December 1, 2009
Issue 16

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. Teizo Fujita on: (a) the role of secreted CCP in AchR clustering, and (b) Recruitment of fH by Neisseria meningitidis using host carbohydrates.

<2>Two complement teams are also presented by Dr. Fujita: one from Tokyo and another from Hungary.

<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.

<4>Updates of the XXIII ICW in NYC (August 1-5, 2010), are included. Please note important dates: (a) abstract deadline-Feb 15;registration deadline-April 30. Please visit the website at :http://www.hsc.stonybrook.edu/ics2010/

EUROPEAN COMPLEMENT NETWORK

FLASH NEWS

Secreted CCP & AchRs-Reporter::T.Fujita

A secreted complement-control-related protein ensures acetylcholine receptor clustering

Gendrel M, Rapti G, Richmond JE and Bessereau J-L;
Nature. 2009; 461: 992-6

To date, the CCP domains, also called as 'sushi' domain or short consensus repeats (SCR), have been identified in regulators of complement activation and complement serine proteases. The main function of CCP domains in complement regulators is serving as receptors for the fragmented C3 and C4.

In this paper, Gendrel M. et al reported a new protein in nematode *Caenorhabditis elegans*, termed LEV-9, which includes eight CCP domains. This protein is structurally similar to some of the complement regulators in humans, and its function relies on a series of CCP domains. LEV-9 is involved in the clustering of levamisole-sensitive heteromeric acetylcholine receptors (L-AchRs) on the cell surface of synapse. The function of LEV-9 is dependent on the interaction with another protein LEV-10, which contains a CUB (C1r/C1s, uEGF, bone morphogenic protein) domain. The CUB domain is also seen in complement serine proteases of the MASP/C1r/C1s family.

Interestingly, about a half of more than 50 genes encoding putative CCP proteins predicted in the mouse genome, are expressed in the central nervous system. The authors suggested that some of the uncharacterized CCP-bearing proteins in mammals might be involved in the organization of the synapse, independently from immune functions.

Neisseria &factor H: Repoorter: T.Fujita

***Neisseria meningitidis* recruits factor H using protein mimicry of host carbohydrate**

Muriel C. Schneider, Beverly E. Prosser, Joseph J. E. Caesar, Elisabeth Kugelberg, Su Li, Qian Zhang, Sadik Quoraishi, Janet E. Lovett, Janet E. Deane, Robert B. Sim, Pietro Roversi, Steven Johnson, Christoph M. Tang and Susan M. Lea.
Nature. 2009; 458:890-893

The complement system plays an important role to protect host from microorganism infection, and activation of complement, in health, is precisely controlled through membrane-bound and soluble plasma-regulatory proteins including complement factor H, a 155 kDa protein composed of 20 domains (termed complement control protein repeats). While some pathogenic microorganisms have evolved a mechanism to avoid immune killing by recruiting host complement regulators, others avoid complement-mediated killing by sequestering factor H to their surface.

The authors present the structure of a complement regulator in complex with its pathogen surface-protein ligand. The study reveals how the important human pathogen *Neisseria meningitidis* subverts immune responses by mimicking the host, using protein instead of charged-carbohydrate chemistry to recruit the host complement regulator, factor H. The structure also indicates the molecular basis of the host-specificity of the interaction between fH and the meningococcus, and informs attempts to develop novel therapeutics and vaccines.

SPOTLIGHT ON TEAMS - I

COMPLEMENT IN TOKYO

Dr. Nonaka's group in the Department of Biological Sciences, Graduate School of Science, at the University of Tokyo focuses on evolution of the complement system and the major histocompatibility complex (MHC).

Starting from identification of C3 in non-mammalian vertebrates such as rainbow trout and lamprey in the 1980's, evolutionary studies of the complement system revealed that the origin of the complement system is much more ancient than that of the adaptive immune system based on lymphocyte/MHC, which was established in a common ancestor of the jawed vertebrates. Our group analyzed two species of urochordate sea squirts, *Halocynthia roretzi* and *Ciona intestinalis*, and found that the orthologs to central complement components of the mammalian complement system with characteristic domain structure such as C3, Bf and MASP constitute an opsonic complement system in sea squirts. More recently, we found the same three genes, C3, Bf and MASP, from a basic eumetazoa, cnidarian sea anemone *Nematostella vectensis*. They were expressed in endoderms of tentacles, pharynx and mesentery, suggesting that they are secreted into coelenteron.

Although the function and activation mechanism of the sea anemone complement system is still to be clarified, these results indicated that the origin of the complement system predated the divergence of the cnidaria and bilateria (protostome plus deuterostome), which occurred approximately 700 million years ago. Whereas all deuterostomes analyzed so far have retained the complement system, many protostomes have lost it secondarily.

Our evolutionary analyses of the genomic structure of MHC inspired by the curious linkage of the C4, C2 and Bf genes in the mammalian MHC revealed the presence of these complement genes in the shark and frog MHC, suggesting that these complement genes were original members of the MHC established in a common ancestor of the jawed vertebrates. Through these evolutionary analyses of MHC, another curious linkage between functionally linked but structurally unlinked genes was recognized between the MHC class Ia genes and the immunoproteasome subunit PSMB8 gene. Now we are focusing on evolutionary analysis of an unprecedentedly long-lasting dimorphism of the PSMB8 gene maintained for more than a hundred million years.

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NOTE: (Photo was taken at alumni reunion in October 2009)

SPOTLIGHT ON TEAMS - II

COMPLEMENT IN BUDAPEST

Péter Závodszky initiated complement research at the Institute of Enzymology of the Hungarian Academy of Sciences in Budapest in the 1980s after his return from the Department of Biochemistry in Oxford. First, the focus was on the interaction of C1 with immune complexes and the structure of C1q. The work was gradually extended to the mechanism of initiation of the classical pathway. This was the site where structural biochemistry was combined with molecular biology, computer modeling and enzyme kinetics. We expressed functionally active recombinant human C1r in a baculovirus-insect cell based expression system. Using deletion and point mutant proteins we determined the function of the individual domains of C1r and investigated the mechanism of the autoactivation. Recently, we determined the crystal structure of the activated catalytic fragment of C1r and refined the functional model of the C1 complex.

In the 1990s Péter Gál extended these studies to the proteases of the lectin pathway**.** Using a combination of techniques including X-ray crystallography and expression of deletion mutants, the substrate and inhibitor specificity of MASP-1 and MASP-2, was determined. MASP-2 combines the activities of C1r and C1s since it can autoactivate and cleave C4 and C2 with high efficiency. In addition, we determined the crystal structure of both the active and zymogen forms of MASP-2 catalytic fragment and showed that the zymogen form has proteolytic activity on protein substrates. MASP-1 cannot initiate the complement cascade alone. However, it can significantly enhance the efficiency of the lectin pathway activation. In collaboration with Bob Sim's group in Oxford, we showed that MASP-1 has more relaxed substrate specificity than the other members of the C1r/C1s/MASPs family of complement proteases. MASP-1 is a thrombin-like enzyme since it can generate fibrin clot by cleaving fibrinogen and factor XIII revealing yet another link between the coagulation and the complement cascades. The crystal structure of the catalytic region of MASP-1 also explains both the relaxed substrate specificity and the thrombin-like properties of MASP-1. Consistent with its thrombin-like activity, MASP-1 can also activate and elicit calcium signal in HUVECs, presumably through the cleavage of a protease activated receptor (PAR4) on the endothelial cell surface.

The crystallization of C1-Inh— a regulator of C1r, C1s, MASP-1, MASP-2 and the plasma kallikrein proteases—has been a major challenge for several decades. Recently, we managed to crystallize the recombinant deglycosylated form of the serpin domain of C1-inhibitor. The structure not only makes possible the explanation of the consequences of different mutations, but it also helps us to interpret the modulating effect of heparin on the C1-inhibitor-protease reactions. Based on the structural biology of the classical and lectin pathways of complement, we are now developing specific, pathway-selective inhibitors that can be used for treatment of diseases such as Alzheimer disease and ischemia reperfusion injury.

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

UPDATES

The XXIII International Complement Workshop (ICW) will be held at the Grand Hyatt in New York City (August 1-5, 2010). In order to make it convenient for *all* the participants, this will be a unique ***all-in-one-site*** meeting, where the teaching day, scientific sessions, and other functions including the Welcome Reception and Gala Dinner will be held on the hotel premises. Although the local organizing committee is doing its level best to make this a very enjoyable and scientifically fruitful meeting, the timely registration and submission of abstracts by all participants, will nonetheless be essential in order to help us run the event smoothly. Therefore, we would like to bring to your attention the following deadlines and updates:

ICW Website: The ICW Website is now open and you can link by either clicking on the website address or copying the address and then pasting it: http://www.hsc.stonybrook.edu/ics2010/

Abstract: The submission site is now open and the deadline for abstract submission is **Feb.15** to ensure publication of the abstracts in "*Molecular Immunology*". Late submissions may be considered for presentation at the meeting but ***may not*** be published in "*Molecular Immunology*".

Conference venue and hotel accommodations: The meetings will be held at the Grand Hyatt in NY City, which has more than 1600 rooms. **Rooms at $209/room** have been reserved for conference participants and their guests. This is indeed an incredible rate for NYC and this ***rate*** will be honored should guests wish to stay an additional week before or after the meetings. Participants ***should*** consider staying at this hotel and reservations can be made by going to the **ICW website** and then clicking first on "hotel accommodation" and then on: http://www.grandnewyork.hyatt.com/groupbooking/nycghgcom2010

Registration: As suggested by many of you, the registration fee has been reduced to **$950**/person for early (before April 30, 2010) registrants and includes: breakfast, lunch, reception and gala dinner. *The registration site will be open soon!*

SCHEDULE

Aug 1: Teaching Day/Welcome Reception
Aug. 2-5: Scientific Meetings
Aug 5: Gala Dinner

LOCAL ORGANIZING COMMITTEE:

B.Ghebrehiwet, R.R. Kew, E.I. Peerschke

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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)