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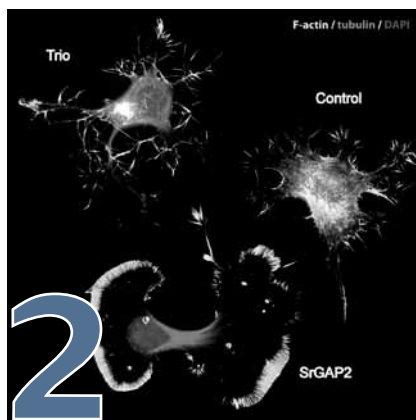
FACTS

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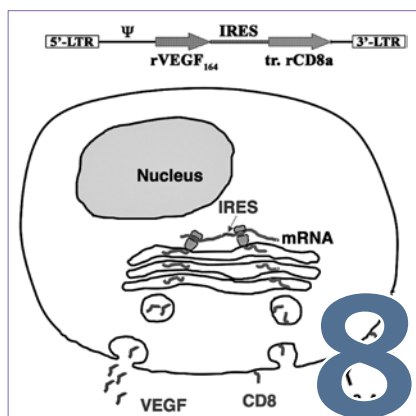
**Cell migration and neuronal differentiation: signaling programs
in space and time | Cell & Gene Therapy: growing vessels
to regenerate tissues | Pferde und Menschen**

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Redaktion

Heidi Hoyermann (Leitung)
 Verena Jäggin

Übersetzungen

Paula Cullen

Layout:

Eric Spaety, Morf Bimo Print AG, Binningen

Publikationen/Publications

Verena Jäggin (Layout)

Mitarbeitende/Colleagues

Verena Jäggin (Layout)

Administration

Manuela Bernasconi

Fotos:

Lena Angman (privat)
 Andrea Banfi (9, 10, 11, 12, 13)
 Stefanie Fritz (privat, GRP)
 Virginie Galati-Fournier (privat)
 Verena Jäggin (8, 27, 28, 34, 35)
 Sabrina Köhli (privat)
 Philipp Müller (privat)
 Marco Osterwalder (privat)
 Olivier Pertz (2, 3, 4, 5, 6, 7)
 Claudia Petit (privat)
 Mathieu Rajalu (Bocher) (privat)

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Redaktion DBM Facts
 Departement Biomedizin
 Hebelstrasse 20
 4031 Basel
 dbmfacts@unibas.ch

EDITORIAL



Radek Skoda
Leiter DBM

Liebe Leserinnen und Leser

Das DBM hatte eine ruhige und erholsame Sommerzeit. Schwerpunkt der nun vorliegenden Herbstausgabe der DBM Facts bilden neben den neuesten Publikationen aus dem DBM die Forschungsdisziplinen von Olivier Pertz und Andrea Banfi. Olivier Pertz führt uns in die Welt der «Cell Migration and Neuritogenesis» (ab Seite 2), Andrea Banfi schildert uns die Herausforderungen in der «Cell and Gene Therapy» (ab Seite 8).

Rund ums Tier geht es bei Stefanie Fritz, die berichtet, wie sie im Rahmen eines internationalen Projektes in Thailand Gibbons auswildert (ab Seite 36), und den drei DBM-Reiterinnen Lena, Sabrina und Claudia, die uns daran teilhaben lassen, wie sie ihre Liebe zum Pferd entdeckten (ab Seite 30).

Schöne Herbsttage und viel Spass bei der Lektüre wünscht Ihnen
Radek Skoda

Dear Readers

The DBM has had a quiet and restorative summer. The emphasis of this Autumnal issue of DBM Facts is on introducing the research disciplines of Olivier Pertz and Andrea Banfi in addition to detailing the newest publications from the DBM. Olivier Pertz brings us into the world of "Cell Migration and Neuritogenesis" (page 2), Andrea Banfi describes the challenges of "Cell and Gene Therapy" to us (page 8).

With Stefanie Fritz it is all about animals, as she describes how she worked on releasing gibbons to the wild as part of an International project in Thailand (page 36); and the three DBM riders Lena, Sabrina and Claudia share with us how they discovered their love of horses (page 30).

Wishing you all a happy autumn and enjoy the read
Radek Skoda

Cell migration and neuronal differentiation: signaling programs in space and time

Introduction

The ability of vertebrate cells to directionally migrate is critical to development, the immune response and wound healing, and its regulation is compromised in pathologies such as metastatic cancer and vascular disease. The capacity of neurons to directionally ex-

tend neuronal processes is crucial for the proper wiring of the brain. A detailed understanding of the signaling events that regulate the cytoskeleton during these complex morphogenetic processes is therefore likely to contribute important insights that could be used to target a number of different pathologies. We are broadly



From left to right

Front row: Erika Fluri (technician), Olivier Pertz, Kyung-Jin Jang (visiting scientist), Katrin Martin (PhD student)

Back row: Georgios Fengos (shared PhD student with D-BSSE), Michel Letzelter (Postdoc), Daniel Feltrin (PhD student), Ludovico Fusco (PhD student)

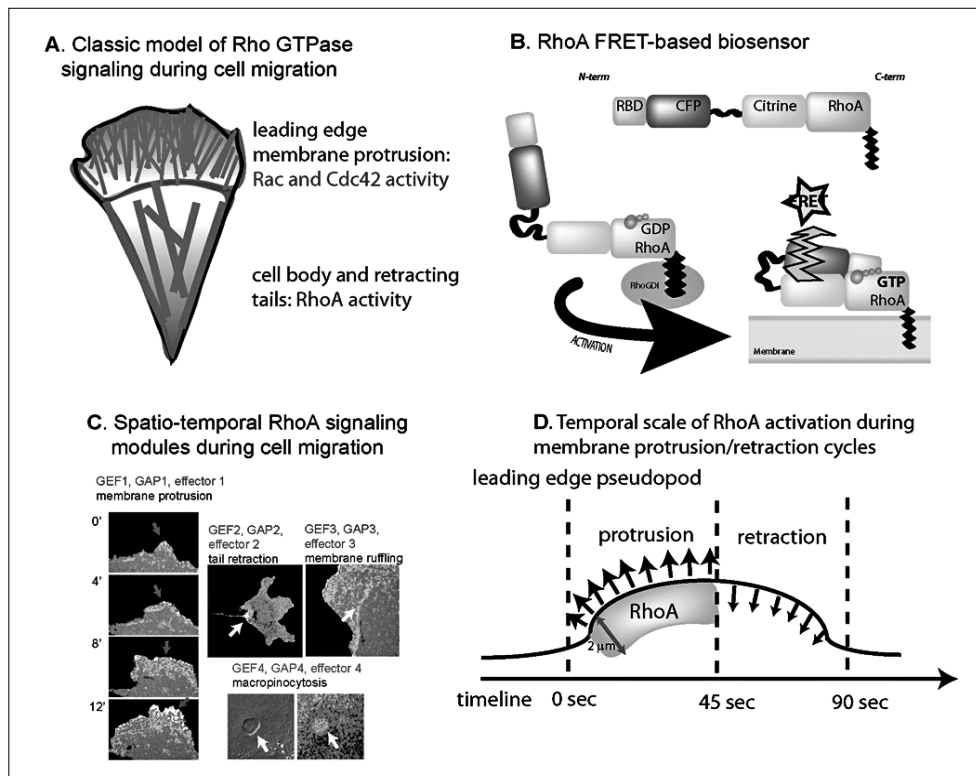


Fig.1. Spatio-temporal RhoA signaling during cell migration.

A. Classic model of Rho GTPase signaling during cell migration.
B. Design of RhoA FRET probe.
C. Different spatio-temporal pools of active RhoA during cell migration.
D. RhoA activation kinetics at the leading edge.

interested in the signaling events that regulate the two processes mentioned above. In particular, our long term goal is to define the spatio-temporal signaling networks that allow migrating cells to extend protrusions called **pseudopods** to produce cell motility. We are also interested in unraveling the signaling programs that allow neurons to extend neuronal processes called **neurites**. Both pseudopods and neurites can protrude from the cell body by using conserved machineries such as the actin and tubulin cytoskeletons, adhesions to the substrate, and polarized membrane trafficking.

Over the past few years, immense progress has been made in understanding the signaling players that regulate such processes. However, despite this wealth of information we still do not understand how multiple signaling components assemble into complex networks and how these networks are organized in space and time to allow the directional extension of pseudopods or of neurites. This is mostly due to limitations of the classical cell biological and biochemical toolbox, most likely reflecting the state of the technology that was used up to now. To unravel these new dimensions, we need novel tools to measure how multiple signaling components are activated in time and space. The goal of our

lab is therefore to design novel technologies that enable studies of the spatio-temporal signaling networks that allow pseudopod and neurite extension to occur. Surprisingly, when we use these new technologies to dissect the signaling mechanisms underlying pseudopod or neurite extension, we observe novel paradigms that are not necessarily in concordance with classic models of signaling. These thus not only enhance further the pre-existing models but also ask for a new conceptual framework.

Rho GTPases and cell migration: from global to spatio-temporal measurements

One of the interests of our lab is to understand spatio-temporal dynamics of the Rho GTPase signaling molecules. Rho GTPases are signaling switches that cycle between a GTP-loaded active and a GDP-loaded inactive conformation. Classic studies in the last 20 years have shown that Rho GTPases are essential signaling switches that regulate the cytoskeleton. This has led to the classic model in which each Rho family GTPase is associated with distinct cytoskeletal and adhesive structures that enable different aspects of cell motility. For example, Rac and Cdc42 activity are thought to regulate mem-

brane protrusion and filopodia formation at the leading edge of migrating cells. In contrast, RhoA has been proposed to regulate assembly of contractile acto-myosin filaments (stress fibers) and focal adhesions which occur in the cell body and at the back of migrating cells (model depicted in Fig.1A). Such a model stems from experiments performed with a classical toolbox that consists of global activity measurements (biochemical pulldown assays of cell populations) and global manipulation of signaling (overexpression of dominant positive and negative mutants and inspection of phenotypes). However, direct measurements of where in the cell Rho GTPases are activated are only emerging. For that purpose, we designed a fluorescence resonance energy transfer (FRET) based probe that enables us to visualize where the small GTPase RhoA is activated in single migrating cells using live cell imaging (1) (Fig.1B). We found two surprising results that are not compatible with the idea of RhoA being constantly activated throughout the back of a migrating cell. **1.** We found that the bulk of RhoA is activated at the leading edge of membrane protrusion. Additionally, we also found pools of RhoA activity at a variety of discrete subcellular locations correlating with different cell behaviors such as tail retraction at the back of the cell, ruffle movement and macropinocytosis (Fig.1C). The different zones of RhoA activation occur on membrane domains that typically span a few microns. Thus, RhoA does not only regulate contractility. Rather, RhoA performs distinct jobs at different places and times in the migrating cell, most likely so by assembling distinct signaling complexes. These different signaling complexes, that we term "spatio-temporal signaling modules", might consist of a variety of upstream regulators (proteins such as Rho GTPase activators: GEFs or inactivators: GAPs) and downstream effectors that allow to perform specific jobs in space and in time. **2.** Another surprising result was the timescale on which Rho GTPase signaling operates. This became obvious when we zoomed in on the spatio-temporal pool of RhoA activity occurring at the leading edge (2). In our cell migration model system, leading-edge advancement occurs in cycles of protrusion and retraction, with one cycle happening in 90 seconds. We found that RhoA is activated directly at the leading edge at the onset of membrane protrusion (for about 45 seconds), but is switched off

during and uncoupled from membrane retraction (the other 45 seconds). Thus, RhoA signaling at the leading edge is cyclic and is switched on and off on timescales of tens of seconds.

The first question that comes to mind is why these results are so different than the classic conceptual framework which has been dominant in the Rho GTPase field in the last 15 years. The answer to that question is simply that the classic Rho GTPase toolbox is not sensitive enough to resolve the spatio-temporal dimensions of Rho GTPase signaling we uncovered using our biosensor. Importantly, this toolbox also often leads to artefactual results. Obviously, the fine activation patterns we observe cannot be measured in activation measurements of a global population in which the dynamic states of thousands of cells are averaged. Similarly, global activation or inhibition of Rho GTPase signaling will not give information about the subtle spatio-temporal pools of active GTPase with different functions we observe. In fact, in such "brute force" experiments, some signaling modules will dominate over others leading to phenotypes that only recapitulate part of the functions of a GTPase (e.g overactivation of RhoA leads to a contractile phenotype and does not give information about a role in pseudopod protrusion). Thus, the discrepancy of our results with the classical model simply results from the fact that signaling events that are intrinsically local and highly regulated in time have been measured or manipulated globally. These findings show the value of precise spatio-temporal measurements of signaling events in the context of dynamic behaviors such as cell migration. Our datasets not only extend previous models but also clearly call for a novel conceptual framework of Rho GTPase signaling. The challenge is now to identify which different proteins assemble specific signaling complexes (modules) in time and space to regulate specific cellular functions (pseudopod extension at the front, tail retraction at the back). Obviously this will not be an easy task using classic biochemical techniques since simple lysis of a cell population will lead to loss of the spatial organization of these complexes observed in the single living cell. Furthermore, any of these local signaling complexes are most likely very low in abundance and occur very transiently in time. Imaging approaches using such biosensors should therefore become in-

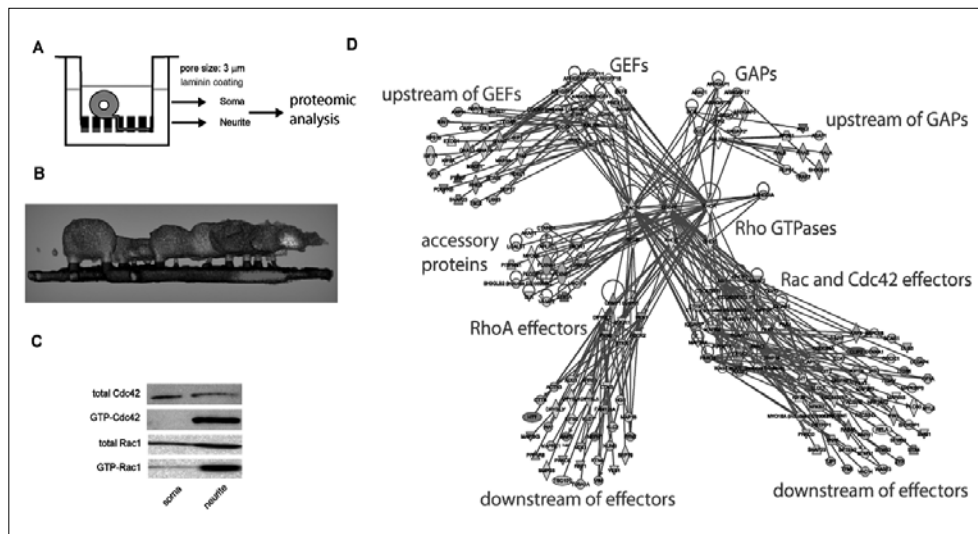


Fig.2. Rho GTPase signaling network in neurite outgrowth.

A. Microporous filter setup for neurite purification.

B. 3D reconstruction of neurons plated on the filter setup.

C. Biochemical analysis of Rac and Cdc42 activity in neurite and soma fractions.

D. Neuronal Rho GTPase signaling network. Hugo gene names of are shown. Each line represents a documented protein-protein interaction. Color intensity is proportional to neurite enrichment of the protein as identified by proteomics.

creasingly used in the future to resolve such dynamic signaling events. One of the technologies we are currently working on is a toolkit that will allow to rapidly design FRET-based sensors for any signaling molecule.

Spatio-temporal biochemistry and proteomics

Obviously, one of the problems with imaging techniques is that it is hard to measure a large amount of signaling components at once. Thus, we thought of getting a biochemical handle by studying signaling in space and time. In the context of neurite outgrowth, we therefore engineered a system that allows large scale purification of neurites in their cellular state of extension from the cell soma. This takes advantage of the classic boyden chamber assay, but instead of using microporous filters with 8 μm pores, in which big cells usually squeeze from the top to the bottom part of the filter, we used filters with 3 μm pores. This precludes the cell body from going to the other side, and enables only neurites to get to the lower part of the filter allowing for their purification (Fig.2A and B). Combining this method with large scale shotgun proteomics (collaboration with Dick Smith, Pacific Northwestern University), we were then able to analyze the subcellular location of 4800 proteins (neurite/soma) (3). We have also extended this technique to purify pseudopod from the cell body of migrating cells. In collaboration with Ruedi Aebersold at the ETHZ, we have resolved the subcellular location, pseudopod or cell body, of 2000 proteins and 2600 phosphorylation events of fibroblasts that are directionally migrating to

different stimuli. This should help us understand at the system biology level the spatio-temporal signaling networks that allow different kinds of directional cell movement. Importantly, such large scale datasets cannot be understood intuitively, and bioinformatic approaches are needed for their characterization. A further step is to understand the flow of information within such networks. For that purpose we are collaborating with Dagmar Iber from the Department of Biosystems and Engineering of the ETHZ, to use mathematical approaches to model the dynamic flux of information in these networks.

