Medical Immunology Campus Erlangen

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

Newsletter Winter 2020

CONTENT

Scientific Highlights

FRIEDRICH-ALEXANDER UNIVERSITÄT ERLANGEN-NÜRNBERG

EDITORIAL

Dear colleagues and friends,

Since its appearance, SARS-CoV-2 is more than ever affecting our lives. At the University Hospital Erlangen, three times as many patients are treated for severe manifestations of COVID-19 as compared to the first infection wave in spring. Due to infections mostly acquired in private settings, we also have much higher numbers of infected personnel. Furthermore, negligence of long-established hygiene rules during work breaks has led to an unprecedented high count of first-degree contact persons, who are then subject to 14-days quarantine orders by the local health authorities. Therefore, I appeal to all of you, clinicians as well as scientists, to strictly follow the existing rules and to reinforce them within your areas of responsibilities.

As immunologists, we are all hoping for the rapid implementation of the COVID-19 vaccines that have successfully passed phase 3 clinical trials. The *European Medical Agency (EMA*) has started review processes on the preclinical and clinical study data from two mRNA vaccines (BNT162b2 from BioNTech/Pfizer; mRNA-1273 from Moderna) and one vector-based vaccine (AZD1222 from Oxford/Astra Zeneca). So far, complete study data that have recently also been published in a peer-reviewed journal (DOI: 10.1056/NEJMoa2034577), are only available from BioNTech/Pfizer so that their vaccine will be the first to be authorized for use in Europe. In parallel to the EMA review, the *Standing Committee on Vaccination (STIKO)* at the Robert Koch Institute is also evaluating the efficacy and safety of the BNT162b2 vaccine and currently finalizes its strictly evidence-based recommendation on COVID-19 vaccination. At the beginning of the rollout, the vaccination will be restricted to persons who have a strongly increased risk to develop severe COVID-19 or to die from the disease. There are several reasons for this prioritization by the STIKO. First, initially the number of available vaccine doses will be limited. In order to reduce the number of fatal cases and to prevent a collapse of intensive care units, hospitals and nursing homes, the most susceptible and exposed people need to be vaccinated (e.g., elderly > 80 years; residents of nursing homes; personnel taking care of COVID-19 patients). Second, at the moment it is unknown whether the BNT162b2 vaccine or any of the other candidates will prevent transmission of SARS-CoV-2 by asymptomatically infected persons. Therefore, highly vulnerable persons can only be reliably protected if they are vaccinated themselves, but not by vaccination of their contacts. Third, the phase 3 clinical approval studies ~~to~~ do not allow to exclude the occurrence of rare severe adverse effects (SAE; < 1:10.000) or the delayed appearance of SAE, as the sizes of the study arms were too small and the observation periods too short. Therefore, vaccination of children and adolescents is presently not recommended based on risk-benefit considerations.

Despite all the restrictions due to the corona pandemic, I wish you and your families a Merry Christmas and all the best for 2021. Hopefully, the new year will allow us to return to a normal way of life.

Prof. Christian Bogdan
Chairman of The Medical Immunology Campus Erlangen

SCIENTIFIC HIGHLIGHTS

Arginase impedes the resolution of intestinal inflammation

Arginase impedes the resolution of colitis by altering the intestinal microbiome and the metabolome

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

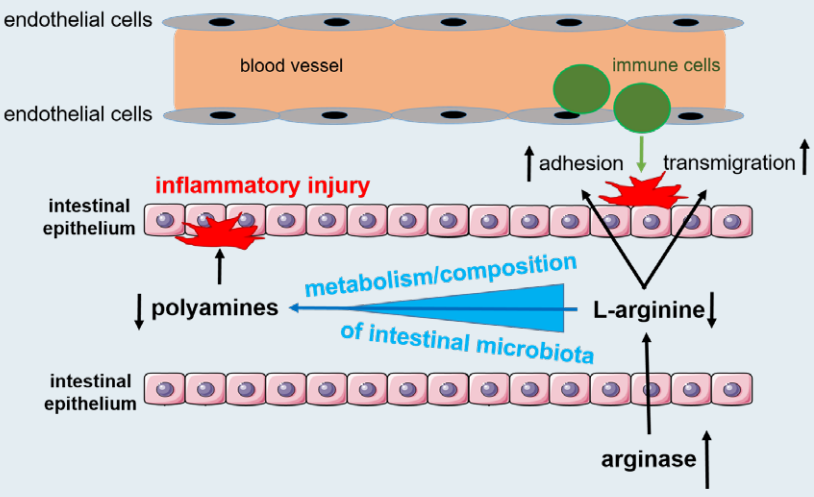
Arginase converts the semi-essential amino acid L-arginine into urea and ornithine, which is a precursor of polyamines that promote cellular growth and tissue remodeling. Besides their enzymatic metabolism, the intraluminal availability of L-arginine and polyamines depends on the diet, the consumption by intestinal microbiota and the turnover of proteins.

