2012-10-29-168 Paratuberculosis databases updated (2012-10-29)
To: (08) Mycobacterial diseases; (23) Veterinary education; (27) Scientific information
____________________________________________________________________________________
A special service of the OIE World Organization for Animal Health
Reference Laboratory for Paratuberculosis, Brno, Czech Republic
How to request full papers from PTB databases

CGN minireviews on mycobacteria as a public health risk

A new series, aimed at stimulating discussion on published literature dealing with the threat to public health posed by mycobacteria. Although some information of global significance has been known for decades, the risk posed by mycobacteria remains underestimated.

Recently published (05) What can be expected from mycobacteria: Latent infection
Go to the minireviews archive 01-05
Go to COMMENTS – DISCUSSION – OPINIONS

Edited by the Reference Laboratory for Paratuberculosis and Avian Tuberculosis World Organization for Animal Health (OIE) and Biomedical Technology, Epidemiology and Food Safety Global Network harbouring in the Veterinary Research Institute, Brno, Czech Republic.
We support the One Health Initiative.

New publications in the PARATUBERCULOSIS database (1303-1314)

Genetic variation for infection status as determined by a specific antibody response against Mycobacterium avium subspecies paratuberculosis in milk of Dutch dairy goats
Journal of Dairy Science, 95, 6145-6151

Classical control strategies based on management restrictions to reduce transmission, culling of infected goats, and vaccination have not been able to eradicate Johne's disease from infected herds. Selective breeding for less susceptibility to disease may be a useful additional tool to contribute to control of the disease. The aim of this study was to estimate genetic variation and heritability for infection status as determined by a specific antibody response against Mycobacterium avium subspecies paratuberculosis in milk of Dutch dairy goats. Milk samples from 950 goats were tested for antibodies specific to Johne's disease by ELISA on 5 consecutive test days, with a time interval of around 3 mo. Test results were coded as infected or not infected according to the instructions of the manufacturer. Heritability of infection status was estimated for 3 data sets to determine the effect of repeated sampling: only test results obtained on the first test day (first-test); the maximum test result of each animal obtained on 1 of the 5 test days (max-test); and all test results per animal, with a maximum of 5 consecutive samplings (all-test). Data sets first-test and max-test were analyzed with a sire model with fixed effects for year of birth and stage of lactation, and random effects for sire and error. For data set all-test, an additional permanent environment effect was included in the model. The estimated heritability on the underlying scale ranged from 0.12 in data set first-test, to 0.09 in data set max-test, to 0.07 in data set all-test

Evaluation of specificity of tuberculosis diagnostic assays in caprine flocks under different epidemiological situations
Research in Veterinary Science, 93, 636-640

The aim of this study was to evaluate the specificity of the most widely used tuberculosis (TB) diagnostic tests, single intradermal tuberculin (SIT) and single comparative intradermal tuberculin (SCIT) tests and interferon-gamma (IFN-gamma) assay in 937 animals from eight
TB-free caprine flocks under different epidemiological situations. Maximum specificity was found using SCIT test (99.4-100% depending on the interpretation criteria) while SIT test and IFN-gamma assay showed a slightly lower overall specificity (97.6-99.2% and 96.4-98.4% respectively). Specificity of the SIT test in a Corynebacterium pseudotuberculosis infected flock was significantly (P < 0.05) lower if a severe interpretation criterion was applied. Similarly, specificity values of SIT test and particularly IFN-gamma assay in a paratuberculosis (PTB)-vaccinated flock were lower than those observed in non-vaccinated flocks. Higher proportion of false positive reactors to TB tests (SIT and IFN-gamma assay) were observed among animals positive in the PTB-ELISA in PTB vaccinated flock. These results demonstrate that TB diagnostic tests show an adequate specificity when performed in goats from TB-free flocks in most situations. However, certain factors such as C. pseudotuberculosis infection and paratuberculosis vaccination can have a negative impact in the most sensitive tests. (C) 2011 Elsevier Ltd. All rights reserved


Mycobacterium avium subsp. paratuberculosis (MAP) is the causal agent of Johne's disease in dairy cattle. Genotyping of MAP is useful to gain a better understanding of the origin of infection, to evaluate regional control programs, to improve diagnostics, and to develop vaccines. In this study 91 MAP isolates mainly from symptomatic dairy cattle in Rhineland-Palatinate (RP, Germany), its neighbor federal states, and Luxembourg were genotyped using Mycobacterial Interspersed Repetitive Units-Variable Number Tandem Repeat (MIRU-VNTR) and Multilocus Short Sequence Repeats (MLSSR). MIRU-VNTR and MLSSR produced 11 and 6 different genotypes among the 91 isolates, respectively. The combined analysis of both methods produced 25 genotypes with an index of discrimination (D) of 0.93 (95% CI: 0.91-0.95). The results revealed the genetic diversity of MAP and the dominance of two MAP genotypes commonly found in Europe, showed the usefulness of MAP genotyping in studies at a regional scale, and provided useful information for control initiatives in RP. (c) 2012 Published by Elsevier Ltd

Nielsen, S.S., Toft, N. (2012) Effect of days in milk and milk yield on testing positive in milk antibody ELISA to Mycobacterium avium subsp paratuberculosis in dairy cattle Veterinary Immunology and Immunopathology, 149, 6-10

Milk samples are becoming more used as a diagnostic specimen for assessment of occurrence of antibodies to Mycobacterium avium subsp. paratuberculosis (MAP). This study assessed the effect of days in milk (DIM) and milk yield on testing positive in a commercial MAP specific milk antibody ELISA among 222,774 Danish Holstein cows. Results showed that odds of testing positive on 1-2 DIM were 9-27 times higher than the rest of lactation, where the chance of testing positive varied less. The reason is most likely a high concentration of non-specific antibodies in colostrum. Consequently, samples from the first couple of DIM should be excluded from MAP testing until further information on their significance is established. Milk yield also had a significant effect on odds of testing positive due to its diluting effect. Inclusion of milk yield in the interpretation of test results could improve the diagnostic value, resulting in more predictable patterns corresponding to progression of infection. (C) 2012 Elsevier B.V. All rights reserved

Plain, K.M., Begg, D.J., de Silva, K., Purdie, A.C., Whittington, R.J. (2012) Enhancement of the interferon gamma assay to detect paratuberculosis using interleukin-7 and interleukin-12 potentiation Veterinary Immunology and Immunopathology, 149, 28-37

A limitation to the widespread application of interferon gamma (IFN-gamma) response assays
has been logistical difficulties, as they must be performed within hours of blood collection. Detection of specific IFN-gamma responses to Mycobacterium avium subspecies paratuberculosis (MAP) as part of the cell-mediated immune response of ruminants with Johne’s disease could aid in diagnosis and control programs. In this study, a modified protocol was developed in which cultures were supplemented with interleukin (IL)-7, a survival factor required to maintain resting T cells, alone or in combination with IL-12 to potentiate IFN-gamma responses and extend blood storage time. The combination of IL-7 and IL-12 was synergistic, giving IFN-gamma responses greater than with IL-12 alone, for sheep blood stored up to 2 days. In a cohort of naturally infected sheep, the same number of animals was identified as test positive using the modified assay (performed after 2 days with IL-7/IL-12 supplementation) as the standard IFN-gamma assay performed on the day of blood collection. The modified assay offered greatest advantage in the detection of early stages of paratuberculosis infection, for sheep with low grade and paucibacillary lesions, and at early time points post-infection. The potentiation protocol allowed for practical shipment of blood samples from farm to laboratory, extending permissible transit times and applicability of IFN-gamma testing to detect Johne’s disease. (C) 2012 Elsevier B.V.. All rights reserved

1308


Risk factors for herds to test positive for Mycobacterium avium ssp paratuberculosis-antibodies with a commercial milk enzyme-linked immunosorbent assay (ELISA) in Ontario and western Canada

Canadian Veterinary Journal-Revue Veterinaire Canadienne, 53, 963-970

The objectives of this study were to identify risk factors associated with i) a Mycobacterium avium subsp. paratuberculosis (MAP)-antibody milk enzyme-linked immunosorbent assay (MAP milk ELISA)-positive herd status, and ii) the within-herd MAP milk ELISA-positive prevalence in Canadian dairy herds. This prospective cohort study was conducted between 2005 and 2009 on 226 herds in Ontario and western Canada, which participated in a voluntary risk assessment (RA)-based Johne's disease control program. Two MAP milk ELISA and risk assessments and a previsit survey were available per herd. The overall farm RA scores alone could not be used to predict whether a herd would test positive for MAP antibodies. However, the results of this study indicated that increasing the likelihood of exposing calves to MAP through certain management practices, as assessed with the RA, increased the likelihood of a herd being test-positive for MAP antibodies

1309


New Emerging and Re-Emerging Bacterial Foodborne Pathogens

Kafkas Universitesi Veteriner Fakultesi Dergisi, 18, 889-898

PDF will not be available, paper in Turkish.

Some newly recognized pathogens have been defined as food-borne pathogens in many parts of the world. Escherihia coli O157:H7, Salmonella Typhimurium Definitive Type 104, Helicobacter pylori, Arcobacter butzleri are the main of these pathogens. Some pathogens, such as Salmonella Enteritidis, Campylobacter jejuni, Vibrio vulnificus, Listeria monocytogenes, Enterobacter sakazakii, Enterococci, Mycobacterium avium subsp. paratuberculosis have been recognized pathogens for many years but have only in the past two decades been determined to be predominantly foodborne. Several factors playing important role in the epidemiology of new emerging and re-emerging food-borne pathogens are changes in the pathogens, economical and technological developments, poverty and pollution, dietary habits, new changes in health sector, demographic changes, increasing in travel and migration and trade in food and animal feed and animals, new food vehicles of transmission. New emerging and re-emerging food-borne pathogens have been implicated with new food vehicles. Foods previously thought to be safe are now considered potentially hazardous. Approaches such as hazard analysisis critical control point, good agricultural practice, good veterinary practice, good manufacturing practice, good distribution practice and good trade practice play important role in reducing and eliminating of food-borne infections
Preventive Veterinary Medicine, 106, 63-74

This study aimed to develop a mathematical model describing the dynamics of paratuberculosis (PTB) in red deer (Cervus elaphus) under pastoral farming conditions in New Zealand. The model examined infectivity differences between ovine and bovine strains of Mycobacterium avium subspecies paratuberculosis (MAP) and seasonality of MAP survival. We also evaluate variable use of pasture and the effect of management interventions on the infection prevalence and annual clinical incidence of PTB. A state-transition model was developed and calibrated to observed data on both prevalence of infection and incidence of clinical PTB. To accommodate specific PTB features for deer, the model included a fast and a slow track for progression of infection to disease. MAP on pasture was the source for horizontal transmission and infected dams for vertical transmission. In the presence of a single strain, an infectivity reduction of up to 80% allowed MAP to persist in the herd (R₀ > 1). For mixed infection by two strains however, a 30% reduction in infectivity of one strain was sufficient to outcompete a strain with lower infectivity, suggesting that mixed infection of MAP strains with different infectivity may not be common in deer. The model showed that seasonal variation of MAP survival on pasture had little impact on transmission dynamics, and that rotational grazing with pasture spelling vs. permanent grazing of the same paddock reduced both infection prevalence and clinical PTB by about 50%. Based on model outputs, early detection of young deer in a high-shedding state was the most effective means of controlling PTB among the tested scenarios. (C) 2012 Elsevier B.V. All rights reserved

Plos One, 7, Article Number: e42127 DOI: 10.1371/journal.pone.0042127 Published: AUG 17 2012

Survival and persistence of Mycobacterium avium subsp. paratuberculosis (MAP) in the intestinal mucosa is associated with host immune tolerance. However, the initial events during MAP interaction with its host that lead to pathogen survival, granulomatous inflammation, and clinical disease progression are poorly defined. We hypothesize that immune tolerance is initiated upon initial contact of MAP with the intestinal Peyer's patch. To test our hypothesis, ligated ileal loops in neonatal calves were infected with MAP. Intestinal tissue RNAs were collected (0.5, 1, 2, 4, 8 and 12 hrs post-infection), processed, and hybridized to bovine gene expression microarrays. By comparing the gene transcription responses of calves infected with the MAP, informative complex patterns of expression were clearly visible. To interpret these complex data, changes in the gene expression were further analyzed by dynamic Bayesian analysis, and genes were grouped into the specific pathways and gene ontology categories to create a holistic model. This model revealed three different phases of responses: i) early (30 min and 1 hr post-infection), ii) intermediate (2, 4 and 8 hrs post-infection), and iii) late (12 hrs post-infection). We describe here the data that include expression profiles for perturbed pathways, as well as, mechanistic genes (genes predicted to have regulatory influence) that are associated with immune tolerance. In the Early Phase of MAP infection, multiple pathways were initiated in response to MAP invasion via receptor mediated endocytosis and changes in intestinal permeability. During the Intermediate Phase, perturbed pathways involved the inflammatory responses, cytokine-cytokine receptor interaction, and cell-cell signaling. During the Late Phase of infection, gene responses associated with immune tolerance were initiated at the level of T-cell signaling. Our study provides evidence that MAP infection resulted in differentially regulated genes, perturbed pathways and specifically modified mechanistic genes contributing to the colonization of Peyer's patch.

avium subsp Paratuberculosis (MAP)
Veterinary Immunology and Immunopathology, 148, 243-251

Johne's disease (JD) is a widespread and economically important chronic inflammatory disease of the small intestine of ruminants caused by Mycobacterium avium subsp. paratuberculosis (MAP). Although there are several techniques available for diagnosis of JD, their sensitivity is questionable. New proteome profiling methods, such as serum/plasma protein fingerprinting by 2-Dimensional Fluorescence Difference Gel Electrophoresis (2D-DIGE), may therefore be useful for identifying novel protein biomarkers of MAP infection. In this study, plasma samples were collected from 380 Holstein cows and screened for the presence of MAP infection using the M.pt. Johne's antibody Kit (IDEXX). Five negative (MAP-), and 5 strongly positive (MAP+) cows were selected for proteomic analysis. Highly abundant proteins were depleted from the plasma samples using the ProteoMiner technology (Bio-Rad) to enhance the resolution of low abundance proteins. Plasma samples from MAP-, MAP+, and a pooled internal control were labelled with different fluorescent dyes and separated based on their isoelectrical point (IP) and then their molecular weight. Gel images of the fluorescent plasma protein maps were acquired using a Typhoon scanner and analyzed using the DeCyder software. Proteins that were differentially expressed were excised from the gels, trypsin digested, and subjected to MS/MS analysis for identification. Six proteins were identified as being up-regulated at least 2-fold in MAP+ cows including: transferrin, gelsolin isoforms alpha & beta (actin binding protein - ABP), complement subcomponent C1r, complement component C3, amine oxidase - copper containing 3 (AOC3), and coagulation factor II (thrombin) (p < 0.05). Two proteins that were down-regulated approximately 2-fold in the MAP+ cows included coagulation factor XIII -B polypeptide (COAFXIII), and fibrinogen gamma chain (FGG) and its precursor. (c) 2012 Elsevier B.V. All rights reserved

Pesquisa Veterinaria Brasileira, 32, 697-700

PDF will not be available, paper in Portuguese.
Paratuberculosis is an important disease of cattle in the state of Paraiba, northeastern Brazil. In the Veterinary Hospital of the Federal University of Campina Grande, five outbreaks of paratuberculosis were diagnosed in the last four years. The objective of this paper is to report the frequency of antibodies against paratuberculosis in different regions of the state of Paraiba, in farms with previous diagnosis of the disease and in farms without diagnosis. The prevalence of antibodies against paratuberculosis, examined by ELISA, in two farms with cases of the disease, was of 72.22% (13/18) and 68.75% (11/16), respectively. Serum samples from 486 healthy cattle from 36 farms without paratuberculosis diagnosis, from three different regions of Paraiba (sertao, cariri, and agreste), were also examined by ELISA. The frequency of antibodies was 10.08 +/- 1.07% (49/486). Antibodies against paratuberculosis were found in 21 (58.33%) out of 36 farms examined. These results suggest that paratuberculosis is an important disease of cattle in the state of Paraiba and that control measures to decrease the prevalence of the disease are necessary.
Medeiros J.M.A., Garino Jr F., Matos R. A. T., Costa V. M. M. & Riet-Correa F. 2012. [Frequency of antibodies against paratuberculosis in cattle in the state of Paraiba.] Frequencia de anticorpos para paratuberculose em bovinos no estado da Paraiba. Pesquisa Veterinaria Brasileira 32(8): 697-700. Hospital Veterinario, Centro de Saude e Tecnologia Rural, Campus de Patos, Universidade Federal de Campina Grande, Patos, PB 58700-000, Brasil. E-mail: franklin.riet@pq.cnpq.br

Gut Pathogens, 4, Article Number: 6 DOI: 10.1186/1757-4749-4-6 Published: JUN 28 2012

Background: Inflammatory Bowel Disease (IBD), which includes both Crohn's disease (CD)
and ulcerative colitis (UC), is caused by a complex interplay involving genetic predisposition, environmental factors and an infectious agent. Mycobacterium avium subsp. paratuberculosis (MAP) is a promising pathogen candidate since it produces a chronic intestinal inflammatory disease in ruminants that resembles CD in humans. MAP is a ubiquitous microorganism, although its presence in the food chain, especially in milk from infected animals, is what made us think that there could be an association between lactase persistence (LP) and IBD. The LCT mutation has brought adaptation to dairy farming which in turn would have increased exposure of the population to infection by MAP. NOD2 gene mutations are highly associated to CD. Methods: In our study, CD and UC patients and controls from the North of Spain were genotyped for the lactase gene (LCT) and for three NOD-2 variants, R702W, G908R and Cins1007fs. MAP PCR was carried out in order to assess MAP infection status and these results were correlated with LCT and NOD2 genotypes. Results: As for LP, no association was found with IBD, although UC patients were less likely to present the T/T-13910 variant compared to controls, showing a higher C-allele frequency and a tendency to lactase non-persistence (LNP). NOD2 mutations were associated to CD being the per-allele risk higher for the Cins1007fs variant. MAP infection was more extended among the healthy controls (45.2%) compared to CD patients (21.38%) and UC patients (19.04%) and this was attributed to therapy. The Asturian CD cohort presented higher levels of MAP prevalence (38.6%) compared to the Basque CD cohort (15.5%), differences also attributed to therapy. No interaction was found between MAP infection and LCT or NOD2 status. Conclusions: We conclude that LP is not significantly associated with IBD, but that MAP infection and NOD2 do show not mutually interacting associations with IBD.

New publications in the **CROHN’S DISEASE AND PARATUBERCULOSIS database** (743-749)

**Serum anti-glycan antibody biomarkers for inflammatory bowel disease diagnosis and progression: A systematic review and meta-analysis** 
Inflammatory Bowel Diseases, 18, 1872-1884

Background: Anti-glycan antibody serologic markers may serve as a useful adjunct in the diagnosis/prognosis of inflammatory bowel disease (IBD), including Crohn’s disease (CD) and ulcerative colitis (UC). This meta-analysis/systemic review aimed to evaluate the diagnostic value, as well as the association of anti-glycan biomarkers with IBD susceptible gene variants, disease complications, and the need for surgery in IBD. Methods: The diagnostic odds ratio (DOR), 95% confidence interval (CI), and sensitivity/specificity were used to compare the diagnostic value of individual and combinations of anti-glycan markers and their association with disease course (complication and/or need for surgery). Results: Fourteen studies were included in the systemic review and nine in the meta-analysis. Individually, anti-Saccharomyces cervisiae antibodies (ASCA) had the highest DOR for differentiating IBD from healthy (DOR 21.1; 1.8247.3; two studies), and CD from UC (DOR 10.2; CI 7.713.7; seven studies). For combination of =2 markers, the DOR was 2.8 (CI 2.23.6; two studies) for CD-related surgery, higher than any individual marker, while the DOR for differentiating CD from UC was 10.2 (CI 5.618.5; three studies) and for complication was 2.8 (CI 2.23.7; two studies), similar to individual markers. Conclusions: ASCA had the highest diagnostic value among individual anti-glycan markers. While anti-chitobioside carbohydrate antibody (ACCA) had the highest association with complications, ASCA and ACCA associated equally with the need for surgery. Although in most individual studies the combination of =2 markers had a better diagnostic value as well as higher association with complications and need for surgery, we found the combination performing slightly better than any individual marker in our meta-analysis. (Inflamm Bowel Dis 2012)

**Changed phagocytic activity and pattern of Fc gamma and complement receptors on blood monocytes in sarcoidosis** 
Human Immunology, 73, 788-794
We have recently revealed that mycobacterial heat shock proteins (Mtb-hsp), involved in forming of immune complexes (CIs), can induce immune response in sarcoidosis (SA). The complexemia may result from inappropriate phagocytosis and clearance of CIs by monocytes with following persistent antigenemia and granuloma formation. Because an aberrant expression of receptors for Fc fragment of immunoglobulin G (Fc gamma R) and complement receptors (CR) on monocytes can be involved in this process, we have evaluated the expression of Fc gamma RI (CD64), Fc gamma RII (CD32), Fc gamma RIII (CD16) and CR1 (CD35), CR3 (CD11b), CR4 (CD11c) receptors on blood CD14(+) monocytes and its phagocytic activity in 24 patients with SA and 20 healthy volunteers using flow cytometry. We found significantly increased expression of all examined Fc gamma R and decreased expression of CD35 and CD11c on CD14(+) monocytes in SA patients vs controls. Significantly increased percentage of CD14(+)CD16(+)CD35(-), CD14(+)CD64(+)CD35(+), CD14(+)CD64(+CD11b(+), CD14(+)CD64(+)CD11c(+) and decreased of CD14(+)CD32(-)CD35(+), CD14(+)CD32(-)CD11b(+), CD14(+)CD32(-)CD11c(+) monocytes' phenotypes was revealed in SA. The total number and percentage of phagocytizing monocytes was significantly increased in SA as compared with controls. In conclusion, altered expression of Fc gamma R and CR on CD14(+) monocytes and its increased phagocytic activity may be responsible for high antigen load, persistent antigenemia and immunocomplexemia in SA patients. (C) 2012 American Society for Histocompatibility and Immunogenetics. Published by Elsevier Inc. All rights reserved

Role for mycobacterial infection in pathogenesis of primary biliary cirrhosis? World Journal of Gastroenterology, 18, 4855-4865

Primary biliary cirrhosis (PBC) is a progressive cholestatic liver disease characterized by the immune-mediated destruction of biliary epithelial cells in small intrahepatic bile ducts. The disease is characterized by circulating antimitochondrial antibodies (AMAs) as well as disease-specific antinuclear antibodies, cholestatic liver function tests, and characteristic histological features, including granulomas. A variety of organisms are involved in granuloma formation, of which mycobacteria are the most commonly associated. This has led to the hypothesis that mycobacteria may be involved in the pathogenesis of PBC, along with other infectious agents. Additionally, AMAs are found in a subgroup of patients with mycobacterial infections, such as leprosy and pulmonary tuberculosis. Antibodies against species-specific mycobacterial proteins have been reported in patients with PBC, but it is not clear whether these antibodies are specific for the disease. In addition, data in support of the involvement of the role of molecular mimicry between mycobacterial and human mitochondrial antigens as triggers of cross-reactive immune responses leading to the loss of immunological tolerance, and the induction of pathological features have been published. Thus, antibodies against mycobacterial heat shock protein appear to cross-recognize AMA-specific autoantigens, but it is not clear whether these autoantibodies are mycobacterium-species-specific, and whether they are pathogenic or incidental. The view that mycobacteria are infectious triggers of PBC is intriguing, but the data provided so far are not conclusive. (c) 2012 Baishideng. All rights reserved

The Innate Immune Protein Nod2 Binds Directly to MDP, a Bacterial Cell Wall Fragment Journal of the American Chemical Society, 134, 13535-13537

Mammalian Nod2 is an intracellular protein that is implicated in the innate immune response to the bacterial cell wall and is associated with the development of Crohn's disease, Blau syndrome, and gastrointestinal cancers. Nod2 is required for an immune response to muramyl dipeptide (MDP), an immunostimulatory fragment of bacterial cell wall, but it is not known whether. MDP binds directly to Nod2. We report the expression and purification of human Nod2 from insect cells. Using novel MDP self-assembled monolayers (SAMs), we provide the first biochemical evidence for a direct, high-affinity interaction between Nod2 and MDP
Survival and persistence of Mycobacterium avium subsp. paratuberculosis (MAP) in the intestinal mucosa is associated with host immune tolerance. However, the initial events during MAP interaction with its host that lead to pathogen survival, granulomatous inflammation, and clinical disease progression are poorly defined. We hypothesize that immune tolerance is initiated upon initial contact of MAP with the intestinal Peyer's patch. To test our hypothesis, ligated ileal loops in neonatal calves were infected with MAP. Intestinal tissue RNAs were collected (0.5, 1, 2, 4, 8 and 12 hrs post-infection), processed, and hybridized to bovine gene expression microarrays. By comparing the gene transcription responses of calves infected with the MAP, informative complex patterns of expression were clearly visible. To interpret these complex data, changes in the gene expression were further analyzed by dynamic Bayesian analysis, and genes were grouped into the specific pathways and gene ontology categories to create a holistic model. This model revealed three different phases of responses: i) early (30 min and 1 hr post-infection), ii) intermediate (2, 4 and 8 hrs post-infection), and iii) late (12 hrs post-infection). We describe here the data that include expression profiles for perturbed pathways, as well as, mechanistic genes (genes predicted to have regulatory influence) that are associated with immune tolerance. In the Early Phase of MAP infection, multiple pathways were initiated in response to MAP invasion via receptor mediated endocytosis and changes in intestinal permeability. During the Intermediate Phase, perturbed pathways involved the inflammatory responses, cytokine-cytokine receptor interaction, and cell-cell signaling. During the Late Phase of infection, gene responses associated with immune tolerance were initiated at the level of T-cell signaling. Our study provides evidence that MAP infection resulted in differentially regulated genes, perturbed pathways and specifically modified mechanistic genes contributing to the colonization of Peyer's patch.

The genetic dissection of various human infectious diseases has led to the definition of inborn errors of human STAT1 immunity of four types, including (i) autosomal recessive (AR) complete STAT1 deficiency, (ii) AR partial STAT1 deficiency, (iii) autosomal dominant (AD) STAT1 deficiency, and (iv) AD gain of STAT1 activity. The two types of AR STAT1 defect give rise to a broad infectious phenotype with susceptibility to intramacrophagic bacteria (mostly mycobacteria) and viruses (herpes viruses at least), due principally to the impairment of IFN-gamma mediated and IFN-alpha/beta mediated immunity, respectively. Clinical outcome depends on the extent to which the STAT1 defect decreases responsiveness to these cytokines. AD STAT1 deficiency selectively predisposes individuals to mycobacterial disease, owing to the impairment of IFN-gamma-mediated immunity, as IFN-alpha/beta-mediated immunity is maintained. Finally, AD gain of STAT1 activity is associated with autoimmunity, probably owing to an enhancement of IFN-alpha/beta-mediated immunity. More surprisingly, it is also associated with chronic mucocutaneous candidiasis, through as yet undetermined mechanisms involving an inhibition of the development of IL-17-producing T cells. Thus, germline mutations in human STAT1 define four distinct clinical disorders. Various combinations of viral, mycobacterial and fungal infections are therefore allelic at the human STAT1 locus. These experiments of Nature neatly highlight the clinical and immunological impact of the human genetic dissection of infectious phenotypes.
Lactase persistence, NOD2 status and Mycobacterium avium subsp. paratuberculosis infection associations to Inflammatory Bowel Disease

Gut Pathogens, 4, Article Number: 6 DOI: 10.1186/1757-4749-4-6 Published: JUN 28 2012

Background: Inflammatory Bowel Disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC), is caused by a complex interplay involving genetic predisposition, environmental factors and an infectious agent. Mycobacterium avium subsp. paratuberculosis (MAP) is a promising pathogen candidate since it produces a chronic intestinal inflammatory disease in ruminants that resembles CD in humans. MAP is a ubiquitous microorganism, although its presence in the food chain, especially in milk from infected animals, is what made us think that there could be an association between lactase persistence (LP) and IBD. The LCT mutation has brought adaptation to dairy farming which in turn would have increased exposure of the population to infection by MAP. NOD2 gene mutations are highly associated to CD. Methods: In our study, CD and UC patients and controls from the North of Spain were genotyped for the lactase gene (LCT) and for three NOD2 variants, R702W, G908R and Cins1007fs. MAP PCR was carried out in order to assess MAP infection status and these results were correlated with LCT and NOD2 genotypes. Results: As for LP, no association was found with IBD, although UC patients were less likely to present the T/T-13910 variant compared to controls, showing a higher C-allele frequency and a tendency to lactase non-persistence (LNP). NOD2 mutations were associated to CD being the per-allele risk higher for the Cins1007fs variant. MAP infection was more extended among the healthy controls (45.2%) compared to CD patients (21.38%) and UC patients (19.04%) and this was attributed to therapy. The Asturian CD cohort presented higher levels of MAP prevalence (38.6%) compared to the Basque CD cohort (15.5%), differences also attributed to therapy. No interaction was found between MAP infection and LCT or NOD2 status. Conclusions: We conclude that LP is not significantly associated with IBD, but that MAP infection and NOD2 do show not mutually interacting associations with IBD.