DBM FACTS

Periodisches Informationsblatt des Departementes Biomedizin
Universität Basel, Universitätsspital Basel und
Universitäts-Kinderspital beider Basel

Dissecting cancer metastasis through the analysis of circulating tumor cells | DBM Scientific Spring Retreat 2016 | Engagement für Kinder in Kamerun!

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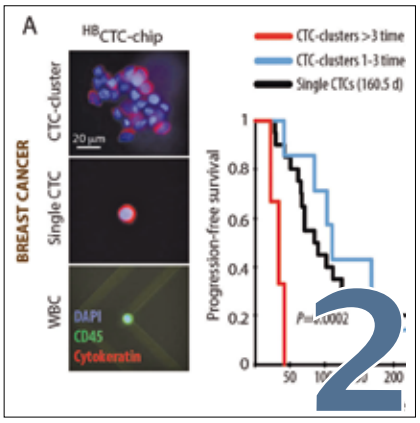
Departement Biomedizin Basel



Dissecting cancer metastasis through the analysis of circulating tumor cells
from Nicola Aceto

DBM Scientific Spring Retreat 2016

Engagement für Kinder in Kamerun!
von Frances Kern

There are three reasons to love lobster: biology, catching, and eating
from Mike Abanto

IMPRESSUM

Redaktion
Heidi Hoyermann

Übersetzungen
Paula Cullen

Layout
Eric Spaety, Morf Bimo Print AG, Binningen

IT-Unterstützung
Niklaus Vogt

Administration
Manuela Bernasconi

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Hebelstrasse 20
4031 Basel
heidi.hoyermann@usb.ch

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Universitätsspital Basel

UNI BASEL

EDITORIAL

Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Die Sommerpause ist zu Ende und das DBM geht weiteren positiven Ereignissen entgegen.
Momo Bentires-Alj wurde auf die Professur für «Experimentell-Chirurgische Onkologie» berufen und nimmt am 01.09.2016 seine Tätigkeit am DBM mit seiner Forschungsgruppe «Breast tumor heterogeneity, metastasis and therapy resistence» auf. Momo kommt vom FMI und wird den Schwerpunkt «Oncology and Cancer Research» verstärken. Wir freuen uns auf den wissenschaftlichen Austausch und heissen ihn und seine Forschungsgruppe herzlich willkommen! Mit Rolf Zeller und Momo Bentires-Alj haben zwei Forscher des DBM einen prestigeträchtigen ERC Advanced Grant erhalten. Wir gratulieren herzlich!
Am 31.08.2016 lädt das DBM zum Summer Symposium, an dem Projektleiter, Postdoktoranden und Doktoranden ihre Forschung präsentieren werden. Am Abend schliesst sich dann das traditionelle Summer Barbecue an. Wir hoffen auf eine zahlreiche Teilnahme!
In der nun vorliegenden Ausgabe erfahren wir von Nicola Aceto mehr über «Dissecting cancer metastasis through the analysis of circulating tumor cells», die Forschung seines Labors «Cancer Metastasis» (ab Seite 2). Die DBM Doktoranden lassen uns teilhaben an ihrer bereits zum vierten Mal stattgefundenen Retreat, dieses Mal in Emmetten (ab Seite 8). Einen Überblick über die neuesten Publikationen erhalten Sie ab Seite 11. Frances Kern, ehemalige und langjährige Mitarbeiterin am DBM, nimmt uns mit nach Kamerun, wo sie mit anderen Helfern ein Waisenhaus betreut (ab Seite 29). Mike Abanto zeigt uns, dass er nicht nur die Biooptik beherrscht, sondern auch ein exzellenter Hummerfischer ist (ab Seite 33).
Viel Freude bei der Lektüre!

Dear Readers

The summer break is over and the DBM moves forward full of positive energy.
Momo Bentires-Alj has been named as professor of Experimental Surgical Oncology and takes up his position in the DBM on 01.09.2016 with his research group "Breast tumor heterogeneity, metastasis and therapy resistence". Momo comes from FMI and will strengthen the Oncology and Cancer Research focal area. We look forward to swapping scientific knowledge and extend the warmest of welcomes to him and his research group. Two researchers at the DBM, Rolf Zeller and Momo Bentires-Alj, have received the prestigious ERC Advanced Grant. Congratulations to them both!
On the 31.08.2016 the DBM invites the project leaders, post doctoral fellows and PhD students to present their studies at the Summer Symposium. This will be wrapped up in the evening by the traditional summer barbecue. We hope to see you all there!
In the following issue we will learn more from Nicola Aceto on "Dissecting cancer metastasis through the analysis of circulating tumor cells", the research of his Cancer Metastasis laboratory (page 2). The PhD students of the DBM let us take part in their retreat in Emmetten, which took place this year for the fourth time (page 8). You can find an overview of the latest publications on page 11. Frances Kern, who was, in the past, a long time member of the DBM community, takes us on a journey to Cameroon where she, and other helpers, are working in an orphanage (page 29). Mike Abanto shows us that he not only excels at microscopy but that he is also an excellent lobsterer (page 33). Happy Reading!

Dissecting cancer metastasis through the analysis of circulating tumor cells

Summary

The Cancer Metastasis lab started in 2015 upon my arrival at the University of Basel from Boston, USA. From the first day, our lab has been embedded in a very dynamic cancer research community in Basel, involving molecular biologists, clinicians, and computational scientists within the DBM as well as in other institutions in town.

Our science focuses on the analysis of circulating tumor cells (CTCs) from both cancer patients and mouse cancer models, to gain insights into the biology of metastasis. CTCs are defined as those cells that detach from a tumor mass in the body and enter the blood circulation, on their way to forming metastasis in a distant site. They are extraordinarily rare compared to blood cells in circulation (approximately one CTC per every billion blood cells!), but their isolation is now possible with specialized devices. In the lab, we combine microfluidics technologies for CTC isolation, human and mouse cancer samples, single cell-resolution next-generation sequencing, molecular and computational biology. These techniques, when combined, allow us to understand important biological features of metastatic cells in circulation, and to identify vulnerabilities of a metastatic disease.

In the long run, we aim to contribute to the development of new therapeutic agents to reduce the metastatic spread of cancer.

What do we know about cancer metastasis?

More than 90% of cancer-related deaths are due to the development of a metastatic disease, corresponding to more than 7 million people each year worldwide (WHO). The search for factors that regulate cancer metastasis began in 1889 when Paget analyzed postmortem data of women who died of cancer, and noticed the high frequency of metastasis to the ovaries and the bone. Paget concluded that metastases only develop when certain tumor cells are compatible with specific distant organs [1]. These observations are the foundation of the highly debated "seed versus soil" theory (i.e. is the cancer cells, or the organ in which they will land that matter the most?), which sharply contrasted the pre-existing theory of Virchow, who postulated that metastasis could be explained by the entrapment of tumor cell emboli in small capillaries [2]. More than a century later, researchers continue their efforts to solve this dilemma, and strive to identify molecular mechanisms driving cancer metastasis, a disease that is still largely incurable [3].

Most of our current understanding of how metastasis occurs derives from experimental mouse models, where the primary tumor site, driver genomic alterations, tumor size and blood/tissues sampling can be engineered and optimized to study the metastatic process. Analysis of these models led us to the notion that metastasis is predominantly achieved by single migratory cancer cells that actively intravasate in the bloodstream and extravasate at distant sites, where they initiate a metastatic lesion [4]. In contrast, studies on histopathological sections of human primary tumors and metastatic deposits have highlighted that most epithelial cancers seem to display the hallmarks of collective invasion into surrounding tissues, including intact cell-cell junctions and cadherin expression [5]. Altogether, this apparent discrepancy between human data and mouse models points to the complexity of blood-borne spread of cancer and the need to dynamically capture cancer cells on their way to forming a metastasis.

Cancer cells that have detached from a primary tumor and enter the blood circulation, on their way to metastasis, are referred to as circulating tumor cells (CTCs). CTCs represent an extraordinary source of information to study metastasis in patients, and an opportunity to identify vulnerabilities of the metastatic process. Since CTCs are extremely rare in circulation compared to blood cells, their isolation has been hampered for many years by technological limitations. Only recently, remarkable advances in microfluidic technologies have made it possible to isolate and characterize this rare population of cells not only in mouse models, but also in human specimens, revealing unexpected (and very exciting!) features.

In the next few lines, I will describe the recent discovery that clusters of CTCs in the blood (a.k.a. CTC-clusters), held together by intercellular junctions, represent highly efficient metastatic precursors [6]. I will also discuss how this finding has opened new questions that are framing our work in the Cancer Metastasis lab, and why CTC analysis may lead to the identification of therapeutic targets for suppressing the spread of cancer.

CTC-clusters in the metastatic process

While single cancer cells in circulation represent the vast majority of CTCs, clusters of CTCs have been first theorized, and then observed several decades ago in patients with cancer [2, 7]. Since then, these clusters have been observed in human cancers of the breast, pancreas, kidney, colon, lung and melanoma. However, their functional role in the metastatic process has remained elusive.

To define whether the presence of CTC-clusters is associated with a poor prognosis, we quantified the abundance of single CTCs and CTC-clusters in the blood of patients with breast and prostate cancer, drawn multiple times over a period of 19 to 53 months at Massachusetts General Hospital in Boston. In patients with breast cancer, the presence of CTC-clusters across more than three timepoints strongly correlated with decreased progression-free survival compared to patients with only single CTCs or in whom clusters were occasionally detected. Even more strikingly, in prostate cancer patients, the presence of one single CTC-cluster during one timepoint correlated with decreased overall survival compared to patients with single CTCs only [6]. These results established that the presence of CTC-clusters correlates with disease progression in patients with breast and prostate cancer (Fig. 1).

Using a mouse model with color-coded primary tumor cells, we also understood that CTC-clusters are rare (2.6-5.8% of total CTC events) but characterized by up to 50-fold increased metastatic potential compared to single CTCs [6]. Further, we determined that virtually all CTC-clusters originate directly from oligoclonal pri-

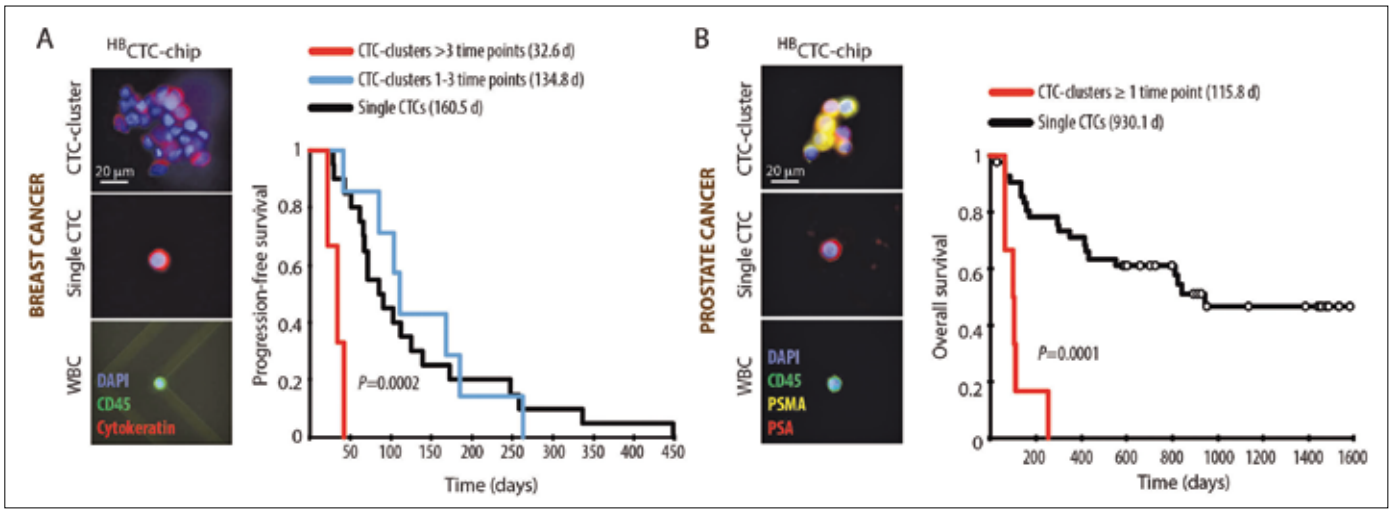

Figure 1: CTC-clusters and poor prognosis. Kaplan-Meier analysis of patient data showing that the presence of CTC-clusters correlates with reduced progression-free survival (A) and overall survival (B) in patients with breast and prostate cancer, respectively.

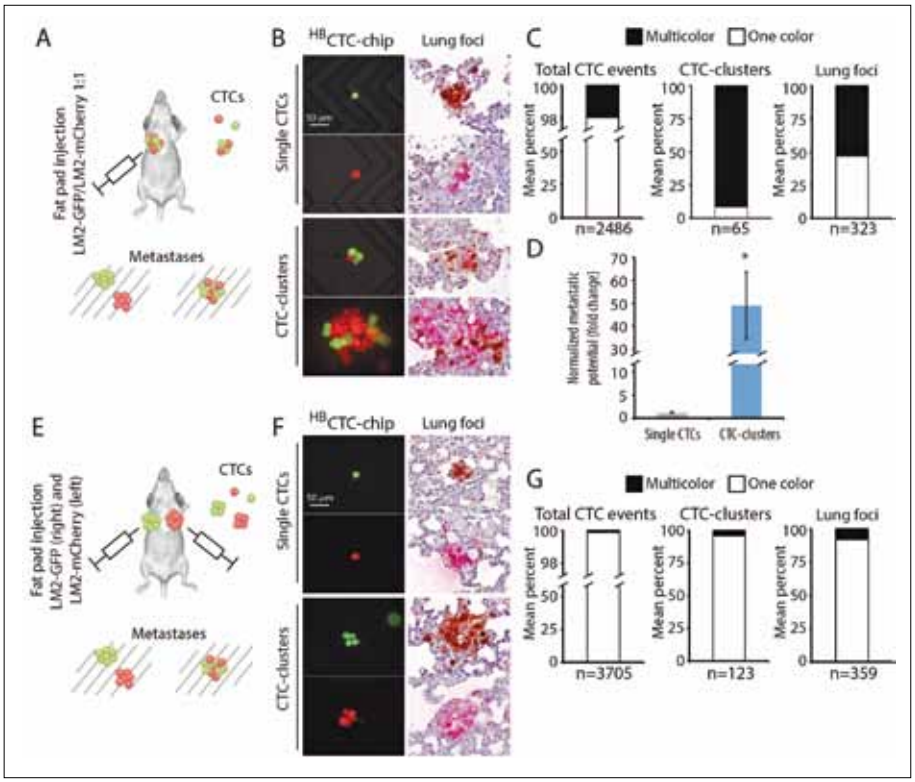

Figure 2: CTC-clusters are oligoclonal metastatic precursors. (A) Schematic of the experiment leading to the spontaneous formation of multicolor CTC-clusters vs monocolor single CTCs from a primary breast tumor. (B) Immunofluorescence images of CTCs (left) and immunohistochemistry staining of metastatic foci (right). (C) Bar graphs showing that the vast majority of CTC-clusters are multicolor and give rise to multicolor metastatic foci. (D) Bar graphs showing that CTC-clusters are up to 50-fold more metastatic than single CTCs. (E) Schematic of the control experiment to assess intravascular aggregation of CTCs. (F) Immunofluorescence images of CTCs (left) and immunohistochemistry staining of metastatic foci (right). (G) Bar graphs showing that over 90% of CTC-clusters and metastatic foci do not derive from aggregation events.

mary tumor cell groupings that enter the circulation, as opposed to be derived from intravascular aggregation of CTCs or the progeny of a single CTC. When injected intravenously, clustered cancer cells are more resistant to apoptosis upon arrival into the lung tissue, than an equal number of single cancer cells [6]. These results highlight the high metastatic propensity of CTC-clusters compared to single CTCs (Fig. 2), and the need to target CTC-clusters, rather than single CTCs, to suppress metastasis.

