March 1, 2010
Issue 17

Focus on Complement

A newsletter of the International Complement Society

About this issue & More

What's inside?

<1>Two flash news, are presented by Dr. Sakari Jokiranta on: (a) Activation of fD by MASP-1, and (b) a novel splice variant of MASP-1 designated MAP-1, which inhibits complement activation.

<2>Two complement teams are also presented by Dr. Jokiranta one from U. Mass in the USA; and another from Helsinki, Finland.

<3>The president of ICS, Mike Pangburn, has two important announcements: (a) call for nominations for Officers of the ICS, and (b) invitation for bids to host the XXIV ICW in 2012. This is a second notice!

<4> A message from the LOC of XXIII ICW, is also included. Please **note** important dates: (a) abstract deadline is March 12, and early registration deadline is April 30. For more information visit the website at: http://www.hsc.stonybrook.edu/ics2010/

EUROPEAN COMPLEMENT NETWORK

FLASH NEWS

MASP-1 activation of fD-Reporter :S. Jokiranta

Essential role of Mannose-binding lectin associated serine protease-1 in activation of the complement factor D

(M Takahashi, Y Ishida, D Iwaki, K Kanno, T Suzuki, Y Endo, Y Homma, and T Fujita. J Exp Med 2010, 207:29-37)

For the activation of the lectin pathway it has previously been shown that MBL-associated serine protease 2 (MASP-2) is essential and responsible for the lectin pathway activation without a contribution of two other MASPs. MASP-1, however, is able to activate MASP-2 and cleave at least C2, C3, factor XIII, and fibrinogen in vitro but the possible physiological significance of these properties has not been shown. To analyze the *in vivo* role of MASP-1 and the alternative splice product of the same gene, MASP-3, Takahashi et al. generated a MASP-1- and MASP-3-deficient mouse model. The surprising primary observation was that the mice had no alternative pathway activity and the reason was revealed to be that plasma factor D was found only as its zymogen form (pro-fD). The role of MASP-1 in cleaving a small peptide from the N-terminus of pro-fD to produce active factor D was thereafter shown using purified proteins *in vitro*.

This report describes an important new link between the lectin and alternative pathways. The results clearly show that in mice, factor D is secreted as a zymogen both *in vivo* and by differentiated adipocytes *in vitro*. Since MASP-1 is essential in factor D activation it is clear that MASP-1 could have a role in lipid metabolism since factor D is essential in generation of acylation-stimulating protein (ASP), i.e. C3a (desArg).

Novel variant of MASP-1- Reporter: S. Jokiranta

A novel MBL/ficolin associated protein is highly expressed in heart and skeletal muscle tissues and inhibits complement activation

(M-O Skjoedt, T Hummelshoj, Y Palarasah, C Honore, C Koch, K Skjodt, and P Garred. J. Biol Chem 2010, Jan 6. [Epub ahead of print])

Similarly to the above reviewed paper, this report also deals with the lectin pathway and MASPs, but the rationale and approach are very different. Skjoedt et al., analyzed proteins associated with MBL and ficolins in human serum and found a new 45-kDa band that reacted with MASP1- and MASP-3-binding antibodies. Using genetic analyses a novel alternative splice variant of the MASP-1 gene was found with exons 1-8 followed by a novel short exon with a stop codon. The resulting protein lacks the serine protease domains but binds to MBL and ficolins and therefore the protein was named MBL/Ficolin-associated protein 1 (MAP-1). This protein was detected in serum and was found to be expressed not only in liver like MASP-1 and -3 but also in skeletal/cardiac muscle and brain. The most important finding in the report is the ability of the recombinant MAP-1 protein to inhibit function of MASP-2 although a great excess of MAP-1 is needed for clear inhibition. Since MAP-1 lacks the protease domains, it certainly cannot replace the proteolytic functions of MASPs. Therefore, it would be interesting to see if it could inhibit the novel function of MASP-1 in factor D activation described by Takahashi.

This report not only provides the first evidence of a novel specific inhibitor/regulator of the lectin pathway, but also warrants further examination of the functions of all the alternative splice variants of the *MASP* genes using various knockout animals.

SPOTLIGHT ON TEAMS - I

COMPLEMENT IN WORCESTER, MASS.

Two groups at the University of Massachusetts in Worcester, study the interactions of complement with the pathogenic Neisseriae. The major focus of **Peter Rice**'s laboratory is *Neisseria gonorrhoeae*, the agent of the sexually transmitted disease, gonorrhea. **Sanjay Ram**'s laboratory focuses on *N. meningitidis*, an important cause of bacterial meningitis and sepsis. Both laboratories actively collaborate to better understand how differences in complement evasion strategies used by these two bacteria that are closely related at the genomic level translate to the distinct diseases they cause.

