1950's, it was shown that a chronic pneumonia infecting British pigs was distinct from swine influenza and, according to filtration studies, thought to be of probable viral origin [41]. In fact, the aetiological agent of this economically important disease was finally identified as another animal mycoplasma presently known as *M. hyopneumoniae* [35].

In human microbiology, when *M. pneumoniae* was isolated from patients with primary atypical pneumonia, using embryonated hens' eggs (a method suitable for virus isolations), this agent was first considered as a pneumotropic virus [26] although it was recognized as a mycoplasma, 18 years later [12].

In comparative pathology, the strange so-called "suckling mouse cataract agent" (SMCA) presently known as *Spiroplasma mirum* has been isolated from ticks using embryonated hens' eggs [15] and considered for a long time as an arbovirus or a slow virus. Finally it was recognized as a mycoplasma [3] and more precisely as a helical mycoplasma or spiroplasma [97]. Plant mycoplasmas were initially thought to be viruses because they were transmitted biologically by sap-sucking insects as is the case for genuine plant viruses as well as for hematophagous arthropod-borne viruses. The plant mycoplasmas now known as phytoplasmas were discovered only in 1967 [25], i.e. 69 years after the cultivation of the first animal mycoplasma [7].

Recently, *M. fermentans* was isolated from AIDS patients and initially described as a "virus-like agent" [54, 55] although its morphology revealed by transmission electron microscopy was obviously that of a mycoplasma. However, this "new" agent was soon recognized as a mycoplasma and given the name *M. incognitus* (sic) [56] before it was properly identified as *M. fermentans* [89].

Thus, the history of viruses and mycoplasmas, mainly before the tissue culture era, was filled with example of confusion between these two types of infectious agents.

Mycoplasmas as frequent contaminants of cell cultures: interference with virological studies

For virologists this represents a more familiar case of mycoplasma/virus association.

Contamination of cell cultures, mainly continuous lines, has been documented since the 1950's [20, 83]. It represents a very serious problem for all those concerned with cell and tissue cultures of any kind. Several general reviews have discussed this question [2, 84] but detection and decontamination of infected cells proved sometimes difficult, if not impossible.

Aseptically obtained cell cultures are generally not contaminated unlike the continuous cell lines which may be infected in 50 to 95 per cent of cases [2]. More than twenty different species of Mycoplasma or Acheloplasma have been identified so far as contaminants, and mixed infection with two or more mycoplasmas is not a rare event. Bovine mycoplasmas (M. arginini, M. bovis, M. bovoculi, etc.) are the most frequently encountered contaminants and the major source of contamination is the commercial bovine serum used in culture media. They are followed in frequency by human oral species such as M. orale, M. hominis and M. salivarium. Human oral mycoplasmas originate from laboratory personnel and are then moved through the laboratory by aerosols, contaminated materials and reagents. Swine mycoplasmas, mainly M. hyorhinis, are also frequently detected [2].

Effects on cultured cells vary from evident consequences [10] with the appearance of a non-specific cytopathic effect (abnormal growth, rounded and degenerated cells, acidification of medium) to covert infection with minimal or inapparent cellular damages [84]. Some mycoplasmas such as M. hyorhinis or M. fermentans are efficient cytadsorbing agents. But in any case, the activities and functions of cells are altered and this may affect the experimental results especially in virus studies, leading to erroneous conclusions, persistent contamination of virus stocks (including reference strains) and virus antibodies.

