Final Program

von-Behring-Röntgen-Symposium 2014

New Concepts in Chronic Disease
Microbes, Metabolism and Inflammation

October 16th – 18th, 2014
Marburg, Germany

Alte Aula, Philipps University Marburg (October 16th, 2014)
Cineplex Marburg (October 17th – 18th, 2014)

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Philipps Universität Marburg

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

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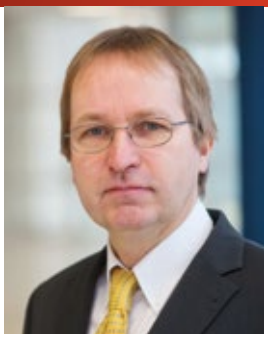
Publisher | For the Scientific Committee:
Universities of Giessen and Marburg
Prof. Dr. Harald Renz

WELCOME ADDRESS



Dear Colleagues,

It is a privilege and great honor to welcome all participants of the von-Behring-Röntgen-Symposium 2014. The theme of this international conference is "New Concepts in Chronic Disease – Microbes, Metabolism and Inflammation". External factors and life style conditions have come into the focus of research on chronic (inflammatory) diseases. Two concepts, the Hygiene hypothesis (endogenous and environmental microbes) and the Biodiversity hypothesis were introduced to explain chronic diseases. I am pleased that the conference committee chaired by Prof. Renz and Prof. Chakraborty invited such a distinguished group of scientists to assemble in Marburg to discuss these timely subjects.

The Philipps-Universität Marburg together with the Justus-Liebig-University Giessen have a longstanding tradition and a strong focus on anti-inflammatory, anti-infective and antibacterial research; so the topic of this symposium fits nicely to the venue of the conference.

May the conference be a success for all of you. I wish you a pleasant stay in Marburg.

Prof. Dr. Ulrich Koert
Vice President for Research, Philipps-University Marburg

WELCOME ADDRESS

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Dear distinguished conference participants,

I am very pleased that there will be again an international and interdisciplinary group of researchers attending the von-Behring-Röntgen-Symposium, which was first held in 2009 and is home at the University of Marburg this year.

As scientists observe, the concerns of chronic (inflammatory) diseases are continually growing. Not only allergies, but also autoimmune diseases, psychiatric diseases and others are on the agenda. Researchers moved from an intrinsic approach to examining external conditions in order to understand this development. The symposium on "New Concepts in Chronic Disease – Microbes, Metabolism and Inflammation" will provide newest insights into the pathogenesis of chronic (inflammatory) diseases, especially on the link between external factors, the role of microbes, and the influence on metabolic and immune functions. Leading international scientists will present latest updates on their research in this area and thus contribute to a better understanding of these diseases.

The excellence of Mittelhessen as a medical location in this field and many others is acknowledged both nationally and internationally, not only since the foundation of the Universities of Marburg and Giessen Research Alliance: The enormous potential of the region is demonstrated by the participation in several German centers for health research as well as large collaborative projects in the Excellence Initiative of the federal and state governments, special research areas of the DFG and the state excellence program LOEWE. Giessen and Marburg represent the third largest university medical center in Germany.

As you can see, Mittelhessen is in many ways a „central" place for medicine in Germany. At this very place, the international symposium shall provide the basis for a network for chronic diseases, promoting scientific communication and exchange. I wish all participants an interesting and rewarding symposium with lots of inspiring academic insights and opportunities to exchange ideas.

Prof. Dr. Joybrato Mukherjee
President of Justus-Liebig-University Giessen

Sehr geehrte Damen und Herren,

wir freuen uns sehr, in diesem Jahr bereits das fünfte von-Behring-Röntgen-Symposium unterstützen zu können. Ich begrüße Sie alle im Namen unserer Stiftung besonders herzlich.

Die Aufgabe der im Jahr 2006 vom Land Hessen gegründeten Von Behring-Röntgen-Stiftung ist die Förderung der Forschung und Lehre an den medizinischen Fachbereichen der Justus-Liebig-Universität Giessen und der Philipps-Universität Marburg. Mit ihrem Stiftungskapital in Höhe von 100 Millionen Euro gehört sie zu den größten Medizinstiftungen in der Bundesrepublik Deutschland.

Seit dem Jahr 2009 fördern wir mit der regelmäßigen Unterstützung von internationalen Symposien gezielt und nachhaltig die wissenschaftliche Kommunikation zu aktuellen medizinischen Forschungsthemen.

Das diesjährige von-Behring-Röntgen-Symposium, das gemeinschaftlich von Marburger und Giessener Wissenschaftlern organisiert wurde, beschäftigt sich mit Highlights aus der Biomedizinischen Forschung in Bezug auf chronische Erkrankungen. Im Mittelpunkt steht die Interaktion zwischen Mikroben, Inflammation und Metabolismus.

Das umfangreiche Tagungsprogramm verspricht eine vielseitige und interessante Auseinandersetzung mit diesem Fachthema. Wir freuen uns, dass es den Organisatoren dabei gelungen ist, viele hochkarätige nationale und internationale Wissenschaftler und Kliniker als Referenten zu gewinnen.

Den Tagungsleitern Herrn Prof. Dr. Harald Renz aus Marburg und Herrn Prof. Dr. Trinad Chakraborty aus Giessen sowie dem wissenschaftlichen Komitee danken wir ganz besonders für ihr großes und sichtbares Engagement.

Allen Teilnehmern und eingeladenen Referenten wünschen wir eine anregende und erfolgreiche Tagung in Marburg, die sicherlich viele neue und gewichtige Impulse für die weitere Arbeit in diesem wichtigen und spannenden Forschungsfeld geben wird und uns allen damit zukünftig viel helfen kann.

Friedrich Bohl
President, Von Behring-Röntgen-Stiftung

WELCOME ADDRESS

Dear Colleagues,

Chronic diseases, in particular, chronic inflammatory conditions, are considered as the new "epidemic of the 21st century". They include autoimmunities, allergies, neurologic diseases, and vascular-metabolic conditions. Recent evidence indicates that the pathogenesis of these diseases share common components including the dysregulation of the immune responses, the contribution of microbes and dysfunction of metabolic pathways.

The Medical Faculties of The Universities in Marburg und Giessen are proud to host this year's von-Behring-Röntgen-Symposium, which is devoted to recent developments in this field. In Marburg we are looking back to more than 100 years of history of excellence in immunology and microbiology research and patient care. In 1901 the first Nobel Award was handed to Emil von Behring for his discoveries in vaccination research. Inflammation and Infection is one of the major priority areas for research and development of our faculty.

The research area of Inflammation and Infection is embedded in an excellent environment including a new research building (Center of Tumor and Inflammation), which was recently opened, the development of state-of-the-art co-facilities for various key technologies, which are shared by several strategic research consortia including The National (German) Lung Center (DZL) and The German Center for Infectious Disease (DZIF) as well as The Universities of Giessen and Marburg Lung Center (UGMLC).

The Medical Faculties are proud that this year's von-Behring-Röntgen-Symposium is devoted to these important diseases and that such a prestigious group of internationally renowned investigators followed our invitation to come to Marburg to present the latest research and discoveries in this area.

Prof. Dr. Helmut Schäfer
Dean, Faculty of Medicine, Philipps-University Marburg

Dear Colleagues,

I welcome you on behalf of the organisers and The Faculty of Medicine of the Justus-Liebig-University to this year's von-Behring-Röntgen-Symposium entitled "New concepts in chronic diseases – Microbes, Metabolism and Inflammation". The von-Behring-Röntgen Foundation was set up in 2006 to support and promote research and teaching at The Medical Faculties of The Universities of Giessen and Marburg. As a key activity it hosts annual international symposia on topics related to profile areas of research at both medical faculties. I am extremely grateful to the members of the Executive Board of the Foundation for their support of this symposium.

Infection, inflammation and immunity are key areas of research at both medical faculties and are funded through competitive research grants obtained from regional, national and international funding agencies. Research into infection and immunity is addressed in a large variety of projects within the German Health Centres, in particular within the German Centre of Infection Research and the German Centre of Lung Research which are located at both faculties. Research into infectious diseases is addressed within the Collaborative Research Centre "RNA viruses" and the transregional Collaborative Research Centre "Innate immunity of the Lung", both of which are funded by the German Science Research Council (DFG). Funding of local research networks in the areas of cancer and inflammation, infertility and reproduction by the LOEWE excellence initiative State of Hessen, European-funded research via the FP8 program or European Research Networks, as well as individual grants from a wide range of institutions are testimonies to the high level of research activity and are the visible signposts of this successful interfaculty research profile.

The prevalence of chronic non-communicable diseases (NCDs) has been increasing over the last 50 years, mostly in industrialized countries. The major NCDs include cardio-vascular disease, metabolic syndrome (obesity, type II diabetes), cancer and chronic lung disease (asthma and allergy). Environmental factors including life style (e. g. nutrition, exercise, stress and others) affect NCDs. This concept has been extended by the perception that the risk of developing NCDs and allergies is determined early in life and led to the

postulation of an early origin of adult disease. Environmental and protective effects on NCDs as described by the Hygiene Hypothesis are thought to include specifically bacteria and bacterial products. Studies in these fields are being fuelled by our ability to carry out genome-based analysis of local microbiota affected by metabolic and immunological processes. It has been demonstrated that diseases like obesity, allergy and neurodegenerative disorders are affected by changes in the composition of the microbiom. The symposium will review the scientific progress in this field.

On behalf of all members of our faculty, I wish you a successful and inspirational symposium with new ideas and rewarding discussions with colleagues and friends. Finally, I wish to take this opportunity to thank the speakers and the participants for their contributions to the meeting, our guests, both national and international for taking valuable time to present their ideas and results, and the organisers of the meeting for putting together an excellent program and for working hard to make it a highlight of the joint activities of The Faculty of Medicine in Giessen and Marburg.

Prof. Dr. Trinad Chakraborty
Dean, Faculty of Medicine,
Justus-Liebig-University Giessen

Dear Colleagues, Dear Fellow Scientists,

The burden of chronic (inflammatory) diseases are constantly rising! This trend is observed for autoimmune diseases, allergies, metabolic conditions, neuro-degenerative and psychiatric diseases, and more. Over the last years, the research focus shifted from the contribution of genetic (intrinsic) factors to the better understanding of changes in life style conditions (external factors). Based on new data, several concepts have been proposed to explain this trend. They include the Hygiene Hypothesis, the role of environmental and endogenous microbes, as well as the Biodiversity Hypothesis. This von-Behring-Röntgen-Symposium aims to update on recent exciting findings on the multi-directional relationship between life style factors, the role of microbes, and the impact on metabolic and immune functions. These important topics will be covered by leading international scientists, who will present the latest update on their research in this area. Therefore, this symposium will provide a state-of-the-art update on the advances in a better understanding of the pathogenesis of chronic (inflammatory) diseases. We are very proud to bring together an international and interdisciplinary group of researchers discussing these topics with us.

We wish you all an inspiring conference!

For The Scientific Committee
Prof. Dr. Harald Renz

CONGRESS VENUES

Congress Venue October, 16th, 2014
Alte Aula, Philipps University Marburg
Lahntor 3
D-35037 Marburg, Germany

Congress Venue October, 17th – 18th, 2014
Cineplex Marburg
Biegenstraße 1
D-35037 Marburg, Germany

CONGRESS HOURS

Thursday, October 16th, 2014
1.00 PM – 6.00 pm
Registration: 12.00 pm
Alte Aula

Friday, October 17th, 2014
8.30 AM – 6.30 pm
Registration: 07.45 am
Cineplex

Saturday, October 18th, 2014
8.30 am – 1.00 pm, Cineplex

SOCIAL PROGRAM

Get-together | Reception & dinner buffet
Thursday, October 16th, 2014
6.00 PM, Alte Aula

Get-together | Reception & dinner buffet – with live music by "Schmachtigallen"
Friday, October 17th, 2014
6.30 PM, Cineplex

LOCATION

CONGRESS SECRETARIAT

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Institute of Laboratory Medicine
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E-Mail: Harald.Renz@uk-gm.de

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ACCREDITATION | CME

The von-Behring-Röntgen-Symposium was certified with 18 CME credits by the 'Landesärztekammer Hessen'. Please do not forget to bring your Barcode-stickers (EFN-No.) for each day.

SPONSORED BY

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Division of Pulmonology, Department of Internal Medicine,
University of Marburg

Michael Zemlin
Children's Hospital, University of Marburg

THURSDAY, OCTOBER 16th, 2014

Alte Aula, Philipps University Marburg

12.00 pm	**Registration**
1.00 pm	**Welcome** Prof. Dr. Ulrich Koert Vice President for Research, Philipps-University Marburg Prof. Dr. Joybrato Mukherjee, President of the Justus-Liebig-University Giessen Friedrich Bohl, President of the Von Behring-Röntgen-Stiftung Prof. Dr. Trinad Chakraborty, Dean Faculty of Medicine, Justus-Liebig-University Giessen Prof. Dr. Helmut Schäfer, Dean Faculty of Medicine, Philipps-University Marburg Prof. Dr. Harald Renz, Chair of the Scientific Committee
1.30 – 3.20 pm	**Environment, Biodiversity and Microbes** Chairs: Werner Seeger, Giessen; Ulrich Steinhoff, Marburg
1.30 pm	**Hygiene hypothesis and chronic inflammatory diseases; Loss of contact with coevolved microorganisms and the pathophysiology depression** Graham Rook, London
2.00 pm	**Surviving in hostile territory: Helicobacter pylori, the gastric microbiota and diseases of the stomach** Sebastian Suerbaum, Hannover
2.30 pm	**Vitamin-D and asthma** Scott Weiss, Boston
3.00 pm	**Bioinformatics – a grand challenge to integrate microbes, metabolism and inflammation** Fiona Brinkman, Vancouver
3.30 pm	**Coffee break**

4.15 – 5.45 pm	**The Gut Microbiome** Chairs: Michael Lohoff, Marburg; Bernhard Schieffer, Marburg
4.15 pm	**Microbiome and inflammation in early life** Hans Bisgaard, Copenhagen
4.45 pm	**Novel insights on how the gut microbiota impacts on experimental thrombus formation** Christoph Reinhardt, Mainz
5.15 pm	**Metagenomics of diabetic foot infections** Trinad Chakraborty, Giessen
5.35 pm	**Control of food-induced inflammation by Peyer's patches** Ulrich Steinhoff, Marburg
6.00 pm	**Get-together | Reception & dinner buffet**

FRIDAY, OCTOBER 17th, 2014

Cineplex Marburg

07.45 am	**Registration & Welcome coffee**
8.30 – 10.20 am	**From Biomarkers to Mechanisms in Neuroinflammation** Chairs: Tilo Kircher, Marburg; Petra Pfefferle, Marburg
8.30 am	**Neurobiological effects of the immune system in the brain** Bernhard Baune, Adelaide
9.00 am	**Biomarkers in psychiatry: Focus on inflammatory processes** Sabine Bahn, Cambridge
9.30 am	**Animal models of developmental neuroinflammation: Relevance to schizophrenia and beyond** Sandra Giovanoli, Zurich
10.00 am	**A metabolic twist in neurodegeneration and neuroinflammation** Carsten Culmsee, Marburg

10.20 pm	**Coffee break**
11.05 – 12.45 pm	**From Hygiene to Biodiversity Hypothesis** Chairs: Markus Neurath, Erlangen; Klaus Preissner, Giessen
11.05 am	**Development of wheezing and atopy: lessons from pediatric cohort studies** James Gern, Madison
11.35 am	**Gut microbes and allergies, including asthma** Shannon Russell, Vancouver
12.05 pm	**The biodiversity hypothesis and chronic inflammatory diseases** Tari Haahtela, Helsinki
12.35 pm	**Allergyprotective effects of environmental bacteria exposure – insights from animal models** Holger Garn, Marburg
12.55 pm	**Lunch & Poster Session**
2.25 – 4.15 pm	**Bacteria, Viruses and Mucosal Inflammation** Chairs: Stephan Becker, Marburg; John Ziebuhr, Giessen
2.25 pm	**Chronic viral infection in disease development** Thaddeus Stappenbeck, St. Louis
2.55 pm	**Preterm versus term neonates: Human immuno-ontogeny with or without microbiota** Michael Zemlin, Marburg
3.15 pm	**Immunopathogenesis of inflammatory bowel diseases** Markus Neurath, Erlangen
3.45 pm	**Impaired immune reactivity – role of exosomal cell-to-cell communication and miRNA networks** Bernd Schmeck, Marburg
4.05 pm	**Coffee break**

4.50 – 6.20 pm	**From Early Development to Chronic Inflammation** Chairs: Elke Roeb, Giessen; Thomas Braun, Bad Nauheim
4.50 pm	**Perinatal challenges and disease development** Petra Arck, Hamburg
5.20 pm	**Inflammation in metabolic disease** Triantafyllos Chavakis, Dresden
5.50 pm	**Molecular control of cardiovascular remodeling processes in chronic disease conditions** Thomas Braun, Bad Nauheim
6.10 pm	**Adipokines as drivers of inflammation** Ulf Müller-Ladner, Giessen
6.30 pm	**Get-together | Reception & dinner buffet – with live music by "Schmachtigallen"**

SATURDAY, OCTOBER 18th, 2014

Cineplex Marburg

8.00 am	**Welcome coffee**
8.30 – 10.20 am	**Environmental Impacts on Allergy and Autoimmunity** Chairs: Philipp Yu, Marburg; Lienhard Schmitz, Giessen
8.30 am	**Microbiota and food allergies** Talal Chatila, Boston
9.00 am	**Epigenetics in inflammatory rheumatic diseases** Steffen Gay, Zurich
9.30 am	**Extracellular RNA as a new alarmsignal in inflammation** Klaus Preissner, Giessen
9.50 am	**Epigenetic control of allergic inflammation** Harald Renz, Marburg

10.10 am	**Early control of Listeria by bactericidal/permeability-increasing protein** Markus Schnare, Marburg
10.30 am	**Coffee break**
11.15 – 12.55 pm	**Gene by Environment Interactions in Psychiatric Disorders** Chairs: Jürgen Hennig, Giessen; Holger Garn, Marburg
11.15 am	**Gene-environment interaction in the origin of the major psychoses** Jim van Os, Maastricht
11.45 am	**Genetic moderator of the first molecular response to stress risk and protective factors for the development of stress-related psychiatric disorders** Elisabeth Binder, Munich
12.15 pm	**Gene environment interactions onto the brain** Tilo Kircher, Marburg
12.35 pm	**Inflammatory risk genes and the brain in affective disorders** Udo Dannlowski, Marburg
12.55 pm	**Poster Awards**
1.00 pm	**End of Symposium**

01

Uncovering new glomerular disease-relevant genes by translational profiling of podocytes in vivo

Ivica Grgic[1,2], Andreas F. Hofmeister[1,2], Giulio Genovese[3,4], Andrea J. Bernhardy[3], Hua Sun[3], Omar H. Maarouf[2], Vanesa Bijol[5], Martin R. Pollak[3,4], Benjamin D. Humphreys[2,6]

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[2] Renal Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3] Division of Nephrology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA
[4] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, Massachusetts, USA
[5] Department of Pathology and Laboratory Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[6] Kidney Group, Harvard Stem Cell Institute, Cambridge, Massachusetts, USA

Identifying new biomarkers and therapeutic targets for podocytopathies such as focal segmental glomerulosclerosis (FSGS) and other inflammatory glomerular diseases requires a detailed analysis of transcriptional changes in podocytes over the course of disease. Here we used translating ribosome affinity purification (TRAP) to isolate and profile podocyte-specific mRNA in two different models of FSGS. Expression of enhanced green fluorescent protein-tagged ribosomal protein L10a in podocytes under the control of the collagen-1α1 promoter enabled podocyte-specific mRNA isolation in a one-step process over the course of disease. This TRAP protocol robustly enriched known podocyte-specific mRNAs. We crossed col1α1-L10a mice with the actn4-/- and actn4+/K256E models of FSGS and analyzed podocyte transcriptional profiles at 2, 6, and 44 weeks of age. Two upregulated podocyte genes in murine FSGS (CXCL1 and DMPK) were found to be upregulated at the protein level in biopsies from patients with FSGS, validating this approach. There was no dilution of podocyte-specific transcripts during disease. These are the first podocyte-specific RNA expression data sets during aging and in two models of FSGS. This approach identified new podocyte proteins that are upregulated in FSGS and will help to define novel biomarkers and therapeutic targets for human glomerular disease.

02

MiR-210 and miR-155 are upregulated in cystic fibrosis cells and involved in Fe-S protein assembly via ISCU downregulation and hemeoxygenase-1 expression via BACH1.

Shashi Chillappagari[1]*, Virajith Garapati[1], Poornima Mahavadi[2], Oliver Stehling[3], Roland Lill[3], Bernd T. Schmeck[1], Markus O. Henke[4]

[1] Institute for Lung Research, Philipps-University Marburg, Marburg, Germany
[2] Department of Internal Medicine, Justus-Liebig-University Giessen, Giessen, Germany
[3] Institut für Zytobiologie, Philipps-Universität Marburg, Marburg, Germany
[4] Comprehensive Pneumology Center, Asklepios Fachkliniken München-Gauting, Germany

Cystic fibrosis (CF) is an inherited lung disorder associated with chronic endobronchial inflammation. Hemeoxygenase-1 (HMOX1), an enzyme involved in heme degradation, is upregulated in inflammation and negatively regulated via the transcription factor BACH1. Here we studied the role of microRNAs (miRs) in the heme metabolism of cystic fibrosis bronchial epithelial cells (CFBE410-), applying qRT-PCR, luciferase promoter assays, immunoblotting, and enzyme activity assays. In comparison to normal human bronchial epithelial cells (16HBE140-) miR-210 and miR-155 were 4- to 5-fold upregulated in CFBE410- cells. MiR-210 has been implicated in the negative regulation of the mitochondrial iron-sulfur (Fe-S) cluster assembly scaffold ISCU, and consistently we found ISCU expression being decreased in CF cells. Accordingly, activities of the Fe-S enzymes aconitase, succinate dehydrogenase, and ferrochelatase (FECH) were also diminished. Despite this latter constraint total heme content was higher in CF than in control cells. Intriguingly, HMOX1 expression in CF cells was severely curtailed, implying that despite the low FECH activity heme formation was in favour of heme degradation. Moreover, we could link HMOX1 expression to TLR4 surface expression via miR-155 which in turn negatively regulates the expression of BACH1. Since TLR4 expression is impaired in CF we applied an TLR4 inhibitor in normal HBE cells and found levels of both miR-155 and BACH1 being increased in a dose-dependent manner. Hence our results suggest that in CF miR-155 is ineffective in repressing BACH1, leading to lowered HMOX1 levels and altered heme catabolism, while miR-210 affects cellular Fe-S assembly with potential general impact on iron homeostasis.

03
Free fatty acids – potential contributors to chronic inflammatory rheumatic diseases

Klaus Frommer[1], Andreas Schäffler[2], Stefan Rehart[3], Ulf Müller Ladner[1], Elena Neumann[1]

[1] Justus-Liebig-University of Giessen, Department of Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany
[2] Justus-Liebig-University of Giessen, Department of Internal Medicine III, Endocrinology, Diabetes, Metabolism, Giessen, Germany
[3] Department of Orthopedics and Trauma Surgery, Markus-Hospital, Frankfurt, Germany

Obesity, a known risk factor for arthritic diseases, increases mechanical stress on joints. Additionally, factors released from adipose tissue probably also contribute to joint damage and this may include free fatty acids (FFA), for which chronically elevated levels have already been linked to inflammatory cardiovascular and metabolic diseases.
To test our hypothesis that FFA play role in arthritic diseases, we investigated the effect of FFA on key effector cells of arthritis. Additionally, involvement of TLR4 in FFA signaling was analyzed.
Synovial fibroblasts (SF) from rheumatoid arthritis (RA), osteoarthritis and psoriatic arthritis patients all responded to FFA stimulation with increased secretion of the proinflammatory cytokine IL 6, the chemokines IL-8 and MCP-1, as well as the matrix-degrading enzymes MMP-1 and MMP-3. There were no significant differences in the effects induced by saturated and unsaturated FFA on RASF. In contrast, human chondrocytes secreted more IL-6 upon stimulation with saturated FFA than with unsaturated FFA. Only higher concentrations of FFA (100 µM, but not 10 µM) were able to induce a significant increase of IL-6 secretion by endothelial cells. Palmitic acid-induced IL-6 secretion of RASF was strongly decreased by blocking intracellular or extracellular TLR4 signaling as well as by blocking FFA transport into the cell.
The data show that FFA are not only part of the energy metabolism but may also contribute to articular inflammation and degradation in arthritis, and this involves TLR4 signaling. Therefore, elevated FFA levels may be another element in the multifactorial pathogenesis of arthritic diseases.

04

Joint regeneration after artificially induced osteoarthritis in the red-spotted Newt Notophthalmus viridescens

Christiane Schönfeld[1], Sony Adhi Susanto[1], Matthias Geyer[1], Carina Schreiyäck[1], Uwe Lange[1], Mario Looso[2], Thomas Braun[2], Ulf Müller-Ladner[1], Elena Neumann[1]

[1] Justus-Liebig-University of Giessen, Internal Medicine and Rheumatology, Kerckhoff-Klinik, Bad Nauheim, Germany
[2] Max-Planck-Institute for Heart and Lung Regeneration, Bad Nauheim, Germany

When tissue damage occurs in mammals, damaged tissue often is not substituted with functional but fibrotic scar tissue which might significantly impair organ function. In contrast, many urodele amphibians have a remarkable regenerative capacity. Damaged tissues or even whole lost appendages will be almost perfectly regenerated. In our working group the red-spotted newt Notophthalmus viridescens has been established as a model organism to study endogenous knee joint regeneration in adult vertebrates. Osteoarthritis (OA)-like symptoms can be induced in these animals by intra-articular injection of collagenase or after surgical removal of articular cartilage. However, joint function is completely restored after approximately 3 months. The underlying mechanisms guiding regeneration are poorly understood. To identify key players involved in knee joint regeneration, a cDNA array was carried out after artificial knee damage in newts. Candidate genes were selected and analyzed on the mRNA level by Real Time PCR and on the protein level by immunohistochemistry (IHC). Several matricellular proteins including tenascin-C (TN-C) were found to be upregulated during the regenerative process. IHC analysis revealed high TN-C expression in the periosteum during the early phase of regeneration. During later stages (>40 days after injury) TN-C expression was also detectable in regenerating cartilage. In ongoing in vitro knock-down experiments in newt-derived cell lines and primary newt cells (chondrocytes/fibroblasts) the effects of TN-C deficiency on cellular behaviour will be further analyzed. In vitro studies might help to identify molecular pathways guiding regeneration and might facilitate the development of new OA treatment options.

05

Lipopolysaccharides induce radiotherapy resistance in non-small cell lung cancer cell lines

Mira Yasemin Gökyildirim[1], Florentine Subtil[2], Ulrich Grandel[1], Gabriele Dahlem[1], Florian Leinberger[2], Rita Engenhart-Cabillic[2], Werner Seeger[3], Ulf Sibelius[1], Friedrich Grimminger[1], Katja Hattar[1]

[1] Medical Clinic IV/V, Department of Internal Medicine, UGMLC, University of Giessen, Germany
[2] Clinic for Radiotherapy and Radiooncology, UGMLC, Philipps-University Marburg, Germany
[3] Medical Clinic II, Department of Internal Medicine, UGMLC, University of Giessen, Germany

Pulmonary infections are common complications in patients with lung cancer and worsen prognosis. The most common pathogens found in patients with lung cancer are gram-negative bacteria. Their virulence is caused by cell wall components, especially by Lipopolysaccharides (LPS). Therefore I analysed, if sensitivity to radiotherapy, is modified by LPS. LPS is known to activate multiple inflammatory pathways in pulmonary epithelial cells. This could induce radiotherapy resistance in lung cancer cells.
In this study, cells of the human adenocarcinoma cell line H1975 as well as of the squamous cell carcinoma cell line H520 were treated with different doses of LPS (0, 0,1, 1 and 10 µg/ml) and exposed to ionizing radiation (0, 1, 2, 4, 6 and 8 Gy).
Ionizing radiation induced a reduction in survival of both cell lines. Interestingly, LPS promotes radiotherapy resistance in the human adenocarcinoma cell line, but not in squamous cell carcinoma. This effect was dose dependent and most pronounced when 10µg/ml LPS were used. In H1975 cells the survival fraction (AUC) increased in the presence of LPS.
When screening for a possible target gene by real-time RT-PCR, the expression of EGFR, IL8, VEGF and COX-2 were not significantly regulated in H1975 cells after irradiation, while EGFR was slightly up-regulated. LPS treatment increases expression of all target genes. Interestingly, VEGF as well as COX-2 and potentially also EGFR seem to be over-additively induced by LPS when cells were irradiated. This might offer one mechanism underlying radiotherapy resistance in response to LPS.

06

C1q/TNF-related protein-3 (CTRP-3) attenuates lipopolysaccharide (LPS)-induced systemic inflammation and adipose tissue Erk-1/-2 phosphorylation in mice in vivo

Andreas Schmid, Jutta Schlegel, Thomas Karrasch, Andreas Schäffler

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Objective: The C1q/TNF-related proteins (CTRPs) comprise a growing family of adiponectin paralogous proteins. CTRP-3 represents a novel adipokine with strong expression in adipose tissue and was shown to inhibit chemokine and cytokine release in adipocytes and monocytes in vitro. The aim of the study was to gain the proof of principle that CTRP-3 is a potent anti-inflammatory adipokine in vivo.
Methods: C57BL/6N mice were treated intraperitoneally (i.p.) with bacterial lipopolysaccharide (LPS) for 2 hours. The effects of a 30 minutes pre-treatment with CTRP-3 i.p. or intravenously (i.v.) on systemic and on epididymal, perirenal and subcutaneous adipose tissue inflammation was analyzed via real-time RT-PCR, ELISA and Western blot analysis.
Results: LPS (1µg i.p.) significantly increased serum IL-6 and MIP-2 levels as well as epididymal adipose tissue expression of IL-6 and MIP-2 in mice, whereas CTRP-3 (10µg i.p.) alone or PBS (i.p.) had no effect. Pre-treatment of mice by CTRP-3 i.p. prior to LPS application significantly attenuated LPS-induced cytokine levels but had no effect on adipose tissue cytokine mRNA expression. In contrast to i.p. application of CTRP-3, systemic i.v. application was not sufficient to inhibit LPS-induced cytokine levels or mRNA tissue expression. CTRP-3 given i.p. significantly attenuated LPS-induced phosphorylation of Erk-1/-2 in inguinal adipose tissue.
Conclusion: The present study shows the proof of principle that the novel adipokine CTRP-3 is a potent inhibitor of LPS-induced systemic inflammation and LPS-induced signalling in adipose tissue in vivo.

07

Streptococcus pneumoniae infection of bronchial epithelial cells induces specific changes in microRNA profile

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Streptococcus pneumoniae is a Gram-positive lactobacillales that usually colonizes the human nasopharynx but is also an important pathogen causing fatal infections like pneumonia. Within the past years it was found that microRNAs (miRNAs) play a crucial role as important transcriptional regulators of gene expression and inflammatory host response in infectious diseases. To date, there are no data addressing miRNA expression after pneumococci infection. For this purpose, we performed a global miRNA expression analysis of human bronchial epithelial cells (Beas-2B) infected with two different multiplicities of infection (MOIs) of S. pneumoniae (strain D39) compared to mock-infected and LTA-stimulated cells by Taqman Low Density Arrays. Out of 759 examined miRNAs we found 356 to be expressed. With regard to the MOIs we identified 19 and 17 significantly deregulated miRNAs after S. pneumoniae infection in contrast to mock infection. To identify miRNAs specific for S. pneumoniae infection we compared the results with LTA-stimulated cells. There, 13 significantly deregulated miRNAs were determined. Out of the aforementioned 19 and 17 miRNAs after S. pneumoniae infection only one and two miRNAs overlapped in LTA-stimulated cells, respectively. This indicates that the miRNA profile after infection varies between cells exposed to diverse MOIs. Furthermore, the results suggest that the miRNA profile is specifically altered in S. pneumoniae infection compared to LTA stimulation. These miRNAs might play an important role in human host response to Streptococcus pneumoniae. Further analysis and greater knowledge of the effect of this deregulated miRNAs within the infection could reveal potential therapeutic targets.
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08
Differential regulation of chitinase-3-like-1 in bacterial and viral infections

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The human lung epithelium is exposed to various pathogens, including the gram-positive bacterium Streptococcus pneumoniae, Influenza A virus (IVA) or Human Rhinovirus (HRV). During inflammation several factors are required for proper regeneration, e. g. Chitinase-3-like-1 (Chi3l1) that is known as a biomarker for several diseases and that predominantly acts in tissue repair and remodelling. Studies have shown that CHI3L1 is involved in bacterial clearance after S. pneumoniae infections but the exact function is still unknown. Furthermore, an indirect regulation of CHI3L1 expression via Notch1, TNFα and NF-κB signalling was identified after Hepatitis C viral infections. Interestingly, there is evidence for the contribution of microRNAs to this signalling pathway. In this study, we investigate the underlying mechanisms that are crucial for function of the chitinase-like glycoprotein. We show that both primary human differentiated bronchial epithelial cells (hBECs) and a bronchial epithelial cell line (Beas-2B) were capable of the expression and secretion of Chi3l1 following exposure to stimuli such as LTA, poly(I:C) and TNFα or infection with S. pneumoniae, IVA or HRV. In time course experiments we observed differential expression of the CHI3L1 transcript in bacterial or viral infections. Interestingly, components of known signalling factors as well as of microRNAs, that potentially target CHI3L1 or NOTCH1 3`UTRs, are regulated differentially within the analysed infections. Further investigations are needed to clarify the role of Chi3l1 and to evaluate its great potential not only as a biomarker in various diseases but also for the development of therapeutic strategies.

09

Differentially expressed miRNAs after legionella pneumophila infection of human macrophages

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Legionella pneumophila (L. p.) is a common cause of severe community-acquired pneumonia. This pathogen replicates primarily within alveolar macrophages and manipulates the host reaction by interfering with intracellular signaling pathways and gene transcription to support its own replication. MicroRNAs (miRNAs) have emerged as critical regulators of mRNAs and are also directly involved in the innate immunity and could therefore have an important function in the regulation of the immune response to Legionella. The aim of this work was to identify deregulated miRNAs following infection by means of small RNA sequencing experiments and advanced bioinformatics analysis to elucidate miRNA-associated pathomechanisms.
Primary blood-derived human macrophages of healthy donors were infected in vitro using the wild type strain L. p. Corby for 24 and 48 hrs, with a multiplicity of infection (MOI) of 0.25. Total RNA was isolated and miRNA libraries were prepared for Illumina small RNA sequencing.
Our analysis revealed infection-specific and statistically significant changes of miRNA expression in human macrophages, such as up-regulation of miR-146a and miR-155, as well as down-regulation of miR-221 and miR-125b. miRNA deregulation seems to be due to transcriptional regulation of miRNA promoters. Overexpression or knock down experiments of miRNAs were performed for functional characterization and showed an influence of selected miRNAs on bacterial replication.
In summary, the results have deepened our insight in the molecular interaction of L. pneumophila and its host cells and might help to establish potential new gene candidates for diagnosis and therapy.