The ability to isolate matched CTC-clusters and single CTCs from the blood of patients with cancer made it possible to compare their expression profile for the first time. Using a single cell-resolution RNA-sequencing approach, we identified genes whose expression was highly enriched in CTC-clusters compared to single CTCs from individual patients. Among the top CTC-cluster genes was plakoglobin, a component of both desmosomes and adherence junctions (Fig. 3). Further, we found that expression of plakoglobin in the primary tumor of patients with breast cancer correlated with decreased progression-free survival, and that plakoglobin was required for CTC-clusters formation and spontaneous metastasis in orthotopic mouse models of breast cancer [6]. Altogether, while leading to exciting new questions, these observations highlight a previously under-appreciated and potentially targetable mechanism of cancer dissemination, i.e. CTC-clustering.

Identifying vulnerabilities of CTC-clusters

Based on the discoveries summarized above, the goal of the Cancer Metastasis lab is to gain insights into the biology of CTC-clusters and to identify their vulnerabilities. To reach this goal, we strive to give an answer to at least three fundamental questions. What leads to the generation of CTC-clusters from an established tumor mass? What are the molecular features of CTC-clusters compared to single CTCs in patients? What can we target on CTC-clusters once they are found in circulation?

To answer these questions, we take a multidisciplinary approach. First, we use microfluidic technology combined with robotics to achieve the isolation of single and clustered (viable) CTCs from the blood of cancer patients and mouse models. Second, we adopt single cell-resolution next generation sequencing and computational biology to define the molecular features

of these cells in circulation. As a last step, we use molecular biology techniques, *ex vivo* cultures and mouse models to validate our findings (Fig. 4). Understanding which signals trigger the release of CTC-clusters from a tumor, what are the signaling events occurring within CTC-clusters, and how to target these clusters effectively may lead to novel approaches to diagnose and to treat metastatic cancers. In the lab, our research plans are focused around these research questions, and can be subdivided into:

1. Targeting cell-cell junctions in CTC-clusters. Recent observations made with molecular analysis of CTCs from cancer patients have led us to the understanding the CTC-clusters are held together by a subset of upregulated cell-cell junction components. Sofia Gkountela (postdoc), Ilona Krol (research technician) and Ramona Scherrer (research technician) in the lab are working on this project, with the goal to define which specific cell-cell junction components are required for CTC-clustering without affecting the architecture of normal epithelia, and most importantly which ones among these will be targetable pharmacologically.

2. Molecular heterogeneity of CTC-clusters and single CTCs. Previous studies have pointed to the oligoclonal nature of CTC-clusters, suggesting that one cluster of cancer cells may be formed by cells with different properties, or even carrying a different subset of mutations. Barbara Szczerba (PhD student) in the lab is using single cell transcriptomics and genomics to quantitatively define the molecular heterogeneity of CTC-clusters isolated from patients with different cancer types. Her work may lead to dissecting the heterogeneity of CTC-clusters, but also to identify important pathways and mutational events that occur during metastatic progression.

3. Signals that trigger CTC generation. While most cancer cells are destined to remain within the established tumor mass, a few will escape and enter the bloodstream. It is currently unknown what events lead to the intravasation of cancer cells in general, and particularly of CTC-clusters. Cinzia Donato (PhD student) and Manuel Scheidmann (PhD student) in the lab will address this question with different approaches. While Cinzia focuses on tumor mircoenvironmental cues that may force cancer cells to intravasate from well-defined areas of the primary tumor, Manuel will take a genome-wide approach to determine which genes are essential (in cancer cells themselves) for the generation of CTC-clusters and metastasis.

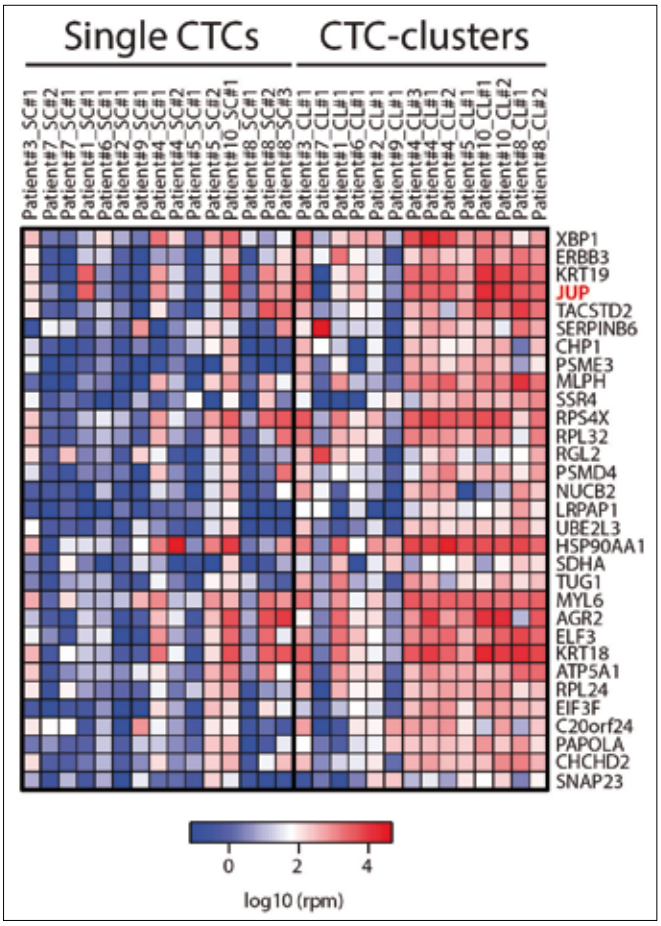

Figure 3: Transcripts upregulated in human CTC-clusters. Heatmap showing the highest upregulated genes (q<0.01) in CTC-clusters compared to matched single CTCs from a total of 10 patients with metastatic breast cancer. The cell-cell junction component plakoglobin (JUP) is highlighted in red. Results are shown in a log10 reads per million (rpm) scale.

4. Single cell resolution interrogation of CTCs and metastatic progression. The possibility to interrogate metastatic cancer cells at the single cell resolution is not only an exceptional opportunity to study the metastatic process, but it is also a challenge from a bioinformatics perspective. Francesc Castro Giner (computational postdoc) and Edward Richards (Intern) will take advantage of their computational skills to identify key networks that support metastatic progression and resistance to therapy.

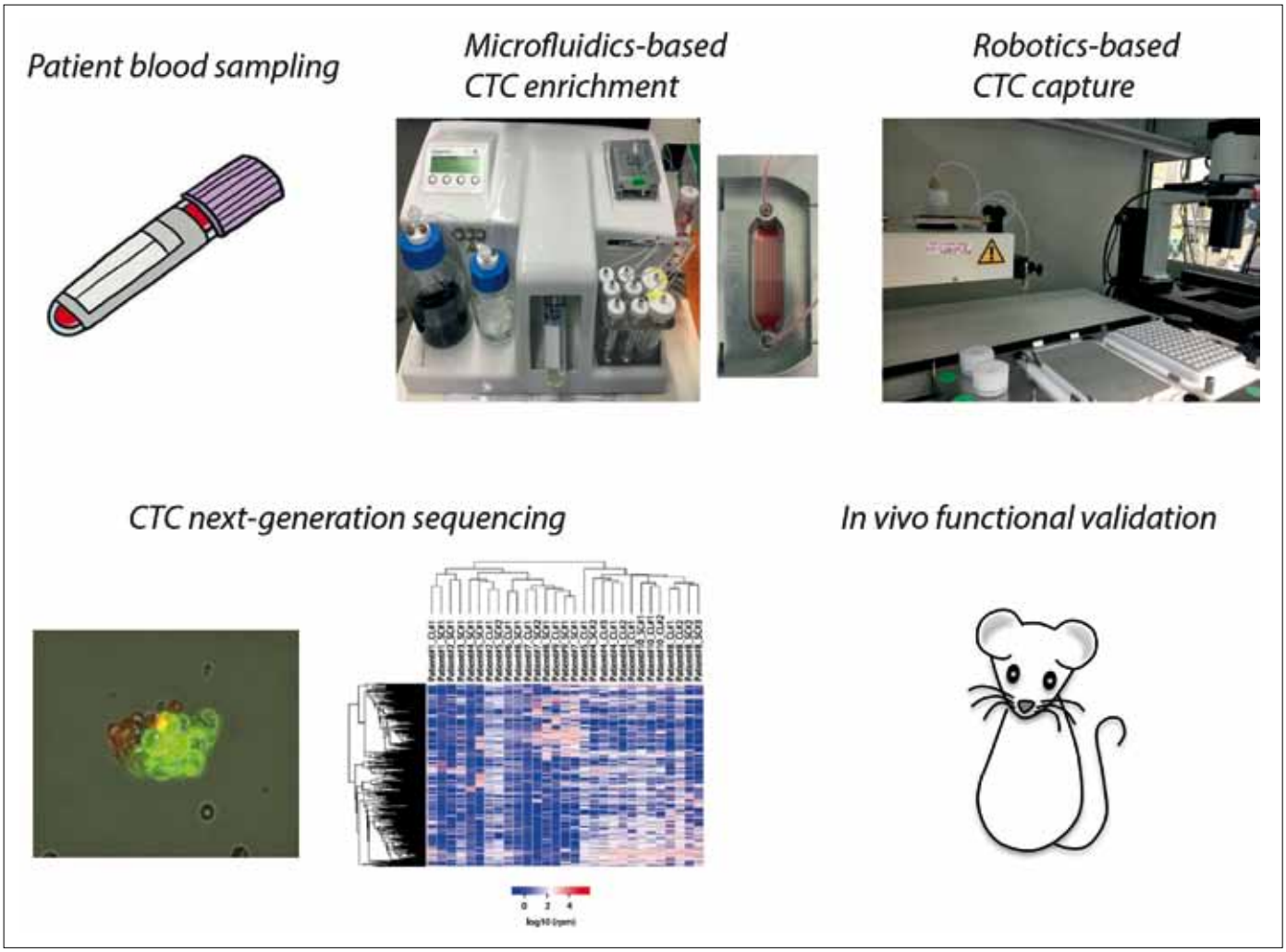

Figure 4: Typical workflow used in the Cancer Metastasis lab to study circulating tumor cells (CTCs) and to identify metastasis-relevant genes.

Outlook and future perspectives

While metastatic cancers are generally treated as if they were a localized disease (i.e. with drugs that reduce proliferation, increase apoptosis, etc.), the ultimate goal of our studies is to develop strategies that are aimed at targeting those pathways that influence the metastatic process itself. In this context, analysis of CTCs is key to dissecting those fundamental mechanisms that underlie cancer dissemination. Understanding what is required for CTC generation and their survival in the blood is of high importance for designing new therapies. While new technologies are finally enabling a detailed molecular analysis of human CTCs, much remains to be learned. Quantitative and molecular approaches on patient specimens are required to deepen our knowledge of these multi-step processes, and pave the way to the development of metastasis-tailored therapies for patients with cancer.

Nicola Aceto

The Cancer Metastasis Group in July 2016.

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DBM Scientific Spring Retreat 2016

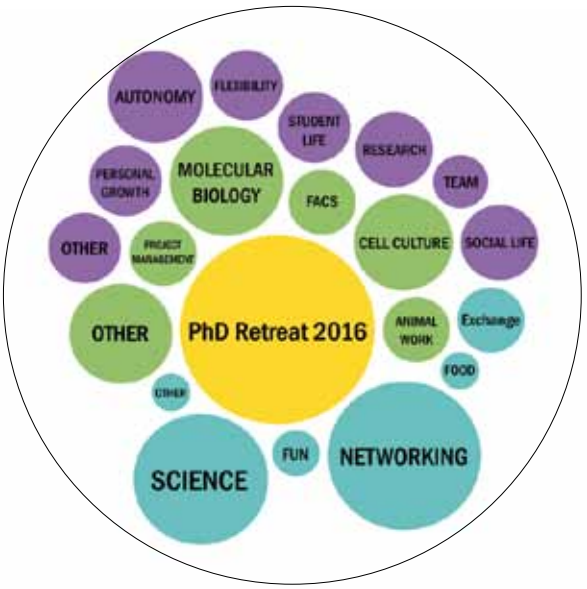
In May 2016, 50 PhD students (and one Master student) stepped away from their benches and set out for the 4th annual DBM PhD retreat.

The retreat is organized by and for PhD students of the International PhD Program in Biomedicine and has been held in different and beautiful locations throughout Switzerland. Participants from all of the DBM's four focal areas present their work to fellow PhD students in either a talk or a poster presentation. Apart from the captivating scientific program, students have the opportunity to socialize and get to know people from different DBM locations over the three-day meeting.

This year the retreat was held at the beautiful Hotel Seeblick in Emmetten. The group arrived early and the day was started with a cross-connective game to break the ice. Here, everybody was encouraged to mingle and interview others about their expectations for the retreat, their field of expertise and their favourite aspect of being a PhD student. Looking at the results, it became clear that the participants have many different skills, but shared their expectations for the upcoming days. In addition, there were obviously many different reasons given to love the PhD life.

During the following two days 19 PhD students from immunology, neurobiology, oncology and stem cells and regenerative medicine gave us insights into their projects in swift 15 minute talks. In between those talks our guest speakers, Dr. Matthias Mehling and Prof. em. Regine Landmann, both held keynote lectures presenting their own research. Dr. Mehling's group is currently working on evaluating lymphocyte migration in patients with Multiple Sclerosis using various interdisciplinary approaches. On the other hand, Professor Landmann, who works on the glycoprotein CD14 in infection models, focused on the most important steps of her scientific work as well as the changes in science that she experienced during her impressive career. Since both talks covered many different areas and aspects of scientific research, the talks were defintiely intriguing for all the participants, no matter their particular fields of research.

At the end of each day the scientific program was closed with a poster session. Best poster presentations and talks were later awarded with the golden pipette. Congratulations again to the winners!



Best Presentation:
- **1st** Sebastian Pigeot
- **2nd** Pascal Forrer
- **3rd** Anna Paczulla

Best Poster:
- **1st** Sandro Nuciforo
- **2nd** Alexander Haumer
- **3rd** Max Mendez

For the evenings the PhD Club also organized a bonfire, an Apéro and a pub quiz that were all well received by everyone. As per usual, on the last day of the retreat there were no presentations scheduled so some people set out on a "patriot walk" to the Rütli meadow, while others tooka trip by cable car up to the Niederbauen to enjoy a light hike and the scenic view over Lake Lucerne.

All in all the retreat was a tremendous success and the PhD Club would like to thank each and every participant for making it so enjoyable. We hope everybody got some new inspiration, had many great conversations and maybe made some new friends!

We also want to give a special thank you to Nicole Schären-Wiemers for her support. It is always a pleasure to work with you and we truly value your sincere dedication to the PhD program and us, its students.

It was a pleasure to have all of you at the retreat and we hope to see many of you again next year!

Your PhD club


DBM Scientific
Spring Retreat
2016

Dissertationen

Am 14. April 2016 konnte **Eleonora Cremonesi** von der Forschungsgruppe „Cancer Immunotherapy“ (Departement Biomedizin Hebelstrasse) ihre Dissertation mit Erfolg beenden. Sie befasste sich in ihrer Dissertation mit dem Thema: „Chemotactic factors underlying tumor infiltration by immunocompetent cells in human colorectal cancer“.

