GfG-Online-Conference 2022

Genetics of Inflammation and Infection

April 4th-April 5th, 2022

Relevance

"The current conference is dedicated to shed light on fundamental genetic mechanisms of inflammatory and infectious events and the involved bacterial, viral and fungal pathogens"

Sparked by the current global pandemic of COVID-19, the field of infection genetics experiences a rapid progress demanding an intense exchange of experience and knowledge.

Accompanying vivid scientific discussions will foster a common understanding of fundamental and newly evolving principles of inflammatory and infectious processes and stimulate novel ideas. Therefore, the scientific program of this conference is not only exciting for experts in the field but also rewarding for everybody interested in infection genetics.

Host of this conference is the Life Sciences Faculty of the Technische Universität Braunschweig with its key research area in infection and drug research. Together with the Helmholtz Centre for Infection Research and the German Collection of Microorganisms and Cell Cultures (DSMZ) as a member institute of the Leibniz Association a strong local infrastructure to organize this conference is provided for this prevailing scientific topic.

The German Genetics Society (GfG)

The German Genetics Society (GfG) is a scientific organization that unites scientists from universities and research institutions as well as from industry and governmental agencies working on all aspects of genetic research. It is also a home for high school teachers and everybody interested in genetics.

The GfG fosters scientific exchange and discussion of actual as well as long-term pressing scientific questions related to the field of genetics and aims for encouraging comprehensive interdisciplinary considerations across genetic disciplines.

The GfG meets this goal by regularly organizing for their members and interested guests international conferences hosting renowned experts and young academics to present their latest findings in a selected key topic of genetic research.

Find out more under: https://www.gfgenetik.de

Chair: Prof. Dr. Gerhard H. Braus
E-Mail: gbraus@gwdg.de
Phone: (+49) (0)551-39-23771

Programme Day 1:

Monday April 4th, 2022	
Poster viewing and visit of industrial exhibition is possible during the entire day in the seminar room	
Time	**Online Main Stage**
8:45	Introduction into conference platform
9:00	Opening Ceremony
9:15	Plenary Session I Title: "Innate or Trained Immunity?" (Chair: Yang Li, MHH Hannover)
9:15	Talk 1 (Prof. Mihai Netea, Limes, University Bonn) "Variation and adaptation in innate immune responses"
9:45	Talk 2 (Prof. Heiner Wedemeyer, MHH Hannover) "Genes and immunity in viral hepatitis: What can we learn from antiviral treatment?"
10:15	Break, Visit of Industrial Exhibition, Visit of Posters
10:45	Plenary Session II Title: "Adaptive or Tissue-Resident Immunity" (Chair: Jochen Hühn, HZI Braunschweig)
10:45	Talk 1 (Prof. Marc Veldhoen, University Lisbon) „Generation, maintenance and activation of tissue resident T cells"
11:15	Talk 2 (Prof. Janneke Samsom, Erasmus Univ. Rotterdam) "Regulating intestinal immune responses to luminal antigens"
11:45	Talk 3 (Goumenaki Pinelopi, MPI Bad Nauheim) „The MyD88 signaling axis regulates the inflammatory response during adult heart regeneration in zebrafish"
12:00	Lunch Break, Visit of Industrial Exhibition, Visit of Posters

13:00	Poster Session I
14:00	Plenary Session III Title: Bacterial Infections I (Chair: Michael Steinert, TU Braunschweig)
14:00	Talk 1 (Prof. Ute Römling, Karolinska Inst. Stockholm) „Cyclic di-GMP signaling of bacterial pathogens“
14:30	Talk 2 (Prof. Franziska Faber, University Würzburg) „RNA biology of *Clostridioides difficile“*
15:00	Coffee Break, Visit of Industrial Exhibition, Visit of Posters
15:30	Plenary Session IV Title: “Inflammasome” (Chair: Michael Steinert, TU Braunschweig)
15:30	Talk 1 (Prof. Mikael Sellin, University Uppsala) "Epithelial Inflammasomes and Gut Bacterial Infection"
16:00	Talk 2 (Prof. Dario Zamboni, Univ. Sao Paulo, Brasil) "Inflammasomes in host response to intracellular pathogens and in the pathogenesis of diseases."
16:30	Talk 3 (Lina Scheithauer, TU Braunschweig) “Zinc metalloprotease ProA of *Legionella pneumophila* promotes bacterial proliferation, tissue degradation and immune evasion in human lung tissue explants”
16:45	Talk 4 (Sibel Oguz, MHH Hannover) „Epidemiology of *Pseudomonas aeruginosa* in people with non-CF-bronchiectasis“
17:00	Coffee Break, Visit of Industrial Exhibition, Visit of Posters
17:30	Max-Delbrück Lecture (Prof. Dr. Ulla Bonas, University Halle) "How bacterial plant pathogens manipulate the host”
18:30	End of Day 1

Programme Day 2:

Tuesday April 5th, 2022		
Poster viewing and visit of industrial exhibition is possible during the entire day in the seminar room		
Time	**Online Main Stage**	
9:00	Plenary Session V Title: "Bacterial Infections II" (Chair: Simone Bergmann, TU Braunschweig)	
9:00	Talk 1 (Prof. Marcus Fulde, FU Berlin) "Random mutagenesis to define new virulence determinants in Streptococcal pathogenesis"	
9:30	Talk 2 (Prof. Jan-Willem Veening, Univ. Lausanne) 30min "Systems and synthetic biology approaches to study pneumococcal pathogenesis".	
10:00	Coffee Break, Visit of Industrial Exhibition, Visit of Posters	
10:30	Plenary Session VI Title: "Neuroinflammation" (Chair: Martin Korte, TU Braunschweig)	
10:30	Talk 1 (Prof. Michael Heneka, DZNE Bonn) „Microglia in Alzheimer's disease: the good, the bad and the ugly"	
11:00	Talk 2 (Lotje de Witte, University Utrecht) „The effects of common genetic variants on the microglia transcriptome"	
11:15	Talk 3 (Dr. Shirin Hosseini, TU Braunschweig) „Respiratory viral infection, neuroinflammation and associated neurodegeneration"	
11:30	Talk 4 (Nadia Soussi-Yanicostas, Université Paris Cité) „Microglia remodelling and neuroinflammation in acute DFP organophosphate poisoning"	
12:00	Lunch Break, Visit of Industrial Exhibition, Visit of Posters	Meet the Prof, Young Scientist Career Counceling (seminar room)