Virus yield of mycoplasma contaminated cells may be affected or not. Some mycoplasmas have no detectable effects on virus growth but other species may depress or even enhance virus replication in infected cells [84]. For instance mycoplasmas can decrease virus yield by depleting the medium of an essential amino acid. Thus, mycoplasma contamination of established lines of human origin, such as KB cells, quickly deplets arginine available in the medium and lowers the plating efficacy of adenovirus type 2 which has an absolute requirement of arginine for growth [85]. Likewise, in hamster and chick embryo fibroblasts or human amnion cells (FL strain) chronically infected by M. arginini, an arginine utilizer, there was a decreased yield of vaccinia virus growth

and this effect might be reverted by addition of arginine to the medium. This decrease was not observed when chronic cell infection was established with *M. hyorhinis*, a non-arginine utilizer [94]. Similar results were observed with another DNA virus, Herpes simplex virus type 1 (HSV1) grown in Vero cells: *M. arginini* decreases the yield of HSV 1 and reversion is obtained by supplementing the medium with arginine while *Acholeplasma laidlawii*, a non-arginine utilizer, has no effect [67]. It has been also shown that contamination of chick embryo cells by *M. gallisepticum* markedly affects the in vitro multiplication of fowlpox virus and modifies the plaque morphology; this mycoplasma also decreases the in vivo infectivity of fowlpox virus for day-old chicks [31]. Conversely, the chronic infection of hamster embryo fibroblasts by *M. arginini* and *M. hyorhinis* increased significantly the yield of two arboviruses, vesicular stomatitis (Indiana strain) and Semliki Forest viruses. This enhancement resulted from a non-arginine dependent depletion of interferon production induced in infected cells by mycoplasmas [92, 93].

Mycoplasma contamination may also have other deleterious effects on the molecular expression of other viruses belonging to the *Herpesviridae* family. For instance some strains of varicella-zoster virus contaminated by *M. hyorhinis* show a greatly reduced immunoreactivity of certain viral glycoproteins possibly by depletion of sugars or interference in glycosylation pathways [42], and the previously reported immunosuppressive effects of human cytomegalovirus in vitro may in fact be due to the presence of the same swine mycoplasma in virus stocks [91].

Finally, *M. orale* inhibits the transforming effect of Rous Sarcoma and Rous-associated viruses in chick embryo fibroblasts, and other mycoplasmas reduce the number of transformed foci in SV-40 and polyoma-infected cells cultures [84].

It is thus clear that mycoplasma contamination of cultured cells and virus stocks may have dileterious effects on many virological studies. From an epidemiological point of view, molecular studies involving the genotyping of obligate intracellular pathogens, including DNA viruses, chlamydias, rickettsias, etc., may lead to erroneous conclusions. Mycoplasmas as a whole are a true "plague" for virologists and other biologists, and only frequent testing of cell cultures can avoid this type of problem.

Infection of mycoplasmas by viruses (bacteriophages) is well documented

Although mycoplasmas (Class Mollicutes) are the smallest and simplest prokaryotes with a genome size of 600–2500 Kbp they have been found to be infected by a number of viruses. Moreover, these specific bacteriophages have been described from different species of mycoplasmas belonging to at least three genera: *Acholeplasma, Spiroplasma* and *Mycoplasma.* Their basic properties, structure and classification have been reviewed in detail by Cole [18, 19], Maniloff et al. [64], Razin [78], Maniloff [65, 66] and Renaudin and Bové [81].

The first known mycoplasma virus, strain *MV-L1*, was described some 25 years ago by Gourlay in England [38] from *Acholeplasma laidlawii*. Soon thereafter the same author described a second mycoplasma virus, strain *MV-L2*, and then a third, strain *MV-L3*, always from *A. laidlawii* [32, 39].

Three spiroplasma viruses, known as *SpV1*, *SpV2* and *SpV3*, have been characterized from *Spiroplasma citri*, the aetiological agent of "stubborn" disease of *Citrus*, an important economical problem worldwide [18], and a fourth spiroplasma virus, *SpV4*, has been isolated from *Spiroplasma melliferum*, a bee pathogen [80]. Other mycoplasma viruses present in different species of the *Mycoplasma* genus (see below) remain to be better characterized [78].

Many mycoplasma viruses resemble classical bacteriophages previously described from wall-covered bacteria but some others, with an enveloped spherial shape and devoid of internal structure, such as *MV-L2* or *L172* strains from *A. laidlawii*, resemble animal viruses [78]. Moreover, they are released from infected cells by budding from the plasma membrane [78], an impossible process for viruses released from rigid, wall-covered cells, such as eubacteria or fungi. Spiroplasma virus SpV1 resembles *E. coli* virus M 13 not only because the two viruses are rod shaped and have double stranded, circular DNA genome, but also because they are lytic and their morphogenesis occurs when the DNA moves through the cell envelope [81].

