The 2013 three Rs Event: Toll like receptors (TLRs),RIG-like receptors (RLRs) and Nod-like receptors (NLR)

Thursday, 19 September 2013
Cineworld: The O2, London, SE10 0DX, UK

The aim of this meeting is to provide an overview of these three families of receptors and provide the most recent advances in the area of innate immune pattern recognition. This event has CPD accreditation and will have a troubleshooting panel session.

Meeting chairs*:* *Dr Martha Triantafilou/Professor Kathy Triantafilou*, Cardiff University School of Medicine, UK

9:00 – 9:45 **Registration**

9:45 – 10:00 **Introduction by the Chairs**: *Dr Martha Triantafilou/Professor Kathy Triantafilou*, Cardiff University School of Medicine, UK

10:00 – 10:30 **Pattern Recognition Receptor recognition of bacterial infection: are all animals created equal?**
Professor Clare Bryant, Professor of Innate Immunity, The University of Cambridge, UK
TLRs and NLRs are important for recognition of bacteria to control infections. These receptors also provide a linke between innate and adaptive immunity, but it is unclear how this occurs in bacterial infection. We use mouse models to study the role of TLRs and NLRs in modulating the adaptive immune response to Salmonella. There are many mammalian species differences in TLRs and NLRs the importance of which are beginning to emerge. We are currently studying how these species differences impact on the recognition of Salmonella infection.

10:30 – 11:00 **Pattern recognition receptor in Gram-negative intracellular infections: friends or foes?**
Dr Pietro Mastroeni, Cambridge University, UK
Pattern recognition receptors are important for the expression of immunity to bacterial infection and modulate aspects of the development of acquired immunity. However in some cases their stimulation can lead immune paralysis and to suppression of the host response.

11:00 – 11:30 **Speakers' photo then mid-morning break and trade show**
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11:30 – 12:00 **Ruminant livestock toll-like receptors: informing TLR evolution and function.**
Professor David Haig, School of Veterinary Medicine and Science, Nottingham University, UK
There are ~1400 breeds of sheep and 1300 breeds of cattle through domestication (around 10,000 years ago). Artificial selection for specific traits accelerated around 200 years ago. Consequently, this provides an opportunity to study TLR evolution and function in a distinct group of mammals closely associated with man. We have studied TLRs 2 and 5 in particular. In TLR5, we identified positive selective pressure in the domesticated ruminant clade suggesting rapid diversifying selection compared to other mammals. Stop codon variants of bovine TLR5 may indicate an alternative function. These and other examples of TLR variation will be presented.

12:00 – 12:45 **Oral Presentations:**

12:00 – 12:15 **Inflammatory Response to Footrot in Sheep**
R. Davenport, C. Haewood, M. Baker and S. Tötemeyer
School of Veterinary Medicine and Science, University of Nottingham, Loughborough, LE12 5RD, UK.

12:15 – 12:30 **The Role of Toll-Like Receptor 2 and 4 in Behcet's Disease Pathogenesis**
N Seoudi[1], L A Bergmeier[1], E Hagi-Pavli[1], D Bibby[2], M A Curtis[2] and F Fortune[1]
[1]Centre for Clinical and Diagnostic Oral Sciences. Institute of Dentistry, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom. [2]Centre for Immunology and Infectious Diseases, The Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom

12:30 – 12:45 **Cholesterol Oxidase of Mycobacterium Tuberculosis Affects the Toll-Like Receptor 2-Mediated Signaling Pathway in Human Macrophages**
Klink M, Brzezinska M, Szulc I, Brzostek A, Kielbik M, Dziadek J
Institute of Medical Biology, Polish Academy of Sciences, Lodowa 106 Str. 93-232 Lodz, Poland

12:45 – 13:45 **Lunch and trade show**
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13:45 – 14:45 **Question and Answer Session**
Delegates will be asked to submit questions to a panel of experts. Questions can be submitted before the event or on the day.

14:45 - 15:15 **Modulation of the innate immune response by C-type lectin receptors**
Professor Dirk Werling, Dept. of Pathology and Infectious Diseases, Royal Veterinary College, UK
Immunity to pathogens critically requires pattern-recognition receptors (PRRs) to trigger intracellular signaling cascades that initiate and direct innate and adaptive immune responses. For some specific sugar-moieties expressed on microbes, these responses are primarily mediated by members of the C-type lectin receptor family. These receptors are uniquely expressed on different antigen presenting cell subsets, but differ clearly in number and structure between species. So far, several members of this family have been identified in a variety of farm- and companion animals. It becomes evident that these receptors bind very specifically sugar-compositions, and this binding stimulates phagocytosis of bound ligand. Interestingly, some pathogens, such as Mycobacteria spp, have actively evolved to potential use these receptor for infection, subsequently leading to the shut-down of intracellular signalling pathways. Here, or recent understanding of CTLR in animals of veterinary importance is highlighted. Furthermore, recent advances in the understanding of the roles and mechanisms of these multifunctional receptors will be explained and the progress in the use of these receptors as targets for the development of new biotherapeutics and vaccines briefly discussed.

15:15 – 15:45 **Afternoon Break**

15:45 – 16:15 **Connecting innate immunity to autoimmunity**
Dr Sandra Sacre, Brighton and Sussex Medical School, UK
Growing evidence suggests that TLRs, may contribute to the pathogenesis of many autoimmune diseases. Initially TLRs were identified by their ability to recognise pathogens, but it was later discovered that they also recognise endogenous ligands present at sites of inflammation or tissue damage. This ability to respond to endogenous molecules has made the TLRs promising candidates to explain the presence of chronic inflammation in the absence of an infection. A role for TLRs in autoimmunity may be due to changes in their expression, function and/or downstream regulation. This presentation will focus on data exploring the possible connections between TLR signalling and sustained inflammation in rheumatoid arthritis.

16:15 – 16:45 **Transcriptome analysis of cigarette smoke extract induced TLR2-dependent activation of human cells.**
Dr Mark Paul-Clark, National heart and Lung Institute, London, UK
Smoking cigarettes causes approximately 5 million deaths world wide each year, and is a risk factor for a number of chronic diseases. We have previously shown that oxidants and cigarette smoke extract (CSE) activate cells in vitro and in vivo, in part via the pattern recognition receptor TLR2. We transfected HEK293 cells with TLR2/6 or control vector were treated with H2O2, CSE and control media for 8h. Expression patterns in HEK293 cells were similar to those obtained from THP-1 cells and PBMCs. Pathway analysis of these cells revealed that inflammation was associated with NRF2-mediated and aryl hydrocarbon receptor signaling pathways.

16:45 - 17:00 **Chairman's summing up**

Keywords: Innate Immunity, DNA sensing, Inflammasome, Type I interferon, RLHs, TLRs, Interferon, rhinovirus, asthma, TLR4, rhinovirus, LPS, TLR, signal transduction, scaffold complexes, NLR, PRR, LPS, Salmonella, Innate Immunity, atherosclerosis, NLRP3, Inflammasome, IL1, infection, immunity TLRS, bacteria, Oxidants, TLRs, Bioinformatics and transcripome, TLR2, TLR5,

ovine, bovine, evolution, Autoimmunity, inflammation, toll-like receptors, rheumatoid arthritis, cytokines, Toll-like receptor, NOD-like receptor, Salmonella

Registration Website: **www.regonline.co.uk/TOLL2012**

About the Chairs

Over the past few years the **Triantafilou group** has been focusing on unravelling the molecular mechanisms behind the innate recognition of bacterial as well as viral pathogens. In particular, we have focused on the involvement of the Toll like receptor (TLR) family of proteins, a recently identified family of pattern recognition receptors (PRRs), in the innate immune sensing. We have the expertise and the research tools for investigating receptor interactions using bioimaging techniques, such a Fluorescence Resonance Energy Transfer (FRET), Fluorescence Recovery after Photobleaching (FRAP), Single Particle Imaging (SPFI), Single Particle Tracking (SPT), Fluorescent Loss in Photobleaching (FLIP) as well as live cell imaging. Using combinations of these techniques, our group has discovered novel concepts in innate immune recognition of microbial ligands by TLRs and co%operating PRRs. We have been one of the first to demonstrate that the single%receptor concept of innate immune recognition is an oversimplified one and that different combinational associations of receptors determine the innate immune response to different microbial pathogens, using a range of non%invasive biophysical techniques. We performed several studies investigating associations of PRRs in response to bacterial products from Helicobacter pylori,Neisseria meningitidis, and bacterial lipopeptides. Furthermore, we demonstrated that membrane microdomains, or "lipid rafts" play an important role in this receptor cluster formation by providing a microenvironment for these interactions to take place. This was the first ever publication demonstrating that TLRs exist and signal within lipid rafts (making this paper one of the most cited papers in the field). We provided the first dynamic picture of TLR engagement by their ligand by determining the lateral diffusion of receptors involved in the innate immune response before and after stimulation by bacterial products . It has helped us understand the organisation, lateral mobility and confinement of PRRs involved in the innate immune response on the plasma membrane. In addition, using fluorescent imaging, we have revealed that TLR2 exists as a heterodimer prior to ligand engagement, as well as its intracellular trafficking and targeting in response to Gram%positive bacterial products. More recently, we have demonstrated that CXCR4 acts as a negative regulator for TLR2 and its significance in the innate recognition of Porphyromonas gingivalis (Hajishengallis et al. 2008). This was the first study demonstrating that TLR2%CXCR4 association can impair innate immune responses. Finally, we have shown that TLR4, TLR7 and TLR8 are involved in sensing viral products. These were the first studies to reveal how enteroviruses are recognised by the innate immune system.

About the Speakers

Clare Bryant is Professor of Innate Immunity at the Department of Veterinary Medicine in the University of Cambridge. Her work focusses on the studying pattern recognition receptor recognition of bacterial infection in different mammalian species.

Pietro Mastroenis' is a Reader at the University of Cambridge. He obtained a Degree in Medicine and Surgery at the Univerisity of Messina, Italy prior to moving to the UK where he obtained a PhD at the Department of Pathology of the University of Cambridge and worked as a postdoctoral Fellow at Imperial College, London. His research has established several landmarks in the fields of pathogenesis of bacterial infections, immunity, immunoevasion and vaccine development. His research group is currently pioneering the use of innovative multidisciplinary approaches towards a global understanding of infection dynamics in the face of immunity and vaccination.

David Haig is currently studying innate immunity and virus pathogenesis and control in livestock animals at the new Veterinary School at the University of Nottingham. He graduated from the University of Glasgow with a B.Sc. in Biochemistry and an M.Sc. and Ph.D. from studying the immunology of nematode infections and mast cell biology. He spent a few years at the WHO Immunology Research and Training Centre at the Instituto Butantan, Sao Paulo, Brazil where he set up a Parasitology laboratory and studied immunity to helminth parasites in rodents. He joined the Moredun Research Institute in 1985 and became Head of Immunology then Head of the Division of Virology before leaving for Nottingham in 2007.

Dirk Werling graduated from the University of Veterinary Medicine in Hannover (Germany) in 1991, and received a PhD (DrMedVet) in Virology at the University of Zuerich. This was followed by a Marie Curie Research Fellowship in the lab of Chris Howard at the Institute for Animal Health (IAH Compton, UK). During this time, he gained a Ph.D. in Immunology (University of London). Dirk Werling then moved back to the ETH Zuerich as a group leader and senior scientist, continuing the work started on bovine innate immune cells. In 2001, he was appointed as assistant professor (tenure track) at the Immunology Division at the Institute of Veterinary Virology (University of Bern) under Thomas Jungi, from where he moved to the RVC in 2003. Since 2007, Dirk Werling is Chair and Professor of Molecular Immunology at the RVC.

Sandra Sacre received her PhD in Physiology from University College London in 2000. Sandra then spent one year working at the Royal Free Hospital (University College London) before moving to the Kennedy Institute of Rheumatology (Imperial College London)

to work on toll-like receptors in rheumatoid arthritis. In 2009, Sandra moved to Brighton and Sussex Medical School (University of Sussex) where she is currently a Senior Lecturer in Molecular Cell Biology. Sandra Sacre's research is focused on the role of innate immunity in musculoskeletal diseases including rheumatoid arthritis and systemic lupus erythamatosus.

Mark Paul-Clark is an accomplished researcher with a number of publications in leading journals. He has established a track record in attracting independent funding and contributes significantly to both postgraduate and undergraduate teaching. Mark Paul-Clark's research focuses upon understanding the process of inflammation with a particular interest in oxidants and the damage they cause. Most recently he has concentrated his research into the area of pattern recognition receptors and inflammation. He completed his PhD with Professor Derek Willoughby before joining Professor Roderick Flower and Professor Mauro Perretti for his postdoctoral training. In 2002 heJoined Professor Jane Mitchell's group to study the role of pattern recognition receptors, including Toll like receptors, in inflammation. Since this time Mark Paul-Clark was awarded a Research Fellowship from the British Lung Foundation and a University award from the Wellcome Trust, with which he will take up an academic lectureship position within Cardiothoracic Pharmacology.

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