Medical Immunology Campus Erlangen

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

Newsletter
Summer 2015

CONTENT

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

EDITORIAL

Dear colleagues and friends,

On May 21, 2015, the Senate Committee on Collaborative Research Centres (CRC) of the DFG approved the grant application for a new CRC at the FAU, focussing on *"Checkpoints for Resolution of Inflammation"*. The first funding period of the CRC1181 will run from July 1, 2015 until June 30, 2019, during which the consortium will receive14 million Euro from the DFG. This is an outstanding success and new milestone in the long-lasting history of immunology research at the FAU and the Universitätsklinikum Erlangen. I would like to express my sincere thanks and heartiest congratulations to Georg Schett, the spokesman of the new CRC, and to Sandra Jeleazcov, the CRC coordinator, for their extraordinary commitment throughout the 2 year preparation phase of this consortium, but also to all project leaders who made this new research center possible.

On June 3, 2015, the EU commission announced that it will not follow the European Citizens' Initiative *"Stop Vivisection"* that aimed to immediately stop any kind of animal experimentation and to abolish the respective EU guideline from 2010. While many immunologists interpreted this decision as a strong statement of the commission against the campaign of animal protectionists, I would like to point out that both the press release and the official communication read differently (http://europa.eu/rapid/press-release_IP-15-5094_en.htm). The commission clearly stated that it adheres to the plan to ultimately phase out all animal testing, which, in my opinion, would close the door on many areas of immunological research.

During the members' assembly of the *Medical Immunology Campus Erlangen* on June 16, Hans-Martin Jäck presented a concept for a Master Program in Immunology at the Medical and Natural Science Faculty of the FAU. After a lively discussion the assembly decided to pursue and support this initiative.

During the past weeks, Sonja Pötzsch and myself put together an extensive report on the activities of our campus, which we had to hand in at the office of the FAU president for research affairs. Every six years, all interdisciplinary centers of the FAU will be evaluated, whether they fulfilled the expectations of the university. One issue (that almost certainly will come up) is the national and international visibility of the center, which in our case could be further improved by specifically mentioning the campus as an additional affiliation in all our publications.

Finally, I would like to draw your attention to the conference *"Infectious Disease Immunology Meets Molecular Microbiology"* which will take place from April 7 to 9, 2016 in the Institute of Clinical Microbiology, Immunology and Hygiene on the occasion of its 150th anniversary. Further information will follow.

I wish you all a relaxing summer period and hope to see you again in October, when our guest seminar series starts again. Please also mark December 1 in your calendar, when Alain Fischer from Paris will give the *Joachim Kalden Lecture 2015*.