13:00	Poster Session II
14:00	Plenary Session VII Title: "Viral Infections" (Chairs: Melanie Brinkmann, TU Braunschweig, Klaus Schughart, HZI Braunschweig)
14:00	Talk 1 (Prof. Adam Grundhoff, HPI Hamburg) „Genetic and Epigenetic Determinants of Herpesvirus Latency"
14:30	Talk 2 (Prof. Xavier Montagutelli, Pasteur Institute, Paris) "Exploring host-virus interactions in genetically diverse Collaborative Cross mice"
15:00	Talk 3 (Prof. Trine Mogensen, Aarhus University) „Life-threatening viral disease in a novel form of autosomal recessive IFNAR2 deficiency in the Arctic"
15:30	Talk 4 (Prof. Dr. Markus Kuhlmann, IPK Gatersleben) „Detection of SARS-CoV-2 derived small RNAs and changes in circulating small RNAs associated with COVID-19"
15:45	Talk 5 (Valerio Laghi, Institut Pasteur, Paris) "Spying on viruses: direct in vivo observation and modelling of the propagation of a neurotropic virus in zebrafish larvae and the role of type I interferons"
16:00	Coffee Break, Visit of Industrial Exhibition, Visit of Posters
16:30	Plenary Session VIII Title: "Fungal Infections") (Chair: Gerhard Braus, University Göttingen)
16:30	Talk 1 (Prof. Axel Brakhage, HKI Jena) „The opportunistic human fungal pathogen *Aspergillus fumigatus*"
17:00	Talk 2 (Prof. André Fleissner, TU Braunschweig) "Conserved cell-cell signaling mechanisms in filamentous fungi"
17:30	Talk 3 (Dr. Daniela Nordzieke, University Göttingen) „Hyphal fusion and autophagy enable proper conidiation and symptom development on maize leaves by *Colletotrichum graminicola*"
17:45	Closing Remarks and Prizes
18:00	End of Conference

Abstracts

Session I:

A homozygous *STING1* gene variant causes STING-associated vasculopathy with onset in infancy (SAVI) in two patients

Rensheng Wan[1], Sandra von Hardenberg[1], Lisa Isabel Olfe[1], Bernd Auber[1], Martin Wetzke[2], Doris Steinemann[1]

[1]Department of Human Genetics, Hannover Medical School, Hannover, Germany
[2]Department of Pediatric Pneumology, Allergology and Neonatology, Hannover Medical School, Hannover, Germany

Background: Stimulator of interferon response cGAMP interactor 1 (*STING1*) gain of function (GoF) variants cause STING-associated vasculopathy with onset in infancy (SAVI; AD inheritance). While most causative heterozygous variants arise *de novo*, Lin et al. (2020) showed that *STING1* variant p.(R281W) causes SAVI only in homozygous state. Here we report two further patients carrying *STING1* homozygous variant p.(R281W).

Methods: Whole exome sequencing (WES) and whole genome sequencing (WGS) were applied respectively to identify causative variant in patient 1 and 2.

Results: *STING1* (NM_198282.3): c.841C>T p.(R281W) was identified in two patients and classified as “pathogenic”. Patient 1 presented with recurrent severe hypoxaemia, hypoventilation, diffuse alveolar hemorrhage, interstitial lung disease, without skin vasculitis. Segregation analysis within the consanguineous family showed that healthy parents and one brother carried variant heterozygously. The interferon signature was highly elevated in patient 1 but not in healthy heterozygous family members. This correlates to published cases displaying that the heterozygous p.(R281W) variant did not affect the interferon signature. No significant improvement was observed after therapy with Janus kinase inhibitor Baricitinib. Patient 2 showed hypoventilation with scarring fibrotic changes, bronchiectasis, tachypnea, failure to thrive with marked dystrophy, hypocalcemia, and also no skin vasculitis.
Conclusion: Our report supports the possibility that p.(R281W) causes an atypical SAVI phenotype without demonstrating vasculopathy. It is important to consider an autosomal recessive inheritance pattern when evidence of STING-associated vasculopathy is given.

Grants: German Research Foundation (DFG) under Germany’s Excellence Strategy - EXC 2155 - RESIST project number 390874280.
R. Wan holds DAAD scholarship.

