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Programmed Host Cell Death and Infectious Process of *Mycoplasma*

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Abstract: A common characteristic of Mycoplasma diseases is their chronicity, Mycoplasma spp. infection have been frequently associated with upper respiratory infections, chronic lung disease , asthma, meningeal encephalitis, mastitis, arthritis, heart problems, sterility, bone problems , oviduct dysfunctions and death in human and different animal species. In former years, changeable expression of membrane antigens has been detected in a number of Mycoplasma spp., resulting in the assumption that immune prevarication may be an important part of the their infection and pathogenesis. It has been determined how the attachment organelle, which mediates the complicated interactions between various adhesins and auxiliary adhesion proteins to mediate the critical first stage of cytoadherence to respiratory tract epithelium. Additionally, it has been demonstrated that inflammatory cytokines cause tissue damage by intracellular localization, direct cytotoxicity, and activation of the inflammatory cascade via Toll-like receptors (TLRs), and inflammosome activation, which causes air passage inflammation. All of these play crucial roles in the infectious process. This paper seeks to provide a thorough assessment of recent developments in our understanding of Mycoplasma pathogenesis with the understanding of its virulence mechanisms.

Keywords: Mycoplasmas, infectious process, programmed cell death, apoptosis.

Introduction: Mycoplasma is the tiniest and most unpretentious cell wall-free parasitic prokaryote, with the capacity for self-reproduction (1). It produces ammonia and induces inflammatory cytokines in immune and non-immune cells similarly to Helicobacter pylori (2). Human genital Mycoplasmas were recovered with a substantial percentage as single infections and/or mixed infections (3, 4). Also, increasing prevalence of antimicrobials resistant such as macrolide-resistant in M. pneumoniae has become a significant problem, which may possibly cause further severe and even extra-pulmonary infections (5), Dogs in Iraq have been found to have Mycoplasma spp. (6). In Basrah governorate of Iraq, infected dogs with Mycoplasma hemocanis, caused emaciation with the possibility of death among infected dogs (7).

Feline mycoplasmosis may cause negative consequences that could result in the death (8), in same context Haemotrophic Mycoplasmas might terminated with highly mortalities of infected sheep of Basrah governorate (9), while (10) found 16.6% M. agalactiae in sheep showed signs of mastitis based on molecular PCR.

However, Mycoplasmosis in newborn calves was detected in Basrah, Iraq, and might lead to huge economic losses, therefore, periodic examination of adult and pregnant cows should be advised. (11). A significant increase lymphocyte, and macrocytic hypochromic type of anemia caused by Mycoplasma wenyonii infection in cattle of Basrah governorate (12)

Many avian species, such as broiler and layer breeds of chickens, turkeys, pigeons, sparrows, finches, falcons, and other bird species are susceptible to the avian mycoplasmosis (13,14). Mycoplasma infections are widespread and are the cause of significant financial losses for the global poultry industry (14). Several world states with modern design poultry facilities have enucleated Mycoplasmas from commercial chickens and breeder flocks; however, avian mycoplasmosis still a real problem in Iraq (15,16), although M.gallisepticum prevention and control by only biosecurity measurements is difficult to achieve Mycoplasma free flock; however, M. gallisepticum vaccines have been used positively in these circumstances to minimize the occurrence and spreading of Mycoplasma (17).

MYCOPLASMA GENOME

The fact that Mycoplasmas have the shortest genomes among bacterial species is assumed to be the result of degenerative evolution, which has reduced genome size from a common gram-positive progenitor through time (18, 19).

The size of Mycoplasma genome is differed from species to another , by using restriction enzymes the genome size of Mycoplasma genitalium was determined, is considered among the smallest genomes ranged from 577 to 590 kb, and is 1 /4 smaller than M. pneumoniae genome (20). While the genome size of many M. gallisepticum strains, both virulent and attenuated strains approximately 1 Mbp (21, 22), with 23 to 40 mol% G+C. (23), however, the genomic size of Mycoplasma penetrans was 1359 kb (24). Despite the small size, Mycoplasma maintained its ability to synthesize DNA,RNA and every protein needed to support its persistence and survival (25). The estimated number of important genes ranged from 256 to 422 depending on the species taken into account and the approach or method (26; 27; 28).

In addition to 20 completed genomes in the class of Mollicutes, (21;29; 30; 31; 32), the genomic DNA of 12 different Mycoplasma species has been fully sequenced and recorded in GenBank such as M. gallisepticum strain Rlow (21), M. hyopneumoniae and M. synoviae (33), M. haemofelis (29), M. pneumonia (30), M. wenyonii strain Massachusetts (34), M. gallinaceum (31), M. genitalium (32) and others. The majority of the mollicutes have two rRNA cistrons, while a small number of species seem to have just one rRNA cistron, that codes for a specific polypeptide in protein synthesis mechanism (35).

Regarding M. gallisepticum, two gene families, pMGA (vlhA) (21), and pvpA (36, 37), translate and encode the primary membrane proteins, as immunogenic proteins (38) Mycoplasma can be influenced by the variations in the expression of pMGA and mgc1 and mgc3 cytoadhesin genes, nevertheless, pMGA genes play a chief role in antigenic variants production and the capability of M. gallisepticum to alter the expression of their antigenic determinants is believed to be an essential mechanism for immune evasion or eluding, host acclimation, and long last persistence (39).