Prof. Christian Bogdan

Chairman of the *Medical Immunology Campus Erlangen*

SCIENTIFIC HIGHLIGHTS

A new function for γδ T cells in anti-viral protection

Control of murine cytomegalovirus infection by γδ T cells

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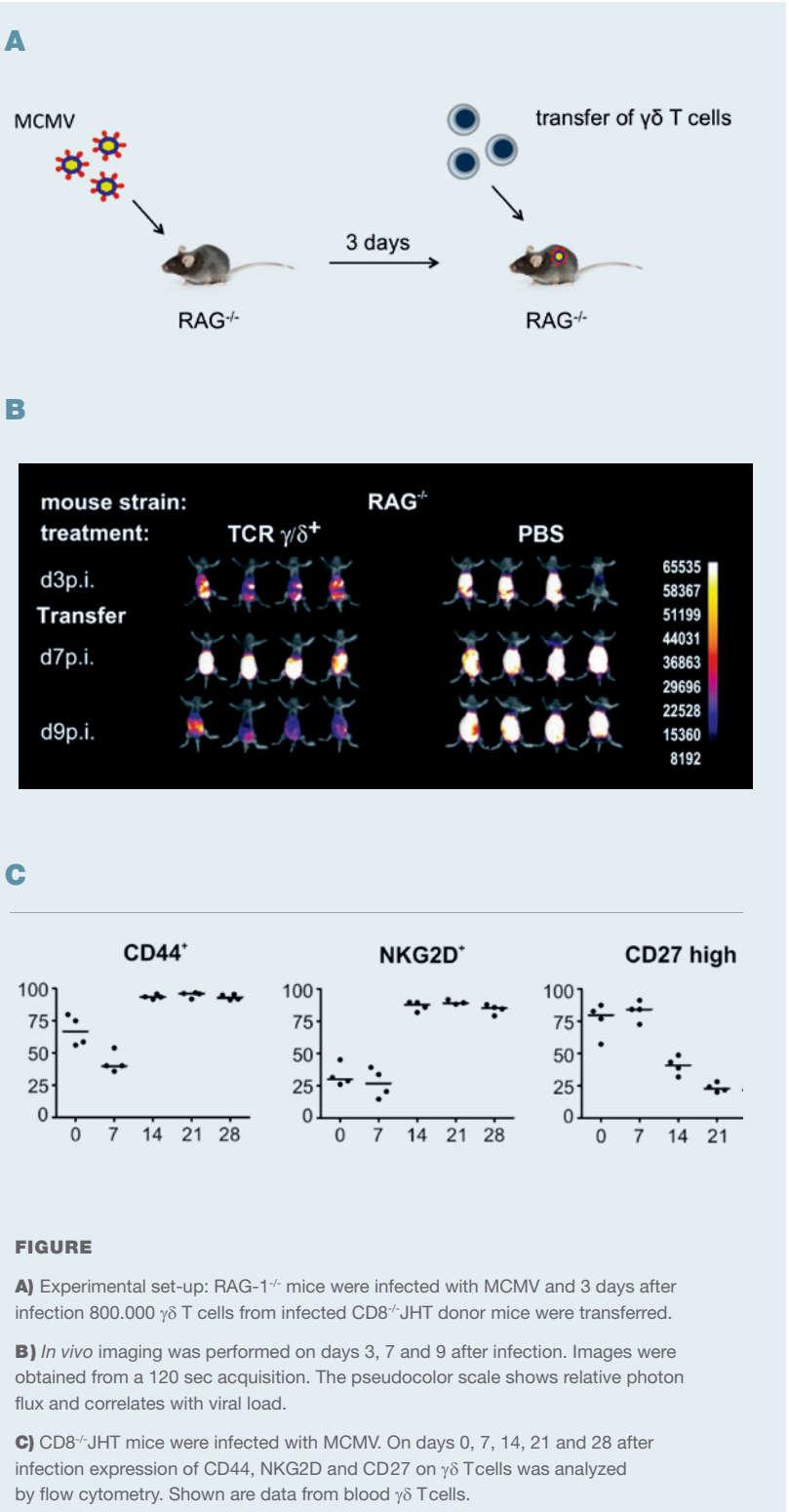
Cytomegalovirus (CMV) is a clinically important pathogen that causes severe disease in immunosuppressed patients and infected newborns. Various layers of innate and adaptive immune responses provide control in cytomegalovirus (CMV) infected individuals and single deficiencies of one immune cell type are compensated by other immune cells.

Here we show that γδ T cells control MCMV infection in the absence of other effector cells of the adaptive immune system. γδ T cells isolated from infected donor mice provide long-term protection in infected RAG-1$^{-/-}$ mice after adoptive transfer. RAG-1$^{-/-}$ mice are devoid of B cells and T cells and usually succumb rapidly to MCMV infection. Furthermore, γδ T cells were able to kill MCMV infected target cells in an *in vitro* assay.

Detailed analyses of γδ T cells in CD8- and B-cell deficient mice after MCMV infection revealed that absolute γδ T cells numbers increase after MCMV infection due to proliferation. Furthermore, γδ T cells undergo a long-lasting phenotypic change. The percentage of CD44^{+} γδ T cells increased, supporting the notion that a large fraction of γδ T cells becomes activated by the MCMV infection. In addition, we observed a long-lasting increase in NKG2D expressing γδ T cells after infection, which are further characterized by the downmodulation of CD27. In target organs, where MCMV is known to persist, a striking change in the γδTCR repertoire can be observed. The CDR3δ length distribution is strongly restricted after MCMV infection and Vγ1^{+} as well as Vγ2^{+} cells expand clonotypically. γδ T cells from infected mice are much better in protection as compared to γδ T cells from naive mice. These data together suggest an adaptive-like response of γδ T cells against MCMV.

Based on their properties, γδ T cells represent promising candidates for a cellular therapy against CMV infection and reactivation for example after organ or hematopoietic stem cell transplantation.

Sell, S. · M. Dietz · A. Schneider · R. Holtappels
M. Mach · T. H. Winkler. 2015.
Control of murine cytomegalovirus infection by gammadelta T cells. *PLoS pathogens* 11: e1004481.



FIGURE

A) Experimental set-up: RAG-1$^{-/-}$ mice were infected with MCMV and 3 days after infection 800.000 γδ T cells from infected CD8$^{-/-}$JHT donor mice were transferred.

B) *In vivo* imaging was performed on days 3, 7 and 9 after infection. Images were obtained from a 120 sec acquisition. The pseudocolor scale shows relative photon flux and correlates with viral load.