Early work (1980s) in the Rice lab, defined how in some instances, the immune response to gonococcus could interfere with the ability of the host's complement system to kill the bacteria. These paradoxical studies led to the characterization of 'blocking' antibodies (Abs) directed against a gonococcal membrane protein called Rmp. Blocking Abs against a lipoprotein of N. *meningitidis* have also been identified recently and are an area of active research in the Ram and Rice labs.

Sialylation of gonococcal lipooligosaccharide (LOS) results in the ability of an otherwise serum sensitive gonococci to resist killing by complement. The ability of sialylated gonococci to bind to host factor H represented the discovery of an important complement evasion strategy. Shortly thereafter, the ability of gonococcal porin to bind to C4b-binding protein (C4BP) was described. Subsequently, several additional microbes were shown to bind to these complement inhibitors to evade killing by complement. *N. meningitidis* also binds to factor H, but in this instance the ligand for factor H was found by the Ram lab to be a lipoprotein that is currently a leading vaccine candidate against serogroup B meningococcal disease. The interaction of complement inhibitors with Neisseriae remains a major focus of interest in the Rice and Ram labs.

Neisseriae infect only humans; development of good animal models to study these diseases has been a challenge. An important related finding has been that evasion of complement by both Neisserial species is restricted to human (and in some strains, chimpanzee) complement. This is because of selective binding of human complement inhibitors to Neisseriae. The development of mice transgenic for human complement inhibitors is currently underway with the objective of improving upon the existing animal models.
N. gonorrhoeae is rapidly becoming resistant to most antimicrobials. The Rice lab, in collaboration with Sunita Gulati's lab, is developing mimitope vaccines against *N. gonorrhoeae*. In addition, novel molecules that divert complement inhibitors away from the bacterial surface and facilitate complement-dependent killing are being engineered and may provide alternatives for the therapy of gonorrhea.
Contact information: Peter Rice (peter.rice@umassmed.edu) Sanjay Ram (sanjay.ram@umassmed.edu)

SPOTLIGHT ON TEAMS - II

COMPLEMENT IN HELSINKI

The thick white snow cover in Finland is now melting down and going into lakes, which will soon warm up for the bright summer days. Like in weather, balance and transition are features of the complement system. Studies on complement have dominated research in the Meri group for the last 20 years. In 1988 Seppo Meri, after finishing his thesis work in Finland, went to Mike Pangburn's lab in Texas, US. The main question was to determine how the alternative pathway discriminates between activators and nonactivators (Meri & Pangburn, PNAS, 1990). Although much progress has been made, the question remains still unsolved. In 1989-90 he went to Peter Lachmann's lab in Cambridge, UK. In collaboration with Paul Morgan he worked out the mechanism of CD59 function.

The Meri group in Helsinki, Finland, has for a long time been interested in sorting out how and why the complement system contributes to disease pathogenesis, how the system is controlled and how pathogenic microbes and tumor cells escape complement attack. They were the first to report complement factor H binding proteins from Borrelia burgdorferi and have observed the same phenomenon with a number of other bacteria, and even with some parasites. Important collaborators have included Peter Zipfel's and Anna Blom's groups plus many others. The Meri group also first observed an interaction of CRP with factor H, and mapped the CRP binding site to SCR domain 7, which later was found to carry the polymorphism that predisposes to age-related macular degeneration (AMD). The polymorphism was found to affect binding to CRP. In tumor studies the Meri group has found that many tumor types resist complement attack by expressing CD46 and CD59, as well as by secreting and binding factor H to their surfaces. They also found that complement-mediated killing was superior to ADCC in rituximab-induced killing of Non-Hodgkin lymphoma cells.

Now the Meri group has nearly 20 members and students. Sakari Jokiranta, one of Seppo's first students, has set up his own group. The students work on microbial evasion of the complement system, have set up a malaria laboratory and continue studies on complement in human diseases and in some animal models. Further information of research in the Meri group can be found at the website of the group: http://www.hi.helsinki.fi/complement. Direct contacts can be made by e-mail: seppo.meri@helsinki.fi. Visitors are always welcome. In July, we will (nearly) all be by the lakeside, so that time is dedicated for relaxation.

XXIII International Complement Workshop
August 1-5, 2010
New York, NY, USA

REMINDER NOTICE #2

The meeting of the XXIII International Complement Workshop (ICW), which will be held at the Grand Hyatt in New York City (August 1-5, 2010), is fast approaching. Although the ICW meeting has been advertised in the last several issues of "***Focus on Complement***", we thought a reminder at this juncture would be appropriate especially since some of the deadlines are already on the horizon. Therefore we would like to direct your attention to the following deadlines:

1. ABSTRACT SUBMNISSION: Friday, March 12, 2010
Please create your login and password by going to the abstract submission site if you have not done so alreay.

2. TRAVEL AWARDS:
To encourage participation of young trainees (Grad students and Postdoctoral Fellows), the ICS will make as many travel awards as possible. Eligibility is based on acceptance of submitted first-authored abstract(s), financial needs, and provision of proof that the applicant is indeed a trainee. Please fill out the *Travel Award Application Form* provided online in the Abstract Submission site and send it to the address given at the bottom of the application form. For your convenience, a copy of the application form is also provided below.

3. EARLY REGISTRATION: Friday, April 30, 2010.
*To take advantage of the early registration fee, you **must** register before this date.*

4. HOTEL RESERVATION: **Friday, June 25, 2010.**
*A limited number of rooms have been blocked at the Grand Hyatt. Reservation is strictly on a first-come-first-served basis. To take advantage of the **special rate**, you need to make reservation before June 25, 2010.*

The ICW website has been designed to link you up with a vast array of entertainment options including museums, monuments, and circle-line cruises around Manhattan. You can make arrangements by clicking on the "Entertainment" to make your own arrangements. Alternatively, the hotel concierge can always help you make arrangements once you are there.

For all other information, please visit the **XXIII ICW Website at:**
http://www.hsc.stonybrook.edu/ics2010/

Message from the President

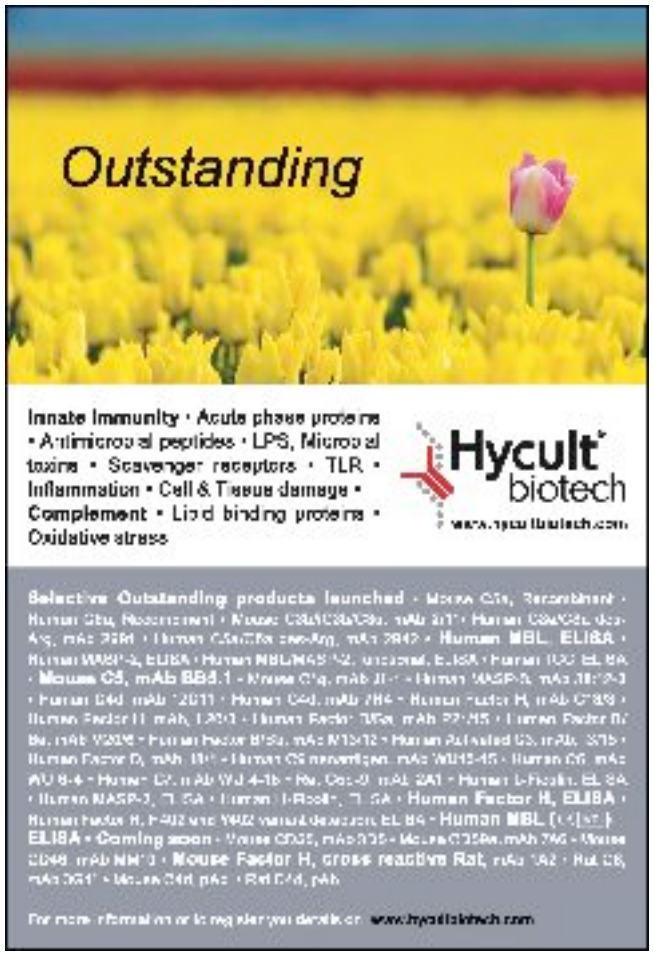
Call for Nomination of New Officers of the ICS

The International Complement Society elects new officers and councilors every two years at its semi-annual meeting. The next meeting will be in New York, Aug. 1-5, 2010. If you or someone you know is willing to serve the complement community as an officer or councilor please submit the name to one of the current ICS officers. A nomination committee will compile the names, verify willingness to serve and prepare a ballot for the election. Nominees must be active ICS members. You are a member if you paid a registration fee for the XXII International Complement Workshop in Basel in 2008. To become a member go to www.Complement.org and click on ICS Membership, send in $50 and the filled in form as instructed on the form.

Call for Bids to Host the International Complement Workshop in 2012

Locations for the next Complement Workshop are being sought. Formal bids will be presented to the society at the meeting in New York. If you are interested in hosting this meeting then review the process on our web site www.Complement.org (double click on Meetings and Bids) or call an officer or councilor to discuss it.

Complement Reagents Corner



Interested in reading previous bulletin issues?

All previous bulletin issues can be freely downloaded from the ICS Homepage : http://www.complement.org
(Publications → Archive)

INTERNATIONAL COMPLEMENT SOCIETY

ICS Travel Award Application Form

Please print legibly or type.

Applicant's Name: _____

Address: _____

City: _____ State/Country: _____ Zip Code: _____

Phone Number: _____ Fax Number: _____

E-mail Address: _____

Trainee Status (check one): Predoctoral — Degree/Year Expected: _____

Postdoctoral — Degree/Year Degree Received: _____

Advisor/Department Chair Certification of Applicant's Trainee Status: I hereby certify that

_____
Name of Trainee

is a registered student or postdoctoral fellow engaged in a research training program.

_____
Name of Advisor/Department Chair

Signature: _____ Date: _____

E-mail Address: _____

International Complement Society

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