Mycoplasma viruses, like other bacteriophages, can persist in two types of carrier states: lysogeny and persistent infection [78].

The old classification of Cole [19] was essentially morphological and listed viruses in four groups: a) Rod-shaped viruses (group L1) with *MV-L1* strain as prototype. b) Spherical enveloped viruses (group L2) with *MV-L2* strain as prototype. c) Short-tailed polyhedral viruses (group L3) with *MV-L3* strain as prototype, and d) Long-tailed polyhedral viruses (group L2) with *S. citri* virus *SpV2*, as prototype. It should be noted, however, that for some of these groups the "prototype" strain is the only known isolate.

The most recent, modern classifications [64–66] of mycoplasma viruses take into account the biophysical and biochemical properties of these viruses. For example, Maniloff [66] listed four single-stranded (ss) DNA and three double-stranded (ds) DNA viruses, plus a number of insufficiently characterized agents from *Acholeplasma modicum* (virus M1), *A. oculi* (virus O1), *M. bovirhinis* (virus Br1), *M. hyorhinis* (virus Hr1) and *M. pulmonis* (virus P1), all with undetermined nucleic acid structure. No RNA phage has so far been identified among mollicutes.

Our present knowledge of some well characterized mycoplasma viruses is summarized in Table 1.

An important question in connection with mycoplasma viruses is whether or not the virus infection may eventually affect the pathogenicity of the infected mycoplasmas [78]. The most convincing evidence of such an effect came from spiroplasmas. It was shown that transmission of *S. citri* infected by virus strain *ai* to periwinkle plants (*Catharantus reseus*) already infected with a highly pathogenic *S. citri* resulted in suppression of symptoms and reduction in the

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Table 1. Some well characterized mycoplasma viruses[a]

Strain	Host	Shape	Size	Nucleic acid	Classification[b]
MV-L1	A. laidlawii	naked rod	16 × 90 nm	1.5×10^6 da, circular ss DNA	Plectrovirus
L172	A. laidlawii	quasi-spherical, enveloped	60–80 nm	14 kb, ss DNA	–
SpV1	S. citri	naked rod	10–15 × 230–280 nm	8.3 kb, circular ss DNA	Plectrovirus
SpV4	S. melliferum	naked, isometric	27 nm	4.4 kb, circular ss DNA	Spiromicrovirus
MV-L2	A. laidlawii	quasi-spherical, enveloped	50–125 nm	12 kb, circular ds DNA	Plasmavirus
MV-L3	A. laidlawii	short-tailed phage	head: 60 nm tail: 10 × 20 nm	39.4 kb, linear ds DNA	–
SpV3	S. citri	short-tailed phage	head: 40 nm tail: 6–8 × 13–18 nm	21 kb, linear ds DNA	Podovirus

[a]In part from Maniloff [66]
[b]According to Francki et al. [29] and Renaudin and Bové [81]

number of viable spiroplasmas [1]. However, the use of this competitive effect to control "stubborn" disease of *Citrus* [82] has never been seriously considered.

Another example of modified spiroplasma pathogenicity as a consequence of virus infection concerns the sex ratio organism (spiroplasma) responsible for male lethality in *Drosophila*. Virus infection of this SRO spiroplasma by SRO viruses resulted in lysis of the microorganism and the infection to be cured [101].

It is probable that other bacteriophages may affect the pathogenic power of mycoplasmas either by inducing variations in surface antigens, secretion of toxins, or more simply by killing the mycoplasma in situ [78].