C) CD8$^{-/-}$JHT mice were infected with MCMV. On days 0, 7, 14, 21 and 28 after infection expression of CD44, NKG2D and CD27 on γδ T cells was analyzed by flow cytometry. Shown are data from blood γδ T cells.

SCIENTIFIC HIGHLIGHTS

AP-1 transcription factor Batf controls colon tumor formation

Batf-dependent Th17 cells are crucial regulators of IL-23 driven colitis-associated colon cancer

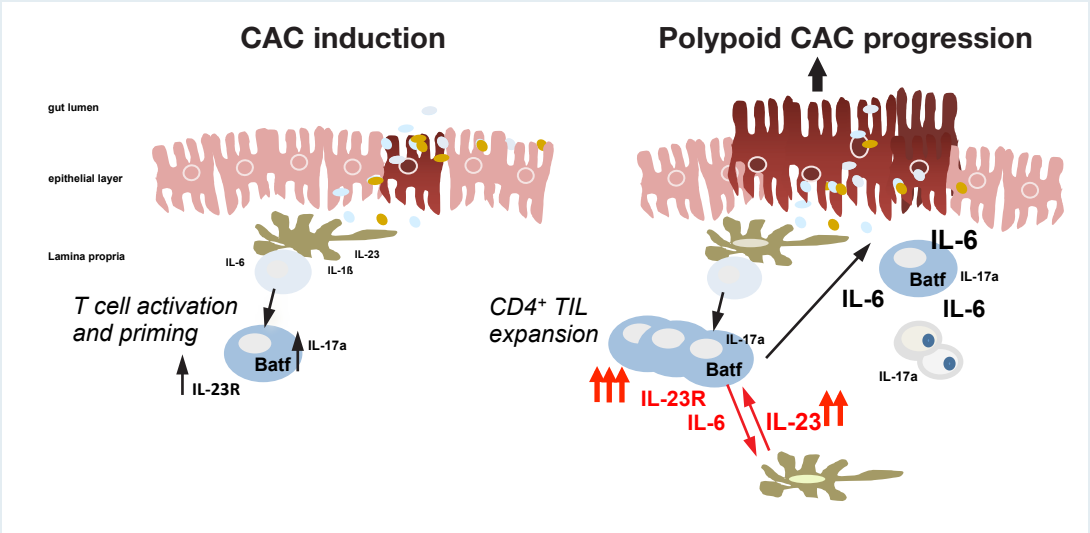
KAI HILDNER
DEPARTMENT OF MEDICINE I, UNIVERSITÄTSKLINIKUM ERLANGEN, FAU ERLANGEN

Inflammatory bowel disease (IBD) is associated with an increased risk to develop colorectal cancer (CRC). While an IL-23$^+$/IL-17a$^+$ tissue microenvironment is linked to a poor prognosis, the selective role of frequently detected tumor-infiltrating IL-17a$^+$CD4$^+$ Tcells (Th17 cells) in the course of the CRC pathogenesis has been poorly understood.

Here, Th17 cells previously described to be dependent on *activating protein 1* (AP-1) transcription factor *basic leucine zipper transcription factor ATF-like* (Batf) were identified to be critical regulators of both sporadic and colitis-associated colon cancer (CAC) formation: Batf$^{-/-}$ mice showed reduced CAC development irrespective of abundant non-Th17 cell-derived IL-17a expression while transgenic Tcells forced to express Batf promoted CAC progression. Mechanistically, Batf controlled IL-23R and IL-6 expression by CD4$^+$ Th17 cells *in vitro* and *in vivo* as Batf$^{-/-}$ tumors lacked IL-17a$^+$IL-23R$^+$IL-6$^+$CD4$^+$ Tcells resulting in reduced intratumoral IL-23 expression. Reconstitution of Batf$^{-/-}$ mice with Hyper-IL6 (consistent of IL-6 bound to soluble IL-6R) restored CAC progression and IL-23 expression invigorating the central role of Batf-dependent IL-6$^+$ Th17 cells in the pathogenesis of IL-23 driven colon cancer formation. Finally, Batf but not Th17 associated *retinoic acid-related orphan receptor gamma* (RORγt) was upregulated in human IBD and CRC tissues. Batf expression correlated with intratumoral IL-23p19 and IL-23R expression and was increased in CRC-infiltrating IL-17a$^+$IL-23R$^+$IL-6$^+$CD4$^+$ T cells.

Together, Batf$^+$IL-23R$^+$IL-6$^+$CD4$^+$ Th17 cells control IL-23 driven colitis-associated tumor formation and the progression of sporadic colon tumors in an IL-17a-independent manner. Batf-dependent Tcells might represent a future therapeutic target limiting CRC progression.

