Medical Immunology Campus Erlangen

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

Newsletter
Spring 2016

CONTENT

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

EDITORIAL

Dear colleagues and friends,

From April 7 to 9, 2016, the Institute of Clinical Microbiology, Immunology and Hygiene at the FAU and University Hospital Erlangen held an international conference on the occasion of the 150th anniversary of the chair. The meeting focused on the two sides of host-microbial interactions: the components of the host immune system that are critical for overcoming acute and chronic infections and the molecular mechanisms by which infectious pathogens manipulate and evade the host defense machinery.

A second reason for this conference was the 75th birthday of Professor Martin Röllinghoff on April 1. Martin Röllinghoff, who was director of the institute from 1983 until 2007, is one of the founding fathers of infectious disease immunology at the FAU Erlangen. Martin was born in Hamburg, brought up in Tübingen, and studied medicine at the universities of Tübingen, Freiburg and Vienna. His career in microbiology and immunology started in 1968, when he became scientific assistant at the Institute of Medical Microbiology of the University of Mainz headed by Prof. Paul Klein. From 1971 to 1973, he was postdoctoral fellow at the Walter and Eliza Hall Institute in Melbourne, Australia. Thereafter, he worked as a group leader at the institute in Mainz until he was appointed as full professor at the FAU in 1983. Together with Prof. Joachim Kalden he initiated the first immunological collaborative research center in Erlangen (SFB 263 "Immunological mechanisms of infection, inflammation and autoimmunity") which was funded by the DFG from 1991 until 2002. Martin has served as Dean of the FAU Medical Faculty from 2001 to 2005. He is member of the National Academy of Science Leopoldina and he was awarded the Order of Merit of the Federal Republic of Germany in 2007. Martin is still regularly attending the Tuesday evening guest seminar series of the *Medical Immunology Campus Erlangen*, closely follows the development of immunology and infectious disease research at the FAU and acts as an advisor in various committees. On behalf of the *Medical Immunology Campus Erlangen,* it is my pleasure to deliver the heartiest congratulations. Ad multos annos, Martin Röllinghoff!

During the past months a group of immunologists of the Department of Biology and the Medical Faculty has actively pursued the plan to initiate a master degree programme in immunology, an idea, which was originally proposed to the *Medical Immunology Campus Erlangen* by Prof. Hans-Martin Jäck. In the meantime, we became aware of an announcement of the *Elite Network Bavaria*, which will sponsor up to five new master programmes in life sciences and medicine. During detailed discussions with the councils of the respective FAU faculties as well as with members of the FAU executive board our concept of an interfaculty master programme on "Integrated Immunology" was very well received. In the forthcoming weeks Falk Nimmerjahn, the designated chairman of the programme, and six other members of the *Medical Immunology Campus* will work on the preapplication, which has to be submitted to the Ministry of Education, Culture, Science and Arts by the end of June.

Prof. Christian Bogdan
Chairman of the *Medical Immunology Campus Erlangen*

SCIENTIFIC HIGHLIGHTS

Stroma sweetens leukemic cells

Stromal cells promote Warburg effect in AML blasts via a CXCL12/CXCR4/mTOR axis

DIMITRIOS MOUGIAKAKOS
DEPARTMENT OF INTERNAL MEDICINE 5, HEMATOLOGY AND ONCOLOGY, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Acute myeloid leukemia (AML) is the most common acute leukemia amongst adults. One of the characteristics of AML blasts is their recurrent contact with the stromal microenvironment in the bone marrow. This stromal contact protects from spontaneous as well as drug-induced cell death. Thereby it paves the way for drug-resistant clones, minimal residual disease, and finally relapses.

Here, we investigated whether stromal cells elicit alterations in the metabolism of AML blasts and aimed to identify potential underlying molecular mechanisms. We observed that stromal contact promoted a metabolic switch in AML blasts away from oxidative phosphorylation towards aerobic glycolysis, the so-called "Warburg" effect. This newly acquired dependency on a high glycolytic flux could be exploited therapeutically as suggested by our data showing that those cells despite being more resistant towards classical chemotherapeutics showed an increased sensitivity towards agents targeting glycolysis.

We identified a novel function of stroma-derived CXCL12 in promoting the "Warburg" effect in AML blasts. This glycolytic shift was mediated by a CXCL12/CXCR4/mTOR signaling axis. Interfering with this pathway using selective inhibitors already represents a clinical approach for overriding stroma-mediated chemoresistance. Targeting glucose metabolism in AML blasts could be therapeutically exploited especially in view of malignant cells finding refuge in the bone marrow niche while turning "glucose addicted".

