December 1, 2011
Issue 24

Focus on Complement

A newsletter of the International Complement Society

EUROPEAN COMPLEMENT NETWORK

About this issue & More

What's inside?

<1>Three flash news, are presented: two articles by Drs. Hyon-Ju Park and John P. Atkinson-independently confirming "CR1 as a sialic-acid independent receptor for *P.falciparum*", and a third one by Dr. Dennis Hourcade on the "3D structure of CR2 in complex with C3d "

<2> Drs. Hyon-Ju Park and John P. Atkinson also present two "Complement Teams": one Team lead by Dr. Uday Kishore at Brunel University in the UK, and the other lead by Dr. Stephen Tomlinson at the Medical University of South Carolina in the US.

<3>. Dr. John Lambris has a message concerning the XXIV International Complement Workshop (ICW). Please also note that you can now get preliminary information about the XXIV ICW meeting in Crete by visiting the website at: www.complement2012.org

FLASH NEWS

CR1 is P.falciparum receptor-Reporter: Atkinson/Park

Complement Receptor 1 Is a Sialic Acid-Independent Erythrocyte Receptor of *Plasmodium falciparum*

Spadafora C, Awandare GA, Kopydlowski KM, Czege J, Moch JK, Finberg RW, Tsokos GC, Stoute JA. PLoS Pathog. 6:e1000968, 2010

P. falciparum merozoites invade erythrocytes through a complex multistep process involving several parasite ligands and their human erythrocyte receptors. For years, glycophorins (surface proteins rich in sialic acid) were the only known host erythrocyte receptors. An alternative erythrocyte receptor was suspected when several strains of both wild isolates and laboratory strains of P. falciparum were able to invade neuraminidase (nm)-treated erythrocytes. By showing significant inhibition of *P. falciparum* invasion into nm-treated erythrocytes in presence of anti-CR1 Fab and soluble full-length complement receptor 1 (sCR1) and by demonstrating a correlation between erythrocyte invasion and CR1 expression in 19 human subjects, this paper indicates that CR1 also serves as an erythrocyte receptor for *P. falciparum*.

CR1 is P.falciparum receptor-Reporter: Atkinson/Park

Complement receptor 1 is the host erythrocyte receptor for *Plasmodium falciparum* PfRh4 invasion ligand

Tham W.H., Wilson D.W., Lopaticki S., Schmidt C.Q., Tetteh-Quarcoo P.B., Barlow P.N., Richard D., Corbin J.E., Beeson J.G., and Cowman A.F. PNAS 107: 17327-17332, 2010

Previously, disruption of PfRh4 gene in a strain of P. falciparum led to an inability of this strain to invade neuraminidase (nm)-treated erythrocytes. Growth assays employing several laboratory strains in setting of anti-PfRh4 antibodies showed 50 to 80% reduction of invasion into nm-treated erythrocytes. In this report, PfRh4 binding to the erythrocyte surface was inhibited in a dose dependent manner by anti-CR1 antibodies and sCR1 in a dose dependent manner. Data from immunoprecipitation, ELISA and SPR experiments supported that PfRh4 and CR1 interact directly. By demonstrating that invasion into nm-treated erythrocytes in human erythrocytes with low CR1 copy number was significantly reduced compared to those with high copy number, additional evidence for CR1 being the predominant receptor in a sialic acid independent invasion pathway was provided.

Note: The two papers establish CR1 as the predominant host sialic acid independent erythrocyte receptor for P. falciparum merozoite invasion. A follow up paper from this group indicates that Site 1 (CCPs 1-3) of CR1 to be essential for PfRh4 binding (Tham, Blood 2011). Site 1 mediates C4b binding and decay accelerating activity for C3 and C5 convertases.

FLASH NEWS (CONTINUATION)

3D structure of C3d/CR2-Reporter: D.Horcade

A Crystal Structure of the Complex Between Human Complement Receptor 2 and its Ligand C3d.

van den Eisen, J. M. and Isenman, D. E. Science, April 29, 2011, vol 332, pp 608-611.

The interaction of complement receptor 2 (CR2) with antigen-bound C3d dramatically enhances the antibody response. Kalli et al. (1991) established that the CR2 SCR 1 and SCR2 domains contain the C3d binding site and Szakonyi et al. presented a crystal structure of the C3d/SCR1-2 complex in 2001. However, the 2001 structure did not agree with earlier biochemical studies of Clemenza and Isenman (2000). Since that time evidence has accumulated that indicates the 2001 structure is non-physiological and likely dependent on the inclusion of zinc acetate in the crystallization protocol. Here van den Eisen and Isenman provide a new structure for the C3d/SCR1-2 complex that conforms to the biochemical data. While the structures of C3d and SCR1-2 individually do not differ from previous models, their relationship is quite different from the 2001 configuration. The new structure features interfaces between both SCR1 and SCR2 and the acidic pocket on the concave surface of C3d, opposite the convex surface which harbors the thioester residues that mediate covalent linkage of C3d to antigen. Hopefully this new work will put an end to the controversy and lead to novel strategies of vaccine development and for the treatment of autoimmunity.

To: The Complement Community

While we have published a retraction, we wanted to be certain the complement community was aware of this development. Properdin levels in mouse blood are not dependent on low level turnover of the alternative pathway. We incorrectly interpreted a pull down assay for mouse properdin. We regret the error and any confusion we have caused in the complement community.

Wu, X., Xu, T.Q., and Atkinson, J.P.: Properdin homeostasis requires turnover of the alternative complement pathway. Proc. Natl. Acad. Sci. USA 107:19444-19448, 2010. *PMCID: PMC2984156.* See retraction, May 2011. We also reported these data at the XXIII International Complement Workshop.

Sincerely,
John P. Atkinson, M.D.
Xiaobo Wu, M.D.

SPOTLIGHT ON TEAMS - I

Complement research in Brunel University, London, UK

The complement research within the Centre for Infection, Immunity and Disease Mechanisms (CIIDM) at the Brunel University, London is overall led by the Centre's Director, Dr Uday Kishore. Dr Kishore, who moved to Brunel University from University of Oxford 5 years ago, carried forward the research he had been conducting with Prof. K.B.M. Reid and Prof. Robert B. Sim at the MRC Immunochemistry Unit, Oxford. Dr Kishore's team (of 15 researchers) focuses on the translational research in the area of asthma, neurodegenerative diseases, pregnancy and tumour immunology. The group also investigates innate immune aspects of host-pathogen interactions (HIV-I, Mycobacterium tuberculosis, Aspergillus fumigatus, malaria parasite and Schistosome).

The complement research group within Dr.Kishore's team is addressing role of complement, especially classical pathway, in neurodegeneration and neuroinflammation, normal and complicated pregnancies, and hypersensitivity. The team also conducts research on novel C1q family members from various lower organisms. Our interest on the aspects of structure-function studies include the gC1q domain of human C1q, thrombospondin repeats of properdin, and CCP modules of factor H, and C1q receptors. Led by Annapurna Nayak, complement inhibitors are being tested to combat the neuroinflammation caused by aggregated proteins in neurodegenerative disorders such as Alzheimer's disease, and will be tested in the models of graft rejection. Led by Dr Anthony Tsolaki, a University Lecturer in Microbiology within CIIDM, his group is investigating interaction between complement and M. tuberculosis. (Photographed are: N. Karbani, A. Qaseem, Dr A. Shastri, E. Marri, Dr U. Kishore, L. Kouser, L.Pednekar, A. Boeteng, Dr J. Ferluga, A. Lokoto, Dr A. Tsolaki and A. Nayak. Other team members, P. Raj and S. Abozaid are missing in the photograph).

SPOTLIGHT ON TEAMS - II

Complement research in Charleston, S. Carolina (USA)

There are four pockets of complement research at the Medical University of South Carolina in Charleston: ***Stephen Tomlinson.*** Early on (New York University), work in the Tomlinson lab was focused on the complement inhibitor, CD59. These studies helped identify the active site of CD59, providing a basis for the species selective activity of the molecule, and better defining the interaction between CD59 and C9. The laboratory has also been at the forefront in the development and characterization of targeted complement inhibitors. Targeting allows effective delivery of complement inhibition while minimizing unwanted systemic effects, and different types of targeted complement inhibitor have been used to better define the role of complement in multiple inflammatory and autoimmune conditions in clinically relevant settings. Current research in the Tomlinson laboratory is fairly broad in scope, but is mostly centered around three themes that concern the role of complement in: 1. Inflammatory and alloimmune responses after ischemia/reperfusion and organ transplantation, 2. CNS injury following stroke or trauma to the spinal cord and, 3. The modulation of anti-cancer immunity. Contact information: tomlinss@musc.edu.

Gary Gilkeson. Work in the Gilkeson laboratory is focused on the role of the alternative complement pathway in mediating disease expression in lupus. Dr. Gilkeson began journey into the complement world in collaboration with Dr. Harvey Colten with studies on the impact of complement factor knockout genotypes on disease expression in lupus mice. His surprising finding was that Factor B deficient mice were significantly protected against development of lupus nephritis and that plasma C3 levels were maintained. He thus began studies on modulating the alternative pathway as a therapeutic strategy in lupus in collaboration both with Michael Holers and with Stephen Tomlinson. His current efforts are in defining the best approach to blocking the alternative pathway in lupus and defining mechanisms by which blocking the alternative pathway effects disease expression. Contact information: Gilkeson@musc.edu. ***Baerbel Rohrer.*** The Rohrer laboratory is investigating mechanisms of photoreceptor degeneration and neuroprotection. Work on complement began from a study aiming to identify commonalities among photoreceptor dystrophies. One key cluster identified included genes involved in complement activation and neuroinflammation, both of which are implicated in age-related macular degeneration (AMD), a focus of the laboratory. Two principle models used in the Rohrer lab to investigate aspects of AMD pathophysiology are light-induced photoreceptor degeneration (to investigate the role of oxidative stress) and argon-laser-induced choroidal neovascularization (CNV; to investigate angiogenesis). Publications from the laboratory show that pathological activation of the alternative pathway is involved in both light-induced degeneration and CNV. More recently, the importance of the classical and lectin pathways in initiating the disease process has been demonstrated, and important interplays between oxidative stress, MMP's and complement identified. Going forward, in vitro models, transgenic mice and complement inhibitors are being utilized in mechanism-based studies and in therapeutic paradigms. Contact information: rohrer@musc.edu. ***Carl Atkinson.*** After a postdoctoral fellowship in the Tomlinson lab, Dr. Atkinson started his own laboratory in 2006, and his focus is organ transplantation and lung diseases. With regard transplantation, the laboratory is investigating how complement impacts overall graft survival through its effects at different stages pre and post-transplantation. An important advance in this area, accomplished in collaboration with the Tomlinson laboratory, was the first description of a mouse model of brain death, and the demonstration that complement activation in the brain dead donor primes immune activation in the donor heart. Another key interest is the role of complement in chronic disease associated with environmental cigarette smoke exposure. Using rodent cigarette smoke exposure models, the Atkinson laboratory has demonstrated a key role for the alternative pathway in acute cigarette smoke induced lung injury. Current studies include investigations into the interplay between cigarette smoke exposure, complement activation and smoking related diseases such as emphysema, asthma and age-related macular degeneration. Contact information: atkinsoc@musc.edu.

ANNOUNCEMENT

XXIV INTERNATIONAL COMPLEMENT WOKSHOP
CRETE, (GREECE)

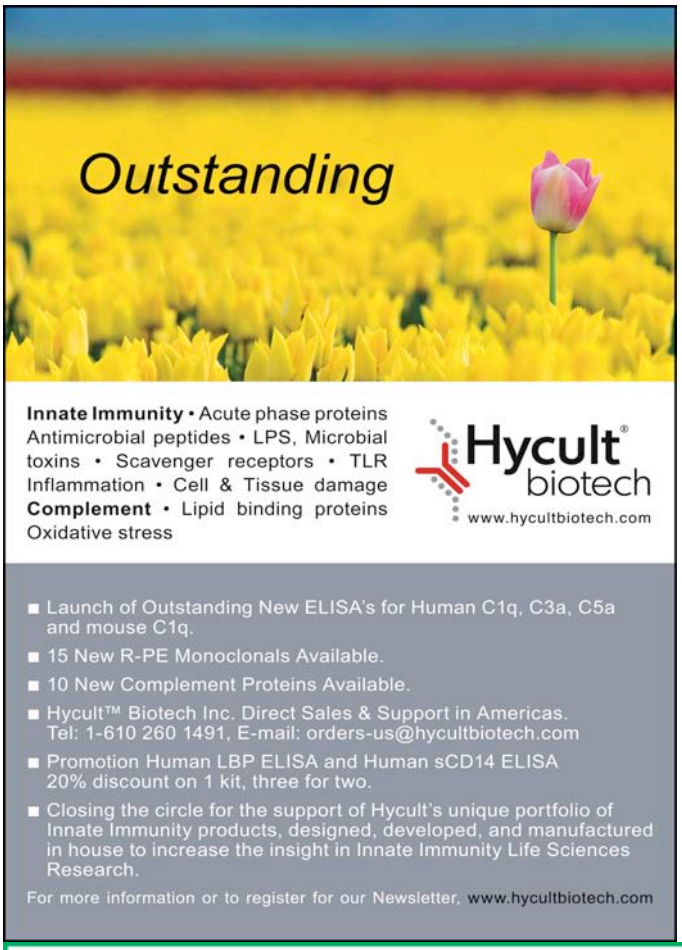
The XXIV International Complement Workshop to be held on October 10-15, 2012, on the scenic island of Crete, Greece, will serve as a timely and lively scientific platform to share the latest research updates, discuss emerging trends and concepts in the field, meet current and future collaborators, and get inspired by new ideas. Submitted abstracts will be peer-reviewed and selected for either an oral presentation in the top-modern conference center, or for the poster sessions. In addition to the scientific highlights, the Greek sun, cuisine, and cultural attractions will certainly contribute to a relaxed and unforgettable workshop experience. The regular registration package will include a wonderful room in a 5-star hotel—located directly on the banks of Mediterranean Sea—, breakfast, lunch, dinner, and coffee breaks, as well as a social program including trips to Cretan highlights and, of course, some dancing.

To recognize outstanding work by younger colleagues in the field and to encourage the participation of young scientists, the International Complement Society is offering several Awards. The Workshop Organizing Committees will select the recipients based on the scientific merit of abstracts of applicants. Abstracts will be selected for presentation in either poster or slide sessions.

For more details please visit www.complement2012.org

On behalf of the Organizing Committee,
John Lambris

Complement Reagents Corner



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