Focus on Complement
A newsletter of the International Complement Society

March 1, 2012
Issue 25

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What’s inside?

1. Three flash news, are presented by Dr. Teizo Fujita on: (a) mutations on Collectin 11 and MASP1 in 3MC syndrome; (b) CL-11 as MASP-1/3 associated collectin with microbial activity and (c) the role of MASP-3 in AP activation.

2. Dr. Fujita also presents two “Complement Teams”: one lead by Dr. G. Stahl, from the Harvard Medical School in Boston, USA, and another lead by Prof. Wakamiya, at Asahikawa Medical University, Japan.

3. Dr. John Lambris shares 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

4. This issue also highlights recent awards and recognition to ICS members as well as advertisement for postdoctoral positions.

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Mutations in lectin complement pathway genes **COLEC11** and **MASP1** cause 3MC syndrome


Recently, a novel missense mutation of **MASP1** gene in the exon encoding the serine protease domain of the protein MASP-3 have been reported to be a cause of the Carnevale, Mingarelli, Malpuech and Michels syndromes (3MC syndrome) (Am. J. Hum. Genet. 87, 679–686 2010). These rare autosomal recessive disorders exhibit a spectrum of developmental features, including characteristic facial dysmorphism, cleft lip and/or palate, craniosynostosis, learning disability and genital, limb and vesicorenal anomalies. Rooryck and colleagues presented an independent confirmation of the above finding and also demonstrated 3MC-causing mutations in another gene, **COLEC11** encoding a protein, collectin kidney 1 (CL-K1 or collectin-11), of the same innate immune defense system, the lectin pathway of complement activation. Their studies on zebrafish further support the developmental influence of mutations in these two genes. Importantly, these findings demonstrate a role for the lectin pathway in fundamental developmental processes and in the etiology of 3MC syndrome.

**Collectin 11 (CL-11, CL-K1) is a MASP-1/3-associated plasma collectin with microbial-binding activity.**


In the lectin complement pathway, MBL and ficolins act as the recognition molecules and associate with MBL-associated serine proteases (MASP-1, MASP-2 and MASP-3). Collectins which consist of collagen region and CRD, play important roles in the innate immune defense against microorganisms. Among collectins, however, only MBL is able to activate the complement system. Selman and colleagues characterize the structural and functional properties of collectin 11 (CL-11 or CL-K1), and found that CL-K1 copurified with MASP-1. The interaction of CL-11 in plasma with MASP-1 and/or MASP-3 was further demonstrated using ELISA. They show that CL-11 binds to intact bacteria, fungi, and viruses. Although MASP-2, which is responsible to activate C4, is not proved to be associated with CL-11, it is conceivable that CL-11 plays a role in activation of the complement system and in the defense against invading microorganisms.
The role of mannose-binding lectin-associated serine protease-3 in activation of the alternative complement pathway.


MBL-associated serine proteases (MASPs) are responsible for activation of the lectin complement pathway. Three types of MASPs (MASP-1, MASP-2, and MASP-3) are complexed with MBL and ficolins in serum. Although MASP-1 and MASP-2 are known to contribute to complement activation, the function of MASP-3 remains unclear. Iwaki and colleagues investigated the mechanism of MASP-3 activation and its substrate using the recombinant mouse MASP-3 (rMASP-3) and several different types of MASP-deficient mice. The recombinant enzyme was activated by incubation with Staphylococcus aureus but not with mannan and GlcNAc. They found that sera from all MASPs-deficient mice showed significantly lower C3 deposition activity on the bacteria compared with that of wild-type serum. The low C3 deposition in sera from all MASPs-deficient mice was probably caused by the low level factor B activation that was ameliorated by the addition of rMASP-3. Furthermore, rMASP-3 directly activated factors B and D in vitro. These results suggested that in addition to MASP-1, MASP-3 triggered the initial activation step of the alternative complement pathway.
Spotlight on teams - I

Complement Team at Harvard Medical School in Boston

The Takahashi and Stahl research groups at HMS are located at Massachusetts General Hospital and Brigham and Women’s Hospital, Harvard Institutes of Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Center for Experimental Therapeutics and Reperfusion Injury. The two groups are located across town from each other and independently funded, but this has not stopped them from intense collaborations over the last ten plus years. Manuscripts from these collaborations have laid the groundwork for the role of MBL in many human diseases.

The work of the Takahashi lab is centered principally on the investigation of MBL and its role in health and disease. Because MBL activates complement, the Takahashi lab became complement researchers, often investigating non-complement centered processes. The lab has developed MBL null mouse lacking both MBL-A and MBL-C, a murine model of the human MBL deficiency, in order to investigate clinically relevant diseases using animal models. We have found in vivo evidence that MBL is involved in many host responses, including antibody-mediated immune reaction, wound healing, coagulation and protection from infection. Our most recent work has demonstrated a possible role for MBL in maintaining brain homeostasis, which further expands our investigation of non-complement related systems. Dr. Wei-Chuan Chang uses in vitro models of infection to study the effects of MBL and MBL-derivatives. Ms. Lorencia Chigweshe is a research associate who assists in a variety of laboratory efforts. Dr. Mykol Larvie is a physician scientist who is studying the function of MBL in amyloid clearance from the brain, a process relevant to Alzheimer’s disease.