Am 23. Juni 2016 stellte sich **David Berner** von der Forschungsgruppe „Molecular Neurobiology Synaptic Plasticity“ (Departement Biomedizin Klingelbergstrasse) den Fragen des Dissertationskomitees. Der Titel seiner Dissertation hiess: „GABAB receptor-associated KCTD proteins as molecular linkers to downstream signaling complexes“.

Seit dem 28. Juni 2016 darf sich **Audrey Lilly von Münchow** von der Forschungsgruppe „Developmental and Molecular Immunology“ (Departement Biomedizin Mattenstrasse) Frau Dr. nennen. Sie befasste sich in ihrer Doktorarbeit mit dem Thema: „New insights into the molecular and cellular requirements of lymphocyte development“.

Auszeichnungen

Venia docendi verliehen

In ihrer Sitzung am 14. April 2016 hat die Regenz der Universität Basel **Christoph Berger** von der Forschungsgruppe “Translational Immunology” (Departement Biomedizin Hebelstrasse) die Venia docendi für Innere Medizin verliehen. In ihrer Sitzung vom 30. Mai 2016 hat die Regenz **Claudia Cavelti-Weder** von der Forschungsgruppe “Translational Diabetes” (Departement Biomedizin Hebelstrasse) die Venia docendi für Endokrinologie/Diabetologie und **Sacha Rotschild** von der Forschungsgruppe Cancer Immunology (Departement Biomedizin Hebelstrasse) die Venia docendi für Medizinische Onkologie erteilt. Sie sind damit befugt, den Titel eines Privatdozenten zu führen.

Swiss Transplant Research Award 2016 an Hans Hirsch

Hans Hirsch von der Forschungsgruppe “Transplantation Virology” (Departement Biomedizin Peterplatz) hat für seine Arbeit: “BK POLYOMAVIRUS REPLICATION IN RENAL TUBULAR EPITHELIAL CELLS IS INHIBITED BY SIROLIMUS; BUT ACTIVATED BY TACROLIMUS THROUGH A PATHWAY INVOLVING FKBP-12” den 1. Preis in BASIC RESEARCH der Swiss Society of Transplantation erhalten.

Das DBM gratuliert ganz herzlich!

AbbVie Swiss HIV cohort grant 2016 an Hans Hirsch und Francesca Compagno

Hans Hirsch und **Francesca Compagno** von der Forschungsgruppe “Transplantation Virology” (Departement Biomedizin Petersplatz) haben für ihre Arbeit “Transmission of JC polymavirus in HIV-infected patients” den AbbVie Swiss HIV cohort grant 2016 erhalten. Der Preis ist mit 20‘000.– CHF dotiert.

Young Investigator Award 2016 an Dino Lüthi

Dino Lüthi von der Forschungsgruppe “Psychopharmacology Research” Departement Biomedizin Hebelstrasse) hat den Young Investigator Award 2016 der European Association of Poison Centers and Clinical Toxicologists an ihrem 36. Internationalen Kongress in Madrid erhalten für seine Arbeit auf dem Gebiet “The hepatoxicity of novel psychoactive substances”.

Cancer Cell 30, 1–16, July 11, 2016 IF 23,214

MLL-AF9 Expression in Hematopoietic Stem Cells Drives a Highly Invasive AML Expressing EMT-Related Genes Linked to Poor Outcome

Vaia Stavropoulou[1], Susanne Kaspar[2,3], Laurent Brault[1], Mathijs A. Sanders[4], Sabine Juge[1], Stefano Morettini[2], Alexandar Tzankov[5], Michelina Iacovino[6], I-Jun Lau[7], Thomas A. Milne[7], Hélène Royo[2], Michael Kyba[8], Peter J.M. Valk[4], Antoine H.F.M. Peters[2,3,*], and Juerg Schwaller[1,*]

Summary

To address the impact of cellular origin on acute myeloid leukemia (AML), we generated an inducible transgenic mouse model for *MLL-AF9*-driven leukemia. MLL-AF9 expression in long-term hematopoietic stem cells (LT-HSC) in vitro resulted in dispersed clonogenic growth and expression of genes involved in migration and invasion. In vivo, 20% LT-HSC-derived AML were particularly aggressive with extensive tissue infiltration, chemoresistance, and expressed genes related to epithelial-mesenchymal transition (EMT) in solid cancers. Knockdown of the EMT regulator ZEB1 significantly reduced leukemic blast invasion. By classifying mouse and human leukemias according to *Evi1/EVI1* and *Erg/ERG* expression, reflecting aggressiveness and cell of origin, and performing comparative transcriptomics, we identified several EMT-related genes that were significantly associated with poor overall survival of AML patients.

[1] Department of Biomedicine, University Children's Hospital (UKBB), University of Basel, 4031 Basel, Switzerland
[2] Friedrich Miescher Institute for Biomedical Research (FMI), Maulbeerstrasse 66, 4058 Basel, Switzerland
[3] Faculty of Sciences, University of Basel, 4031 Basel, Switzerland
[4] Department of Hematology, Erasmus University Medical Center, 3015 CE Rotterdam, the Netherlands
[5] Institute for Pathology, University Hospital Basel, 4031 Basel, Switzerland
[6] Department of Pediatrics, LA Biomedical Research Institute, Torrance, CA 90502, USA
[7] MRC Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, NIHR Oxford Biomedical Research Centre Programme, University of Oxford, Oxford OX3 9DS, UK
[8] Department of Pediatrics, Lillehei Heart Institute, University of Minnesota, Minneapolis, MN 55455, USA
[*] Co-senior author

Immunity **Immunity** 44, 1–13, June 21, 2016 IF 21,561

Memory CD8$^+$ TCells Require Increased Concentrations of Acetate Induced by Stress for Optimal Function

Maria L. Balmer[1], Eric H. Ma[2,3], Glenn R. Bantug[1], Jasmin Grählert[1], Simona Pfister[4], Timo Glatter[5], Annaïse Jauch[6], Sarah Dimeloe[1], Emma Slack[7], Philippe Dehio[1], Magdalena A. Krzyzaniak[8], Carolyn G. King[9], Anne-Valérie Burgener[1], Marco Fischer[1], Leyla Develioglu[1], Réka Belle[1], Mike Recher[6], Weldy V. Bonilla[8], Andrew J. Macpherson[10], Siegfried Hapfelmeier[4], Russell G. Jones[2,3] and Christoph Hess[1]

Summary

How systemic metabolic alterations during acute infections impact immune cell function remains poorly understood. We found that acetate accumulates in the serum within hours of systemic bacterial infections and that these increased acetate concentrations are required for optimal memory CD8$^+$ T cell function in vitro and in vivo. Mechanistically, upon uptake by memory CD8$^+$ T cells, stress levels of acetate expanded the cellular acetyl-coenzyme A pool via ATP citrate lyase and promoted acetylation of the enzyme GAPDH. This context-dependent post-translational modification enhanced GAPDH activity, catalyzing glycolysis and thus boosting rapid memory CD8$^+$ T cell responses. Accordingly, in a murine *Listeria monocytogenes* model, transfer of acetate augmented memory CD8$^+$ T cells exerted superior immune control compared to control cells. Our results demonstrate that increased systemic acetate concentrations are functionally integrated by CD8$^+$ T cells and translate into increased glycolytic and functional capacity. The immune system thus directly relates systemic metabolism with immune alertness.

[1] Department of Biomedicine, Immunobiology, University of Basel, 4031 Basel, Switzerland
[2] Goodman Cancer Research Centre, McGill University, Montreal, QC, H3A 1A3, Canada
[3] Department of Physiology, McGill University, Montreal, QC, H3G 1Y6, Canada
[4] Institute for Infectious Diseases, University of Bern, 3010 Bern, Switzerland
[5] Proteomics Core Facility, Biozentrum, University of Basel, 4056 Basel, Switzerland
[6] Department of Biomedicine, Immunodeficiency, University of Basel, 4031 Basel, Switzerland
[7] Institute of Microbiology, Swiss Federal Institute of Technology Zurich, 8093 Zurich, Switzerland
[8] Department of Biomedicine, Division of Experimental Virology, University of Basel, 4009 Basel, Switzerland
[9] Department of Biomedicine, Transplantation Immunology, University of Basel, 4031 Basel, Switzerland
[10] Maurice Müller Laboratories (DKF), Universitätsklinik für Viszerale Chirurgie und Medizin Inselspital, University of Bern, 3010 Bern, Switzerland

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Biochemical reconstitution of TET1–TDG–BER-dependent active DNA demethylation reveals a highly coordinated mechanism

Alain R. Weber[1], Claudia Krawczyk[1], Adam B. Robertson[2], Anna Kuśnierczyk[3], Cathrine B. Vågbø[3], David Schuermann[1], Arne Klungland[2] & Primo Schär[1]

Cytosine methylation in CpG dinucleotides is an epigenetic DNA modification dynamically established and maintained by DNA methyltransferases and demethylases. Molecular mechanisms of active DNA demethylation began to surface only recently with the discovery of the 5-methylcytosine (5mC)-directed hydroxylase and base excision activities of ten–eleven translocation (TET) proteins and thymine DNA glycosylase (TDG). This implicated a pathway operating through oxidation of 5mC by TET proteins, which generates substrates for TDG-dependent base excision repair (BER) that then replaces 5mC with C. Yet, direct evidence for a productive coupling of TET with BER has never been presented. Here we show that TET1 and TDG physically interact to oxidize and excise 5mC, and proof by biochemical reconstitution that the TET–TDG–BER system is capable of productive DNA demethylation. We show that the mechanism assures a sequential demethylation of symmetrically methylated CpGs, thereby avoiding DNA double-strand break formation but contributing to the mutability of methylated CpGs.

[1] Department of Biomedicine, University of Basel, Mattenstrasse 28, Basel CH-4058, Switzerland.
[2] Department of Molecular Microbiology, Oslo University Hospital, Rikshospitalet, NO-0372 Oslo, Norway.
[3] Proteomics and Metabolomics Core Facility, PROMEC, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, NO-7489 Trondheim, Norway.

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3CAPS – a structural AP-site analogue as a tool to investigate DNA base excision repair

David Schuermann[1], Simon P. Scheidegger[2], AlainR. Weber[1], Magnar Bjørås[3,4], Christian J. Leumann[2] and Primo Schär[1]

Abstract

Abasic sites (AP-sites) are frequent DNA lesions, arising by spontaneous base hydrolysis or as intermediates of base excision repair (BER). The hemiacetal at the anomeric centre renders them chemically reactive, which presents a challenge to biochemical and structural investigation. Chemically more stable AP-site analogues have been used to avoid spontaneous decay, but these do not fully recapitulate the features of natural AP-sites. With its 3´-phosphate replaced by methylene, the abasic site analogue 3CAPS was suggested to circumvent some of these limitations. Here, we evaluated the properties of 3CAPS in biochemical BER assays with mammalian proteins. 3CAPS-containing DNA substrates were processed by APE1, albeit with comparably poor efficiency. APE1-cleaved 3CAPS can be extended by DNA polymerase β but repaired only by strand displacement as the 5´-deoxyribophosphate (dRP) cannot be removed. DNA glycosylases physically and functionally interact with 3CAPS substrates, underlining its structural integrity and biochemical reactivity. The AP lyase activity of bifunctional DNA glycosylases (NTH1, NEIL1, FPG), however, was fully inhibited. Notably, 3CAPS-containing DNA also effectively inhibited the activity of bifunctional glycosylases on authentic substrates. Hence, the chemically stable 3CAPS with its preserved hemiacetal functionality is apotent tool forBERresearch and apotential inhibitor of bifunctional DNA glycosylases.

[1] Department of Biomedicine, University of Basel, Mattenstrasse 28, CH-4058 Basel, Switzerland,
[2] Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012 Bern, Switzerland,
[3] Department of Microbiology, Oslo University Hospital and University of Oslo, Rikshospitalet, PO Box 4950 Nydalen, N-0424 Oslo, Norway and
[4] Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, PO Box 8905, N-7491 Trondheim, Norway

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Targeting Metabolic Symbiosis to Overcome Resistance to Anti-angiogenic Therapy

Laura Pisarsky[1,*], Ruben Bill[1,*], Ernesta Fagiani[1], Sarah Dimeloe[1], Ryan William Goosen[1], Jörg Hagmann[1], Christoph Hess[1], and Gerhard Christofori[1]

Summary

Despite the approval of several anti-angiogenic therapies, clinical results remain unsatisfactory, and transient benefits are followed by rapid tumor recurrence. Here, we demonstrate potent anti-angiogenic efficacy of the multi-kinase inhibitors nintedanib and sunitinib in a mouse model of breast cancer. However, after an initial regression, tumors resume growth in the absence of active tumor angiogenesis. Gene expression profiling of tumor cells reveals metabolic reprogramming toward anaerobic glycolysis. Indeed, combinatorial treatment with a glycolysis inhibitor (3PO) efficiently inhibits tumor growth. Moreover, tumors establish metabolic symbiosis, illustrated by the differential expression of MCT1 and MCT4, monocarboxylate transporters active in lactate exchange in glycolytic tumors. Accordingly, genetic ablation of MCT4 expression overcomes adaptive resistance against anti-angiogenic therapy. Hence, targeting metabolic symbiosis may be an attractive avenue to avoid resistance development to anti-angiogenic therapy in patients.

[1] Department of Biomedicine, University of Basel, 4058 Basel, Switzerland
[*] Co-first author

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mTORC1 Inhibition Corrects Neurodevelopmental and Synaptic Alterations in a Human Stem Cell Model of Tuberous Sclerosis

Veronica Costa[1,*], Stefan Aigner[1,*], Mirko Vukcevic[5,*], Evelyn Sauter[1], Katharina Behr[5], Martin Ebeling[2], Tom Dunkley[2], Arno Friedlein[2], Sannah Zoffmann[3], Claas A. Meyer[3], Frédéric Knoflach[1], Sebastian Lugert[1], Christoph Patsch[3], Fatiha Fjeldskaar[1], Laurie Chicha-Gaudimier[4], Anna Kiialainen[2], Paolo Piraino[6], Marc Bedoucha[1], Martin Graf[3], Sebastian Jessberger[7], Anirvan Ghosh[1], Josef Bischofberger[5], and Ravi Jagasia[1]

Summary

Hyperfunction of the mTORC1 pathway has been associated with idiopathic and syndromic forms of autism spectrum disorder (ASD), including tuberous sclerosis, caused by loss of either TSC1 or TSC2. It remains largely unknown how developmental processes and biochemical signaling affected by mTORC1 dysregulation contribute to human neuronal dysfunction. Here, we have characterized multiple stages of neurogenesis and synapse formation in human neurons derived from TSC2-deleted pluripotent stem cells. Homozygous TSC2 deletion causes severe developmental abnormalities that recapitulate pathological hallmarks of cortical malformations in patients. Both $TSC2^{+/-}$ and $TSC2^{-/-}$ neurons display altered synaptic transmission paralleled by molecular changes in pathways associated with autism, suggesting the convergence of pathological mechanisms in ASD. Pharmacological inhibition of mTORC1 corrects developmental abnormalities and synaptic dysfunction during independent developmental stages. Our results uncouple stage-specific roles of mTORC1 in human neuronal development and contribute to a better understanding of the onset of neuronal pathophysiology in tuberous sclerosis.