One of the primary forces behind microbial innovation was the occurrence of

horizontal gene transfer (HGT) and was enables the transfer of substantial gene groups, referred to as genomic islands (GIs), between bacteria (25). But Mycoplasma was not taken into account until the 1990s Due to the small size of their genome and the prevalent evolutionary theory, which was exclusively based on sequential gene losses (40). However, HGT has appeared in a number of gene clusters, certain of which encode virulence elements in Mycoplasmas (41). For example, two loci were found in the M. agalactia strain 5632 by Island Viewer 4. (42) that code for Vpma family surface proteins (43), are involved in immune evasion and colonization (44, 45).

ANTIGENIC STRUCTURE

About two-thirds of the components of the membrane are made up of proteins, with the remaining lipids having different molecular weights (40). The high frequency of antigenic variety and the capacity for outer surface protein phase divergence are universal characteristics of many pathogenic Mycoplasmas, which facilitate immune evasion. (46). For instance, in terms of pathogenicity, transmissibility, and immunogenicity, for instance, M. gallisepticum isolates differ greatly from one another in accordance with phenotypic and genotypic features (47). The key membrane proteins on the surface of the organism, known as adhesins, are the virulence factors, they play a crucial function in attaching to the host epithelial cell receptors, allowing Mycoplasma to colonize and subsequently start the infection process (48). In general, these components (surface lipoproteins) are typically related to antigenic diversity, tissue attachment, gliding motion activity, and the transportation of nutritive ingredients (49).

In M. gallisepticum the GapA protein is the primary cell adhesin able to act in synchrony with additional cytoadherence associated proteins CrmA, (21, 50, 51). and Mgc2 protein which confines to the attachment process (52), as showed by some studies, both GapA and CrmA are the most essential for pathogenicity of M. gallisepticum enabling strong adherence to the epithelial respiratory tissues (53,54), and also responsible for hemadsorption (55). with additional cytoadherence associated proteins which are connected to phase diversity pMGA (21), and pvpA proteins (36, 37).

Another lipoprotein that has been linked to M. gallisepticum's pathogenicity is Mycoplasma specific lipoprotein A (MslA) (22). Additionally, MG1142 homology to OsmC-like protein has a role in the virulence of M. gallisepticum and survival by increased resistance of hydroperoxide in the host tissue (56).

PROGRAMMED CELL DEATH

There are a variety of ways for Mycoplasma to evade the host's innate and adaptive immune systems, these include biological mimicry, capsules, complement inhibition, latent forms hidden within phagosomes, hypervariable antigenicity, phase variance, blocking phagolysosome fusibility, and inducing apoptosis in immune cells (57). In addition, it is capable of mutation in small repeat sequences of the DNA strand (25), As a result, there is a decrease in the ability of immune system to detect Mycoplasma, which leads to increased resistance and a longer survival period (58). The membrane lipoproteins of Mycoplasma, or pathogen associated molecular patterns (PAMPs), have the capacity to bind to the Toll-like receptors (TLRs), which are part of pattern recognition receptors (PRRs), or body cell receptors of the natural immune system, are essential for recognizing invasive microorganisms and initiating the natural and adaptive immune response processes, which are expressed by B and T lymphocytes, monocytes, macrophages, neutrophils or heterophils, dendritic cells, fibroblasts, endothelial and epithelial cells, (59), also a pathogen sensitizes cytosolic receptors called nucleotide-binding oligomerization domain like receptors (NOD) (60), act as microbial sensor for provoking antimicrobial immune response (61), pro-inflammatory cytokine secretion is stimulated in part by the NF-κB pathway, which is controlled by the TLRS 1 and 2 (62), however, M. pneumoniae was proved to stimu,ate NF-κB through TLR1, TLR2, and TLR6. (63). Due to the interaction between TLRs and Mycoplasma PAMPs, Mycoplasmas stimulate the macrophages' ability to lyse cells, and increase IL-8 secretion by bronchial epithelial cells (64), while Shimizu and copartners showed increased in production of TNF-α with M. genitalium infection (62), in another study M. genitalium infection cause the release of IL-6, IL-8 and secretion of granulocyte-monocsyte (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) was

considerably increased, so the infection may result in persistent inflammation of affected tissues (65). Moreover, as stated by Chen and colleagues they demonstrated substantial reduction of the CD8+ lymphocytes in the thymus of infected chickens with M. gallisepticum, in addition to decreased DNA and mitochondrial function of thymus (66), in addition, the inflammasome is activated in the chicken thymus by reactive oxygen species (ROS), PAMPs, or Damage-associated molecular patterns (DAMPs), it is also believed that the TLR-2/MyD88/NF-κB signaling pathways play a role in this process (66).

Additionally, according to Li and colleagues (2019) (67), M. gallisepticum can inhibit autophagocytosis, a mechanism that eliminates damaged components, and induce oxidative stress and apoptosis in thymus tissue cells. Additionally, maybe there is no interception to assuming that Mycoplasma follows the same mechanism as the rest of the bacteria in terms of being rich in lipoproteins, as it has been proven that bacterial lipoproteins are able to induce the release of adenosine triphosphate (ATP) from host cells responding to pathogenic infections (68) and accumulate near the inflamed tissues (69 De Marchi etal., 2019), which in turn causes inflammation and is linked to cell cytotoxicity or apoptosis as a result of ATP binding to cell membrane protein called purinergic P2X7 receptors (70,71), by inducing the inflammasome, a group of proteins that causes the maturation and release of pro-inflammatory cytokines as well as the release of reactive nitrogen and oxygen, which is followed by the release of IL1 and IL18, which contribute to the inflammation process (70). Also activated P2X7R induces apoptosis by activating caspases 3 and 7 following a massive Ca+2 intake (72) and leading to the up regulation of IL-1expression (73).

INFECTIOUS PROCESS

Here we will explain the infection process of one of the types of Mycoplasma that infects poultry. Concerning M. gallisepticum, cell adhesion to the chicken tracheal epithelium is caused by capsular components (blebs or tip structures) (74), which is followed by epithelial penetration and cilia dysfunction (17). Almost all chicken populations are commonly affected by M. gallisepticum infection, though the intensity and duration of the illness vary depending on the season and age (75). Additionally, M. gallisepticum colonization

can become more severe due to prior damage to respiratory epithelial layers caused by a number of concurrent pathogens, including viruses such the LPAI subtype H3N8 virus (76), or subtype H9 (77), Newcastle virus (ND) (57), infectious bronchitis virus (IB) (78), or E. coli (79), as well as immunodepression, unfavorable environmental factors like poor ventilation, subtle temperature changes, and numerous other stressors (75), leading to complex chronic respiratory infections (80) with significant morbidity and mortality rates and low weight, particularly during colder months.

Most susceptible birds to severe infection are malnourished birds and those who live in houses with high levels of ammonia and nitrites, which in turn damage and destroy the mucous membranes. and decrease macrophage and natural killer cell activity, all these factors facilitate M. gallisepticum colonization and increase the severity of the infection (82). Age also has a significant impact on the severity of Mycoplasmosis, for example, while chickens are infected with M. gallisepticum when they are younger than 4 weeks they develop a more serious disease (57).

Mycoplasmas can persist in one primary host for a long time, making diseased hosts the main sources of Mycoplasmas, i.e, long-lasting carrier status is a common characteristic (75). In addition, cysteine proteases (CysP) of M. gallisepticum were confirmed to degrade IgG and present another practical way for a protracted period of the livability of M. gallisepticum, leading to the chronic nature of infection and carrier status of chicken (83).

As previously demonstrated by several studies, the attachment through sialic acid residues of the epithelial cells respiratory tract and colonization are prerequisites for the pathogenic processes and robust immune response, and some hints of evidence may suggest that lesions of the respiratory system are fundamentally caused by the host immunity and inflammatory response during infection rather than by direct effect of Mycoplasma toxins or membrane elements (84), early interactions between M. gallisepticum and pulmonary epithelial cells, which promote macrophage cell migration, inflammatory cytokine production, and chemokine gene expression, may be related to the initiation of the inflammatory response and the progression

of lesions (85). As a result of cellular infiltrations and edema in the trachea, M. gallisepticum infections result in epithelial necrosis and exfoliation, ciliostasis, and de-ciliation, as well as increased epithelial thickness (76). It has been demonstrated that M. gallisepticum invades non-phagocytic host cells (86), producing toxic byproducts for the host immune system, including hydrogen peroxide and nitric oxide, which damage host epithelial cells (72) and negatively affect the function and integrity of epithelial cells as well as the B and T cell functions (87). Although, most Mycoplasmas are extracellular (88) however, M. gallisepticum and, M. penetrans M. pneumoniae, M. genitalium can invade and survive in host cells as well as M. fermentans can reside in non-phagocytic cells (89).

REFERENCES

1. Weisburg, W. G., Tully, J. G., Rose, D. L., Petzel, J. P., Oyaizu, H., Yang, D., Mandelco, L., Sechrest, J., Lawrence, T. G., & Van Etten, J. (1989). A phylogenetic analysis of the mycoplasmas: basis for their classification. Journal of bacteriology, 171 (12), 6455–6467. doi.org/10.1128/jb.171.12.6455-6467.1989

2. Al-Essa , S.H. F., Al-Ghazawi, G. J., Jumaa, Z. K.and and Lapteva , An. V.(2021). Isolation and Identification of Mycoplasmas from Patients with Gastro-Intestinal Disease in Basrah Hospitals. Clin Schizophr Relat Psychotses. 15S: 6, doi: 10.3371/CSRP.HSJG.080921.

3. Al-Mosawi, R.M. (2009). Signs and symptoms of urethritis and cervicitis among women with or without genital mycoplasma infection in governorate of Basrah. Journal of Basrah Researches (Sciences) 35,(3):48-58.

4. Al-Mosawi, R.M. (2019). Genital Mycoplasmas among Women in the Province of Basrah with an Evaluation of their Role in Some Cases. Global Journal of Medical Research: C Gynecology and Obstetrics. 19, 1 Vers. 1.0 .

5. Meyer Sauteur, P. M., Unger, W. W., Nadal, D., Berger, C., Vink, C., & van Rossum, A. M. (2016). Infection with and Carriage of Mycoplasma pneumoniae in Children. Frontiers in microbiology, 7, 329. doi.org/10.3389/fmicb.2016.00329.

6. Hasso, S. A. (2007). A review of confirmed pathogen of dogs and cats in Iraq . Basrah Journal of Veterinary Research,.6,(2):156 162.

7. Jarad, A. and Abed, F. A. (2020).Clinical and diagnostic studies of hemo-mycoplasmosis in dogs at Basrah, Iraq. Biochemical and Cellular Archives.. 20, (2): 6171-6175.

8. Jabbar S. L., and Al. Amery M. A.Y. (2020). Diagnostic study of hemoplasmosis in cats in Basrah city-Iraq. Basrah Journal of Veterinary Research, 19,

3,48 55. Proceeding of the 17th International Conference. College of Veterinary Medicine. University of Basrah. Iraq.

9. Abed, F. A., Alsaad, K. M. (2017). Clinical, hematological and diagnostic studies of hemomycoplasma infection (Mycoplasma ovis) in sheep of Basrah govenorate . Basrah Journal of Veterinary Research.16,(2):284 301.

10. Noomi , B. S. , Hadi, K. A., , Khalaf , H.Y., , Abdulaali Azeez, A. , Jaafar, N. A.,, Al-refaai, H. A. N. (2018). Investigation of M. agalactiae and study its effects on some hematological and biochemical parameters in sheep and goats infected with mastitis Basrah Journal of Veterinary Research. 17,.3,2018 Proceeding of 6th International Scientific Conference, College of Veterinary Medicine University of Basrah, Iraq.

11. Alsaad, K. M. Lafta, M. H. Jarad A. and Ali, D. H. (2018).Acute Hemotropic Mycoplasmosis Of Newborn Calves In Basrah, Iraq. IOSR Journal of Agriculture and Veterinary Science (IOSR-JAVS) 11, 4 Ver. I, 28-33.

12. Jarad,. A and Alsaad K. M. (2016).Clinical , hematological and diagnostic studies of Mycolasma wenyonii infection in cattle of Basrah governorate , Iraq. Basrah Journal of Veterinary Research.15,(4):37 53.

13. Gharaibeh, S., and Hailat, A. (2011). Mycoplasma gallisepticum experimental infection and tissue distribution in chickens, sparrows and pigeons. Avian Pathology.40, 349-354.

14. Prajapati, A., Subhashree, N., Susan, J., Reddy, M., Yogisharadhya, R., and Patil, S. (2018). Prevalence of M. gallisepticum and M. synovae in Poultry- India Perspective. International Journal of Current Microbiology and Applied Sciences. 7 (5):2213-2220.

15. Ali, AJ. (2019). Isolation, identification and some aspects pathogenicity of Mycoplasma gallisepticum in broiler chickens. A doctoral dissertation, University of Bagdad, Coll. Vet. Med. Iraq.

16. Al-Mahmoudi, A. H. J., Hammadi, H.A., Ayyez, H. N., Al-Ibadi, I. N. A., Mutter, H.M., and Neamah, A. J. (2020). Mycoplasma gallisepticum based phylogenetic studies of infected chicken farms in Iraq . Plant Archives, 20 , (2): 4279-4282.

17. Kleven, S.H., (2008). Control of avian Mycoplasma infections in commercial poultry. Avian Diseases. 52, 367- 374.

18. Pilo, P., Frey, J., and Vilei, E. (2007). Molecular mechanisms of pathogenicity of Mycoplasma mycoides subsp. mycoides SC. Veterinary Journal. 174, 513-521.

19. Maniloff, J. (1992). Phylogeny of Mycoplasmas. Mycoplasmas Molecular Biology and Pathogenesis (Maniloff J, McElhaney RN, Finch LR & Baseman JB, eds): pp. 549–559. American Society for Microbiology, Washington, DC.

20. Su, C. J., & Baseman, J. B. (1990). Genome size of Mycoplasma genitalium. Journal of bacteriology, 172(8), 4705–4707. doi.org/10.1128/jb.172.8.4705-4707.1990.

21. Papazisi, L., Gorton, T., Kutish, G., Markham, P., Browning, G., Nguyen, D., Swartzell, S., Madan, A., Mahairas, G., and Geary, S. (2003). The complete genome sequence of the avian pathogen Mycoplasma gallisepticum strain R(low). Microbiology. 149, 2307-2316.

22. Szczepanek, S., Frasca, Jr., S. Schumacher, V., Liao, X., Padula, M., Djordjevic, S., and Geary, S. (2010). Identification of lipoprotein MslA as a neoteric virulence factor of Mycoplasma gallisepticum. Infection and Immunity. 78,3475-3483.

23. Razin, S., and Hayflick, L. (2010). Highlights of Mycoplasma research-. An historical perspective. Biologicals. 38(2): 183-190.

24. Sasaki, Y., Ishikawa, J., Yamashita, A., Oshima, K., Kenri, T., Furuya, K., Yoshino, C., Horino, A., Shiba, T., Sasaki, T., and Hattori, M. (2002). The complete genomic sequence of Mycoplasma penetrans, an intracellular bacterial pathogen in humans. Nucleic acids research. 30, 5293-5300.

25. Citti, C., Baranowski E., Dordet-Frisoni, E., Faucher, M., and Nouvel, LX. (2020). Genomic Islands in Mycoplasmas. Genes, 11, 836; doi:10.3390/genes11080836.

26. Mushegian, A. R., & Koonin, E. V. (1996). A minimal gene set for cellular life derived by comparison of complete bacterial genomes. Proceedings of the National Academy of Sciences of the United States of America. 93(19), 10268–10273. doi.org/10.1073/pnas.93.19.10268.

27. Hutchison, C. A., Peterson, S. N., Gill, S. R., Cline, R. T., White, O., Fraser, C. M., Smith, H. O., & Venter, J. C. (1999). Global transposon mutagenesis and a minimal Mycoplasma genome. Science (New York, N.Y.), 286 (5447): 2165–2169. doi.org/10.1126/science.286.5447.21

28. Dybvig, K.; Lao, P.; Jordan, D.S.; Simmons, W.L. (2010). Fewer essential genes in mycoplasmas than previous studies suggest. FEMS Microbiological. Letters., 311, 51–55. doi.org/10.1111/j.1574-6968.2010.02078.x

29. Barker, N., Helps, R., Peters, R., Darby,C., Radford,D., Tasker, S. (2011). Complete genome sequence of Mycoplasma haemofelis, a hemotropic Mycoplasma. Journal of Bacteriology. 193(8): 2060-2061.

30. Kenri, T., Horino, A., Matsui, M., Sasaki, Y., Suzuki, S., Narita, M., Ohya, H., Okazaki, N., Shibayama, K. (2012). Complete genome sequence of Mycoplasma pneumoniae type 2a strain 309, isolated in Japan. Journal of Bacteriology. 194 (5): 1253-4. doi: 10.1128/JB.06553-11.

31. Abolnik, C. and Beylefeld A. (2015). Complete genome sequence of Mycoplasma gallinaceum. Genome Announcements. 3(4): e00712-15.

32. Fookes, C., Hadfield, J., Harris, S., Parmar, S., Unemo, M., Jensen, S., and Thomson, R. (2017). Mycoplasma genitalium: whole genome sequence analysis, recombination and population structure. BMC genomics. 18(1): 993.

33. Vasconcelos, A., Ferreira, H., Bizarro, C., Bonatto, S., Carvalho, M., Pinto, P., and et al., (2005). Swine and Poultry Pathogens: the Complete Genome Sequences of Two Strains of Mycoplasma hyopneumoniae and a Strain of M. synoviae. Journal of Bacteriology. 187,(16): 5568–557.

34. Dos Santos, P., Guimaraes, A., Nascimento, N., SanMiguel, P., and Messick, J.(2012). Complete Genome Sequence of Mycoplasma wenyonii Strain Massachusetts. Journal of Bacteriology. 194, (19): 5458-5459..

35. Razin, S., Barile, M. F., Harasawa, R., Amikam, D., & Glaser, G. (1983). Characterization of the mycoplasma genome. The Yale journal of biology and medicine, 56(5-6): 357–366.

36. Yogev, D., Menaker, D., Strutzberg, K., Levisohn, S., Kirchhoff, H., Hinz, K.-H. & Rosengarten, R. (1994). A surface epitope undergoing high-frequency phase variation is shared by Mycoplasma gallisepticum and Mycoplasma bovis. Infection and Immunity. 62, 4962-4968

37. Boguslavsky, S., Menaker, D., Lysnyansky, I., Liu, T., Levisohn, S., Rosengarten, R., Garcia, M., and Yogev, D. (2000). Molecular characterization of the M. gallisepticum pvpA gene which encodes a putative variable cytadhesin protein. Infection and Immunity. 68,3956-3964.

38. Levisohn, S., Rosengarten, R., and Yogev, D. (1995). In vivo variation of Mycoplasma gallisepticum antigen expression in experimentally infected chickens. Veterinary Microbiology. 45,219–231.

39. Noormohammadi, A. (2007). Role of phenotypic diversity in pathogenesis of avian Mycoplasmosis. Avian Pathology. 36,439-444.

40. Razin, S., Yogev, D., and Naot, Y. (1998). Molecular biology and pathogenicity of Mycoplasmas. Microbiology and Molecular Biology Reviews. 62,1094-1156.

41. Sirand-Pugnet, P., Lartigue, C., Marenda, M., Jacob, D., Barré, A., Barbe, V., Schenowitz, C., Mangenot, S., Couloux, A., Segurens, B., de Daruvar, A., Blanchard, A., & Citti, C. (2007). Being pathogenic, plastic, and sexual while living with a nearly minimal bacterial genome. PLoS genetics, 3(5): e75. doi.org/10.1371/journal.pgen.0030075.

42. Bertelli, C., Laird, M. R., Williams, K. P., Simon Fraser University Research Computing Group, Lau, B. Y., Hoad, G., Winsor, G. L., & Brinkman, F. (2017). IslandViewer 4: expanded prediction of genomic islands for larger-scale datasets. Nucleic acids research, 45(W1), W30–W35. doi.org/10.1093/nar/gkx343.

43. Nouvel, L. X., Marenda, M., Sirand-Pugnet, P., Sagné, E., Glew, M., Mangenot,

S., Barbe, V., Barré, A., Claverol, S., & Citti, C. (2009). Occurrence, plasticity, and evolution of the vpma gene family, a genetic system devoted to high-frequency surface variation in Mycoplasma agalactiae. Journal of bacteriology, 191(13): 4111–4121. doi.org/10.1128/JB.00251-09.

44. Glew, M. D., Papazisi, L., Poumarat, F., Bergonier, D., Rosengarten, R., & Citti, C. (2000). Characterization of a multigene family undergoing high-frequency DNA rearrangements and coding for abundant variable surface proteins in Mycoplasma agalactiae. Infection and Immunity, 68(8): 4539–4548. doi.org/10.1128/IAI.68.8.4539-4548.2000.

45. Chopra-Dewasthaly, R., Spergser, J., Zimmermann, M., Citti, C., Jechlinger, W., & Rosengarten, R. (2017). Vpma phase variation is important for survival and persistence of Mycoplasma agalactiae in the immunocompetent host. PLoS pathogens, 13(9): e1006656. doi.org/10.1371/journal.ppat.1006656.

46. Browning, G. F. M. S. Marenda, P. F. Markham, A. H. Noormohammadi, and K. G. Whithear. (2010). In, Pathogenesis of Bacterial Infections in Animals, Fourth Edition, Edited by Carlton L. Gyles, John F. Prescott, J. Glenn Songer, and Charles O. Thoen, Blackwell Publishing, Pp549-565. USA.

47. Grodio, J., Hawley, D., Osnas, E., Ley, D., Dhondt, K., Dhondt, A., and Schat, K. (2012). Pathogenicity and immunogenicity of three M. gallisepticum isolates in house finches (Carpodacus mexicanus). Veterinary Microbiology. 155(1): 53–61.

48. Mudahi-Orenstein, S., Levisohn, S., Geary, S., and Yogev, D. (2003). Cyt-adherence-deficient mutants of Mycoplasma gallisepticum generated by transposon mutagenesis. Infection and Immunity. 71,3812-3820.

49. Miyata, M. (2005). Gliding motility of Mycoplasmas, the mechanism cannot be explained by current biology. In, Mycoplasmas Molecular Biology Pathogenicity and Strategies for Control, A. Blanchard and G. Browning, eds. Horizon Bioscience, Wymondham, United Kingdom. 137-163.

50. Keeler, C., Jr., Hnatow, L., Whetzel, P., & Dohms, J. (1996). Cloning and characterization of a putative cytadhesin gene (mgc1) from Mycoplasma gallisepticum. Infection and Immunity. 64, 1541-1547.

51. Goh, M., Gorton, T., Forsyth, M., Troy, K., and Geary S. (1998). Molecular and biochemical analysis of a 105 kDa Mycoplasma gallisepticum cytadhesin (GapA). Microbiology. 144 (Pt 11): 2971-2978.

52. Hnatow, L., Keeler, Jr., C., Tessmer, L., Czymmek, K., and Dohms J. (1998). Characterization of Mgc2 , a Mycoplasma gallisepticum cytadhesin with homology to the M. pneumoniae 30-kilodalton protein P30 and Mycoplasma genitalium P32. Infection and Immunity. 66,3436-3442.

53. Papazisi, L., Silbart, L., Frasca Jr., S., Rood, D., Liao, X., Gladd, M., Javed, M., and Geary, S. (2002a). A modified live M. gallisepticum vaccine to protect chickens from respiratory disease. Vaccine. 20,3709–3719.

54. Papazisi, L., Frasca, Jr., S., Gladd, M., Liao, X., Yogev, D., and Geary, S. (2002b). GapA and CrmA co-expression is essential for Mycoplasma gallisepticum cytadherence and virulence. Infection and Immunity. 70,6839-6845.

55. Winner, F., Markova, I., Much, P., Lugmair, A., Siebert-Gulle, K., Vogl, G., Rosengarten, R., and Citti, C. (2003). Phenotypic switching in M. gallisepticum hemadsorption is governed by a high-frequency, reversible point mutation. Infection and Immunity. 71,1265-1273.

56. Jenkins, C., Samudrala, R., Geary, S., and Djordjevic, S. (2008). Structural and functional characterization of an organic hydroperoxide resistance protein from Mycoplasma gallisepticum. Journal of Bacteriology. 190,2206-2216.

57. Finlay, B. B., & McFadden, G. (2006). Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell, 124(4): 767–782. doi.org/10.1016/j.cell.2006.01.034.

58. Majumder, S., Zappulla, F., Silbart, L. (2014). Mycoplasma gallisepticum Lipid Associated Membrane Proteins Up-regulate Inflammatory Genes in Chicken Tracheal Epithelial Cells via TLR-2 Ligation through an NF-κB Dependent Pathway. PLoS one 9(11): e112796.

