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MYCOPLASMOSIS AND IMMUNITY OF FISH AND REPTILES

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Mollicute and vertebrate host origins
4. Mycoplasmosis of poikilotherms
4.1. Pathogens and commensals
4.2. Pathobiology
4.2.1. Chronic infection
4.2.2. Acute infection
5. Immunity of poikilotherms
5.1 Innate defenses
5.1.1. Histaminergic cells
5.1.2. Antimicrobial peptides
5.1.3. Complement and pattern recognition receptors
5.1.4. Phagocytes and natural killer cells
5.1.5. Peptide regulatory factors
5.1.6. Fever
5.2 Adaptive defenses
5.2.1. Lymphoid tissues and lymphocytes
5.2.2. Major histocompatibility receptors, lymphocyte receptors, and antibodies
5.2.3. Immune memory
6. Perspective
7. Acknowledgments
8. References

1. ABSTRACT

Advances in molecular phylogenetics have enabled reconstruction of the most likely chronology of events in prokaryotic evolution and correlation with the paleontologic record with increasing precision. Mycoplasmas probably evolved from clostridial ancestors by genome reduction leading to obligate parasitism of host cells. The vertebrate hosts present at the time of the origin of mycoplasmas about 400 million years ago were fish, and later amphibians and reptiles, whose descendants possess most elements of vertebrate innate and adaptive immunity. Successful colonization of those poikilothermous ("cold-blooded") hosts must have involved adaptation to those defenses, shaping mycoplasma-host interactions for more than 125 million years before the earliest emergence of mammals. That history illuminates one aspect of the potential significance of mycoplasmosis of poikilothermous vertebrates to health and disease of other hosts including humans.

2. INTRODUCTION

The class *Mollicutes* includes the genus *Mycoplasma*, the smallest free-living cells with the smallest genomes among eubacteria (1). Evolutionary reduction of mycoplasmal genomes from clostridial ancestors (2) likely promoted increasingly fastidious dependence on exogenous nutrients obtainable by parasitic colonization of host cells. Mycoplasmas have a spectrum of relationships with vertebrate hosts which extends from innocuous commensals to etiologies of fulminant lethal disease. They are important human pathogens especially of the respiratory and urogenital tracts (3), and are also responsible for economically significant diseases of animals including ruminants, swine, poultry, and laboratory rodents (4). Mycoplasmosis is predominantly associated with slowly progressive subclinical, subtle, or chronic diseases, caused or exacerbated by host responses elicited by colonization of mucosal, serosal, or serosynovial surfaces (5). Mechanisms of pathogenicity in all hosts are poorly understood beyond the generalizations that host responses to mycoplasmal cytadherence exacerbate disease, and variation in certain cell-surface antigens can occur with high frequency in mycoplasmas (6). Mycoplasmas can modulate host cell cytokine and lymphokine expression, possibly through intracellular effects induced by colonization of the host cell's surface. For those reasons, interactions with host innate and adaptive immune systems is a dominant topic of current mycoplasmology.

Table 1. Characterized mycoplasmas cultured from fish or reptiles

Mycoplasma	Known susceptible hosts	Effect of colonization
Mycoplasma mobile	Freshwater fish (*Tinca tinca*)	Acute erythrodermatitis, necrotizing gill lesions
Mycoplasma agassizii	Tortoises (*Gopherus* and *Testudo* spp.) And turtles (*Terrapene carolina*)	Chronic upper respiratory tract disease
Mycoplasma alligatoris	Alligators (*Alligator mississippiensis*) and caimans (*Caiman latirostris*)	Acute multisystemic inflammatory disease
Mycoplasma crocodyli	Crocodiles (*Crocodylus niloticus*)	Polyarthritis, sub-acute pneumonia
Mycoplasma testudinis	Tortoises (*Testudo graeca*)	Commensal

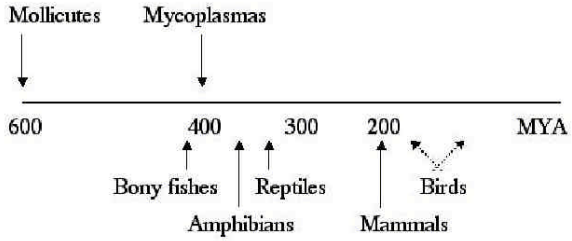

Figure 1. The reconstructed chronology of the origins of mollicutes and their vertebrate hosts. MYA = million years ago.