Patients with inflammatory bowel disease (IBD) exhibit an enhanced expression and activity of arginase in colonic tissues. However, it is only incompletely understood, whether arginase ~~contributes~~ to epithelial tissue injury, intestinal dysbiosis and the disrupted L-arginine metabolism in IBD.

We observed that an arginine-free chow accelerated experimental colitis in mice while a dietary supplementation with L-arginine promoted the resolution of intestinal inflammation. Unexpectedly, arginase-deletion in hematopoietic and endothelial cells accelerated the recovery from colitis as well. Protection from disease as seen in arginase-deficient animals was similarly observed in L-arginine-supplemented wild-type litters and was associated with an accumulation of intraluminal polyamines, decreased inflammatory cytokine production, reduced inflammatory cell extravasation and compositional changes in the intestinal microbiota. Fecal microbiota transfers (FMTs) from wild-type litters supplemented with L-arginine restored the anti-inflammatory phenotype in recipient mice to a comparable extent as FMTs from arginase-knockout donors, suggesting the intraluminal microbiota as source for protective polyamine production. Vice versa, dietary L-arginine restriction abolished the anti-colitogenic effect of arginase-deletion, suggesting that protection is related to an increased availability of L-arginine, microbial polyamine production and the expansion of anti-inflammatory microbiota.

Thus, in summary our data suggest arginase and L-arginine as novel targets for clinical intervention in IBD patients.

Baier J., Gansbauer M., Giessler C., Arnold H., Muske M., Schleicher U., Lukassen S., Ekici A., Rauh M., Daniel C., Rtmann A.H., Schmid B., Tripal P., Dettmer K., Oefner P.J., Atreya R., Wirtz S., Bogdan C. and Mattner J. 2020. Arginase impedes the resolution of colitis by altering the microbiome and metabolome. J Clin Invest. 130.11: 5703–5720



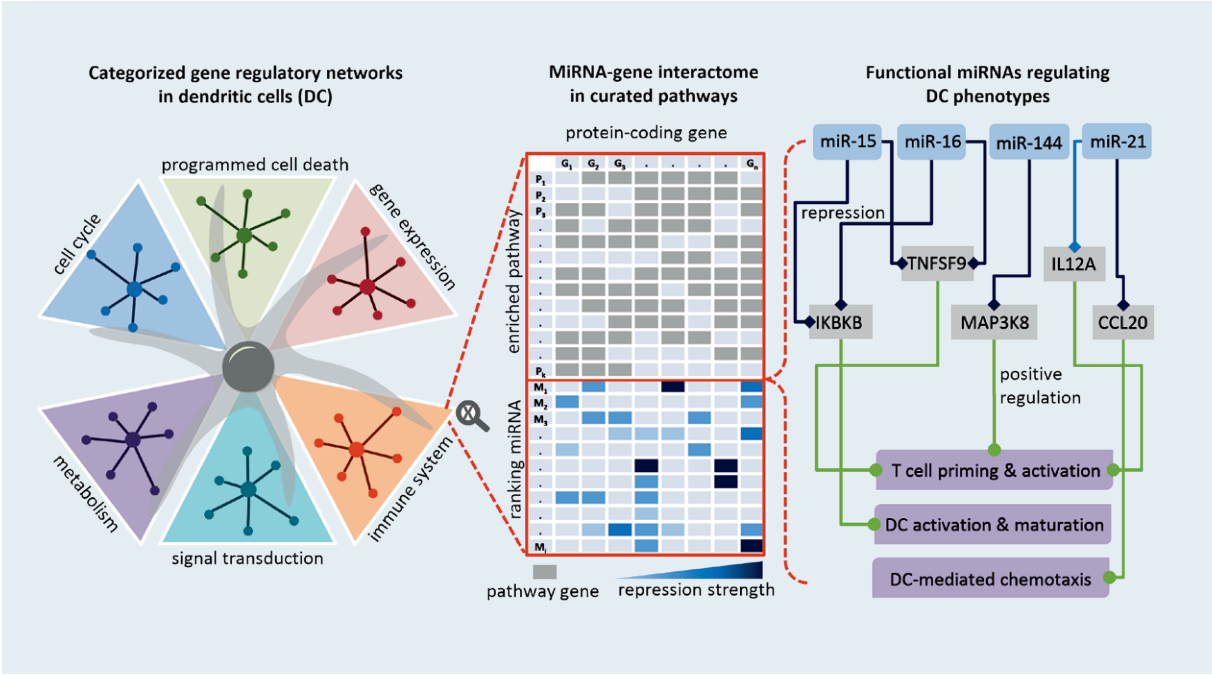
Overview over the pathological changes in the gut induced by arginase expression and subsequent L-arginine deficiency. The consumption of L-arginine by arginase lowers the diversity of the intestinal microbiota and the production of polyamines, resulting in an augmented adhesion and extravasation of inflammatory immune cells and accelerated intestinal epithelial injury. *(Adapted from Baier et al., JCI 2020)*

