Medical Immunology Campus Erlangen

An Interdisciplinary Center
of the Friedrich-Alexander-Universität
Erlangen-Nürnberg

Newsletter
Summer 2019

CONTENT

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

EDITORIAL

Dear colleagues and friends,

on March 9, 2009, the inaugural assembly of the *Medical Immunology Campus Erlangen* took place. 33 immunologists and scientists from related areas of research participated in the meeting which led to the formal foundation of this interdisciplinary center of the Friedrich Alexander University Erlangen-Nürnberg. Prof. Bernhard Fleckenstein, the former director of the Institute of Clinical and Molecular Virology, was the father of this initiative that was approved by the University Council on February 13, 2009. 10 years later, the *Medical Immunology Campus Erlangen* has more than 100 members. Although one of its key goals, i. e. to succeed in the Federal Excellence Initiative, has not yet been reached, the Campus turned out to be a highly fruitful platform for the immunologists in Erlangen. Over 300 lectures by national and international scientists have taken place under the umbrella of the *Medical Immunology Campus*. A series of DFG-funded research consortia, such as the Collaborative Research Centers 643, 796 and 1181, the Transregios 130, 221 and 241, the Research Training Group 1660 and the Research Unit 2886, have been established by or with the contribution of members of the *Medical Immunology Campus Erlangen*. The latest achievement is the Research Training Group 2504 on new antiviral strategies, which was approved by the DFG in May 2019 and will start its work later in October (see separate report in this newsletter). Congratulation to Prof. Klaus Überla and the participating scientists for this success!

The scientists of the *Medical Immunology Campus Erlangen* are devoted to translational research linking mouse and human studies. Both the logo and the acronym of the Campus *(MICE)* already point to the fact that mouse research is absolutely essential for the current and future projects within the Campus. Unfortunately, a number of factors have been starting to jeopardize our work. These include the limited space for mouse keeping in the Preclinical Experimental Animal Center (PETZ), the urgent need for more qualified animal caregivers, the increasing difficulties in obtaining final approval for the animal studies in a timely manner, differing and non-harmonized assessments on the categorization and stress grading of mouse lines, and decisions of authorities that are difficult to understand. It is time that we exchange our experiences and develop a strategy of solution. The topic will be on the agenda in the forthcoming members´ assembly.

I wish you all a relaxing summer break and hope to see you again in October, when the guest seminar series starts. Please also mark November 19 as the date for the next *Joachim Kalden Lecture* in your calendar.

Christian Bogdan

Prof. Christian Bogdan
Chairman of The Medical Immunology Campus Erlangen

SCIENTIFIC HIGHLIGHTS

T cells at the 'driver's seat' of intestinal inflammation

Hobit- and Blimp-1-driven CD4+ tissue resident memory T cells control chronic intestinal inflammation

SEBASTIAN ZUNDLER, MARKUS NEURATH
DEPARTMENT OF MEDICINE 1, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

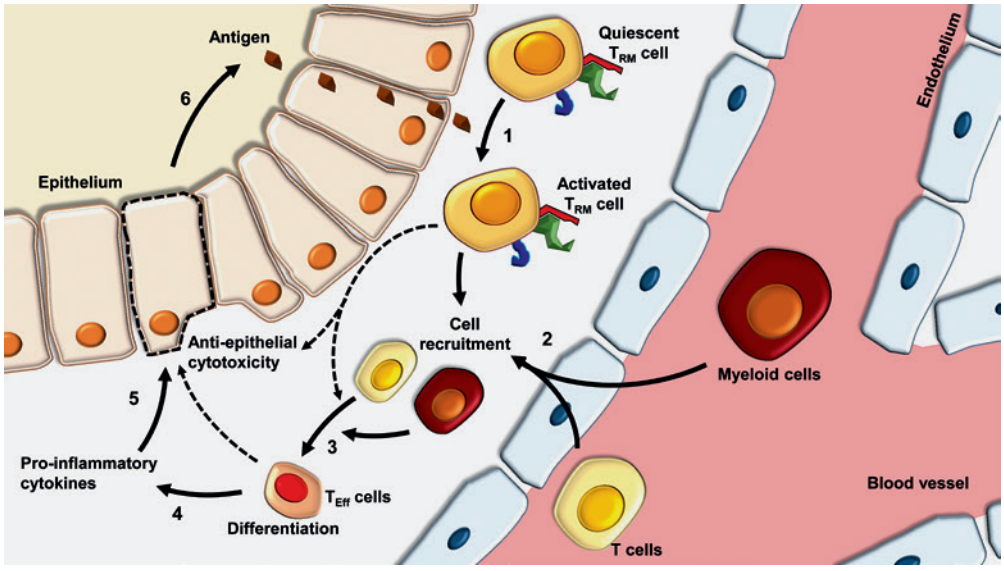
T cells play a central role in the pathogenesis of inflammatory bowel disease (IBD). Although so-called tissue resident memory T cells (TRM cells) had previously been shown to mediate host protection in viral infections, their function in IBD remained elusive. Thus, we set out to explore their role in chronic intestinal inflammation.

