A Publication of the International Endotoxin and Innate Immunity Society

ENDOTOXIN NEWSLETTER

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IEIIS - INTERNATIONAL ENDOTOXIN & INNATE IMMUNITY SOCIETY

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A Letter from the IEIIS President

Dear IEIIS Members,

Another year is coming to an end and I hope everyone had a productive and joyous 2017. I know some of you have been concerned about research grants (I certainly have been myself), and I am crossing my fingers for better times in 2018. Let us hope that everyone gets to their senses and doubles the research funding available for the next year!

2018 is lining up to be a good year society-wise. We have our biennial meeting in Arizona USA October 14-16, and I am looking forward to seeing many of you in person there. The meetings are a key component of society life and help people to stay in touch. Many members have long-term friendships and collaborations, and new ones to be made. As you know, the 2018 meeting is joint with SLB. The program that has been put together reflect interests from both societies, and some new topics, and the organizers (David Underhill, Darren Lee and myself) hope there is something in the program for everyone. There is a substantial registration discount for IEIIS members, so please register as a member! Membership (now on a 2-year basis) will instantly pay off. Please see more info on the IEIIS web site at www.IEIIS.org

Sheraton Grand at Wild Horse Pass Resort
Chandler, Arizona USA

These newsletters are also an important component of IEIIS. We are aiming for new issues in the next year. Our new newsletter editor, Jason Barker; and also Nancy Pollman are contributing with time and energy towards newsletters, kudos to them. Note that we have included summaries of recent articles of interest to the community, written by various Society councilors. Let us know what you think of it.

In new issues of the newsletters we also hope to have focus on some of the IEIIS members. If you want to write a short piece about a particular member, please let Jason and me know.

2017 was a biennial meeting off-year, but we were involved in some activities, including the Tollerant event in Italy (see page 7 in the newsletter) and Innate Immunity Day at UMass. I am hoping we can have more of these events going forward in meeting off-years as this is important to keep the society vibrant each year!

Otto Holst also has some info with regard to our great journal *Innate Immunity*, which is now open access (with reduced publishing fee for IEIIS members).

I am hoping to see all of you in Arizona in October!
Happy holidays and all the best wishes
for the new year.

Best regards,

Egil Lien
IEIIS President 2016-2018

Inside this issue:

IEIIS/SLB Joint Meeting 2018

by Egil Lien

Myeloid Cells: Development, Environment and Inflammation

Chairs: David Underhill (IEIIS/SLB), Darren Lee (SLB), Egil Lien (IEIIS)

We are excited to present the 15th biennial IEIIS meeting and 51st annual SLB meeting in a beautiful Southwestern US setting, a short travel (20-30 minutes) from Phoenix. This is the 4th time IEIIS and SLB (Society for Leukocyte Biology) join forces – past joint meetings (2006, 2010, 2014) have been very successful.

We are assembling a great program. Proposed session topics include: Inflammation and cell death in host-pathogen interactions; Myeloid cell development, differentiation and novel functions; Ligands of Innate Immunity: structure and function; Metabolism and physiology in inflammation; Best of JLB and Innate Immunity; Neutrophils and phaogocyte functions; Metabolism and Physiology in inflammation; Leukocytes in immune privilege sites; inflammatory signaling; host receptors and microbes; the Microbiome in inflammation and immunity. There are also some pre-meeting sessions October 13 that are interesting.

October 14-16, 2018

The Sheraton Grand at Wild Horse Pass, Chandler, Arizona USA

SAVE THE DATES!

Confirmed speakers include: Sergio Grinstein, Stefanie Vogel, David Underhill, Darren Lee, Mary Dinauer, Lee-Ann Allen, Janelle Ayres, Daniel McVicar, Neal Silverman, Ilhem Messaoudi, Otto Holst, Helen Goodridge, Bob Ernst, Ken Murphy, Jessica Hamerman, Eric Perlman, Jon Kagan, Ed Miao, Neal Silverman, Yan Shi, Kensuke Miyake, Trude Flo, Julie Blander, Egil Lien, Gabriel Nunez, Dawn Bowdish.

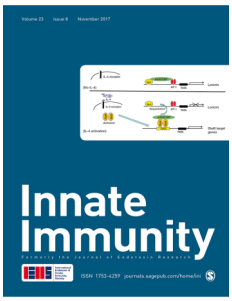
There are plenty of opportunities for presenting your work! We will have plenary sessions, break-out sessions, selected oral presentations from abstracts, award presentations, and of course plenty of time for networking and ▲

Innate Immunity Converts to Open Access

Otto Holst,
Editor-in-Chief

Innate Immunity will convert to open access publication from January 2018.
With that, there will be a number of benefits introduced to authors and IEIIS members, like:

- No author page charges
- Different access options which enable universal free access to all papers published in the journal
- An Article Processing Charge (APC) of $1,800 payable on acceptance
- 20% Discount on the APC for IEIIS members
- An initial introductory APC of 50% ($900) in 2018
- APC waivers for authors in low-income countries
- Authors will be offered a Creative Commons Licensing agreement (they retain full copyright, and have more control over rights to distribute and re-use their material)



Changing the journal to open access will neither affect the editorial policy nor the quality of the journal. Innate Immunity will still be run by the current editorial team, ensuring strict peer-review and high ethical standards, plus fast speeds to first decision. Free color online will continuously be offered. Authors will for sure benefit from open access publication resulting in high visibility and exposure.

We look forward to receiving your valuable manuscripts!

Renew Your Membership Now!

https://www.ieiis.org/Membership%20subscription

IEIIS members are entitled to a 20% reduced article processing rate for the society's official journal *Innate Immunity* as well as a discounted registration rate to attend the society's highly-regarded biennial international scientific and business meeting. The meeting sites alternate between the USA, Japan, and Europe, providing international opportunities for scientific interaction with researchers in wide-ranging and related areas of work.

Other benefits of membership include:

- **Joining a network of experienced scientists who can give advice and help on project and career issues/development**
- **Speaking/presenting at internationally attended meetings**
  (2018 meeting joint with SLB: October 14-16, Arizona, USA)
- **New 2-year discounted membership rate**
- **Involvement in smaller meetings during main meeting off-years**
  A unique opportunity for trainees, and young and mid-level investigators to meet with highly accomplished scientists whose seminal discoveries underpin the fields of endotoxin biology and innate immunity
- **Ability to apply for student travel grants for the IEIIS biennial meetings**
  Includes up to $750 USD and a waiver of registration fees
- **IEIIS Newsletter**
  News about members and meetings; special articles and contact information
- **Opportunities**
  Become involved via Council or committee membership
- **Vote in IEIIS elections**

Transitions

Many of you know **Tim Sellati, PhD,** a long-time IEIIS member and officer, who is currently the Membership Chair. Among his main research interests are immune responses to Francisella bacteria and to spirochetes such as Borrelia burgdorferi, the Lyme disease bacterium. He spent several years in Albany, New York as part of the Albany Medical College. He has most recently been working at Southern Research as a Chair of the Infectious Diseases Department, but has now decided to try something new. As of late 2017 he started as a research chief at the Global Lyme Alliance, where he will be responsible for directing funding at different levels as the Chief Scientific Officer. We wish him the best of luck in his new job. His new email address is: timothy.sellati@gla.org

People in Focus

Holger Heine, PhD, is at Research Center Borstel close to Hamburg in Germany. He has served in different functions for IEIIS, including scientific councilor, and is now responsible for the IEIIS web site. If you see any changes to the web site that you like, please let Holger know! He has worked with TLRs and innate immune responses to different microbes, and lately he has focused on bacteria suspected to modify susceptibilities to allergy. The studies raise questions about current levels of cleanliness in our modern lives, and whether microbes found in farm environments can protect towards allergies.

Amy Hise, MD, is the current IEIIS Treasurer, an important position. She is also a scientific councilor. She is at Case Western Reserve University in Cleveland, OH where she does research and clinical work. Many of you will know her work on endosymbionts and TLR recognition in filariasis and River Blindness; and on innate immune responses including inflammasome activation during fungal infections, establishing oral models for *Candida albicans* challenge. Among other projects, she has also studied immunity to Rift Valley Fever virus.

The International Workshop "Molecular Aspects of Host/Microbe dialogue"

Naples, 5-7 June 2017

by Francesco Peri

The international workshop "Molecular aspects of host/microbe dialogue", an event within the European project TOLLerant (www.tollerant.eu), was organized in Naples from the 5th to the 7th June 2017. TOLLerant is an ITN Marie Slodowska Curie (MSC) action funded by the Horizon 2020 European programme. One of the goals of the ITN actions of the European Union is to provide to young recruited PhD students a multidisciplinary environment and to train them to basic research and to industrial and entrepreneurial skills.

The aim of the organizers was, however, to extend this meeting beyond the TOLLerant consortium, allowing the participation of early stage researchers (ESRs) and well-established scientists from IEIIS and other International networks and societies. The workshop took place in a unique historical venue: the "Complesso dei SS. Marcellino e Festo", an ancient church attached to the old cloister (property of the University of Napoli) located in the heart of Naples.

The majority of participants were from TOLLerant and Immunoshape MSCA-ITN actions, two projects based on chemical approaches to immunology and focused, respectively, on the study of ligand/Toll-like receptors and sugar/lectins interactions. Other scientists from European and extra-European countries as well as IEIIS members attended the meeting.

The molecular interactions at the basis of infection and innate immunity were the unifying topics of the lectures. During the two-day meeting different approaches and strategies were presented, reflecting the different scientific areas and expertise of the speakers, ranging from computational and medicinal chemistry, to biophysics, micros-copy, biochemistry, molecular biology, pharmacology and microbiology.

The first session focused on molecular aspects of sugar/lectine interactions. Cristina Nativi, from the University of Florence (Italy), analyzed from a chemical and structural point of view the role of multivalency in the molecular recognition of sugars and other antigens by the receptors of immune system, in particular lectins.

In the same context, Javier Rojo from the Instituto de Investigaciones Químicas (IIQ-CSIC) in Seville, Spain, presented recent data on glycodendritic systems (based on multiple presentation of mannose sugar) as inhibitors of DC-SIGN-dependent pathogen-cell interaction (http://immunoshape.eu/glycosystems-laboratory). Finally, Niels-Christian Reichardt (CIC-bioma GUNE, Bilbao, Spain) presented the most recent achievements of the MSCA project "Immunoshape" that he coordinates (www.immunoshape.eu).

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PIs Group

Some Participants

The International Workshop "Molecular Aspects of Host/Microbe dialogue"

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The Immunoshape ITN consortium is focused on the study and development of selective carbohydrate immunomodulators Targeting C-type Lectin Receptors on Antigen Presenting Cells.

The second session focused on TLR/ligand interactions in innate immunity and host/microbe interactions from different perspectives. Sonsoles Martin-Santamaria (CIB-CSIC, Madrid, Spain, partner of TOLLerant) showed in an exhaustive way the last achievements in the computational study of Toll-like Receptor conformations, interaction with ligands and other receptors MD2 and CD14. Koichi Fukase (University of Osaka, Japan) presented and discussed the synthesis of immunologically relevant prokaryotic and eukaryotic glyco-conjugates. Grisha Pirianov, from the Anglia Ruskin Cambridge University (UK), presented very recent data on the property of new synthetic molecules to negatively regulate in vitro and in vivo haematopoietic and non-haematopoietic vascular TLR4 signalling in response to sterile inflammation.

This second session continued with the presentations by Francesco Peri (University of Milano-Bicocca, Milano, coordinator of TOLLerant), discussing about the possibility to study TLR pathways by using high affinity, small molecule ligands. Flaviana Di Lorenzo, from the University of Naples, presented the recently determined chemical structures of Gram-negative bacterial lipopolysaccharides (LPS) and their biological activity. Maria Lina Bernardini (University of Rome – La Sapienza, Italy) discussed the molecular recognition of pathogen associated molecular patterns by pattern recognition receptors, included TLRs. Roman Jerala (University of Lujbljana, Slovenia, partner of TOLLerant) outlined and analyzed new mechanisms of regulation of MyD88-mediated signaling in innate immunity. Finally, Thomas Huser (University of Bielefield, Germany, partner of TOLLerant) gave insight into the use of super-resolution fluorescence microscopy for studying molecular events associated to innate immunity and receptor activation and signaling.

The atmosphere of the meeting was stimulating, jovial and friendly. Early stage young researchers and senior scientists belonging to different European networks had the opportunity to share ideas and set up new collaborative interactions.

Last but not least, a rich and well-organized social program, including dinner at the romantic restaurant "La Scialuppa" on Napoli's Castle, and the visit to Napoli underground, certainly contributed to creating a positive environment that favored the consolidation and the beginning of new social and scientific interactions.

Visiting Napoli Sotterranea (underground)

See page 2 for more details on this meeting

IN THE LITERATURE

In this issue of the IEIIS Newsletter we are introducing a new feature: brief summaries, written by Society councilors, of articles of likely interest to IEIIS members. Let us know how you like it and if you would like to contribute.

The Role of lipid A Modifications in Plant Pathogenesis

Bob Ernst

Article: The Very Long Chain Fatty Acid (C26:25OH) Linked to the Lipid A Is Important for the Fitness of the Photosynthetic *Bradyrhizobium* Strain ORS278 and the Establishment of a Successful Symbiosis with *Aeschynomene* Legumes.

Nicolas Busset[1], Flaviana Di Lorenzo[2], Angelo Palmigiano[3], Luisa Sturiale[3], Frederic Gressent[1], Joël Fardoux[1], Djamel Gully[1], Clémence Chaintreuil[1], Antonio Molinaro[2], Alba Silipo[2] and Eric Giraud[1]* (2017) Front Microbiol 8:1821.

[1] Institut de Recherche pour le Développement, LSTM, UMR IRD, SupAgro, INRA, Université de Montpellier, CIRAD, Montpellier, France, [2] Dipartimento di Scienze Chimiche, Complesso Universitario Monte Sant'Angelo, Università di Napoli Federico II, Naples, Italy, [3] Istituto per i Polimeri, Compositi e Biomateriali IPCB, Consiglio Nazionale delle Ricerche, Catania, Italy

Discussants: Courtney E. Chandler and Bob Ernst

Department of Microbial Pathogenesis, University of Maryland, Baltimore, 650 W. Baltimore Street, 8th Floor South, Baltimore, MD, 21201, USA

Bradyrhizobium are Gram-negative bacilli that exist either free-living in soil or enclosed in nodules on the roots of leguminous plants such as those of the genus *Aeschynomene*. Their lipid A structure is unique from other rhizobia in that it can contain very long-chain fatty acids (VLCFAs, C26 or greater), which can be linked to a sterol-like hopanoid molecules. It is thought that these modifications help promote membrane rigidity and protection against external stresses during their dual life styles. The biosynthesis underlying VLCFA addition to lipid A is largely unknown. Recently, Busset *et al.* described the mechanism by which the VLCFA-related synthesis gene, *lpxXL* encodes an acyltransferase in *Bradyrhizobium* strain ORS278 that is responsible for the addition of a 26-carbon fatty acid to its lipid A. Mutants lacking LpxXL activity showed decreased ability to cope with various stresses including low pH, high temperature, antimicrobial peptides, and high osmolarity. Additionally, *lpxXL* mutants showed reduced ability to establish symbioses with *Aeschynomene* species. This highlights the importance of lipid A structure and VLCFAs for both the free-living and symbiotic life cycles of *Bradyrhizobium* and provides more insight into the biosynthesis pathway of these unique lipid A modifications. *Bradyrhizobium* are important nitrogen fixers for their symbiotic partners, making them of interest in agricultural and food science settings. Better understanding of the mechanism that promote symbiosis help advance our understanding of membrane-host interactions and bacterial-symbiont fitness.

BECC method for rational design of vaccine adjuvants

Susu Zughaier

Article: Rationally Designed TLR4 Ligands for Vaccine Adjuvant Discovery.

Kelsey A. Gregg[a] Erin Harberts,[a] Francesca M. Gardner,[a] Mark R. Pelletier,[a]* Corinne Cayatte,[c] Li Yu,[b] Michael P. McCarthy,[c] Jason D. Marshall,[c]* Robert K. Ernst[a] mBio; June 2017 Volume 8 Issue 3 e00492-17

Department of Microbial Pathogenesis, University of Maryland School of Dentistry, Baltimore, Maryland, USA[a]; Statistical Sciences, MedImmune, Gaithersburg, Maryland, USA[b]; Vaccine Platform Group, MedImmune, Gaithersburg, Maryland, USA[c]

Discussant: Susu Zughaier, PhD

College of Medicine, Qatar University, Doha, Qatar

Since the discovery of alum as the first effective vaccine adjuvant, research effort in this field has captured a new height following many decades of dormancy. Novel vaccine adjuvants both licensed or in advanced stages of clinical trials are the fruit of this research.

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IN THE LITERATURE

BECC method for rational design of vaccine adjuvants, *cont'd.*

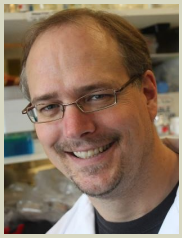
These adjuvants enhance innate immune responses to vaccines that in turn enhance adaptive immune responses. Therefore, some of the currently licensed vaccine adjuvants are TLR ligands e.g. monophosphoryl lipid A (MPLA) as a TLR4 ligand. MPLA is a modified lipid A structure that can induce innate immune responses but without the toxicity of the cytokine storm hence serves as a good vaccine adjuvant. The principle of enzymatically modifying lipid A structures is elegantly presented by Kelsey et al (mBio; June 2017 Volume 8 Issue 3 e00492-17). Authors describe a method that utilizes a set of bacterial enzymes involved in LPS biosynthesis pathway to generate rationally designed and functionally diverse lipid A structures. Bacterial enzymatic combinatorial chemistry (BECC) method capitalizes on the collective knowledge of previously discovered enzymes in various gram-negative bacteria (*Yersinia pestis*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Francisella novicida*, *Acinetobacter baumannii*, and *Leptospira intorregans*) and their role in modifying lipid A structures. For example, enzymes that add or remove a modification from lipid A head groups such as PhoP/Q that adds an aminoarabinose or LmtA that adds methyl group consequently affecting lipid A binding to MD-2 as a prerequisite of TLR4 dimerization and activation. Other enzymes are acyl trasferases that add fatty acyl chains with different length to lipid A disaccharide backbone such as PagP, LpxL, LpxM/MsbB, and LpxT that determine acylation pattern and consequently impact lipid A potency i.e. influence TLR4 signaling. Authors used an avirulent strain of *Yersinia pestis* to genetically add or remove specific lipid A structure modifying enzymes to generate a TLR4-based vaccine adjuvants. Using BECC method two penta-acylated bisphosphorylated lipid A candidates demonstrated favorable characteristics as promising vaccine adjuvants. The two lipid A candidates stimulated moderate cytokine release and induced co-stimulatory molecules expression required for effective antigen presentation.

This paper presents BECC method that can generate a set of diverse lipid A structures that can be utilized in vaccine adjuvants discovery. It remains to be seen whether these modified lipid A structures can exert differential activation of TLR4-TRIF and MyD88 signaling pathways. This collection of lipid A modified structures can be a useful tool to further dissect TLR4 signaling pathways for immune modulators and adjuvant therapies discovery.

An MsbA::LPS complex and Two LptB2FG Structures Redefine the LPS Transport Mechanism

Discussant: Russel E. Bishop

Department of Biochemistry and Biomedical Sciences, and the Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton ON, L8S 4K1 Canada. Address correspondence to: bishopr@mcmaster.ca



Russel Bishop

The first ATP-binding cassette transporter structure to be solved was that of the lipopolysaccharide (LPS) transporter MsbA. Despite the stereochemical inversion in that now infamous first report (*1*), the corrected structure from 2007 ultimately revealed "open" and "closed" conformations and a mechanistic model dubbed "alternating access with a twist" (*2*). LPS was manually docked to show steric compatibility with a mechanism for its passage from the inner leaflet of the cytoplasmic membrane toward an internal chamber within the open conformation of MsbA. The closed nucleotide bound conformation of MsbA could not accommodate this type of passage. Fast forward ten years and advances in single-particle cryo-electron microscopy, combined with the use of lipid-nanodisc-embedded MsbA, have enabled Maofu Liao and co-workers to delineate the conformational transitions that occur in MsbA as it traps and flips LPS (*3*); surprisingly, LPS almost completes its trans-bilayer passage before it flips in the external leaflet, as is effectively illustrated in the provided supplementary video.

Ten years ago, we had only a vague idea about how lipopolysaccharide (LPS) is transported from the periplasmic side of the bacterial inner membrane to the extracellular surface of the outer membrane. Today, the seven components of the LPS transport (Lpt) machinery have all been functionally identified and structurally characterized. The soluble periplasmic protein LptA ushered in the structural biology of the Lpt apparatus in 2008, which is marked by the publication of the structure of LptA from *Escherichia coli*. The group led by Zongchao Jia at Queen's University in Kingston, Ontario, Canada, demonstrated that LptA folded into a beta-jellyroll structure that displays a lipophilic groove; the LptA subunit can stack upon itself to create a filament where the lipophilic groove continuously spirals along its axis (*4*). Intensive collaborative investigations into LPS transport began in earnest and led to the general conclusion, reported last year by Kahne, Silhavy and co-investigators (*5*), that the energetics and genetics of individual Lpt components dictated that they likely all engaged in a complex in order to bridge the two membranes and functioned as a kind of molecular PEZ-dispenser for LPS (*5*).

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IN THE LITERATURE

The Lpt complex model was confirmed structurally for the outer membrane in 2014, when two competing groups published structures of the outer membrane LptDE complex. The group led by Changjiang Dong at the University of East Anglia, in Norwich, UK, solved a partial structure of the LptDE complex from *Salmonella typhimurium*, but provided functional analysis that helped to explain how LPS emerged in the external leaflet of the outer membrane (*6*). The group led by Yihua Huang at the Chinese Academy of Sciences, in Beijing, China, then published a complete structure of LptDE from *Shigella flexneri*, but did not include extensive functional analysis (*7*). Although the two groups were clearly competing on the same project, their combined contributions made for a much more compelling story than did either of their independent manuscripts, both of which were published together in the same issue of *Nature*.

We now know that the LptA filament delivers LPS into the LptDE complex in the outer membrane. What remains to be structurally characterized is the engine that drives LPS transport; namely, the $LptB_2FG$ complex, an ATP-binding cassette transporter specifically adapted to extract LPS from the periplasmic leaflet of the inner membrane and to inject LPS into the LptA filament. In the summer of 2017, the same two competing groups led by Yihua Huang and Changjiang Dong have done it again. The Huang group published the structure of the $LptB_2FG$ complex from *Pseudomonas aeruginosa* (*8*), while the Dong group published the homologous structure from *Klebsiella pneumoniae* (*9*). These latest contributions were published in different journals a few months apart, but again, their combined contributions were much more compelling because each group had captured the $LptB_2FG$ complex in two structurally distinct conformational states. It is now apparent that LPS is transported by a novel "alternating lateral access" mechanism that has been summarized in a recent review by the Dong group (*10*); this review includes a supplementary video to help visualize how LPS is transported between the two bacterial membranes.

The last remaining piece of the Lpt apparatus is an intact structure of LptC, an inner membrane protein with a beta-jellyroll domain that has only been characterized in the absence of its membrane domain. We can still look forward to understanding how LptC interfaces between $LptB_2FG$ and LptA, but the mostly complete picture of the Lpt apparatus that we see today represents a remarkable achievement in the structural biology of LPS transport. $LptB_2FG$ now represents a subset of ABC transporters specialized in extracting lipids from the external membrane leaflet, whereas MsbA represents another subset of ABC transporters specialized in flipping lipids across membranes. ATP binding and hydrolysis is coupled to the repositioning of LPS within the membrane by distinctly different molecular transitions occurring within MsbA and $LptB_2FG$, revealing novel strategies to selectively inhibit LPS transport at both leaflets of the cytoplasmic membrane.

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IN THE LITERATURE

Inflammasome Activation by Bacterial Outer Membrane Vesicles Requires Guanylate Binding Proteins

Finethy, R., S. Luoma, N. Orench-Rivera, E. M. Feeley, A. K. Haldar, M. Yamamoto, T. D. Kanneganti, M. J. Kuehn, and J. Coers (2017) MBio 8(5):e01188-17.

Jason Barker

Discussant: Jason H. Barker

Departments of Internal Medicine and Microbiology, Inflammation Program, University of Iowa

In the last ten years, it has been appreciated that cytoplasmic LPS can stimulate inflammatory cell death (pyroptosis) via detection by caspases-4/5/11. This system, the noncanonical inflammasome, thus acts in concert with the TLR4/MD-2 system, which mediates inflammatory responses to extracellular or intravacuolar LPS. An open question is the means whereby LPS reaches the cytosol so as to access cytosolic caspases. In some cases, microbes actively disrupt the phagosome or endosome, but it is clear that noncanonical inflammasome caspases can mediate LPS-dependent responses to microbes that lack systems that disrupt vacuoles and, intriguingly, to Gram-negative bacterial outer membrane vesicles (OMVs). Finethy et al. now shed some light on the question, reporting that guanylate-binding proteins (GBPs) are required for efficient caspase-11 activation by OMVs. GBPs are interferon-induced dynamin-like proteins that have been implicated in a variety of cellular processes, including phagosome rupture and membrane trafficking. Macrophages from mice deficient in a section of chromosome 3 (GBP^{chr3}-/-, thus lacking GBPs 1,2,3,5 and 7) or from mice deficient in GBP2 did not undergo pyroptosis in response to purified OMVs. Mice deficient in GBPs were partially protected against intra-peritoneal *E. coli* infection, suggesting that disruption of GBP function could be beneficial in the treatment of sepsis.

Importantly, the mechanism of cytosolic escape remains a mystery. Whether OMVs are exposed to the cytosol intact or whether they are processed by the host remains unclear. Given that purified LPS does not activate the noncanonical inflammasome in the absence of manipulations to disturb the cytoplasmic membrane, some unique aspect of OMV structure, composition, and/or shape appears to stimulate particular handling by the host. Dynamin-like proteins have been implicated in not just vesicle trafficking, but also membrane fusion, scission, and remodeling, suggesting that OMVs may undergo major alterations after they are ingested. A separate report in 2016 (Man et al., *Cell*) implicated the interferon-inducible protein, IRGB10, in noncanonical inflammasome activation and observed its GBP-dependent association with the Gram-negative bacterial membrane. Thus, future studies will need to determine which host factors are involved in LPS detection and whether the host alters OMV composition.

Where to Ask . . .

Need to update your address information? Want to pay your dues but are not sure how? You can get answers to these and all other questions related to your IEIIS membership from the following locations:

To contact the Society for any inquiry, email us at **IEIIS@aol.com** or contact one of these individuals directly:

Membership
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