10

The effect of an anti inflammatory vagus nerve stimulation on the cellular immune response in the rat brain during systemic inflammation

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Previous experiments indicated that stimulation of the vagus nerve has modulating, anti-inflammatory effects on the cellular immune response in the blood and the spleen, stabilising brain function. However, in these studies, underlying mechanisms remained largely unknown. Here, we aimed to investigate the potential effects of vagus nerve-stimulation for immune-to-brain communication focused on neurophysiological readouts and leukocyte migration to the brain during severe septic-like endotoxemia.
Systemic inflammation was induced by intravenous administration of lipo-polysaccaride (LPS; 5mg/kg). Animals received either no manipulation of the vagus nerve, vagus nerv stimulation, vagotomy or vagotomy plus vagus nerve stimulation of the distal trunk. Somatosensory evoked potentials (SEP) and evoked flow velocity response (EFVR) were measured as indicators of brain function and neurovascular coupling, respectively. 4.5 hours after LPS challenge animals were sacrificed and blood and brains collected for further analyses using immunohistochemistry, ELSIA as well as PCR.
LPS induced a decline of SEP-amplitudes and EFVR indicating a disturbance of brain function and microcirculation. This response was recovered by vagus nerve stimulation in LPS-treated animals. As for peripheral organs, LPS-stimulated neutrophil counts increased in the brain and colocalized with intercellular adhesion molecule (ICAM)-1 while they decreased in the circulation. Interestingly, vagal stimulation reduced colocalisation between neutrophil granulocytes and ICAM-1 and decreased nuclear translocation of the brain cell activation marker nuclear factor interleukin (NF-IL)6. Overall, our findings suggest beneficial, anti-inflammatory effects of vagus nerve stimulation on neurophysiological parameters that potentially are due to reduced interaction of neutrophil granulocytes with brain endothelial cells and decreased brain cell NF-IL6-activation.

11

CSF signaling via the peripheral CSF outflow pathway – an underscored pathophysiological link in neuroinflammation

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In virology it is established that neuroinflammation is triggered by antigen transported via the CSF outflow pathway (PCOP) along peripheral nerves, to join the interstitial tissue fluid, then taken up into the lymph, to develop within the peripheral lymph nodes a CNS specific immune reaction.
Review about a rarely studied phenomenon involving literature from 1872 – 2014 and recent studies.
Results: CSF cells can follow the CSF outflow at the cribriform plate (Goldmann et al 2006), which has in the meanwhile been shown in number of studies, taking place apparently also along spinal nerves (Schmitt et al 2011).
There is apparent plausibility that beyond proteins also microparticles and exosomes may have the ability to follow the PCOP along brain nerves and peripheral nerves. In addition, CSF signaling may take place at various sites of the widely distributed PCOP and accordingly might play an important role in the regulation of neuroinflammation in general, which was up to now nearly not specifically investigated (Bechter 2011). We recently showed that the physiological CSF outflow velocity in quiet sitting posture is about 10 cm per hour along all lumbar nerves and involves considerable CSF volumes (Bechter & Schmitz 2014).
Many though preliminary findings demonstrate increasing evidence that CSF signaling via the PCOP, but also at the PCOP is an underscored if not for long time unnoticed pathophysiological link in neuroinflammation of potentially considerable importance.

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Autistic-like behavior and altered epigenetic markers in mice lacking the Post-synaptic Scaffolding Protein SHANK1

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Autism spectrum disorders (ASD) are a class of neurodevelopmental disorders characterized by persistent social communication deficits across multiple contexts, together with repetitive patterns of behavior. Among the most promising ASD candidate genes is the SHANK gene family, including SHANK1. To study contribution of SHANK1 mutations to ASD symptoms throughout development, Shank1+/+, Shank1+/-, and Shank1-/- mice were compared in behavioral assays developed to detect social communication deficits and aberrant cognitive phenotypes as pups, juveniles, and adults. When assessing isolation-induced ultrasonic vocalizations (USV) as a measure for communication during early development, call rate exhibited the typical inverted U-shaped developmental pattern in all genotypes. However, Shank1-/- pups were found to be developmentally delayed and characterized by a less prominent inverted U-shaped call emission pattern, reflecting an overall reduction in USV. Those deficits in Shank1-/- mice were even more prominent when pups were tested across various social contexts. As juveniles, social approach and recognition were evident irrespective of genotype. In contrast, object recognition was affected by Shank1 deletion, with Shank1-/- mice not showing a preference for the novel object. In addition, alterations in certain epigenetic markers were found in the hippocampi of juvenile Shank1-/- mice. In adulthood, Shank1-/- males and controls displayed normal social approach, but impaired social recognition. Object recognition was additionally impaired in adult Shank1-/- males. Conversely, adult Shank1-/- females exhibited deficits in social recognition only. In summary, present findings indicate that Shank1 deletions lead to communication deficits and an aberrant cognitive phenotype, together with age- and sex-dependent effects on social behavior.

13

Oldie but goldie? Advanced paternal age as a risk factor for social deficits: from rats to humans

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Advanced paternal age (APA) is considered as a risk factor for neuropsychiatric disorders, such as autism (ASD). To study APA effects on brain and behavior, a large cohort of healthy subjects was investigated with the schizotypal personality questionnaire (SPQ-B) and the NEO-FFI. It was found that APA had linear effects on SPQ-B scores as well as neuroticism after controlling for maternal age, subjects' age, sex and level of education. Moreover, APA was linearly correlated with increased grey matter volume in the right parahippocampal cortex and right inferior frontal cortex. However, despite the fact that epidemiological studies demonstrated an association between APA and neuropsychiatric disorders, the underlying causality is not yet understood since experimental evidence in humans is not feasible. Therefore, we recently developed a rat model, comparing offspring from young (2 months) and old (12 months) fathers, while maternal age was the same in both conditions (2 months). By means of this detailed and longitudinal study, we found that rats from old fathers display behavioral alterations with relevance to all ASD core symptoms, including social communication deficits and impaired reversal learning. Furthermore, we observed alterations in the psychomotor response to drugs of abuse, in particular amphetamine. These findings indicate that at least part of the APA effects obtained in humans are not due to differences in personality traits or socio-economic status, but may be linked to reduced quality of spermatocytes due to epigenetic modifications or accumulating genetic deficits, i.e. mutations, as a consequence of "copy errors" during cell division.

14

Effects of urban upbringing on grey matter volume, white matter microstructure and executive functioning in healthy subjects

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Urban upbringing is one of the best-replicated environmental risk factors for schizophrenia. While the exact mechanisms are not well understood, a number of studies recently found effects on brain structure and stress-related function caused by urban upbringing as well as current urban living. The aim of the present study was to further elucidate the effects of urban upbringing on grey matter structure, fiber tract integrity and cognition in a large sample.
Two hundred ninety subjects were scanned with 3-Tesla and tested with a neuropsychological test battery. Urban upbringing was assessed and correlated with these measures.
Urban upbringing had a negative effect on executive functioning, bilateral dorsolateral prefrontal grey matter volume and fractional anisotropy in the left superior longitudinal fasciculus, left corticospinal tract and left superior corona radiate.
These results are comparable to findings in subjects at high risk for psychosis and first episode schizophrenia. The data may point to urban upbringing influencing brain structure and cognition in healthy subjects which may make them more liable to the outbreak of psychosis. Thus, this study is a step toward a better understanding of the role environmental factors play in the aetiology of schizophrenia.

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Social stress and delusions: how environmental factors predict the occurrence and intensity of delusions

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Psychopathological symptoms of psychosis, most prominently delusions and hallucinations, can be found in the general population and are onceptualized as a continuum (Freeman et al., 2011; Nuevo et al., 2012; Os, Hanssen, Bijl, & Ravelli, 2000). In accordance with the vulnerability –stress model, risk factors for the occurrence of psychopathological symptoms have been investigated: Negative affect and withdrawal from activities increase the risk for subsequent delusional moments whereas the presence of family or acquaintances reduces the occurrence of delusional moments (Myin-Germeys, Nicolson, & Delespaul, 2001). On the other hand, strong connections between the occurrence of delusions and self-esteem were found (Kesting, Mehl, Rief, Lindenmeyer, & Lincoln, 2011; Thewissen, Bentall, Lecomte, van Os, & Myin-Germeys, 2008) The present study explores whether the occurrence of delusions is influenced by environmental factors (presence of familiy, friends, social inclusion / exclusion) in a healthy sample (n = 35). Data were collected with a structured diary technique, the Experience Sampling Method (ESM). Participants answered questions on an IPod about psychopathological symptoms, mood-states, environmental context and self-evaluation (self-esteem, self-acceptance and self-stigma) ten times a day within a random interval of 80 minutes for six days. In general, persons reported more severe delusions and other psychopathological symptoms if they were surrounded by other persons, but this did not depend on the quality of the relationship. Moreover, delusions occurred more often if persons felt social exclusion, e. g. less acceptance by their social contacts. Finally, delusions were more pronounced in situations if persons felt self-stigmatized or reported low-self-esteem. In order to reduce delusional symptoms in patients with psychosis it might be useful for CBT interventions to focus more closely on the improvement of their social contacts and the reduction of self-stigmatization.

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Parental sampling of nasal and stool microbiome in a birth cohort – a feasibility study

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Studying development of microbiome during early childhood requires frequent sampling of biomaterials preferably by the parents themselves. In preparation of a birth cohort study focusing on infections, microbiome and development of immunity, we conducted a feasibility study. Parents of children 1-3 years old were recruited through kindergartens in Braunschweig for a three month study in winter of 2013 and asked to fill out a daily diary on respiratory and gastrointestinal infections as well as perform nasal and dirty nappy swabs every month. The samples were mailed to our study center and stored at -80 °C. Advertising the study by flyers and presenting the study to parents, we recruited parents of 75 children (~8% of those who could be potentially reached by flyers) for this rather intensive observational study. Of those who participated over 80 % provided samples for analysis of nasal or stool microbiome. Asked about acceptability of collecting samples, most parents gave positive feedback. Over 50% reported that could imagine to participate in a long term study with daily symptom diaries and frequent collection of biosamples. Our findings demonstrate that while only a small proportion of the corresponding population is willing to participate in such study. Those who participate are able to collect regular samples. In the end of 2014, we will start recruitment for an infectiological birth cohort in Braunschweig and Hannover. We expect to win 500-1000 participants until 2016.

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Folate status as a modifier of epigenetic profile in human neonatal CD4+ T cells

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Normal immune development in early life is important for the protection against inflammatory diseases such as allergies. Changes in the dynamics of gene-environment interactions in early life are implicated in the rising of disease predisposition. Exposure to different environmental factors during pregnancy can play a very important role in the development of immune response. In the present study we sought to examine the effects of high in utero exposure to folate on neonatal epigenetic profiles of genes associated with allergic inflammation. 23 neonates were selected from a large prospective cohort including the two extremes of maternal folate levels. Different epigenetic modifications, including DNA methylation and histone acetylation were analyzed at allergy-associated genes. Furthermore, cytokine levels were measured following both polyclonal and allergen specific stimulation of cord blood mononuclear cells. There was a bias toward a Th2 phenotype by looking at the whole cohort epigenetic profile. Histone acetylation on both H3 and H4 histones at the GATA3 locus and H4 acetylation at the IL9 locus was increased in children born to mothers with high folate levels together with decreased acetylation at the IFNG locus in the same group. Cytokine levels were not significantly differed between the two groups. Nevertheless, cytokine ratios of Th2/Th1 showed an increase in the high folate group. Maternal folate as a known methyl donor is likely influencing the development of the fetal immune system by modifying epigenetic marks like histone acetylation. High folate levels render allergy-associated genes more permissive for transcription and might thus affect disease development later in life.

18
Microbiome of the neonatal lung

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Asymptomatic bacterial colonisation starts immediately after birth, but it is unknown if this is also true for the lung. Bacterial infections of the lung are a major cause of morbidity, especially in preterm infants, and are involved in development of chronic lung disease.
To investigate the microbiome of the neonatal lung, we analysed 48 tracheal aspirates from intubated, preterm and term neonates. In addition to conventional microbiological culture and microscopy, bacterial 16S ribosomal DNA was amplified via PCR followed by denaturing high-performance liquid chromatography on a WAVE System (Transgenomic, Omaha, Nebraska) for molecular diagnosis.
16 different bacterial species were identified in the tracheal aspirates. We did not observe an overall difference in sensitivity for both methods, concerning types of species found and number of positive results. Both the conventional analysis and the genomic approach revealed at least one bacterial species in 36% of the samples, respectively. However, the two methods yielded consistent findings only in 66 % of the positive samples. 29% of the infants with bacteria in their tracheal aspirates had clinical and laboratory signs of systemic infection. Patients with pulmonary colonization developed a chronic lung disease (Bronchopulmonary Dysplasia) significantly more often than uncolonized patients (p=0,048). In one patient, a genomically detected Lactobacillus crispatus could not be grown in conventional culture although bacteria were seen by microscopy.
The neonatal lung is not sterile as assumed formerly. Further studies have to differentiate between germs of the physiological flora, non-invasive colonization and infection and their prognostic significance.

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The gut microbiota induces expression of bone morphogenic proteins via toll-like receptors 4 and 5 in the small intestinal mucosa

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Colonization of germfree (GF) mice is associated with shortening and widening of villus structures and increased vascularization in the distal small intestine. Bone Morphogenic Proteins (BMPs) are regulators of the angiogenic balance. Here, we identify BMPs as microbiota-triggered angiogenic factors that might contribute to stabilization of intricate capillary networks in the small intestinal mucosa. We confirmed that transcript levels of the vascular marker PECAM-1 are increased in presence of gut microbiota (conventionally-raised mice; CONV-R and conventionally-derived mice; CONV-D) compared with GF controls, in accordance with enhanced vascularization in the small intestine of colonized mice. Transcript levels of BMPs 2, 7 and 9 and the receptor BMP type 2 (BMPR2) were significantly increased in CONV-R mice compared with GF controls. Toll-like receptor (TLR) signaling is enhanced in the small intestine of CONV-R mice since mRNA levels of adapter molecules such as MYD88 and TRIF were increased in CONV-R mice. To infer whether BMPs are regulated through TLR signaling, we examined BMPs mRNA expression comparing Tlr4-/- and Tlr5-/- C57BL6 mice with WT controls. We found BMP2, BMP7 and BMPR2 transcript levels significantly decreased in the small intestine of TLR4-/- animals. Similarly, transcript levels of BMP4 and BMP7 were reduced in TLR5-/- mice. Decreased BMP mRNA levels were accompanied by reduced mRNA levels of PECAM-1 in the small intestine of Tlr4-/- and Tlr5-/- mice. Our data suggest a novel pathway which regulates the expression of BMPs via TLR4 and TLR5 and may be involved in microbiota-induced vascular remodeling in the small intestinal mucosa.

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The commensal microbiota alters intestinal coagulation factor synthesis and supports arterial thrombus formation

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Recent advances have implied the intestinal microbiota in mucosal angiogenesis triggered by coagulation factor signaling and in atherosclerosis development. Coagulation as a hemostatic process not only restores vascular integrity but also unleashed to initiate thrombus formation to prevent dissemination of invading pathogens. It is unknown whether presence of microbiota alters coagulation factors in the small intestine. Here, we pioneer to probe if the absence of microbial colonization could affect hemostasis and experimental thrombus formation. To assess the effect of microbiota in coagulation activation we analyzed Tissue Factor (TF)-dependent Factor Xa (Fxa) activity in small intestinal lysates of germfree (GF) and conventionally-raised (CONV-R) mice. We found that TF-dependent coagulation activation in small intestinal lysates and TF surface localization in enterocytes were increased in CONV-R mice compared with GF counterparts. In line with increased TF/FVIIa dependent zymogen activation in colonized mice we found decreased FIX and FX protein in small intestinal tissues of CONV-R mice compared with GF controls. In contrast liver expression of FIX and FX was not changed. To further investigate if the intestinal microbiota impacts on hemostasis we measured tail bleeding times of GF and CONV-R mice. Hemostasis is disturbed in the absence of microbiota as tail bleeding was prolonged in GF mice. Furthermore, we analyzed experimental thrombus formation with a ferric chloride injury model at the carotid artery in GF and CONV-R mice. Time to occlusion was prolonged in GF mice. Our results suggest that the intestinal microbiota affects coagulation initiation in the small intestine and we report that hemostasis and experimental thrombus formation is systemically altered in GF mice.

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Intracellular movement of Listeria monocytogenes in the absence of actin-based motility

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The facultative intracellular bacterium Listeria monocytogenes (Lm) is the causative agent of listeriosis. Following invasion, the bacterium escapes from the phagosome into the cytoplasm where it expresses the surface protein ActA. Three regions of the ActA molecule viz., a putative actin-binding motif, a Arp2/3 (actin related protein 2/3) recruiting motif and four proline-rich repeats binding Ena/VASP (enabled homolog/vasolidator-stimulated phosphoprotein) are required for actin-based intracellular motility. Arp2/3 binds monomeric actin and catalyzes actin nucleation. Ena/VASP binds actin filaments and the actin-binding protein profilin. The resulting formation of actin tails provides bacterial motility. Intracytosolic replicating ActA-negative bacteria form clumps as their motility is impaired. However a ActA mutant devoid for the three regions required for actin-based motility showed two interesting phenotypes: First, mutant bacteria showed a higher invasion rate even when compared to wild-type Lm and second, these strains were present as widely dispersed individual bacteria in the host cytosol. We performed studies with different inhibitors and determined that chemically induced depolarization of the microtubuli abolished the separation of individual bacteria to from clumps. These results suggest that Lm uses microtubuli for intracellular movement and that this activity is mediated by a region(s) on ActA that is/are distinct from regions required for actin-based motility.

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BPI-like proteins induce type 1 fimbriae in different enterobacteriaceae

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Adhesion to biotic and abiotic surfaces such as epithelia or catheters plays an important role in the life cycle and pathogenesis of many bacteria and is mediated by a vast number of different adhesive structures. In this study we aimed to analyze the influence of BPI/PLUNC proteins on the adhesion of several bacteria from the family of Enterobacteriaceae.
The influence of recombinant murine short and long PLUNC1 on bacterial adhesion was analyzed via a quantitative in vitro assay and fluorescence microscopy. To identify specific genes involved in the adhesion of the bacteria gene deletions via Lambda Red-recombination were introduced.
Some genera of Enterobacteriaceae, such as Salmonella Typhimurium and Escherichia coli, surprisingly showed increased adhesion in the presence of several members of the BPI/PLUNC family of proteins.
The observed induction of adhesion could be inhibited by the addition of mannose or methyl α-D-mannopyranoside, known inhibitors of type 1 fimbriae. Moreover adhesion was no longer induced by any of the proteins, if strains deficient for fimA, the major structural component of type 1 fimbriae, were used.
Some Enterobacteriaceae like S. Typhimurium and E. coli respond to the presence of antimicrobial proteins (AMPs) from the BPI/PLUNC family by fimbrial adhesion. This could be a strategy of the pathogens to escape the activity of these AMPs by enforced attachment.

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Retinopathy of prematurity – from bench to bedside and back

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Infants born with less than 1500g or before 32 weeks gestational age (GA) are at risk of serious health problems caused by oxygen exposure such as retinopathy of prematurity (ROP) or periventricular leukomalacia (PVL).
The aim of this project was to characterize the oxygen related morphological and functional changes of the retina due to altering oxygen pressure during the early development of retinal vessels.
Firstly, we started the GRANIT study (Giessen retinal maturation study in former premature infants) to characterize morphological and functional alterations of the retina in school age children with a history of prematurity. We developed the software DIOCTA (device independent OCT analysis) for in depth characterization of morphological changes in the retina of these children. Secondly, we analysed the retinal vessel damage in a rat model of PVL provoked by unilateral carotis ligation (UCL) at post natal day (P)6 together with different hypoxic and hyperoxic conditions.
Infants born preterm, regardless of whether they developed a clinically relevant ROP or not, had a significant risk of developing a non-physiologic fovea and showing decreased central visual function. Rats, which received UCL, developed significant vessel damage and retarded plexus outgrowth at P11 through P21 together with delayed vascular remodelling.
Absence of foveal development and retarded vascular remodelling indicate a generally changed retinal maturation following unphysiological oxygen supply during retinal vessel development. We currently prepare a clinical study to characterize the growth factor VEGF and the oxygen radical levels in different body fluids of preterm infants to shed further light on this pathomechanism.

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Effects of cigarette smoke extract-conditioned medium on T helper cell development and differentiation in vitro

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Chronic obstructive pulmonary disease (COPD) is a highly prevalent inflammatory disease of the lung associated with increasing mortality rates throughout the world. Cigarette smoke exposure has been identified as most common cause of COPD, however, the underlying pathogenetic mechanisms are still poorly understood. Most recently, autoimmune mechanisms and a role of Th1/Th17 have been proposed to be involved in induction and/or perpetuation of the inflammatory processes. Based on these observations we hypothesized that cigarette smoke drives T cells preferentially into a Th1/Th17 direction and reduces numbers of Tregs.
To test this hypothesis, we analyzed the influence of cigarette smoke extract-conditioned medium (CSE) on the development of naïve and differentiating T cells in vitro. Activity of Th subsets was determined by intracellular FACS staining, secretion assays and cytokine cytometric bead assays.
CSE delays the proliferation but promotes the differentiation of Th1 cells. After 3 days of differentiation with CSE there were less IFNγ+ cells, however, remains Th1 cells were more active and produced significantly more IFNγ.
In parallel, CSE directly inhibited the development of Tregs. Application of CSE in a late stage of differentiation preferentially stabilized/promoted an already established Th17 phenotype in contrast to a Th1 phenotype.
In future, subsequent analyses will be performed to further characterize the influence of cigarette smoke exposure on Th cell differentiation processes and the course of inflammatory reactions in vivo.

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Effect of chronic inflammation by metabolic syndrome on male fertility

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The metabolic syndrome (MetS) is a disease cluster of obesity, hypertension, dyslipidaemia and glucose intolerance resulting from nutritional overflow with concomitant chronic and systemic inflammation. It is not clear whether inflammatory pathways are activated in the reproductive system as well. Db/db mice are characterized by massive obesity caused by a dysfunctional leptin receptor. In the present experiment they were bred together with heterozygous controls. At 6, 12 and 24 weeks (wk) of age testes was retrieved for histochemistry and real-time quantitative polymerase chain reaction [qPCR] gene expression. Epididymis was taken for sperm counts. Male db/db mice were morbidly obese and exhibited impaired reproductive function. Declining sperm density and increased percentage of immotile sperm were evident in 24 wk old mice. Morphological spermatogenesis appeared to be normal, but reduced InSL3 positivity was observed indicating lack of Leydig cells. Low testosterone level was detected in db/db mice, together with low mRNA expression of steroidogenic enzymes. With qPCR, we identified macrophage- and several endoplasmic reticulum (ER) stress-related genes that were expressed at higher level in db/db testos than in controls at all time points. Among these were activating transcription factor 3 (Atf3), activating transcription factor 4 (Atf4), and ER DnaJ homolog 4 (Erdj4). The results of the current study show that ER stress in testis may play a role in obese male mice infertility via impairment of Leydig cell function.

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The role of IL-6 in microbial mediated asthma protection

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Exposure of mice with the gram-negative bacterium Acinetobacter lwoffii F78 leads to an attenuated asthmatic phenotype in an acute as well as in a prenatal model. Exposed mice exhibit an increased production of pro-inflammatory cytokines like IL-6 and TNFα (local and systemic).
To analyze the role of pro-inflammatory cytokines in A. lwoffii mediated asthma-protection IL-6 ko mice were exposed to A. lwoffii F78 before and during OVA sensitization and challenge. Additionally, naïve $CD4+$ T cells were treated with supernatant from A. lwoffii preconditioned macrophages.
IL-6 ko mice exhibit an exacerbated asthmatic phenotype compared to wt mice with strong airway inflammation and high numbers of eosinophils. This is not changed by A. lwoffii exposure in the IL-6 ko background.
In addition the number of other inflammatory cell like lymphocytes and neutrophils is increased. Induction of IL-17 can be observed after A. lwoffii application in wt mice but not of IL-6 ko mice. In vitro treatment of naïve T cells with A. lwoffii preconditioned media from macrophages (containing high levels of IL-6) leads to the induction of IL-17 and IL-10 producing T cells leading to the idea that IL-6 is needed for the induction of anti-inflammatory IL-17 and IL-10 producing T cells.

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A single influenza virus infection protects of allergic airway inflammation in the OVA-mouse model

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Asthma and other chronic airway inflammatory diseases are heavily affected by airway viral infections. Epidemiological and clinical data display contradictory effects in terms of asthma prevention and asthma exacerbation in already diseased patients. The molecular basis of these phenotype-modifying virus-host interactions, however, is still largely unknown. We describe a prevention model of influenza airway infection followed by succeeding ovalbumin based airway inflammation model in Balb/c mice. A single infection using the pandemic HH/09 H1N1 causes a quick influx and activation of CD4 and CD8 T-cell populations into the lung, peaking at day 8-12 post infection combined with a pronounced TNF-α, IFN-γ and IL-6 secretion pattern. Virus-specific tetramer-positive cytotoxic T- and effector memory cells peak in the lung at day 12 followed by a migration into spleen. Even 60 days post infection, tetramer-positive cytotoxic T-cells were detected in both lung and spleen. A subsequent OVA-sensitization protocol starting from 12 days post infection followed by OVA challenge resulted in decreased severity of a range of allergic airway inflammation parameters (e. g. eosinophilia $p<0.05$, IL-5 and IL-13 $p<0.01$, goblet cell hyperplasia $p<0.05$) compared to the OVA-treated group without a preceding influenza infection. CD8 memory cell subpopulations displayed a characteristic redistribution pattern, and further in-vitro analysis points towards a protective role based on cross-reactive sequence recognition. Delineation of the underlying molecular and cellular rearrangements during virus infection will lead to a better understanding of the development and regulation of chronic inflammation and should identify novel targets for prevention of asthma induction and exacerbation.

28
The impact of short chain fatty acid receptors in modulating allergic mucosal immune responses

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Microbial organisms influence the immune system of the host not only by bacterial components but also by virulence factors and fermentation products such as short chain fatty acids (SCFA). It has been shown that SCFA exert immune-modulatory functions, promotes the development of Tregs, dampen inflammatory pathways in macrophages and DCs and serve as a growth factor for the integrity of the intestinal epithelium and cellular health. However it remains unclear whether SCFA also play a role in the development of pulmonary inflammatory processes. The aim of this study was to investigate the effects of HDM induced allergic inflammation in SCFA receptor deficient mice (Ffar2/3 KO mice) by evaluating the role of SCFA in inducing/preventing experimental asthma. Moreover, the communication between mucosal surfaces of gut and lung was analyzed.
We found that in naive situation Ffar2/3-deficient mice do not show decreased frequencies in peripheral Foxp3+ Treg population. Moreover, Infiltration of inflammatory cells in the airways after airborn allergen exposure is independent of SCFA R expression. Surprisingly, airborn HDM exposure significantly decreases Treg frequencies only in the mLN of Ffar2/3-KO mice. Here we show that airborn exposure to house dust mite (HDM) increases the frequency of Tregs in lungs independently of SCFA receptor expression (GPR 41/43) and absence of SCFA receptors did not affect the inflammatory airway response. Unexpectedly, mice lacking SCFA receptors show a marked decrease of Tregs in mesenteric lymph nodes (mLN) during allergic airway response. These findings show the dependency of intestinal Tregs upon SCFA and suggest that Tregs migrate between both mucosal sites.

29
Vitamin-D deficiency augments cytokine expression in murine Th2 cells

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Vitamin-D (Vit-D) possesses immunmodulatory functions and Vit-D deficiency has been associated with severity of chronic inflammatory diseases. In asthmatic patients, this condition is linked to exacerbations and high IgE levels. Studies, assessing the effect of Vit-D supplementation on immune regulation, provide contradictory results and raise the need for deeper analysis of the underlying molecular mechanisms. To investigate the importance of Vit-D and its receptor (VDR) in Th2-driven diseases, we used Balb/c mouse models of Ovalbumin induced allergic airway inflammation (acute and chronic), combined these with FACS-sorting of distinct live T-helper (Th) subsets (Th1, Th2 and Treg) from inflamed lungs and microarray analyses. Functional studies were performed with WT (Vit-D sufficient diet), WT/Vit-D deprived (Vit-D deficient diet from 3rd trimester of pregnancy) and VDR-knockout (KO) mice on C57BL/6J background in the in vitro system of differentiating Th-cells. Microarray results revealed 5-fold higher expression of VDR in Th2 cells compared to naïve T cells, Th1 and Treg cells, implicating a specific function of Vit-D in Th2 cells. In vitro experiments revealed that Th-cells, deficient in Vit-D signaling, displayed lower IFN-γ (Th1) and IL-4 (Th2) levels. In contrast, loss of Vit-D signals in Th2 cells augmented IL-5, IL-6 and IL-13 levels compared to wild type cells. Here we show that Th2 cells in murine allergic airway inflammation can respond to Vit-D signals. We further demonstrate that Vit-D is able to mediate cell and cytokine specific effects and is needed for dampening the expression of disease promoting cytokines.

30
Effects of Gata3-targeted DNAzyme treatment in an oxazolone-induced mouse model of chronic inflammatory skin disease

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The transcription factor GATA-3 is a crucial element in T helper cell type 2 (Th2)-differentiation and activation. Therefore, targeting GATA-3 could be of high therapeutic value in predominantly Th2-driven diseases like atopic dermatitis (AD). We developed a GATA-3 specific molecule called hgd40, which as a DNAzyme combines the sequence specificity of anti-sense molecules with catalytic RNA-cleaving activity. A water/oil/water emulsion was created especially to facilitate stability and penetration of the skin barrier for topically applied DNAzymes. The efficacy of this treatment was tested in a sub-acute oxazolone-induced mouse model modified to mimic an AD-like condition of prolonged Th2-dominated skin inflammation. Treatment with hgd40 significantly decreased oxazolone-induced skin swelling and reduced CD4 cell influx into the challenged skin as compared with vehicle-only placebo or non-functional DNAzyme control. Further analysis of pathological development in this model indicates reduced GATA-3 mRNA levels after hgd40 treatment early in the course of disease. These results show the GATA-3 targeted DNAzyme-based topical therapy to be a valid approach for the treatment of AD-like inflammatory skin conditions.

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Systemic characterization of macrophage phenotypes in allergic airway inflammation

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Macrophages are central players in lung pathology with both regulatory and effector properties. Besides activation toward the M1 subtype (classic activation), alternatively activated M2 macrophages have been implicated in pneumonia and allergy. Recently, microRNAs (miRNAs) have emerged as a regulatory network with great impact on cellular organization and function. We investigate the role of miRNAs in macrophage polarization and associated diseases. Here, we analyzed the systemic RNA phenotype of murine lung macrophages in allergic airway inflammation. We aim to compare these findings to prototypical in vitro polarized human blood-derived macrophages in order to assess the disease-associated polarization status in the mouse model.

We established FACS protocols to define and separate different macrophage subsets and polarization phenotypes. In vitro polarized human macrophages were purified by CD80 (M1) or CD23 (M2) positive selection. Macrophages from the bronchoalveolar lavage fluid (BALF) and lung homogenate of mice with acute OVA-induced eosinophilic airway inflammation were sorted on the basis of CD11 and SiglecF, and total RNA was analyzed subsequently. Differential miRNA expression could be observed that seems to be tissue- and asthma dependent, as illustrated by principal component analysis (PCA). In the interstitial macrophage fraction, up-regulation of the M1-associated miR-155-5p and down-regulation of the equally M1-associated miR-146a-5p was observed, among others. On mRNA level, prominent markers of alternative macrophage activation were found to be up-regulated, such as Arginase (Arg1) and the IL4-induced Retnla (FIZZ1), CCL17 and Mgl2. This signature suggests a limited M2-like polarization profile, in accordance with the TH2-skewed environment in eosinophilic airway inflammation.

POSTER AWARDS

The Scientific Committee identified the most highly ranked abstracts selected for the Poster Sessions in each category and acknowledge their achievement with a Poster Award (250-500 Euro for each rewarded poster). All abstracts accepted in advance will be considered for this award. Award Presentation Ceremony will take place on Saturday, October 18, 2014. Poster prizes will be awarded after the final session of the symposium only to authors who are personally present!

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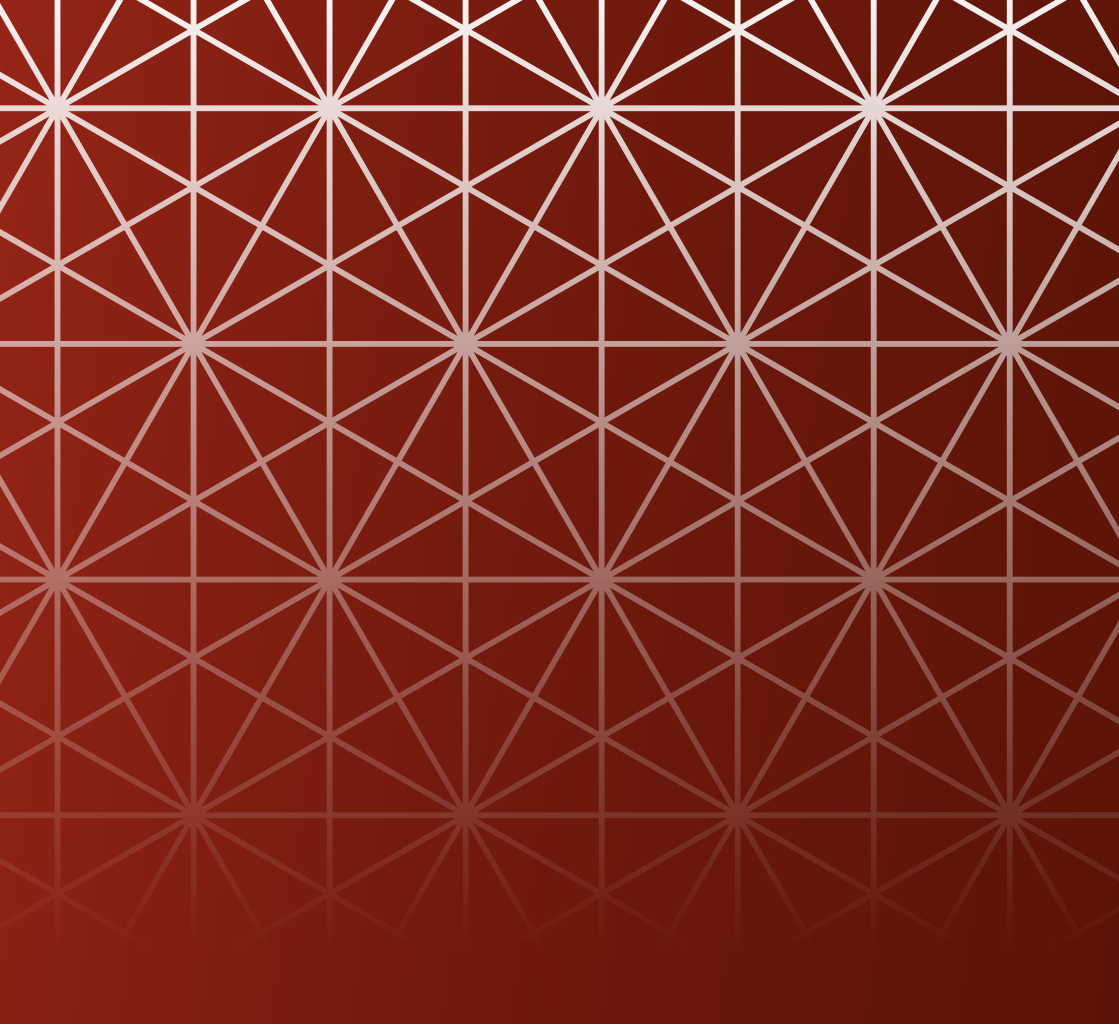
IMPORTANT CHARACTERS IN THE HISTORY OF MARBURG

Marburg is a medieval city with many steps and narrow streets that has many unexpected cultural facets and celebrities who lived and studied in this city.

We encourage you to discover some of these secrets on your own – below is a small list of places worth to be visited during your stay.

1207 – 1231	Elisabeth von Thüringen (Saint Elisabeth/Elisabeth church)
1527	Philipps University, Marburg (first protestant university)
1711 – 1765	Michail Lomonossow (founder of the Moscow university)
1785 – 1863	Gebrüder Grimm (Grimm tales)
1850 – 1918	Ferdinand Braun (cathode-ray tube, Nobel Prize in physics, 1909)
1811 – 1899	Robert Bunsen (spectral analysis, Bunsen burner)
1854 – 1917	Emil von Behring (serum therapy, first Nobel Prize of medicine, 1901)
1879 – 1968	Otto Hahn (nuclear fission, Nobel Prize in chemistry, 1944)
1880 – 1930	Alfred Wegener (continental drift)
1890 – 1960	Boris Pasternak (Russian poet and novelist, Nobel Prize for literature, 1958)



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