Dear Readers,

Welcome to the September 2017 issue of ‘Focus on Complement’. This 47th issue of FoC contains the following:

- Joshua Thurman reviews publications for the News Flash describing evidence for complement factor H related proteins in IgA nephropathy, and results from a Phase II trial of a C5aR antagonist in ANCA-associated vasculitis.

- The Complement research teams around the world series featuring Dr Peter Heeger in New York, as well as Dr Richard Smith, in Iowa, USA.

- Two news items regarding the American Association of Immunology (AAI) annual meetings, and a SUNY complement meeting report.

- Three upcoming complement meeting announcements.

If you would like to contribute with an article to a future issue or have suggestions for a subject theme, please contact Trent Woodruff (t.woodruff@uq.edu.au) or Michael Holers (Michael.Holers@ucdenver.edu).
NEWS FLASH (reported by Dr. Joshua Thurman, USA)

News Flash 1:


Although the function of the factor H related proteins (FHRs) is still under intense investigation, experiments have shown that FHRs 1 and 5 can competitively inhibit factor H from regulating the alternative pathway on tissue surfaces. Mutations in the FHRs may increase the potency of the FHRs to compete with factor H and cause complement dysregulation, but normal variations in the levels of these proteins may also contribute to the risk of disease. IgA nephropathy is a kidney disease characterized by complement activation within the kidney, and genome wide association studies have previously found that deletion of FHRs 1 and 3 are associated with protection against IgA nephropathy. Two groups recently examined whether the converse is true – whether increased levels of FHR1 would increase the risk of developing the disease. Both groups found that FHR1 levels are higher in IgA nephropathy patients with two CFHR1 alleles than in healthy control subjects with two CHFR1 alleles. In both studies, elevated FHR1 levels were also associated with indicators of disease severity or the increased rate of disease progression. Interestingly, a decline in kidney function seemed to increase FHR1 levels, possibly causing a feedback loop whereby a loss of kidney function could reduce alternative pathway regulation and lead to further kidney injury. This may also be a mechanism by which a decrease in kidney function could exacerbate other alternative pathway-mediated diseases. Deletion of the CFHR1 gene is protective for age-related macular degeneration (AMD), for example. Patients with AMD and decreased kidney function may have higher FHR1 levels in the plasma than patients with normal kidney function. Such an effect could link kidney disease with accelerated retinal injury, although this has not yet been studied.
News Flash 2:

Randomized Trial of C5a Receptor Inhibitor Avacopan in ANCA-Associated Vasculitis.

Complement activation contributes to the pathogenesis of dozens of different diseases, but therapeutic complement inhibition is still used in only a relatively small number of patients. Eculizumab has been approved for the treatment of paroxysmal nocturnal hemoglobinuria and for atypical hemolytic uremic syndrome, both of which are very rare diseases. Additional complement inhibitory drugs are currently in clinical development, however, and the efficacy of these drugs is being tested in new diseases. Jayne et al. recently published the results of a Phase II randomized, placebo-controlled trial of avacopan, a C5a receptor antagonist, in ANCA-associated vasculitis. The study enrolled and randomized 61 patients. The three different treatment protocols were cyclophosphamide or rituximab plus: 1) placebo and high dose corticosteroids, 2) reduced dose corticosteroids plus avacopan, or 3) avacopan without corticosteroids. The patients were treated with the study drug for 12 weeks, and were then followed for an additional 12 weeks off the medication. Treatment response was evaluated using clinical activity scores, and the response rates for the three treatment groups at the end of 12 weeks were 70, 86, and 81%, respectively. The study was designed as a noninferiority trial. Based on the results, the authors concluded that treatment with avacopan is noninferior to treatment with the standard, steroid-containing regimen. Of note, though, patients that received avacopan responded more quickly than patients in the corticosteroid-only group. The rate of adverse events was similar in each group, and one patient in each group developed a severe infection. Interestingly, patients that received avacopan without corticosteroids had a higher rate of lymphopenia. This finding may have been caused by the drug. The authors noted, though, that it is also possible that the lymphopenia was caused by cyclophosphamide or rituximab, but that lymphopenia was masked in patients who received corticosteroids. Corticosteroids are associated with a wide range of different side effects, and quality of life scores were significantly better in the steroid-free group than in the high dose steroid group. Based on the results of this study, complement inhibitors appear to be an effective treatment for ANCA vasculitis, and they may also allow clinicians to reduce the use of corticosteroids in this and other inflammatory diseases.
Focus on Complement

COMPLEMENT TEAMS AROUND THE WORLD

Complement Research in New York, USA: The team of Dr. Peter Heeger

Dr. Heeger’s research group has been continuously funded through the National Institutes of Health for >20 years in the field of basic and translational transplantation immunobiology. He currently leads an international multicenter consortium, Clinical Trials in Organ Transplantation, which is conducting clinical trials to assess the utility of noninvasive biomarkers to predict outcomes and guide treatment strategies in transplant recipients. The lab’s basic science research interests involve mechanisms of allograft injury and tolerance, focusing on interactions between the complement system and T lymphocytes. In conjunction with collaborators the work demonstrated that a) cognate interactions between T cells and antigen presenting cells (both human and mouse) cause production of alternative pathway complement components, b) cell surface downregulation of decay accelerating factor (DAF/CD55) permits the immune cell-derived complement to activate locally yielding C3a and C5a, and c) these anaphylatoxins ligate their receptors on both interacting partners (paracrine and autocrine), together inducing effector T cell activation, promoting effector T cell differentiation. The same mechanisms simultaneously and locally inhibit induction and function of regulatory T cells. C3aR/C5aR absence or blockade limits effector T cell expansion and promotes regulatory T cells, thereby shifting the immune balance away from potent effector immune and toward immune tolerance. The effects apply in vivo in the contexts of organ transplantation, graft versus host disease, autoimmunity (experimental allergic encephalomyelitis, autoimmune diabetes) and pathogen induced immune responses. Work published in 2017 additionally showed that Toll-like receptor initiated activation of antigen presenting cells, required for optimal T cell activation, is dependent upon immune cell-derived complement. Together with ongoing work by other laboratories, the data support the conclusion that the immune cell derived complement functions independent of serum complement to crucially regulate adaptive T cell immune responses in mice and humans.

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Complement Research in Iowa, USA: The team of Dr. Richard Smith

Research and development in Molecular Otolaryngology and Renal Research Laboratories (MORL) at University of Iowa focuses on two ultra-rare complement-mediated renal diseases, C3 glomerulopathy (C3G) and atypical hemolytic uremic syndrome (aHUS). Each disease affects about 1-2 persons per million.

The overarching goal of the MORL is to improve the care of these patients through two initiatives. First, we complete cutting-edge diagnostic studies in patients to quantitate the degree and type of complement deregulation; identify autoantibodies that function as acquired drivers of disease; and screen complement genes for pathogenic/likely pathogenic genetic variants. Collectively, these tests allow us to provide to clinicians a comprehensive picture of the degree of the complement deregulation in their patients.

Second, we target research efforts to refine our understanding of the underlying disease pathophysiology. Examples include whole exome sequencing to look at rare and novel variant load at the gene and pathway level; studies of complement activity and control in the microenvironment of the glycalyx and the glomerular endocapillary pore; long-range sequencing to interrogate complex genomic regions like the CFHR family cluster; molecular modeling to refine our understanding of missense genetic variants and the role of small molecules as complement inhibitors; and gene therapy studies to identify novel treatment opportunities to cure these diseases.

Our complement journey started more than two decades ago, although it was not until 2008 that the MORL formally launched clinically validated functional studies using patient serum and plasma. Currently, we offer an extremely comprehensive autoantibody panel that includes testing for factor H autoantibodies, factor B autoantibodies, C3 nephritic factors, C4 nephritic factors and C5 nephritic factors, among others. We have also established multiple assays to measure levels of complement proteins and their split products, which has allowed us to define unique and disease-specific complement ‘signatures’. For example, DDD and C3GN, the two signature types of C3G, have commonalities but also differences that enable us to identify one from the other and determine where along the complement cascade the deregulation is occurring.

Our genetic studies have skyrocketed. No longer constrained by the limitations of Sanger sequencing, we have developed a variety of targeted genetic panels for clinical and research use; we have validated multiplex ligation-dependent probe amplification over the complete CFH-CFHR region; we have developed long-range sequencing methods for difficult-to-sequence regions; and we have completed whole exome and whole genome sequencing on a large number of patients.

To improve the clinical care of patients, a large multidisciplinary team of MORL scientists and clinicians meets weekly (Renal Group Meeting) to assist clinicians in the care of their patients by reviewing genetic and functional data in the context of each patient’s phenotype. As different complement-targeting strategies emerge, the MORL has also established itself as a leader in the development of complement-targeted therapeutics by collaborating with other investigators, small startups, and large pharmaceutical companies.
The MORL is proud of its unique resources (either in vitro or in vivo) that have allowed us to work closely with clinicians to improve patient care, advance our understanding of these diseases, and work with industry to meet requirements for preclinical drug development.

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SUNY attracts complement to Buffalo.

The State University of New York (SUNY) ‘conversations in disciplines’ grant awarded to Jessy Alexander and Stephan Judex brought together SUNY and other local complementologists to bring awareness to the new directions the field of complementology was taking. The meeting began with opening remarks by Anne Curtis, Charles and Mary Bauer Professor and Chair & SUNY Distinguished Professor followed by ICS past president Prof Andrea Tenner, plenary speaker, who gave an overview of where the complement field was headed, its intricacies, complexities and novelties. Julia Koeppe presented data on the interactions of complement C3 with thrombomodulin, a protein which is best known for its regulatory role in blood clotting using hydrogen/deuterium exchange mass spectrometry (HDXMS) and fluorescence spectroscopy, while Sriram Neelamegham using bioengineering approaches presented studies on the role of complement and VWF in regulation of blood cell and vascular endothelial cell function. Ming Zhang demonstrated the role of C3 in myocardial necrosis during ischemia reperfusion injury, a setting where C3 migrates intracellularly and determines the fate of the cell. Jessy Alexander revealed the role of macrophages and complement in factor H mediated glomerulonephritis while Janmeet Saini reported that hiPSC-derived RPE cells from AMD donors show significantly increased complement and inflammatory factors, and that nicotinamide (NAM) inhibited the increased complement levels ameliorating the pathology. That gC1qR is key for cell proliferation especially in a cancer setting was revealed by Berhane Ghebrehiwet, while Supriya Mahajan introduced us to the role of complement in HIV brain. Christoph Licht gave an update on the diagnosis and management of aHUS in the clinic, while Lori Morton discussed the close alignment of academia and pharma and gave an insight into the process. Richard Quigg closed the meeting and thanked the attendees. Although the meeting ended, the effects continue with the beginning of new collaborations and the renewal of existing ones.

L to R: Jessy Alexander, Anne Curtis, Berhane Ghebrehiwet, Richard Quigg, Supriya Mahajan, Andrea Tenner, James Jarvis, Julia Koeppe, Janmeet Saini, Lori Morton, Christoph Licht, Ming Zhang, Lee Chaves.
The American Association of Immunology (AAI) annual meeting

The American Association of Immunology (AAI) annual meeting is one of the most important events under the aegis of the AAI. It is important to the community of members and the field at large. During the last annual meeting (IMMUNOLOGY 2017™) over 2,000 abstracts were submitted and there were ~4,000 attendees. The AAI annual meeting is the largest gathering of immunologists held annually world-wide. ICS Board member, Dr. Viviana Ferreira, was recently appointed to serve on the AAI Program Committee for a term of three years. This committee fulfills the very important role of setting the scientific tone of each year’s meeting and meets once a year during the annual meeting (held in Spring). During this meeting, the committee selects three Distinguished Lecturers, eight Major Symposia topics and corresponding chairs, and considers any special sessions or themes that may be especially timely. To this end, the group reviews recent annual meeting trends regarding topics represented, suggests chairs and speakers, considers opportunities for new and young investigators and underrepresented scientists, and more. This helps ensure that the annual meeting continues to flourish in terms of representing the field comprehensively, showcasing the finest and most cutting-edge science, and offering attendees the best possible value - professionally and socially. Please go to http://www.aai.org/About/Committees/Program to view the current composition of the committee. ICS members are encouraged to contact Dr. Ferreira (viviana.ferreira@utoledo.edu) with suggestions on how to promote the complement field and the ICS in the context of the AAI meetings.

ANNOUNCEMENTS

On behalf of the organizing committee, Professor Peter Garred invites members of the complement community and beyond to the 17th European Meeting on Complement in Human Disease. The meeting will take place in Copenhagen, Denmark from September 8th to 12th 2017. For the final program, accommodation and travel information, please see http://emchd2017.dk
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DATE CLAIMER: SEPT 16-20, 2018; 27th INTERNATIONAL COMPLEMENT WORKSHOP

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