Session II:

The MyD88 signaling axis is required for adult heart regeneration in zebrafish

Pinelopi Goumenaki, Stefan Günther, Didier Y.R. Stainier
Max Planck Institute for Heart and Lung Research, Department of Developmental Genetics, Ludwigstraße 43, 61231 Bad Nauheim, Germany

Inflammation is triggered immediately after cardiac injury, and it has been hypothesized to promote regeneration in regenerative models such as zebrafish. Myeloid differentiation factor 88 (MyD88) is a central adaptor molecule for the Toll-like receptor and interleukin-1 receptor signaling pathways, both of which are essential regulators of inflammation. However, how specific inflammatory components, such as MyD88, regulate the early inflammatory phase after cardiac injury remains unclear. In this project, we are testing the hypothesis that the MyD88 signaling axis plays a central role in the initiation of the inflammatory response after injury and that this early response is required for cardiac regeneration in zebrafish. Our data indicate that zebrafish lacking functional MyD88 display features linked to impaired cardiac regeneration potential, including reduced immune cell recruitment to the injured tissue and reduced coronary endothelial cell proliferation at the border zone. Additionally, transcriptomic analysis reveals that *myd88* mutants exhibit a downregulation of immune-related processes after cardiac cryoinjury. To understand the mechanisms activated downstream of MyD88, we identified via this transcriptomic analysis potential effectors of the MyD88 signaling pathway (*il1b, cxcl18b, itln1)* and are studying their role with gain- and loss-of-function tools. To determine the cell types in which MyD88 signaling plays a role during cardiac regeneration, we are using a transgenic approach to block MyD88 function in a cell type-specific manner. This project will provide further insights into the cellular and molecular mechanisms involved in the early inflammatory response during zebrafish cardiac regeneration. By modulating specific immune components and their response to injury, we could potentially improve the regeneration outcome in mammalian models including humans.

Session III:

Cyclic di-GMP signaling of bacterial pathogens

Ute Römling
Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

Cyclic di-GMP is a ubiquitous second messenger present in the majority of bacterial species. Thereby, the protein domains, GGDEF, EAL and HD-GYP domains, which mediate the synthesis and hydrolysis of cyclic di-GMP belong to the most abundant protein domain superfamilies. Within one bacterial genome, individual GGDEF and EAL domains are distinctively diverse with the amino acid sequence most similar to homologous proteins of identical domain structure in distantly related bacterial species. In pathogens such as *Salmonella typhimurium* causing self-limiting gastroenteritis, we have demonstrated that cyclic di-GMP is directing the motility/sessility life style transition equally as the transition between acute and chronic infection. Thereby, the ability to form biofilms is traded versus acute virulence. However, we have also recently observed that within the gamma-proteobacteria, the cyclic di-GMP signaling system has almost disappeared from species belonging to the Morganellaceae family, with the uropathogen and environmental species *Proteus mirabilis* to harbor only one diguanylate cyclase. The reason for the lack of the cyclic di-GMP signaling system remains mysterious in these free living bacteria with an approximate genome size as *Escherichia coli*. On the other hand, a diguanylate cyclase is present in animal pathogenic and probiotic species of the genus *Streptococcus* on a horizontally transferred genomic island. The co-occurrence of the diguanylate cyclase with a cellulose-(like) synthase in streptococcal and *Proteus* species points to post-translational activation of cellulose biosynthesis by cyclic di-GMP as an ecologically important ancient signaling pathway highly conserved even in many of today’s diverse bacterial species.

Session IV:

Epidemiology of *Pseudomonas aeruginosa* in people with non-CF-bronchiectasis

S. Oguz[1,2], IM. Lüdemann[1,2], I. Rosenboom[1,3], L. Sedlacek[4], F. Ringshausen[2,5,6], T. Welte[2,5,6], B. Tümmler[1,6], N. Cramer[1,2]

[1]Clinical Research Group 'Pseudomonas Genomics', Clinic for Paediatric Pneumology, Allergology and Neonatology, Hannover Medical School
[2]German Center for Infection Research (DZIF), Hannover
[3]Research Core Unit Genomics, Hannover Medical School
[4]Institute for Medical Microbiology and Hospital Epidemiology, Hanover Medical School
[5]Dept for Respiratory Medicine, Hannover Medical School
[6]Biomedical Research in Endstage and Obstructive Lung Disease Hannover (BREATH), Hannover Member of the German Center for Lung Research (DZL), Hannover Medical School

Pseudomonas aeruginosa is a gram-negative bacterium belonging to the group of γ-proteobacteria.
As an opportunistic pathogen, *P. aeruginosa* causes both acute and chronic infections and is one of the most common triggers of nosocomial infections. Patients with serious underlying lung diseases such as cystic fibrosis (CF), bronchiectasis or chronic obstructive pulmonary disease (COPD) are often affected.
In bronchiectasis, one or more of the bronchi are abnormally widened leading to mucus plugging, which predisposes to colonization with opportunistic pathogens such as *P. aeruginosa* and the emergence of a vicious cycle of infection, inflammation and lung remodeling.
Our studies intended to genotype the *P. aeruginosa* population in non-CF-bronchiectasis, which were isolated from patients at Hannover Medical School over the last couple of years. We cultivated in total 261 isolates of the strain collection, extracted the genomic DNA and prepared fragment libraries for Next Generation Sequencing via NovaSeq. After sequencing with an average genome coverage at the regions of interest of about 200-fold, the reads were trimmed, assembled to scaffolds and aligned to the PA14 genome reference sequence. "Multilocus Sequence Types" (MLST) were derived from the genomic data by identifying sequence variants in seven highly conserved housekeeping genes and compared with the MLST entries of the Pseudomonas genome database.
Three MLST types (ST17, ST253 and ST395) occurred most frequently in non-CF-bronchiectasis. These sequence types also belong to the most common sequence types among isolates from other human pulmonary chronic infections. In conclusion, the spectrum of frequent MLST types in bronchiectasis matches with that in other chronic lung infections.

