Focus on Complement

December 1, 2014
Issue 36

International Complement Society

European Complement Network

Dear readers,

Welcome to the December 2014 issue of 'Focus on Complement'. This 36th issue of FoC contains:

- **Seasonal greetings and Presidential message**
- **Obituary on Dr. Michael Loos**
- **Flash News** presenting two recent papers showing that Von Willebrand Factor can act as a cofactor in complement regulation and describing a novel activation mechanism for the Lectin pathway
- **The Complement research teams around the world series** featuring the teams of Drs. Markus-Huber Lang in Germany and Veronique Fremeaux-Bacchi in France
- Part I of the **Meeting Report** on the 25th ICW held in September 2014 in Rio de Janeiro
- Complement meetings announcement

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Claudia Kemper or Zvi Fishelson; Claudia.kemper@kcl.ac.uk, lifish@post.tau.ac.il

Seasonal Greetings and Presidential message

◈ **The 25th International Complement Workshop** took place September 14-18, 2014 in beautiful Rio de Janeiro, Brazil, at the Copacabana and was hosted by Dr. Denise Tambourgi (Instituto Butantan, San Paulo) and colleagues. The remote venue imposed relatively higher travel expenses; nevertheless, 155 senior ICS members and 90 postdocs and students participated in this excellently organized conference and made it highly productive and rich in novel findings and concepts. The meeting was organized in 10 Scientific Sessions plus 3 Plenary Sessions in which selected invited speakers presented an overview of their work. The respective session chairs summarized the highlights of each session and these summaries will be presented partly in this issue of Focus on Complement and partly in the next issue. We thank all session chairs for their contribution during the meeting and for summarizing their sessions for us all to read and remember. Special thanks go to all teachers in the Teaching Day!

◈ During the meeting the ICS presented **Young Investigator Awards** to Suzan Rooijakkers and Trent Woodruff for their work on complement and bacterial interplay and the role of anaphylatoxins in immune homeostasis, respectively. An **ICS Merit Award** was given to Claudia Kemper for outstanding contributions to complement research. Travel and Poster Awards were given to 34 students and postdocs who scientifically excelled in their abstracts or posters. Congrats again!

◈ **Election for ICS Board members** was held during the 25th ICW and the ICS members elected Michael Holers for President-Elect and re-elected Claudia Kemper as Secretary and Wenchao Song as Treasurer for 2 additional years. Peter Zipfel and Michael Kirschfink were elected as new board members. Congratulation to all! Thanks to Paul Morgan (ICS President 2010-12) and Tom-Eirik Mollnes whose term on the board has ended, for their valuable contributions to the ICS over the years.

◈ Decisions from the **ICS Board meeting** in Rio:
1. The ICS will join the IUIS, International Union of Immunological Societies, as an affiliated organization (with WHO and FOCIS).
2. The full ICS Board will serve as the Complement Nomenclature Committee and as an IUIS sub-committee on Complement Nomenclature.
3. ICS Young Investigator Awards will have an age limit of 40 years and the exclusion of acting ICS Board members from nomination has been be omitted.

◈ At the end of this month I will retire from my duties as ICS President and Andrea Tenner will take over as ICS President for the next two years. Good luck, Andrea! I am very grateful for the assistance and cooperation of all ICS Board members. Special thanks go to Claudia Kemper, ICS Secretary and Editor of 'Focus on Complement' and Wenchao song, ICS Treasurer, for their efficient and intensive efforts to keep our society functional, flourishing and 'on the map'.

◈ I wish you and your families wonderful holidays and New Year filled with prosperity, joy and peace!

Zvi Fishelson

OBITUARY

REMEMBERING MICHAEL LOOS (1941 – 2014)

Dr. Michael G. Loos, Professor of Medical Microbiology, passed away unexpectedly on November 12, 2014.

Trained as a pharmacist and microbiologist, Michael started his career in science at the Institute of Medical Microbiology at the University of Mainz, Germany, where he was awarded his Ph.D. in 1969. Encouraged by his mentor Professor Paul Klein, he joined Tibor Borsos at the NIH in Bethesda in 1971/1972, working on the activation of the early components of the classical pathway of complement. Back in Mainz, his interest started to focus on the interaction of C1 and bacteria, eventually demonstrating an antibody independent activation of the classical pathway by various polyanionic molecules. In collaboration with clinicians and scientists from various countries he described the molecular and genetic basis in C1q and C1 inhibitor deficiencies and the existence of autoantibodies against C1q and C1 inhibitor in patients with rheumatoid arthritis, SLE and acquired C1 inhibitor deficiency type II.