Mycoplasmas/viruses interactions in viral diseases

Animal diseases

Infectious diseases of multiple aetiology are frequent in veterinary medicine. Those which associate mycoplasmas and viruses pose difficult problems because it is very hard if not impossible to assess the actual role played by each agent acting as a part of the "pathogenic complex": interference, indifference, facilitation, synergy or, more simply, addition of the damaging effects of individual pathogens.

In this respect, the muddled aetiology of the "avian respiratory disease complex", reviewed by Jordan [48], represents a paradigm. At least four different pathogens could be involved, either alone or in combination: Newcastle disease (ND) virus, a paramyxovirus, infectious bronchitis (IB) virus, a coronavirus, infectious laryngotracheitis (ILT) virus, a herpesvirus, *M. gallisepticum* and, eventually, other mycoplasmas, avian reoviruses and adenoviruses. All the listed viruses, mainly ND virus, may express considerable variation in virulence, from highly pathogenic devastating strains, to very mild ones inducing asymtomatic infections [48].

From epidemiological data and a number of experimental results [21, 51], it clearly appears that association of respiratory viruses and *M. gallisepticum* (or other bacteria) results in more severe or prolonged disease for poultry, especially turkeys and broilers. Thus, viral damage of the tracheal epithelium induced by ND virus enhances the multiplication of *M. gallisepticum* in the trachea of experimentally infected chickens [21]. Likewise, production of prolonged corysa and rales was observed in adult poultry exposed to IB virus 31 days after infection with *M. gallisepticum*. However, interactions between ILT virus and "PPLO" were not documented, and avian reoviruses exerted no influence on the course of the disease in young chickens infected by *M. gallisepticum* 24 h previously. On the contrary, the combined infection of laying hens with *M. gallisepticum* and avian adenoviruses caused a fall in egg production greater than that induced by viruses alone, suggesting a synergistic effect [6]. Consequences of an eventual decrease in interferon synthesis or a possible immunosuppressive effect of mycoplasma infection on the course of viral diseases of poultry were not considered in the Jordan's review [48].

More recently, according to a large serological survey which included 71 California meat-turkey flocks, it was demonstrated that flocks where antibodies to ND virus and/or *Mycoplasma meleagridis* were detected, had an increased risk of outbreak of fowl cholera [11].

Concerning the "endemic calf pneumonia", an enzootic pneumonia with high mortality occurring primarily in housed dairy calves, it was established that infections with bovine respiratory syncytial virus and parainfluenza type 3 virus are followed by secondary, sometimes fatal, invasion of the lungs by mycoplasmas. However, pneumotropic species of mycoplasmas isolated from calves i.e., *M. bovis*, *M. dispar* and *Ureaplasma dispar*, can be pathogenic for calves in the absence of viruses or other bacteria [9]. Thus, in this bovine disease the role of respiratory mycoplasmas and other bacteria (*Pasteurella*, *Haemophilus*) seems limited to a secondary aggravation of the viral pathology.

Likewise, "Enzootic pneumonia of swine" occurs worldwide with a high morbidity (30 to 80%) but a near zero mortality in slaughter pigs. The primary aetiological agent, *M. hyopneumoniae* (formerly *M. suipneumoniae*) was not described until 1967 [36]. The disease is frequently complicated by viral or bacterial infections which can exacerbate the generally mild symptoms due to the mycoplasma.

Another example of complex interrelations between mycoplasmas and viruses in animal pathology concerns the massive death in seals (pinnipeds) recently observed in Europe, Asia and the USA. During the summer of 1988, about 18 000 harbor seals (*Phoca vitulina*) died of pneumonia during an epizootic occurring in the North sea and Baltic sea [23, 24]. The cause of the disease was a "new" morbillivirus closely related to canine distemper virus, called phocine distemper virus (PDV) [74]. PDV was also found infecting grey seals (*Halichoerus grypus*). Interestingly, in the former U.S.S.R., another mass death related to a morbillivirus has been previously reported from Lake Baikal seals (*Phoca sibirica*) in 1987 [40]. Since serological surveys have shown that canine distemper virus antibody was prevalent in crabeater seals (*Labodon carcinophagus*) in the Antartic [5], the viral aetiology of these massive epizootics was largely accepted. This appeared particularly founded because, in 1979 and 1980, an epizootic of pneumonia has killed at least 445 harbor seals along the New England seabord, in northeastern USA, during which an influenza virus (A/Seal/Mass/1/80) has been isolated from the lungs of deceased seals [33].