Session IV:

Epithelial Inflammasomes and Gut Bacterial Infection

M.E. Sellin, University of Uppsalla, Department of Medical Biochemistry and Microbiology, Sweden

The gut epithelium has a large surface for nutrient and fluid uptake, but must also provide a barrier against tissue-invading pathogens, such as Salmonella bacteria. Work by us and others has shown that Salmonella invasion of intestinal epithelial cells (IECs) is efficiently sensed by epithelial inflammasomes – including the NAIP/NLRC4/Caspase-1/8 inflammasome that detects flagellin and type-III-secretion system components, and the Caspase-4/11 inflammasome that detects cytosolic LPS. Epithelial inflammasome activation elicits a swift cell death response and fuels extrusion of infected IECs into the lumen. In this talk, I present our recent findings from studies of the epithelial inflammasome response to infection in mice and intestinal epithelial organoids. By time-lapse imaging, we find that NAIP/NLRC4/Caspase-1 activation triggers prompt epithelial contractions and the densification of IEC packing around a Salmonella invasion site. This response, which involves the pore-forming protein Gasdermin D and myosin-II, precedes the IEC extrusion step. I present a temporal model for how inflammasome activation can drive elimination of infected IECs without compromising epithelial barrier integrity. Absence of this early defense causes excessive translocation of bacteria to deeper tissues and sparks a hyperinflammatory state that destroys mucosal tissue architecture.

Session IV:

Zinc metalloprotease ProA of *Legionella pneumophila* promotes bacterial proliferation, tissue degradation and immune evasion in human lung tissue explants

Scheithauer L.[1], Thiem S. [1], Ünal C.M. [1], Dellmann A. [2], Steinert M. [1]
[1]Technische Universität Braunschweig, Institute of Microbiology, Braunschweig, Germany
[2]Klinikum Braunschweig, Pathology, Braunschweig, Germany

Legionnaires' disease is a severe, atypical pneumonia caused by the human lung pathogen *Legionella pneumophila*. The bacterium is well-adapted to colonize man-made water systems and, after inhalation, to replicate inside alveolar macrophages. By developing and applying a unique infection model for Legionnaires' disease, we were able to characterize the zinc metalloprotease and versatile bacterial virulence factor ProA in human lung tissue explants (HLTEs). These vital specimens were obtained from patients undergoing lobe- or pneumectomy because of lung cancer. Infection studies with a *proA*-deletion mutant showed that the extracellular protease activity facilitates proliferation and transmigration of *L. pneumophila* in pulmonary tissue. For the first time, histological analysis revealed inflammation and thickening of alveolar septa as a direct consequence of ProA-mediated derangement and degradation of human collagen IV at the basal lamina. Furthermore, an increased susceptibility of the *proA*-deficient mutant to human serum revealed a central role of the protease in antagonizing humoral immune defense. Ongoing studies also indicate that ProA is able to reduce TLR5-mediated activation of the NF-κB signaling pathway and subsequent cytokine secretion due to the efficient cleavage of bacterial flagellin monomers. Overall, we demonstrated that ProA contributes to the pathogenesis of Legionnaires' disease by destroying human pulmonary tissue, promoting replication and dissemination of *L. pneumophila*, and antagonizing host defense mechanisms via a diverse spectrum of bacterial or host specific targets.

Session V:

Systems and synthetic biology approaches to study pneumococcal pathogenesis

Jan-Willem Veening, University of Lausanne, Faculty of Biology and Medicine, Department of Fundamental Microbiology, Switzerland

Pathogenic bacterial phenotypes are the product of intracellular changes and interactions among numerous molecules of various regulatory (omics) levels, such as transcripts, proteins and metabolites. Multiomics approaches are therefore warranted to fully uncover how such phenotypes arise and cause disease. Here, we constructed integrated transcriptome, proteome and essentialome profiles of the important opportunistic human pathogen *Streptococcus pneumoniae* for various *in vitro* growth conditions mimicking environmental factors of its vital human host niches, such as the nasopharynx (colonization), lungs (pneumonia) and cerebral spinal fluid (meningitis). To this end, genome-wide operon essentiality was quantified by an optimized CRISPRi-seq approach. The observed profiles were condition-specific, confirming pneumococcal niche adaptation flexibility on multiple regulatory levels. Surprisingly, no correlation was found between gene essentiality and expression, neither on the transcript nor on the protein level. This suggests that CRISPRi-seq data might be more informative than expression data to identify novel therapeutic targets. To define potential universal protective antigens, we performed CRISPRi-seq in a murine model of flu superinfection and identified the highly conserved pneumococcal genes spv_0960 (lafB) and spv_0004 (ychF) as novel virulence factors. Vaccination with recombinant LafB protein was highly immunoprotective in mice during superinfection and depends on Th17-mediated immunity. Importantly, LafB vaccination protected against non-vaccine serotypes 15A and 24F paving the way for a universal pneumococcal vaccine.

Session VI:

Microglia remodelling and neuroinflammation in acute DFP organophosphate poisoning

Nadia Soussi-Yanicostas
NeuroDiderot, Inserm U1141, Université Paris Cité, Hôpital Robert Debré, Paris, France. Contact: nadia.soussi@inserm.fr

Organophosphates (OPs) comprise highly toxic molecules widely used as pesticides but also warfare nerve agents, and existing countermeasures are lifesaving but do not alleviate all long-term neurological sequelae, making OP poisoning a public health concern worldwide and the search for fully efficient antidotes an urgent need. OPs cause irreversible acetylcholinesterase (AChE) inactivation, inducing the so-called cholinergic syndrome characterized by peripheral manifestations and epileptic seizures associated with permanent psychomotor deficits. Beyond immediate neurotoxicity, recent data also identified neuroinflammation and microglia activation as two processes that likely play an important, albeit poorly understood, role in the physiopathology of OP intoxication and its long-lasting consequences. To get insights into the response of microglia to OP poisoning, we used a previously described model of OP diisopropylfluorophosphate (DFP) intoxication of zebrafish embryos that reproduces almost all the defects seen in poisoned humans and preclinical models, including acetylcholinesterase inhibition, neuron epileptiform hyperexcitation and increased neuronal death. Here, we investigated *in vivo* the consequences of acute DFP exposure on microglia morphological and behavioural changes, and expression of a set of pro- and anti-inflammatory cytokines. We also took advantage of a genetic microglia ablation method to evaluate the role of microglia in the OP-induced neuropathology. We first showed that DFP intoxication rapidly induced deep microglia phenotypic remodelling resembling that seen in M1-type activated macrophages and characterized by an amoeboid morphology, reduced branching and increased mobility. DFP-intoxication also caused massive expression of pro-inflammatory cytokines Il-1ß and Il-8, and, to a lesser extent, immuno-modulatory cytokine Il-4, suggesting complex microglia reprogramming that included, but not limited to, neuroinflammatory activities. Thus, microglia appeared as an interesting therapeutic target to identify molecules reducing microglia activation, which could be used to complement existing OP antidote cocktails.

Key words: Microglia, Neuroinflammation, organophosphate poisoning, microglia in vivo imaging, diisopropylflurorphoshate (DFP), zebrafish, cytokines.

Session VII:

Exploring host-virus interactions in genetically diverse Collaborative Cross mice

Xavier Montagutelli, Institut Pasteur, Université de Paris, Mouse Genetics Laboratory, France

The control of infectious disease in human and animals primarily relies on vaccines and drugs targeting the infectious agent. Although very potent, these countermeasures do not consider host spontaneous mechanisms of resistance or tolerance to infections. Understanding host-pathogens interactions is critical to decipher the pathophysiology of infectious diseases and to develop host-directed preventive and therapeutic strategies. Analyzing response to infections in genetically diverse hosts is a powerful, hypothesis-free approach to identify genes which play key roles in host-pathogens interactions. In mice, the Collaborative Cross, a collection of inbred strains with genetic diversity similar to humans, provides an optimal platform to achieve this aim. Taking examples from bacterial and viral infections, we will illustrate the contribution of the Collaborative Cross strains for improving models of human infectious diseases and identifying polymorphic host genes modulating susceptibility to pathogens.

Session VII:

Life-threatening viral disease in a novel form of autosomal recessive IFNAR2 deficiency in the Arctic

Trine H. Mogensen, Department of Biomedicine, Aarhus University, Aarhus, Denmark and Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark

Type I interferons (IFN-I) play a critical role in human antiviral immunity, as demonstrated by exceptionally rare deleterious variants of IFNAR1 or IFNAR2. We investigated five children from Greenland, Canada and Alaska presenting with viral disease, including life-threatening COVID-19 or influenza, in addition to meningoencephalitis and/or haemophagocytic lymphohistiocytosis following live-attenuated viral vaccination. Affected individuals bore the same homozygous IFNAR2 c.157T>C, p.Ser53Pro missense variant. Although absent from reference databases, p.Ser53Pro occurred with a minor allele frequency of 0.034 in their Inuit ancestry. The serine to proline substitution prevented cell surface expression of IFNAR2 protein, small amounts of which persisted intracellularly in an aberrantly glycosylated state. Cells exclusively expressing the p.Ser53Pro variant lacked responses to recombinant IFN-I and displayed heightened vulnerability to multiple viruses in vitro – a phenotype rescued by wild-type IFNAR2 complementation. This novel form of autosomal recessive IFNAR2 deficiency reinforces the essential role of IFN-I in viral immunity. Our findings may have public health implications, including development of strategies for population screening, prophylaxis, and management of viral infections and live attenuated vaccines in these populations.

Session VII:

Detection of SARS-CoV-2 Derived Small RNAs and Changes in Circulating Small RNAs Associated with COVID-19

Claudius Grehl+1, Christoph Schultheiß+2, Katrin Hoffmann3, Mascha Binder2, Thomas Altmann4, Ivo Grosse1 & Markus Kuhlmann4

+ Authors contribute equally to this work

Affiliations
1 Martin Luther University Halle-Wittenberg, Institute of Computer Science, Von Seckendorff-Platz 1, 06120 Halle (Saale), Germany
2 Department of Internal Medicine IV, Oncology/Hematology, Martin-Luther-University Halle-Wittenberg, 06120 Halle (Saale), Germany
3 Institute of Human Genetics, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany
4 Heterosis, Department of Molecular Genetics, Leibniz Institute of Plant Genetics and Crop Plant Research (IPK), OT Gatersleben, Stadt Seeland, Germany.

Cleavage of double-stranded RNA is described as an evolutionary conserved host defense mechanism against viral infection. Small RNAs are the product and triggers of post transcriptional gene silencing events. Up until now, the relevance of this mechanism for SARS-CoV-2-directed immune responses remains elusive. Herein, we used high throughput sequencing to profile the plasma of active and convalescent COVID-19 patients for the presence of small circulating RNAs. The existence of SARS-CoV-2 derived small RNAs in plasma samples of mild and severe COVID-19 cases is described. Clusters of high siRNA abundance were discovered, homologous to the nsp2 3'-end and nsp4 virus sequence. Four virus-derived small RNA sequences have the size of human miRNAs, and a target search revealed candidate genes associated with ageusia and long COVID symptoms. These virus-derived small RNAs were detectable also after recovery from the disease. The additional analysis of circulating human miRNAs revealed differentially abundant miRNAs, discriminating mild from severe cases. A total of 29 miRNAs were reduced or absent in severe cases. Several of these are associated with JAK-STAT response and cytokine storm.

Session VII:

Characterizing the role of the HCMV UL35-UL82 complex during the antiviral innate immune response

Ramya Ramani[1], Markus Fabits[1,2], Markus Stempel[1,2], Joop van den Heuvel[3], Wulf Blankenfeldt[4], Melanie M. Brinkmann[1,2]

As all herpesviruses, the Human Cytomegalovirus (HCMV) exhibits a temporally-regulated gene expression cascade, and establishes latent and lifelong infection. In certain permissive cell types, HCMV infection can kickstart the lytic replication cycle, characterized by the activation of the HCMV Major Immediate Early Promoter (MIEP) and subsequent expression of viral Immediate Early (IE) genes followed by Early and Late proteins. Pattern recognition receptors (PRR) detect HCMV upon cell entry and establish an antiviral state within the infected cell. Consequently, HCMV has to modulate the host response to successfully establish an infection. Critical for the manipulation of cellular processes to favor lytic replication of HCMV are tegument proteins that are delivered directly into the cell upon virus entry. Two tegument proteins of HCMV, UL82 and UL35, individually antagonize the PRR-mediated type I IFN response at the level of the cGAS adapter protein STING and the downstream kinase TBK1, respectively (1, 2). Interestingly, UL35 and UL82 were also shown to interact and cooperatively activate transcription from the HCMV Major Immediate Early Promoter (MIEP) that kickstarts the viral lytic replication cycle (3). We observed that, as opposed to singular expression, co-expression of UL35 and UL82 inhibited IFNβ transcription downstream of the critical transcription factor IRF3 in a cooperative manner, and co-localized in close proximity to promyelocytic leukemia nuclear bodies (PML-NBs) that are important players of intrinsic immunity. However, UL82-mediated inhibition of IFNβ transcription was independent of its interaction with Daxx, a component of PML-NBs, suggesting a different mode of action to evade the type I IFN response. To obtain a broader picture of UL35/UL82-regulated gene expression and biological consequences of SUMOylation, we currently perform RNA- sequencing and SUMOylation assays, respectively. Due to the important role of UL35 and UL82 during HCMV infection regarding modulation of the host response and viral replication, the UL35-UL82 complex is a promising target for small molecule inhibitors in treating HCMV infection.

References:

(1) Fu et al., 2017, Cell Host and Microbe
(2) Fabits et al., 2020, Microorganisms
(3) Schierling et al., 2004, Journal of Virology

Session VII:

Identification of murine 2‘-5‘-oligoadenylate synthetase-like protein 2 (mOASL2) as a restriction factor for murine gammaherpesvirus-68 (MHV68) infection

*Viktoria Vögele*1*, Markus Stempel1,2, Melanie M. Brinkmann1,2*

1 Technische Universität Braunschweig, Institute of Genetics, Braunschweig, Germany
2 Helmholtz Centre for Infection Research, Viral Immune Modulation Research Group, Braunschweig, Germany

Murine gammaherpesvirus-68 (MHV68) is a member of the *Gammaherpesvirinae* subfamily and closely related to the oncogenic Kaposi’s sarcoma-associated herpesvirus (KSHV). Due to KSHV’s specificity to its human host, MHV68 is a widely used model system to study gammaherpesvirus pathogenesis *in vivo*. Both viruses encode for an ORF55 protein, a member of the herpesviral U44 superfamily. Human cytomegalovirus (HCMV) UL71 belongs to the U44 superfamily and is required for efficient secondary envelopment of new virions [1]. Moreover, it was shown that UL71 interacts with human 2’-5’-oligoadenylate synthetase-like protein (hOASL) [2]. hOASL is an interferon-stimulated gene (ISG). Unlike its orthologues hOAS1/2/3, hOASL contains a catalytically inactive nucleotidyl transferase (NTase) domain and two C-terminal ubiquitin-like (Ubl) domains [3]. It still exerts antiviral activity against some viruses, but its role for gammaherpesviral infections is poorly characterized. The function of its two murine homologues, mOASL1 and mOASL2, remains to be elucidated.

Here, we investigated the role of mOASL2 during MHV68 infection. By co-immunoprecipitation and immunofluorescence analysis, we could show that mOASL2 interacts and colocalizes with various members of the U44 superfamily in the cytoplasm. Furthermore, we investigated the role of the C-terminal Ubl domains of mOASL2, showing that this domain is not involved in the interaction with U44 family members. Since mOASL2 was shown to inhibit the DNA sensor cyclic GMP-AMP synthase (cGAS) [3], we analyzed the type I interferon (IFN) response of MHV68-infected mOASL2 knock-out (KO) macrophages. Interestingly, MHV68 infection did not induce detectable levels of type I IFN, while viral growth was significantly enhanced in mOASL2 KO macrophages compared to WT cells. These findings suggest that mOASL2 restricts MHV68 independent of the type I IFN response.

Hence, we currently hypothesize that mOASL2 could impact stages before or during the secondary envelopment of newly generated MHV68 particles by interacting with ORF55.

[1] Schauflinger, M. et al. *Journal of virology* (2011), doi:10.1128/JVI.01540-10
[2] Nobre, L. V et al. *eLife* (2019), doi:10.7554/eLife.49894
[3] Ghosh, A. et al. *Immunity* (2019), doi:10.1016/j.immuni.2018.12.013

Session VIII:

The opportunistic human fungal pathogen *Aspergillus fumigatus*

Axel Brakhage, HKI Jena, Molekulare und Angewandte Mikrobiologie

For several pathogenic fungi, it has been shown that they can survive for some time intracellularly, *i.e*., in human cells even of the immune system. This way they can hide from the immune system. Another important aspect is that available antimycotics do not sufficiently reach these intracellular pathogens. Recently, we have elucidated the mechanisms how the important fungal pathogen *Aspergillus fumigatus* manipulates the maturation of phagosomes of macrophages thus allowing spores (conidia) to survive for some time in phagosomes. We showed that lipid-raft microdomains are essential components of phagolysosomal membranes of macrophages and depend on flotillins. Genetic deletion of flotillins demonstrates that the assembly of both major defense complexes vATPase and NADPH oxidase requires membrane microdomains. Furthermore, we discovered a new virulence mechanism leading to dysregulation of membrane microdomains by melanized wild-type conidia of *A. fumigatus* resulting in reduced phagolysosomal acidification. We identified a single nucleotide polymorphism (SNP) in the human *FLOT1* gene resulting in heightened susceptibility for invasive aspergillosis in hematopoietic stem-cell transplant recipients. Collectively, flotillin-dependent microdomains on the phagosomal membrane play an essential role in protective antifungal immunity. We also developed strategies to target these hidden fungi by antifungal compounds using nanocontainers.
Essential immune cells for defense against fungal infections are neutrophilic granulocytes. Recently, we discovered the long distance killing mechanism of neutrophils on *A. fumigatus*. When in contact with *A. fumigatus*, neutrophils produce specific antifungal extracellular vesicles that contain a distinct set of antimicrobial proteins. Antifungal extracellular vesicles attack fungal hyphae and can even enter the cytoplasm of hyphae thereby killing the fungus. They hold great promise for a novel therapy against *A. fumigatus*.

Session VIII:

Conserved cell-cell signaling mechanisms in filamentous fungi

Hamzeh Hammadeh, Antonio Serrano, Valentin Wernet, Natascha Stomberg, Davina Hellmeier, Martin Weichert, Ulrike Brandt, Bianca Sieg, Konstantin Kanofsky, Reinhard Hehl, Reinhard Fischer, André Fleißner

In many filamentous ascomycete fungi, germinating spores cooperate and fuse into supracellular structures, which further develop into the mycelial colony. Our earlier studies revealed that interacting spore germlings of the model fungus *Neurospora crassa* employ an unusual signaling mechanism, which we termed “cellular dialog”. In this process, the two fusion partners coordinately take turns in signal emission and signal receiving. This unique cellular behavior involves the alternating recruitment of two conserved signaling complexes to the plasma membrane. To test if this mechanism is conserved in other fungi, we investigated cell fusion in the plant pathogenic grey mold *Botrytis cinerea* and the nematode-trapping species *Arthrobotrys flagrans.* In both species, cell-cell communication and fusion were also mediated by the cell dialog mechanism. When *N. crassa* and *B. cinerea* spores are mixed, interactions between the two species are frequently observed, which result in mutual interspecies attraction and cell-cell contact. However, interspecies fusion has never been observed. These findings suggest that the so far unknown signal and receptor that mediate cell-cell communication are also conserved, and that so far uncharacterized downstream mechanisms have evolved, that prevent interspecies fusion after cell-cell contact. In addition, we found that the presence of *N. crassa* can reprogram developmental decisions in *B. cinerea*. In the grey mold, cell fusion and pathogenic growth appear to be mutually exclusive. When confronted with *N. crassa*, however, *B. cinerea* also undergoes fusion under growth conditions, which usually trigger infectious growth. We hypothesize that the pathogenic development may be suppressed in the presence of the so far unknown fusion signals.

Session VIII:

Hyphal fusion and autophagy enable proper conidiation and symptom development on maize leaves by *Colletotrichum graminicola*

Daniela Nordzieke[1]

[1]*Georg-August University Gottingen, Institute of Microbiology and Genetics, Department of Genetics of Eukaryotic Microorganisms, Gottingen, Germany*

The hemibiotrophic fungus *Colletotrichum graminicola* is a maize pathogen infecting several plant tissues like leaves, stems, and roots. Responsible for *Z. mays* infection are two morphological distinct asexual spores, oval and falcate conidia.

Hyphal and germling fusion is a common phenomenon in ascomycetous fungi. Due to the formed hyphal network, this process enables coordinated development, interaction with plant hosts and efficient nutrient distribution. Recently, our lab showed a positive correlation of germling fusion with the formation of penetrating hyphopodia on maize leaves outgoing from *C. graminicola* oval conidia. To investigate the probable interconnectivity of these processes, we have generated a deletion mutant in *Cgso*, which homologs are essential for cellular fusion in other fungal species. Indeed, plant infection studies combined with microscopy revealed a significant decrease in symptom development of the ΔCgso mutant on maize leaves. However, hyphopodia development was not affected, indicating that both processes are not directly connected. Instead, we were able to link the decreased symptom development to a reduced formation of acervuli, asexual fruiting bodies of *C. graminicola*, which give rise to falcate conidia. Monitoring of a fluorescent labelled autophagy marker eGFP-CgAtg8 revealed a high autophagy activity in hyphae surrounding acervuli. Since the ΔCgso mutant shows no hyphal fusions at these sites, we conclude that efficient nutrient transport of degraded cellular material by hyphal fusions enables proper acervuli maturation and symptom development on leaves.

Appendix

Sponsors:

The GfG would like to thank the following companies for their support of the conference:

New England Biolabs GmbH
Brüningstrasse 50 | Geb. B852
65926 Frankfurt am Main
Tel: +49 (0) 69/ 305-23140 | 0800/ BIOLABS (246-5227)
Fax: +49 (0) 69/ 305-23149 | 0800/ BIOLABX (246-5229)
www.neb-online.de

Contact:

Kristin Schnettler
Mobil: +49 (0) 170/ 246-5550
schnettler@neb.com

Carl Roth GmbH + Co. KG
Schoemperlenstr. 3-5
D-76185 Karlsruhe
T: +49 511 388 3270
F: +49 511 388 3270
www.carlroth.com

Contact:

Dr. Volker Jacobs
M: +49 172 738 5762
V.Jacobs@carlroth.de

Aufnahmeantrag: Ich beantrage, mich als Mitglied in die Gesellschaft für Genetik e.V. aufzunehmen.

Meine Adressdaten:	
Anrede*:	
Namenstitel:	
Titel:	
Vorname*:	
Nachname*:	
Adresszusatz:	
Bundesland*:	
Geburtstag*:	
Straße*:	
PLZ*:	
Ort*	
Postland (nur Ausland):	
Telefon:	
Mobil:	
Email*:	

Bei Teilnahme am SEPA-Lastschriftverfahren unterschreiben Sie bitte die SEPA-Einzugsermächtigung, die Sie ausfüllen und sofort wieder hochladen können. Sollten Sie keine digitale Unterschrift haben, drucken Sie die Einzugsermächtigung aus, unterschreiben und scannen sie ein oder schicken diese per Post an uns. Um Ihren Antrag schneller bearbeiten zu können, füllen Sie bitte dennoch Ihre eigene IBAN und BIC in diesem Formular aus.

Ihre Bankverbindung:	
IBAN*:	
BIC:	
Kontoinhaber*:	

Ich akzeptiere die Vereinssatzung und habe die Hinweise zum Datenschutz gelesen.

* Pflichtfeld

Ort, Datum

Unterschrift

Bitte senden Sie Ihre schriftliche Anmeldung an: Gesellschaft für Genetik e.V. c/o Georg-August-University Göttingen/ Prof. Dr. Gerhard H. Braus/ Institute of Microbiology and Genetics/ Department Molecular Microbiology and Genetics/ Grisebachstraße 8/ D-37077 Göttingen (Germany). Einen Online-Aufnahmeantrag finden Sie im Internet unter: https://ememberline.de/vbio/mg_anmeldungGfG.php

DoktorandInnenenpreis der Gesellschaft für Genetik

Elisabeth-Gateff-Preis 2022

"Im Laufe meiner wissenschaftlichen Laufbahn bin ich mit einigen schönen Preisen geehrt worden - diese Förderung und finanzielle Unterstützung möchte ich nun an junge Forscher weitergeben"

sagt Elisabeth Gateff, die Leiterin des Instituts für Genetik an der Mainzer Universität war und seit 1998 im Ruhestand ist.

In jedem Jahr werden DoktorandInnen für herausragende Arbeiten auf dem Feld der Genetik mit dem nach ihr benannten Preis ausgezeichnet.

Sie hat ihre Preisgelder des Meyenburg-Preises, des Deutschen Krebspreises und des ihr überreichten Prince-Hitachi-Preises für diesen Zweck gespart und seit dem Jahr 2000 für den Doktoranden-Preis der Gesellschaft für Genetik zur Verfügung gestellt.

In den Jahren zuvor wurden die Preise großzügigerweise von der Firma Boehringer Ingelheim zur Verfügung gestellt.

Weitergehende Informationen zu den PreisträgerInnen der vergangenen Jahre sowie zu ihren Arbeiten sind zu finden unter: https://www.gfgenetik.de/doktorandenpreis

Ausschreibung

Für das Jahr 2022 wird der Elisabeth-Gateff-Preis zum 28. Mal ausgeschrieben. Der DoktorandInnen-Preis der Gesellschaft für Genetik ist mit 3.000 EUR dotiert.

Interessierte WissenschaftlerInnen mit herausragenden Promotionsarbeiten können sich bis zu 1,5 Jahre nach der Promotion direkt bewerben oder von dritter Seite vorgeschlagen werden. Stichtag: Datum der Promotionsurkunde

Bewerbungen aus allen Teilgebieten der Genetik sind willkommen, zum Beispiel:

- Molekulare Genetik
- Evolutionsgenetik
- Molekularbiologie
- Entwicklungsgenetik
- Neurogenetik
- Humangenetik
- Genomik
- Epigenetik

u.a.m.

Die Arbeit, die in deutscher oder englischer Sprache abgefasst sein kann, muss auf einem Gebiet der Genetik angesiedelt und zum überwiegenden Teil in Deutschland oder von deutschen DoktorandInnen im Ausland angefertigt sein.

Bewerbungen bzw. Vorschläge müssen in elektronischer Form eingereicht werden. Sie müssen enthalten:

- die Dissertationsschrift
- eine Zusammenfassung mit Erläuterungen zur Bedeutung der Arbeit
- eine Publikationsliste
- einen Lebenslauf

Bitte geben Sie an, ob Sie Mitglied der GfG oder einer anderen Fachgesellschaft sind.

BewerberInnen oder die vorschlagende Person müssen Mitglied der Gesellschaft für Genetik sein.

Die eingereichten Arbeiten werden von einer Jury bestehend aus Vorstands- und Beiratsmitgliedern der Gesellschaft für Genetik bewertet.

Die Verleihung des Preises erfolgt jeweils im Rahmen der Jahrestagung der Gesellschaft für Genetik bei der PreisträgerInnen die Promotionsarbeit in einem Vortrag vorstellen.

Teilnahme

Bewerbungen bzw. Vorschläge müssen bis spätestens **30. Juni 2022** beim Präsidenten der Gesellschaft für Genetik eingereicht werden:

Prof. Dr. Gerhard H. Braus
Georg-August-University Göttingen
Institute of Microbiology and Genetics
Department Molecular Microbiology and Genetics
Grisebachstraße 8
D-37077 Göttingen (Germany)

Email: gbraus@gwdg.de

https://www.gfgenetik.de/doktorandenpreis
https://www.gfgenetik.de