Punkenburg, E. · T. Vogler · M. Buttner · K. Amann · M. Waldner · R. Atreya · B. Abendroth · J. Mudter · S. Merkel · E. Gallmeier · S. Rose-John · M.F. Neurath · K. Hildner. 2015. Batf-dependent Th17 cells critically regulate IL-23 driven colitis-associated colon cancer. *Gut* 10.1136/gutjnl-2014-308227



MODEL
Regulation of colitis- associated colon cancer (CAC) induction and progression by Batf-expressing T cells. **Left:** Upon continuous colitis activity and malignant transformation Batf positively regulates IL-23R expression by CD4$^+$ T cells (blue) rendering these T cells increasingly responsive to IL-23 secreted by tumor-associated APC (green). **Right:** IL-23 drives polypoid colon tumor progression via T cells while intratumoral IL-23 expression levels are at least in part maintained by local effectors like IL-6 provided by Batf-dependent IL23R$^+$ Tcells.

NEWS AND UPDATES

International Day of Immunology

“Pirates of the Immunobay – Adventure Immune System” was this year’s theme for the international Day of Immunology, which was organized by doctoral students of the DFG research training groups GK1660 and IRTG TRR130. Every year at the end of April, the EFIS arranges this event to inform the public about immunological topics focusing on vaccination.

This year, everything was based on a pirate adventure to arouse the interest of children.

Furthermore, a kids’ activity station with different games and handicraft work was set up as well as a microscopy station for observing several pathogens.

All in all, it was a very successful event with satisfied attendees and a lot of positive feedback. We would be pleased to welcome many interested people to the next Day of Immunology 2016.

Lastly, we would like to thank the “Deutsche Rote Kreuz” who supported the event.

Written by Anne Hahn, Alexandra Weise, Tobit Steinmetz

UPCOMING EVENTS

MICE Immunological Colloquium Summer 2015

Tuesdays, 5.15 pm

13. 10. 2015
awaiting confirmation of speaker

20. 10. 2015
Prof. Thomas Brocker
Institute for Immunology, Ludwig-Maximilians-Universität Munich
Title to be announced

27.10.2015
Prof. Andrés Hidalgo
Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain
Title to be announced

03. 11. 2015
No seminar – Fall vacation

10.11.2015
Prof. Robert Zeiser
Klinik für Innere Medizin I, Universitätsklinikum Freiburg
“Pathomechanisms of intestinal acute GvHD”

17.11.2015
Univ.-Prof. Dr. Tobias Bopp
Institute for Immunology, University Medical Center of the Johannes Gutenberg-University Mainz
“Context- and Tissue-specific Regulation of Immunity and Tolerance by Protein Kinase CK2”

24.11.2015
Prof. Irmgard Förster
LIMES-Institut, Bonn
Title to be announced

01.12.2015
Joachim Kalden Lecture 2014
Prof. Alain Fischer
Hôpital Necker-Enfant Malades, Paris, France
Title to be announced

08.12.2015
awaiting confirmation of speaker

15.12.2015
Prof. Marc Schmidt-Supprian
Technische Universität München
Title to be announced

12.01.2016
awaiting confirmation of speaker

19.01.2016
Dr. Helmut Jonuleit
Department of Dermatology, Johannes Gutenberg-University Mainz
Title to be announced

26.01.2016
Dr. Chiara Romagnani
Deutsches Rheuma-Forschungszentrum (DRFZ), Berlin
“Adaptive traits of NKG2C+ NK cell expansions in HCMV seropositive individuals

02.02.2016
Prof. Ernst Werner
Innsbruck Medical University Center for Chemistry and Biomedicine (CCB)
Title to be announced

Further Conferences and Events of Interest

September 11 – 13, 2015
29th Annual Conference of the European Macrophage and Dendritic Cell Society (EMDS)
Krakow, Poland
www.macrophage.de/meetings.htm

September 27 – 30, 2015
67. Jahrestagung der DGHM
Münster

October 4 – 9, 2015
7th Autumn School - Current Concepts in Immunology
Merseburg

April 7 – 9, 2016
International Conference – Infectious Disease Immunology Meets Molecular Microbiology on the Occasion of the 150th Anniversary of the Foundation of the Institute
Erlangen

To celebrate next year´s 150th anniversary of the Microbiology Institute in Erlangen, we will host an international conference titled Infectious Disease Immunology Meets Molecular Microbiology. The number of participants will be limited to 120. There will be no parallel sessions. The conference will comprise 16 invited main talks and 20-25 shorter talks given by scientists from the University of Erlangen and other German or European universities working in the field of infectious disease immunology and microbiology.

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Publisher

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Please note that the authors are responsible for the content of their contributions.

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