This conclusion, however, may have to be revised. Several seal herpesviruses were also isolated from pneumonic harbor seals during the 1988 epizootic in northern Europe [30, 73] together with a large number of mycoplasma strains [50]. These mycoplasmas were believed to be responsible for increasing the death rate among seals [50] and soon afterwards they were recognized as two new species named *M. phocarhinis* and *M. phocacerebrale* [34]. Moreover, by a remarkable coincidence, another new species of mycoplasma, *M. phocidae*, unrelated to the European ones, was isolated from sick harbor seals during the 1979–1980 north-American epizootic [87]. Howeover, the actual role of

M. phocidae in the seal disease remains to be established; it is likely to be minimal [87].

AIDS

Probably much more important for the understanding of mycoplasma/virus interactions, at the molecular level, is the hypothesis recently developed in the USA [60] and France [68] concerning an eventual role of human mycoplasmas in the pathogenesis of AIDS. This problem was considered sufficiently important to be fully discussed during a recent symposium held in the USA [96]. Indeed, this is not a theoretical debate since it was considered that AIDS is not only a viral disease due to HIV-1 and HIV-2 but essentially a multifactorial infection with multiple overlapping phases and this concept may have important repercussion in therapy [28]. Mycoplasmas, as several other bacteria and viruses, could represent certain factors or co-factors operating at different stages of the natural history of the disease [70, 76].

A number of mycoplasma species such as *M. fermentans* (*incognitus* strain), *M. penetrans*, *M. pirum* or *M. genitalium* have been repeatedly detected in or isolated from AIDS and also non-AIDS patients [17, 22, 43, 49, 54, 56, 57, 59]. Antibodies to *M. fermentans* were detected with a high frequency in HIV-infected patients [99]. Basically, the metabolism of these mycoplasmas apparently does not differ from that of other, more fully characterized species. Pollack et al. recently [77] noted that they lack cytochromes, the tricarboxylic acid cycle and portions of the hexose mono-phosphate shunt. Their pathogenic potential might proceed from the generation of toxic oxygenated products that could damage the host cell membrane [77]. The question may thus be asked: What is the role of mycoplasmas in AIDS; are they only a part of many opportunistic infectious agents isolated from immunocompromised AIDS patients or synergistic, precipitating co-factors?

From a clinical point of view, it was sometimes found that there was a steady link between HIV infection and the presence of *M. fermentans* or *M. pirum* in urine [22, 70] or blood [43] of patients, but in other surveys it was observed that *M. fermentans* occurred in similar proportion among HIV sero-positive and HIV sero-negative patients [49]. Moreover, no association was observed between the infection by *M. fermentans* and the stage of the disease, CD4 count or HIV-load [49]. Other authors also find no correlation between *M. fermentans* infection and HIV clinical stages [43], an argument against an action of the mycoplasma at a particular stage of the disease.

However, the fact [99] that a higher frequency of antibodies to *M. fermentans* was found in sera from HIV-1-infected patients with AIDS (40%) than in sera from HIV-1-negative controls (1%) argues for a possible role of mycoplasmas in the progression of AIDS, a theory advanced as early as 1989 by Lo et al. [54] and developed since 1990 by Montagnier et al. [68, 69].

In addition, *M. fermentans* causes a fatal systemic disease in non-human primates [55] and *M. penetrans* appears as a possible pathogen since it exhibits

a tip-like structure which allows it to attach to and penetrate in human and animal cells [57, 59]. Furthermore, *M. penetrans* is apparently actively transmitted among homosexual males and epidemiologically linked with Kaposi's sarcoma in homosexual men with AIDS, a correlation not observed with another species, *M. genitalium* [100].