[1] Roche Pharmaceutical Research and Early Development, Neuroscience Ophthalmology and Rare Diseases Discovery & Translational Area, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland
[2] Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland
[3] Roche Pharmaceutical Research and Early Development, Therapeutic Modalities, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland
[4] Department of Neurosurgery, Universita¨ tsspital Basel, ZLF 20 Hebelstrasse, 4031 Basel, Switzerland
[5] Department of Biomedicine, University of Basel, Pestalozzistrasse 20, 4056 Basel, Switzerland
[6] Pvalue Research SRL, 29015 Castel San Giovanni, Italy
[7] Brain Research Institute, Faculty of Medicine and Science, University of Zurich, 8057 Zurich, Switzerland
[*] Co-first author

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Expression of inhibitory receptors on intratumoral T cells modulates the activity of a T cell-bispecific antibody targeting folate receptor

Jens Schreiner[a,*], Daniela S. Thommen[a,b,*], Petra Herzig[a], Marina Bacac[c], Christian Klein[c], Andreas Roller[d], Anton Belousov[d], Victor Levitsky[c], Spasenija Savic[e], Wolfgang Moersig[f], Franziska Uhlenbrock[a], Viola A. Heinzelmann-Schwarz[g], Pablo Umana[c], Pavel Pisa[c], M. von Bergwelt-Baildon[h], Didier Lardinois[f], Philipp Müller[a,*], Vaios Karanikas[c,*], and Alfred Zippelius[a,b,*]

Abstract

T-cell bispecific antibodies (TCBs) are a novel therapeutic tool designed to selectively recruit T-cells to tumor cells and simultaneously activate them. However, it is currently unknown whether the dysfunctional state of T-cells, embedded into the tumor microenvironment, imprints on the therapeutic activity of TCBs. We performed a comprehensive analysis of activation and effector functions of tumor-infiltrating T-cells (TILs) in different tumor types, upon stimulation by a TCB targeting folate receptor 1 and CD3 (FolR1-TCB). We observed a considerable heterogeneity in T-cell activation, cytokine production and tumor cell killing upon exposure to FolR1-TCB among different FolR1-expressing tumors. Of note, tumors presenting with a high frequency of PD-1^{hi} TILs displayed significantly impaired tumor cell killing and T-cell function. Further characterization of additional T-cell inhibitory receptors revealed that PD-1^{hi} TILs defined a T-cell subset with particularly high levels of multiple inhibitory receptors compared with PD-1^{int} and PD-1^{neg} T-cells. PD-1 blockade could restore cytokine secretion but not cytotoxicity of TILs in a subset of patients with scarce PD-1^{hi} expressing cells; in contrast, patients with abundance of PD-1^{hi} expressing T-cells did not benefit from PD-1 blockade. Our data highlight that FolR1-TCB is a promising novel immunotherapeutic treatment option which is capable of activating intratumoral T-cells in different carcinomas. However, its therapeutic efficacy may be substantially hampered by a pre-existing dysfunctional state of T-cells, reflected by abundance of intratumoral PD-1^{hi} T-cells. These findings present a rationale for combinatorial approaches of TCBs with other therapeutic strategies targeting T-cell dysfunction.

[a] Laboratory of Cancer Immunology, Department of Biomedicine, Basel, Switzerland;
[b] Department of Medical Oncology, University Hospital Basel, Basel, Switzerland;
[c] Roche Pharma Research and Early Development, Roche Innovation Center Zurich, Schlieren, Switzerland;
[d] Roche Pharma Research and Early Development, Roche Innovation Center Penzberg, Roche Innovation Center Penzberg, Penzberg, Germany;
[e] Institute of Pathology, University Hospital Basel, Basel, Switzerland;
[f] Department of Surgery, University Hospital Basel, Basel, Switzerland;
[g] Department of Gynecology and Obstetrics, University Hospital Basel, Basel, Switzerland;
[h] Klinik I für Innere Medizin, Klinikum der Universität zu Köln, Germany
*These authors contributed equally to this work.

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BK Polyomavirus Replication in Renal Tubular Epithelial Cells Is Inhibited by Sirolimus, but Activated by Tacrolimus Through a Pathway Involving FKBP-12

H. H. Hirsch[1,2,3], K. Yakhontova[1], M. Lu[1] and J. Manzetti[1]

BK polyomavirus (BKPyV) replication causes nephropathy and premature kidney transplant failure. Insufficient BKPyV-specific T cell control is regarded as a key mechanism, but direct effects of immunosuppressive drugs on BKPyV replication might play an additional role. We compared the effects of mammalian target of rapamycin (mTOR)-and calcineurin-inhibitors on BKPyV replication in primary human renal tubular epithelial cells. Sirolimus impaired BKPyV replication with a 90% inhibitory concentration of 4 ng/mL by interfering with mTOR–SP6-kinase activation. Sirolimus inhibition was rapid and effective up to 24 h postinfection during viral early gene expression, but not thereafter, during viral late gene expression. The mTORC-1 kinase inhibitor torin-1 showed a similar inhibition profile, supporting the notion that early steps of BKPyV replication depend on mTOR activity. Cyclosporine A also inhibited BKPyV replication, while tacrolimus activated BKPyV replication and reversed sirolimus inhibition. FK binding protein 12kda (FKBP-12) siRNA knockdown abrogated sirolimus inhibition and increased BKPyV replication similar to adding tacrolimus. Thus, sirolimus and tacrolimus exert opposite effects on BKPyV replication in renal tubular epithelial cells by a mechanism involving FKBP-12 as common target. Immunosuppressive drugs may therefore contribute directly to the risk of BKPyV replication and nephropathy besides suppressing T cell functions. The data provide rationales for clinical trials aiming at reducing the risk of BKPyV replication and disease in kidney transplantation.

[1] Transplantation & Clinical Virology, Department of Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland
[2] Division Infection Diagnostics, Department of Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland
[3] Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

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Characterization of Immunodominant BK Polyomavirus 9mer Epitope T Cell Responses

M. Cioni[1,*], C. Leboeuf[1,*], P. Comoli[2], F. Ginevri[3] and H. H. Hirsch[1,4,5]

Uncontrolled BK polyomavirus (BKPyV) replication in kidney transplant recipients (KTRs) causes polyomavirus-associated nephropathy and allograft loss. Reducing immunosuppression is associated with clearing viremia and nephropathy and increasing BKPyV-specific T cell responses in most patients; however, current immunoassays have limited sensitivity, target mostly $CD4^+$ T cells, and largely fail to predict onset and clearance of BKPyV replication. To characterize BKPyV-specific $CD8^+$ T cells, bioinformatics were used to predict 9mer epitopes in the early viral gene region (EVGR) presented by 14 common HLAs in Europe and North America. Thirty-nine EVGR epitopes were experimentally confirmed by interferon-γ enzyme-linked immunospot assays in at least 30% of BKPyV IgG–seropositive healthy participants. Most 9mers clustered in domains, and some were presented by more than one HLA class I, as typically seen for immunodominant epitopes. Specific T cell binding using MHC class I streptamers was demonstrated for 21 of 39 (54%) epitopes. In a prospective cohort of 118 pediatric KTRs, 19 patients protected or recovering from BKPyV viremia were experimentally tested, and 13 epitopes were validated. Single HLA mismatches were not associated with viremia, suggesting that failing immune control likely involves multiple factors including maintenance immunosuppression. Combining BKPyV load and T cell assays using immunodominant epitopes may help in evaluating risk and reducing immuno-suppression and may lead to safe adoptive T cell transfer.

[1] Transplantation and Clinical Virology, Department Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland
[2] Pediatric Hematology/Oncology, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
[3] Nephrology, Dialysis and Transplantation Unit, IRCCS G. Gaslini Institute, Genova, Italy
[4] Division of Infection Diagnostics, Department Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland
[5] Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland
[*] The first authors contributed equally to this work.

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Long-term safety and stability of angiogenesis induced by balanced single-vector co-expression of PDGF-BB and $VEGF_{164}$ in skeletal muscle

Roberto Gianni-Barrera[1,2], Maximilian Burger[1,2,3], Thomas Wolff[1,2,4], Michael Heberer[1,2], Dirk J. Schaefer[3], Lorenz Gürke[4], Edin Mujagic[1,2,4] & Andrea Banfi[1,2]

Therapeutic angiogenesis by growth factor delivery is an attractive treatment strategy for ischemic diseases, yet clinical efficacy has been elusive. The angiogenic master regulator VEGF-A can induce aberrant angiogenesis if expressed above a threshold level. Since VEGF remains localized in the matrix around expressing cells, homogeneous dose distribution in target tissues is required, which is challenging. We found that co-expression of the pericyte-recruiting factor PDGF-BB at a fixed ratio with VEGF from a single bicistronic vector ensured normal angiogenesis despite heterogeneous high VEGF levels. Taking advantage of a highly controlled gene delivery platform, based on monoclonal populations of transduced myoblasts, in which every cell stably produces the same amount of each factor, here we rigorously investigated a) the dose-dependent effects, and b) the long-term safety and stability of VEGF and PDGF-BB co-expression in skeletal muscle. PDGF-BB co-expression did not affect the normal angiogenesis by low and medium VEGF doses, but specifically prevented vascular tumors by high VEGF, yielding instead normal and mature capillary networks, accompanied by robust arteriole formation. Induced angiogenesis persisted unchanged up to 4 months, while no tumors appeared. Therefore, PDGF-BB co-expression is an attractive strategy to improve safety and efficacy of therapeutic angiogenesis by VEGF gene delivery.

[1] Cell and Gene Therapy, Department of Biomedicine, Basel University, Basel, Switzerland.
[2] Department of Surgery, Basel University Hospital, Basel, Switzerland.
[3] Plastic, Reconstructive, Aesthetic and Hand Surgery, Basel University Hospital, Basel, Switzerland.
[4] Vascular Surgery, Basel University Hospital, Basel, Switzerland.

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Oestrogen receptor β regulates epigenetic patterns at specific genomic loci through interaction with thymine DNA glycosylase

Yun Liu[1,*], William Duong[2,7,*], Claudia Krawczyk[2], Nancy Bretschneider[3], Gábor Borbély[4], Mukesh Varshney[6], Christian Zinser[4], Primo Schär[2] and Joëlle Rüegg[2,4,5,*]

Abstract

Background: DNA methylation is one way to encode epigenetic information and plays a crucial role in regulating gene expression during embryonic development. DNA methylation marks are established by the DNA methyltransferases and, recently, a mechanism for active DNA demethylation has emerged involving the ten-eleven translocator proteins and thymine DNA glycosylase (TDG). However, so far it is not clear how these enzymes are recruited to, and regulate DNA methylation at, specific genomic loci. A number of studies imply that sequence-specific transcription factors are involved in targeting DNA methylation and demethylation processes. Oestrogen receptor beta (ERβ) is a ligand-inducible transcription factor regulating gene expression in response to the female sex hormone oestrogen. Previously, we found that ERβ deficiency results in changes in DNA methylation patterns at two gene promoters, implicating an involvement of ERβ in DNA methylation. In this study, we set out to explore this involvement on a genome-wide level, and to investigate the underlying mechanisms of this function.

Results: Using reduced representation bisulfite sequencing, we compared genome-wide DNA methylation in mouse embryonic fibroblasts derived from wild-type and ERβ knock-out mice, and identified around 8000 differentially methylated positions (DMPs). Validation and further characterisation of selected DMPs showed that differences in methylation correlated with changes in expression of the nearest gene. Additionally, re-introduction of ERβ into the knock-out cells could reverse hypermethylation and reactivate expression of some of the genes. We also show that ERβ is recruited to regions around hypermethylated DMPs. Finally, we demonstrate here that ERβ interacts with TDG and that TDG binds ERβ-dependently to hypermethylated DMPs.

Conclusion: We provide evidence that ERβ plays a role in regulating DNA methylation at specific genomic loci, likely as the result of its interaction with TDG at these regions. Our findings imply a novel function of ERβ, beyond direct transcriptional control, in regulating DNA methylation at target genes. Further, they shed light on the question how DNA methylation is regulated at specific genomic loci by supporting a concept in which sequence-specific transcription factors can target factors that regulate DNA methylation patterns.

Correspondance: joelle.ruegg@swetox.se
*Yun Liu and William Duong have contributed equally to this work

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Flt3 Ligand Regulates the Development of Innate Lymphoid Cells in Fetal and Adult Mice

Anne Baerenwaldt[1,2], Nicole von Burg[1,2], Matthias Kreuzaler[3], Selina Sitte[4], Edit Horvath[1,2], Annick Peter[1,2], David Voehringer[4], Antonius G. Rolink[3], and Daniela Finke[1,2]

Flt3 ligand (Flt3L) promotes survival of lymphoid progenitors in the bone marrow and differentiation of dendritic cells (DCs), but its role in regulating innate lymphoid cells (ILCs) during fetal and adult life is not understood. By using Flt3L knockout and transgenic mice, we demonstrate that Flt3L controls ILC numbers by regulating the pool of $\alpha4\beta7^-$ and $\alpha4\beta7^+$ lymphoid tissue inducer cell progenitors in the fetal liver and common lymphoid progenitors in the bone marrow. Deletion of *flt3l* severely reduced the number of fetal liver progenitors and lymphoid tissue inducer cells in the neonatal intestine, resulting in impaired development of Peyer's patches. In the adult intestine, NK cells and group 2 and 3 ILCs were severely reduced. This effect occurred independently of DCs as ILC numbers were normal in mice in which DCs were constitutively deleted. Finally, we could show that administration of Flt3L increased the number of $NKp46^-$ group 3 ILCs in wild-type and even in $Il7^{-/-}$ mice, which generally have reduced numbers of ILCs. Taken together, Flt3L significantly contributes to ILC and Peyer's patches development by targeting lymphoid progenitor cells during fetal and adult life.

[1] University of Basel Children's Hospital, 4056 Basel, Switzerland;
[2] Developmental Immunology, Department of Biomedicine, University of Basel, 4058 Basel, Switzerland;
[3] Developmental and Molecular Immunology, Department of Biomedicine, University of Basel, 4058 Basel, Switzerland;and
[4] Department of Infection Biology, University Clinic of Erlangen, Friedrich Alexander University Erlangen-Nuremberg, 91054 Erlangen, Germany

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Anti-C1q Autoantibodies from Systemic Lupus Erythematosus Patients Induce a Proinflammatory Phenotype in Macrophages

Sophia Thanei[1], and Marten Trendelenburg[1,2]

Anti-C1q autoantibodies (anti-C1q) are frequently found in patients with systemic lupus erythematosus (SLE) and correlate with the occurrence of proliferative lupus nephritis. A previous study of anti-C1q in experimental lupus nephritis demonstrated an important role for FcgRs in the pathogenesis of lupus nephritis, suggesting a direct effect on phagocytes. Therefore, we developed an in vitro model to study the effect of SLE patient–derived anti-C1q bound to immobilized C1q (imC1q) on human monocytederived macrophages (HMDMs) obtained from healthy donors and SLE patients. HMDMs were investigated by analyzing the cell morphology, LPS-induced cytokine profile, surface marker expression, and phagocytosis rate of apoptotic Jurkat cells. Morphologically, bound anti-C1q induced cell aggregations of HMDMs compared with imC1q or IgG alone. In addition, anti-C1q reversed the effect of imC1q alone, shifting the LPS-induced cytokine release toward a proinflammatory response. FcγR-blocking experiments revealed that the secretion of proinflammatory cytokines was mediated via FcγRII. The anti-C1q–induced inflammatory cytokine profile was accompanied by a downregulation of CD163 and an upregulation of LPS-induced CD80, CD274, and MHC class II. Finally, HMDMs primed on bound anti-C1q versus imC1q alone displayed a significantly lower phagocytosis rate of early and late apoptotic cells accompanied by a reduced Mer tyrosine kinase expression. Interestingly, anti-C1q–dependent secretion of proinflammatory cytokines was similar in SLE patient–derived cells, with the exception that IL-10 was slightly increased. In conclusion, anti-C1q induced a proinflammatory phenotype in HMDMs reversing the effects of imC1q alone. This effect might exacerbate underlying pathogenic mechanisms in lupus nephritis.