Taken together, our findings suggest a microenvironmental glycolytic shift that is mediated by CXCL12/CXCR4/mTOR signaling. Interfering with this pathway or glucose metabolism in AML blasts could represent a novel strategy for targeting the stromal niche's protective effects.

M. Braun, M. Qorraj, M. Buttner, F.A. Klein, D. Saul, M. Aigner, W. Huber, A. Mackensen, R. Jitschin, D. Mougiakakos. 2016.
CXCL12 promotes glycolytic reprogramming in acute myeloid leukemia cells via the CXCR4/mTOR axis. *Leukemia* DOI: 10.1038/leu.2016.58

Bone Marrow

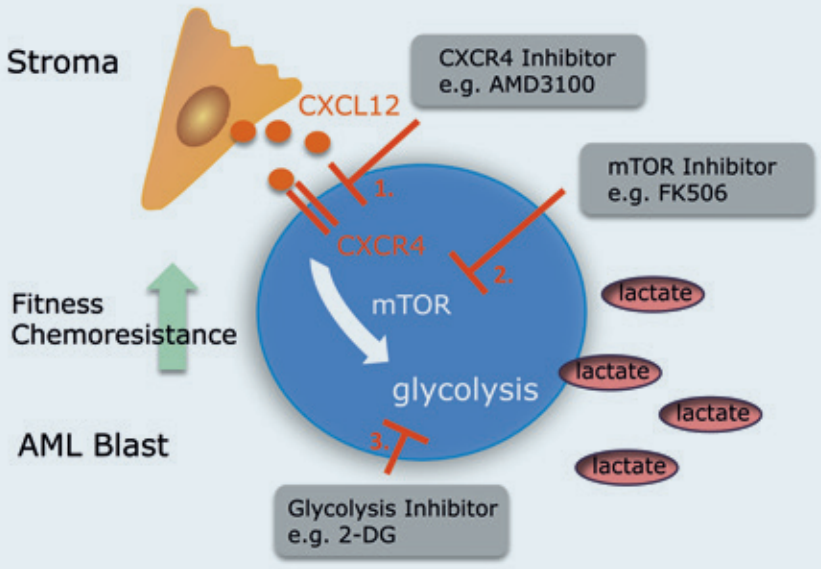

Figure: Metabolic interplay in AML. Based on our observations we propose the following model for the interaction between AML blasts and bone marrow stroma. Stromal cells secrete CXCL12 that binds to its cognate receptor CXCR4 found on AML blasts. Subsequent signal transduction results in an activation of mTOR and an increased glycolytic rate. This metabolic shift is accompanied by increased fitness and resilience towards standard chemotherapeutics of AML blasts. Interfering with this pathway (1. and 2.) or the glucose metabolism (3.) in AML blasts could represent a viable option for targeting the stromal niche's protective effects and remains to be further elucidated.

SCIENTIFIC HIGHLIGHTS

Enzymatic lipid oxidation shapes the adaptive immune response

12/15-Lipoxygenase-mediated phospholipid-oxidation regulates DC maturation and prevents autoimmune disease

TOBIAS ROTHE, GERHARD KRÖNKE
DEPARTMENT OF INTERNAL MEDICINE 3, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Dendritic cells (DCs) act as sentinels that constantly survey our body for infection. Upon recognition of a pathogen, DCs undergo rapid maturation, which subsequently allows them to initiate and orchestrate T cell-driven immune responses. However, DC maturation must be tightly regulated in order to avoid random T cell activation, which would eventually result in an immune response against self-antigens and autoimmune disease. Mechanisms that maintain a DC activation threshold during the steady state and counteract uncontrolled maturation are incompletely understood. Our analyses showed that immature DCs constantly modified their membrane phospholipids via 12/15-lipoxygenase (12/15-LO)-mediated enzymatic lipid oxidation. During the steady state, these oxidative membrane modifications prevented DCs from spontaneous maturation via triggering the antioxidative stress response and activation of the transcription factor NRF2. Downregulation of 12/15-LO, in turn, was necessary for full-blown DC maturation after toll-like receptor-induced activation of DCs. Deletion of the 12/15-LO-encoding gene or pharmacologic inhibition of 12/15-LO in murine or human DCs accelerated maturation and shifted their cytokine profile, thereby favoring the differentiation of pathogenic and autoreactive Th17 cells. 12/15-LO-deficient mice were accordingly prone to Th17-mediated autoimmune diseases such as experimental autoimmune encephalomyelitis, a model for human multiple sclerosis. Our findings thus reveal an unexpected role of enzymatic lipid oxidation during the shaping of the adaptive immune response and the maintenance of self-tolerance.

T. Rothe, F. Gruber, S. Uderhardt, N. Ipseiz, S. Rossner, O. Oskolkova, S. Bluml, N. Leitinger, W. Bicker, V.N. Bochkov, M. Yamamoto, A. Steinkasserer, G. Schett, E. Zinser, and G. Kronke. 2015. 12/15-Lipoxygenase-mediated enzymatic lipid oxidation regulates DC maturation and function. The Journal of Clinical Investigation 125:1944–1954.

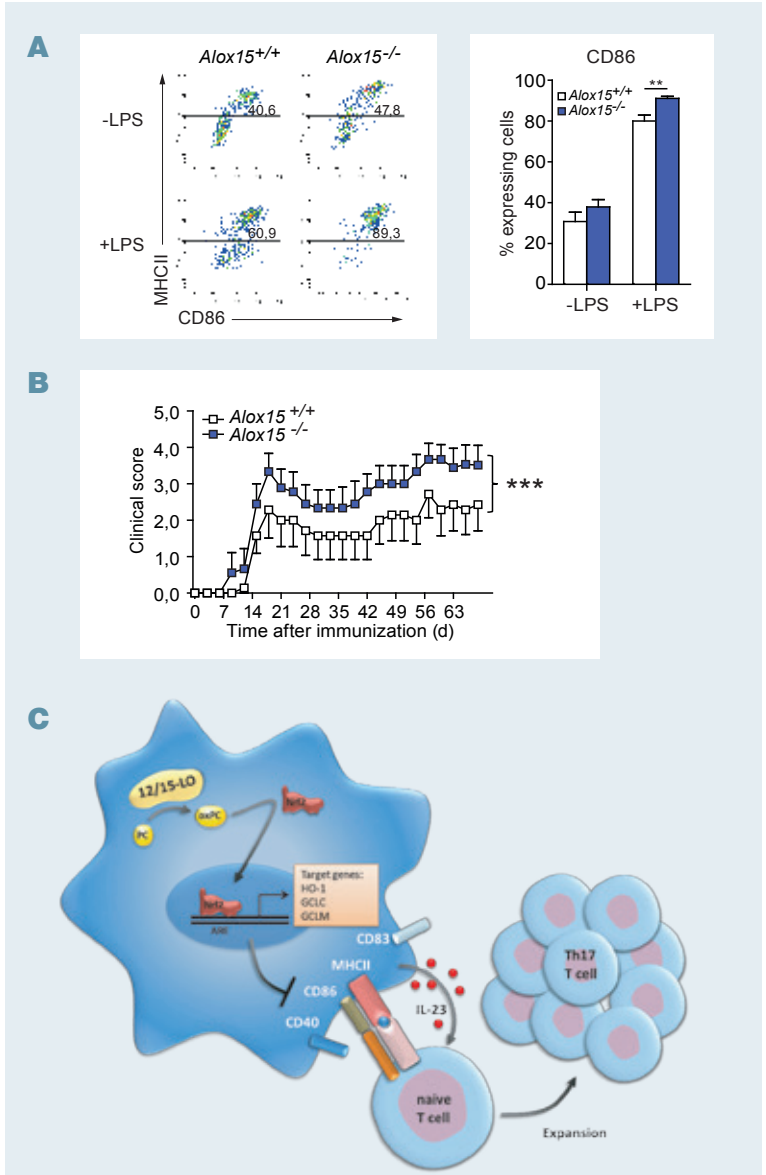

Figure: 12/15-lipoxygenase-mediated lipid oxidation blocks DC maturation and Th17-driven (auto)immunity.

A) Analysis of the maturation status of wild-type (Alox15$^{+/+}$) and 12/15-lipoxygenase-deficient (Alox15$^{-/-}$) DCs. **B)** Clinical disease course of mice after induction of experimental autoimmune encephalomyelitis. **C)** 12/15-lipoxygenase (12/15-LO)-mediated oxidation of membrane phosphatdylcholine (PC) results in the activation of the transcription factor Nrf2 and the induction of the anti-oxidative stress response, which interferes with DC maturation, interleukin-23 (IL-23) production and Th17 differentiation.

SCIENTIFIC HIGHLIGHTS

Survivin regulates intestinal homeostasis

Survivin controls cellular homeostasis in the intestinal stem cell niche

EVA MARTINI, CHRISTOPH BECKER
DEPARTMENT OF MEDICINE 1, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

The intestinal epithelium builds a protective shield against potential pathogens and antigens to prevent direct contact of these to the subjacent immune system. To maintain this barrier function, it is essential to tightly regulate the balance of cell death and proliferation of intestinal epithelial cells. The IAP (inhibitor of apoptosis) family member survivin/BIRC5 is particularly interesting in this respect as it has been described as a regulator of both of these homoeostatic mechanisms. Survivin is highly expressed during embryogenesis and in many cancer types, but only little is known about its role in adult gut tissue.

We found that survivin is not only expressed during embryonic gut development but also exclusively expressed in stem and progenitor cells in intestinal crypts of adult mice. Induced deletion of survivin in intestinal epithelial cells resulted in weight loss, severe destruction of tissue integrity and mucosal inflammation. Furthermore we could observe decreased regenerative proliferation in the epithelium of survivin-deficient (survivin$^{i\Delta IEC}$) mice as well as the development of enlarged nuclei. Intestinal epithelial cells furthermore showed characteristic markers for DNA- damage and dysregulated chromosomal segregation. Using various technical approaches, survivin deletion was shown to result in mitotic catastrophe, a process occurring as a consequence of mitotic failure. Furthermore, absence of survivin specifically in Lgr5 expressing cells resulted in stem cell death.

Taken together, our data highlight a role of survivin as a central regulator in the intestinal stem cell niche and showed that survivin is essential for the proper assembly of the mitotic spindle in rapidly dividing intestinal epithelial cells. Survivin is therefore a crucial molecule for the maintenance of intestinal tissue homeostasis.

E. Martini, N. Wittkopf, C. Gunther, M. Leppkes, H. Okada, A.J. Watson, E. Podstawa, I. Backert, K. Amann, M.F. Neurath, C. Becker. 2016. Loss of survivin in intestinal epithelial progenitor cells leads to mitotic catastrophe and breakdown of gut immune homeostasis. *Cell Reports* 14:1062 – 1073.

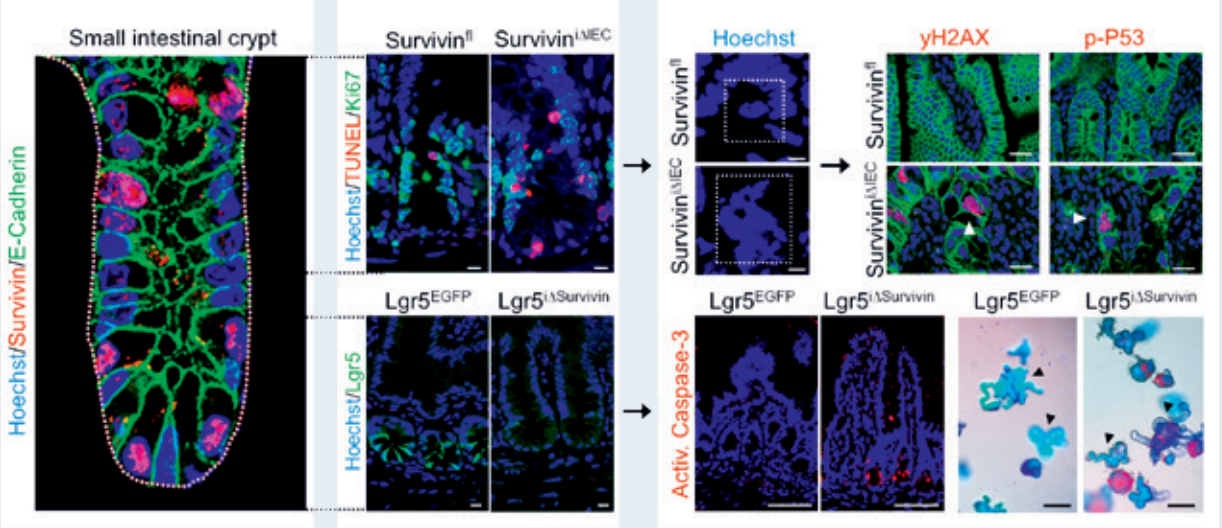

Figure:

A) Expression pattern of survivin (red) in epithelial cells (green) of the small intestinal crypt. Nuclei were counterstained with Hoechst (blue).

B) Upper panel: Deletion of survivin in intestinal epithelial cells leads to enhanced cell death in transit-amplifying cells (Ki67; green) shown by TUNEL staining (red). **Lower panel:** Expression of Lgr5 in the small intestinal crypt (Lgr5^{EGFP}) is reduced when survivin is deleted (Lgr5$^{i\Delta Survivin}$). Nuclei were counterstained with Hoechst (blue).

C) Upper panel: Deletion of survivin results in aberrant mitosis shown by enlarged nuclei in survivin$^{i\Delta IEC}$ mice when compared to controls (survivin^{fl}). Signs of mitotic catastrophe could be detected by up-regulated phosphorylation of H2AX (red) and P53 (red) in epithelial cells (green) of survivin$^{i\Delta IEC}$ mice. **Lower panel:** Reduced expression of Lgr5^{EGFP} (green) could be connected with enhanced cell death shown by activated caspase-3 (red) in survivin-deficient Lgr5 stem cells (Lgr5$^{i\Delta Survivin}$) in the small intestine as well as in small intestinal organoids. Nuclei were counterstained with Hoechst (blue).

SCIENTIFIC HIGHLIGHTS

CD101 inhibits the expansion of colitogenic T cells

Identification of CD101 as a novel marker for inflammatory bowel disease activity and regulatory T cell function

JOCHEN MATTNER
INSTITUTE FOR CLINICAL MICROBIOLOGY, IMMUNOLOGY AND HYGIENE, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

Disturbances in T cell homeostasis contribute to the pathogenesis of inflammatory bowel diseases (IBD). However, the mechanisms underlying the inhibition of regulatory T cell (Treg) function and/or the propagation of colitogenic T lymphocytes in these devastating diseases have remained largely unknown.

Compared to other T cell populations, Tregs express unique sets of costimulatory molecules at steady state. One of these abundantly expressed molecules is CD101, which is absent from naïve T cells. Although CD101 exerts negative-costimulatory effects *in vitro*, its function *in vivo* has remained poorly defined. As CD101 is primarily expressed on immune cells within intestinal tissues, we characterized its function in a T cell transfer model of chronic colitis.

We observed that T cells, once adoptively transferred, expressed CD101, correlating with an increased FoxP3-expression. While the expression of CD101 on T cells was sufficient for the differentiation of Tregs and the inhibition of T cell proliferation, sustained IL-10-production and optimal Treg function required CD101-expression by myeloid cells. Compared to T cells from wild-type mice, a transfer of CD101$^{-/-}$ T cells caused more severe colitis and was associated with an expansion of IL-17-producing T cells. Finally, IBD patients showed a reduced CD101-expression on myeloid cells and T lymphocytes which correlated with an enhanced IL-17-production and disease activity and thus reflected the data obtained in the T cell transfer mouse model. In summary, our data identify CD101 as novel IBD disease activity marker and critical regulator of intestinal T cell homeostasis in both mouse and human IBD.

R. Schey, H. Dornhoff, J.L. Baier, M. Purtak, R. Opoka, A.K. Koller, R. Atreya, T.T. Rau, C. Daniel, K. Amann, C. Bogdan, J. Mattner. 2016. CD101 inhibits the expansion of colitogenic T cells. *Mucosal Immunology*
DOI: 10.1038/mi.2015.139