Functionally probing a Rho GTPase signaling network regulating neurite outgrowth

Indeed, our proteomics approaches only provide a list of the potential components that regulate neurite outgrowth (or pseudopod extension). While using bioinformatic approaches, it is possible, to some extent, to guess how these components are wired in a coherent signaling network, additional functional data is desired to understand how these components assemble specific spatio-temporal signaling modules. The central dogma of Rho GTPase signaling tells us that Rac1 and Cdc42 regulate neurite extension. Accordingly, using the neurite purification assay with pulldown assays, we find that active Rac1 and Cdc42 are virtually confined to the extending neurite (Fig.2C). However, bioinformatic mining of the neurite proteomic dataset identified a potential Rho GTPase signaling network than was

much more complex than previously anticipated. This network of 220 proteins (Fig.2D) consists of different Rho GTPases, their upstream activators: GEFs, inactivators: GAPs, proteins that are further upstream of these regulators, downstream effector and their targets and further proteins that are interacting with Rho GTPases. Obviously, again, such a complexity is not compatible with the classic framework, but fits with our FRET experiments that show a high modularity in Rho GTPase signaling.

To dissect this complex Rho GTPase interactome, and understand how specific components interact to form signaling modules, we are using RNA interference to systematically knockdown each signaling component in this network and observe how this impacts neurite outgrowth. Our results are in marked contrast with experiments in which signaling is globally manipulated (such as overexpression of dominant-negative Rac or Cdc42 mutants which lead to loss of neurite outgrowth). Instead, our initial results (based on the knockdown of about 15 candidates) show that when we target one by one the different components of this complex network, only specific functions of neurite outgrowth are affected and loss of neurite outgrowth is never observed. The subtle phenotypes we observe require high sensitivity

readouts to characterize them. In some cases, the phenotypes are visible using high resolution snapshots of the cytoskeleton at steady state. For example in Fig.3, knockdown of the GAP *SrGAP2* leads to a hyperstabilization of filopodia at the cell periphery and on the growth cone. Knockdown of GEF *Trio* leads to aberrantly elongated filopodia. However, in most cases, the whole morphodynamic history of neurite outgrowth (e.g. a timelapse movie of the neurite outgrowth process) is needed to understand the phenotype. For example, the *Trio* siRNA phenotype shows highly unstable neurite outgrowth, with very frequent neurite retraction events. The *SrGAP2* phenotype displays complete loss of neurite retraction events that are however present in wild-type cells.

From a technical point of view, this means that to understand how our network of 220 proteins is wired in signaling modules, we need to produce a timelapse movie for each disturbed state. Our working hypothesis is that RNA interference of proteins that are part of a given signaling module will lead to a spectrum of similar phenotypes. We have now built a high-throughput imaging pipeline that allows that. The next problematic step is the quantitation of this large amount of movies. For that purpose, we are collaborating with the group of Pascal Fua (EPFL) to use computer vision methods to automatically quantitate different morphodynamic parameters relevant to neurite outgrowth in these timelapse movies. We are also collaborating with the group of Francois Fleuret to use machine learning methods to be able to classify the different phenotypes using the multiple morphodynamic parameters extracted from the computer vision techniques. This common effort will allow the dissection of how the Rho GTPase interactome is organized in spatio-temporal signaling modules regulating functions such as filopodia formation, neurite extension, retraction, guidance and branching. This will ultimately provide an integrated framework on how all these functions co-operate to fine tune the neurite outgrowth process.

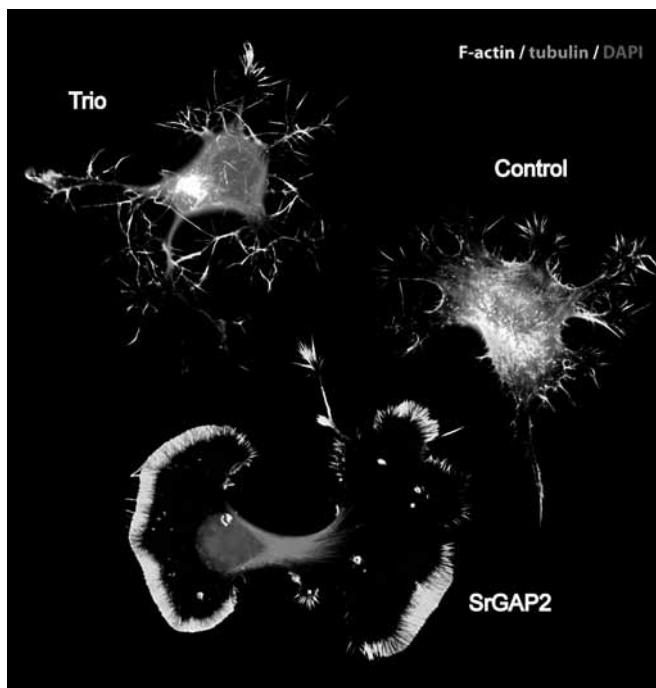


Fig.3. Cytoskeletal phenotypes of selected proteins from the Rho GTPase interactome.

Engineer precise microenvironments to kill the noise in the dish

One difficulty of studying signaling at the single cell level in comparison with biochemical measurements

of cell populations is the large amount of cellular noise. This proves especially true when studying cell migration and neurite outgrowth, in which a large spectrum of cellular behaviors (migration speed, directionality, ...) and shapes often make it difficult to compute an average phenotype. One reason for this is most likely that the dish environment does not recapitulate the precise stimuli that cells encounter *in vivo*, and thus that the cells are somewhat confused. To try to get rid of this cellular noise, we are engineering specific microenvironments to mimic the extracellular cues that the cells observe *in vivo*. This should increase the robustness of the processes we are studying and should allow to standardize cellular behaviors for single cell imaging experiments. In the cell migration system, this means generating highly defined gradients of chemokines that migrating cells observe *in vivo*. This necessitated state of the art microfabrication techniques and was possible through a collaboration with Noo Li Jeon at the National University in Seoul (South Korea). An interesting result is that when a migrating cell encounters such a chemokine gradient, it assembles a completely different cytoskeleton and uses different morphodynamics for its motility, than when this chemokine is applied globally (as one performs in a classic biochemical experiment). Thus, reading a chemokine gradient triggers different signaling networks than with uniform stimulation. We are currently characterizing this novel type of cell migration that was not observed before because of lack of technology. Importantly, such robust behaviors also mean robust signaling events and this should greatly facilitate the spatio-temporal signaling events we are studying using our FRET-based probes.

We also are studying the effect of extracellular matrix (ECM) geometry on cell behavior. In the typical cell migration and neurite outgrowth setups, surfaces are coated with ECM proteins and provide the cells with two dimensional environments that do not recapitulate the 3D organization of the ECM observed *in vivo*. Such ECM environments typically occur as fibrillar or basement membrane structures with highly defined size features on the nanometer scale. In that respect, we found that when the ECM protein laminin is presented to the cell under the form of ridges with nanometric size features, neurons can read this topology and align neurites along

these ridges. An unexpected bonus is that neurite outgrowth is much more robust. We have identified the cellular mechanism that allows the cell to read this ECM geometry and found that it depends on the filopodia of the neurite growth cone. On 2D environments, unrestricted access to the ECM allows filopodial adhesion to the substrate in all directions. On the ridge substrate, filopodia can either align or not on the ridges. Using timelapse microscopy, we find that aligned filopodia are stable whereas unaligned filopodia are not. Filopodia thus stochastically scan the pattern until they are aligned. A signaling crosstalk between aligned and non-aligned filopodia allows for stabilization of filopodia and neurite outgrowth in the pattern direction. This not only gives novel insights in the field of neuronal guidance but also paves the way for the design of novel nanostructured scaffolds for nerve injury and repair.

Olivier Pertz

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Cell & Gene Therapy: growing vessels to regenerate tissues



From left to right

Front row: Silvia Reginato, Veronica Sacchi, Marianna Trani, Uta Helmrich, Elena Groppa

Back row: Roberto Gianni' Barrera, Andrea Banfi, Ludovic Melly, Jeroen Geurts

Therapeutic angiogenesis

Atherosclerotic cardiovascular disease is the most frequent cause of death in the western world. Despite advances in medical and surgical therapy, the morbidity and mortality of coronary heart disease and peripheral artery disease remain very high. There is no medical therapy to halt or reverse the process of atherosclerotic vessel obstruction. Interventional revascularization by balloon dilatation or stenting is frequently not possible, or has poor long-term results. Surgical revascularization by coronary artery bypass or femoro-popliteal bypass is often not feasible because of diffuse vessel disease or unacceptably high operative morbidity and mortality.

Therapeutic angiogenesis aims at restoring blood flow to ischemic tissues by the generation of new vessels. Vascular endothelial growth factor (VEGF) is the most potent and specific angiogenic factor. Despite encouraging preclinical and early clinical results, the results of placebo-controlled clinical trials of VEGF gene therapy have been disappointing and clear clinical benefit has yet to be established. In particular, VEGF delivery appears to have a very limited therapeutic window *in vivo*, such that low doses are safe, but mostly inefficient, and higher doses become rapidly unsafe. In fact, uncontrolled expression leads to deleterious effects, such as the growth of vascular tumors (angiomas) and increased leakiness of the new vessels, leading to tis-

sue swelling (edema). While long-term and high-level VEGF expression carries the potential for serious and life-threatening side effects, short-term expression has been shown to lead to unstable vessels, which promptly regress following cessation of the angiogenic stimulus. A better understanding of the molecular and cellular mechanisms regulating the angiogenic process is clearly needed in order to fully exploit the potency of VEGF for therapeutic purposes while avoiding its deleterious effects.

Our research focuses on the basic principles controlling the physiological generation of normal and functional blood vessels and their translation into rational strategies to treat ischemic diseases and to improve the vascularization of tissue engineered grafts. We use precursor cells genetically engineered to express controlled levels and combinations of angiogenic factors, in order to provide both vascular growth and tissue regeneration, combining the specific advantages of cell and gene therapy (Figure 1).

Controlled expression of VEGF

We have found that the therapeutic window of VEGF delivery does not depend on the total dose administered, but rather on its levels of expression in the microenvironment around each producing cell (Figure 2). In fact, since VEGF remains tightly localized in tis-

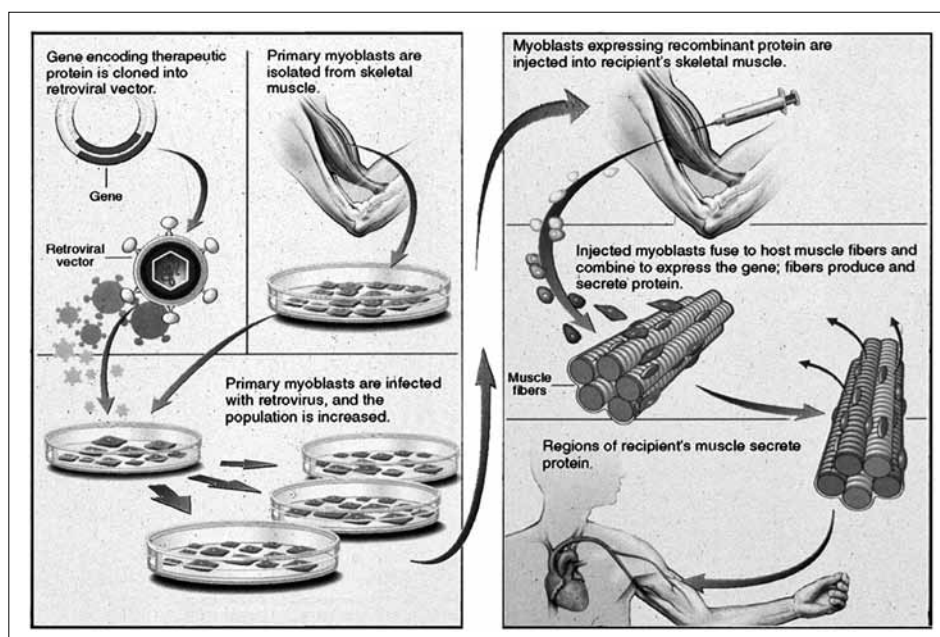


Figure 1. Myoblasts as gene vectors.

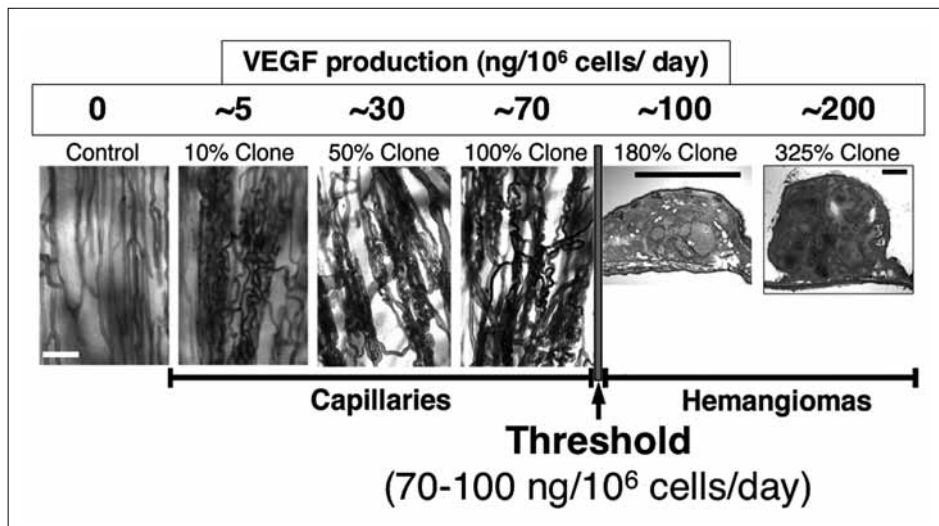


Figure 2. If the microenvironmental distribution of VEGF expression levels is controlled by implanting clonal populations of transduced progenitors, in which every cell produces the same VEGF amount, a dose-dependent threshold between normal and aberrant angiogenesis becomes apparent and a wide range of doses reproducibly induce normal capillaries.

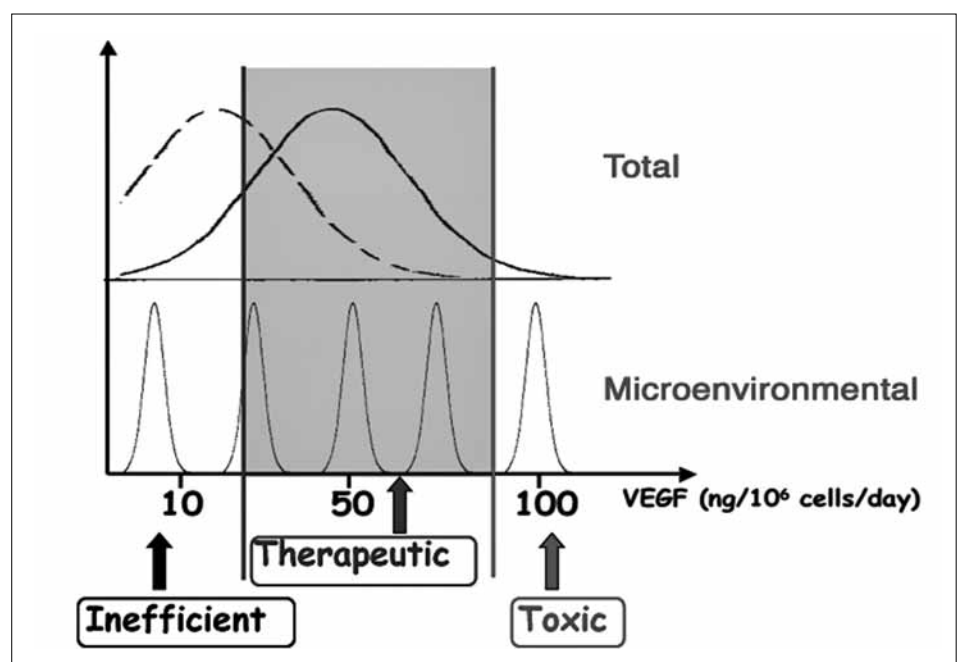
sue after being secreted, different growth factor concentrations do not average with each other, even between neighbouring muscle fibers. Therefore, a few “hotspots” of high expression are sufficient to cause angioma growth even if the total VEGF dose is rather low. This finding helps to explain the apparent difficulty to achieve a manageable therapeutic window in clinical trials of VEGF gene therapy. In fact, currently employed gene therapy methods, such as direct injection of constitutive adenoviral and plasmid vectors, only allow control on the total dose (titer) of gene delivered, but not the distribution of microenvironmental levels *in vivo*. Therefore, in order to avoid even rare “hotspots” of

expression, the total dose must be kept low and efficacy is wasted (Figure 3).

In order to translate this biological concept into a clinically applicable approach, in collaboration with Dr. Heidi Misteli, Dr. Thomas Wolff, Dr. Edin Mujagic and Prof. Lorenz Gürke (Vascular Surgery, USB), we have recently developed a high-throughput FACS-based technology that allowed us to identify and rapidly purify progenitors expressing specific VEGF levels from a heterogeneous population after genetic modification *in vitro* (Figure 4). Populations of mouse muscle progenitors purified in this way induced only safe and efficient

Figure 3. Conceptual representation of the clinical implications of the data shown in Figure 2. If only the total dose delivered can be controlled, but not microenvironmental distribution, therapeutic efficacy will not be achieved in order to avoid rare areas of expression above the threshold that result in angioma formation (broad distribution of VEGF levels on top panel).

When homogeneously distributed doses can be delivered, the microenvironmental distribution can be tightly controlled and efficacy achieved without risk of deleterious effects (narrow distribution of VEGF levels in bottom panel).



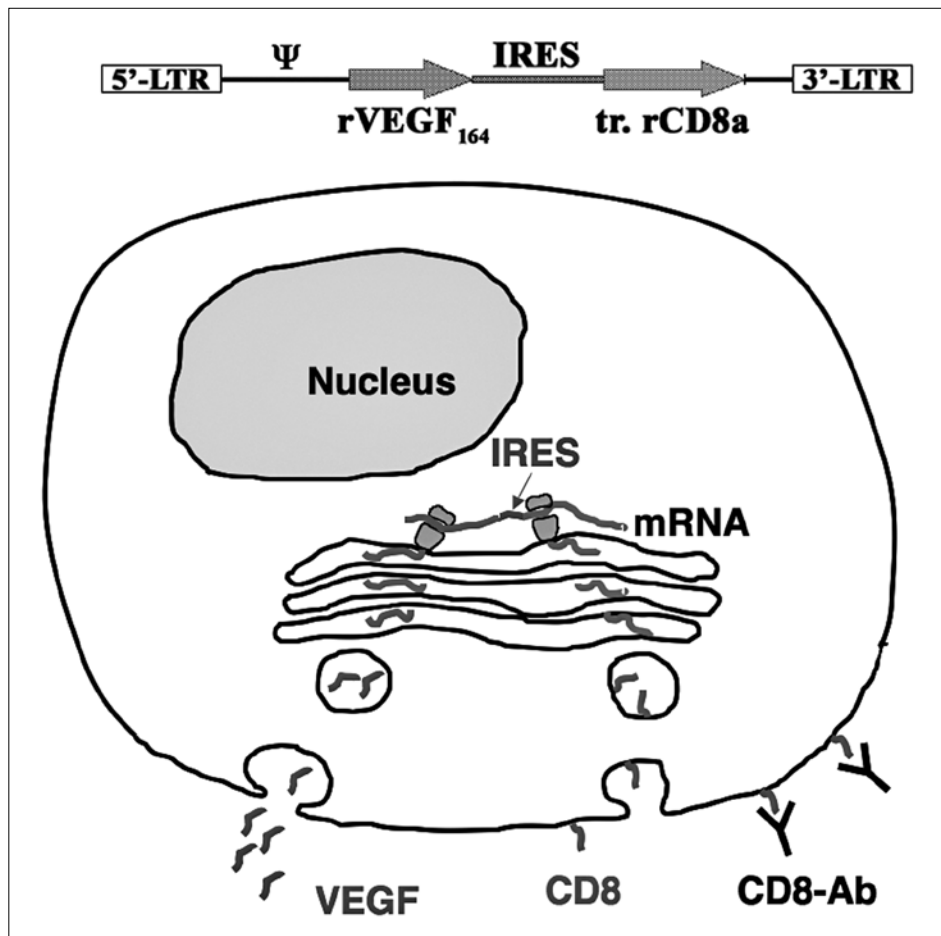


Figure 4. In order to purify by FACS myoblasts expressing a specific amount of VEGF, the VEGF gene was coupled to that of a truncated form of CD8a through an Internal Ribosomal Entry Site (IRES) sequence in a bicistronic retroviral construct. After infection of the primary myoblasts, both genes are co-expressed in each cell at a fixed ratio from the bicistronic mRNA, so that the amount of VEGF secreted (left side) is correlated to that of truncated CD8a retained on the cell surface (right side), which can be quantified by staining with an anti-CD8a antibody (CD8-Ab). (Art by Dr. T. Wolff)

angiogenesis both in normal and ischemic muscle, while angioma growth was completely avoided. In preparation for a future clinical application, we are currently establishing this technology for the use of primary human myoblasts, isolated from individual patients and genetically modified *in vitro* to express human VEGF by the use of safer and clinically-approved gene delivery vectors based on lentiviruses.

In a separate project, in collaboration with Dr. Ludovic Melly and Prof. Friedrich Eckstein (Cardiac Surgery, USB), we are investigating the possibility of inducing controlled angiogenesis in a model of myocardial infarction with a similar cell-and-gene-therapy approach. The goal is to restore blood flow to areas of tissue where cardiac cells are still alive, but not working properly due to insufficient oxygen and nutrient supply. Because myoblasts have been shown to possibly induce serious disturbances of the rhythm (arrhythmias) when implanted in the heart, we are genetically modifying

and FACS-purifying human multipotent mesenchymal progenitors from adipose tissue to provide controlled VEGF expression in the heart.

A further situation where insufficient vascularization represents a fundamental bottleneck for the development of novel therapies is tissue engineering. In fact, when progenitor cells, for example osteo-progenitors capable to regenerate bone, are seeded on appropriate scaffolds, they will survive and differentiate *in vivo* only if reached by the host's vascular supply, which takes place only for constructs up to a few millimeters in size, whereas clinically relevant constructs need to reach dimensions of several centimeters. In collaboration with Dr. René Largo and Prof. Dirk Schäfer (Plastic and Reconstructive Surgery, USB), we are pursuing strategies to achieve rapid vascularization of the inner core of clinical-size osteogenic grafts in order to improve bone formation, by using transduced bone marrow-derived osteoprogenitors expressing controlled VEGF levels.

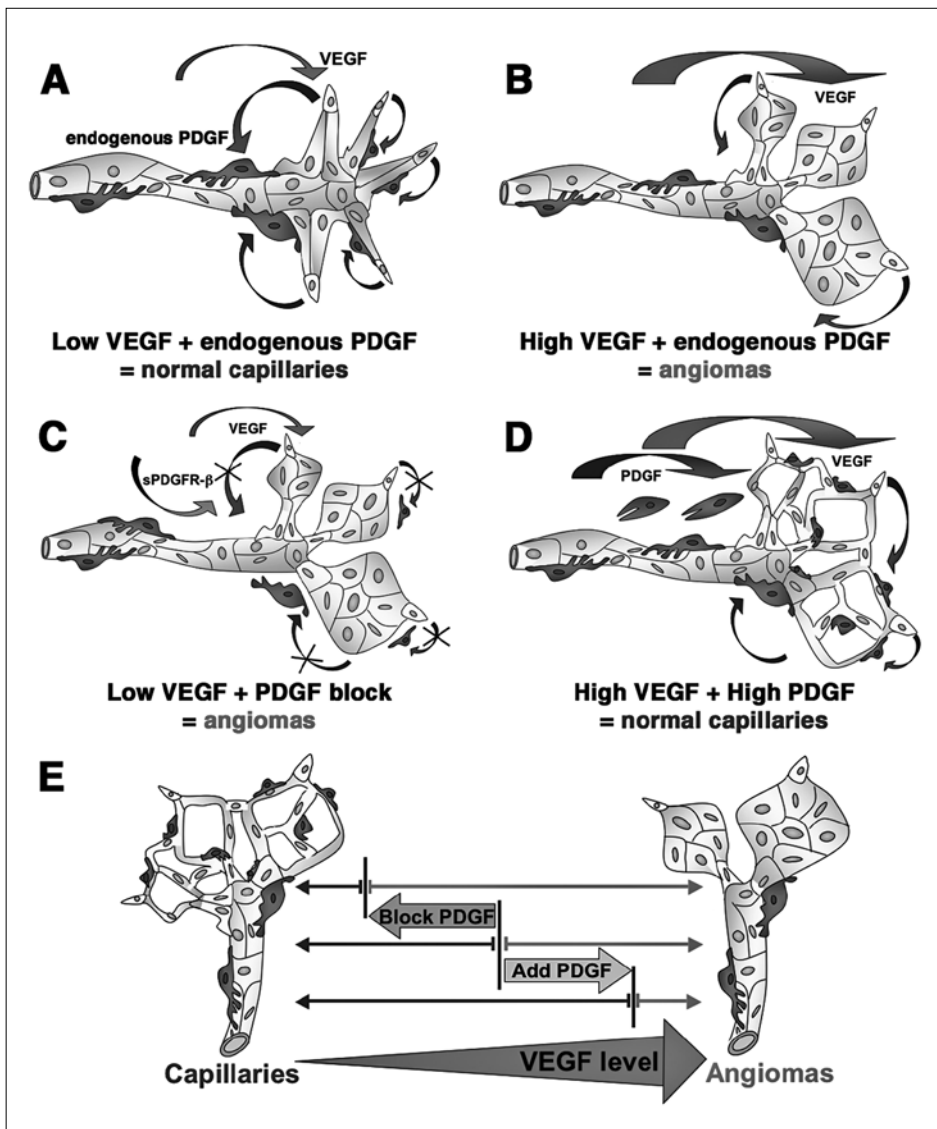


Figure 5. Model for PDGF-BB modulation of VEGF dose-dependent angiogenesis. Normal mature capillaries are induced by microenvironmental VEGF levels up to a discrete threshold, above which angiomas grow instead. However, this threshold depends on the balance between VEGF and PDGF-BB signaling and it can shift to higher or lower VEGF levels if endogenous PDGF-BB signaling is stimulated or blocked, respectively. (Art by Dr. N. Di Maggio)

Co-expression of VEGF and PDGF-BB

VEGF can induce normal capillaries at low levels and angiomas at high levels and the transition between normal and aberrant angiogenesis does not occur gradually, but rather as an all-or-none response across a threshold VEGF dose. However, we found that such threshold is not an intrinsic property of VEGF dose, but depends on the balance between VEGF-induced endothelial stimulation and vascular maturation mediated by pericyte recruitment by Platelet-Derived Growth Factor-BB (PDGF-BB; Figure 5). In particular, we found that if VEGF and PDGF-BB are co-expressed in a coordinated fashion from myoblasts infected with a single retroviral vector, so that each transduced cells expresses the same

ratio of the two factors, only homogeneous normal angiogenesis is induced despite heterogeneous and high VEGF expression levels. Therefore, we are testing the hypothesis that PDGF-BB co-expression can overcome the requirement for control on the microenvironmental level distribution of VEGF and make direct gene therapy approaches with adeno- and adeno-associated-viral vectors, which are unsuitable to VEGF alone, safe and efficacious.

Other projects are aimed at understanding the mechanism by which PDGF-BB modulates VEGF-induced angiogenesis and specifically at how the early phases of vascular induction and remodelling are differentially regulated in the crucial first few days after factor

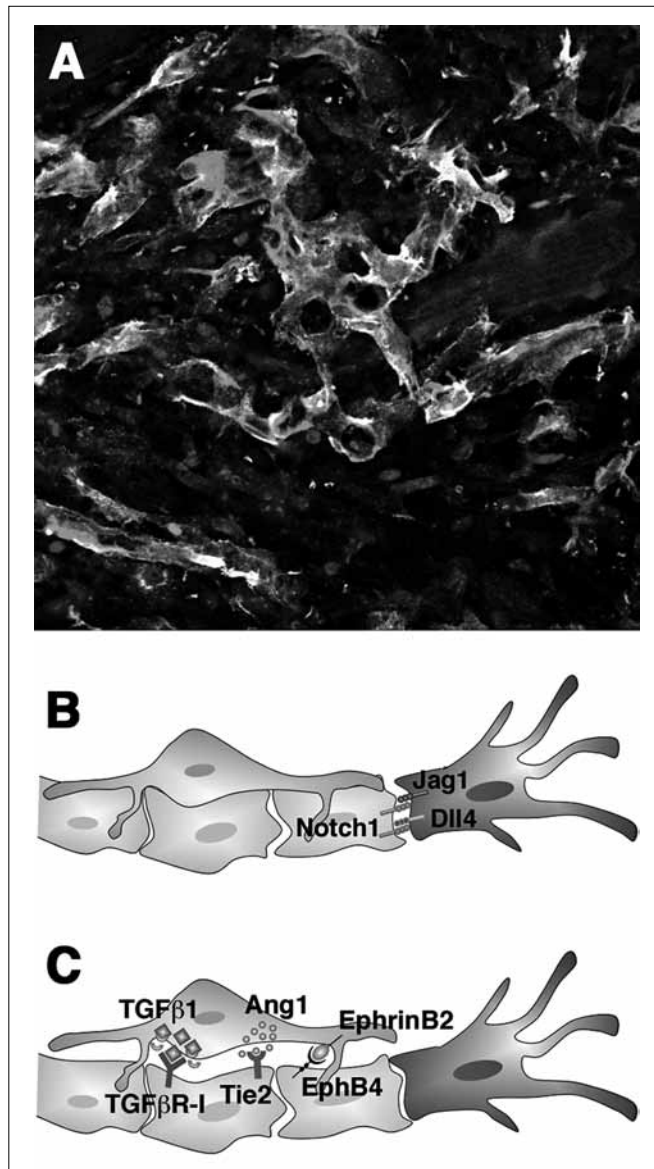


Figure 6. (A) In the first few days after the start of VEGF expression, endothelial cells (stained here in red for the marker CD31) initially form transient vascular structures that are then remodelled to either normal capillaries or aberrant angiomas. The remodeling stage is controlled by the association with pericytes (stained in green for the marker NG2). (B-C) These complex morphogenetic events involve the coordinated exchange of signals both between neighbouring endothelial cells, especially through the Notch pathway, to determine which will become tip (in red) and which stalk cells (in yellow), and between pericytes (in orange) and endothelium.

expression (Figure 6a). In this setting, we are investigating whether dose-dependent co-expression prevents angioma growth and leads instead to normal capillary networks by regulating the Notch signaling pathway, which controls the endothelial cell fate decision to become a sprouting tip cell or a circumferentially growing

stalk cell (Figure 6b). On the other hand, we also aim to dissect the role of pericytes and specific pericyte-mediated signaling pathways in the normalization of VEGF-induced angiogenesis by PDGF-BB (Figure 6c). For this purpose, we are co-expressing truncated and secreted forms of the specific receptors (so called “Factor-Traps”) together with specific levels of VEGF alone or together with PDGF-BB.

Combining these different approaches, we aim to understand which signals control the proper and physiological morphogenesis of new blood vessels in skeletal muscle, both in terms of factor dose, duration and mode of presentation in the angiogenic microenvironment. This knowledge is hoped to provide the basis for the rational design of biology-oriented strategies for therapeutic angiogenesis.

Andrea Banfi

Selected publications by DBM members

Below you can find the abstracts of recent articles published by members of the DBM. The abstracts are grouped according to the impact factor of the journal where the work appeared. To be included, the papers must meet the following criteria:

1. The first author, last author or corresponding author (at least one of them) is a member of the DBM.
2. The DBM affiliation must be mentioned in the authors list as it appeared in 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 primarily concentrating on original articles. 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.

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Deadline for the next issue is October 31, 2010.

Blood

blood

115, 3960–3965, 2010

IF 10,6

Natural killer–cell receptor polymorphisms and posttransplantation non-Hodgkin lymphoma

M. Stern^{1,2}, G. Opelz³, B. Döhler³ and C. Hess^{1,4}

Abstract:

Posttransplantation non-Hodgkin lymphoma is a life-threatening complication after transplantation. Although pharmacologically suppressed adaptive immunity plays a major role in its development, the role of innate immunity in posttransplantation lymphoma is unknown. We assessed the 158 V/F polymorphism in the Fc- γ receptor 3A gene (*FCGR3A*), killer cell immunoglobulin-like receptor (KIR) genotype, KIR ligand status, and a single nucleotide polymorphism affecting the production of interferon- γ (IFN- γ ; +874 A/T) in 236 patients with posttransplantation lymphoma reported to the Collaborative Transplant Study. In addition, polymorphisms in the interleukin-10 (IL-10) and transforming growth factor- β (TGF- β) genes previously associated with lymphoma development were also typed. Using a split-cohort approach, gene/allele fre-

quency was related to the 5-year patient survival after the diagnosis of lymphoma and compared with 100 control solid organ transplant recipients. *FCGR3A* and KIR genotype significantly influenced survival after diagnosis of posttransplantation lymphoma: the hazard of dying was reduced in homozygous carriers of the high-affinity V allele (hazard ratio 0.49, 95% confidence interval 0.29–0.82, $P = .006$), whereas carrying a genotype including *KIR2DL2/KIR2DS2* increased the risk of dying (hazard ratio 1.49, 95% confidence interval 1.07–2.05, $P = .02$). KIR ligands and cytokine polymorphisms had no effect on survival. None of the genetic loci analyzed emerged as risk factors for lymphoma development.

¹ Immunobiology Laboratory, Department of Biomedicine, University Hospital Basel, Basel, Switzerland

² Stem Cell Transplant Team, University Hospital Basel, Basel, Switzerland

³ Collaborative Transplant Study, University of Heidelberg, Heidelberg, Germany

⁴ Medical Outpatient Department, University Hospital Basel, Basel, Switzerland

T-cadherin is present on endothelial microparticles and is elevated in plasma in early atherosclerosis

M. Philippova¹, Y. Suter², S. Toggweiler², A. W. Schoenenberger³, M. B. Joshi¹, E. Kyriakakis¹, P. Erne² and T. J. Resink¹

Abstract:

Aims: The presence of endothelial cell (EC)-derived surface molecules in the circulation is among hallmarks of endothelial activation and damage *in vivo*. Previous investigations suggest that upregulation of T-cadherin (T-cad) on the surface of ECs may be a characteristic marker of EC activation and stress. We investigated whether T-cad might also be shed from ECs and in amounts reflecting the extent of activation or damage.

Methods and results: Immunoblotting showed the presence of T-cad protein in the culture medium from normal proliferating ECs and higher levels in the medium from stressed/apoptotic ECs. Release of T-cad into the circulation occurs *in vivo* and in association with endothelial dysfunction. Sandwich ELISA revealed negligible T-cad protein in the plasma of healthy volunteers (0.90 ± 0.90 ng/mL, $n = 30$), and increased levels in the plasma from patients with non-significant atherosclerosis (9.23 ± 2.61 ng/mL, $n = 63$) and patients with chronic coronary artery disease (6.93 ± 1.31 ng/mL, $n = 162$). In both patient groups there was a significant ($P = 0.043$) dependency of T-cad and degree of endothelial dysfunction as measured by reactive hyperaemia peripheral tonometry. Flow cytometry

analysis showed that the major fraction of T-cad was released into the EC culture medium and the plasma as a surface component of EC-derived annexin V- and CD144/CD31-positive microparticles (MPs). Gain-of-function and loss-of-function studies demonstrate that MP-bound T-cad induced Akt phosphorylation and activated angiogenic behaviour in target ECs via homophilic-based interactions.

Conclusion: Our findings reveal a novel mechanism of T-cad-dependent signalling in the vascular endothelium. We identify T-cad as an endothelial MP antigen *in vivo* and demonstrate that its level in plasma is increased in early atherosclerosis and correlates with endothelial dysfunction.

¹ Department of Biomedicine, Laboratory for Signal Transduction, Basel University Hospital, ZLF 316 Hebelstrasse 20, CH 4031, Basel, Switzerland

² Division of Cardiology, Kantonsspital Luzern, Luzern, Switzerland

³ Department of Geriatrics and General Internal Medicine, University of Bern Hospital, Inselspital Bern, Switzerland

Distinct Roles of Hand2 in Initiating Polarity and Posterior Shh Expression during the Onset of Mouse Limb Bud Development

A. Galli¹, D. Robay¹, M. Osterwalder¹, X. Bao², J.D. Bénazet¹, M. Tariq³, R. Paro^{3,4}, S. Mackem² and R. Zeller¹

Abstract:

The polarization of nascent embryonic fields and the endowment of cells with organizer properties are key to initiation of vertebrate organogenesis. One such event is antero-posterior (AP) polarization of early limb buds and activation of morphogenetic Sonic Hedgehog (SHH) signaling in the posterior mesenchyme, which in turn promotes outgrowth and specifies the pentadactylous autopod. Inactivation of the *Hand2* transcriptional regulator from the onset of mouse forelimb bud development disrupts establishment of posterior identity and *Shh* expression, which results in a skeletal phenotype identical to *Shh* deficient limb buds. In wild-type limb buds, *Hand2* is part of the protein complexes containing *Hoxd13*, another essential regulator of *Shh* activation in limb buds. Chromatin immunopre-

cipitation shows that *Hand2*-containing chromatin complexes are bound to the far upstream *cis*-regulatory region (ZRS), which is specifically required for *Shh* expression in the limb bud. Cell-biochemical studies indicate that *Hand2* and *Hoxd13* can efficiently transactivate gene expression via the ZRS, while the *Gli3* repressor isoform interferes with this positive transcriptional regulation. Indeed, analysis of mouse forelimb buds lacking both *Hand2* and *Gli3* reveals the complete absence of antero-posterior (AP) polarity along the entire proximo-distal axis and extreme digit polydactyly without AP identities. Our study uncovers essential components of the transcriptional machinery and key interactions that set-up limb bud asymmetry upstream of establishing the SHH signaling limb bud organizer.

¹ Developmental Genetics, Department of Biomedicine, University of Basel, Basel, Switzerland

² Cancer and Developmental Biology Laboratory, National Cancer Institute, Bethesda, Maryland, United States of America

³ Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland

⁴ Faculty of Sciences, University of Basel, Basel, Switzerland

PNAS

PNAS

107, 13924–13929, 2010

IF 9,4

NMDA receptor-dependent GABA_B receptor internalization via CaMKII phosphorylation of serine 867 in GABA_{B1}

N. Guetg¹, S. A. Aziz¹, N. Holbro², R. Turecek¹, T. Rose², R. Seddik¹, M. Gassmann¹, S. Moes⁴, P. Jenoe⁴, T. G. Oertner², E. Casanova¹ and B. Bettler¹

Abstract:

GABA_B receptors are the G-protein-coupled receptors for GABA, the main inhibitory neurotransmitter in the brain. GABA_B receptors are abundant on dendritic spines, where they dampen postsynaptic excitability and inhibit Ca²⁺ influx through NMDA receptors when activated by spillover of GABA from neighboring GABAergic terminals. Here, we show that an excitatory signaling cascade enables spines to counteract this GABA_B-mediated inhibition. We found that NMDA application to cultured hippocampal neurons promotes dynamin-dependent endocytosis of GABA_B receptors. NMDA-dependent internalization of GABA_B receptors requires activation of Ca²⁺/Calmodulin-dependent protein kinase II (CaMKII), which associates with GABA_B receptors in vivo and phosphorylates serine 867 (S867) in the intracellular C terminus of the GABA_{B1} subunit. Blockade of either CaMKII or phosphorylation of S867 renders GABA_B receptors refractory to NMDA-mediated internalization. Time-lapse two-photon imaging of organotypic hippocampal slices reveals that activation of NMDA receptors removes GABA_B receptors within minutes from the surface of dendritic spines and shafts. NMDA-dependent S867 phosphorylation and internalization is predominantly detectable with the GABA_{B1B} subunit isoform, which is the isoform

that clusters with inhibitory effector K⁺ channels in the spines. Consistent with this, NMDA receptor activation in neurons impairs the ability of GABA_B receptors to activate K⁺ channels. Thus, our data support that NMDA receptor activity endocytoses postsynaptic GABA_B receptors through CaMKII-mediated phosphorylation of S867. This provides a means to spare NMDA receptors at individual glutamatergic synapses from reciprocal inhibition through GABA_B receptors.

¹ Department of Biomedicine, Institute of Physiology, Pharmazentrum, University of Basel, 4056 Basel, Switzerland

² Friedrich Miescher Institute for Biomedical Research, 4058 Basel, Switzerland

³ Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, 142 20 Prague, Czech Republic

⁴ Biozentrum, University of Basel, 4056 Basel, Switzerland

Human Molecular Genetics

HUMAN
MOLECULAR
GENETICS

19, 2936–2946, 2010

IF 7,4

Methylation profile of *TP53* regulatory pathway and mtDNA alterations in breast cancer patients lacking *TP53* mutations

Z. Barekati¹, R. Radpour¹, C. Kohler¹, B. Zhang¹, P. Toniolo^{2,3}, P. Lenner⁴, Q. Lv⁵, H. Zheng^{6,7} and X. Y. Zhong¹

Abstract:

The present study investigated promoter hypermethylation of *TP53* regulatory pathways providing a potential link between epigenetic changes and mitochondrial DNA (mtDNA) alterations in breast cancer patients lacking a *TP53* mutation. The possibility of using the cancer-specific alterations in serum samples as a blood-based test was also explored. Triple-matched samples (cancerous tissues, matched adjacent normal tissues and serum samples) from breast cancer patients were screened for *TP53* mutations, and the promoter methylation profile of *P14^{ARF}*, *MDM2*, *TP53* and *PTEN* genes was analyzed as well as mtDNA alterations, including D-loop mutations and mtDNA content. In the studied cohort, no mutation was found in *TP53* (DNA-binding domain). Comparison of *P14^{ARF}* and *PTEN* methylation patterns showed significant hypermethylation levels in tumor tissues ($P < 0.05$ and < 0.01 , respectively) whereas the *TP53* tumor suppressor gene was not hypermethylated ($P < 0.511$). The proportion of *PTEN* methylation was significantly higher in serum than in the normal tissues and it has a significant correlation to tumor tissues ($P < 0.05$). mtDNA analysis revealed 36.36% somatic and 90.91% germline mutations in the D-loop region and also significant mtDNA depletion in tumor

tissues ($P < 0.01$). In addition, the mtDNA content in matched serum was significantly lower than in the normal tissues ($P < 0.05$). These data can provide an insight into the management of a therapeutic approach based on the reversal of epigenetic silencing of the crucial genes involved in regulatory pathways of the tumor suppressor *TP53*. Additionally, release of significant aberrant methylated *PTEN* in matched serum samples might represent a promising biomarker for breast cancer.

¹ Laboratory for Gynecological Oncology, Women's Hospital/Department of Biomedicine, University of Basel, Switzerland

² Department of Obstetrics & Gynecology, New York University School of Medicine, New York, USA

³ Institute Universitaire de Médecine Sociale et Préventive, CHUV, Lausanne, Switzerland

⁴ Department of Oncology, Umeå University Hospital, S-90185 Umeå, Sweden

⁵ Department of Breast Surgery,

⁶ Department of Oncology, State Key Laboratory of Biotherapy and Cancer Center and

⁷ Laboratory of Molecular Diagnosis of Cancer, West China Hospital/West China School of Medicine, Sichuan University, Chengdu, China

The Journal of Neuroscience

The Journal of Neuroscience

30, 10233–10242, 2010

IF 7.2

Fast Sodium Channel Gating Supports Localized and Efficient Axonal Action Potential Initiation

C. Schmidt-Hieber^{1,2} and J. Bischofberger^{2,3}

Abstract:

Action potentials (APs) are initiated in the proximal axon of most neurons. In myelinated axons, a 50-times higher sodium channel density in the initial segment compared to the soma may account for this phenomenon. However, little is known about sodium channel density and gating in proximal unmyelinated axons. To study the mechanisms underlying AP initiation in unmyelinated hippocampal mossy fibers of adult mice, we recorded sodium currents in axonal and somatic membrane patches. We

demonstrate that sodium channel density in the proximal axon is 5 times higher than in the soma. Furthermore, sodium channel activation and inactivation are 2 times faster. Modeling revealed that the fast activation localized the initiation site to the proximal axon even upon strong synaptic stimulation, while fast inactivation contributed to energy-efficient membrane charging during APs. Thus, sodium channel gating and density in unmyelinated mossy fiber axons appear to be specialized for robust AP initiation and propagation with minimal current flow.

¹ Wolfson Institute for Biomedical Research, University College London, London, WC1E 6BT, United Kingdom,

² Physiologisches Institut der Universität Freiburg, Abteilung I, D-79108 Freiburg, Germany

³ Department of Biomedicine, Physiological Institute, University of Basel, CH-4056 Basel, Switzerland

The Journal of Immunology

The Journal of
Immunology

183, 3512–3521, 2009

IF 5.6

Autoantibodies against Complement C1q Specifically Target C1q Bound on Early Apoptotic Cells

C. Bigler¹, M. Schaller¹, I. Perahud¹, M. Osthoff^{1,2} and M. Trendelenburg^{1,2}

Abstract:

Autoantibodies against complement C1q (anti-C1q) are frequently found in patients with systemic lupus erythematosus (SLE). They strongly correlate with the occurrence of severe lupus nephritis, suggesting a pathogenic role in SLE. Because anti-C1q are known to recognize a neoepitope on bound C1q, but not on fluid-phase C1q, the aim of this study was to clarify the origin of anti-C1q by determining the mechanism that renders C1q antigenic. We investigated anti-C1q from serum and purified total IgG of patients with SLE and hypocomplementemic urticarial vasculitis as well as two monoclonal human anti-C1q Fab from a SLE patient generated by phage display. Binding characteristics, such as their ability to recognize C1q bound on different classes of Igs, on immune complexes, and on

cells undergoing apoptosis, were analyzed. Interestingly, anti-C1q did not bind to C1q bound on Igs or immune complexes. Neither did we observe specific binding of anti-C1q to C1q bound on late apoptotic/necrotic cells when compared with binding in the absence of C1q. However, as shown by FACS analysis and confocal microscopy, anti-C1q specifically targeted C1q bound on early apoptotic cells. Anti-C1q were found to specifically target C1q bound on cells undergoing apoptosis. Our observations suggest that early apoptotic cells are a major target of the autoimmune response in SLE and provide a direct link between human SLE, apoptosis, and C1q.

¹ Clinical Immunology Laboratory, University Hospital Basel, Basel, Switzerland

² Internal Medicine, University Hospital Basel, Basel, Switzerland

Ceramic materials lead to underestimated DNA quantifications: a method for reliable measurements

E. Piccinini, N. Sadr and I. Martin

Abstract:

Abstract: In the context of investigating cell-material interactions or of material-guided generation of tissues, DNA quantification represents an elective method to precisely assess the number of cells attached or embedded within different substrates.

Nonetheless, nucleic acids are known to electrostatically bind to ceramics, a class of materials commonly employed in orthopaedic implants and bone tissue engineering scaffolds. This phenomenon is expected to lead to a relevant underestimation of the DNA amount, resulting in erroneous experimental readouts. The present work aims at (i) investigating the effects of DNA-ceramic bond occurrence on DNA quantification, and (ii) developing a method to reliably extract and accurately quantify DNA in ceramic-containing specimens.

A cell-free model was adopted to study DNA-ceramic binding, highlighting an evident DNA loss (up to 90%) over a wide range of DNA/ceramic ratios (w/w). A phosphate buffer-based (800mM) enzymatic extraction

protocol was developed and its efficacy in terms of reliable DNA extraction and measurement was confirmed with commonly used fluorometric assays, for various ceramic substrates. The proposed buffered DNA extraction technique was validated in a cell-based experiment showing 95% DNA retrieval in a cell seeding experiment, demonstrating a 3.5-fold increase in measured DNA amount as compared to a conventional enzymatic extraction protocol.

In conclusion, the proposed phosphate buffer method consistently improves the DNA extraction process assuring unbiased analysis of samples and allowing accurate and sensitive cell number quantification on ceramic containing substrates.

Departments of Surgery and of Biomedicine, University Hospital Basel, Basel, Switzerland

Frequent Calcium Oscillations Lead to NFAT Activation in Human Immature Dendritic Cells

M. Vukcevic¹, F. Zorzato^{1,3}, G. Spagnoli² and S. Treves^{1,3}

Abstract:

Spontaneous Ca^{2+} oscillations have been observed in a number of excitable and non-excitable cells, but in most cases their biological role remains elusive. In the present study we demonstrate that spontaneous Ca^{2+} oscillations occur in immature human monocyte-derived dendritic cells but not in dendritic cells stimulated to undergo maturation with lipopolysaccharide or other toll like-receptor agonists. We investigated the mechanism and role of spontaneous Ca^{2+} oscillations in immature dendritic cells and found that they are mediated by the inositol 1,4,5-trisphosphate receptor as they were blocked by pretreatment of cells with the inositol 1,4,5-trisphosphate receptor antagonist Xestospingon C and

2-aminoethoxydiphenylborate. A component of the Ca^{2+} signal is also due to influx from the extracellular environment and may be involved in maintaining the level of the intracellular Ca^{2+} stores. As to their biological role, our results indicate that they are intimately linked to the “immature” phenotype and are associated with the translocation of the transcription factor NFAT into the nucleus. In fact, once the Ca^{2+} oscillations are blocked with 2-aminoethoxydiphenylborate or by treating the cells with lipopolysaccharide, NFAT remains cytoplasmic. The results presented in this report provide novel insights into the physiology of monocyte-derived dendritic cells and into the mechanisms involved in maintaining the cells in the immature stage.

¹ Departments of Anaesthesia and Biomedicine, Basel University Hospital, Basel 4031, Switzerland

² Institute of Surgical Research, Basel University Hospital, Basel 4031, Switzerland

³ Department of Experimental and Diagnostic Medicine, General Pathology Section, University of Ferrara, Ferrara 44100, Italy

Aids


 AIDS
 Official Journal of the International AIDS Society

24, 2287–2289, 2010

IF 4,9

Virosomal influenza-vaccine induced immunity in HIV-infected individuals with high versus low CD4⁺ T-cell counts: clues towards a rational vaccination strategy

S. Fritz¹, E. Mossdorf², B. Durovic¹, G. Zenhausern¹, A. Conen², I. Steffen⁴, M. Battegay², R. Nüesch² and C. Hess^{1,3}

Abstract:

In a prospective influenza-vaccination trial we show that HIV-infected individuals with CD4⁺ T-cell counts less than 350 µl were distinct from HIV-infected individuals with more than 350 CD4⁺ T-cell counts/µl, and from HIV-negative individuals, in that an influenza-specific immunoglobulin M-response was absent and expansion of interferon-γ-secreting CD4⁺ T cells was impaired. By contrast, immunoglobulin G-responses were induced in all study groups. These data suggest that establishing broad influenza-specific (immunoglobulin G) B-cell memory prior to severe immunodeficiency is important.

¹ Immunobiology Laboratory, Department of Biomedicine, Basel University, Basel, Switzerland

² Division of Infectious Diseases and Hospital Epidemiology, Basel, Switzerland

³ Medical Outpatient Department, University Hospital Basel, Basel, Switzerland

⁴ Institute for Medical Microbiology, Basel University, Basel, Switzerland

British Journal of Dermatology

BJD

British Journal of Dermatology

163, 353–363, 2010

IF 4,3

T-cadherin loss induces an invasive phenotype in human keratinocytes and squamous cell carcinoma (SCC) cells in vitro and is associated with malignant transformation of cutaneous SCC in vivo

D. Pfaff¹, M. Philippova¹, S.A. Buechner², K. Maslova¹, T. Mathys², P. Erne³ and T.J. Resink¹

Abstract:

Background: Cadherins play important roles in controlling keratinocyte growth, differentiation and survival. Atypical glycosylphosphatidylinositol-anchored T-cadherin (T-cad) is highly expressed in the basal keratinocyte layer of skin. The role of T-cad in keratinocyte biology and pathology is unclear.

Objectives: To define the role of T-cad in the pathogenesis of cutaneous squamous cell carcinoma (SCC) through gain-of-function and loss-of-function studies in vitro and through examination of T-cad expression patterns in human cutaneous SCC specimens in relation to histological classification of degree of tumour differentiation.

Methods: In vitro studies employed lentiviral-mediated overexpression/silencing of T-cad in normal human keratinocyte (HaCaT) and SCC (A431) cell lines, monolayer and multicellular spheroid culture models, cell morphology analyses and assays of random motility and invasion. Immunohistochemistry was performed on skin specimens from patients with actinic keratosis, Bowen disease or SCC.

Results: In vitro, silencing of T-cad induced a morphologically elongated and disorganized cell phenotype, increased random motility and markedly enhanced invasive potential. Overexpression of T-cad induced a morphologically spread and compact cell phenotype and blunted invasive potential. In vivo, regional loss of T-cad expression was more frequent and prominent in SCC classified as moderately-to-poorly differentiated than in SCC classified as well differentiated. However, in both categories aberrant and/or absence of T-cad expression was associated with histological features of a potentially more malignant and invasive phenotype of cutaneous SCC.

Conclusions: T-cad is a controlling determinant of SCC phenotype and invasive behaviour and its loss is associated with the process of malignant transformation from noninvasive to invasive SCC.

¹ Department of Biomedicine, Laboratory for Signal Transduction, Lab. 316, Basel University Hospital, CH 4031 Basel, Switzerland

² Blumenrain 20, CH 4051 Basel, Switzerland

³ Division of Cardiology, Kantonsspital Luzern, CH 6000 Lucerne, Switzerland

Biochemical Pharmacology

Biochemical
Pharmacology

79, 1200–1209, 2010

IF 4,3

Effect of simvastatin on cholesterol metabolism in C2C12 myotubes and HepG2 cells, and consequences for statin-induced myopathy

P. J. Mullen¹, B. Lüscher¹, H. Scharnagl², S. Krähenbühl¹ and K. Brecht¹

Abstract:

The mechanism of statin-induced skeletal muscle myopathy is poorly understood. We investigated how simvastatin affects cholesterol metabolism, ubiquinone levels, and the prenylation and N-linked glycosylation of proteins in C2C12 myotubes. We used liver HepG2 cells for comparison, as their responses to statins are well-characterized in terms of their cholesterol metabolism (in contrast to muscle cells), and statins are well-tolerated in the liver. Differences between the two cell lines could indicate the mechanism behind statin-induced myopathy. Simvastatin reduced de novo cholesterol production in C2C12 myotubes by 95% after 18 h treatment. The reduction was 82% in the HepG2 cells. Total cholesterol pools,

however, remained constant in both cell lines. Simvastatin treatment similarly did not affect total ubiquinone levels in the myotubes, unlike in HepG2 cells (22% reduction in CoQ10). Statin treatment reduced levels of Ras and Rap1 prenylation in both cell lines, whereas N-linked glycosylation was only affected in C2C12 myotubes (21% reduction in rate). From these observations, we conclude that total cholesterol and ubiquinone levels are unlikely to be involved in statin-mediated myopathy, but reductions in protein prenylation and especially N-linked glycosylation may play a role. This first comparison of the responses to simvastatin between liver and skeletal muscle cell lines may be important for future research directions concerning statin-induced myopathy.

¹ Division of Clinical Pharmacology & Toxicology, Department of Research, University Hospital Basel, Hebelstrasse 20, CH-4031 Basel, Switzerland

² Department of Clinical Chemistry, University of Graz, Graz, Austria

Cellular Signalling

Cellular
Signalling

22, 1308–1316, 2010

IF 4,1

T-cadherin attenuates the PERK branch of the unfolded protein response and protects vascular endothelial cells from endoplasmic reticulum stress-induced apoptosis

E. Kyriakakis¹, M. Philippova¹, M. B. Joshi¹, D. Pfaff¹, V. Bochkov², T. Afonyushkin², P. Erne³ and T. J. Resink¹

Abstract:

Endoplasmic reticulum (ER) stress activated by perturbations in ER homeostasis induces the unfolded protein response (UPR) with chaperon Grp78 as the key activator of UPR signalling. The aim of UPR is to restore normal ER function; however prolonged or severe ER stress triggers apoptosis of damaged cells to ensure protection of the whole organism. Recent findings support an association of ER stress-induced apoptosis of vascular cells with cardiovascular pathologies. T-cadherin (T-cad), an atypical glycosylphosphatidylinositol-anchored member of the cadherin superfamily is upregulated in atherosclerotic lesions. Here we investigate the ability of T-cad to influence UPR signalling and endothelial cell (EC) survival during ER stress. EC were treated with a variety of ER stress-inducing compounds (thapsigargin, dithiothreitol, brefeldin A, tunicamycin, A23187 or homocysteine) and induction of ER stress validated by increases in levels of UPR signalling molecules Grp78 (glucose-regulated protein of 78 kDa), phospho-eIF2 α (phosphorylated eukaryotic initiation factor 2 α) and CHOP (C/EBP homologous protein). All compounds also increased T-cad mRNA and protein levels. Overexpression or silencing of T-cad in EC respectively attenuated or amplified the ER stress-induced

increase in phospho-eIF2 α , Grp78, CHOP and active caspases. Effects of T-cad-overexpression or T-cad-silencing on ER stress responses in EC were not affected by inclusion of either N-acetylcysteine (reactive oxygen species scavenger), LY294002 (phosphatidylinositol-3-kinase inhibitor) or SP6000125 (Jun N-terminal kinase inhibitor). The data suggest that upregulation of T-cad on EC during ER stress attenuates the activation of the proapoptotic PERK (PKR (double-stranded RNA-activated protein kinase)-like ER kinase) branch of the UPR cascade and thereby protects EC from ER stress-induced apoptosis.

¹ Department of Biomedicine, Laboratory for Signal Transduction, Basel University Hospital, Hebelstrasse 20, CH 4031 Basel, Switzerland

² Center for Biomolecular Medicine and Pharmacology, Department of Vascular Biology and Thrombosis Research, Medical University of Vienna, Schwarzschanerstrasse 17, 1090 Vienna, Austria

³ Division of Cardiology, Cantonal Hospital Luzern, CH 6000 Luzern, Switzerland

Diabetes, Obesity and Metabolism

DIABETES, OBESITY
AND METABOLISM

12, 356–359, 2010

IF 4.1

Metformin induces glucose uptake in human preadipocyte-derived adipocytes from various fat depots

M. Fischer¹, K. Timper^{1,2}, T. Radimerski¹, K. Dembinski¹, D. M. Frey³, H. Zulewski^{1,2}, U. Keller^{1,2}, B. Müller⁴, M. Christ-Crain^{1,2} and J. Grisouard¹**Abstract:**

To evaluate the effect of metformin on basal and insulin-induced glucose uptake in subcutaneous and visceral preadipocyte-derived adipocytes from obese and non-obese patients, preadipocytes were obtained from subcutaneous and visceral fat depots during abdominal surgery. Differentiation efficiency was evaluated by measurement of intracellular triglyceride accumulation. Preadipocyte-derived adipocytes were treated with metformin (1 mM) for 24 h with or without the addition of insulin (100 nM) for 20 min and glucose uptake was measured. In cells from each donor, intracellular triglyceride accumulation was more abundant in subcutaneous preadipocyte-derived adipocytes than in visceral preadipocyte-derived adipocytes ($p < 0.001$). Insulin stimulated glucose uptake in subcutaneous preadipocyte-derived adipocytes from both non-obese and obese patients ($p < 0.001$ vs. basal). In visceral preadipocyte-derived adipocytes, insulin did not increase basal glucose uptake. In subcutaneous preadipocyte-derived adipocytes from non-obese and obese patients, metformin alone increased glucose uptake to 2.7 ± 0.2 ($p < 0.001$) and 2.1 ± 0.1 fold ($p < 0.001$) respectively. Metformin increased glucose uptake in visceral preadipocyte-derived adipocytes from non-obese (1.7

± 0.1 fold vs. basal, $p < 0.001$) and obese (2.0 ± 0.2 fold vs. basal, $p < 0.001$) patients. Combined treatment with metformin and insulin increased glucose uptake in subcutaneous preadipocyte-derived adipocytes from both non-obese and obese patients ($p < 0.001$ vs. insulin alone). In preadipocyte-derived adipocytes glucose uptake is induced by metformin independent of the fat depot origin of the preadipocytes (subcutaneous or visceral) and the obesity state of the patients (non-obese or obese). In adipocytes, metformin seems to induce glucose uptake independent of insulin suggesting an alternative mechanism of action of this drug.

¹ Department of Biomedicine, University Hospital Basel, CH-4031 Basel, Switzerland² Division of Endocrinology, Diabetes and Clinical Nutrition, University Hospital Basel, CH-4031 Basel, Switzerland³ Department of Surgery, Division of General Surgery and Surgical Research, University Hospital Basel, CH-4031 Basel, Switzerland⁴ Department of Internal Medicine, Kantonsspital Aarau, CH-5001 Aarau, Switzerland

Osteoarthritis and Cartilage

Osteoarthritis
and Cartilage

18, 1067–1076, 2010

IF 3.9

Are ankle chondrocytes from damaged fragments a suitable cell source for cartilage repair?

C. Candrian^{1,2}, S. Miot^{1,3}, F. Wolf^{1,3}, E. Bonacina⁴, S. Dickinson⁵, D. Wirz⁶, M. Jakob³, V. Valderrabano³, A. Barbero^{1,3} and I. Martin^{1,3}**Abstract:**

Objective: To characterize the post-expansion cartilage-forming capacity of chondrocytes harvested from detached fragments of osteochondral lesions (OCLs) of ankle joints (Damaged Ankle Cartilage Fragments, DACF), with normal ankle cartilage (NAC) as control.

Design: DACF were obtained from six patients (mean age: 35 years) with symptomatic OCLs of the talus, while NAC were from 10 autopsies (mean age: 55 years). Isolated chondrocytes were expanded for two passages and then cultured in pellets for 14 days or onto HYAFF®-11 meshes (FAB, Italy) for up to 28 days. Resulting tissues were assessed histologically, biochemically [glycosaminoglycan (GAG), DNA and type II collagen (CII)] and biomechanically.

Results: As compared to NAC, DACF contained significantly lower amounts of DNA (3.0-fold), GAG (5.3-fold) and CII (1.5-fold) and higher amounts of type I collagen (6.2-fold). Following 14 days of culture in pellets, DACF-chondrocytes generated tissues less intensely stained for

Safranin-O and CII, with significantly lower GAG contents (2.8-fold). After 28 days of culture onto HYAFF®-11, tissues generated by DACF-chondrocytes were less intensely stained for Safranin-O and CII, contained significantly lower amounts of GAG (1.9-fold) and CII (1.4-fold) and had lower equilibrium (1.7-fold) and dynamic pulsatile modulus (3.3-fold) than NAC-chondrocytes.

Conclusion: We demonstrated that DACF-chondrocytes have inferior cartilage-forming capacity as compared to NAC-chondrocytes, possibly resulting from environmental changes associated with trauma/disease. The study opens some reservations on the use of DACF-derived cells for the repair of ankle cartilage defects, especially in the context of tissue engineering-based approaches.

¹ Department of Biomedicine, University Hospital Basel, Switzerland² Department of Surgery, Ospedale Regionale di Lugano, Switzerland³ Department of Surgery, University Hospital Basel, Switzerland⁴ IRCCS Istituto Ortopedico Galeazzi, Milano, Italy⁵ Department of Cellular and Molecular Medicine, University of Bristol, School of Medical Sciences, University Walk, UK⁶ Laboratory for Orthopaedic Biomechanics, University of Basel Faculty of Medicine, Switzerland

Regulation of Podocyte Survival and Endoplasmic Reticulum Stress by Fatty Acids

J. Sieber¹, M. T. Lindenmeyer², K. Kampe¹, K. N. Campbell³, C. D Cohen², H. Hopfer¹, P. Mundel³ and A. W. Jehle¹

Abstract:

Apoptosis of podocytes is considered critical in the pathogenesis of diabetic nephropathy (DN). Free fatty acids (FFAs) are critically involved in the pathogenesis of diabetes mellitus type 2, in particular the regulation of pancreatic β -cells survival. The objectives of this study were to elucidate the role of palmitic acid, palmitoleic, and oleic acid in the regulation of podocyte cell death and endoplasmic reticulum (ER) stress. We show that palmitic acid increases podocyte cell death, both apoptosis and necrosis of podocytes in a dose and time-dependent fashion. Palmitic acid induces podocyte ER stress leading to an unfolded protein response

(UPR) as reflected by the induction of the ER chaperon immunoglobulin heavy chain binding protein (BiP) and proapoptotic C/EBP (CCAAT/enhancer binding protein) homologous protein (CHOP) transcription factor. Of note, the monounsaturated palmitoleic and oleic acid can attenuate the palmitic acid-induced upregulation of CHOP, thereby preventing cell death. Similarly, gene silencing of CHOP protects against palmitic acid induced podocyte apoptosis. Our results offer a rationale for interventional studies aimed at testing whether dietary shifting of the FFA balance towards unsaturated FFAs can delay the progression of DN.

¹ Department of Biomedicine, Molecular Nephrology, University Hospital, Basel, Switzerland

² Institute of Physiology with Center of Integrative Human Physiology, University of Zürich, Zürich, Switzerland

³ Division of Nephrology, University Hospital Zürich, Zürich, Switzerland

⁴ Department of Medicine, University of Miami, Miller School of Medicine, Miami, Florida, USA

⁵ Institute of Clinical Pathology, University Hospital, Basel, Switzerland,

⁶ Department of Internal Medicine, Kantonsspital Bruderholz, University of Basel, Basel, Switzerland

Activated endothelial cells induce neutrophil extracellular traps and are susceptible to NETosis-mediated cell death

A. K. Gupta¹, M. B. Joshi², M. Philippova², P. Erne³, P. Hasler⁴, S. Hahn¹ and T. J. Resink²

Abstract:

Neutrophil interaction with activated endothelial cells (EC) is required for transmigration. We examined consequences of this interaction on NETosis. Co-culture of activated EC with neutrophils induced neutrophil extracellular trap (NET) formation, which was partially dependent on production of IL-8 by activated EC. Extended neutrophil/EC co-culture resulted in EC damage, which could be abrogated by inclusion of either diphenyl-eneiodonium to inhibit the NADPH oxidase pathway required for NETosis, or DNase to disrupt NETs. These findings offer new insight into mechanisms whereby NETs trigger damage to the endothelium in sepsis, small vessel vasculitis and possibly the villous trophoblast in preeclampsia.

¹ Laboratory for Prenatal Medicine, University Women's Hospital, Department of Biomedicine, University Hospital, Switzerland

² Laboratory for Signal Transduction, Department of Biomedicine, Basel University Hospital, Switzerland

³ Department of Cardiology, Kantonsspital Luzern, Switzerland

⁴ Department of Rheumatology, Kantonsspital Aarau, Switzerland

Functional Properties of RYR1 Mutations Identified in Swedish Patients with Malignant Hyperthermia and Central Core Disease

M. Vukcevic¹, M. Broman², G. Islander², M. Bodelsson², E. Ranklev-Twetman², C. R. Müller³ and S. Treves¹

Abstract:

Background: A diagnosis of malignant hyperthermia susceptibility by in vitro contraction testing can often only be performed at specialized laboratories far away from where patients live. Therefore, we have designed a protocol for genetic screening of the RYR1-cDNA and for functional testing of newly identified ryanodine receptor 1 (RYR1) gene variants in B lymphocytes isolated from peripheral blood samples drawn at local primary care centers.

Methods: B lymphocytes were isolated for the extraction of RYR1-mRNA and genomic DNA and for establishment of lymphoblastoid B cell lines in 5 patients carrying yet unclassified mutations in the RYR1. The B lymphoblastoid cell lines were used to study resting cytoplasmic calcium concentration, the peak calcium transient induced by the sarco(endo)plasmic reticulum Ca-ATPase inhibitor thapsigargin, and the dose-dependent calcium release induced by the ryanodine receptor agonist 4-chloro-m-cresol.

Results: It was possible to extract mRNA for cDNA synthesis and to create B lymphocyte clones from all samples. All B lymphoblastoid cell lines carrying RYR1 candidate mutations showed significantly increased resting cytoplasmic calcium levels as well as a shift to lower concentrations of 4-chloro-m-cresol inducing calcium release compared with controls.

Conclusions: Peripheral blood samples are stable regarding RNA and DNA extraction and establishment of lymphoblastoid B cell lines after transportation at ambient temperature over large distances by ordinary mail. Functional tests on B cells harboring the newly identified amino acid substitutions indicate that they alter intracellular Ca²⁺ homeostasis and are most likely causative of malignant hyperthermia.

¹Department of Anaesthesia and Biomedicine, Basel University Hospital, Basel, Switzerland

²Department of Anaesthesiology and Intensive Care, Lund University Hospital, Lund, Sweden

³Department of Human Genetics, Biocentre, University of Würzburg, Würzburg, Germany

The plasma carnitine concentration regulates renal OCTN2 expression and carnitine transport in rats

R. Schürch^{1,2,3}, L. Todesco^{1,2}, K. Novakova^{1,2}, M. Mevissen³, B. Stieger⁴ and S. Krähenbühl^{1,2}

Abstract:

Previous findings in rats and in human vegetarians suggest that the plasma carnitine concentration and/or carnitine ingestion may influence the renal reabsorption of carnitine. We tested this hypothesis in rats with secondary carnitine deficiency following treatment with N-trimethyl-hydrazine-3-propionate (THP) for 2 weeks and rats treated with excess L-carnitine for 2 weeks. Compared to untreated control rats, treatment with THP was associated with an approximately 70% decrease in plasma carnitine and with a 74% decrease in the skeletal muscle carnitine content. In contrast, treatment with L-carnitine increased plasma carnitine levels by 80% and the skeletal muscle carnitine content by 50%. Treatment with L-carni-

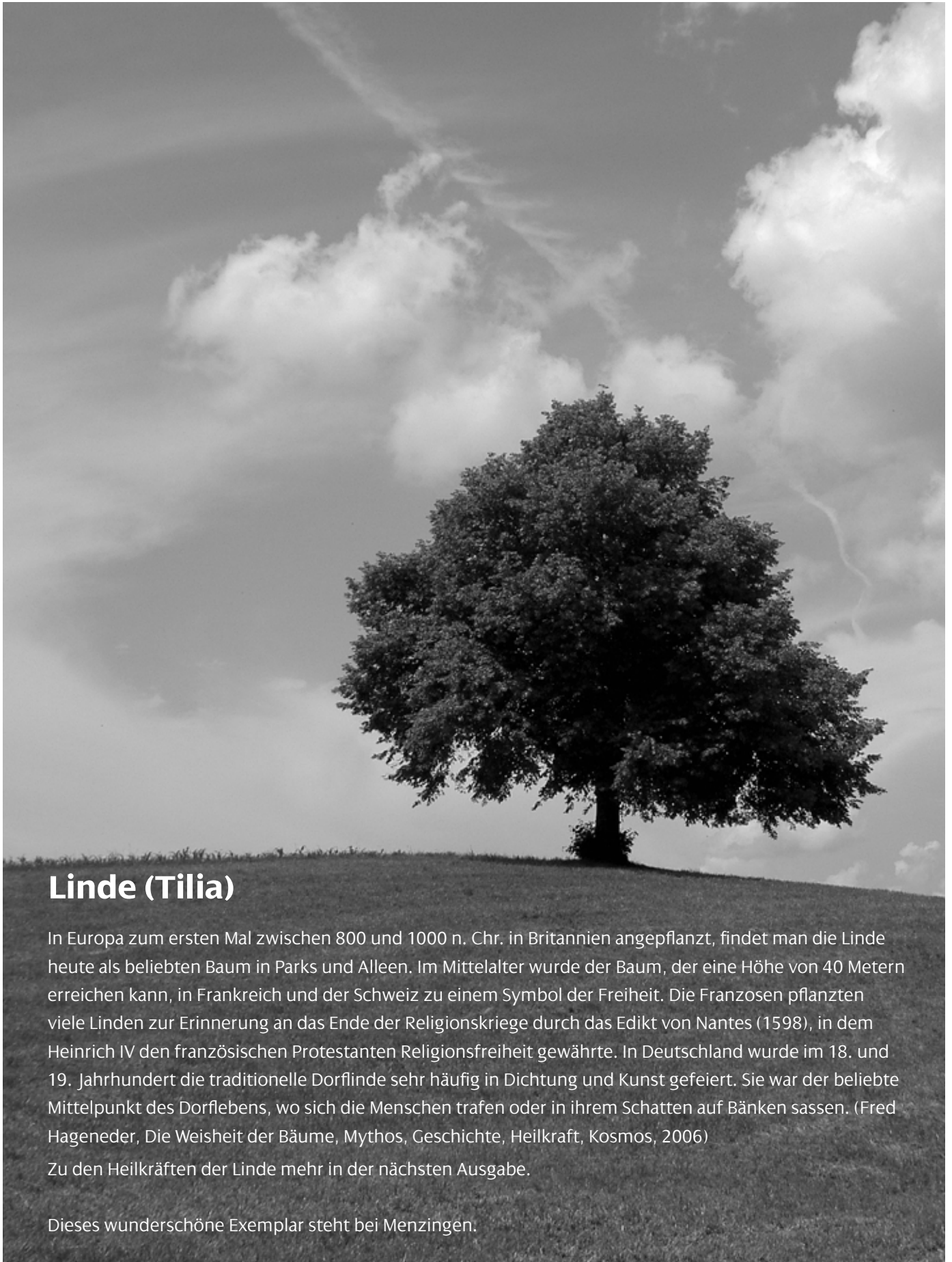
tine affected neither the activity of carnitine transport into isolated renal brush border membrane vesicles, nor renal mRNA expression of the carnitine transporter OCTN2. In contrast, in carnitine deficient rats, carnitine transport into isolated brush border membrane vesicles was increased 1.9-fold compared to untreated control rats. Similarly, renal mRNA expression of OCTN2 increased by a factor of 1.7 in carnitine deficient rats, whereas OCTN2 mRNA expression remained unchanged in gut, liver or skeletal muscle. Our study supports the hypothesis that a decrease in the carnitine plasma and/or glomerular filtrate concentration increases renal expression and activity of OCTN2.

¹ Division of Clinical Pharmacology and Toxicology, University Hospital and University of Basel, Switzerland

² Department of Biomedicine and Swiss Center of Applied Human Toxicology (SCAHT), University Hospital and University of Basel, Switzerland

³ Division of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Berne, Switzerland

⁴ Division of Clinical Pharmacology and Toxicology, University Hospital, Zurich, Switzerland



Linde (Tilia)

In Europa zum ersten Mal zwischen 800 und 1000 n. Chr. in Britannien angepflanzt, findet man die Linde heute als beliebten Baum in Parks und Alleen. Im Mittelalter wurde der Baum, der eine Höhe von 40 Metern erreichen kann, in Frankreich und der Schweiz zu einem Symbol der Freiheit. Die Franzosen pflanzten viele Linden zur Erinnerung an das Ende der Religionskriege durch das Edikt von Nantes (1598), in dem Heinrich IV den französischen Protestanten Religionsfreiheit gewährte. In Deutschland wurde im 18. und 19. Jahrhundert die traditionelle Dorflinde sehr häufig in Dichtung und Kunst gefeiert. Sie war der beliebte Mittelpunkt des Dorflebens, wo sich die Menschen trafen oder in ihrem Schatten auf Bänken sassen. (Fred Hageneder, Die Weisheit der Bäume, Mythos, Geschichte, Heilkraft, Kosmos, 2006)

Zu den Heilkräften der Linde mehr in der nächsten Ausgabe.

Dieses wunderschöne Exemplar steht bei Menzingen.

Zur Pensionierung von Cordula Nitsch



Zum 31. Juli 2010 ist Frau Prof. Cordula Nitsch als Extraordinaria für Neuroanatomie am Anatomischen Institut der Universität Basel emeritiert. Seit 1987 (d.h. für 23 Jahre) leitete sie die Abteilung Neuroanatomie im Institut. Cordula Nitsch studierte Medizin in Frankfurt/M. und Wien und dissertierte am Max-Planck-Institut für Hirnforschung in Frankfurt. Ein wichtiges Thema ihrer Forschung war die Reaktion des Gehirns auf Schädigungen, insbesondere bei Epilepsie und Schlaganfällen. Nach ihrer Promotion forschte Frau Prof. Nitsch zunächst für mehrere Jahre in Tokio und am NIH in Bethesda, Maryland. Anschliessend ging sie an das Anatomische Institut in München, wo sie sich für Anatomie und Neuroanatomie

habilitierte. Als sie 1987 nach Basel berufen wurde, war sie die erste von extern berufene Professorin in der Medizinischen Fakultät. Ihr Hauptforschungsgebiet blieb auch in Basel die Anpassungsfähigkeit (heute "Plastizität" genannt) des Gehirns. Der ihrer wissenschaftlichen Arbeit zu Grunde liegende interdisziplinäre Ansatz führte sie in Basel zur Gründung und Leitung des "Multilingual Brain" Projektes, in dem sie gemeinsam mit Sprachforschern und Neuroradiologen die Auswirkungen von Mehrsprachigkeit auf die Sprachzentren des Gehirns untersuchte. Neben ihrer wissenschaftlichen Arbeit ist Frau Prof. Nitsch stark engagiert im Bereich der Gender Studies. In den vergangenen 23 Jahren repräsentierte Frau Prof. Nitsch die Neuroanatomie an der Universität Basel und unterstützte mit ihrem neuroanatomischen Fachwissen die Forschung vieler Kolleginnen und Kollegen. In der Lehre vermittelte sie den Medizinstudenten ein fundiertes und aktuelles Bild des Aufbaus und der Funktionsweise des menschlichen Gehirns. Wir wünschen ihr alles Gute für den neuen Lebensabschnitt und noch viele Jahre aktives Wirken.

Josef Kapfhammer und Rolf Zeller

Dissertationen

Seit dem 24. Juni 2010 darf sich **Vara Prasad Kolla** von der Forschungsgruppe Prenatal Medicine (Departement Biomedizin USB) Herr Dr. nennen. Er befasste sich in seiner Dissertation mit dem Thema: „Identification of screening biomarkers for chromosomal anomalies and pregnancy-related disorder using quantitative plasma proteomics“.

Am 28. Juni 2010 hat **Tanja Radimerski** von der Forschungsgruppe Metabolism (Departement Biomedizin USB) ihre Dissertation erfolgreich abgeschlossen. Der Ti-

tel ihrer Doktorarbeit hiess: „The regulation of calcitonin genes upon bacterial infection and sepsis in human adipocytes“.

Am 15. Juli 2010 stellte sich **Heike Himmelreich** von der Forschungsgruppe Exp. Hematology (Departement Biomedizin USB) dem Dissertationskomitee. Der Titel ihrer Dissertation lautete: „Regulation of expression of ULBP1, a ligand for the activating immunoreceptor NKG2D, and its influence on the cytotoxic function of natural killer cells against human leukemia“.

Ausbildungen

Tamara Wenger, Versuchstierpflegerin am Departement Biomedizin USB, hat nach zweijähriger verkürzter Ausbildung am 5. Juli 2010 die Lehrabschlussprüfung zur Versuchstierpflegerin erfolgreich bestanden.

Auszeichnungen

Déjérine-Dubois-Preis an Jochen Kinter

Jochen Kinter von der Forschungsgruppe Neuromuscular Research (Departement Biomedizin USB) hat den Déjérine-Dubois-Preis der Schweizerischen Neurologischen Gesellschaft für seine Arbeit „Drug screening for Motonic Dystrophy type 1“ erhalten.

Herzliche Gratulation an alle!

eSIROP – the Research Network

As an academic scientist you surely are familiar with the situation: for every door to knowledge that is opened, ten new doors appear that are closed. You'd like most to open all ten and follow their paths but often you are limited by time and the lack of help.

To find this help there is now a new tool. About 6 months ago, the University of Basel was integrated into the web portal SiROP – the Student Research Opportunities Program.

SiROP is a non-profit organization that works for better networking among researchers and students and cultivates young academics. SiROP began about 8 years ago as a pilot project at the ETH in Zurich. The network now consists of 15 member institutions. Several renowned institutions are among them – including the universities of Basel and Zurich as well as the Technical University of Munich. Researchers can announce the projects for which they need students' help. These can be small sub-projects, which complement larger projects, but projects can also be presented which can be used for a masters or doctoral thesis. The online database func-

tions as an employment broker but is fashioned to the needs of the researchers. By means of a systematic search function, SiROP simplifies the search for academic staff.

Not only researchers profit from the possibility of finding motivated staff from the web portal; students benefit as well. They can gain an understanding of practical research during their study period and will be able to make better decisions regarding their future development. Integration into routine research procedures enriches the experience of the students and for the researchers it often means a new and fresh view of current projects.

The vision of SiROP is to have the platform used for a standard search for project staff. In order to increase its attractiveness, more top universities in Europe should be recruited into the network in the future.

Katrin Bühler
Head of SiROP University of Basel

**DEPARTEMENT
BIOMEDIZIN
USB**



Selina Burch
Ocular Pharmac. & Physiology



Alessia Colone
Exp. Immunology



Sofia Contin
Tissue Engineering



Karol Czaja
Immunotherapy



Cuddapah Sunku Kesava
Prenatal Medicine



Elham Khanicheh
Cardiovasc. Mol. Research



Sébastien Lalevee
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Cancer- & Immunobiology

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Adrian Hermann
Developmental Genetics



Frederic Laurent
Developmental Genetics



Dario Speziale
Developmental Genetics

INSTITUT FÜR MEDIZINISCHE MIKROBIOLOGIE



Sylvia Balogh
Molecular Diagnostics

Ausserdem haben angefangen:

INSTITUT FÜR MEDIZINISCHE MIKRO- BIOLOGIE

Bryan Rupinski,
Transplantation Virology
Claudia Möller,
Molecular Diagnostics

DEPARTEMENT BIOMEDIZIN USB

Michaela Ramser,
Cardiobiology

Congratulations

Das DBM gratuliert ganz herzlich!

**Apolline
Rajalu -
Bocher**

Geboren am
8.5.2010



Yannis Müller

Geboren am 21.6.2010



**Noah Galati-Fournier mit
Bruder Mathias**

Geboren am 23.6.2010

***Herzlich
willkommen,
allerseits!***

Pferde und Menschen

Man muss nicht Marion Gräfin Dönhoffs «Kindheit in Ostpreussen» gelesen haben, um zu verstehen, welche Bedeutung diese Tiere für uns Menschen haben können. Und doch war der Auslöser für die Artikelreihe diese Lektüre. Eindrücklich beschreibt die grosse alte Dame des deutschen Journalismus, wie sie im harten Winter 1945 mit ihrem Trakehner-Hengst Alarich vor Stalins Soldaten von Ostpreussen nach Westfalen flieht. Ohne ihren treuen Gefährten, der später in keiner Würdigung fehlen darf, hätte sie diese Strapazen nicht überlebt.

Was Pferde für unsere DBM-Reiterinnen Lena Angman, Sabrina Köhli und Claudia Petit in der heutigen Zeit bedeuten, beschreiben sie nachfolgend:

Lena Angman:

Ever since I was a child, I was fascinated by horses. Maybe it came from watching too many western movies then, or maybe it was just because of its majestic appearance, I really don't know. The possibilities for horseback riding out in the Swedish countryside in the fifties were reduced to hanging out at the farms at the time of the harvest. We could then ride on top of the hay wagon, and maybe occasionally sit on the horse's back when the work was done. It would take many, many years before I would be able to get any closer than that to these fantastic animals.

So in the beginning of the nineties, the thought of the western movies arouse again, and I felt a deep desire to finally start riding. I wanted to do western riding!

Unfortunately it was not easy then to find a stable that would do this type of teaching. I settled for English riding.

I wanted to become excellent RIGHT AWAY not



realizing, that it take years and years to become a fully fledged rider. I am not so sure today that it is ever possible. After all a horse is a living creature, not an object. Besides, all are different, just as human beings are.

Anyway, I got started by taking a 30min private lesson at 7 am every morning before work for 6 weeks. I loved it! We had a group lesson once a week, where our ability was constantly increased, and it was great fun to study a program for our show riding at Christmas. Dressed up in costumes, mastering the difficult passages to lively music, we were mighty proud of our ability to "master the dressage figures" in front of a large audience.

Then of course I wanted more, I wanted to experience trekking. France was our choice. The stable organized a 7 day tour in Burgundy (Avalon-Beaune). Suddenly I realized how little I knew about how a horse functions outside of the "arena". However, I survived without any accidents, and it sure had awakened my appetite for more.

The very same year I went for a 14 day tour from Bordeaux to Avignon. That proved to be bit harder than I had expected. We crossed the Cevennes, and since I have an anxiety of heights, it gave me all kinds of situations to master. There is truly no place else where you will gather so much experience and understanding about riding then during these trips. Of course one must take many lessons first to minimize dangerous situations, but the real terrain ability is gathered here.

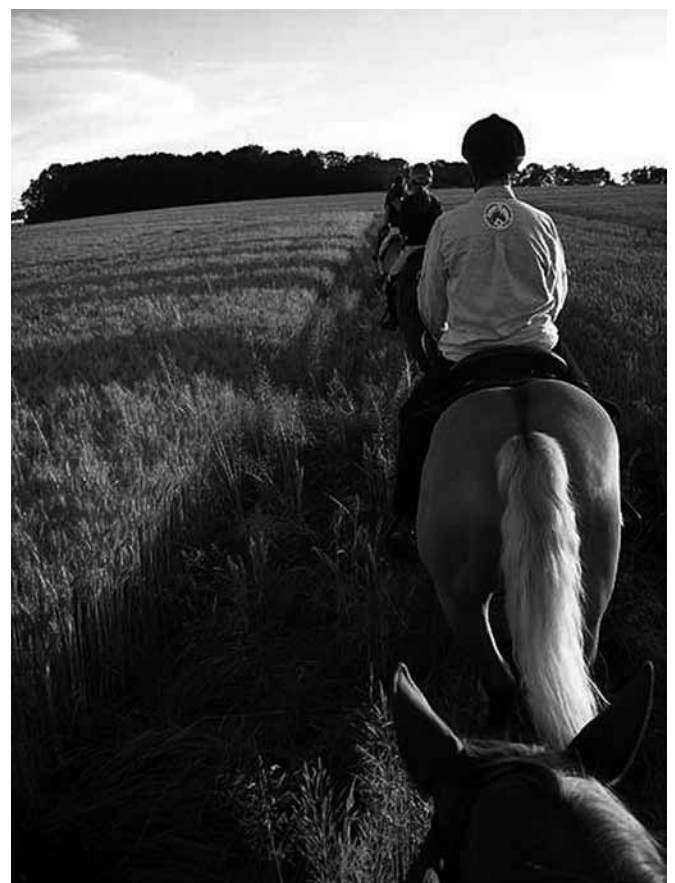
The following year I went on the 3rd trip, so far my favourite one, Paris to Bordeaux, a 600km trip which meant at least 10 hours or more in the saddle every day. The hoses were transported by truck to Fontainebleau which was the starting point. Our sparse luggage was loaded on the truck, that also transported food for the horses during the trek. For night quarters we were extremely flexible, served everything from luxurious hotel rooms to a very simple roof-over-our-heads. We began our ride through the Loire valley with its castles and surrounding forests, where in earlier days the owners spend their time hunting. We had lots of opportunities for long gallops. Then came the agricultural district with fields of corn and sunflowers as far as one could see.

Approaching the coast there were the orchards rich on all kinds of fruits. Finally, reaching the coast, we had reserved tickets on the ferry crossing the Gironde. Prior to our arrival, there had been a flood, so we were running. The captain had been informed that we were on our way and passing the bay at a fast gallop. The traffic had been stopped in order for us to have free passage to the ship. We boarded and were mighty proud standing on deck with our comrades, the horses. They showed absolutely no fear and we celebrated the successful day with an Apéro, while the other passengers were taking pictures.

The rest of the way down to Bordeaux consisted of sandbanks, where we for three whole days we could gallop to our hearts content. Having reached our final destination we all got a good night's sleep in the city. The following day, our companions the

horses were loaded on to the truck, while we took a flight, back to Basel.

During a trip like this you get so close to your horse, that you could actually spend the night next to it in the hay without any fear. It becomes clear to you what a fantastic animal it is. It becomes your comrade. Since then I have kept improving my skills both in the "arena" and out on the "terrain". Fortunately riding is possible up to a very old age and I know I will keep it up as long as I can.



Sabrina Köhli:

Den ersten Kontakt mit Pferden hatte ich mit etwa acht Jahren, als meine Kollegin und ich in den Sommerferien auf einem Bauernhof aushalfen. Nach dem Ausmisten des Stalles stand das Striegeln der Pferde auf dem Programm. Als Belohnung durften wir dann ein paar Runden auf dem Pferd reiten.

Mit dreizehn Jahren durfte ich endlich, nach langen Diskussionen mit meinen Eltern, Reit-Un-

terricht nehmen. Die Reitlehrerin hatte sich nicht der weitverbreiteten, klassischen Reitweise verschrieben, sondern der Western-Reiterei. Wie der Marlboro-Man sitzen Westernreiter lässig im Sattel. Damals hätte ich nie geglaubt, wie viel Arbeit sich dahinter für Reiter und Pferd verbirgt. Zuerst wird lange geübt, um richtig im Sattel zu sitzen, so dass man ausbalanciert ist und sich nicht mit den Beinen am Pferd festklammert. Erst danach lernte ich, mein Pferd zu lenken, entscheidend dabei ist das richtige Timing. Jedes Signal vom Reiter muss im Rhythmus der Bewegung des Pferdes gegeben und im richtigen Moment wieder weg genommen werden. Für mich hatte sich damals eine ganz neue, faszinierende Welt geöffnet. Mit einem Schmunzeln gebe ich zu, dass Reiten «eine Wissenschaft für sich ist».

Nach der Matur fuhr ich ins Elsass in die Reitferien. Die Reise wurde von meiner Reitlehrerin organisiert. Wir waren eine Gruppe von sechs Reitschülern und hatten die Pferde aus unserem Stall nach Frankreich transportiert. Unsere Zimmer waren auf einem Hof nahe Waltenheim, wo wir mit köstlichem Essen und die Pferde mit saftigem Gras verwöhnt wurden. Jeden Morgen ritten wir entlang von Mohnblumen übersäten Feldern und durchquerten den Tarzenwald auf Sumpfwegen. Richtige Abenteuerstimmung kam auf, als wir im Galopp von springenden Rehen begleitet wurden. Ich bin gespannt auf meine nächsten Reitferien im Herbst!



Claudia Petit:

Vor elf Jahren habe ich mir meinen Jugendtraum erfüllt, ich fing mit Reiten an. Erste Reitstunde, gleich mal Pferd putzen und satteln unter Anleitung. Dann aufsteigen, und die ersten Schritte hoch zu Ross und an der Loge meistern (Pferd an langer Führleine, so dass die Lehrerin darüber Kontakt zum Pferd hat). Das war erst einmal Gymnastik auf dem Pferd, Vertrauen gewinnen (in sich und das Pferd), Bewegung erfahren, an die Höhe gewöhnen, und den Augenblick geniessen! Mein Pferd, ein erfahrener Freiburger Hengst, ist total gutmütig und Anfänger gewöhnt. Nach der Reitstunde geht es dann ans Absatteln, Pferd putzen und versorgen!

Wie bekommt man jetzt 600 kg Pferd vorwärts, nach links oder rechts, eventuell auch in eine schnellere Gangart? Nur am Zügel ziehen, nein, so geht das nicht. Man muss mit den Beinen und dem Becken das Pferd antreiben, und das Ganze auch noch gleichzeitig (knifflig). Nach dem Reiten spürt man Muskeln, die man vorher gar nicht kannte! Auch schläft man nach einer Reitstunde (frische Luft und Bewegung) immer sehr gut ein!

Was immer wieder einmal passieren kann: Man fliegt vom Pferd! Mir ist es noch nicht häufig passiert, dafür fünfmal in einer Reitstunde (Stall-Rekord...)!

Nach ca. drei Jahren musste ich feststellen, dass es mit meinen Reitkünsten nicht mehr weiter geht. Nur eine Reitstunde in der Woche ist zuwenig, um

vorwärts zu kommen! Frust machte sich bemerkbar und ich dachte schon ans Aufhören. Dann kamen die Reitferien in der Lüneburger Heide, diese haben mich wieder motiviert! Bei zweimaligem Reiten pro Tag macht man plötzlich wieder echte Fortschritte! In der Heide habe ich mit «meinem» Haflinger Freundschaft geschlossen, mit ihm auszureiten, war ein wahrer Genuss. Wenn die vier Beine unter dir anfangen zu arbeiten, dann geht es ab wie der Blitz!

Zurück aus den Ferien und voll motiviert ging es auch wieder vorwärts mit meinem Reitkönnen.

Nicht nur das Reiten an sich ist etwas Magisches. Kommt man in den Stall, umfängt einen der Geruch von Heu, Pferd und Leder. Die Atmosphäre hat etwas Beruhigendes in der Hektik des Alltags. Es geht geschäftig zu im Stall, aber es herrscht eine Ruhe, die sich auch auf dich selbst überträgt und die man mit nach Hause nimmt. Was einem auch hilft, das Reiten zu erlernen, ist eine gute Kondition! Und da ich früher noch Handball spielte, konnte ich es zwar nicht besser, aber länger!



«Die wahre Geschichte vom Pferd»

Heidi fragt die potentiellen Autorinnen an:

Liebe Mädels, Reiterinnen, Pferdenärrinnen

In der nächsten Ausgabe der DBM Facts möchten wir gerne «die Geschichte vom Pferd» erzählen und hoffen auf Eure Unterstützung! Jede von Euch hat eine Seite, Inhalt völlig frei, sie soll nur von Pferden handeln und mit Euch zu tun haben. Eine Wegleitung zum Verfassen des Artikels lege ich bei, eine Illustration wäre auch schön. Allerletzter Redaktionsschluss wäre der 20. August 2010. Können wir mit Euch rechnen? Gebt mir doch bitte kurz Bescheid :-)

Ganz lieben Dank und herzliche Grüsse

Heidi

Karin Brecht antwortet:

Liebe Heidi,

ich sollte mich wohl freuen, dass ich auserkoren wurde, etwas vom Pferd zu erzählen? :o) Noch hoffe ich, dass ich nur durch ein Versehen auf den Adressverteiler geraten bin. Wärest Du mir sehr böse, wenn ich für die nächste DBM Ausgabe einen Rückzieher machen würde? Ich bin zur Zeit so eingespannt, der Tag müsste 30 Stunden haben, und ich würde nicht rund kommen. Und dann noch vom Pferd...(unter uns, ich finde, Pferde sind ein echter Irrtum in der Evolution). Ich will mich nicht generell drücken, ich wäre einfach froh um ein paar Monate Aufschub. Wäre das okay für Dich?

Ganz herzliche Grüsse,

Karin

Heidi:

Karin, man hat mir gesagt, Du würdest reiten ... stimmt das etwa nicht?

Karin:

Oh, Heidi, da hat man Dir aber einen grossen Bären aufgebunden ... oder sollte ich sagen, man hat Dir eins vom Pferd erzählt? Nichts gegen Pferde und nichts für ungut :o)

Liebe Grüsse,

Karin

Des Nachts in dunklen Gassen

Mit Nachtwächter Rudolf Streiff unterwegs durch das dunkle und geheimnisvolle «Kleine Venedig» Basels

«Hört Ihr Leut' und lasst Euch sagen, unsere Glock' hat neun geschlagen», stimmungsvoller könnte der Auftakt unseres Rundgangs durch St. Alban, auf Basel-deutsch Dalbe, an diesem lauen Sommerabend im Juli 2010 nicht sein. Seine Hellebarde und sein Horn hat der Nachtwächter zu Hause gelassen, einzig eine Laterne begleitet ihn bei seinen einsamen Rundgängen, bei denen er für Ruhe und Ordnung zu sorgen hat.

An diesem Abend ist er nicht allein: Etwa dreissig Co-Wächter, von 10 bis 80 Jahre alt, Einheimische



und Zugereiste, folgen dem Licht und der Stimme des Mannes, der heute Nachtwächter Rudolf Streiff verkörpert: David Bröckelmann. Schauspieler, Sprecher, Kabarettist und Imitator. Ihn allein zu erleben, ist ein Vergnügen. Ihn vor der Kulisse St. Albans zu erleben, ein Genuss. Germanistenherzen schlagen höher bei seinem Repertoire und nicht nur sie, der Dialog mit dem Publikum macht den Kleinen eben soviel Spass wie den Grossen.

Wir hören von vergessenen Gestalten, lauschen Episoden von früheren Begebenheiten und erleben das mittelalterliche St. Alban zum Greifen nah. So erfahren wir von den Beginen, einer religiösen Gemeinschaft von Frauen ohne Ordensanschluss, und von Hermann Hesses kurzem Intermezzo 600 Jahre später im «Haus zum Sausewind», der morgens früh die vorbei ratternden Pferdefuhrwerke nicht ertragen konnte, den rivalisierenden Gruppen, die eine Heimat im Haus «Zum hohen Dolder» fanden, lernen Helena Hoffmann-Merian (anmutig dargestellt von Salomé Jantz) kennen, deren Gatte als Musketier zu Pferd in der preussischen Armee dient und deren Herz sich völlig unstandesgemäss zu unserem Nachtwächter und dem Leben hinzugezogen fühlt. Ich kann mir ihre zänkische Köchin und ihren langweiligen Gemahl lebhaft vorstellen.

Wir vernehmen, wie man im Kloster St. Alban über Menschen zu Gericht sass, selbst wenn sie nur einen Krug Wasser mehr aus dem Brunnen genommen hatten, als ihnen zustand, betrachten im Laternenschein die alten Gemäuer der St. Alban-Kirche, die 1356 dem schweren Erdbeben zum Opfer fiel und heute serbisch-orthodoxen Gläubigen Heimat bietet, schleichen ehrfürchtig vorbei an alten Grabsteinen ins St. Alban-Tal



(Dalbeloch), den Kanälen entlang, die die Mühlen betrieben und St. Alban den Beinamen «Kleines Venedig» eingetragen haben, hin zum letzten Stück der Basler Stadtmauer, bevor unser Rundgang am St. Alban-Tor endet.

Es ist Viertel nach zehn und dunkel geworden. Mit ein paar Geschichten zum Abschied und «Ich möchte noch ein paar Nächte Zeit» schliesst Rudolf Streiff unsere Führung ab. «Ich auch», denke ich, so schön wie an diesem Abend habe ich Basel noch nie erlebt.

Heidi Hoyerermann

Wer mehr wissen möchte: Der Rundgang kostet pro Person 30 CHF (Kinder/Jugendliche 6 bis 16 Jahre 20 CHF) und wird organisiert von:

Basel Tourismus, Guided Tours, Aeschenvorstadt 36, 4010 Basel, Tel. 061/268 68 32, Fax 061/268 68 75, guidedtours@basel.com

Weitere Führungen: Erdbeben, Pest und Tod (Der Chronist Nicolaus von Waldighoffen und dessen Schreiber Peter führen durch eine dunkle Zeit, in der die Erde bebte, die Stadt brannte und die Pest wütete). Hinter verschlossenen Türen (Dienstmädchen Emma Munzinger nimmt die Besucher mit auf ihren Weg in einen vornehmen Basler Haushalt).

Wer David Bröckelmann und Salomé Jantz im Theater sehen möchte:

Theater am Weg, Margarethenstrasse 98, 4102 Binningen, Tel. 0041 79 611 44 35, www.Theater-am-weg.ch



Phuket – from another perspective

The Gibbon Rehabilitation Project

Before starting my PhD-studies, I decided to do some volunteer work. A friend of mine referred me to an associate professor at the University of Erlangen who arranged contacts with different volunteer organizations. Finally, I decided to go to Phuket (Thailand) to join the Gibbon Rehabilitation Project (GRP), a program under the "Wild Animal Rescue Foundation (WARF)". It is an organisation that runs several projects throughout Thailand.

The aim of the GRP is to bring white-handed gibbons, which were kept in captivity, back to the forest. The problem in Thailand is that baby gibbons are captured and sold as pets or they are often used as tourist attractions. For example in the tourist zones of Patong, baby gibbons are used by locals to lure tourists to have photos taken with them after paying a fee. In order to capture a baby gibbon, hunters have to shoot the mother. By doing so, often both the mother and the baby gibbon fall from the tree and do not survive. That is one of the reasons why the species is endangered.

For gibbons raised in captivity the problems start when they reach sexual maturity. They become very aggressive and attack their owners. When this happens, most owners abandon the gibbons and some of them are just left on the street. So, from time to time, the GRP would receive phone calls with information on the location of abandoned gibbons. After several years at the station, they hopefully can be released back to the forest. However, the gibbons have to "find" a mate, have a baby and then they can be released as a family. The GRP only releases families and not single gibbons, because past studies have shown an increased success rate when



families are released together. However, it is often not easy to find the right mate for the gibbons. Or sometimes, they are too used to human company and they have problems forming bonds with other gibbons. This is the main reason why any physical contact is forbidden between gibbons and volunteers, including grooming or hugging them.

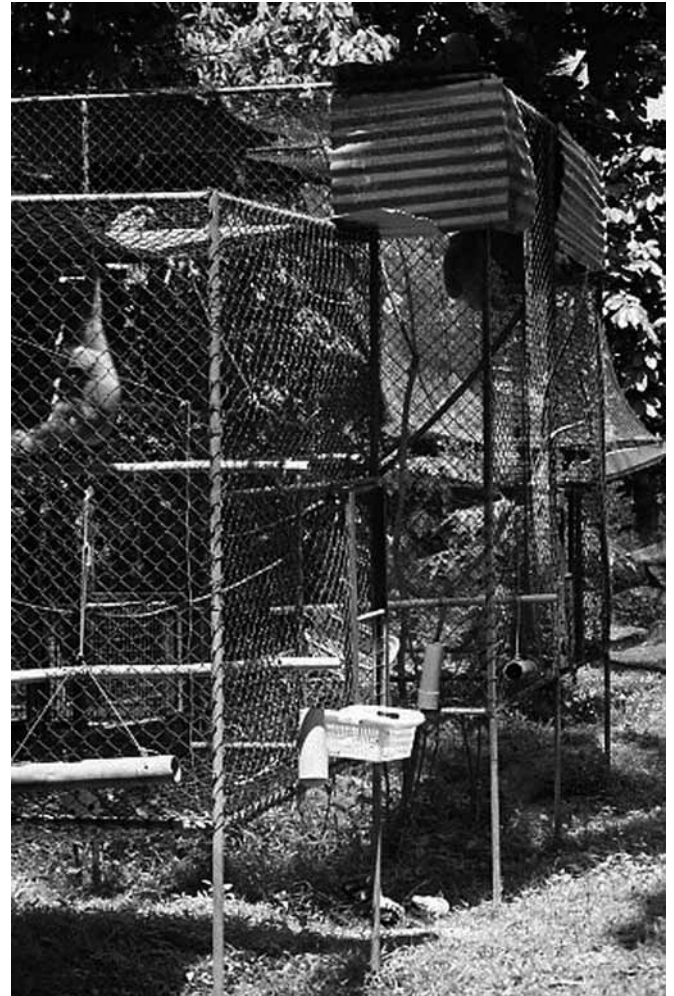
At first I was confused about having to pay for volunteering but that seemed to be quite normal. I had to pay 1.000 Dollars for 8 weeks, food not included. Later I un-

derstood why – the WARF is financed by its volunteers, by donations, visitors, and the government. Because I had to pay a fee, to save money, I booked a flight to Bangkok, which was much cheaper than a direct flight to Phuket and decided to take the train to Phuket after a short stay in Bangkok. So, I could not tell the co-ordinators the time of my arrival but I thought it would not be a problem because I had the address of the GRP-station. After arriving at the Phuket train station, I realized there was no bus going to the GRP-station. Nonetheless, I took a taxi and the driver brought me directly to the middle of the island, into the rainforest. It was unbelievably hot and humid and I was scared that I had to spend 8 weeks in that humid area. Fortunately, I found a guy who told me that we were housed at the release station and he brought me to a village some kilometres away. The volunteers and most of the staff lived together at the accommodation. Luckily, the climate there was much more agreeable.

I got an introduction on the rules and I was very impressed on how strict they were. I had to agree that if I overslept and missed work twice, they could kick me out. After this introduction I was shown my room. Normally all volunteers had to share a room with two people. But when I arrived there were only a few volunteers, so luckily I had a room on my own for some time. Two of the four bathrooms were broken, therefore all people living there had to share the remaining bathrooms. Somehow it all worked out.

During work there were several tasks that the volunteers had to perform and strictly adhere to. My most favourite of these tasks was the “quarantine”. This is the place where new gibbons were housed for the first few weeks. There the gibbons received a full medical examination. Gibbons, which would be released, had to be negative for Herpes, HIV and Hepatitis. If they were positive, they would be brought to a sister project at Ranong.

After 3 months, the newcomers were brought to the Rehabilitation site. At this place they had to learn natural behaviour by watching other gibbons and they had to eat food commonly found in the wild. This second task was also interesting to do and always needed sev-



eral volunteers to work together. The tasks there were to feed the gibbons and clean the bottom of the cages.

The third and most boring job was at the “Education Centre”. There, we either had to sell t-shirts, etc or to guide tourists in the centre. Selling something meant more finance for the project. Another possibility to support the project was to adopt a gibbon. That means that people pay a yearly fee and they receive news about their “adopted gibbon”.

We “educated” the tourists by telling them not to have their photos taken with threatened species because tourists who give money are unknowingly supporting gibbon hunting.

The most fascinating experience for me was when volunteers had the opportunity to go with the Thai staff to build cages in the forest. These cages were needed if a gibbon family is released in the forest. First the gibbons were brought to a cage in the centre of their “future

forest". Every time a family is released they had to get adapted to the forest before they were finally released. Additionally, during their first two days of release two Thai staff members stayed there to survey their first steps in the wilderness.

Finally I would like to emphasize that I had a great time and I really enjoyed it. Although I have to confess that several things did not come easy for me: one of which was to live in a very small village. The bus only came by three times a day. If you had your day off, it was not easy to leave the village. Most of the times I hitchhiked, but I did not like doing it on my own. But often there was no alternative.

Another issue that I had to get used to was passing time after work, which ended at 3pm. The volunteers and the staff normally "hung out" at the station. There, we spent our leisure time chatting or reading, unfortunately it was really difficult to talk with most of the Thai staff



because their English was very poor and they only knew a few expressions and basic sentences.

Lastly, the biggest issue for me were the snakes. At the beginning I thought, I just had to be extra careful when I was in the forest or at the "rehab". But a week before my departure, a volunteer almost stepped on a baby cobra at our house. Luckily one of the staff killed it. As it turned out, the village had serious problems with cobras in the past. These snakes are very poisonous: If you are bitten by it, you will probably not have enough time to reach the hospital. The reason why there were so many cobras is that they live in the mangroves near the village and they do not have a lot of natural predators. After this, I was very careful in the bathroom because it had a big hole and some snakes were found there in the past.

Like always, the farewell was not very easy (especially as the baby gibbons were very cute), but luckily I could spend some time by travelling before returning home.

Stefanie Fritz



Marco Osterwalder, Developmental Genetics

“Better poor in Aargau, than wealthy anywhere else” – saying

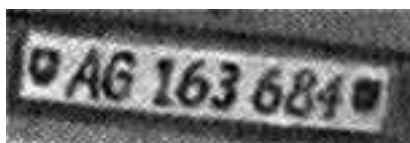
It was a peculiar observation that I made during the first days of my master studies in the lab of Prof Rolf Zeller. So far I had realized that I had gotten into a good, international lab with friendly and committed people, introducing me to the thoroughly interesting field of limb development. But now I stared at a poster hanging in a preferential spot in the lab and somehow something was strange. It was not the dinosaur crossing a motorway that was clearly the eye-



catcher and reminded me of a passion in childhood. Why was there a nuclear power plant pictured in the background? And why did the crashed car have an AG (Aargau) licence plate? Growing up in Müh-
lau (who doesn't know it?), a little village in the southeast of that particular canton AG, my parents showed me early on the open-air treasures of nature in the nearby nature reserve – that was when I got interested in biology. However, AG in Switzerland is not only fa-



mous for its spectacular meadows and rivers but also for the nuclear power plants, terminal storage of hazardous waste, motorways and in particular car drivers (AG: «Achtung Gefahr»). Was this indeed the more or less secret message of the creator of that picture? Anyway, my lamenting about that in the group did not help. They instead pointed out to me that a certain



“Planet Aargau” was part of the Star Wars universe. Well, I will spare you the details.

Back to the past: after mandatory

school I choose emphasis on languages such as Ancient Greek and Latin at the Alte Kantonsschule Aarau (Aarau is the capital of Aargau) that, by the way, harboured as a scholar none other than Albert Einstein in the late 19th century. Despite the charm of ancient languages my inner emphasis was directed all the more towards the fascinating mechanisms underlying the functionality of organs or whole organisms. Soon I left the aargauish planet, commuting daily to Basel by train to study molecular biology at the Biocenter. There I learned a lot of intriguing facts, being impressed the most by the molecular mechanisms underlying



animal development and microbial biology. As the mouse is an excellent model system and its embryonic development is, in many aspects, remarkably similar to that in humans, I was searching for a lab combining developmental biology with mouse genetics. Indeed I found exactly what I was looking for. I was very pleased to join the Zeller group of the Developmental Genetics Department at Mattenstrasse for my master studies. Being captivated by the work with genetically manipulated mouse embryos and the huge potential the mouse model holds, I finally decided to stay in the same group for my PhD as people, resources and scientific environment at the institute were really promising.

In the Zeller group our key players are genes bearing characteristic names such as Sonic Hedgehog, Gremlin, Hand2, Gli3 or Smad4. In particular we are interested in the composition and the architecture of the gene regulatory networks that are guiding the outgrowth of the limb - the machinery that generates a fully functional limb from

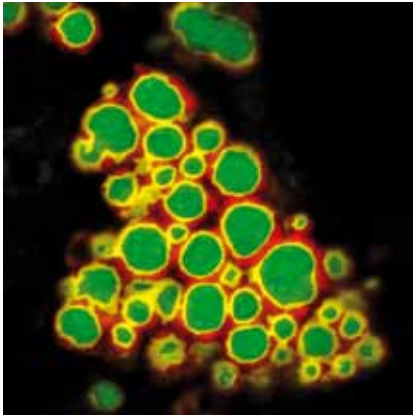
a minute bulge of undifferentiated mesenchymal cells in the lateral embryonic flank. Almost like an additional body axis, the forming locomotion organ extends, tightly regulated over time and space, driving cells to exquisitely acquire the fate of specific cell types including cartilage, bone, tendons and dermis. To investigate these complex processes we combine mouse genetics with limb culture, biochemistry and mathematical modelling. Hereby the use of genetic tools based on tailored manipulation of the mouse genome is critical. Thus, to overcome the limitations in manipulating our favourite genes, we have recently developed a method we called dRMCE that allows the use of conventional conditional alleles to be modified further very efficiently. After presenting my work in the Mouse Genetics and Genomics meeting in 2009, we established a collaboration with a group from the Sanger Institute in Hinxton that is part of the EUCOMM consortium, and found that thousands of these conditional alleles are actu-

ally compatible with our method. This now provides easy access to the generation of tagged proteins, reporter or Cre lines under the control of endogenous regulatory sequences. In the two and a half years of my PhD I was involved in a recent publication about the Hand2 gene and its role in the developing limb bud. Hopefully, I will soon also have a first author paper describing the dRMCE technique. Thanks to this genetic trick, my favourite protein is endogenously tagged and can be analysed in a genome-wide context in differentiating ES cells as well as in the mouse embryo, and these studies will be the main focus of the last part of my PhD. Moreover we now use dRMCE in the lab to introduce other custom modifications into our favourite genes.

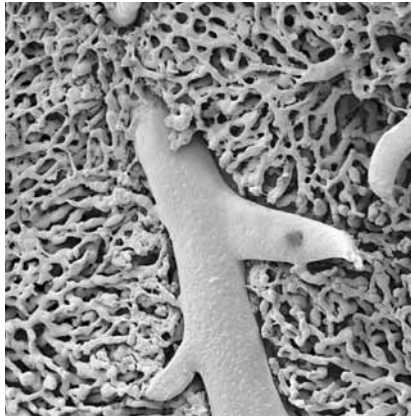
As you can imagine, in the course of dRMCE experiments I spent a lot of time under the reign of ES cells – and believe me, they behave better when exposed to Metallica sound waves.

VORSCHAU PREVIEW

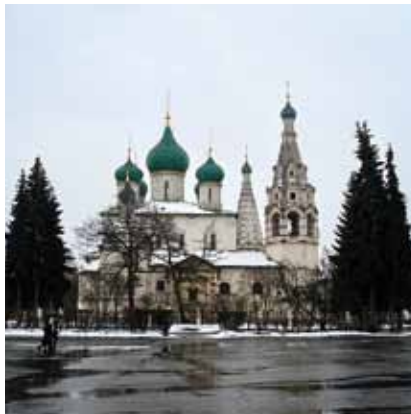
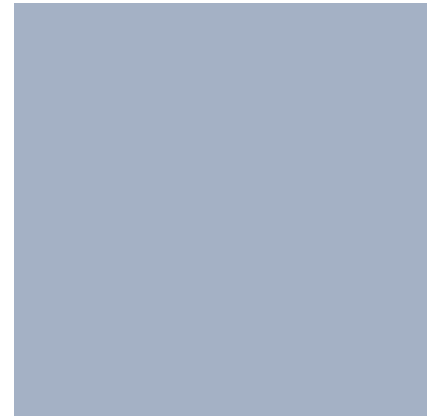
In der nächsten Ausgabe ...



... erfahren wir von Hans Hirsch, welche Herausforderungen die Transplantation Virology bietet



... erzählt uns David Semela, womit sich die Liver Biology beschäftigt



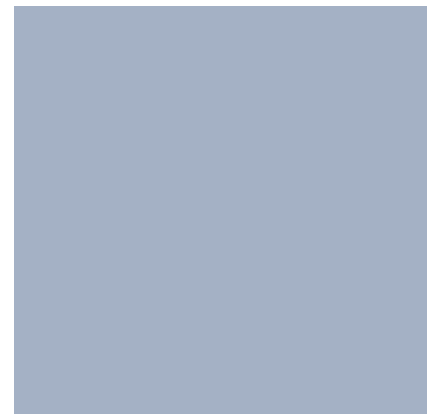
... erleben wir Orthodoxe Weihnachten



... reisen wir mit Verena Jäggin noch weiter Richtung Osten



... und lernen schliesslich mit Anna Marsano fernöstliche Meditationstechniken kennen



Das weisse Spitzchen

Ein blendendes Spitzchen blickt über den Wald,
Das ruft mich, das zieht mich, das tut mir Gewalt:

«Was schaffst du noch unten im Menschengewühl?
Hier oben ist's einsam! Hier oben ist's kühl!

Der See mir zu Füßen hat heut sich enteist,
Er kräuselt sich, flutet, er wandert, er reist.

Die Moosbank des Felsens ist dir schon bereit,
Von ihr ist's zum ewigen Schnee nicht mehr weit!»

Das Spitzchen, es ruft mich, sobald ich erwacht,
Am Mittag, am Abend, im Traum noch der Nacht.

So komm ich denn morgen! Nun lass mich in Ruh!
Erst schliess ich die Bücher, die Schreine noch zu.

Leis' wandelt in Lüften ein Herdegeläut:
«Lass offen die Truhen! Komm lieber noch heut.»

Conrad Ferdinand Meyer (1825–1898)