SCIENTIFIC HIGHLIGHTS

Re-engineering of dendritic cells with non-coding RNAs

Network- and systems-based re-engineering of dendritic cells with non-coding RNAs for cancer immunotherapy

JULIO VERA-GONZÁLEZ
DEPARTMENT OF DERMATOLOGY, FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN



Due to their coordinative role in adaptive immune responses, dendritic cells (DCs) have been used as cell-based therapeutic vaccination against cancer. The capacity of DCs to induce a therapeutic immune response can be enhanced by re-wiring of cellular signaling pathways with microRNAs (miRNAs). Since the activation and maturation of DCs is controlled by an interconnected signaling network, we deploy an approach that combines RNA sequencing data and systems biology methods to delineate miRNA-based strategies that enhance DC-elicited immune responses.

The capacity of DCs to induce an immune response can be improved by molecular engineering. We enhanced the immunostimulatorxy activity of DCs through electroporation with mRNA encoding a constitutively active variant of IKKβ (caIKK), a kinase upstream of NF-κB that is a key regulator of the immune response. Through RNA sequencing of IKKβ-matured DCs that is currently being tested in a clinical trial on therapeutic anti-cancer vaccination, we identified 44 differentially expressed miRNAs. According to a network analysis, most of these miRNAs regulate targets that are linked to immune pathways, such as cytokine and interleukin signaling. We employed a network topology-oriented scoring model to rank the miRNAs, analysed their impact on immunogenic potency of DCs, and identified dozens of promising miRNA candidates, with miR-15a and miR-16 as the top ones. The results of our analysis are presented in a database that constitutes a tool to identify DC-relevant miRNA-gene interactions with therapeutic potential (www.synmirapy.net/dc-optimization).

Taken together, our approach enables the systematic analysis and identification of functional miRNA-gene interactions that can be experimentally tested for improving DC immunogenic potency.

Lai X, Dreyer F, Cantone M, Eberhardt M, Gerer K, Jaitly T, Uebe S, Lischer C, Ekici A, Wittmann J, Jäck HM, Schaft N, Dörrie J, Vera J. 2021. Network- and systems-based re-engineering of dendritic cells with non-coding RNAs for cancer immunotherapy. Theranostics.;11(3)1412–1428. doi:10.7150/thno.53092

SCIENTIFIC HIGHLIGHTS

ZEB1/YAP/AP-1 – a good cooperation with bad outcome

Genome-wide cooperation of EMT transcription factor ZEB1 with YAP and AP-1 in breast cancer

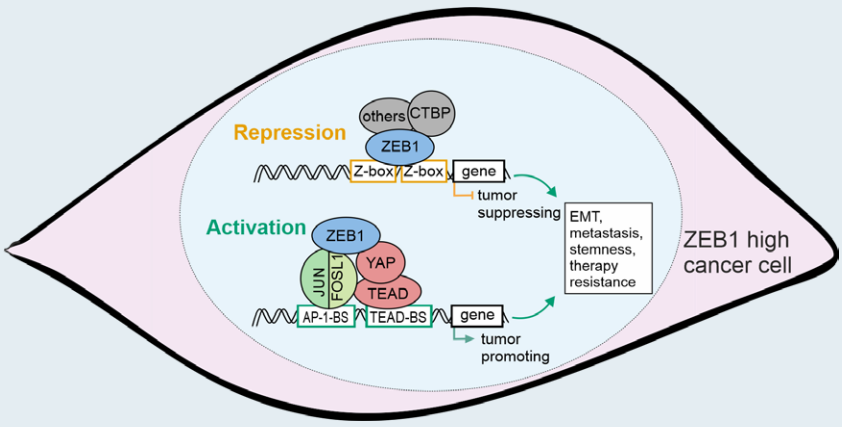
SIMONE BRABLETZ & THOMAS BRABLETZ
DEPARTMENT OF EXPERIMENTAL MEDICINE I, FAU ERLANGEN-NÜRNBERG