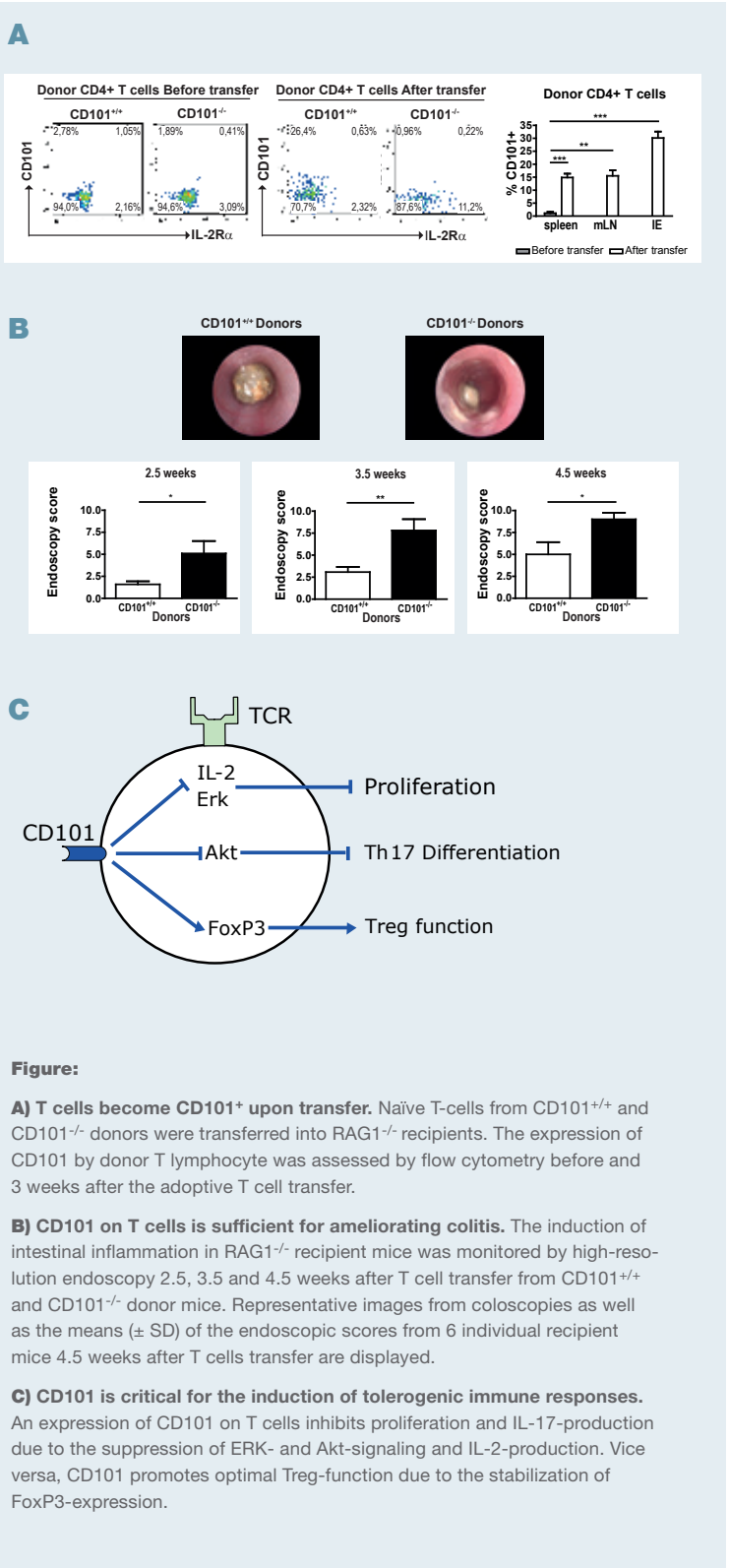

Figure:

A) T cells become CD101^{+} upon transfer. Naïve T-cells from CD101$^{+/+}$ and CD101$^{-/-}$ donors were transferred into RAG1$^{-/-}$ recipients. The expression of CD101 by donor T lymphocyte was assessed by flow cytometry before and 3 weeks after the adoptive T cell transfer.

B) CD101 on T cells is sufficient for ameliorating colitis. The induction of intestinal inflammation in RAG1$^{-/-}$ recipient mice was monitored by high-resolution endoscopy 2.5, 3.5 and 4.5 weeks after T cell transfer from CD101$^{+/+}$ and CD101$^{-/-}$ donor mice. Representative images from coloscopies as well as the means (± SD) of the endoscopic scores from 6 individual recipient mice 4.5 weeks after T cells transfer are displayed.

C) CD101 is critical for the induction of tolerogenic immune responses. An expression of CD101 on T cells inhibits proliferation and IL-17-production due to the suppression of ERK- and Akt-signaling and IL-2-production. Vice versa, CD101 promotes optimal Treg-function due to the stabilization of FoxP3-expression.

