The hypothesis postulating that Mycobacterium avium paratuberculosis (MAP) is the cause of Crohn’s disease (CD) has been circulating for many years. Advances in molecular techniques, such as polymerase chain reaction and culture methods, have enabled researchers to demonstrate that there is an association between MAP and CID. Recently, genome-wide association studies have identified novel susceptibility genes for CD, which are critical for generation of an adaptive immune response that is protective against intracellular pathogens, including M. tuberculosis infection. However, the role of MAP as a cause of CD suffered a setback with the report that administration of antimycobacterial therapy failed to lead to a sustained response in CD patients. Accordingly, this review sought neither to confirm nor refute this, but instead to survey recent literature on the role of MAP in CD. (C) 2009 The WJG Press and Baishideng. All rights reserved.

Decrease of Johne’s disease prevalence and incidence in six Minnesota, USA, dairy cattle herds on a long-term management program
Preventive Veterinary Medicine, 88, 128-137

The objective of this prospective longitudinal field study was to describe changes in prevalence of seroconversion and fecal shedding and changes in incidence rate of seroconversion, fecal shedding and culling of milk cows for clinical signs of Johne’s disease (JD) in six Minnesota (USA) herds participating the JD Demonstration Herd Project (JDDHP) from 2000 to December 2005. Changes in prevalence and incidence rate were evaluated in light of the owner’s compliance to the JDDHP using a risk assessment (RA) score. Adult cows were tested regularly using serum ELISA and bacterial fecal culture to evaluate progress made throughout the control program. Logistic regression was used to evaluate the association between the risk for a cow to test positive and the year on the program. After 5 years of follow-up, the proportion of cows that tested positive to serum ELISA and fecal culture (all positive cultures as well as moderate to heavy shedders only) decreased significantly from the first to the last year (8-3.1%, 10.4-5.6% and 3.1-1.5%, respectively). Cox proportional hazards regression was used to evaluate change of incidence rate across birth cohorts. Birth cohorts were defined by birth date of the animals with the reference cohort or oldest cohort being already 12-24 months of age at the onset of the long-term management program. All cohorts were censored at 45 months of age. Compared to cows from the reference cohort, cows from cohorts that could have benefitted from the JDDHP in their young age (less than 12 months of age at the start of the program or born later) were significantly less at risk of seroconversion and fecal shedding (hazard ratios for seroconversion, any fecal shedding and heavy shedders less than 0.63, 0.67 and 0.62, respectively). For the three herds achieving good management changes with a risk assessment score under 30 at their last year of the study, the cohorts that were born after the program was instituted did better than those born before the start of the program, implying that the program could have helped around birth as well for those herds. This study suggests that reduction of environmental contamination of heifers up to a year of age may have had some impact on the success of the program. The JDDHP appears more beneficial for herds achieving a better reduction of their RA score with a decrease risk for infection in very young calves. (c) 2008 Elsevier B.V. All rights reserved.
Comparison of bacterial culture, histopathology, and immunohistochemistry for the diagnosis of Johne's disease in culled dairy cows

Journal of Veterinary Diagnostic Investigation, 20, 51-57

Paired samples of formalin-fixed, paraffin-embedded ileum and lymph node from 204 culled dairy cows were investigated for evidence of infection by Mycobacterium avium subsp. paratuberculosis. Of the samples, 151 were from animals that were tissue-culture positive for M. avium subsp. paratuberculosis, and 53 were from animals that were tissue and fecal culture negative. From the culture-positive animals, M. avium subsp. paratuberculosis was isolated from 78 samples of ileum and from 107 samples of lymph node. Ziehl-Neelsen acid-fast and immunoperoxidase stained slides were examined for 15 minutes each. Acid-fast organisms were identified in 7 of 78 (8.97%) and 6 of 106 (5.61%) culture-positive ileum and lymph node samples, respectively. Immunohistochemical (IHC) analyses of the same tissues identified infection in the ileum of 9 of 78 (11.54%) and in the lymph node of 5 of 106 (4.67%) culture-positive tissues. All tissues from culture-negative animals tested negative when using acid-fast and IHC staining. The sensitivity of these 2 tests in detecting M. avium subsp. paratuberculosis in culled dairy cows was not significantly different, and the tests exhibited substantial to almost perfect agreement. Both tests were much less sensitive than bacterial culture, detecting less than 6% of tissues positive compared with culture.

Prevalence and characterization of bovine viral diarrhea virus in the white-tailed deer population in Indiana

Journal of Veterinary Diagnostic Investigation, 20, 71-74

Bovine viral diarrhea (BVD) is one of the economically important diseases of cattle. For many years, different types of vaccines have been commercially available, yet this disease is hard to control in high-density population areas. Detection and isolation of bovine viral diarrhea virus (BVDV) from any potential reservoir is vital, especially when considering virus eradication from a herd or locale. One potential source is wild ruminants. Ear notches and lymph nodes were collected from the wild population of white-tailed deer (Odocoileus virginianus) during deer hunting season in Indiana and tested for BVDV with a commercial BVD antigen capture enzyme-linked immunosorbent assay. Two samples out of 745 collected samples were positive, and subsequently cp and ncp BVDV was isolated from 1 ear notch and 1 lymph node. These isolates were genotyped as type la and 16 based on sequence analysis of the 5' untranslated region (U-I-R). The results of the present study indicate that the prevalence of BVDV in the white-tailed deer population of Indiana is about 0.3%. Wild ruminants infected with BVDV should be taken into consideration during an eradication program of BVDV from the livestock population.

Mycobacterium avium Genes MAV_5138 and MAV_3679 Are Transcriptional Regulators That Play a Role in Invasion of Epithelial Cells, in Part by Their Regulation of CipA, a Putative Surface Protein Interacting with Host Cell Signaling Pathways

Journal of Bacteriology, 191, 1132-1142

The Mycobacterium avium complex (MAC) is an important group of opportunistic pathogens for birds, cattle, swine, and immunosuppressed humans. Although invasion of epithelial cells lining the intestine is the chief point of entry for these organisms, little is known about the mechanisms by which members of the MAC are taken up by these cells. Studies with M. avium have shown that cytoskeletal rearrangement via activation of the small G-protein Cdc42 is involved and that this activation is regulated in part by the M. avium fadD2 gene. The fadD2 gene indirectly regulates a number of genes upon exposure to HEp-2 cells, including transcriptional regulators, membrane proteins, and secreted proteins. Overexpression of two fadD2-associated regulators (MAV_5138 and MAV_3679) led to increased invasion of HEp-2 cells, as well as altered expression of other genes. The protein product of one of the regulated genes, named CipA, has domains that resemble the PXXP motif of human Piccolo proteins, which bind SH3 domains in proteins involved in the scaffold complex formed during cytoskeletal rearrangement. Although CipA was not detected in the cytoplasm of HEp-2 cells exposed to M. avium, the recombinant protein was shown to be potentially expressed on the surface of Mycobacterium smegmatis incubated with HEp-2 cells and, possibly, to interact with human Cdc42. The interaction was then confirmed by showing that CipA activates Cdc42. These results suggest that members of the M. avium complex have a novel role in epithelial cell invasion.
mechanism for activating cytoskeletal rearrangement, prompting uptake by host epithelial cells, and that this mechanism is regulated in part by fadD2, MAV_5138, and MAV_3679


Therapeutic vaccine comprising Mycobacterium HSP70
Expert Opinion on Therapeutic Patents, 19, 95-99

Background: Mycobacterium avium ssp. paratuberculosis is the causative agent of Johen's disease. This infection of the small intestine is a global problem in the livestock industry. Bacterial shedding by infected but subclinical animals, and transmission via the fecal or intrauterine route and through colostrum and/or milk, make containment and eradication of this disease highly problematic. Current vaccine strategies are ineffective and no effective therapy is available. Objective: Within the broader scope of therapeutic uses of recombinant heat-shock protein 70 (HSP70), the present article evaluates the claim of patent WO08040691. Conclusion: The patent under comment here covers the ability of recombinant Mycobacterium avium ssp. paratuberculosis (MAP) HSP70, when administered in conjunction with an adjuvant, to result in a significant reduction in bacterial shedding in cattle infected with MAP. Furthermore, its administration does not mask diagnostic assays, allowing clinical diagnosis to be maintained.


Serological survey of selected infectious diseases in mouflon (Ovis aries musimon) from south-central Spain
European Journal of Wildlife Research, 55, 75-79

Serum samples from 101 mouflons (Ovis aries musimon) collected from July 2002 to January 2006 were tested for antibodies against Anaplasma spp., Brucella spp., bovine viral diarrhea virus, Chlamydophila abortus, Coxiella burnetti, Mycobacterium avium ssp. paratuberculosis, and Maedi-Visna virus. Mouflon came either from extensive farms or high ungulate density fenced hunting estates. Antibodies were detected against Anaplasma spp. (22.2%), C. burnetti (4.0%), M. avium ssp. paratuberculosis (1.0%) and C. abortus (1.0%). According to our results, mouflons could participate as a wild reservoir in the epidemiology of Anaplasma spp. infection and maybe Q fever, but they do not seem to contribute in the epidemiology of the rest of the studied infectious diseases in south-central Spain.


Seroprevalence of Mycobacterium avium paratuberculosis infection in French goat herds: preliminary results
Epidemiologie et Sante Animale, 2008, No 53, 121-128

A survey was conducted to estimate the prevalence of Mycobacterium avium paratuberculosis (Map) infection in goat herds in France. All the animals older than 6 months (n = 9420) from 80 goat-herds were tested using an absorbed ELISA. The apparent and true prevalences have been respectively measured and estimated both at herd and individual levels. The within-herd prevalence was also estimated. The true prevalence at herd level was estimated at 57%, while the individual true prevalence was estimated at 5.6% with 95% CI = [5.1 - 6.0] in the study population. The true within-herd prevalence was 11.29 +/- 7.66%. Nearly half of the infected herds had a true within-herd prevalence higher than 10%. Despite the lack of data from one important area (Rhone-Alpes), the results of this survey showed that infection by Map is widespread in French goat herds and provide the first epidemiological descriptive data necessary to the implementation for any control program against this disease.


Discovery of Stable and Variable Differences in the Mycobacterium avium subsp paratuberculosis Type I, II, and III Genomes by Pan-Genome Microarray Analysis
Applied and Environmental Microbiology, 75, 676-686
Mycobacterium avium subsp. paratuberculosis is an important animal pathogen widely disseminated in the environment that has also been associated with Crohn's disease in humans. Three M. avium subsp. paratuberculosis genomotypes are recognized, but genomic differences have not been fully described. To further investigate these potential differences, a 60-mer oligonucleotide microarray (designated the MAPAC array), based on the combined genomes of M. avium subsp. paratuberculosis (strain K-10) and Mycobacterium avium subsp. hominisuis (strain 104), was designed and validated. By use of a test panel of defined M. avium subsp. paratuberculosis strains, the MAPAC array was able to identify a set of large sequence polymorphisms (LSPs) diagnostic for each of the three major M. avium subsp. paratuberculosis types. M. avium subsp. paratuberculosis type II strains contained a smaller genomic complement than M. avium subsp. paratuberculosis type I and M. avium subsp. paratuberculosis type III genomotypes, which included a set of genomic regions also found in M. avium subsp. hominisuis 104. Specific PCRs for genes within LSPs that differentiated M. avium subsp. paratuberculosis types were devised and shown to accurately screen a panel (n = 78) of M. avium subsp. paratuberculosis strains. Analysis of insertion/deletion region INDEL12 showed deletion events causing a reduction in the complement of mycobacterial cell entry genes in M. avium subsp. paratuberculosis type II strains and significantly altering the coding of a major immunologic protein (MPT64) associated with persistence and granuloma formation. Analysis of MAPAC data also identified signal variations in several genomic regions, termed variable genomic islands (vGIs), suggestive of transient duplication/deletion events. vGIs contained significantly low GC% and were immediately flanked by insertion sequences, integrases, or short inverted repeat sequences. Quantitative PCR demonstrated that variation in vGI signals could be associated with colony growth rate and morphology.

New publications in the CROHN’S DISEASE AND PARATUBERCULOSIS database (253-255)


The hypothesis postulating that Mycobacterium avium paratuberculosis (MAP) is the cause of Crohn's disease (CD) has been circulating for many years. Advances in molecular techniques, such as polymerase chain reaction and culture methods, have enabled researchers to demonstrate that there is an association between MAP and CID. Recently, genome-wide association studies have identified novel susceptibility genes for CD, which are critical for generation of an adaptive immune response that is protective against intracellular pathogens, including M. tuberculosis infection. However, the role of MAP as a cause of CD suffered a setback with the report that administration of antimycobacterial therapy failed to lead to a sustained response in CD patients. Accordingly, this review sought neither to confirm nor refute this, but instead to survey recent literature on the role of MAP in CD. (C) 2009 The WJG Press and Baishideng. All rights reserved


Introduction Over two decades ago, T helper cells were classified into its functional subsets. Soon after the classical observation of Mosmann et al., immunologists agreed to accept the Th1/Th2 paradigm of the T helper subsets. Each subset is not only characterized by its specific cytokines pattern and effector functions but also by their properties to counter regulate each other’s functions. This classification helped to understand the complex principles of T helper cell biology and allowed us to comprehend different immune reactions in context of Th1 and Th2 subsets. Discussion Although Th1 subsets thought to be the crucial player for most of the organ-specific autoimmune diseases like multiple sclerosis and type-1 diabetes but the loss of Th1 dominant cytokine, IFN-gamma did not prevent the development of autoimmunity which raised the possibility of involvement of other Th subsets, different from Th1 cells in the induction of autoimmunity. Conclusion Recently, a new subset of Th cells that predominantly produce IL-17 and induce autoimmunity has been discovered, and it is believed that this subset may be the major cell type involved in orchestrating tissue inflammation and autoimmunity. Recent data propose that the differentiation factors of Th17 cells reveal a link with induction of Foxp3(+) regulatory T cells. Here, we review the interplay between Th17 and Foxp3(+) T-reg cells and Tr1 cells during autoimmune inflammatory reaction.
Mycobacterium avium subsp. paratuberculosis is an important animal pathogen widely disseminated in the environment that has also been associated with Crohn's disease in humans. Three M. avium subsp. paratuberculosis genomotypes are recognized, but genomic differences have not been fully described. To further investigate these potential differences, a 60-mer oligonucleotide microarray (designated the MAPAC array), based on the combined genomes of M. avium subsp. paratuberculosis (strain K-10) and Mycobacterium avium subsp. hominisuis (strain 104), was designed and validated. By use of a test panel of defined M. avium subsp. paratuberculosis strains, the MAPAC array was able to identify a set of large sequence polymorphisms (LSPs) diagnostic for each of the three major M. avium subsp. paratuberculosis types. M. avium subsp. paratuberculosis type II strains contained a smaller genomic complement than M. avium subsp. paratuberculosis type I and M. avium subsp. paratuberculosis type III genomotypes, which included a set of genomic regions also found in M. avium subsp. hominisuis 104. Specific PCRs for genes within LSPs that differentiated M. avium subsp. paratuberculosis types were devised and shown to accurately screen a panel (n = 78) of M. avium subsp. paratuberculosis strains. Analysis of insertion/deletion region INDEL12 showed deletion events causing a reduction in the complement of mycobacterial cell entry genes in M. avium subsp. paratuberculosis type II strains and significantly altering the coding of a major immunologic protein (MPT64) associated with persistence and granuloma formation. Analysis of MAPAC data also identified signal variations in several genomic regions, termed variable genomic islands (vGIs), suggestive of transient duplication/ deletion events. vGIs contained significantly low GC% and were immediately flanked by insertion sequences, integrases, or short inverted repeat sequences. Quantitative PCR demonstrated that variation in vGI signals could be associated with colony growth rate and morphology.