[1] Laboratory of Clinical Immunology, University Hospital Basel, CH-4031 Basel, Switzerland; and
[2] Division of Internal Medicine, University Hospital Basel, CH-4031 Basel, Switzerland

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The Immune-Metabolic Basis of Effector Memory CD4$^+$ T Cell Function under Hypoxic Conditions

Sarah Dimeloe[1], Matthias Mehling[1,2], Corina Frick[1], Jordan Loeliger[1], Glenn R. Bantug[1], Ursula Sauder[3], Marco Fischer[1], Réka Belle[1], Leyla Develioglu[1], Savaş Tay[2], Anja Langenkamp[4], and Christoph Hess[1]

Effector memory (EM) CD4$^+$ T cells recirculate between normoxic blood and hypoxic tissues to screen for cognate Ag. How mitochondria of these cells, shuttling between normoxia and hypoxia, maintain bioenergetic efficiency and stably uphold antiapoptotic features is unknown. In this study, we found that human EM CD4$^+$ T cells had greater spare respiratory capacity (SRC) than did naive counterparts, which was immediately accessed under hypoxia. Consequently, hypoxic EM cells maintained ATP levels, survived and migrated better than did hypoxic naive cells, and hypoxia did not impair their capacity to produce IFN-γ. EM CD4$^+$ T cells also had more abundant cytosolic GAPDH and increased glycolytic reserve. In contrast to SRC, glycolytic reserve was not tapped under hypoxic conditions, and, under hypoxia, glucose metabolism contributed similarly to ATP production in naive and EM cells. However, both under normoxic and hypoxic conditions, glucose was critical for EM CD4$^+$ T cell survival. Mechanistically, in the absence of glycolysis, mitochondrial membrane potential ($\Delta\Psi$m) of EM cells declined and intrinsic apoptosis was triggered. Restoring pyruvate levels, the end product of glycolysis, preserved $\Delta\Psi$m and prevented apoptosis. Furthermore, reconstitution of reactive oxygen species (ROS), whose production depends on $\Delta\Psi$m, also rescued viability, whereas scavenging mitochondrial ROS exacerbated apoptosis. Rapid access of SRC in hypoxia, linked with built-in, oxygen-resistant glycolytic reserve that functionally insulates $\Delta\Psi$mand mitochondrial ROS production from oxygen tension changes, provides an immune-metabolic basis supporting survival, migration, and function of EM CD4$^+$ T cells in normoxic and hypoxic conditions.

[1] Immunobiology, Department of Biomedicine, University of Basel, 4031 Basel, Switzerland;
[2] Department of Biosystems Science and Engineering, Swiss Federal Institute of Technology in Zurich, 4058 Basel, Switzerland;
[3] Microscopy Center, Biocenter, University of Basel, 4056 Basel, Switzerland; and
[4] Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center, 4070 Basel, Switzerland

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Functional characterization of orbicularis oculi and extraocular muscles

Marijana Sekulic-Jablanovic[1,2], Nina D. Ullrich[3], David Goldblum[4], Anja Palmowski-Wolfe[4], Francesco Zorzato[1,2,5], and Susan Treves[1,2,5]

The orbicularis oculi are the sphincter muscles of the eyelids and are involved in modulating facial expression. They differ from both limb and extraocular muscles (EOMs) in their histology and biochemistry. Weakness of the orbicularis oculi muscles is a feature of neuromuscular disorders affecting the neuromuscular junction, and weakness of facial muscles and ptosis have also been described in patients with mutations in the ryanodine receptor gene. Here, we investigate human orbicularis oculi muscles and find that they are functionally more similar to quadriceps than to EOMs in terms of excitation–contraction coupling components. In particular, they do not express the cardiac isoform of the dihydropyridine receptor, which we find to be highly expressed in EOMs where it is likely responsible for the large depolarization-induced calcium influx. We further show that human orbicularis oculi and EOMs express high levels of utrophin and low levels of dystrophin, whereas quadriceps express dystrophin and low levels of utrophin. The results of this study highlight the notion that myotubes obtained by explanting satellite cells from different muscles are not functionally identical and retain the physiological characteristics of their muscle of origin. Furthermore, our results indicate that sparing of facial and EOMs in patients with Duchenne muscular dystrophy is the result of the higher levels of utrophin expression.

[1] Department of Anesthesia and
[2] Department of Biomedicine, Basel University Hospital, 4031 Basel, Switzerland
[3] Institute of Physiology and Pathophysiology, Department of Cardiovascular Physiology, University of Heidelberg, 69120 Heidelberg, Germany
[4] Eye Clinic, Basel University and Basel University Hospital, 4031 Basel, Switzerland
[5] Department of Life Sciences and Biotechnology, General Pathology Section, University of Ferrara, 44100 Ferrara, Italy

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Cell Growth Dynamics in Embryonic and Adult Mouse Thyroid Revealed by a Novel Approach to Detect Thyroid Gland Subpopulations

Sanjay Gawade[1], Carlos Mayer[1], Katrin Hafen[1], Thomas Barthlott[1], Werner Krenger[1], and Gabor Szinnai[1,2]

Background: The thyroid is composed of endocrine epithelial cells, blood vessels, and mesenchyme. However, no data exist thus far on absolute cell numbers, relative distribution, and proliferation of the different cell populations in the developing and mature thyroid. The aim of this study was therefore to establish a flow cytometry protocol that allows detection and quantification of discrete cell populations in embryonic and adult murine thyroid tissues.

Methods: Cell-type anti-mouse specific antibodies were used for erythroid cells (Ter119), hematopoietic cells (CD45), epithelial cells (EpCam/CD326, E-cadherin/CD324), thyroid follicular cells and C-cells (Nkx2-1), endothelial cells (Pecam/CD31, Icam-1/CD54), and fibroblasts (PDGFRa/CD140a). Proliferating cells were detected after labeling with 5-bromo-2¢-deoxyuridine (BrdU). For flow cytometry analyses, micro-dissected embryonic (E) and adult thyroids were pooled (E13.5, $n = 25$; E15.5, $n = 15$; E17.5, $n = 15$; adult, $n = 4$) in one sample.

Results: The absolute parenchymal cell numbers per mouse thyroid ($M \pm SD$), excluding the large number of $CD45^+$ and $Ter119^+$ cells, increased from 7425 ± 1338 at E13.5 to 271,561 ± 22,325 in adult tissues. As expected, $Nkx2\text{-}1^+$ cells represented the largest cell population in adult tissues (61.2 ± 1.1%). Surprisingly, at all three embryonic stages analyzed, thyroid follicular cells and C-cells accounted only for a small percentage of the total thyroid cell mass (between 4.7 ± 0.4% and 9.4 ± 1.6%). In contrast, the largest cell population at all three embryonic stages was identified as PDGFRa/$CD140a^+$ fibroblasts (61.4 ± 0.4% to 77.3 ± 1.1%). However, these cells represented the smallest population in adult tissues (5.2 ± 0.8%). Pecam/$CD31^+$ endothelial cells increased from E13.5 to E15.5 from 3.7 ± 0.8% to 8.5 ± 3.0%, then remained stable at E17.5 and adult tissues. Proliferation rates were sizable during the entire organogenesis but differed between cell populations, with distinct proliferative peaks at E13.5 in epithelial cells (32.7 ± 0.6% $BrdU^+$ cells), and at E15.5 in endothelial cells (22.4 ± 2.4% $BrdU^+$ cells). Fibroblasts showed aconstant proliferation rate in embryonic tissues. In adult tissues, BrdU+ cells were between 0.1% and 0.4% in all cell types.

Conclusions: Using a novel flow cytometry–based method, a previously unobserved highly dynamic growth pattern of thyroid cell populations during embryogenesis was uncovered. This approach will provide a useful new tool for cell function analyses in murine thyroid disease models.

[1] Pediatric Immunology, Department of Biomedicine, University of Basel, Basel, Switzerland.
[2] Pediatric Endocrinology, University Children's Hospital Basel, University of Basel, Basel, Switzerland.

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Preventing Implant-Associated Infections by Silver Coating

Richard Kuehl[a,b], Priscilla S. Brunetto[c], Anne-Kathrin Woischnig[a], Massimo Varisco[c], Zarko Rajacic[a], Juerg Vosbeck[d], Luigi Terracciano[d], Katharina M. Fromm[c], Nina Khanna[a,b]

Implant-associated infections (IAIs) are a dreaded complication mainly caused by biofilm-forming staphylococci. Implant surfaces preventing microbial colonization would be desirable. We examined the preventive effect of a silver-coated titanium-aluminum-niobium (TiAlNb) alloy. The surface elicited a strong, inoculum-dependent activity against *Staphylococcus epidermidis* and *Staphylococcus aureus* in an agar inhibition assay. Gamma sterilization and alcohol disinfection did not alter the effect. In a tissue cage mouse model, silver coating of TiAlNb cages prevented perioperative infections in an inoculum-dependent manner and led to a 100% prevention rate after challenge with 2 X 10^6 CFU of *S. epidermidis* per cage. In *S. aureus* infections, silver coating had only limited effect. Similarly, daptomycin or vancomycin prophylaxis alone did not prevent *S. aureus* infections. However, silver coating combined with daptomycin or vancomycin prophylaxis thwarted methicillin-resistant S. aureus infections at a prevention rate of 100% or 33%, respectively. Moreover, silver release from the surface was independent of infection and occurred rapidly after implantation. On day 2, a peak of 82 μg Ag/ml was reached in the cage fluid, corresponding to almost 6X the MIC of the staphylococci. Cytotoxicity toward leukocytes in the cage was low and temporary. Surrounding tissue did not reveal histological signs of silver toxicity. *In vitro*, no emergence of silver resistance was observed in several clinical strains of staphylococci upon serial subinhibitory silver exposures. In conclusion, our data demonstrate that silver-coated TiAlNb is potent for prevention of IAIs and thus can be considered for clinical application.

[a] Infection Biology Laboratory, Department of Biomedicine, University and University Hospital of Basel, Basel, Switzerland;
[b] Division of Infectious Diseases and Hospital Epidemiology, University Hospital of Basel, Switzerland;
[c] Department of Chemistry, University of Fribourg, Switzerland;
[d] Institute of Pathology, University Hospital of Basel, Basel, Switzerland

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PDGF-BB induces PRMT1 expression through ERK1/2 dependent STAT1 activation and regulates remodeling in primary human lung fibroblasts

Qingzhu Sun[a,b], Li Liu[a], Jyotshna Mandal[b], Antonio Molino[c], Daiana Stolz[b], Michael Tamm[b], Shemin Lu[a], Michael Roth[b]

Abstract
Tissue remodeling of sub-epithelial mesenchymal cells is a major pathology occurring in chronic obstructive pulmonary disease (COPD) and asthma. Fibroblasts, as a major source of interstitial connective tissue extracellular matrix, contribute to the fibrotic and inflammatory changes in these airways diseases. Previously, we described that protein arginine methyltransferase-1 (PRMT1) participates in airway remodeling in a rat model of pulmonary inflammation. In this study we investigated the mechanism by which PDGF-BB regulatesPRMT1 in primary lung fibroblasts, isolated from human lung biopsies. Fibroblasts were stimulated with PDGF-BB for up-to 48 h and the regulatory and activation of signaling pathways controlling PRMT1 expression were determined. PRMT1 was localized by immunohistochemistry in human lung tissue sections and by immunofluorescence in isolated fibroblasts. PRMT1 activity was suppressed by the pan-PRMT inhibitor AMI1. ERK1/2 mitogen activated protein kinase (MAPK) was blocked by PD98059, p38 MAPK by SB203580, and STAT1 by small interference (si) RNA treatment. The results showed that PDGF-BB significantly increased PRMT1 expression after 1 h lasting over 48 h, through ERK1/2 MAPK and STAT1 signaling. The inhibition of ERK1/2 MAPK or of PRMT1 activity decreased PDGF-BB induced fibroblast proliferation, COX2 production, collagen-1A1 secretion, and fibronectin production. These findings suggest that PRMT1 is acentral regulator of tissue remodeling and that the signaling sequence controlling its expression in primary human lung fibroblast is PDGF–ERK–STAT1. Therefore, PRMT1 presents a novel therapeutic and diagnostic target for the control of airway wall remodeling in chronic lung diseases.

[a] Department of Biochemistry and Molecular Biology, Xi'an Jiaotong University Health Science Center, Xi'an, Shaanxi 710061, PR China
[b] Pneumology and Pulmonary Cell Research, Department of Biomedicine, University and University Hospital Basel, Basel 4031, Switzerland
[c] Dept of Respiratory Diseases, University of Naples, Federico II, Naples, Italy

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T-cadherin promotes vascular smooth muscle cell dedifferentiation *via* a GSK3β-inactivation dependent mechanism

Agne Frismantiene, Boris Dasen, Dennis Pfaff, Paul Erne, Therese J. Resink, Maria Philippova

Abstract

Participation of the cadherin superfamily of adhesion molecules in smooth muscle cell (SMC) phenotype modulation is poorly understood. Immunohistochemical analyses of arterial lesions indirectly suggest up-regulated expression of atypical glycosylphosphatidylinositol-anchored T-cadherin on vascular SMCs as a molecular indicator of the dedifferentiated/proliferative phenotype. This study investigated the role of T-cadherin in SMC phenotypic modulation. Morphological, molecular and functional SMC-signature characteristics of rat, porcine and human arterial SMCs stably transduced with respect to T-cadherin upregulation (Tcad+) or T-cadherin-deficiency (shTcad) were compared with their respective control transductants (E-SMCs or shC-SMCs). Tcad+-SMCs displayed several characteristics of the dedifferentiated phenotype including loss of spindle morphology, reduced/disorganized stress fiber formation, decay of SMC-differentiation markers (smooth muscle α-actin, smooth muscle myosin heavy chain, *h*-caldesmon), gain of SMC-dedifferentiation marker calmodulin, reduced levels of myocardin, nuclear-to-cytoplasmic redistribution of the myocardin related transcription factors MRTFA/B and increased proliferative and migratory capacities. T-cadherin depletion enforced features of the differentiated SMC phenotype. PI3K/Akt is a major signal pathway utilized by T-cadherin in SMCs and we investigated mTORC1/S6K1 and GSK3β axes as mediators of T-cadherin-induced dedifferentiation. Inhibition of mTORC1/S6K1 signalling by rapamycin suppressed proliferation in both E-SMCs and Tcad+-SMCs but failed to restore expression of contractile protein markers in Tcad+-SMCs. Ectopic adenoviral-mediated co-expression of constitutively active GSK3β mutant S9A in Tcad+-SMCs restored the morphological and molecular marker characteristics of differentiated SMCs and normalized rate of proliferation to that in control SMCs. In conclusion our study demonstrates that T-cadherin promotes acquisition of the dedifferentiated phenotype *via* amechanism that is dependent on GSK3β inactivation.