We found that TRM cells are increased in patients with IBD and display a pro-inflammatory phenotype. Their abundance correlates with previous disease duration and patients with high levels of $CD4^+CD69^+CD103^+$ TRM cells had substantially shorter flare-free survival than patients with low levels.

In several experimental mouse models, deficiency of Hobit and Blimp-1 alleviated the course of colitis although the number of TRM cells was not affected. However, RNA sequencing showed that genes associated with the recruitment of various and, in particular, innate leukocyte populations are downregulated in Hobit- and Blimp-1-deficient mice. This was validated on mRNA, protein and cell level and, consistently, we found reduced levels of pro-inflammatory cytokines released by innate immune cells and downstream T helper cells. Moreover, depletion of TRM cells co-expressing Hobit together with a transgenic diphtheria toxin receptor by application of diphtheria toxin and of P2X7-expressing TRM cells by ligation with NAD led to reduced colitis severity.

Together, our data suggest that TRM cells play a crucial role in human IBD and experimental colitis. Mechanistically, they seem to control an adaptive-innate crosstalk mechanism governing the recruitment and differentiation of other immune cell subsets.

Zundler S, Becker E, Spocinska M, Slawik M, Parga-Vidal L, Stark R, Wiendl M, Atreya R, Rath T, Leppkes M, Hildner K, Lopez-Posadas R, Lukassen S, Ekici AB, Neufert C, Atreya I, van Gisbergen K and Neurath M F. (2019). Hobit- and Blimp-1-driven CD4(+) tissue-resident memory T cells control chronic intestinal inflammation. *Nat Immunol 20:288–300.*



Model of adaptive-innate crosstalk controlled by TRM cells Once a quiescent TRM cell residing in the gut is activated by its cognate antigen (1), it secretes chemokines leading to the recruitment of other immune cells of the innate and adaptive immune system (2). These cells secrete cytokines inducing the differentiation of pro-inflammatory T cell subsets (3), which produce further pro-inflammatory cytokines (4). The mediators released by all these immune cells lead to anti-epithelial cytotoxicity (5), facilitating further translocation of IBD antigens (6) which ultimately results in a vicious cycle. Dashed lines indicate potential additional direct effects of T_{Eff} and T_{RM} cells on anti-epithelial cytotoxicity and of T_{RM} cells on T_{Eff} cell differentiation.