Dr. Stahl’s lab has a long history in studying mediators of disease and is classically trained as a cardiovascular physiologist/pharmacologist. His lab studies the role of complement, particularly the MBL complex, in ischemia/reperfusion (I/R) injury and the resulting inflammation, coagulopathy and vascular injury associated with the disease process. Currently the lab is funded to investigate the role of the MBL complex in vivo and in vitro in coagulation abnormalities associated with oxidative stress. Dr. Vasile Pavlov uses in vivo murine models to study I/R injury and coagulation defects in the many complement deficient and transgenic lines in the lab. Ms. Ying S. Tan assists in these studies by providing in vitro models of whole blood aggregation as well as immunohistochemical applications to identify novel mechanisms. A second major focus of the lab involves the role of complement in acute hyperglycemia-induced vasculopathy and ventricular remodelling. Dr. Chenhui Zou studies the complement pathways and components involved in hyperglycemia-induced cardiomyopathy. Dr. Zou’s ongoing work will be pivotal to identify promising therapeutic targets aimed at mitigating hyperglycemia-induced microvascular dysfunction and myocardial remodelling. Ms. Margaret Morrissey assists in all aspects of the lab, as the Stahl lab manager and animal colony veterinary technician. Ms. Heather Kearney keeps the lab grounded by assisting the Stahl lab as its Administrative Assistant.

Both laboratories invite collaborations and visits from other labs at any time.

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Front row (L/R): Vasile Pavlov, Kazue
Takahashi, Mykol Larvie, Greg Stahl, Chenhui
Zou. Back row: Heather Kearney, Lorencia
Chigweshe, Ying Tan, Wei-Chuan (Claudia)
Chang, Margaret Morrissey
Spotlight on teams - II

Novel collectin team at Asahikawa Medical University in Asahikawa, JAPAN

At Asahikawa Medical University located in the heart of Hokkaido, Japan, our research laboratory is directed by Professor N. Wakamiya, a member of the American Society for Microbiology, and the main research topic is the study on biological functions of collectin families. In 1992, we reported the findings from our first collectin study that conglutinin of the bovine collectin family neutralizes the infection of influenza virus due to its lectin activity. In 1999, using a reverse genetic method, our laboratory discovered collectin liver 1 (CL-L1) as the 4th member of the collectin family. Then, we found collectin placenta 1 (CL-P1) as another new collectin member, which is expressed on vascular endothelial tissues. It acts as a scavenger receptor to endocytose oxidized LDL and phagocytose microbes. Finally, we found collectin kidney 1 (CL-K1) as the 6th member of the collectin family, which is mainly produced in the liver and pulmonary tissues. These new collectin members are different from the classical type of collectins such as MBL (mannose-binding lectin), SP-A (surfactant protein A), and SP-D (surfactant protein A). The collectin genes of CL-L1, CL-P1, and CL-K1 are designated as COLEC10, COLEC12, and COLEC11, respectively. Recently, we have cloned a zebrafish CL-P1 and demonstrated by its knockdown study that zCL-P1 is implicated in vasculogenesis and body formation. Furthermore, it has been found that CL-K1 may be a third candidate to activate the lectin pathway following MBL and ficolin. Also, it has been discovered that gene mutations of CL-K1 and MASP-3 cause the rare autosomal recessive disease 3MC syndrome, demonstrating unique characteristics of high arched eyebrows, ptosis, cleft palate, cleft lip, down-turned mouth, cognitive impairment, growth deficiency, and an insufficiency of craniosynostosis. Accumulating results of these new collectin members suggest that they play roles in significant biological functions in development and vascular homeostasis other than those of innate immunity. The recent focus of our laboratory is to clarify the molecular basis of biological functions in novel collectins. We hope to devote our new findings to the health of human beings.

Dr. Katsuki Ohtani, Associate Professor, leads a group working on the murine biological functions in CL-P1 and CL-K1 using knockout mice. Drs. Kenichiro Mori and Yasuyuki Matsuda, Assistant Professors, are also studying CL-P1 and CL-L1 functions.

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Dear Colleagues,

The **XXIV International Complement Workshop** will be held on **October 10-15, 2012**, on the scenic island of **Crete, Greece**. It 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 wonderful room accommodations in a 5-star hotel—located directly on the banks of the Mediterranean Sea—, breakfast, lunch, dinner, and coffee breaks, as well as a social program including trips to Cretan highlights and, of course, some dancing.

Rarely before has the field of complement research seen such dramatic changes and exciting developments than during the past decade. Driven by seminal discoveries ranging from molecular to clinical aspects, and fueled by recent progress in the therapeutic intervention in complement-mediated diseases, novel insights into the function of complement appear at an increasingly rapid pace. New players in the network have been discovered, and several functional aspects have been redefined or extended, recently. At the same time, we are coming to realize that the physiological spectrum of complement by far exceeds host antimicrobial defense and that the complement network is highly intertwined with a variety of bodily systems. Open and vivid scientific discussions, the integration of new research ideas and talents, and the interaction with peripheral fields can further drive complement research to new horizons.

**The keynote speakers of the meeting are:**

**Alberto Mantovani, M.D.** Professor, University of Milan Scientific Director, Istituto Clinico Humanitas.

**Hans J. Müller-Eberhard Memorial Lecture:** *The humoral arm of innate immunity: recurrent themes and regulatory pathways*

**Shankar Subramaniam, Ph.D.** Professor and Chair Department of Bioengineering, University of California, San Diego.

**Systems Biology and Innate Immunity**

**Joe Nadeau, Ph.D.** Director of Research and Academic Affairs of the Systems Biology Institute, Seattle.

**Tipping complex systems from disease to health: genetic and dietary influences on metabolic disease, cancer and inflammation**

**Additional speakers will be selected from the submitted abstracts**

The deadline for receipt of abstracts, early registration, and hotel reservations is **July 1, 2012**. Please note that the cost of the registration fee is **575 Euro** and hotel accommodations from **85-110 Euro/night**.

Additional information will be sent only to people who respond to this announcement and pre-register.
on-line. For your convenience and to expedite the communication process, registration materials, including abstract and hotel reservation forms, are available on the web site. Information on Crete, travel to Greece, hotel accommodations, etc. is also available on the web site. Updated information will be available through this site.

http://www.complement2012.org or http://www.aegeanconferences.org

To pre-register to the conference please visit:
https://www.aegeanconferences.org/registOpen.do?method=open

To encourage the participation of young scientists, the following Trainee Travel Awards will be available to offset a portion of the travel expenses to the Conference:
- Trainee Travel Awards
- The Lambris Complement Training Award (LCTA)
- Young Investigator Awards for Research in Complement

For more information please visit the workshop’s website.
We look forward to welcoming you in Crete for a scientifically stimulating and socially enjoyable meeting.

Best personal regards,

Local Organizing Committee

John D. Lambris (www.lambris.com)
University of Pennsylvania, USA
Chair of the Organizing Committee

George Hajishengalis
University of Louisville, USA

Daniel Ricklin
University of Pennsylvania, USA

Program Committee

The Program Committee will consist primarily of ICS Board members (see www.complement.org), and possibly a few ad hoc members. The committee will select the abstracts for presentation, travel awards, and the keynote speakers. The Chair of the Program Committee is the current President of the ICS, Dr. Paul B. Morgan, University of Wales College of Medicine. The other members are as follows:

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Matthew C. Pickering (Imperial College, Hammersmith, UK)
Santiago Rodriguez de Cordoba (Centro de Investigaciones Biologicas, Spain)
Wenchao Song (University of Pennsylvania, USA)
RECENT AWARDS AND RECOGNITION of ICS MEMBERS

John Atkinson, M.D., Washington University School of Medicine—will be recognized at the upcoming 99th AAI Annual Meeting, “IMMUNOLOGY 2012™” May 4-8, Boston, Massachusetts; with the AAI-Award for Human Immunology Research “For significant, sustained achievement in immunology research pertinent to human disease pathogenesis, prevention, and therapy”.

Agustin Dalmaso, M.D., U of Minnesota Minneapolis—received the Honorary Award of the International Xenotransplantation Association at the biennial Congress of the Association in Miami, FL, October 23-26, 2011. The award was given to Dr. Dalmaso in recognition of his many scientific contributions that have revealed the pivotal role of complement in xenograft injury and accommodation and have contributed significantly to the advancement of our field. Dr. Dalmaso gave a presentation summarizing his contributions, recent progress in xenotransplantation and the clinical perspectives of the field.

POSTDOCTORAL POSITIONS

AVAILABLE: A post-doctoral position is available at the Department of Pediatrics, Lund University, Lund, Sweden. The laboratory studies complement and Shiga toxin-producing E. coli infections in the induction of the renal disease hemolytic uremic syndrome. The ideal candidate should be highly motivated, be able to work independently and have a record of publications. The candidate should have good knowledge in the field of complement and experience of in vivo experiments using primarily mice. The applicant should be experienced with cell cultures, immunological methods (ELISA, immunoblotting, flow cytometry) and immunohistochemistry/immunofluorescence. For more information please contact Professor Diana Karpman at diana.karpman@med.lu.se

LOOKING: “I am looking for a post-doctoral position in complement research. I have graduated from Eotvos Lorand University, MSc in Biology in 2001 and was awarded with a PhD degree in Immunology at the Semmelweis University, Hungary in 2005. I have over 4 years postdoctoral experience in the field of immunology and molecular biology. I have experience in antibody development and analysis, I used ELISA, ELISPOT, Western blot and BiaCore methods routinely and have a good practice with primary cell cultures and flow cytometry. In the past few years I have worked for the Institut de Biologie Structural, Grenoble, France as a Marie Curie postdoctoral grant holder under the supervision of Gerard Arlaud. After a maternity leave I would like to return in science and continue my research carrier.” Contact Dr. Adrienn Biro; ADRIENN_BIRO@YAHOO.COM
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