At the cellular level, it was shown that *M. hyorhinis* contamination of lymphocyte cultures suppressed the HIV-1 reverse transcriptase (RT) activity [98] whereas the treatment of HIV-1 infected CEM cells with antimycoplasmal tetracyclines resulted in increased RT activity of HIV-1 [52]. In fact, it was recently shown that the drastic inhibition of HIV-1 RT as a consequence of mycoplasma contamination was due to a soluble protein with a molecular mass about 70 Kda, present in the particle-free supernatants of contaminated cultures. This RT-inhibitor had a strong DNase activity on both linear and circular DNas [27]. Such nuclease activity has been already postulated to explain RT depression observed in mycoplasma contaminated murine hybridoma cell lines producing types A and C retroviral particles [63]. On the other hand, antibody directed against the binding site of *M. genitalium* inhibited or reduced the infectivity of HIV-1 and HIV-2 in the same cells [69] and an unidentified mycoplasma significantly reduced the CD4 expression, with a consequent inhibition of gp 120 binding and HIV infection in CEM cells [75].

However, mixed infection of A3.01 cells by both *M. fermentans* and HIV-1 resulted in the disappearence of syncytia but an increased cytocidal effect, despite little or no RT activity and the apparent normal assembly of VIH virions [58]. A synergy in cell killing was also observed in U937 cells doubly infected with *M. fermentans* and HIV-1 or HIV-2 [53]. Cell lysates of *M. fermentans*, *M. genitalium* and *M. pneumoniae* stimulate the HIV-1 replication through selective activation of CD4+ T lymphocytes [90].

From these different in vitro studies it is clear that several mycoplasma species could interfere, though along different pathways, with the replicative cycle of human immunodeficiency viruses. Nevertheless, the actual effects of mycoplasmas on the natural history of HIV infection and AIDS remains to be clarified [70]. It is not impossible that progression of the disease may result from more subtle interactions of these organisms (and others) with the immune system of the host rather than from the direct cytopathic effect of the HIV lentiviruses.

For instance, mycoplasmas could act on the immune system by means of their antigens or superantigens, inducing a programmed cell death or apoptosis in activated infected or non infected TH cells [37]. These antigenic stimuli could also induce a chronic activation of the immune system and a deep de-regulation of the complex interrelation of cytokines, especially TNF-α and IL 2 or IL 6 interleukines [16, 28, 71]. It is noteworthy that mycoplasmas provoke the production of TNF-α and other cytokines in lymphocytes and macrophages, thus enhancing the in vitro HIV replication [16].

Such pathogenicity studies in AIDS seem more realistic than experiments conducted only in vitro which account essentially for the effect of mycoplasmal

infections on the replicative cycle of HIV-1 or HIV-2 in a peculiar type of lymphocyte cells line.

Concluding remarks

If one takes into account the various data mentioned above as well as the fact that infection of a mosquito by a spiroplasma may reduce its vector competence for Eastern equine encephalitis virus [95] or that another mosquito spiroplasma, *S. taiwanense* may be used as a biological control agent against dangerous mosquito-borne viral diseases [13, 44–46], it becomes clear that the associations between mycoplasmas and viruses appear multiple and sometimes extremely complex.

From a historical point of view, these associations have evolved from persistent confusions in the past sometimes still present today, to genuine interactions, since mycoplasmas are now implicated as possible co-factors in AIDS.

Viral diseases of cattle and poultry, especially those affecting the respiratory tract, are frequently aggravated by concurrent or subsequent mycoplasmal infections. On the contrary, the eventual role of mycoplasmas in the natural history and progression of AIDS appears fundamentally distinct because the human disease is multifactorial (but not multi-aetiological) in nature and that the mycoplasmas could exert their deleterious effects directly within the immune system, already assaulted by a T lymphotropic lentivirus.

Thus, it is not unreasonable to think that the studies presently performed on the pathogenesis of this terrifying disease could result in a better understanding of mycoplasma-virus interactions in other hosts, including lower invertebrates, plants and insects as well.

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