Michael engaged himself in the teaching of students of medicine, pharmacy, biology and immunology. As a result of this, he attracted students for his research group "the C1 family" and supplied them with the tools of the trade for their M.D., Ph.D. and diploma projects. The German term for Ph.D. supervisor is "Doktorvater". And yes indeed, Professor Loos was a father to us by caring, stimulating, and supporting us to find our own scientific, professional and personal careers.

From 1995-1998 he was elected Vice-President for Science of the Johannes Gutenberg-University of Mainz. Despite this demanding task he continued research on various aspects of C1 and MBL. Michael has been an active member of the International Complement Society and the European Complement Network throughout many years. Together with Ken Reid and Maurice Colomb he organized the legendary International Workshops on C1 and the Collectins. Everyone who attended these meetings will remember the dynamic, cordial and fruitful atmosphere that Michael was able to create.

Dearly loved, greatly missed and truly unforgettable – Thank you Michael

His former students and colleagues "Die Loosianer"

FLASH NEWS

NEWS FLASH 1:

Von Willebrand Factor is a cofactor in complement regulation. *Feng S, Liang X, Kroll MH, Chung DW, Afshar-Kharghan V. Blood, 2014 Nov 13. pii: blood-2014-06-585430.*

The complement and coagulation systems interact as exemplified by proteins with dual coagulation and complement functions, such as thrombomodulin that enhances activation of protein C and degradation of anaphylatoxins, or Factor H that acts as a cofactor for cleavage of C3b and von Willebrand Factor (vWF). Similarly, several complement proteins interact with hemostatic factors. This raises the possibility that vWF binding might also alter complement regulation by FH and, incidentally, vWF mutations have been identified in patients with atypical hemolytic uremic syndrome (aHUS). The group of Vahid Afshar-Kharghan recently discovered that vWF acts as a cofactor for Factor I-mediated cleavage of complement C3b, thereby shutting down complement activation. The complement regulatory function of vWF multimers depends on their size. Smaller vWF multimers enhance cleavage of C3b but large and ultra-large vWF (ULvWF) multimers have no effect on C3b cleavage and permit default complement activation. We conclude that normal plasma vWF multimers prevent complement activation and steer the complement pathway towards generation of inactivated C3b (iC3b). ULvWF multimers, as are present in patients with thrombotic microangiopathy, lack an inhibitory effect on complement and permit complement activation. The results are consistent with recent reports of complement activation in patients with thrombotic thrombocytopenia purpura. Mild-reduced ADAMTS-13 activity is also detected in other thrombotic micropathies, including aHUS and sepsis, suggesting that larger vWF multimers in these conditions may increase complement activation. ***Reported by Bo Nilsson, Uppsala University, Sweden***

NEWS FLASH 2:

Complement activation by ligand-driven juxtaposition of discrete pattern recognition complexes. *Søren E. Degn, Troels R. Kjaer, Rune T. Kidmose, Lisbeth Jensen, Annette G. Hansen, Mustafa Tekin, Jens C. Jensenius, Gregers R. Andersen, and Steffen Thiel. PNAS, 2014 Sep 16;111(37):13445-50.*

In this study, Søren Degn and coworkers suggest a new mechanism for the activation of complement and show that the lectin pathway is activated by ligand-driven juxtaposition of discrete pattern recognition complexes. It has long been held that classical pathway activation occurs through conformational changes in the macromolecular initiating complexes upon pattern recognition and it has been proposed that the same principle holds also for complement activation through the lectin pathway. This long-standing paradigm has now been challenged in this current study. The lectin pathway is activated by the pattern recognition molecules (PRMs), MBL and ficolins, complexed with the proteases MASP-1 and MASP-2. MASP-1 can only cleave C2, whereas MASP-2 can cleave both C4 and C2, imposing an absolute requirement for MASP-2 in activation of the pathway. The investigation of Degn *et al*. was prompted by the recent demonstration that MASP-1 is the exclusive activator of MASP-2 under physiological conditions (Heja *et al*., PNAS 2012, Degn *et al*., JI 2012). Because the predominant tertameric form of MBL carries only a single MASP homodimer, this suggested that activation of MASP-2 by MASP-1 would have to occur through PRM-driven juxtaposition on ligand surfaces. Indeed, Degn *et al*. find that MBL tetramers binding either MASP-1 or MASP-2, can still drive activation when bound on a ligand surface, They also found that discrete PRM/MASP complexes, i.e. H-ficolin/MASP-1 and MBL/MASP-2, activate when bound on mixed ligand surface - suggesting that different PRMs cooperate in recognizing and eliminating pathogens. They furthermore show that PRM ligand binding does not directly escort a transition of MASP from zymogen to active enzyme. Rather, activation is induced by clustering of the complexes. Thus their data support a clustering-based mechanism of activation, akin to that of cellular receptors, and fundamentally different from the conformational model suggested for the classical pathway of complement. ***Reported by Bo Nilsson, Uppsala University, Sweden***

COMPLEMENT TEAMS AROUND THE WORLD

Complement in Germany: Prof. Markus Huber-Lang's Team

The picturesque city of Ulm in the South of Germany is relatively small, yet it is the home to the world's highest church tower and was the birthplace of Albert Einstein.
Within the last decade, *complement research on cellular trauma* became a crucial pillar at the University of Ulm, driven by a group around a trauma-surgeon. After completing medical school and his first clinical training at the University of Freiburg, Germany, *Markus Huber-Lang* went to Peter Ward, USA, for a postdoc-fellowship between 1998−2000, where he investigated the role of complement in acute lung injury and sepsis, finding various detrimental effects of C5a.
Markus Huber-Lang then "squared the circle" as clinician and researcher by receiving training and working as a general and trauma surgeon side by side with translational research activities and building-up a complement lab. His young team was subsequently granted the Emmy Noether excellence program (by the German Research Foundation) with a focus on C5a-induced dysfunction after tissue trauma and during sepsis, where many involved pathways could be described.
In 2000, Markus Huber-Lang became a Professor for Clinical and Experimental Trauma-Immunology and the leader of the Research Unit KFO200, addressing the early danger response after trauma. In close collaboration with complement experts (J. Lambris, T.E. Mollnes, B. Nilsson, P. Ward, J. Köhl, G. Stahl, A. Blom, P. Zipfel, and M. Ratajczak among many others) the Huber-Lang group is interested in the intensive cross-talk of the complement and coagulation systems and in defining new exogenous complement activation pathways. Moreover, the group has recently addressed the role of complement in fracture healing and regenerative processes in close collaboration with A. Ignatius, Ulm University. An overall effort of the Huber-Lang team is to bridge the lab findings and clinical reality in acute critical illnesses (including hemorrhagic shock, polytrauma, sepsis and multi-organ dysfunction) for reliable immune-monitoring of patients. The final aim of the team effort is to find effective complement-modulatory approaches to improve the (surgical) management of critically ill patients and their outcome.
Currently, the Huber-Lang group has almost a dozen members plus students. Daniel Rittirsch and Michael Flierl, two of Huber-Lang's first students, have meanwhile established their own group. Visitors are always welcome; we are located close to the Alps and Austria, less than 4 hours travel from Italy. In August, we will (nearly) all be by the Mediterranean Sea, so that time is dedicated to relaxation and philosophizing on how to complement life.

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Complement in France: Dr. Veronique Fremeaux-Bacchi's Team

Dr. Veronique Fremeaux-Bacchi's "Complement and diseases" team was established about 10 years ago in Paris, France. It is situated at two different geographic locations. The research group is in the Cordeliers Research Center (CRC, INSERM UMRS1138) while the diagnostic and genetic exploration laboratory is in the European Georges Pompidou Hospital.