59. Takeuchi, O. and Akira, S. (2010). Pattern Recognition Receptors and Inflammation. Cell. 140, 805–820.

60. Browning, G., and Citti, C. (2014) Mollicutes. Molecular Biology and Pathogenesis. caister Academic Press.

61. Elinav, E., Strowig, T., Henao-Mejia, J., and Flavell, R. (2011). Regulation of the antimicrobial response by NLR proteins. Immunity. 34(5):665-679.

62. Shimizu, T., Kida, Y. and Kuwano, K. (2008). A triacylated lipoprotein from Mycoplasma genitalium activates NF-κB through Toll-like receptor 1 (TLR1) and TLR2. Infection and Immunity. 76(8): 3672-3678.

63. Shimizu, T., Kida, Y., & Kuwano, K. (2005). A dipalmitoylated lipoprotein from Mycoplasma pneumoniae activates NF-kappa B through TLR1, TLR2, and TLR6. Journal of Immunology (Baltimore, Md. : 1950), 175(7): 4641–4646. doi.org/10.4049/jimmunol.175.7.4641.

64. Chen, Z., Shao, X., Dou, X., Zhang, X., Wang, Y., Zhu, C., et al. (2016). Role of the Mycoplasma pneumoniae/ interleukin-8 / neutrophil axis in the pathogenesis of pneumonia. PLoS One. 11, e0146377.

65. McGowin, C., Ma L., Martin D., Pyles R. (2009). Mycoplasma genitalium-encoded MG309 activates NFkappaB via Toll-like receptors 2 and 6 to elicit pro inflammatory cytokine secretion from

human genital epithelial cells. Infection and Immunity. 77(3): 1175- 81.

66. Chen, C., Li, J., Zhang, W., Shah, S., & Ishfaq, M. (2020). Mycoplasma gallisepticum triggers immune damage in the chicken thymus by activating the TLR-2/MyD88/NF-κB signaling pathway and NLRP3 inflammasome. Veterinary Research. 51(1), 52. doi.org/10.1186/s13567-020-00777-x.

67. Li J, Qiao Z, Hu W, Zhang W, Shah SWA, Ishfaq M (2019) Baicalin mitigated Mycoplasma gallisepticum-induced structural damage and attenuated oxidative stress and apoptosis in chicken thymus through the Nrf2/HO-1 defence pathway. Veterinary Research . 50:83.

68. Di Virgilio, F.; Adinolfi, E. (2017). Extracellular purines, purinergic receptors and tumor growth. Oncogene. 36, 293–303.

69. De Marchi, E.; Orioli, E.; Pegoraro, A.; Sangaletti, S.; Portararo, P.; Curti, A.; Colombo, M.P.; Di Virgilio, F.; Adinolfi, E. (2019). The P2X7 receptor modulates immune cells infiltration, ectonucleotidases expression and extracellular ATP levels in the tumor microenvironment. Oncogene. 38, 3636–3650.

70. Savio, L., Mello, P., da Silva, C., and Coutinho-Silva, R. (2018). The P2X7 receptor in inflammatory diseases, angel or demon? Frontiers in Pharmacology. 9,52. doi, 10.3389/fphar.2018.00052.

71. Acuna, C.; Capelli, C.; Coddou, C.; Escobar, A.; Imarai, M.; Yohana, L.; Lopex, X.; Rios, M.; Lopez, M. (2014). WO2013023319A1—In Vitro Method for Modifying the Depletion Profile of Treg Cells Present in a Total Splenocyte Population of a Biological Sample by Means of the Isolation, Culturing and Exposure Thereof to an Atp and Polymixin b Medium. U.S. Patent 14/181,810, 18 December.

72. Zhang, W., Liu, Y., Zhang, Q., Waqas, S., Wu, Z., Wang, J., Ishfaq, M., and Li, J. (2020). Mycoplasma gallisepticum Infection Impaired the Structural Integrity and Immune Function of Bursa of Fabricius in Chicken, Implication of Oxidative Stress and Apoptosis. Frontiers in Veterinary Science. 7,225.

73. Liu, Y.; Xiao, Y.; Li, Z. (2011). P2X7 receptor positively regulates MyD88-dependent NF-_B activation. Cytokine., 55, 229–236.

74. Bencina, D. (2002). Haemagglutinins of pathogenic avian mycoplasmas. Avian Pathology. 31, 535-547.

75. Raviv, Z., and Ley, D. (2013). Mycoplasma gallisepticum infection. In, Diseases of Poultry. D.E. Swayne, J.R. Glisson, L.R. McDougald, L.K. Nolan, D.L. Suarez and V.L. Nair, eds. Wiley-Blackwell, Ames, Iowa. pp 877-893.

76. Stipkovits, L., Glavits, R., Palfi, V., Beres, A., Egyed, L., Denes, B., Somogyi, M., and Szathmary, S. (2012). Pathologic lesions caused by co-infection of M. gallisepticum and H3N8 low pathogenic avian influenza virus in chickens. Veterinary Pathology. 49(2) 273-283.

77. Al- Dabhawe, A.H., Kadhim, H.M. S. and Samaka, H.M. (2013). Molecular detection of infectious bronchitis virus and it is relation with avian influenza virus (H9) and Mycoplasma gallisepticum from different geographical regions in Iraq. Iraqi Journal of Veterinary Sciences. 27(2): 97-101.

78. Landman, W., and Feberwee, A. (2004). Aerosol - induced Mycoplasma synoviae arthritis, the synergistic effect of infectious bronchitis virus infection. Avian Pathology. 33, 591 – 598.

79. Ley, D. H. (2003). "Mycoplasma gallisepticum Infection" in Diseases of Poultry, Y.M. Saif, H.J. Barnes, A.M. Fadly, J.R. Glisson, L.R. McDougald, D.E. Swayne., Eds., pp 722-744, Iowa State University Press, Ames, Iowa, USA,11th edition.

80. Kleven, S. H. (1998). Mycoplasmas in the etiology of multifactorial respiratory disease. Poultry Science. 77,1146-1149.

81. Peebles, E., Branton, S., Burnham, M., and Gerard, P. (2003). Influences of supplemental dietary poultry fat and F-strain Mycoplasma gallisepticum infection on the early performance of commercial egg laying hens. Poultry Science. 82, 596 – 602.

82. .Gaunson, J., Philip, C., Whithear, K., and Browning, G. (2006). Age related differences in the immune response to vaccination and infection with Mycoplasma gallisepticum. Vaccine. 24, 1687-169254.

83. Cizelj, I., Bercic, R., Dusanic, D., Narat, M., Kos, J., Dovc, P., and Bencina, D. (2011). Mycoplasma gallisepticum and M. synoviae express a cysteine protease CysP, which can cleave chicken IgG into Fab and Fc. Microbiology. 157, 362–372.

84. Ferguson-Noel, N., and Noormohammadi, A. (2013). Mycoplasma synoviae infection. In, Diseases of Poultry, 13th ed. D.E. Swayne, J.R. Glisson, L.R. McDougald, L.K. Nolan, D.L. Suarez and V.L. Nair, eds. Blackwell-Wiley Publishing, Ames, IA. pp 900 - 906.

85. Majumder, S., and Silbart, L. (2016). Interaction of Mycoplasma gallisepticum with chicken tracheal epithelial cells contributes to macrophage chemotaxis and activation. Infection and Immunity. 84, 266 –274.

86. Vogl, G., Plaickner, A., Szathmary, S., Stipkovits, L., Rosengarten, R., and Szostak, M. (2008). Mycoplasma gallisepticum invades chicken erythrocytes during infection. Infection and Immunity. 76,71-77.

87. Cartner S., Lindsey, R., Gibbs-Erwin, J., Cassel, G., Simecka, J. (1998). Roles of innate and adaptive immunity in respiratory mycoplasmosis. *Infection and Immunity.* 66(8):3485–3491.

88. Wise, K., Foecking, M., Röske, K., Lee, Y., Lee, Y., Madan, A., and Calcutt, M. (2006). Distinctive repertoire of contingency genes conferring mutation-based phase variation and combinatorial expression of surface lipoproteins in M. capricolum subsp. capricolum of the M. mycoides phylogenetic

cluster. *Journal of Bacteriology*. 188, 4926-4941.

89. Rottem, S. (2003). Interaction of Mycoplasmas with host cells. *Physiological Reviews. 83,* 417-432.

موت خلايا المضيف المبرمج والعملية الخمجية للمفطورات

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الخلاصة

السمة المشتركة في امراض المفطورات هي الحالة المزمنة للإصابة وقد ارتبطت امراض المفطورات بالتهابات الجهاز التنفسي ، وأمراض الرئة المزمنة ، والربو القصبي ، والتهاب الدماغ السحائي ، والتهاب الضرع ، والتهاب المفاصل ، ومشاكل القلب ، والعقم ، ومشاكل العظام ، واضطرابات قناة البيض ، والموت في البشر وأنواع الحيوانات المختلفة. ولقد تم تحديد كيفية عمل بنية عضي الارتباط بخلايا الكائن الحي المضيف ، والتي تتوسط العديد من التفاعلات المعقدة بين مختلف المواد المسؤولة عن الارتباط اضافة الى بروتينات الالتصاق المساعدة الثانوية لتسهيل المرحلة الحرجة الأولى من الالتصاق الخلوي بظهارة الجهاز التنفسي او التناسلي. وقد ثبت أيضًا أن التواجد داخل الخلايا ، والتسمم الخلوي المباشر ، وتنشيط مسارات الاحداث الالتهابية من خلال المستقبلات (TLRs) ، والتي تسبب تطور افات الأنسجة الناجمة عن السيتوكينات الالتهابية ، وتنشيط الانفلاسوم ، الذي يسبب التهاب القنوات التنفسية العليا ، حيث كلها تلعب أدوارًا حاسمة في التسبب في تطور ونشؤ المرض. تسعى هذه المراجعة إلى تقديم تقييم شامل للتطورات الأخيرة في فهمنا لإمراضية المفطورات مع فهم آليات ضراوتها .

الكلمات المفتاحية: المفطورات، العملية الخمجية, موت الخلايا المبرمج