SCIENTIFIC HIGHLIGHTS

PU.1 controls fibroblast polarization and tissue fibrosis

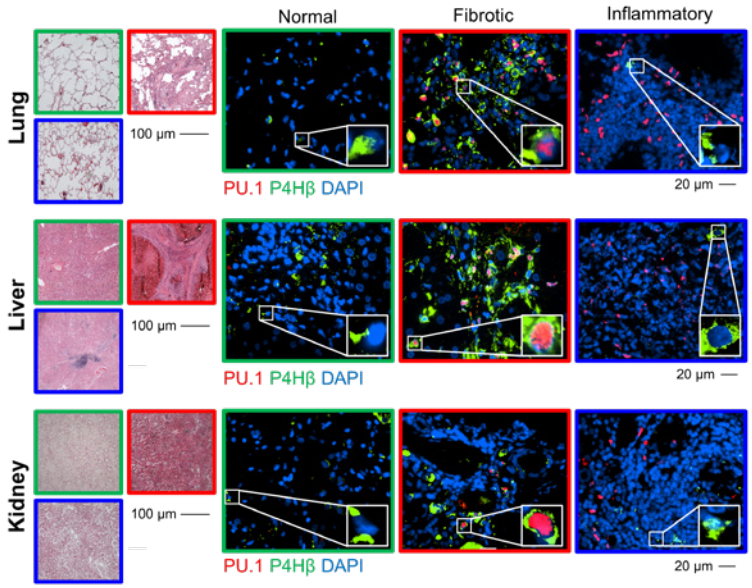
THOMAS WOHLFAHRT, SIMON RAUBER, GEORG SCHETT, JÖRG HW DISTLER, ANDREAS RAMMING
DEPARTMENT OF MEDICINE 3, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Fibroblasts are the most abundant cells of the stroma. These cells still remain poorly characterized. It has therefore been notoriously challenging to find appropriate targets to influence fibroblast function. Fibroblasts are highly pleomorphic and can acquire functionally almost opposing phenotypes and functions in the context of different diseases. In fibrotic diseases, they differentiate into a highly matrix-producing contractile phenotype promoting progressive accumulation of extracellular matrix and thereby predominantly contribute to severe tissue fibrosis. In contrast, in chronic inflammatory diseases such as rheumatoid arthritis, fibroblasts acquire a matrix-degrading, catabolic phenotype characterized by the release of matrix-degrading enzymes along with pro-inflammatory mediators. Until now, the reasons underlying those opposing functional phenotypes of fibroblasts have remained enigmatic.

A bioinformatic screen of promoter regions of fibrotic genes derived from a database of skin samples taken from patients with systemic sclerosis – a prototypic fibrotic disease – revealed a potential role for PU.1 in fibrosis. PU.1 is a well-characterized transcription factor known to have a central function in the development of B cells and myeloid cells, but little was known about its effect on fibroblasts, fibrosis and extracellular matrix remodeling.

The new data show that PU.1 is a checkpoint of fibroblast polarization involved in a wide range of fibrotic diseases. PU.1 was effectively silenced in fibroblasts of normal tissue and during physiological tissue repair. Epigenetic mechanisms accounted for differential PU.1 activity in the different fibroblast subpopulations, including histone methylation marks in the upstream regulatory element and promoter of PU.1. MicroRNA miR-155, which is associated with various inflammatory diseases, inhibited PU.1 in inflammatory fibroblasts. The loss of epigenetic and posttranscriptional control led to upregulation of PU.1 and allowed the development of fibroblasts with a “profibrotic” phenotype. This differentiation into profibrotic fibroblasts was associated with the transcription of numerous pro-fibrotic mediators and the development of fibrotic tissue remodeling in several organs including skin, lung, liver and kidney. Pharmacological and genetic inhibition of PU.1 reprogrammed matrix-producing profibrotic fibroblasts into resting fibroblasts and thereby efficiently terminated fibrotic tissue remodeling.

Wohlfahrt T, Rauber S, Uebe S, Luber M, Soare A, Ekici A, Weber S, Matei AE, Chen CW, Maier C, Karouzakis E, Kiener HP, Pachera E, Dees C, Beyer C, Daniel C, Gelse K, Kremer AE, Naschberger E, Sturzl M, Butter F, Sticherling M, Finotto S, Kreuter A, Kaplan MH, Jungel A, Gay S, Nutt SL, Boykin DW, Poon GMK, Distler O, Schett G, Distler JHW and Ramming A. (2019).
PU.1 controls fibroblast polarization and tissue fibrosis. Nature 566:344 –349.