Our team focuses on fundamental and translational research linking complement to disease pathogenesis. We study the genetic, cellular and molecular mechanisms of complement-induced renal diseases, with a particular emphasis on atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathies (C3G, dense deposit disease and C3 glomerulonephritis). Thanks to our large network of clinicians and the aHUS and C3G working groups, we established one of the largest cohorts of aHUS and C3G patients in the world. We discovered Factor I and C3 genetic abnormalities in aHUS patients and were the first to identify an autoimmune form of aHUS, associated with anti-Factor H autoantibodies. Recently, we identified diacylglycerol kinase e (DGKE) as a new gene, unrelated to the complement cascade, contributing to aHUS. We developed a platform to study the structure-function relationships of disease-associated genetic and acquired abnormalities in complement proteins and their pathological relevance. This allowed us to characterize the functional consequences and pathogenic role of a large number of mutations in C3, Factor B, Factor I and Factor H genes as well as anti-Factor H autoantibodies found in the French patients with aHUS or C3G. We have established international collaborations to analyze the pathogenic role of all identified mutations in the components of the C3 convertase C3 and FB. We currently seek to identify the mechanisms, leading to generation of auto-antibodies against complement proteins in aHUS and C3G as well as characterization of their functional consequences and disease relevance. A more recent axis of our research is related to the study of the pathophysiological role and mechanisms of complement-mediated cellular injury and the participation of complement to the intravascular cell-cell interactions in case of inflammation, hemolysis and thrombosis.

We have established a cellular model of aHUS and we study of the link between complement overactivation and the expression of a pro-thrombotic phenotype of the endothelium in the context of aHUS as well as the molecular and cellular mechanisms of complement activation by heme and the role of hemolysis as a secondary 'hit for aHUS. Finally, in close collaboration between diagnostic and research groups we contributed to the new disease classification of the C3 glomerulopathies and seek to identify new diagnostic and prognostic markers for complement-mediated diseases to improve strategies of patient management.

We are passionate complementologists, approaching complement from different perspectives and we often welcome foreign young researchers for collaborative projects in our lab. This diversity allows us an active exchange of ideas and an interdisciplinary research.

Research group: *Olivia May (MD, M2 student), Tania Rybkine (engineer), Maria-Chiara Marinozzi (PhD student), Nicolas Merle (PhD student), Sophie Chauvet (MD, PhD student), Veronique Fremeaux-Bacchi (MD, PhD, team leader), Remi Noe (engineer student), Lubka Roumenina (PhD), Marie-Agnes Dragon-Durey (MD, PhD), Romain Paule (MD, M2 student), Shambhuprasad K Togarsimalemath (PhD student)*

***Diagnostic Lab**: Paula Vierra Martins (engineer), Anne-Marie Courchinoux (technician), Pauline Bordereau (technician), Fabienne Beury (technician), Stephanie Ngo (technician), Stephane Roncelin (technician), Marie-Agnes Dragon-Durey (deputy), Veronique Fremeaux-Bacchi (Head of Diagnostic Complement laboratory), Nelly Poulain (technician).*

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ANNOUNCMENTS - COMPLEMENT MEETINGS

THE ROYAL SOCIETY hosts the meeting '**Complement: Driver of inflammation and therapeutic target in diverse diseases**' in Buckinghamshire, UK, February 23/24 2015. For further information please see the meeting web page:

https://royalsociety.org/events/2015/02/complement-therapeutic/ or contact:

Professor B. Paul Morgan, Institute of Infection and Immunity, School of Medicine, Cardiff University; E-mail: MorganBP@cardiff.ac.uk

The **15th European Meeting on Complement in Human Disease (EMCHD)** will take place in Uppsala, Sweden, the 27th to 30th of June 2015. Abstract submission is open and the submission deadline is the 29th of January 2015.

For further information, please go to the meeting web page:

https://akkonferens.slu.se/emchd2015/

15th European Meeting on Complement in Human Disease

MEETING REPORT – ICW 2014 IN RIO DE JANEIRO

Below are summaries of the Plenary and Scientific sessions of the 25th ICW, composed by each session chairpersons. 'Second part' of the summaries will be published in the next Issue.

PLENARY SESSIONS

Plenary Session I: Hans J. Müller-Eberhard Memorial Lecture – Prof. Victor Nussenzweig *(Chair: Charlie Vogel, Hawaii, USA)*

The sixth Hans J. Müller-Eberhard Memorial Lecture was given by Victor Nussenzweig, MD, PhD, the Hermann M. Biggs Professor of Pathology at New York University, NY, USA, and Professor at the Universidade Federal de São Paulo, São Paulo, Brazil. Dr. Nussenzweig received his MD and PhD (in parasitology) from the University of São Paulo. After joining the faculty oft the University of São Paulo, and a postdoctoral fellowship at the Pasteur Institute in Paris, France, Dr. Nussenzweig joined the Department of Pathology at New York University in 1963, where he has remained a faculty member for 50 years. Since 2013, he has rejoined his alma mater and now splits his time between New York and São Paulo. In his lecture, entitled "Control of Complement Activation and the Malaria Parasite" Dr. Nussenzweig gave an overview of his two key scientific areas of expertise, the complement system and the malaria parasite *Plasmodium* and emphasized some of his key contributions to the fields. In a 1977 paper in the *Journal of Experimental Medicine*, he elegantly differentiated the roles of different C3 receptors in the mechanism of phagocytosis, while in the last two decades, he focused on developing a vaccine against malaria, based on the seminal observation of a sporozoite surface protein, described in a 1980 *Science* manuscript. The lecture proved scientifically stimulating and entertaining and attested to Dr. Nussenzweig's ongoing strong scientific vigor and conviction.

Plenary session II: Prof. Mauro Teixeira

(Chair: Carmen van den Berg, Cardiff, UK)

Prof. Mauro Teixeira from the Federal University of Minas Gerais (UFMG), Brazil, gave a seminar on therapeutic intervention targeting platelet activating factor (PAF) and C5a in various pathologies. Mauro studied Medicine at UFMG and subsequently went to London for PhD studies with Paul Hellewell (1992-1994). He remained in London for further 3 years as postdoctoral fellow at the London School of Tropical Hygiene and after his return to UFGM set up his own research group. His main research interests are the mechanism and control of infection (e.g. by trypanosomes, dengue and influenza) and inflammation and the role of chemokines, eosinophils and neutrophils in these processes. His interest also covers the complement system and he presented here on the role of PAF and C5a receptors in diseases. He showed that PAFR is an important mediator of inflammation and a potential target for therapeutic intervention. Importantly, PAFR activation has distinct biological effects: PAFR genetic deletion increased parasitemia and pathology by Trypanosoma Cruzi and Leishmania, suggesting a protective effect here but in animal models of Dengue fever, Influenza and Malaria, inhibition of PAFR function protected from pathology. Additional data presented suggest also that timing of PAFR activation is important. Prof. Teixeira then showed that C5a contributes to tissue-destructive inflammatory responses to Influenza: Influenza A increased C5a concentrations in bronchoalveolar lavage fluids. This could be reduced with the tick-derived inhibitor of C5 activation OMCI and yielded concomitant decrease in neutrophil and macrophage infiltration and lung injury. Also usage of a novel C5aR antagonist (DF2593) in mouse models of hypernociception reduced both mechanical and thermal hypernociception further supporting the key role of C5a as a therapeutic target.

Plenary session III: Prof. Ricardo Gazzinelli
(Chair: Sanjay Ram, Boston, USA)
Ricardo T. Gazzinelli is a professor of biochemistry and immunology at Universidade Federal de Minas Gerais, Brazil, and a senior investigator at Fundação Oswaldo Cruz, Brazil, as well as an adjunct professor at the University of Massachusetts Medical School, USA. His research focuses on the mechanisms by which the innate immune system mediates host resistance to infection with protozoan parasites. More recently, he and his group have investigated the role of Toll-like receptors and inflammasomes in malaria. In this engaging lecture, Prof. Gazzinelli discussed the key roles of innate immune receptors in immune surveillance by sensing *Plasmodium* spp. and initiating the protective immune responses. However, the innate immune system can also overreact to pathogens and mediate deleterious effects with specific clinical manifestations. In this lecture, he lectured on the role of immune-complexes in the systemic inflammation and pathogenesis in patients with acute malaria. He demonstrated that these immune complexes contain parasite DNA and activate NLRP3-, AIM2, and NLRP12-inflammasomes and induces the release of IL-1β and other proinflammatory cytokines through stimulation of a subset of $CD16^{+}CD14^{+}$ monocytes. This immune stimulation decreases after treatment of the acute infection. He finalized his session with a discussion on how these events mediate both host resistance to infection and the pathogenesis of malaria.

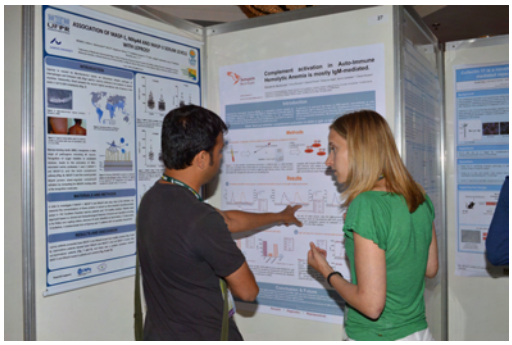
SCIENTIFIC SESSIONS
Session I: Complement in Host – Pathogen Interaction
(Chairs: T. Sakari Jokiranta, Helsinki, Finland and Peter F. Zipfel, Jena, Germany)
This session started with the Young Investigator Award Lecture from Suzan H. M. Rooijakkers from Utrecht, the Netherlands. Suzan Rooijakkers reported on the intriguing molecular interplay that *S. aureus* uses to intervene, control, and modulate host complement attack. She presented current data which reveal how efficiently this bacterium controls complement and pointed out particular novel interference with cellular response and modulation of the terminal pathway. E.T.M Berends (Abstract 139) from the same group in Utrecht summarized novel experimental approaches on C5 convertase formation and on the identification of docking sites on the C5 convertase complex relevant for microbial interference. A.K. Gautam (Abstract 140) from Arvind Sahus' group showed detailed structure function analyses of the viral complement evasion protein Kaposica and identified the protein modules and amino acids that mediate complement evasion by Kaposica. D. Stapels (Abstract 141) from Utrecht, the Netherlands, summarized novel data how the extracellular adherence protein (Eap) from *S. aureus* interferes with both the classical and lectin pathways. Eap blocked activation of C4 by binding to C4b and thereby competing with C2 and V. Agarwal (Abstract 142) from Anna Blom's group showed that phosphoglycerate kinase of *S. pneumoniae* is a moonlighting protein that controls the terminal complement pathway by binding to C5, C7, and C9. C. Schmidt (Abstract 152) together with the group of W.H. Tham from Melbourne, Australia, showed that Pf92 protein on merozoites of malaria parasite acquire the soluble complement regulator factor H to the cell surface leading to immune evasion, while A. Barrios (Abstract 148) showed related features for the parasitic helminth *E. granulosus*. The acellular laminated layer consisting of mucins and various proteins provides an interesting structure to study complement evasion and to identify relevant immune evasion proteins of this cestode. In summary, this session presented novel insight into the complex molecular interplay that microbial pathogens use to interfere with complement in all levels - and suggests that additional molecular aspects will be unraveled in the furture and give further insights of this complex ad important topic.

Session II: Complement Activation and Function
(Chairs: B. Paul Morgan, Cardiff, UK and Teizo Fujita, Fukushima, Japan)
The title of this session encompasses many things but to the considerable relief of the chairs, there was a clear theme and focus through the session. Four presentations considered the C3 convertase components and regulators, three described aspects of the lectin pathway, while one explored novel activities of the membrane attack complex. Paul Barlow from Edinburg University (Abstract 107) described a pneumococcal surface protein (PspCN) that binds Factor H (FH) with picomolar affinity through a site in SCRs 8-10. This binding site, unique to FH, is remote from the "active" regions of FH. PspCN locks FH in a novel "activated" conformation resulting in increased C3b and C3d binding and enhanced decay accelerating activity. PspCN thus represents a new bacterial evasion strategy, capturing a regulator but also enhancing its activity to facilitate survival. Elizabeth Rodriguez from Stephen Perkin's group (Abstract 110) analysed the transition from C3 to C3b using solution X-ray and neutron scattering and analytical ultracentrifugation of native and hydrolysed C3, C3b, C3c and C3d. Under low salt conditions, C3c and C3d were closely apposed in C3b, held together by a salt bridge and disrupted in high salt causing C3c and C3d to move apart. They pinpointed a mutation that disrupted the bridge causing loss of binding. The C3S/F polymorphism, a R80G change, will similarly impact the bridge, perhaps providing a structural explanation for published functional differences between variants. Ruodan Nan from the same group (Abstract 109) used similar structural tools to investigate FH-C3b structure. Crystal structures suggest that FH binding to C3b involves multiple sites of interaction. A solution structure-derived molecular model showed FH adopting an extended conformation overlaying C3b in a 1:1 complex with the major FH binding site residing in the C3d domain. Maiken Henriksen from Soren Hansen's lab (Abstact 103) reported that CL-K1 was purified from plasma with CL-L1, and that these complexes are associated with MASP-1/3 and MASP-2, resulting in activation of the lectin pathway. Steffen Thiel (Abstract 099) described the activation mechanism of the lectin pathway: oligometric forms of MBL carry a single MASP homodimer and intercomplex activation occurs between discrete MBL or ficolin/MASP complexes. Minoru Takahashi (Abstract 184) from Teizo Fujita's group analysed the activation of proDf using two sera of 3MC syndrome: one has neither MASP-1 nor MASP-3 and another has MASP-1 but not MASP-3. Both sera show neither alternative pathway nor proDf activation, demonstrating clearly that MASP-3 is responsible for the proDf activation. Finally, Michal Lusthaus from the Fishelson lab (Abstract 102) explored similarities between MAC- and TNF-induced cell killing: TNF activates receptor-activated protein kinases 1 and 3 (RIP1; RIP3) to trigger cell death. RIP3 inhibition rendered cells resistant to MAC killing and MAC formation triggered rapid association of RIP1 and RIP3, an essential step in RIP-mediated cell death. The data suggest a novel mechanism of MAC-triggered cell death distinct from the "traditional" view of pore-induced lytic killing.

Session III: Complement and Disease I
(Chairs: Andrea Tenner, Irvine, USA and Veronique Fremeaux-Bacchi, Paris, France)
This session focussed on the regulation of complement activation in tissue. DAF is one of the most critical membrane complement regulators in humans and studies in DAF-deficient mice have revealed considerable insight into the mechanism for anti-FH autoantibody induced aHUS. Wenhhao Song's group (Abstract 053) reported here that renal disease induced by a murine anti-FH CCP20 autoantibody was dependent on C3, Factor B, Factor D, C5a receptor 1 (C5aR1) and Fc receptor but not on C4, C3a receptor or C6. However, when alternative pathway amplification was uncontrolled in acute renal injury in DAF-deficient mice, the murine anti FH antibody injury was mediated by the membrane attack complex independent of C5aR.

The data presented by Joshua Thurman (Abstact 045) showed that IgM deposition in the kidney contributes to pathogenicity and severity of glomerulopathy. The authors used $FH^{-/-}$ mice with and without B cells (ie. with or without IgM) and demonstrated that natural IgM binds to injured glomeruli in this model of C3 glomerulopathy and that B cell-deficient mice were protected from renal damage. Veronique Fremeaux-Bacchi (Abstract 036) described different types of large deletions and gene conversion events identified in the French atypical Hemolytic Uremic Syndrome. After a summary of already published non-allelic homologous recombination between CFH and CFHR1 genes, new pathogenic gene conversion resulting from the transfer of genetic information between CFH and CFR1 functional genes were described.

David Tran from Wuding Zhou's group in London (Abstract 29) demonstrated that ischemia reperfusion damage in the kidney requires collectin-11, an activator of the lectin complement pathway. They showed that collectin-11 is expressed by, and can bind to, stressed kidney epithelia, and that the binding of collectin-11 activates complement in the presence of serum in a MASP2-dependent fashion. Mutants of the ARMS2 gene that lower expression of this protein have been associated with age-related macular degeneration (AMD). Christine Skerka (Abstract 015) presented evidence that ARMS2 was synthesized and secreted by macrophages and microglial cells and that this protein binds to late apoptotic and necrotic cells, recruits properdin and enhances the deposition of C3b and subsequent clearance dying cells by phagocytes. Finally, Hayley Lavender from Chris Tang's group (Abstract 146) presented data in which *N. meningitides* serum sensitivity was increased upon the addition of complement Factor H (CFH)3, which they showed competes with CFH for binding to the bacterial surface lipoprotein, fHbp, and antagonizes the C' regulatory activity of CFH. Variants of fHbp with increased affinity for CFH3 showed lower survival in serum, implicating a role for host genetic variability (via CFH3 levels or function) in susceptibility to this infection.



COMPLEMENT REAGENT RESOURCES