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New book

Kazda, J., Pavlik, I., Falkinham III, J.O., Hruska, K. (Eds.)
The Ecology of Mycobacteria: Impact on Animal's and Human's Health
Springer 2009 (February), Approx. 260 p., Hardcover

New publications in the PARATUBERCULOSIS database (451)

On-farm spread of Mycobacterium avium subsp paratuberculosis in raw milk studied by IS900 and F57 competitive real time quantitative PCR and culture examination
International Journal of Food Microbiology, 128, 250-257

A rapid, cheap and sensitive detection method of Mycobacterium avium subsp. paratuberculosis (MAP) in raw milk was needed for routine usage. We developed two duplex real time qPCR systems specific for MAP detection. These real time qPCR assays amplify the multicopy element IS900 for qualitative analysis and the single copy element F57 for quantitative analysis. Both assays incorporate an internal amplification control amplified with the same primers as the targets and the same probes are used in both assays. The specificity of the assays was confirmed by the testing of 6 different MAP isolates, 12 isolates of other mycobacteria or bacterial species and 4 different mammalian DNAs. The sensitivity of the developed assays and isolation efficiency were demonstrated through the analysis of raw milk samples artificially contaminated with MAP cells and with plasmids containing cloned fragments of the targets (IS900 and F57). The developed assays for milk analysis were applied to samples from one farm with two faecal shedding cows. Three hundred and forty five individual milk samples were tested by real time qPCR assays and by cultivation. Hundred and eleven (32.5%) individual milk samples were positive by the real time qPCR, no milk sample was culture positive. The spread of MAP in individual, tank and bulk tank milk samples was also monitored. (C) 2008 Elsevier B.V. All rights reserved

New publications in the CROHN’S DISEASE AND PARATUBERCULOSIS database (231-237)

Systemic lupus erythematosus association with tuberculosis - Critical review
Revista Portuguesa de Pneumologia, 14, 843-855

The author provides a critical analysis of systemic lupus erythematosus associated with tuberculosis. A brief review of the lupus-tuberculosis association is also given, and stresses that extra-pulmonary TB is the most usual form of TB in these cases. Other issues considered are the heat shock proteins of Mycobacterium tuberculosis HSP70KDa and HSP65KDa families and TLR2, TLR4, TLR9 that can be involved in interaction between bacilli antigen and host tissue causing autoimmune induction by lupus. The author concludes that early diagnosis and
appropriate management are mandatory in SLE associated with TB in areas where TB is endemic.

In vivo enzymatic modulation of IgG glycosylation inhibits autoimmune disease in an IgG subclass-dependent manner
Proceedings of the National Academy of Sciences of the United States of America, 105, 15005-15009

IgG antibodies are potent inducers of proinflammatory responses. During autoimmune diseases such as arthritis and systemic lupus erythematosus, IgG autoantibodies are responsible for the chronic inflammation and destruction of healthy tissues by cross-linking Fc receptors on innate immune effector cells. The sugar moiety attached to the asparagine-297 residue in the constant domain of the antibody is critical for the overall structure and function of the molecule. Removal of this sugar domain leads to the loss of the proinflammatory activity, suggesting that in vivo modulation of antibody glycosylation might be a strategy to interfere with autoimmune processes. In this work, we investigated whether removal of the majority of the IgG-associated sugar domain by endoglycosidase S (EndoS) from Streptococcus pyogenes is able to interfere with autoimmune inflammation. We demonstrate that EndoS injection efficiently removes the IgG-associated sugar domain in vivo and interferes with autoantibody-mediated proinflammatory processes in a variety of autoimmune models. Importantly, however, we observed a differential impact of EndoS-mediated sugar side chain hydrolysis on IgG activity depending on the individual IgG subclass.

Identification of a receptor required for the anti-inflammatory activity of IVIG
Proceedings of the National Academy of Sciences of the United States of America, 105, 19571-19578

The anti-inflammatory activity of intravenous Ig (IVIG) results from a minor population of the pooled IgG molecules that contains terminal alpha 2,6-sialic acid linkages on their Fc-linked glycans. These anti-inflammatory properties can be recapitulated with a fully recombinant preparation of appropriately sialylated IgG Fc fragments. We now demonstrate that these sialylated Fcs require a specific C-type lectin, SIGN-R1, (specific ICAM-3 grabbing non-integrin-related 1) expressed on macrophages in the splenic marginal zone. Splenectomy, loss of SIGN-R1(+)+ cells in the splenic marginal zone, blockade of the carbohydrate recognition domain (CRD) of SIGN-R1, or genetic deletion of SIGN-R1 abrogated the anti-inflammatory activity of IVIG or sialylated Fc fragments. Although SIGN-R1 has not previously been shown to bind to sialylated glycans, we demonstrate that it preferentially binds to 2,6-sialylated Fc compared with similarly sialylated, biantennary glycoproteins, thus suggesting that a specific binding site is created by the sialylation of IgG Fc. A human orthologue of SIGN-R1, DC-SIGN, displays a similar binding specificity to SIGN-R1 but differs in its cellular distribution, potentially accounting for some of the species differences observed in IVIG protection. These studies thus identify an antibody receptor specific for sialylated Fc, and present the initial step that is triggered by IVIG to suppress inflammation.

Quantitative Dynamic Models of Arthritis Progression in the Rat
Pharmaceutical Research, 26, 196-203

This comparison employs mathematical disease progression models to identify a rat model of arthritis with the least inter-animal variability and features lending to better study designs. Arthritis was induced with either collagen (CIA) or mycobacterium (AIA) in either Lewis or Dark Agouti (DA) rats. Disease progression was monitored by paw edema and body weight. Models with production, loss, and feedback components were constructed and population analysis using
NONMEM software was employed to identify inter-animal variability in the various disease progression parameters. Onset time was the only parameter different within all four groups (DA-AIA 11.5 days, DA-CIA 16.5 days, Lewis-AIA 11.9 days, Lewis-CIA 13.9 days). The loss-of-edema rate constant was 20% slower in DA (0.362 h\(^{-1}\)) than Lewis (0.466 h\(^{-1}\)) rats. Most models exhibited peak paw edema 20 days post-induction. Edema in CIA returned to 150% of the initial value after the disease peaked. DA rats displayed more severe overall responses. No statistical differences between groups were observed for inter-animal variation in disease onset, progression and severity parameters. Onset time varies and should be noted in the design of future studies. DA rats may offer a more dynamic range of edema response than Lewis rats.

Nucleic Acid from Saliva and Salivary Cells for Noninvasive Genotyping of Crohn’s Disease Patients
Genetic Testing, 12, 587-589

CARD15 genes carrying the 3020insC frameshift polymorphism encode a truncated CARD15 protein that is unresponsive to bacterial muramyl dipeptide, and are strongly associated with increased susceptibility to Crohn’s disease (CD). In this study we established that CARD15 gene sequences encompassing the major 3020insC polymorphism could be readily amplified from the DNA found in saliva. In addition, CARD15 RNA sequences can be readily derived from the cellular component of saliva, which is primarily comprised of buccal epithelial cells. Our results demonstrate that saliva is a readily accessible source of DNA and RNA for genotyping CD patients for variants of the CARD15 gene, representing an alternative source of nucleic acid to that obtained from venous blood.

The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: a review of the literature
British Journal of Dermatology, 159, 1217-1228

Biologics that antagonize the biological activity of tumour necrosis factor (TNF)-alpha, namely infliximab, etanercept and adalimumab, are increasingly used for treatment of immune-mediated inflammatory diseases, including psoriasis, worldwide. TNF-alpha antagonists are known to increase the risk of reactivation and infection, particularly of infections with intracellular bacteria such as Mycobacterium tuberculosis. More frequently these agents are given to patients with viral infections. Viral hepatitis and human immunodeficiency virus infections are often present in these patients, with a considerable geographical variation. Other concomitant viral infections such as herpes, cytomegalovirus and varicella zoster virus may occur much more frequently than tuberculosis or leprosy. General recommendations about the management related to possible problems associated with anti-TNF-alpha treatment and these viral infections are lacking. This short review will give an overview of the most recent data available on the effects of anti-TNF-alpha therapy on viral infections with a particular focus on patient management and screening recommendations.

Lectin-epithelial interactions in the human colon
Biochemical Society Transactions, 36, 1482-1486

Similar changes in glycosylation occur in the colonic epithelium in inflammatory conditions such as ulcerative colitis and Crohn’s disease and also in colon cancer and precancerous adenomatous polyps. They include reduced length of O-glycans, reduced sulfation, increased sialylation and increased expression of oncofetal carbohydrate antigens, such as sialyl-Tn (sialyl alpha 2-6GalNAc), and the TF antigen (Thomsen-Friedenreich antigen) Gal beta 1-3GalNAc alpha-
Ser/Thr. The changes affect cell surface as well as secreted glycoproteins and mediate altered interactions between the epithelium and lectins of dietary, microbial or human origin. Different TF-binding lectins cause diverse effects on epithelial cells, reflecting subtle differences in binding specificities e.g. for sialylated TF; some of these interactions, such as with the TF-binding peanut lectin that resists digestion, may be biologically significant. Increased TF expression by cancer cells also allows interaction with the human galactose-binding lectin, galectin-3. This lectin has increased concentration in the sera of patients with metastatic cancer and binds TF on cancer cell surface MUC1 (mucin 1), causing clustering of MUC1 and revealing underlying adhesion molecules which promote adhesion to endothelium. This is likely to be an important mechanism in cancer metastasis and represents a valid therapeutic target. Tools are now available to allow fast and accurate elucidation of glycosylation changes in epithelial disease, characterization of their potential lectin ligands, whether dietary, microbial or human, and determination of the functional significance of their interactions. This should prove a very fruitful area for future research with relevance to infectious, inflammatory and cancerous diseases of the epithelia.