2012-11-23-176 Paratuberculosis databases updated (2012-11-23)
To: (08) Mycobacterial diseases; (23) Veterinary education; (27) Scientific information
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New publications in the PARATUBERCULOSIS database (1324-1329)

    Crohn’s disease
    Lancet, 380, 1590-1605

Crohn’s disease is a relapsing systemic inflammatory disease, mainly affecting the gastrointestinal tract with extraintestinal manifestations and associated immune disorders. Genome wide association studies identified susceptibility loci that-triggered by environmental factors-result in a disturbed innate (ie, disturbed intestinal barrier, Paneth cell dysfunction, endoplasmic reticulum stress, defective unfolded protein response and autophagy, impaired recognition of microbes by pattern recognition receptors, such as nucleotide binding domain and Toll like receptors on dendritic cells and macrophages) and adaptive (ie, imbalance of effector and regulatory T cells and cytokines, migration and retention of leukocytes) immune response towards a diminished diversity of commensal microbiota. We discuss the epidemiology, immunobiology, amd natural history of Crohn's disease; describe new treatment goals and risk stratification of patients; and provide an evidence based rational approach to diagnosis (ie, work-up algorithm, new imaging methods [ie, enhanced endoscopy, ultrasound, MRI and CT] and biomarkers), management, evolving therapeutic targets (ie, integrins, chemokine receptors, cell-based and stem-cell-based therapies), prevention, and surveillance

    Uptake and Persistence of Mycobacterium avium subsp paratuberculosis in Human Monocytes
    Infection and Immunity, 80, 3768-3775

Mycobacterium avium subsp. paratuberculosis is a bacterium sometimes found in human blood and tissue samples that may have a role in the etiology of Crohn's disease in humans. To date, however, there have been few studies examining the interactions of these bacteria with human cells. Using the THP-1 human monocytic cell line, this study shows that the uptake and trafficking of M. avium subsp. paratuberculosis in human cells is cholesterol dependent and that these bacteria localize to cholesterol-rich compartments that are slow to acidify. M. avium subsp. paratuberculosis bacteria containing phagosomes stain for the late endosomal marker Rab7, but recruitment of the Rab7-interacting lysosomal protein that regulates the fusion of bacterium-containing phagosomes with lysosomal compartments and facilitates subsequent bacterial clearance is significantly reduced. Disruption of phagosome acidification via this mechanism may contribute to M. avium subsp. paratuberculosis persistence in human cells, but there was no evidence that internalized M. avium subsp. paratuberculosis also affects the survival of bacteria taken up during a secondary phagocytic event

    Detection of Mycobacterium Avium Subspecies Paratuberculosis in Several Herds of Arctic Caribou (Rangifer Tarandus Ssp.)
    Journal of Wildlife Diseases, 48, 918-924

Mycobacterium avium subspecies paratuberculosis (MAP) is a common pathogen in domestic ruminants that causes granulomatous inflammation of the small intestine leading to emaciation and wasting. Clinical disease (Johne's disease) is also reported for several wild ruminant species. Between 2007 and 2009 we collected 561 fecal samples from caribou (Rangifer tarandus ssp.) representing 10 herds of migratory caribou, two herds of caribou from
Greenland, and three populations of boreal woodland caribou. Feces were tested for MAP by bacterial culture and PCR targeting the IS900 insertion sequence. In total, 31 samples from eight different populations representing all three ecotypes were found positive for MAP by PCR, with one sample from the Riviere-aux-Feuilles herd also being culture positive for the type II (cattle) strain. The proportion of positive animals was particularly high in the Akia-Maniitsiq herd in Greenland, and Riviere-aux-Feuilles and Riviere-George herds in northeastern Canada (2:3.4, 11.5, and 10.0%, respectively). Our results indicate that MAP is present in several caribou herds of different ecotypes in northern Canada and Greenland and that MAP circulates within wildlife populations that do not have ongoing contact with domestic livestock. The epidemiology, pathogenicity, and effects on the health of caribou in northern ecosystems remain unknown FULL PAPER PDF NOT AVAILABLE