SCIENTIFIC HIGHLIGHTS

Induction of the memory IgE response

The extracellular domains of IgG1 and T cell-derived IL-4/IL-13 are critical for the polyclonal memory IgE response in vivo

ADRIANA TURQUETI-NEVES, DAVID VÖHRINGER
DEPARTMENT OF INFECTION BIOLOGY, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN

IgE-mediated activation of mast cells and baso-phils contributes to protective immunity against helminths but also causes allergic responses. The development and persistence of IgE responses are poorly understood which is in part due to the low number of IgE-producing cells. In our work, we used next generation sequencing to uncover a striking overlap between the IgE and IgG1 repertoires n helminth-infected or OVA/alum-immunized wild-type BALB/c mice. The memory IgE response after secondary infection induced a strong increase of IgE^+ plasma cells in spleen and lymph nodes. In contrast, germinal center B cells did not increase during secondary infection. Unexpectedly, the memory IgE response was lost in mice where the extracellular part of IgG1 had been replaced with IgE sequences. Adoptive transfer experiments revealed that $IgG1^+$ B cells were required and sufficient to constitute the memory IgE response in recipient mice. T cell-derived IL-4/IL-13 was required for the memory IgE response but not for expansion of B cells from memory mice.

Taken together, our results reveal a close relationship between the IgE and IgG1 repertoires *in vivo* and demonstrate that the memory IgE response is mainly conserved at the level of memory $IgG1^+$ B cells. Therefore, targeting the generation and survival of allergen-specific $IgG1^+$ B cells could lead to development of new therapeutic strategies to treat chronic allergic disorders.

A. Turqueti-Neves, M. Otte, C. Schwartz, M.E. Schmitt, C. Lindner, O. Pabst, P. Yu, D. Voehringer. 2015. The extracellular domains of IgG1 and T Cell-derived IL-4/IL-13 are critical for the polyclonal memory IgE response *in vivo*. *PLoS Biology* 13:e1002290.

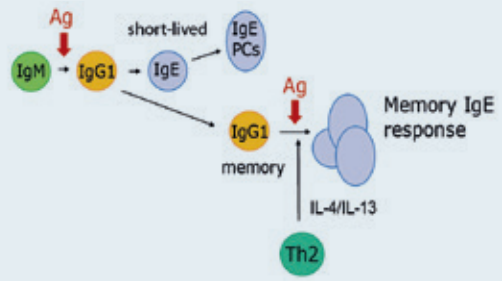

Figure: Primary type 2 immune responses elicit IgG1- and IgE-switched germinal center B cells and plasma cells. IgE-switched B cells appear to be rather short-lived and cannot give rise to a memory IgE response. In contrast, IgG1-switched B cells form a pool of memory cells which undergo a second class switch recombination to IgE upon secondary encounter of the same antigen and this response requires IL-4/IL-13 from T cells.

PEOPLE

Prof. Dr. med. Gerhard Krönke

Appointment as W2 Professor for Translational Immunology at the Department of Medicine III – Rheumatology and Immunology of the Universitätsklinikum Erlangen

Gerhard Krönke obtained his M.D. at the Medical University of Vienna, Austria in 2002. After his post-doctoral studies in Vienna and in Charlottesville, Virginia, USA, he came to the Universitätsklinikum Erlangen in 2006 and started working on the molecular mechanisms of inflammatory bone damage. Prof. Krönke became research group leader in 2009 in the Nikolaus Fiebiger Center of Molecular Medicine focusing his research on the enzyme 12/15-lipoxygenase and its function during the regulation of inflammation, immunity, and self-tolerance. In 2014, Prof. Krönke succeeded in obtaining the renowned ERC starting grant worth 1,5 Mio Euro for the duration of five years.

We congratulate Gerhard Krönke on his appointment as W2 Professor for Translational Immunology and wish him good luck and success for his future.

NEWS AND UPDATES

April 7 – 9, 2016
INTERNATIONAL CONFERENCE

Infectious Disease Immunology Meets Molecular Microbiology Institute for Clinical Microbiology, Immunology and Hygiene

To celebrate the 150th anniversary of the chair at the Institute of Clinical Microbiology, Immunology and Hygiene at the FAU Erlangen-Nürnberg and the Universitätsklinikum Erlangen, an international conference titled Infectious Disease Immunology Meets Molecular Microbiology was held from April 7 to 9, 2016 in the lecture hall and seminar room of the institute.

The meeting started with an opening speech by the Dean of the Medical Faculty of the FAU, Prof. Jürgen Schüttler, followed by welcome addresses by the chairmen of the conference, Prof. Christian Bogdan (FAU) and Prof. Werner Solbach (University of Lübeck). Some of the key topics included were microbial metabolism and virulence, antiviral immunity, antibacterial immunity, antiprotozoan immunity and therapy, immunity to helminths, antifungal immunity and therapy, and mechanisms of immune escape and disease. These topics were covered in seven symposia by 19 invited distinguished scientists. Alongside these 19 scientifically exciting presentations, 21 short oral presentations by international and local experts in the field as well as current and former members of the Microbiology Institute gave fascinating insights in the various fields of molecular microbiology and infectious disease immunology. In all, the conference brought together 110 scientists from eight different countries (Austria, Switzerland, France, Italy, Ireland, UK, USA and Australia).

From left: Prof. Christian Bogdan and Prof. Werner Solbach (Chairmen of the conference) with Prof. Martin Röllinghoff at the speakers' dinner

During the social event on Friday evening, which took place in the seminar room of the institute and was beautifully framed by music performed by Markus Werner (bassoon) and by Rudolf Götzfried (piano), Prof. Bogdan, the chairman of the meeting, briefly summarized the historical milestones of the past 150 years of the Microbiology Institute and paid tribute to Prof. Martin Röllinghoff, the former director of the institute, who celebrated his 75th birthday on April 1. He also thanked all the PhD students, technicians, administrative staff of the institute who helped during the conference and particularly acknowledged the untiring assistance by Dr. Sonja Pötzsch in planning and organizing the conference during the past 9 months as well as the technical and computer support by Hasso Schueler.

At the end of the conference, Prof. Bogdan expressed his thanks to all speakers, chairpersons and participants for their scientific contributions and for making this conference an enjoyable, memorable and scientifically rewarding meeting.

UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Summer 2016

Tuesdays, 5.15 pm

14. 06. 2016
Prof. Dr. Christina Zielinski
Institut für Medizinische Mikrobiologie, Immunologie und Hygiene, Technische Universität München

"Regulation of human T helper cell subsets by the microenvironment in heath and disease"

21.06. 2016
Prof. Patrick Bäuerle
MPM Capital, Cambridge Office

"T Cell-engaging Antibodies for Cancer Therapy"

28.06. 2016
Prof. Thomas Weichhart
Medizinische Universität Wien

"mTOR and macrophage homeostasis"

12. 07. 2016
Martin Kriegel, MD, PhD
Yale School of Medicine, New Haven, USA

Title to be announced

Further Conferences and Events of Interest

August 21 – 26, 2016
International Congress of Immunology
Melbourne, Australia
www.ici2016.org

September 11 – 14, 2016
68. Jahrestagung der DGHM
Ulm

September 21 – 23, 2016
30th Annual Conference of the European Macrophage and Dendritic Cell Society (EMDS)
Amsterdam, The Netherlands
www.macrophage.de

September 27 – 30, 2016
46th Annual Meeting of the German Society for Immunology
Hamburg
www.immunology-conference.de

October 5 – 7, 2016
Interdisciplinary Forum on Virulence Mechanisms of Phyto- and Human-Pathogenic Fungi

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene

This international symposium brings together renowned experts of molecular mycology to discuss distinct as well as common principles of fungal virulence and infections affecting plants and patients. Besides a plenary talk given by Prof. Dr. Regine Kahmann from the MPI of Terrestrial Microbiology in Marburg, regular sessions with invited speakers, short talks by upcoming researchers in the field, and a poster exhibition will provide an up-to-date overview on this exciting topic of infection research.

Medical Immunology Campus Erlangen

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

Publisher
Medical Immunology Campus Erlangen
An Interdisciplinary Center of the Friedrich-Alexander-Universität Erlangen-Nürnberg

Dr. rer. nat. Sonja Pötzsch (Scientific Coordinator)

Mikrobiologisches Institut – Klinische Mikrobiologie, Immunologie und Hygiene

Universitätsklinikum Erlangen
Friedrich-Alexander-Universität Erlangen-Nürnberg
Wasserturmstraße 3/5 · 91054 Erlangen

Phone +49. 9131. 85. 225 71
Fax +49. 9131. 85. 225 73

Mail Sonja.Poetzsch@uk-erlangen.de
www.mice.uni-erlangen.de

Conceptual Design and Editor
Dr. rer. nat. Sonja Pötzsch V.i.S.d.P.

Subscription via Email to:
Sonja.Poetzsch@uk-erlangen.de

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

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

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG