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Illuminating the latest advances in innate immunity on the island of the sun god

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The latest Aegean Conferences workshop on innate immunity (Rhodes, Greece) discussed recent developments that suggest that innate immune mechanisms are not restricted to providing first-line defense or instructing the development of adaptive immunity, but additionally permeate and influence diverse physiological and homeostatic processes.

Helios (Greek for ‘sun’) was worshipped as a god by the Ancient Greeks, especially in Rhodes. As the god of light, Helios saw and knew everything and is identified with Phoebus (‘Shining’) Apollo, who signified intellect and rationality. The Aegean island of Rhodes was the location of the 7th International Aegean Conference on Innate Immunity (4–9 July 2010), where leading scientists from all over the world gathered to illuminate the latest developments in the field.

Innate immunity came into the spotlight when its instructive role in the initiation of the adaptive immune response was established in the late 1990s/early 2000s [1]. This coincided with the 1st International Aegean Conference on Innate Immunity (Santorini, Greece, 11–15 October 2000). Since then, continuous progress in the field has led to the understanding that innate immune mechanisms additionally permeate and influence diverse physiological processes, such as synapse maturation in the CNS, angiogenesis, mobilization of hematopoietic stem/progenitor cells, tissue regeneration and lipid metabolism [2]. Not surprisingly, therefore, deregulation in the sensing or effector functions of innate immunity can lead to pathological disorders that are not necessarily or directly related to host defense against infection or other types of insult. The workshop covered these emerging concepts, both at the basic and applied/translational level. The topics discussed included Toll-like receptors (TLRs) and other pattern-recognition receptors, complement and its crosstalk with other physiological systems,

inflammatory mechanisms and diseases, natural killer (NK) cells, innate–adaptive interactions and host–pathogen interactions.

Pattern recognition, TLRs & downstream signaling & functions

Our understanding of pattern recognition as a mechanism of innate immune sensing continues to grow as more receptors and ligands are identified and the associated signaling pathways become elucidated. Of equal importance is the role of pattern-recognition molecules in physiological and pathophysiological conditions. Alberto Mantovani (Istituto Clinico Humanitas, Milan, Italy) reviewed recent studies from his laboratory showing that pentraxin 3 (PTX3) is a versatile soluble pathogen-recognition molecule that mediates between the soluble and cellular arms of innate immunity. Produced upon TLR stimulation, PTX3 binds complement components, cell adhesion molecules and selected microbes. This allows PTX3 to regulate complement activation, control neutrophil trafficking and promote innate immunity against infection. C1q and the mannose-binding lectin (MBL) are important complement components with a major role in apoptotic cell clearance. Recent evidence presented by Andrea Tenner (University of California, Irvine, CA, USA), shows that both C1q and MBL, independently of complement activation, can bind to and promote the clearance of oxidized and acetylated low-density lipoprotein. Pulmonary collectins protect the lungs from a variety of insults. In

this context, Francis McCormack (University of Cincinnati, OH, USA) showed that administration of keratinocyte growth factor upregulates the alveolar levels of collectins (surfactant proteins A and D) and promotes the clearance of lung pathogens such as *Pseudomonas aeruginosa*. Gerardo Vasta (University of Maryland Biotechnology Institute, MD, USA) talked about the F-type lectins (found in invertebrate and vertebrate species) and their roles in innate immune recognition and other biological processes, including fertilization.

Terje Espevik (Norwegian University of Science and Technology, Trondheim, Norway) presented evidence that phagosome-associated TLR4 is actually recruited from the endocytic recycling compartment, rather than from the cell membrane as previously thought. This TLR4 trafficking mechanism is moreover essential for the induction of IFN- β production. Steve Gerondakis (Burnet Institute, Melbourne, Australia) presented a bioinformatics analysis of how NF- κ B and ERK-dependent gene expression is coordinated in response to TLR4 signaling. Patricia Fitzgerald-Bocarsly (New Jersey Medical School, NJ, USA) described a mechanism whereby plasmacytoid dendritic cells internalize cell-free or cell-associated viral antigens to endosomally located TLRs, which signal for IFN- α production; in this process, TLR9 plays an important role in signaling but not in the uptake of viral antigens.

Pattern-recognition molecules are also involved in the pathogenesis of inflammatory diseases and are thus targeted for therapeutic intervention. MBL was previously implicated as the initiator of complement activation following reperfusion of ischemic organs. Now studies by Gregory Stahl (Harvard Medical School, MA, USA) implicate MBL in the setting of acute hyperglycemia and diabetes, and MBL inhibition may provide an approach to prevent this disease. Tom Mollnes (University of Oslo, Oslo, Norway) presented data indicating that antibody neutralization of CD14 has a stronger anti-inflammatory effect than inhibition of the TLR4-associated MD-2 in a whole human blood model of *Escherichia coli*-induced sepsis.

Complement crosstalk interactions in health & disease

Besides its traditional role in tagging and eliminating pathogens, complement is increasingly recognized as participating in or controlling diverse immune and other physiological processes [2]. John Lambris (University of Pennsylvania, PA, USA) presented findings from a multidisciplinary approach, which support the concept that complement has versatile roles in inflammatory, developmental and homeostatic processes. Emphasis was given to the ability of complement components to crosstalk with coagulation and TLR systems, whereas deregulation of these finely tuned interactions leads to immunopathology. This in turn renders the complement system an appropriate target for therapeutic intervention against a variety of diseases. Bo Nilsson (Uppsala University, Uppsala, Sweden) discussed recent developments regarding the interplay between complement and platelet activation, and presented a complement activation mechanism induced by platelet-derived chondroitin sulfate. The role of complement in hematopoietic stem/progenitor cell

mobilization was substantiated by recent findings implicating C5 cleavage fragments and the terminal complement pathway in this process (Marius Ratajczak; University of Louisville, KY, USA). A mechanism for complement activation after severe tissue injury was presented by Marcus Huber-Lang (Ulm University, Ulm, Germany). Specifically, severe tissue injury activates the factor VII-activating protease, which in turn cleaves C3 and C5, leading to the generation of functional C3a and C5a. A new role was identified for C5a, which negatively regulates IL-17A in macrophages (Peter Ward, University of Michigan, MI, USA); mice deficient in C5a receptors (C5aR and C5L2) generate higher levels of IL-17A in lipopolysaccharide/TLR4-induced sepsis and consequently display higher mortality than wild-type controls. The crosstalk interactions of complement with other signaling pathways do not simply serve physiological functions but may also be exploited by pathogens to subvert immunity. In this regard, a novel crosstalk mechanism between C5a receptor and TLR2 was described by George Hajishengallis (University of Louisville, KY, USA), which is instigated by bacteria and undermines the ability of macrophages to clear infections. Peter Zipfel (Hans Knoell Institute, Jena, Germany) discussed the importance of complement regulation for proper innate immune responses against pathogens and for the prevention of immunopathology (e.g., hemolytic uremic syndrome and age-related macular degeneration). However, although the alternative pathway has been implicated in age-related macular degeneration, the same pathway appears to be protective in retinopathy by promoting the resolution of neovascular tufts (Kip Connor; Harvard Medical School).

The findings from these presentations further support the notion that complement is a reasonable target for therapeutic intervention against a variety of diseases. C3 inhibition using the drug compstatin in a baboon model of *E. coli*-induced sepsis inhibited the proinflammatory and procoagulant response and protected against organ damage (Florea Lupu; University of Oklahoma Health Sciences Center, OK, USA). Complement drug discovery is facilitated by the latest advances in the structure, dynamics and binding characteristics of complement components. Federico Forneris (University of Utrecht, Utrecht, The Netherlands) presented the crystal structure of the pro-convertase of the alternative pathway (C3bB) in complex with factor D, which provides useful information for potential structure-based drug design for complement inhibitors. Daniel Ricklin (University of Pennsylvania, PA, USA) discussed the significance of structural and biophysical studies to characterize the interaction of complement with bacterial complement inhibitors, such as the extracellular fibrinogen-binding protein of *Staphylococcus aureus*, which is the first identified allosteric complement inhibitor. Brian Geisbrecht (University of Missouri–Kansas City, MO, USA) presented structure–function studies on the C3b-binding interactions of *Staphylococcal* complement inhibitor, which provide useful templates for the design of novel complement-targeted therapeutics. *S. aureus* also secretes a C5- and IgA-binding protein (termed SSL7) which is thought to block both C5a-induced neutrophil chemotaxis and Fc α receptor I-mediated phagocytosis. A 3D structural model of SSL7-C5-IgA-Fc was

presented by Paul Ramsland (Burnet Institute, Melbourne, Australia) suggesting how a virulence factor can act as a blocking bridge between innate and adaptive immunity.

Dendritic cells, NK cells & innate–adaptive crosstalk

It is now firmly established that innate immune cells do not work by simply buying the host time before adaptive immunity kicks in. Rather, they are also involved in sophisticated interactions that initiate and regulate the adaptive response. As a consequence, deregulation of this finely balanced innate–adaptive crosstalk may have a negative impact on homeostasis. Jörg Köhl (University of Lübeck, Lübeck, Germany) described how anaphylatoxins regulate T helper differentiation by acting on antigen-presenting cells either autonomously or through crosstalk with TLRs. He also presented recent evidence that C5aR signaling on macrophages, but not dendritic cells (DCs), promotes Th17 development and the induction of autoimmune arthritis. Matyas Sandor (University of Wisconsin–Madison, WI, USA) described how DCs survey chronic mycobacterial granulomas and interact with T cells to induce local tolerance but also systemic immunity. Zsuzsanna Fabry (University of Wisconsin–Madison) presented evidence for a major role of brain DCs in regulating inflammatory T-cell recruitment in the CNS and the development of experimental autoimmune encephalitis. Alessandro Moretta (University of Genova, Genova, Italy) described how NK cells respond to environmental stimuli to shape and regulate T-helper responses, whereas Michael Caligiuri (Ohio State University, OH, USA) and Christian Munz (University of Zurich, Zurich, Switzerland) discussed how DCs regulate NK cell function in mucosal surfaces. Ana Angulo (Institut d'Investigacions Biomediques August Pi i Sunyer, Barcelona, Spain) discussed recent developments concerning the role of NK cells against cytomegalovirus infection and how this pathogen may be evading the NK response. Lorenzo Moretta (University of Genova) focused on NK exploitation to cure high-risk leukemias. *KIR* genes interact with HLA class I molecules to regulate NK cell activation. John Trowsdale (University of Cambridge, Cambridge, UK) presented a high-throughput KIR typing system for investigating polymorphic HLA/KIR combinations and their role in disease.

Inflammatory diseases

George Kollias (B.S.R.C. 'Alexander Fleming', Vari, Greece) presented recent studies that suggest that synovial fibroblasts, far from being secondary effectors, are actually instrumental in the pathogenesis of rheumatoid arthritis, even in the absence of professional inflammatory cells or an adaptive immune response. In this regard, synovial fibroblasts can initiate the pathologic cascade by sensing triggers such as TLR ligands. Youhai Chen (University of Pennsylvania) showed evidence for member-specific functions of NF- κ B proteins and suggested that targeted inhibition of Rel alone was sufficient to mitigate autoimmune encephalitis. Xiaoxia Li (Cleveland Clinic Foundation, OH, USA) outlined a novel signaling mechanism for IL-17-induced autoimmune encephalitis dependent upon the E3 ligase Act1. An integrated view of how neutrophil-expressed Fc γ receptor IIA, C5aR and lymphocyte function-associated antigen-1 may interact to promote rheumatoid

arthritis was proposed by Naotake Tsuboi (Harvard Medical School). Hydar Ali (University of Pennsylvania) identified the presence of mas-related gene (Mrg) receptors (MrgX2 and MrgX4) in human mast cells and showed data suggesting that these receptors may contribute to innate immunity as well as modulating allergic and inflammatory responses. Laura Sepp-Lorenzino (Merck research laboratories, PA, USA) discussed siRNAs as a potential therapeutic modality after their encapsulation into liposomal nanoparticles. Current efforts are focusing on improving delivery efficiency while reducing potential toxicity. Janet Read (Potter Anderson & Corroon LLP, DE, USA) talked about the necessity of patenting and commercializing academic inventions.

Host–pathogen interactions

The session included studies on innate host–pathogen interactions in both mammalian and lower organism models. Elizabeth Grice (NIH, MD, USA) presented her work to characterize microbial communities in healthy skin and chronic diabetic wounds and to integrate the microbiome with the host transcriptional response. These studies may serve as a basis for understanding the role of microbiota in disease and have the potential for developing novel drugs and treatments. Jennifer van Velkinburgh (National Center for Genome Resources, NM, USA) presented an omics-based study that identified a distinct transcriptional response in sepsis survivors and sepsis death. Sepsis patients who go on to die display decreased transcription of 1326 genes in the blood, including genes for neutrophil recruitment, oxidative burst, immune response and inflammation resolution. A novel pore-forming protein, perforin-2, which kills invasive intracellular bacteria, was presented by Ekhard Podack (University of Miami, FL, USA). George Christophides (Imperial College, London, UK) described a mosquito defense machinery in the hemolymph (blood) that is equivalent to the vertebrate complement. Although the mechanisms of complement activation in the mosquito complement display substantial differences from complement activation in vertebrates, the effector functions appear to be similar and range from phagocytosis to lysis of pathogenic intruders. Beatriz Novoa (Instituto de Investigaciones Marinas, Vigo, Spain) presented a zebrafish model to study septic shock and lipopolysaccharide tolerance. Microarray analysis revealed similarities with the transcriptional response in mammalian sepsis; strikingly, chemokine (C-X-C motif) receptor 4 was shown to downregulate TLR responses, as previously shown in mouse and human cells [3]. Goutam Gupta (Los Alamos National Laboratory, NM, USA) described specific examples of transgenic plants that express innate defense molecules that can provide resistance against plant pathogens like *Xylella fastidiosa*.

At the meeting, ten Young Investigator Presentation Awards were presented to Andriani Daskalaki (Max Planck Institute for Molecular Genetics, Berlin, Germany), Brandon Garcia (University of Missouri, MO, USA), Elizabeth Grice (NIH, MD, USA), Praveen Papareddy (Lund University, Lund, Sweden), Jayme Souza-Neton (Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA), Andas Spaan (University of Utrecht), Yani Kaconis (Leibniz-Center for Medicine and Biosciences, Borstel, Germany), Federico Forneris (University

of Utrecht), Daniel Ricklin (University of Pennsylvania) and Jennifer Van Velkinburgh (National Center for Genome Resources, NM, USA).

The conference concluded with a tribute to another Greek deity, Dionysus the god of wine and dance, who complemented and balanced Apollo's intellect and rationality in the Greek world. The meeting succeeded in bringing together scientists and engaging them in informal discussions and exchange of ideas, and was renewed for June 15–20 2011 in Chania, Crete.

Information resources

- Aegean conferences: www.aegeanconferences.org

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- University of Louisville: Oral health and systemic disease research group: <http://research.louisville.edu/oralhealth/george>
 - John D Lambris, PhD: www.lambris.com

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