Department of Biomedicine, Laboratory for Signal Transduction, Basel University Hospital and University of Basel, Basel, Switzerland

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Dynamic spatio-temporal contribution of single β5t+ cortical epithelial precursors to the thymus medulla

Carlos E. Mayer[1,*], Saulius Žuklys[1,*], Saule Zhanybekova[1], Izumi Ohigashi[2], Hong-Ying Teh[1], Stephen N. Sansom[3], Noriko Shikama-Dorn[1], Katrin Hafen[1], Iain C. Macaulay[4], Mary E. Deadman[6], Chris P. Ponting[4,5], Yousuke Takahama[2] and Georg A. Holländer[1,6]

Intrathymic T-cell development is critically dependent on cortical and medullary thymic epithelial cells (TECs). Both epithelial subsets originate during early thymus organogenesis from progenitor cells that express the thymoproteasome subunit β5t, a typical feature of cortical TECs. Using in vivo lineage fate mapping, we demonstrate in mice that β5t$^+$ TEC progenitors give rise to the medullary TEC compartment early in life but significantly limit their contribution once the medulla has completely formed. Lineage-tracing studies at single cell resolution demonstrate for young mice that the postnatal medulla is expanded from individual β5t$^+$ cortical progenitors located at the cortico-medullary junction. These results therefore not only define a developmental window during which the expansion of medulla is efficiently enabled by progenitors resident in the thymic cortex, but also reveal the spatio-temporal dynamics that control the growth of the thymic medulla.

[1] Department of Biomedicine, University of Basel, Basel, Switzerland
[2] Division of Experimental Immunology, Institute for Genome Research, University of Tokushima, Japan
[3] The Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK
[4] Wellcome Trust Sanger Institute-EBI Single Cell Genomics Centre, Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK
[5] MRC Functional Genomics Unit, Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK
[6] Department of Paediatrics and the Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK
[*] These authors contributed equally to this work.

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In Vitro Characterization of Psychoactive Substances at Rat, Mouse, and Human Trace Amine-Associated Receptor 1[S]

Linda D. Simmler, Danièle Buchy, Sylvie Chaboz, Marius C. Hoener, and Matthias E. Liechti

Abstract

Trace amine-associated receptor 1 (TAAR1) has been implicated in the behavioral effects of amphetamine-type stimulant drugs in rodents. TAAR1 has also been suggested as a target for novel medications to treat psychostimulant addiction. We previously reported that binding affinities at TAAR1 can differ between structural analogs of psychostimulants, and species differences have been observed. In this study, we complement our previous findings with additional substances and the determination of functional activation potencies. In summary, we present here pharmacological in vitro profiles of 101 psychoactive substances at human, rat, and mouse TAAR1. *p*-Tyramine, β-phenylethylamine, and tryptamine were included as endogenous comparator compounds. Functional cAMP measurements and radioligand displacement assays were conducted with human embryonic kidney 293 cells that expressed human, rat, or mouse TAAR1. Most amphetamines, phenethylamine, and aminoindanes exhibited potentially physiologically relevant rat and mouse TAAR1 activation ($EC_{50} < 5\ \mu M$) and showed full or partial ($E_{max} < 80\%$) agonist properties. Cathinone derivatives, including mephedrone and methylenedioxypyrovalerone, exhibited weak ($EC_{50} = 5–10\ \mu M$) to negligible ($EC_{50} > 10\ \mu M$) binding properties at TAAR1. Pipradrols, including methylphenidate, exhibited no affinity for TAAR1. We found considerable species differences in activity at TAAR1 among the highly active ligands, with a rank order of rat > mouse > human. This characterization provides information about the pharmacological profile of psychoactive substances. The species differences emphasize the relevance of clinical studies to translationally complement rodent studies on the role of TAAR1 activity for psychoactive substances.

Division of Clinical Pharmacology and Toxicology, Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland (L.D.S., M.E.L.); and Neuroscience Research, Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel, Switzerland (D.B., S.C., M.C.H)

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Pharmacokinetics and pharmacodynamics of γ-hydroxybutyrate in healthy subjects

Matthias E. Liechti[1], Boris B. Quednow[2],Evangelia Liakoni[1], Dario Dornbierer[2],Robin von Rotz[2], Maria Salomé Gachet[3], Jürg Gertsch[3], Erich Seifritz[2] and Oliver G. Bosch[2]

Aims

γ-Hydroxybutyrate (GHB) is used as a treatment for narcolepsyand alcohol withdrawal and as a recreational substance. Nevertheless, there are limited data on the pharmacokinetics and pharmacokinetic-pharmacodynamic relationships of GHB in humans. We characterized the pharmacokinetic profile and exposure-psychotropic effect relationship of GHB in humans.

Methods

Two oral doses of GHB (25 and 35 mg kg^{-1}) were administered to 32 healthy male subjects (16 for each dose) using a randomized, placebo-controlled, cross-over design.

Results

Maximal concentrations of GHB were (geometric mean and 95% CI): 218 (176–270) nmol ml^{-1} and 453 (374–549) nmol ml^{-1} for the 25 and 35 mg kg^{-1} GHB doses, respectively. The elimination half-lives (mean ± SD) were 36 ± 9 and 39 ± 7 min and the AUC_{∞} values (geometric mean and 95% CI) were 15 747 (12 854–19 290) and 40 113 (33 093–48 622) nmol/min ml^{-1} for the 20 and 35 mg kg^{-1} GHB doses, respectively. Thus, plasma GHB exposure ($AUC_{0-\infty}$)rose disproportionally (+40%) with the higher dose. γ-Hydroxybutyrate produced mixed stimulant-sedative effects, with a dose-dependent increase in sedation and dizziness. It did not alter heart rate or blood pressure. A close relationshipbetween plasma GHB exposure anditspsychotropic effectswas found, with higher GHB concentrations associated with higher subjective stimulation, sedation, and dizziness. No clockwise hysteresis was observed in the GHB concentration effect plot over time (i.e., no acute pharmacological tolerance).

Conclusion

Evidence was found of a nonlinear dose-exposure relationship (i.e., no dose proportionality) at moderate doses of GHB. The effects of GHB on consciousness were closely linked to its plasma exposure and exhibited no acute tolerance.

[1] Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel CH-4031, Switzerland,
[2] Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, Zurich CH-8032, Switzerland and
[3] Institute of Biochemistry and Molecular Medicine, University of Bern, Bühlstrasse 28, Bern CH-3012, Switzerland

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Effect of L-carnitine supplementation on the body carnitine pool, skeletal muscle energy metabolism and physical performance in male vegetarians

Katerina Novakova[1,2,*], Oliver Kummer[1,2,*], Jamal Bouitbir[1,2,*], Sonja D. Stoffel[1], Ulrike Hoerler-Koerner[1], Michael Bodmer[1,2], Paul Roberts[1,2], Albert Urwyler[3], Rolf Ehrsam[1], Stephan Krähenbühl[1,2]

Abstract

Purpose More than 95 % of the body carnitine is located in skeletal muscle, where it is essential for energy metabolism. Vegetarians ingest less carnitine and carnitine precursors and have lower plasma carnitine concentrations than omnivores. Principle aims of the current study were to assess the plasma and skeletal muscle carnitine content and physical performance of male vegetarians and matched omnivores under basal conditions and after L-carnitine supplementation.

Results Sixteen vegetarians and eight omnivores participated in this interventional study with oral supplementation of 2 g L-carnitine for 12 weeks. Before carnitine supplementation, vegetarians had a 10 % lower plasma carnitine concentration, but maintained skeletal muscle carnitine stores compared to omnivores. Skeletal muscle phosphocreatine, ATP, glycogen and lactate contents were also not different from omnivores. Maximal oxygen uptake (VO_2max) and workload (P_{max}) per bodyweight (bicycle spiroergometry) were not significantly different between vegetarians and omnivores. Sub-maximal exercise (75 % VO_2max for 1 h) revealed no significant differences between vegetarians and omnivores (respiratory exchange ratio, blood lactate and muscle metabolites). Supplementation with L-carnitine significantly increased the total plasma carnitine concentration (24 % in omnivores, 31 % in vegetarians) and the muscle carnitine content in vegetarians (13 %). Despite this increase, P_{max} and VO_2max as well as muscle phosphocreatine, lactate and glycogen were not significantly affected by carnitine administration.

Conclusions Vegetarians have lower plasma carnitine concentrations, but maintained muscle carnitine stores compared to omnivores. Oral L-carnitine supplementation normalizes the plasma carnitine stores and slightly increases the skeletal muscle carnitine content in vegetarians, but without affecting muscle function and energy metabolism.

[1] Division of Clinical Pharmacology and Toxicology, University Hospital Basel, CH-4031 Basel, Switzerland
[2] Department of Biomedicine, University of Basel, Basel, Switzerland
[3] Department of Anesthesia, University Hospital Basel, Basel, Switzerland
[*] These authors contributed equally to this work

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Neuregulin-1β promotes glucose uptake via PI3K/Akt in neonatal rat cardiomyocytes

Laura Pentassuglia, Philippe Heim, Sonia Lebboukh, Christian Morandi, Lifen Xu, and Marijke Brink

Nrg1β is critically involved in cardiac development and also maintains function of the adult heart. Studies conducted in animal models showed that it improves cardiac performance under a range of pathological conditions, which led to its introduction in clinical trials to treat heart failure. Recent work also implicated Nrg1β in the regenerative potential of neonatal and adult hearts. The molecular mechanisms whereby Nrg1β acts in cardiac cells are still poorly understood. In the present study, we analyzed the effects of Nrg1β on glucose uptake in neonatal rat ventricular myocytes and investigated to what extent mTOR/Akt signaling pathways are implicated. We show that Nrg1β enhances glucose uptake in cardiomyocytes as efficiently as IGF-I and insulin. Nrg1β causes phosphorylation of ErbB2 and ErbB4 and rapidly induces the phosphorylation of FAK (Tyr^{861}), Akt (Thr^{308} and Ser^{473}), and its effector AS160 (Thr^{642}). Knockdown of ErbB2 or ErbB4 reduces Akt phosphorylation and blocks the glucose uptake. The Akt inhibitor VIII and the PI3K inhibitors LY-294002 and Byl-719 abolish Nrg1β-induced phosphorylation and glucose uptake. Finally, specific mTORC2 inactivation after knockdown of rictor blocks the Nrg1β-induced increases in Akt-p-Ser^{473} but does not modify AS160-p-Thr^{642} or the glucose uptake responses to Nrg1β. In conclusion, our study demonstrates that Nrg1β enhances glucose uptake in cardiomyocytes via ErbB2/ErbB4 heterodimers, PI3Kα, and Akt. Furthermore, although Nrg1β activates mTORC2, the resulting Akt-Ser^{473} phosphorylation is not essential for glucose uptake induction. These new insights into pathways whereby Nrg1β regulates glucose uptake in cardiomyocytes may contribute to the understanding of its regenerative capacity and protective function in heart failure.

Department of Biomedicine, University of Basel and University Hospital Basel, Basel, Switzerland

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Perception,diagnosis and management of BK polyomavirus replication and disease in paediatric kidney transplant recipients in Europe

Lars Pape[1,*], Burkhard Tönshoff[2,*] and Hans H. Hirsch[3,4,5,*], Members of the Working Group 'Transplantation' of the European Society for Paediatric Nephrology

Abstract

Background: BK polyomavirus (BKPyV)-associated nephropathy remains a challenge to the success of kidney transplantation, but its impact varies in different transplant programmes.

Methods: We investigated current practice through a webbased questionnaire made available by the European Society for Paediatric Nephrology (ESPN).

Results: A total of 90 physicians (23% of 391 active members) from 27 countries participated in the study. BKPyV-associated nephropathy is seen in 1–5% of patients annually with treatment success in 30–60%, and graft loss in 10%. Quantitative BKPyV load testing is available to >90% of physicians. Screening is performed in urine alone in 26%, in urine and blood in 37% and in blood alone in 37%. Most physicians (47%) screen at month 1,2,3,6,9 and12 post-transplant. For patients with baseline renal function and plasma BKPyV loads of 10000–1000000 copies/mL, 50% report performing renal biopsies prior to intervention. Intervention consists of reducing immunosuppression first with mycophenolate (Myc) in 40%, first with calcineurin inhibitors (CNI) in 29% or with both in 31%. Changing immunosuppressive drugs is considered mainly for biopsy-proven nephropathy consisting of discontinuation of Myc in 75%, and switching from CNI to mTOR inhibitors (52%). Cidofovir, intravenous immunoglobulin G, leflunomide and fluoroquinolones are used in less than one-third of this group. Furthermore, 66% of participants see a need for new antiviral drugs and new immmunosuppressive strategies, and almost 90% are willing to participate in future observational and interventional trials.

Conclusion: This ESPN survey suggests that prompt translation of a positive screening test into reducing immunosuppression could improve outcomes.

[1] Department of Paediatric Nephrology, Hannover Medical School, Hannover, Germany,
[2] Department of Paediatrics I, University Children's Hospital Heidelberg, Heidelberg, Germany,
[3] Transplantation & Clinical Virology, Department Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland,
[4] Infection Diagnostics, Department Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland and
[5] Infectious Disease & Hospital Epidemiology, University Hospital Basel, Basel, Switzerland
[*] All authors contributed equally to this manuscript.

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Impact of Cytochrome P450 2D6 Function on the Chiral Blood Plasma Pharmacokinetics of 3,4-Methylenedioxymethamphetamine (MDMA) and Its Phase I and II Metabolites in Humans

Andrea E. Steuer[1], Corina Schmidhauser[1], Eva H. Tingelhoff[1], Yasmin Schmid[2], Anna Rickli[2], Thomas Kraemer[1], Matthias E. Liechti[2]

Abstract

3,4-methylenedioxymethamphetamine (MDMA; ecstasy) metabolism is known to be stereoselective, with preference for S-stereoisomers. Its major metabolic step involves CYP2D6-catalyzed demethylenation to 3,4-dihydroxymethamphetamine (DHMA), followed by methylation and conjugation. Alterations in CYP2D6 genotype and/or phenotype have been associated with higher toxicity. Therefore, the impact of CYP2D6 function on the plasma pharmacokinetics of MDMA and its phase I and II metabolites was tested by comparing extensive metabolizers (EMs), intermediate metabolizers (IMs), and EMs that were pretreated with bupropion as a metabolic inhibitor in a controlled MDMA administration study. Blood plasma samples were collected from 16 healthy participants (13 EMs and three IMs) up to 24 h after MDMA administration in a double-blind, placebo-controlled, four-period, cross-over design, with subjects receiving 1 week placebo or bupropion pretreatment followed by a single placebo or MDMA (125 mg) dose. Bupropion pretreatment increased the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from 0 to 24 h (AUC_{24}) of *R*-MDMA (9% and 25%, respectively) and S-MDMA (16% and 38%, respectively). Bupropion reduced the C_{max} and AUC_{24} of the CYP2D6-dependently formed metabolite stereoisomers of DHMA 3-sulfate, DHMA 4-sulfate, and 4-hydroxy-3-methoxymethamphetamine (HMMA sulfate and HMMA glucuronide) by approximately 40%. The changes that were observed in IMs were generally comparable to bupropion-pretreated EMs. Although changes in stereoselectivity based on CYP2D6 activity were observed, these likely have low clinical relevance. Bupropion and hydroxybupropion stereoisomer pharmacokinetics were unaltered by MDMA co-administration. The present data might aid further interpretations of toxicity based on CYP2D6-dependent MDMA metabolism.

[1] Department of Forensic Pharmacology & Toxicology, Zurich Institute of Forensic Medicine, University of Zurich, Zurich, Switzerland,
[2] Psychopharmacology Research, Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland

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A 'Too Negative' ANA Test Predicts Antibody Deficiency

Mike Recher[1], Christoph T. Berger[2], Thomas Daikeler[3], Christoph Hess[4], and Ingmar A. F. M. Heijnen[5]

Antibody deficiency can occur in the setting of a primary immunodeficiency or secondary due to a variety of underlying causes. Primary antibody deficiencies (PAD) are rare genetically determined diseases that typically manifest with susceptibility to bacterial infections, most commonly of the respiratory tract [1]. PAD are also associated with autoimmune complications, non-malignant lymphoproliferation, granuloma formation, various types of lung disease (e.g. bronchiectasis, interstitial lung disease) and malignancy [1]. These heterogeneous manifestations may precede clinical susceptibility to infection. Diagnosis of PAD requires exclusion of secondary antibody deficiencies (SAD), such as drug-induced hypogammaglobulinemia, renal protein loss, or rare entities such as thymoma-associated hypogammaglobulinemia (Good Syndrome) [2].

The diagnosis of antibody deficiency is straight forward, as quantification of serum immunoglobulins (IgG, IgM, IgA, and IgG subclasses) is broadly available [3]. In some cases, other laboratory findings hint at antibody deficiency, such as a low gamma-fraction in the serum electrophoresis, or unexplained lymphopenia [3]. Nevertheless, diagnosis of antibody deficiency is missed in a substantial proportion of affected subjects, likely due to lack of awareness of PAD amongst healthcare professionals. Hence, being aware of any other lab finding that might be associated with the diagnosis of PAD may help reduce the number of unidentified patients and thereby prevent infection or autoimmunity-related morbidity.

Anti-nuclear antibodies (ANA) are autoantibodies targeting nuclear constituents that can be found at elevated titers in various autoimmune diseases. Given their clinical relevance, and the variable presentation of ANA associated diseases, testing of ANA is commonly ordered in patients with inflammatory disease or autoimmune Phenomena. ANA -testing is usually performed by the indirect immunofluorescence assay (IIFA) on HEp-2 cells which is at present the gold standard technique to detect ANA (Fig. 1a, b) [4]. A positive ANA -test is usually defined as a detectable nuclear immunofluorescence staining at a serum pre-dilution of at least 1:40 (Fig. 1b).

[1] Immunodeficiency Clinic, Medical Outpatient Unit, and Immunodeficiency Lab, Department Biomedicine, University Hospital, Petersgraben 4, 4031 Basel, Switzerland
[2] Medical Outpatient Clinic and Translational Immunology, Department Biomedicine, University Hospital, Petersgraben 4, 4031 Basel, Switzerland
[3] Rheumatology, University Hospital, Petersgraben 4, 4031 Basel, Switzerland
[4] Clinical Immunology, Medical Outpatient Unit, and Immunobiology lab, Department Biomedicine, University Hospital, Petersgraben 4, 4031 Basel, Switzerland
[5] Division Medical Immunology, Laboratory Medicine, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland

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Acute Effects of Lysergic Acid Diethylamide on Circulating Steroid Levels in Healthy Subjects

P. Strajhar[1,*], Y. Schmid[2,*], E. Liakoni[2], P. C. Dolder[2,3], K. M. Rentsch[3], D. V. Kratschmar[1], A. Odermatt[1,*] and M. E. Liechti[2,*]

Lysergic acid diethylamide (LSD) is a serotonin 5-hydroxytryptamine-2A ($5\text{-}HT_{2A}$) receptor agonist that is used recreationally worldwide. Interest in LSD research in humans waned after the 1970s, although the use of LSD in psychiatric research and practice has recently gained increasing attention. LSD produces pronounced acute psychedelic effects, although its influence on plasma steroid levels over time has not yet been characterised in humans. The effects of LSD (200 lg) or placebo on plasma steroid levels were investigated in 16 healthy subjects using a randomised, double-blind, placebo-controlled, cross-over study design. Plasma concentration– time profiles were determined for 15 steroids using liquid-chromatography tandem mass-spectrometry. LSD increased plasma concentrations of the glucocorticoids cortisol, cortisone, corticosterone and 11-dehydrocorticosterone compared to placebo. The mean maximum concentration of LSD was reached at 1.7 h. Mean peak psychedelic effects were reached at 2.4 h, with significant alterations in mental state from 0.5 h to > 10 h. Mean maximal concentrations of cortisol and corticosterone were reached at 2.5 h and 1.9 h, and significant elevations were observed 1.5–6 h and 1–3 h after drug administration, respectively. LSD also significantly increased plasma concentrations of the androgen dehydroepiandrosterone but not other androgens, progestogens or mineralocorticoids compared to placebo. A close relationship was found between plasma LSD concentrations and changes in plasma cortisol and corticosterone and the psychotropic response to LSD, and no clockwise hysteresis was observed. In conclusion, LSD produces significant acute effects on circulating steroids, especially glucocorticoids. LSD-induced changes in circulating glucocorticoids were associated with plasma LSD concentrations over time and showed no acute pharmacological tolerance.

[1] Division of Molecular and Systems Toxicology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland.
[2] Division of Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel, Basel, Switzerland.
[3] Laboratory Medicine, University Hospital Basel, Basel, Switzerland.
[*] These authors contributed equally to the study.

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IDH mutation is associated with higher risk of malignant transformation in low-grade glioma

Severina Leu[2], Stefanie von Felten[3], Stephan Frank[4], Jean-Louis Boulay[1], Luigi Mariani[1,2]

Abstract Acquisition of *IDH1* or *IDH2* mutation (*IDH*-mut) is among the earliest genetic events that take place in the development of most low-grade glioma (LGG). *IDH*-mut has been associated with longer overall patient survival. However, its impact on malignant transformation (MT) remains to be defined. A collection of 210 archived adult LGG previously stratified by *IDH*mut, *MGMT* methylation (*MGMT*met), 1p/19q combined loss of heterozygosity (1p19qloh) and TP53 immunopositivity (TP53pos) status was analyzed. We used multistate models to assess MT-free survival, considering one initial, one transient (MT), and one absorbing state (death). Missing explanatory variables were multiply imputed. Overall, although associated with a lower risk of death (HR_{DEATH} = 0.35, P = 0.0023), *IDH*mut had a non-significantly higher risk of MT (HR_{MT} = 1.84; P = 0.1683) compared to *IDH* wild type (*IDH*wt). The double combination of *IDH*mut and *MGMT*met and the triple combination of *IDH*mut, *MGMT*met and 1p/19qloh, despite significantly lower hazards for death (HR_{DEATH} versus *IDH*wt: 0.35, P = 0.0194 and 0.15, P = 0.0008, respectively), had non-significantly different hazards for MT. Conversely, the triple combination of *IDH*mut/*MGMT*met/ TP53pos, with a non-significantly different hazard for death, had a significantly higher hazard for MT than *IDH*wt (HR_{MT} versus *IDH*wt: 2.83; P = 0.0452). Although *IDH*-mut status is associated with longer overall patient survival, all *IDH*mut/*MGMT*met subsets consistently showed higher risks of MT than of death, compared to *IDH*wt LGG. This supports the findings that molecular events relevant to *IDH* mutations impact early glioma development prior to malignant transformation.

[1] Laboratory of Brain Tumor Biology, Department of Biomedicine, University Hospital Basel, Room 7009, PharmaCenter, Klingelbergstrasse 50-70, 4056 Basel, Switzerland
[2] Neurosurgery Clinic, University Hospital Basel, Basel, Switzerland
[3] Clinical Trial Unit, University Hospital Basel, Basel, Switzerland
[4] Division of Neuropathology, Institute of Pathology, University Hospital Basel, Basel, Switzerland
Severina Leu and Stefanie von Felten are co first authors and Jean-Louis Boulay and Luigi Mariani are co last authors.

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2. Department of Biomedicine and University of Basel affiliation must be mentioned in authors list as published by the journal.
3. The final version of the article must be available (online pre-publications will be included when the correct volume, page numbers etc. becomes available).

We are focussing on original publications. Due to page constraints, abstracts of publications that appeared in lower ranked journals may not be able to be included. Review articles are generally not considered, unless they appeared in the very top journals (e.g. Cell, Science, Nature, NEJM, etc.). The final decision concerning inclusion of an abstract will be made by the chair of the Department of Biomedicine.

If you wish that your article will appear in the next issue of DBM Facts please submit a pdf file to the Departmental Assistant, Manuela Bernasconi: manuela.bernasconi@unibas.ch

Deadline for the next issue is October31, 2016.

Zwetschgenmarmelade

Zutaten

1 1/2 kg Zwetschgen
750 g Gelierzucker (2:1)
2 Tüte/n Vanillinzucker
200 ml Rotwein, trockener
1 TL Zimt

Zubereitung

Arbeitszeit: ca. 1 Std. / Schwierigkeitsgrad: simpel / Kalorien p. P.: keine Angabe

Die Zwetschgen waschen, entsteinen und in kleine Stücke schneiden (nicht pürieren!). Mit dem Vanillinzucker in einen grossen Topf geben, den Gelierzucker einrieseln lassen und unter Rühren zu Kochen bringen. 3–4 Minuten unter Rühren weiter kochen.

Den Topf vom Herd nehmen, Zimt und Rotwein unterrühren und die Marmelade sofort heiss in Gläser füllen und diese fest verschliessen.

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Applied Microbiology Research
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Transplantation Virology

Ralph Duhr, PhD

May 5, 1985 – July 7, 2016
(PhD student in the Laboratory of Tissue Engineering October 2011 – December 2015)

Ralph passed away on a sunny day. He was happy as always and after greeting his wife Danielle with a sweet "I love you", left home for a run. Unfortunately, he did not come back. Although Ralph had no adverse health conditions, on this day he experienced a sudden heart arrhythmia, from which he did not recover.

There are no words that can express the sadness felt by all of us. Throughout his PhD studies, Ralph was a true joy to work with. A gifted student, a trusted colleague, a respected mentor, and most of all, a dear friend. He was a highly professional scientist and engineer: determined, intelligent, confident, pragmatic, and reliable. Ralph was a person capable of delicate gestures, always available and willing to help everyone, capable of enriching others, thanks to his intelligence, kindness, and unique sense of humor. When one so young and capable is taken from us, we are reminded of the beauty of life and friendship, which should be lived as intensely and generously as Ralph did: he had an impact on those around him and made the world a brighter place, without bringing his person on the forefront.

We will remember Ralph in the state of running, of living his life in a professional, personal and spiritual movement. Ralph continues to remind us that we cannot remain in our protected positions, where we feel safe and comfortable. We cannot rest in front of the mystery of life, clung to our religious beliefs or to our claims to be non-believers.

Ralph dealt with the difficulties of work and life without complaining, always with a smile and struggling to find a logic explanation. But when this was really impossible, we remember him lifting his shoulders and his hands in sign of surrender. Ralph's short but intense life remains as a symbol to us: it indicates that in our run towards truth and fulfillment, it's only when our heart surrenders, that it may find a secret path to reach the mystery of life and to experience the vicinity to God and to our beloved.

Ivan Martin and David Wendt on behalf of Ralph's lab friends

Engagement für Kinder in Kamerun!

Mein Name ist Frances Kern. Ich habe 29 Jahre in einem Forschungslabor im DBM (vormals DF) gearbeitet. Nach einer sehr erfüllten und bereichernden Zeit hatte ich die Chance, mich mit 58 Jahren pensionieren zu lassen. Mein Wunsch «Etwas Neuem Raum zu geben», manifestierte sich in Kürze und wurde zu meiner neuen Herausforderung! Kurz gesagt wurde ich Vorstandsmitglied eines Vereins, der sich für Waisenkinder in Kamerun einsetzt. Die Initiative zu diesem Verein geht auf die tatkräftige Arbeit von Virginie Nke (Schweizerin/Kamerunerin) zurück, welche sich schon seit Jahren um die Belange der Kinder eines Waisenheims in Mbalmayo kümmerte. Sie initiierteAnfang 2013 gemeinsam mit vier Mitgliedern die Gründung von CAREDOR Suisse.

Das Waisenheim Caredor (Centre d'Accueil et de Resocialisation des Enfants Desherites et Orphelins de Ngallan- Malbayo, Kamerun) wurde 1984 vom Ehepaar Bessala gegründet. Was mit wenigen Kindern begann, ist heute zu einer täglichen Herausforderung, wenn nicht gar Überforderung herangewachsen. Aktuell leben 38 Kinder zwischen 3 und 21 Jahren im Heim. Hinzu kommen rund 10 Kinder, die als Tagesbesucher vor Ort sind.

2 Euro pro Kind pro Tag

Als kleines Hilfswerk leisten wir direkte Arbeit vor Ort. 100% aller Mitgliederbeiträge und Spenden fliessen direkt in unsere Projekte. Kamerun ist ein wunderschönes, aber sehr armes Land. So be-

Kinder vom Heim

Dr. Zusi mit Diego

trägt das Durchschnittseinkommen rund 70 Euro pro Monat. Menschen leben von der Hand in den Mund, und wenn sie sich mal ein Bier leisten wollen, müssen sie einen ganzen Tageslohn von 2 Euro berappen. Milch ist praktisch unerschwinglich, sie kostet pro Liter ebenfalls 2 Euro.

Waisen in Kamerun gehören zu den Allerärmsten. Entsprechend gross war dann auch der Kulturschock bei unserem ersten Besuch 2013 vor Ort. So waren die hygienischen Verhältnisse mehr als nur prekär, was sich zusammen mit einer sehr einseitigen und oft nicht genügenden Ernährung im Gesundheitszustand der Kinder widerspiegelte. Hautflöhe, Malaria, Röteln, Durchfall, Sehstörungen, schlechte Zähne und teilweise angeborene Behinderungen – um nur einige Krankheiten zu nennen – gehören zu den ganz normalen Herausforderungen im Heim.

Dank einer guten Kooperation mit einem italienischen Privatspital in Mbalmayo konnten wir erreichen, dass die Waisen von Caredor Zugang zu medizinischer Versorgung bekommen. Diese Kooperation war nur dank einer äusserst grosszügigen Spende aus einer Basler Stiftung möglich. Das bedeutet konkret, dass jeden Monat eine Ärztin im Waisenheim alle Kinder untersucht und die Kinder im Krankheitsfall dank einem persönlichen Batch freien Zugang zum Spital haben, was ihnen im Notfall die medizinische Versorgung garantiert. Keine Selbstverständlichkeit in Kamerun!

Die Hygiene im Heim ist katastrophal. Es mangelt an allem: Platz, Infrastruktur wie Toiletten oder Duschen. Das Dach rinnt und in den Schlafzimmern gibt es keine Fenster.

Grundsätzlich ist das Waisenheim auf sich selbst gestellt. Ausser einigen unregelmässigen Spenden von Naturalien oder etwas Geld von Kirche oder privaten Sponsoren, gibt es keine Unterstützung. Die Regierung ist korrupt und das Sozialministerium kümmert sich nicht um die Belange des Heims. Es ist zum Verzweifeln.

Und so wird den Kindern aus Mangel an finanziellen Mitteln eine Suppe auf Basis von Mais oder Maniok sowie abwechslungsweise ein Stück Weissbrot mit einer Art Nutella, ergo viel Zucker verabreicht, was in beiden Fällen einer gesunden Ernährung nicht zuträglich ist und ausser viel Karies und Vitaminmangel nichts bringt!

Ein Stück Kuchen für alle.

Die Nahrung ist eine sehr grosse Herausforderung. Auch hier konnten wir einen Meilenstein in der konkreten Hilfe setzen: Dank einer weiteren äusserst grosszügigen Spende einer anderen Basler Stiftung, können wir die Ernährung für 3 Jahre garantieren. Vor Ort versuchen wir die angestellte Köchin, eine durch und durch gute Seele, in einer ausgewogenen und gesunden Ernährung zu unterrichten, was langsam zu funktionieren scheint!

Das ist vor Ort alles andere als selbstverständlich, obwohl Nahrungsmittel grundsätzlich vorhanden wären... Nur leider sind sie sehr teuer, eine direkte Folge der Globalisierung!

Insgesamt haben wir pro Kind und pro Tag für alle Ausgaben (inkl. Miete, Elektrizität, Wasser, Nahrung, Medizin, Betreuung und Schule) 2 Euro Budget zur Verfügung.

Kleine Highlights

Was ursprünglich eine Spende einer Gönnerin aus Basel war, hat sich institutionalisiert: Wir bringen jedes Jahr an einem Sonntag fünf grosse Kuchen ins Heim, was immer ein etwas abenteuerliches Unterfangen ist: Es beginnt bereits am Samstag in der Bäckerei Acropol bei der Bestellung der 5 Torten, was gut eine Stunde dauert! Tags darauf verstauen wir bei mind. 30°C die Torten dann alle im Kofferraum. Und hoffen, ohne allzu grossen Verkehrsstau, wo man gerne mal 1 Stunde in der brütenden Hitzte steht, aus Yaounde raus zu kommen, um in 40 Min. Mbalmayo zu erreichen. Die leuchtenden Kinderaugen, wenn jedes Kind ein grosses Stück Kuchen vor sich hat, ist jeweils sehr berührend und lässt uns den ganzen Aufwand rasch vergessen.

Ein weiteres Highlight ist «unser» Guillaume, ein Vollwaise. Ein 20 jähriger junger Mann, der wegen einer blöden Geschichte aus dem Heim gejagt wurde. Für ihn ein traumatisches Erlebnis, mit dem er beinah nicht klar kam, war für ihn das Heim doch von Klein an sein zu Hause, die vielen Kinder sei-

Coiffeursalon

ne Brüder und Schwestern. Wir unterstützen ihn nun mittels einer Patenschaft und finanzieren seine Zimmermiete und die Schule. Sein Essen verdient er sich selbst, indem er einen kleinen Coiffeursalon unterhält. Er hat mich vor 2 Jahren kurzerhand als seine Mutter adoptiert und uns dieses Jahr mit einer riesen Überraschung empfangen! Er ist Vater geworden, seine Freundin hat soeben das Krankenschwester Diplom erlangt und ich habe den Status der Grossmutter des 3 monatigen Yarell erhalten!

Solche Erlebnisse sind nebst all den Problemen, die sich uns tagtäglich stellen einfach herzerwärmend! Wir geniessen die speziell schönen Momente auch immer innerhalb des Teams und gönnen uns am Abend nach einem anstrengenden Tag jeweils ein gutes kamerunesisches Bier und geniessen unseren Fisch vom Grill, der immer frisch am Strassenrand vis à vis von unserem Hotel zubereitet und von Hand gegessen wird!

Ex-FCB-Star Thimothé Atouba und unser Netzwerk

Dank Virginie's kamerunesischen Wurzeln sind wir in Yaounde bereits gut etabliert, was unserer Arbeit sehr zuträglich ist! So bauen wir von Jahr zu Jahr unser Netzwerk aus. Wir arbeiten vor Ort mit einer Vertrauensperson zusammen. Ein junger Mann, der derzeit seinen Master in Recht ab-

Guillaume und Baby

schliesst, sorgt für unsere Sicherheit, chauffiert uns in seinem alten Mercedes quer durch die Strassen Yaoundes, «rettet» uns mit seinem Humor, wenn's mal ganz bitter wird und ist für uns vor Ort treuhänderisch tätig. Zudem haben wir im Heim ein paar Betreuungspersonen sowie eine Köchin angestellt – zu Minilöhnen –, die bei der täglichen Betreuung der Kinder mithelfen.

Und dieses Jahr haben wir mit dem ehemaligen FCB-Star und Kameruner Thimothé Atouba eine ganz besondere Begegnung genossen! Wir sind sehr stolz auf diesen Kontakt! In unserem Blog auf unserer Homepage unter www.caredor.org können Sie in Kürze weitere interessante News über diese Begegnung und vor allem auch über die Beziehung zwischen Atouba und Caredor nachlesen. Atouba oho – Atouba ohohohoh…!!!

Wir sind auf finanzielle Hilfe angewiesen

Wir sind auf finanzielle Hilfe von aussen angewiesen. Bitte helfen Sie uns, indem Sie Mitglied werden oder eine Spende leisten. Wir haben viele offene Projekte und Patenschaften, die Sie gerne unterstützen können. Wir garantieren als kleiner Verein, dass 100% der Spenden direkt unseren Projekten zu Gute kommen, indem wir mindestens 1–2 mal pro Jahr vor Ort sind und an der Optimierung der Lebensumstände der Waisen mitarbeiten. Setzen Sie sich doch bitte mit einem unserer Vorstandsmitglieder in Verbindung unter www.caredor.org.

Unsere Projekte sind vielfältig: Auto, Latrinen, Nahrung, Löhne. Und unsere Patenschaften sind konkret: Ausbildung zu Chauffeur, Sekretärin, Architekt. Zudem haben wir ein für uns gigantisches Vorhaben im Auge: Den Bau eines Hauses zur Ausbildung von Waisen im Agrarbereich, ein vielgefragter Job vor Ort.
MedizinerInnen sind jederzeit für einen Einsatz vor Ort im Spital willkommen. Melden Sie sich bei uns, wir stellen gerne den Kontakt her. Das Spital in Mbalmayo ist froh um jede Unterstützung!

Frances Kern

Team mit Timothy Atouba

There are three reasons to love lobster: biology, catching, and eating

Biology.

When I was a kid, I heard this story about lobsters:

Catch a migrating lobster, drive by boat thirty nautical miles in any direction and release the lobster. What happens? It swims back to where you caught it. It swims back even if you are fifty kilometers away and the lobster is blinded.

I thought this was a fisherman's tale well dressed in an experiment until I stumbled across this Nature paper (1). Lobsters do indeed use magnetic, or 'true' navigation.

The other legend I heard was that in the old days, before overfishing, lobsters migrated single file, in a chain several kilometers long. Fishermen would put a big net in front and the lobsters walked in one by one, by the thousands. I have yet to find the Nature papers examining lobster chain length or gullibility.

The beautiful crustaceans, Panulirus argus, provide an unending list of amazing biology, from life cycle, to neurophysiology, to migration experiments. But for this article, you only need to know that I am talking about spiny lobsters. Not the ones with big claws. They have legs for walking forward, tails for the occasional backwards swim, and they are delicious – if you can catch them.

Catching.

You get up at 4a.m. and load the boat with snorkeling and scuba gear, and with lobster nets and tickle sticks – all the devices for catching. On the way to breakfast you pick Key limes, avocadoes, mangoes, and bananas. At 5 a.m. the house is swarming with neighbors, friends, and relatives sipping a coffee and

packing bags for a day on the boat – the more people on the boat, the more lobster you can catch.

We push the boat from the dock at 5.30, and just before 6 we anchor over a reef a few kilometers from shore. The reef would have been scouted days before by dragging a small human (my younger brother) behind the boat until he finds a high density of lobster per reef area.

Once you have a reef to explore, you have to swim down and find the lobsters. My parents always scuba dive and my brothers and I snorkel. We all get into the water at sunrise, but the water is still dark - so dark that you can see the bioluminescent plankton and fish.

Lobsters tend to migrate at night and then hide inside reefs during the day. So finding lobster during the day can be tricky. Either you see their antennae sticking out of the reef, or you see have to swim down and look under the reef ledges and into the holes. You can also follow groupers (large and tasty fish that eat lobster), which tend to follow the lobsters.

Once you locate a lobster you swim down with a net and tickler stick. The net is maybe 50cm in diameter and the tickle stick is about 1.5m long. You lure a lobster out of the reef with the fine art of 'tickling'. In the best situation, tickling is this: you tap the lobster from behind with a stick and it moves forward; tap it on the right and it moves left; and so on – it moves away from where you tickle. After a seductive tickle, the lobster is out and you net it. Once it's in the net, you grab it with a gloved hand and swim it to the surface. Either you throw the lobster to a friend on the boat, or you carry it around with you in bag.

A good catch is up to 100 lobsters. We also catch a lot of fish while lobstering, particularly groupers. Groupers have a fine mix of intelligence and stupidity. They are clever enough to follow lobster fishers, but stupid enough to get so close to fishermen as to be easily netted.

After a full day or a full boat, we head home. This is usually after 3 to 6 hours of swimming for lobster, about an hour or two of boat travel, and a few hours of loading and unloading the boat as well as preparing the catch. It's a long day. You know you will eat fish that is a few hours fresh. So you are hungry by dinnertime.

Eating.

We freeze the majority of the catch because lobsters keep flavor and texture well, and perhaps even tenderize under freeze-thaw cycling – and we cant eat 100 in a day. The ones we eat are decapitated, deveined, and then taken to the kitchen. They sit in a bowl with olive oil, a little salt and pepper, and maybe some garlic and local herbs. We normally add Key lime at some point because Key limes are a local fruit and integrated into most Keys and Caribbean cuisines.

Between catching, cleaning, and prepping the fish and tending to the boat, there is little time before dinner. If there is time, I nap or catch up on reading. The Keys are a good place to nap (famous for so called 'Keys-disease', a compulsive form of napping or laziness), and they are a good to place to read if you are a Hemmingway fan. Much of Hemmingway's writing is based on his experience in the Keys, Bahamas and Cuba – all are within 75 to 150 km of each other. The book 'Islands in stream' (2) is set in the Bahamas, but the fishing and the terrain described is the same as the Keys, particularly where we are, which is the most northern, most remote and least populated Key.

We tend to grill most fish on the barbeque. My parents are not strict charcoal and wood barbequeurs, and use a gas grill. This allows for better reproducibility and control – they say. They have a method of time and temperature for cooking any fish perfectly well. Lobsters, for example, are cooked on a high temperature for 6 minutes. While the fish grill, we prepare the sides. A chutney of mango, lime and coriander is a typical side. Salads often contain the Caribbean avocado, which is a much bigger (and more flavorful) version of the one bought here. Rice is often cooked with Caribbean (spicier and with tomato) or Mexican (with beans) styles.

There is no local wine, but pairing with anything dry and white seems to work – my mom would recommend a pinot grigio. There are several decent Caribbean beers, which picked up the craft from European (and English) colonizations. Normally we have a beer watching the sunset and then wine with dinner.

It's hard to stay up late, when you wake at four and swim for several hours. A day lobstering is as hard as any in the Alps. However, there are still a few late nights. Late-night fishing in the summer can be excellent: inshore for the late tides, and offshore for full moon spawning cycle of snappers. We also sometimes stay up a little later eating and drinking - one of our neighbors makes ice-cream and a digestif from Key limes – both can keep you up a little longer than you planned. But no matter how late it goes, we always find it easy to wake up early for another day of lobster.

Mike Abanto

Ref:

Nature **421**, 60-63 (2 January 2003) | doi:10.1038/nature01226; Received 6 June 2002; Accepted 7 October 2002

Simon and Schuster 1970. Islands in the stream, by Ernest Hemingway.

Today: Timo Dörflinger, DBM IT

My name is Timo Dörflinger and I'm 23 years old. I'm from Grenzach-Wyhlen and I've been happily working at the DBM-IT since September 2015.

As child I drew every day and initially I wanted to work as a media designer or something like that. But when in school I discovered IT and wanted to work with computers.

I started my IT-apprenticeship in 2011 at Novartis in Basel and finished it successfully in 2015. It was a really good time. Every six months I moved to a different IT-department at Novartis. Some of them were support groups and some of them were software-development groups. It was a good mix. But Novartis never adopt their apprentices so on finishing I had to search for a new job.

Because I wanted to build on the education I received in my apprenticeship I started a dual course of study in the summer of 2015. This means that in addition to working at the DBM I now attend this course two evenings a week and all day on Saturday. It's interesting to do some projects with people from different jobs and of different ages and it's exciting to see how different characters solve a problem or work together.

The Dragonboat – My hobby

Paddling in the Dragonboat is my biggest hobby and I would therefore like to show you more of the Dragonboat. Many people mix up paddling with rowing. But these are two different sports. With paddling you have only one paddle and paddle forward. With rowing you have two skulls and row backward.

The boat

There are two types of the Dragonboat. First there is the normal Dragonboat. The boat itself is about 12 meters long and almost one meter wide in the middle. The boat has 10 benches with space for up to 20 paddlers.

There is also the "Smallboat". It isn't really smaller but has only 5 benches for up to 10 paddlers. Because it is almost the same weight and size but is manned by just half the number of people, it's more difficult to paddle.

We are guided by a steersman because the boat is too big to be handled by just the paddlers. During competitions and championships, we also are supported by a drummer, as you can see in the picture. People think that the drummer is responsible for beating the rhythm. However, it is actually the paddlers on the first bench in the front of the boat who are responsible for setting the rhythm, which is then assumed by all other paddlers and the drummer.

For the past two years my position has been on the right side of the first bench so I set the rhythm for both the start-up phase and the main part of the race. For short race distances we have a faster rhythm in the boat and for longer distances we have a slower rhythm.

Training

Because we train on the Rhine we can't be on the water the whole year round. In the winter months, between November and February in particular, it's too cold. We therefore have our own little gym where

we can train through the winter to keep fit. We train four times a week. This is necessary because we take part in the "German Dragonboat Championship" and many other competitions every year. We need the training because we want to be successful at these competitions and we want to qualify for the "European Club Crew Championship" and the "World Club Crew Championship" where the best teams from each country paddle against each other. We were at the "World Club Crew Championship" in Italy two years ago and at the "European Club Crew Championship" in Genève last summer . It was a great experience to paddle again teams from Australia, China, America and so on and we were more successful than we expected.

Competitions and Championships

A competition or a championship takes place over two or three days. On the first day there are the 200-meter sprint races. For 200 meters we take around 1.20 min. On the second day there are the 500-meter sprint races. We finish the 500 meters in about 2.30 min.

On every competition day there are 2 to 4 races. The exact number depends on whether we reach the final or lose in the first two rounds.

If there is a third day, then there will be the long distance races over 2000 or 4000 meters. If there isn't a third day, then the long distance races are held between the 200 and 500 meter races as was the case at the last "German Dragonboat Championship" in the middle of June this year with the Smallboat. Our team started in different performance classes. We had five 200 meter races followed by the 4000-meter race on the same day. On the following day we had five 500-meter races. That was a really tough weekend.

The 2000 or 4000 meter races are "hunting" races where all boats start one after another in 10 second steps. The aim is to reach the finish as quickly as possible, but another goal is to overtake the boat in front of you while not getting overtaken by the boat behind you. At the German championship some weeks ago we were able to overtake the boat in front of us over the 4000-meter distance. That is really hard because every team is fighting to overtake and not get overtaken, but it's a lot of fun. For the 4000 meters we took around 20 minutes.

At the end of the season, around October, it's the time for the really long distance races. Then we have competitions over roughly 8 and 11 kilometers and these are also "hunting" races. For such a competition we need up to one hour. One really famous competition over 8 kilometers takes place in Bern every year. And because it's in October we have once even been paddling as it was snowing.

For me the sport is a great counterbalance to my job and the dual course of study.

DBM Summer Symposium

August 31, 2016

8:00 – 13:15
Kleiner Hörsaal, ZLF, Hebelstrasse 20

Presentations by DBM postdocs, PhD students and project leaders

DBM Summer Barbecue

August 31, 2016

16:30 – 21:30
Kraftwerkinsel Birsfelden

For DBM members only

Ohne Heimat sein,
heisst leiden.

(F. M. Dostojewski)