PU.1 expression in fibroblasts from normal human tissues and tissues affected by inflammatory or fibrotic diseases
Representative confocal immunofluorescent microscopy images of lung, liver and kidney biopsy specimens stained for PU.1 (red), CD45 or P4Hβ (green), and DAPI (blue)

SCIENTIFIC HIGHLIGHTS

Restriction of citrate is a HIF1α-dependent anti-microbial effector mechanism of macrophages

Limitation of TCA cycle intermediates represents an oxygen-independent, nutritional antibacterial effector mechanism of macrophages

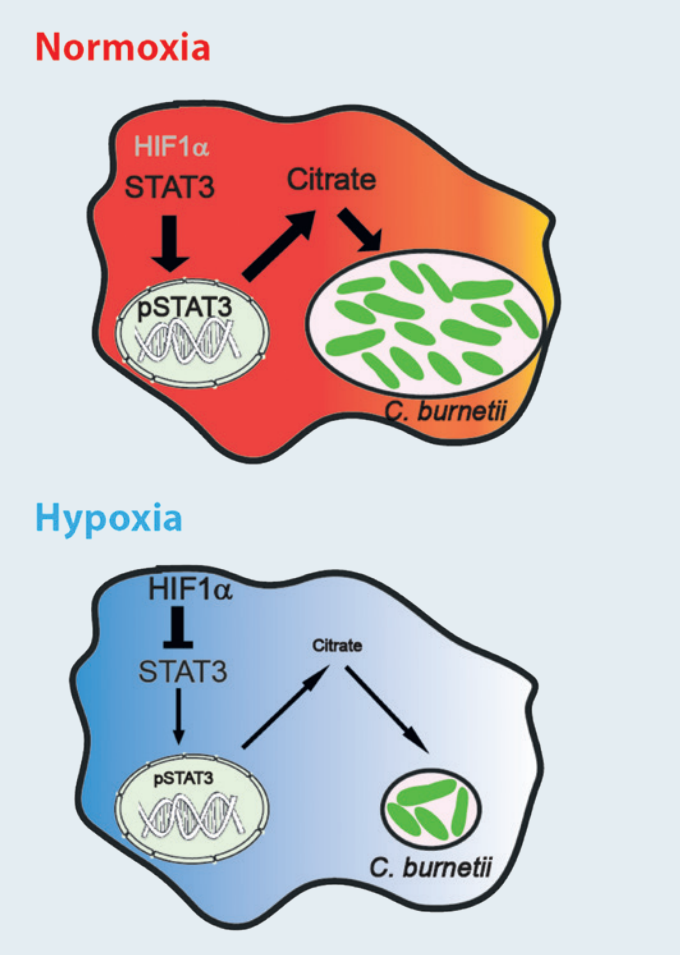
ANJA LÜHRMANN
MICROBIOLOGY INSTITUTE, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

The tissue microenvironment is an important regulatory factor of organ and cell function. As the oxygen tension in infected and inflamed tissue is low, oxygen (O_2)-dependent antimicrobial defenses are impaired. However, how pathogen control works under oxygen deficiency is unclear. To get insight into this question, we investigated the infection of macrophages with the obligate intracellular pathogen *Coxiella (C.) burnetii*, the causative agent of the zoonotic disease Q fever.

Our work demonstrated that *Coxiella burnetii* only replicated in macrophages under normoxic (21% O_2) conditions. Under hypoxia (0.5% O_2), which predominates in infected tissues, HIF1α inhibited STAT3 activation, which in turn reduced the intracellular citrate content. A lack of citrate led to the inhibition of *C. burnetii* proliferation and to the induction of bacterial persistence. Since the persistence of *C. burnetii* plays a key role in the development of chronic Q fever, these findings provide new insights into the pathogenesis of this disease, for which a curative and well-tolerated therapy is still missing.

This is the first report that the regulation of citrate concentration by the transcription factor HIF1α represents a strategy of host cell defense of macrophages against intracellular pathogens. The pharmacological targeting of these signaling pathways might be a new way of fighting *C. burnetii* and potentially other infectious diseases.

Hayek I, Fischer F, Schulze-Luehrmann J, Dettmer K, Sobotta K, Schatz V, Kohl L, Boden K, Lang R, Oefner P J, Wirtz S, Jantsch J and Lührmann A. (2019). Limitation of TCA cycle intermediates represents an oxygen-independent nutritional antibacterial effector mechanism of macrophages. *Cell Rep* 26: 3502–3510 e6.

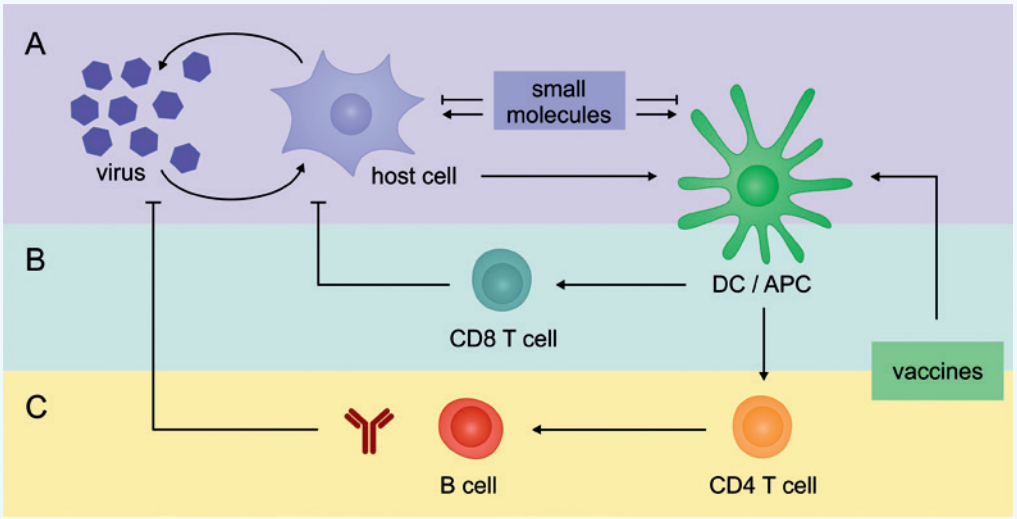


HIF1α-mediated inhibition of *C. burnetii* replication in hypoxic macrophages

NEWS AND UPDATES

RTG2504 “Novel antiviral approaches” starts its training and research program in October 2019

The Medical Immunology Campus Erlangen congratulates Prof. Klaus Überla on the approval of the new DFG-funded Research Training Group



The GRK2504 research programme includes and combines antiviral strategies ranging from small molecules inhibiting viral replication (A) to cellular (B) and humoral (C) immune responses.

The extensive gain of knowledge in virology and immunology during the last two decades provides a wealth of candidate antiviral targets and approaches, but prevention and treatment options for many viral infections remain unsatisfactory. The DFG-funded research training group RTG2504 therefore focuses on novel antiviral strategies that bridge expertise in antiviral chemotherapy and immune intervention. Its educational objective combines knowledge on both, basic and translational research concepts for innovative antiviral therapies. Our research projects cover interference with viral replication and transmission, exploitation of intrinsic and innate immune responses, and the optimization of vaccination and adoptive cell therapy strategies. The complementary expertise of our principle investigators offers the opportunity for vivid exchange and efficient cooperative, application-oriented developments.

The training concept combines profound, internationally oriented scientific education with an early exposure to important aspects of translational research. Selected through a competitive recruitment procedure, junior researchers graduated in life sciences or trained in medicine are accompanied throughout their doctoral projects by a supervisor and two mentors. Regular seminars and retreats covering the topics of the the RTG 2504 enhance scientific exchange and cooperation among the training members, supervisors and the international exchange partners. Courses with external trainers enforce transferable skills required to efficiently communicate scientific contents. Training with regard to translational procedures comprise workshops on legal and patent issues as well as industrial approaches to product development, courses on clinical studies, and a visit to a biotechnological or pharmaceutical company. Thus, all training members are enabled to efficiently and successfully pursue their scientific projects and, in parallel, become acquainted with translational concepts, which are important for their future professional careers. For FAU master graduates, our cooperation with the Ragon Institute of MGH, MIT and Harvard offers the possibility to pursue doctoral training in the USA.

Please visit the RTG 2504 homepage for further information on the projects and on current announcements:
www.virologie.uk-erlangen.de/grk2504

UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Winter 2019/20

Tuesdays, 5.15 pm

15.10.2019
Prof. Jörg Köhl
Institute for Systemic Inflammation Research, Universität zu Lübeck
to be announced

22.10.2019
Prof. David Hildeman
Cincinnati Children's Hospital Medical Center
to be announced

29.10.2019
Prof. Alexander Visekruna
Institut für Medizinische Mikrobiologie und Krankenhaushygiene, Philipps-Universität Marburg
Regulation of the mucosal immune system by dietary and microbial factors

19.11.2019
Joachim Kalden Lecture 2019
Prof. Dolores Schendel
Medigene AG, Martinsried
My Journey to Join the Frontline in TCR-T Immunotherapies

03.12.2019
Dr. Andreas Hutloff
Chronische Immunreaktionen, Deutsches Rheuma-Forschungszentrum Berlin (DRFZ)
T cell / B cell interactions in chronically inflamed tissues

07.01.2020
Dr. Silvia Portugal
Department of Infectious Diseases, Parasitology, Heidelberg University Hospital
Plasmodium falciparum dry season reservoir: a long hide and seek game

14.01.2020
PD Dr. Marta Rizzi
Klinik für Rheumatologie und Klinische Immunologie, Universitätsklinikum Freiburg
to be announced

21.01.2020
Prof. Stefanie Kürten
Institut für Anatomie und Zellbiologie, Uniklinikum Erlangen
to be announced

04.02.2020
Dr. Christoph Klose
Charité - Universitätsmedizin Berlin
to be announced

03.03.2020
Dr. Sebastian Winter
Department of Microbiology, UT Southwestern Medical Center; Dallas, TX, USA
Microbiota Metabolism and Intestinal Inflammation

Conferences and Events of Interest

September 4 – 6, 2019 · Cottbus
27. Jahrestagung der Deutschen Gesellschaft für Immungenetik
www.dgi2019.de

September 10 –13, 2019 · München
II Joint Meeting of the German Society for Immunology (DGfI) and the Italian Society of Immunology, Clinical Immunology and Allergology (SIICA)
www.immunology-conference.de

September 12 –14, 2019 · Marseille, France
33rd Annual Conference of the European Macrophage and Dendritic Cell Society (EMDS)
www.emds2019.com

September 18 – 21, 2019 · Brussels, Belgium
2019 Focused Meeting of the European Society for Immunodeficiencies (ESID 2019)
www.esidmeeting.org

October 2 – 4, 2019 · Lyon, France
4th International Cancer Symposium
www.crclsymposium2019.fr

October 27 – 29, 2019 · Ghent, Belgium
International Society for Vaccines Annual Congress 2019
www.isvcongress.org

March 4 – 6, 2020 · Burg Rothenfels
Meeting des AK Infektionsimmunologie

March 12 – 14, 2020 · Sonthofen, Bayern
Meeting des AK Biologie der B-Lymphozyten
www.isvcongress.org

March 18 – 19, 2020 · Resort Schwielowsee, Potsdam
Meeting des AK Klinische Immunologie

March 8 – 11, 2020 · Leipzig
72. DGHM-Jahrestagung 2020, 6. Gemeinsame Tagung von DGHM und VAAM
www.dghm-kongress.de

March 25 – 28, 2020 · Berlin
30th Annual Meeting of the Society for Virology
www.virology-meeting.de

April 18 – 21, 2020 · Paris, France
30th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
www.eccmid.org/eccmid_2020

May 14 – 16, 2020 · Halle/Saale
Meeting des AK Tumorimmunologie

May 20 – 24, 2020 · Athens, Greece
12th International Congress on Autoimmunity
www.autoimmunity.kenes.com

May 27 – 30, 2020 · Mallorca, Spain
2nd International Congress of Micro-Immunotherapy
www.icomi2020.org

July 2 – 3, 2020 · Marburg
Meeting des AK T-Zellen

October 11 – 15, 2020 · Queensland, Australia
16th International Symposium on Dendritic Cells 2020
www.dc2020symposium.com

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We are looking forward to suggestions for the next MICE newsletter.
Please send material to:
Sonja.Poetzsch@uk-erlangen.de

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