Mycoplasmas are ubiquitous, but different species usually exhibit strict natural host and tissue tropism, so the significance of mycoplasmosis of poikilothermous ("cold-blooded") fish or reptiles to human health and disease may not seem obvious. However, the recently reconstructed chronology of their rRNA sequence variations suggests that mycoplasmas originated from streptococci following an evolutionary trajectory that began approximately 600 million years ago (MYA; 1, 3, 7). Therefore, whatever host defenses mycoplasmas encountered when they first had the opportunity to colonize fish approximately 400 MYA, and reptiles 325 MYA, may have delimited vertebrate mycoplasmosis by the time mammals and birds emerged as potential hosts more than 125 million years later. This review briefly summarizes mycoplasmosis and the elements of innate and adaptive immunity of poikilothermous vertebrates, to draw attention to their probable significance in the history of mycoplasma-host interactions and the potentially broad relevance of mycoplasmosis of those classes to health and disease of other vertebrate hosts including humans.

3. MOLLICUTE AND VERTEBRATE HOST ORIGINS

The chronology of events in the evolution of mollicutes and their Gram-positive ancestors was recently reconstructed from phylogenetic trees based on 16S rRNA nucleotide sequences (7). The rate of increase in the number of branch lineages, a measure of the rate of branch evolution, was calibrated to geologic time in part by assuming the origins of facultative and obligate aerobes coincided with the increasing abundance of oxygen in Earth's atmosphere about 1600 MYA. The results suggested that the first mollicutes originated from streptococci about 600 MYA, and that mycoplasmas diverged from a distal branch about 400 MYA (Figure 1). Further, in contrast to mollicutes such as phytoplasmas, whose plant hosts were already widespread and diverse at the time the bacteria emerged, the rates of evolution among mycoplasmal branches later increased during periods correlated with milestones in the emergence of vertebrate host niches.

Ancestral vertebrates (conodonts) and primitive fish were present in Earth's oceans during the Ordovician period 440-500 MYA. Cartilaginous fish appeared about 450 MYA. Bony fish date to the late Silurian period 410 MYA. By the early Devonian period 400 MYA all major groups of bony fish were present, and before the end of the Devonian 360 MYA terrestrial vertebrates had evolved from lobe-finned bony fish. The oldest known terrestrial vertebrates were primitive amphibians whose fossil remains have been found in late Devonian deposits about 360 million years old. During the mid-Carboniferous period, about 325 MYA, labyrinthodont amphibians evolved the ability to lay amniotic eggs, the key event in the origin of reptiles during the Carboniferous period. For perspective, mammal-like cynodont reptiles, the ancestors of the first mammals, appeared during the late Triassic period about 200 MYA. The origin of birds from reptiles remains more obscure, but occurred not later than the Cretaceous period 65-150 MYA and possibly as early as the Jurassic period 150-200 MYA (8, 9).

4. MYCOPLASMOSIS OF POIKILOTHERMS

4.1. Pathogens and commensals

Two-thirds of the vertebrates on Earth are fish, making them the most abundant potential vertebrate hosts for mycoplasmas. Mycoplasma-like colonies developed with high frequency on American Type Culture Collection (ATCC) medium 988 (SP4) agar inoculated with minced gill tissues from a variety of freshwater fish, and acholeplasmas have been detected frequently in fish cell cultures, but to date only one species of piscine mycoplasma has been culturable on artificial media (Table 1). *Mycoplasma mobile* (10) was isolated from the gills of a tench (*Tinca tinca*) with gill erythrodermatitis. Most *M. mobile* cells are flask-shaped and have remarkably rapid gliding motility. The species grows between 17 and 30 °C. Colonies adsorb piscine and mammalian erythrocytes and are hemolytic. In experimental fish inoculation studies, *M. mobile* caused mild to severe erythrodermatitis and necrotizing lesions of gill epithelium, which were rarely fatal, and in other studies caused necrosis of gill and mammalian tracheal explants (11-15). Its natural prevalence and route of transmission are unknown. Its unique 16S rRNA gene nucleotide sequence indicated it is a member of the *Mycoplasma hyorhinis* phylogenetic clade.

Mycoplasma agassizii (16) is widespread in free-ranging *Gopherus* spp. tortoise populations throughout North America and *Testudo* spp. tortoises in Europe, which have been separated since the breakup of the Laurasian continent approximately 100 MYA. It has also been isolated from a free-ranging box turtle (*Terrapene carolina bauri*) in North America, and detected by 16S rRNA gene-based PCR-RFLP in. several other species of captive chelonians (our unpublished data). It causes chronic upper respiratory tract disease (URTD) characterized by rhinitis and conjunctivitis (17-19). The cells are pleomorphic and non-motile. They grow slowly but readily between 20 and 35 °C. The organism adsorbs and weakly agglutinates mammalian and reptilian erythrocytes. Its seroprevalence varies from 0 to 90% among isolated turtle and tortoise populations in North America. Its transmission seems to be horizontal by direct contact or fomites. Its unique 16S rRNA gene nucleotide sequence indicated it is another member of the *M. hyorhinis* phylogenetic clade, where its closest known relative is *M. mobile* (20).

A yet-unnamed mycoplasma, ATCC accession 700618 (20), is indistinguishable from *M. agassizii* by morphology, metabolic tests, or ELISA of infected tortoise plasma. However, it has a unique 16S rRNA gene nucleotide sequence which suggested it is a member of the *Mycoplasma fermentans* phylogenetic clade, within which it has no obvious close relative. The proposed species grows slowly between 22 and 30 °C. It also causes URTD of tortoises, and seems to have a geographic distribution in North America similar to, but with lower prevalence than, *M. agassizii*.

Mycoplasma alligatoris (21) causes acute fatal multisystemic inflammatory disease including necrotizing synovitis, hepatitis, myocarditis, meningitis, and necrotizing pneumonia of American alligators (*Alligator mississippiensis*) and at least one closely-related Central and South American crocodilian (*Caiman latirostris*; 22-25). The cells are pleomorphic. The species grows between 22 and 34 °C, with remarkably rapid growth between 30 and 34 °C. Limited data suggest that a natural reservoir for this acutely lethal pathogen may be crocodilians only distantly related to alligators (specifically including *Crocodylus siamensis*), in which the organism can be merely commensal, and that its prevalence among captive and wild crocodilians is low. Its unique 16S rRNA gene nucleotide sequence indicated it also is a member of the *M. fermentans* phylogenetic clade.

Mycoplasma crocodyli (26) was associated with multiple independent outbreaks of polyarthritis and sub-acute pneumonia of captive Nile crocodiles (*Crocodylus niloticus*) in Zimbabwe (27-29). Its pathogenicity in other crocodilians remains unknown. The cells are pleomorphic and non-motile. The species grows between 25 and 42 °C, with fastest growth at 37 °C, showing that host-range determinants of the mollicutes which infect poikilotherms are not necessarily as trivial as growth temperature restrictions. The organism adsorbs and lyses mammalian erythrocytes. Its unique 16S rRNA gene nucleotide sequence indicated it is yet another member of the *M. fermentans* phylogenetic clade, within which *M. alligatoris* is its very close relative (98% 16S rRNA gene nucleotide sequence identity).

Another yet-unnamed mycoplasma was associated with severe proliferative lymphocytic tracheitis and pneumonia of captive Burmese pythons (*Python molurus bivittatus*; 30). The proposed species has been detected in multiple independent cases by electron microscopy and PCR. Primary cultures grew slowly in SP4 broth at 30 °C, but subcultures grew very poorly on SP4 agar, and a pure clone has not yet been obtained. Its unique 16S rRNA gene nucleotide sequence indicated it is another member of the *M. hyorhinis* phylogenetic clade, where its closest known relatives are *M. agassizii* and ATCC 700618.

Mycoplasma testudinis (30), the first mycoplasma cultured from a reptile (a Greek tortoise, *Testudo graeca*), seems to be a non-pathogenic commensal of the excretory tract. Some cells possess a polar bleb but are non-motile. The species grows between 20 and 35 °C. The organism did not adsorb or agglutinate avian or mammalian erythrocytes but was hemolytic. Its natural prevalence and route of transmission are unknown. Its unique 16S rRNA gene nucleotide sequence indicated it is a member of the *Mycoplasma pneumoniae* phylogenetic clade. *Acholeplasma laidlawii*, generally considered to be a nonpathogenic commensal of vertebrates, was isolated from the choanae of a moribund *Gopherus* tortoise (20).

An uncharacterized mycoplasma was cultured from a gharial (*Gavialis gangeticus*) in India that died with pneumonia (32). An uncharacterized mycoplasma was detected by culture and PCR during an epizootic of pneumonia among captive green tree pythons (*Morelia viridis*) in Indonesia (E.R. Jacobson, personal communication). Several additional unique 16S rRNA gene polymorphisms, indicative of still more uncharacterized mycoplasmas, have been detected by mollicute-specific PCR-RFLP of choanal lavage specimens from captive and free-ranging *Geochelone*, *Gopherus*, and other tortoises (our unpublished data). Although to date there are no credible reports of mycoplasmas being isolated from amphibians (33), to paraphrase Razin (34), the main factor for detecting mycoplasmas in any vertebrate host seems to be the willingness of mycoplasmologists to invest the resources required to isolate and characterize the mycoplasmas.

4.2. Pathobiology

4.2.1. Chronic infection

The best-studied chronic mycoplasmal infection of a member of this class of hosts is tortoise URTD (17-19). *Mycoplasma agassizii* adhere intimately to ciliated mucosal epithelial cells which line the ventrolateral surfaces of the choanae, but are not found attached to the multilayered, non-ciliated glandular olfactory epithelium which lines the dorsal nasal passages. There is no evidence of intracellular invasion of non-phagocytic cells, which may play a role in immune system evasion in chronic mycoplasmosis of other hosts (35), or of dissemination from the upper respiratory tract. The mechanism of

attachment is unknown, although *M. agassizii* does not possess a prominent attachment organelle (6). The potential specific mechanisms of cytopathic effects on host cells following cytadherence, including enzymatic or oxidative damage, metabolic dysregulation, toxins, or collateral damage from induced immune responses, remain to be investigated for this disease. Tortoise tracheal ring explants cultured and inoculated *in vitro* showed marked ciliostasis following mycoplasmal cytadherence. Attachment *in vivo* elicits severe disruption of the normal tissue architecture and function, with focal loss of ciliated epithelium, mucosal hyperplasia, and infiltration of mononuclear leukocytes and phagocytic granulocytes. Normal olfactory mucosa becomes replaced with proliferating mucous epithelial cells, and proliferating basal cells may project into the underlying lamina propria. The lesions slough large amounts of epithelial and inflammatory cells, which accumulate in a symptomatic mucopurulent nasal discharge that also includes infectious mycoplasmas, or form caseous material which can completely occlude the nasal airways. Chronically infected tortoises remain intermittently symptomatic for many years, but may eventually become debilitated by cachexia.

4.2.2. Acute infection

The best-studied acute mycoplasmal infection of a member of this class of hosts occurs in adult alligators (22, 23) and caimans (24), which may succumb to multisystemic inflammatory disease including necrotizing pneumonia, severe pericarditis and necrotizing myocarditis, lymphocytic interstitial nephritis, lymphocytic periportal hepatitis, splenic hyperplasia, pyogranulomatous meningitis, and necrotizing synovitis as early as one week following infection with *M. alligatoris*. Twelve-week-old hatchling alligators inoculated by intratracheal instillation of as few as 10^3 colony-forming units of *M. alligatoris* developed disseminated mycoplasmal infection of blood, lung, limb joints, and brain within 2 weeks, causing lesions similar to those of adults including acute multifocal brainstem hemorrhage (L.J. Richey, University of Florida Ph.D. dissertation, 2001). Lesion severity correlates with large numbers of *M. alligatoris* cells in affected tissues, suggesting that a spreading factor contributes to its virulence.

5. IMMUNITY OF POIKILOTHERMS

Microbial colonization of ancient vertebrates must have involved interactions with their innate and adaptive immune defenses. The defenses of ancient hosts cannot be studied directly, but they may be inferred from what is known about their modern descendants. The following sections show that modern poikilotherms possess defenses against infection comparable to those of modern mammals and birds. The significance specifically to mycoplasmosis, if known, is noted briefly for each potential defense mechanism described below. It seems likely that mycoplasmas had the opportunity to adapt to each of these forms of defense during a period of at least 125 million years before the earliest emergence of mammals.

5.1. Innate defenses

5.1.1. Histaminergic cells

Fish and reptile tissues are rich in mast cells (eosinophilic granulocytes) but 20-fold lower than mammals and birds in stored tissue histamine (36). Fish lack basophils, but reptiles possess antigen-specific immunoglobulin-bearing basophils which degranulate with histamine release in a calcium-, temperature-, and antigen concentration-dependent fashion (37, 38). However, both fish and reptiles show little cardiovascular response to histamine injection (but may respond to other vasoactive amines), and leukocyte migration from peripheral blood seems to be independent of vascular permeability.

5.1.2. Antimicrobial peptides

Amphipathic peptide ionophores (piscidins, pleurocidin, pardaxin) present in skin mucus and mast cells of some bony fish (39, 40) are bactericidal against Gram-positive and Gram-negative bacteria. At least 11 families of antimicrobial peptides (magainin, ranatuerin, esculentin, brevinin, temporin, palustrin, ranalexin, etc.) have been isolated from the skin secretions of a variety of amphibians (41, 42). Structurally and functionally similar antimicrobial peptides were effectively bactericidal or bacteriostatic against diverse mollicutes including acholeplasma, mycoplasma, and spiroplasma (43). The effects observed included plasma membrane depolarization, inhibited protein processing, and loss of spiroplasma helicity and motility.

5.1.3. Complement and pattern recognition receptors

All activation and effector pathways of the mammalian complement system are present and well-developed in bony fish, amphibians, and reptiles (44, 45). Fish and reptiles in fact have even more diversity in their complement system than mammals and birds do, manifested as multiple highly-polymorphic isoforms of C3 that differ in their binding efficiencies to complement-activating surfaces. This is speculated to expand their immune recognition capabilities (46). Mycoplasmas activate complement by both the classical and alternative pathways. Several species of mycoplasma have been shown to be susceptible to lysis by activated complement. Complement is also involved in mammalian antibody- and phagocyte-mediated killing of mycoplasmas (4).

Toll-like pathogen-associated molecular pattern recognition receptors, homologous to those which modulate transmembrane immune signaling in mammals and birds, have yet to be thoroughly investigated in poikilotherms (47, 48). However, elements of the Toll intracellular peptide signal cascade exist in bony fish (49). The macrophage-activating lipopeptide 2 of *M. fermentans* is one example of a well-characterized ligand for a mammalian Toll-like receptor (TLR2; 50).

5.1.4. Phagocytes and natural killer cells

Fish, amphibians, and reptiles possess monocytes and macrophages similar to those of mammals and birds (51-55). The macrophages are phagocytic, process and present antigens, and are a source of cytokines. The phagocytic granulocytes of fish and reptiles which are

Table 2. Characterized cytokines of poikilothermous vertebrates

Fish	Amphibians	Reptiles
Interferon	Interleukin-1	Interferon
Interleukin-1	Interleukin-2	Interleukin-1
Interleukin-2	Transforming growth factor beta	Transforming growth factor beta
Interleukin-8		
Transforming growth factor beta		
Tumor necrosis factor alpha		

functionally equivalent to mammalian neutrophils are called heterophils. The acute response to bacterial infection in fish and reptiles consists of local accumulation of heterophils which degranulate and act as a foreign body, eventually becoming surrounded by macrophages to form a granuloma (56). Suppurative exudates do not become liquified as pus, but instead accumulated degranulated heterophils form caseous material which accumulates in hollow spaces. In mammals, macrophages are believed not to ingest mycoplasmas in the absence of opsonization (4), but this process has not been studied in fish or reptiles.

Fish macrophages and heterophils produce microbicidal reactive oxygen intermediates including superoxide anion, singlet oxygen, hydroxy radical, and hydrogen peroxide in a typical respiratory burst following stimulation (57-59). Nitric oxide (NO) produced by macrophages is a source of nitrogen radicals which have antimicrobial effects. A cytokine-inducible isoform of NO synthase (iNOS) present in fish macrophages was activated by infection with the Gram-negative piscine pathogen *Edwardsiella ictaluri* (60), or by macrophage exposure to bacterial lipopolysaccharide or mitogen-stimulated fish kidney leukocyte culture supernatant (61). The gill is a major site of soluble and particulate antigen uptake in fish. Expression of iNOS was induced rapidly in gill, and later and for a shorter duration in kidney, following injection or bath challenge with the Gram-positive piscine pathogen *Renibacterium salmoninarum* (62) The response could be enhanced by prior immunization, showing that macrophages resident in the respiratory epithelium may play a role in local innate immunity. Infection with *Mycoplasma gallisepticum* and *M. hyorhinis* has been shown to stimulate NO production by cultured avian monocytes (63).

Nonspecific cytotoxic leukocytes, or natural killer (NK)-like cells, which kill cells that do not express receptors specifying self, are well-studied in a wide variety of fish species (64, 65). Adult *Xenopus* splenocytes display NK-like activity toward tumor cell targets (66).

5.1.5. Peptide regulatory factors

Mycoplasmas can be powerful modulators of vertebrate peptide regulatory factor and receptor expression in complex interactions with colonized host cells (4, 6). Research on the cytokines of fish, amphibians, and reptiles (49, 67-70; Table 2) has been hampered to date by lack of specific reagents and functional assays, but genomic and proteomic analyses especially of fish promise rapid advancements in understanding the peptide regulatory factors and their receptors of poikilotherms in the near future. In addition, a number of CC and CXC chemokine (small pro-inflammatory protein) genes have already been cloned from fish (49). The existence of signaling pathways similar to those known in mammals, and their significance in generation and regulation of immune responses of poikilothermous vertebrates, may be inferred from what is known about the acute phase response (71), inflammation, and lymphocyte activation in fish, amphibians, and reptiles.

5.1.6. Fever

The peripheral thermosensory and hypothalamic integrative neural pathways are the same for homeotherms and poikilotherms, but fish and reptiles respond with behavioral instead of metabolic effectors to control body temperature (72-75). Fever in poikilotherms stimulates inflammation, increases antibody production, and decreases serum iron availability. The initiation of phagocytosis in fish and reptiles is relatively temperature insensitive, but granuloma formation and wound healing is faster at higher temperatures (56). Parameters like the ID_{50} and LD_{50} of microbial pathogens are temperature-specific for fish and reptiles. For example, fish and lizards challenged with *Aeromonas* infection, then allowed to develop behavioral fever, experienced a 92% survival rate. The same treatment but with antipyresis led to 100% mortality (72).