Despite major progress in cancer treatment, metastatic disease is still the main cause for cancer related deaths. On their way from the primary tumor to the formation of distant metastases, cancer cells need to be highly plastic, to cope with a wide variety of environmental conditions. This plasticity is conferred by partial and reversible activation of the embryonic epithelial to mesenchymal transition (EMT)-program elicited by a group of core EMT-transcription factors like ZEB1 that is known to play a crucial role in tumor invasion and metastasis.

ZEB1 was first described as a transcriptional repressor. However, subsequent studies revealed that ZEB1 directly activated transcription in conjunction with different co-factors. In line with this, our group recently published that ZEB1 interacts with the Hippo pathway effector YAP in aggressive breast cancer cells to activate common target genes.

To better understand these two modes of action, we performed a genome-wide ZEB1 binding study in triple negative breast cancer cells. We identified ZEB1 as a novel interactor of the AP-1 factors FOSL1 and JUN and showed that, together with the Hippo-pathway effector YAP, they form a transactivation complex, predominantly activating tumor-promoting genes, thereby synergizing with its function as a repressor of epithelial genes. High expression of ZEB1, YAP, FOSL1 and JUN marks the aggressive claudin-low subtype of breast cancer, indicating the translational relevance of our findings. Thus, our results link critical tumor-promoting transcription factors: ZEB1, AP-1 and Hippo-pathway factors. Disturbing their molecular interaction may provide a promising treatment option for aggressive cancer types.

Feldker N., Ferrazzi F., Schuhwerk H., Widholz S. A., Guenther K., Frisch I., Jakob K., Kleemann J., Riegel D., Bönisch U., Lukassen S., Eccles R. L., Schmidl C., Stemmler M. P., Brabletz T. and Brabletz S. 2020
Genome-wide cooperation of EMT transcription factor ZEB1 with YAP and AP-1 in breast cancer. EMBO J, 39, e103209



Model of dual modes of transcriptional regulation by ZEB1

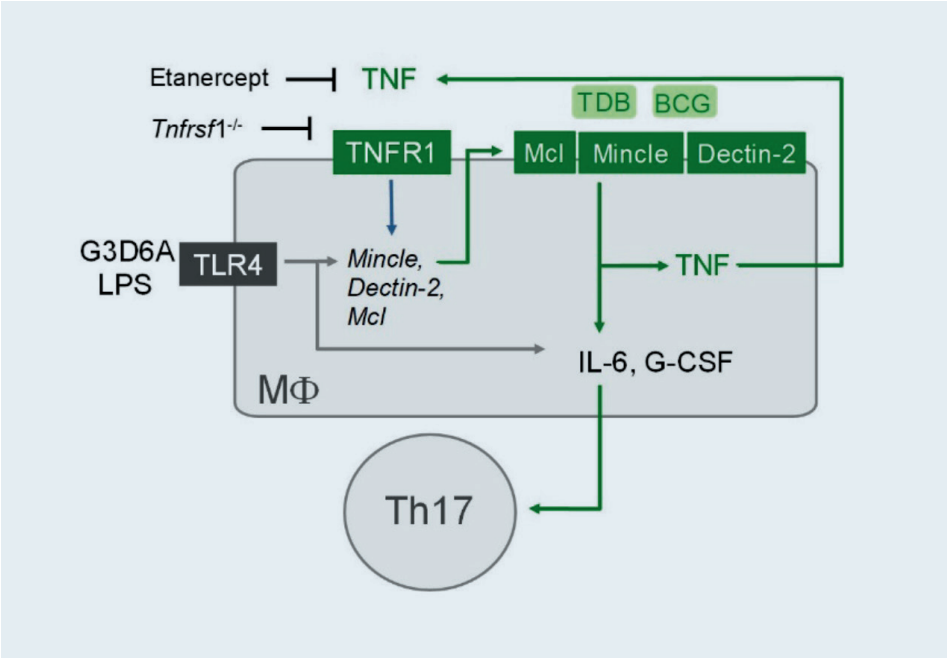
To act as a transcriptional repressor of epithelial differentiation genes, ZEB1 binds to DNA via a dual E-box motif (Z-Box) and recruits co-repressors like CTBP. Within the same cell, recruitment of ZEB1 by YAP and the AP-1 factors FOSL1 and JUN turns ZEB1 into a transcriptional activator of tumor-promoting genes. Together, both modes of ZEB1 action exerted in the same cell contribute to cancer aggressiveness. Orange box: ZEB1-specific E-box motif. Green boxes: AP-1 and TEAD binding sites.