The authors describe the first paratuberculosis case in mouflon (Ovis musimon) in Hungary. Pathologically the small intestine was thickened, and the pathogen was demonstrated by histological examination FULL PAPER PDF NOT AVAILABLE


Phagosome maturation is a highly organized and sequential process that results in the formation of a microbicidal phagolysosome. This results in crucial contributions to innate and adaptive immunity through pathogen clearance and antigen presentation. Thus, it is important to understand the regulatory networks that control the extent and nature of phagosome maturation. PI3Ks are lipid kinases that catalyze the phosphorylation of the 3' position of the inositol ring. This enzyme family is divided into three classes based on structure and substrate preferences. Previously, only the class III PI3K, hVps34, was thought to contribute to phagosome maturation. Recent evidence, however, suggests important contributions by class I PI3Ks in bringing about the diverse phagosome maturation phenotypes. Class I PI3Ks have also been implicated in the activation of Rab GTPases that function in phagosome maturation, such as Rab14. In addition, recent studies have illuminated the overlap between phagosome maturation and autophagy, which itself is regulated by multiple classes of PI3K. Taken together, a picture of phagosome maturation is emerging in which multiple classes of PI3Ks are involved in modulating maturation phenotypes. This review summarizes the known contributions of PI3Ks to phagosome maturation. Special emphasis is placed on the impact of PI3Ks on different maturation outcomes stemming from the engagement of diverse phagocytic receptors and on Rab and Ca2+ signaling cascades. J. Leukoc. Biol. 92: 553-566; 2012


Paratuberculosis (Johne's diseases) is responsible for massive economic losses to dairy industry, both in the industrially advanced as well as in the developing countries. To detect its occurrence in cattle and buffaloes locally, blood and tissue samples from clinically weak and grossly suspected slaughtered animals were collected from two abattoirs of Jhang, municipal area, Pakistan. Acid-fast smear staining, gross/histopathology and indirect ELISA were done for the detection of Mycobacterium avium subsp. paratuberculosis (MAP). Total 134 samples illustrating gross pathological lesions were collected, only 11.19% (cattle: 6.67%, buffaloes: 12.5%) showed acid fast bacilli through smear staining and were taken as confirmed cases. Thickening of intestines alone was not a reliable indicator of Johne's disease. Tissue sections from intestines and mesenteric lymph nodes from these acid fast positive animals were stained with hematoxylin & eosin (H&E) and Ziehl Neelsen (ZN) methods. Sum of (15/134) impression smear staining as well as (15/15) tissue sections of the intestines were found ZN positive, and only 6.7% of impression smears and 100% of tissue sections of mesenteric lymph nodes showed acid fast bacilli. Through ELISA, two cattle and five buffaloes (07/134) gave positive optical densities, while one cattle and seven buffaloes (08/134) were judged as doubtful. It is concluded that infection of MAP can be identified by histopathology and ELISA.
The present study was the first record of paratuberculosis among the dairy animals slaughtered at Jhang abattoirs. The objective was to compare different methods for the diagnosis of Johne's disease. (C) 2012 PVJ. All rights reserved FULL PAPER PDF NOT AVAILABLE

New publications in the CROHN'S DISEASE AND PARATUBERCULOSIS database (754-757)


The immune system is exquisitely balanced. It has the ability to effectively respond to and control infections while at the same time preventing inappropriate responses to self and environmental antigens. When this response goes awry, either through a failure to activate the immune response, or failure to terminate it, inflammatory pathology results. Posttranslational modifications (PTMs) such as ubiquitination and phosphorylation help ensure that the delicate balance underlying immune signal transduction is maintained. Ubiquitination and phosphorylation affect localization, activity, stability, and interactions of various components of the immune signal transduction machinery. Moreover, ubiquitination and phosphorylation are tightly linked, with one PTM affecting the other. Therefore, in order to find potential therapies for many immune-related pathologies, it is necessary to understand not only how the immune response is activated by ubiquitination and phosphorylation, but also how it is regulated by these PTMs at different stages of the response. An excellent system to study such activation and regulation is the NOD2 pathway. Dysregulation of NOD2 signaling is involved in the pathogenesis of a variety of inflammatory disorders including Crohn's disease, early onset sarcoidosis, and Blau syndrome. More recently NOD2 has been implicated in the development of autoimmune disease, allergy and asthma. This review will focus on what is currently known about how ubiquitination and phosphorylation regulate NOD2 signaling with particular emphasis on novel in vitro substrates which may serve as potential in vivo therapeutic targets for hyperactive NOD2 states. This article is part of a Special Issue entitled: Ubiquitin Drug Discovery and Diagnostics. (c) 2012 Elsevier B.V. All rights reserved


Mycobacterium avium subsp. paratuberculosis is a bacterium sometimes found in human blood and tissue samples that may have a role in the etiology of Crohn's disease in humans. To date, however, there have been few studies examining the interactions of these bacteria with human cells. Using the THP-1 human monocytic cell line, this study shows that the uptake and trafficking of M. avium subsp. paratuberculosis in human cells are cholesterol dependent and that these bacteria localize to cholesterol-rich compartments that are slow to acidify. M. avium subsp. paratuberculosis bacteria containing phagosomes stain for the late endosomal marker Rab7, but recruitment of the Rab7-interacting lysosomal protein that regulates the fusion of bacterium-containing phagosomes with lysosomal compartments and facilitates subsequent bacterial clearance is significantly reduced. Disruption of phagosome acidification via this mechanism may contribute to M. avium subsp. paratuberculosis persistence in human cells, but there was no evidence that internalized M. avium subsp. paratuberculosis also affects the survival of bacteria taken up during a secondary phagocytic event


Respiratory syncytial virus (RSV) is a major cause of lower respiratory tract infections in infants, with remarkable variability in disease severity. An exaggerated proinflammatory
response and influx of leukocytes is part of the pathogenesis of severe RSV disease. Here, we show an increase in proinflammatory cytokine production by human immune cells after stimulation with RSV and muramyl dipeptide (MDP), which is recognized by nucleotide-binding oligomerization domain containing 2 (NOD2). PBMCs from Crohn’s disease patients homozygous for the 3020insC mutation in the NOD2 gene did not show a synergistic response to stimulation with RSV and MDP, suggesting that NOD2 is essential for the observed synergy. Further experiments aimed at identifying the viral ligand indicated that viral RNA plays an essential role in the recognition of RSV. Stimulation with RSV or Poly(I:C) induced IFN-beta expression, which resulted in an increased expression of the viral receptors TLR3 and RIG-I, as well as an increased NOD2 expression. Our data indicate that IFN-beta induction by viral RNA is an essential first step in the increased proinflammatory response to MDP. We hypothesize that the enhanced proinflammatory response to MDP following RSV infection may be an important factor in determining the outcome of the severity of disease.

NOD2 Signaling and Role in Pathogenic Mycobacterium Recognition, Infection and Immunity
Cellular Physiology and Biochemistry, 30, 953-963

The Mycobacterium pathogens acquire additional properties to expand their pathogenicity and existence spaces. The interaction between pathogenic Mycobacterium components and receptors of host innate immune system is critical for the infection outcome, particularly for the macrophage activation. NOD2 (Nucleotide binding oligomerization domain 2), an intracellular pathogen recognition sensor, attenuates two key putative host bacterial killing mechanisms: interfering the production of TNF-alpha and inducing resistance to apoptosis. Multiple evidences have shown that NOD2 acts as a non-redundant recognition system of Mycobacterium, a successful pathogen with many mechanisms to evade host immunity and leading to insidious disease. Understanding the complex interaction between host and pathogen mediated by NOD2 signaling, might provide novel insight into the pathogenesis of pathogenic Mycobacterium and inform the development of more effective vaccines and therapeutics. (C) Copyright c 2012 S. Karger AG, Basel

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