5.2. Adaptive defenses

5.2.1. Lymphoid tissues and lymphocytes

Although fish do not have bone marrow, the fish kidney is its histological equivalent. The liver is the other major lymphopoetic organ of fish (76, 77). Bone marrow, spleen and thymus are the sources of lymphocytes in adult reptiles (77-81). Reptile spleen notably lacks the germinal centers essential for B-cell clonal selection and antibody affinity maturation in mammals (77). In mammals, germinal center formation is dependent on the cytokine "lymphotoxin alpha", which has not yet been detected in fish or reptiles. Fish and reptiles also lack true lymph nodes. There is abundant mucosal-associated lymphoid reticulum in all poikilotherms. All possess T- and B-lymphocytes.

5.2.2. Major histocompatibility receptors, lymphocyte receptors, and antibodies

Major histocompatibility (MH) class I and II receptor genes, and T-lymphocyte receptor genes, in fish and amphibians are similar to those of mammals (82, 83). Fish MH receptors are expressed in cells and tissues comparable to those of mammalian MH receptors. Their presence and functional equivalence in reptiles can be inferred from known elements of innate imunity and lymphocyte functions (84).

The major antibody isotypes present in fish and reptiles are IgM (the primordial ancestor of all immunoglobulins), IgY (the ancestor of IgG and IgE), and a

low molecular-weight form of IgY lacking the Fc region (IgY?Fc; 85-87). Tetra- and penta-polymeric IgM is the predominant serum immunoglobulin of fish. The IgM is the secretory antibody found in cutaneous mucus of fish, produced locally by lymphocytic infiltrates abundant in epithelium. Skin mucus IgM titer can increase after bath immunization, with no change in serum titer (88). In reptiles, a sequential serum IgM-IgY response and some affinity maturation is observed, but the antibodies are believed to have generally lower affinity and less diversity than antibodies of mammals and birds (89-92). Antibody production in poikilotherms is influenced by temperature (93-97), season (97-101), and hormones (102-110) in a complex manner. In adult reptiles, mycoplasmal infection elicits a humoral immune response to numerous mycoplasmal antigens after about six weeks (25, 111), consistent with the rate of response to other antigens (112), but specific antibody titers following mucosal or systemic mycoplasmal infection seem to be much lower in reptiles than in mammals or birds. Alligators exposed to a sub-lethal dose of *M. alligatoris* sustained specific antibody titers for more than six years (although it is formally possible that the animals remained latently infected; our unpublished data). Maternal specific anti-*M. agassizii* antibodies are passively transferred through tortoise egg yolk, and may persist at low levels in hatchling tortoises as long as one year (113).

5.2.3. Immune memory

Fish and reptiles exhibit humoral anamnestic responses (51, 52, 76, 78, 88, 114), and an antigen-specific cell-mediated anamnestic response has been shown in lymphocyte proliferation assays of experimentally immunized green sea turtles (*Chelonia mydas*; 115). Tortoises chronically infected with respiratory mycoplasmosis more rapidly developed more severe signs of disease following experimental reinoculation than naïve tortoises did following an initial inoculation (18).

6. PERSPECTIVE

Fish, amphibians, and reptiles must have been the first vertebrate hosts encountered by mycoplasmas. They experience the same range of effects of mycoplasmosis that mammals and birds do, and they possess elements of immunity comparable to those of mammals and birds. Though there are also some notable differences from mammals and birds, such as the timing of adaptive immune responses, the limited data available specifically regarding immunity against mycoplasmas suggest that the defenses of poikilotherms are not esoteric or deficient. Therefore, comparative mycoplasmology of poikilothermous vertebrates can be directly relevant to other hosts, including humans, at many levels including the biology of the mycoplasmas, the mycoplasma-host interactions, the diseases of the hosts, and the epidemiology of those diseases. Many aspects of mycoplasmal colonization which have not yet been studied in poikilotherms, especially the roles of innate defenses and immune signaling following infection, also remain to be elucidated in other hosts.

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