SCIENTIFIC HIGHLIGHTS

TNF is essential for MINCLE expression: a new function for an old cytokine in innate immunity

TNF is essential for mycobacteria-induced MINCLE expression, macrophage activation and Th17 adjuvanticity

ROLAND LANG
INSTITUTE OF MICROBIOLOGY – CLINICAL MICROBIOLOGY, IMMUNOLOGY AND HYGIENE,
FAU ERLANGEN-NÜRNBERG, UNIVERSITÄTSKLINIKUM ERLANGEN



During the last decade, myeloid C-type lectin receptors (CLR) such as Dectin-1, Mincle and Dectin-2 have emerged as an important class of pattern recognition receptors during fungal and bacterial infections. Several CLR binding ligands derived from the mycobacterial cell wall are upregulated on macrophages by microbial stimuli, increasing the sensitivity and magnitude of the response to infection. The work by Judith Schick and colleagues from Erlangen, Munich, Düsseldorf, Borstel and Copenhagen now demonstrates that upregulation of the cord factor-receptor MINCLE in macrophages depends on the cytokine TNF. *In vivo*, deletion or pharmacologic blockade of TNF prevented the Th17-inducing adjuvant activity of the synthetic MINCLE ligand TDB. These findings implicate the regulation of MINCLE and related CLR as a new mechanism underlying the increased risk to develop tuberculosis during treatment with TNF blockers, e.g. in patients with autoimmune diseases like rheumatoid arthritis and inflammatory bowel disease. Downregulation of Dectin-2 family CLR by TNF blockade may also contribute to impairment of vaccination responses, a question that will be investigated in a PhD project in the new GRK 2599 FAIR starting in January 2021.

Schick J., Schafer J., Alexander C., Dichtl S., Murray P.J., Christensen D., Sorg U., Pfeffer K., Schleicher U. and Lang R. 2020. Cutting Edge: TNF Is Essential for Mycobacteria-Induced MINCLE Expression, Macrophage Activation, and Th17 Adjuvanticity. J Immunol. 205. 2: 323–328

UPCOMING EVENTS

Immunological Colloquium of the Medical Immunology Campus Erlangen – Winter 2020/21 Tuesdays, 5.15 pm

12.01.2021 (9:00 Uhr)

Dr. Johannes Mayer
Malaghan Institute of Medical Research,
Wellington, New Zealand

Development of functional Th2-promoting dendritic cell subsets in naïve skin requires innate IL-13

19.01.2021

Prof. Bernd Bodenmiller
Department of Quantitative Biomedicine,
University of Zurich, Switzerland

~~*Titel wird noch bekannt gegeben*~~

~~(engl. to be announced?)~~

26.01.2021

Prof. Bruno Silva-Santos
Instituto de Medicina Molecular,
Universidade de Lisboa, Portugal

Functional and metabolic dichotomy of pro-inflammatory gamma-delta T cell subsets

09.02.2021

Prof. Reuben Tooze
School of Medicine,
University of Leeds, UK

~~*Titel wird noch bekannt gegeben*~~

~~(engl. to be announced?)~~

16.02.2021

Prof. Dietmar Zehn
School of Life Sciences Weihenstephan,
Technical University of Munich

Mechanisms controlling the differentiation of proliferation competent and terminally differentiated cells in acute and chronic infection.

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 (FAU)

www.mice.fau.de

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

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

Contact

For subscriptions and suggestions for the next MICE newsletter please contact

Dr. Sonja Pötzsch
Mikrobiologisches Institut –
Klinische Mikrobiologie,
Immunologie und Hygiene
Universitätsklinikum Erlangen
FAU Erlangen-Nürnberg

Wasserturmstraße 3/5
91054 Erlangen

Phone +49. 9131. 85. 225 71
Fax +49. 9131. 85. 225 73
E-Mail Sonja.Poetzsch@uk-erlangen.de

FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG