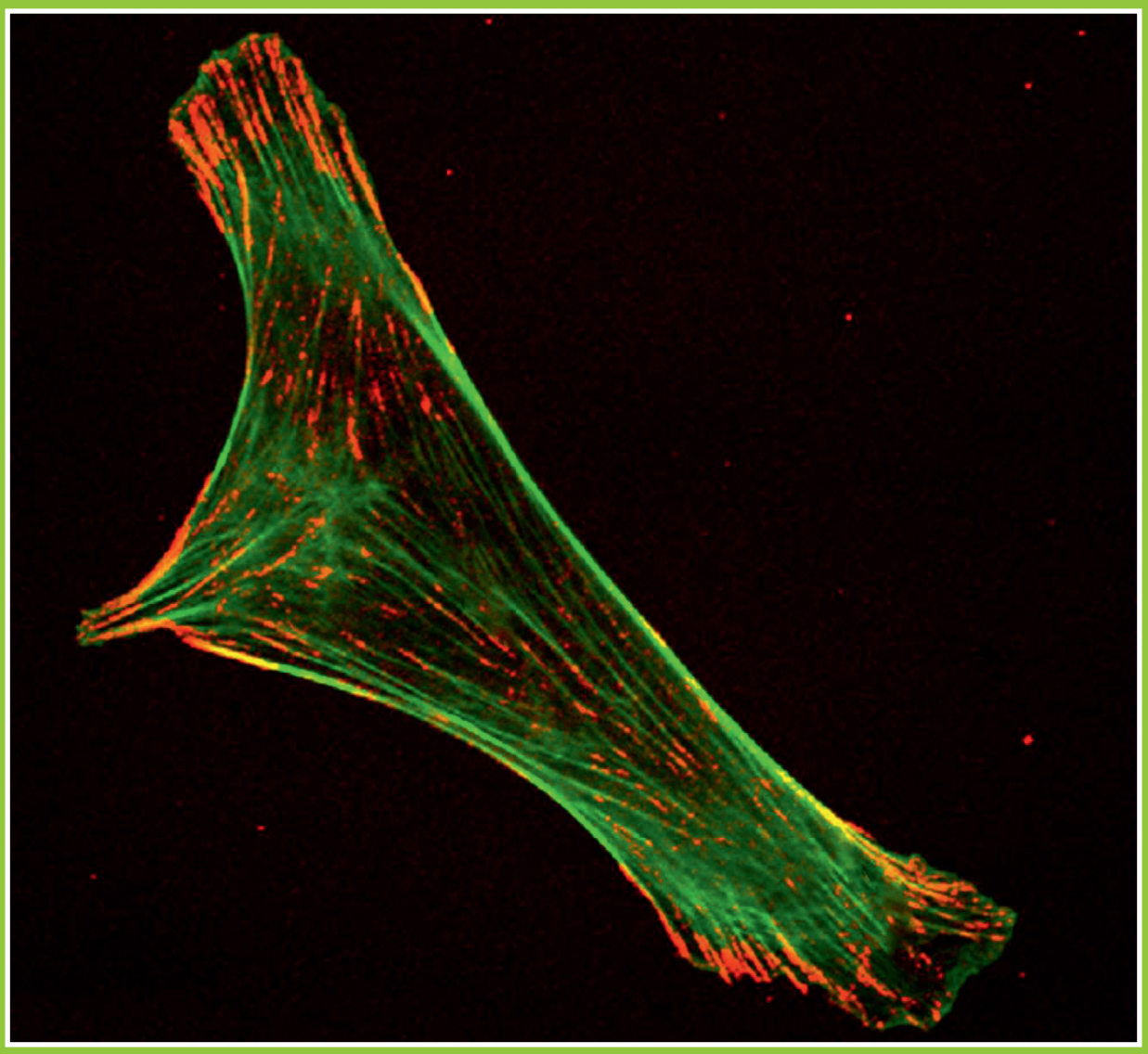
Cell News

Newsletter of the German Society for Cell Biology

full electronic version

Volume 41, 1/2015



International Meeting in Cologne

March 24-27, 2015

– Full Program –

DGZ

The moment your data change scientific minds.

This is the moment we work for.

Revolutionize Your Confocal Imaging

Discover the new ZEISS LSM 8 family of fast linear scanning confocals with GaAsP detection and Airyscan. It offers high sensitivity, speed and 1.7× higher resolution in all three dimensions. Combine ZEISS LSM 800 and LSM 880 with Airyscan to perform quantitative imaging in life sciences.

ZEISS

We make it visible.

www.zeiss.com/lsm

CONTENT

Newsletter of the German Society for Cell Biology

Office:
Sabine Reichel-Klingmann
c/o Deutsches Krebsforschungs-zentrum (DKFZ)
Im Neuenheimer Feld 280
69120 Heidelberg
Tel.: 0 62 21 /42-34 51
Fax: 0 62 21 /42-34 52
E-Mail: dgz@dkfz.de
Internet: www.zellbiologie.de

Cover image: Integrin-linked kinase is required for focal adhesion maturation, cellular force generation and extracellular matrix deposition
Immunofluorescence analysis of paxillin as a marker for focal adhesions and F-actin in fibroblasts. Wild type fibroblasts display small focal complexes (arrow), focal adhesions (open arrowhead), and fibrillar adhesions (arrowhead), which are tightly connected to the actin cytoskeleton. Note lack of focal complexes and fibrillar adhesions, reduced amount of actin stress fibers, and accumulation of large peripheral focal adhesions (open arrowhead) in ILK-deficient cells. Scale bar 25 mm. See article by Jessica Morgner and Sara A. Wickström

Dear colleagues,

we are right in front of our biggest annual event, the International Meeting of the German Society for Cell Biology. Reserve the dates from March 24 – 27 and come to Cologne! You can still register at **http://congress.cpb.de/1/index.php?id=586** or through the link on our website www.zellbiologie.de. You'll find the final exciting program (**http://congress.cpb.de/1/Scientific-Program.583.0.html**) in this issue of Cell News. For the first time, we have also included very interesting satellite symposia organized by young investigators starting already on Tuesday morning. Furthermore, we will celebrate the 40th anniversary of our society in an outstanding plenary symposium on past and present breakthroughs in cell biology with Harald Herrmann, Jan Ellenberg, Jennifer Lippincott-Schwartz and Matthias Mann. In addition to the scientific program, we will have a party on Thursday evening and an absorbing industrial exhibition. Don't miss the chance to visit the booths of our exhibitors, as there are many interesting things to learn from them. Keep in mind that our meetings are financed through the continuous support of our industrial exhibitors. Only if they receive attention from the meeting participants in Cologne, they will want to come back to our next year's international meeting in Munich.

We cannot think about our own anniversary without giving credits to the founder of the DGZ, Prof. Werner W. Franke (DKFZ, Heidelberg), who recently celebrated his 75th birthday. On this occasion, he gave a very enjoyable talk at the DKFZ dealing with "Ten major problems of the cell and molecular biology of normal and diseased cells". Enjoy a video footage of his talk at Youtube (**https://www.youtube.com/watch?v=t4AqChyR_f4&feature=youtu.be**).

Once again I would also like to invite YOU to contribute to Cell News. If you want to write an article about your work, a book review or a journal club article, don't hesitate to contact us. Note that it is free of charge and the copyright is completely yours. You'll find instructions to authors at **http://zellbiologie.de/cellnews/for-authors**. Last but not least an organizational announcement: from this year on, we will retrieve your membership fees in the second quarter of the year.

See you in Cologne and all the best,
Ralph Gräf

DGZ Member Meeting 2015

We are inviting all members to attend our next member meeting that will take place on

Thursday, March 26, 2015, 13:00

at the International Meeting of the DGZ in Cologne, venue: University of Cologne, Hörsaalgebäude **(room: Hall F)**, Gebäudenummer (Building No.) 105, Universitätsstraße 35, 50931 Köln.

Agenda:

1. Confirmation of the minutes of the last year's DGZ member meeting 2014
2. The president's annual report
3. Financial report
4. The auditors' report
5. Approval of the executive board
6. „Other"

Last Announcement

International Meeting of the German Society for Cell Biology (DGZ)

March 24 – 27, 2015 in Cologne, Germany

Dear Ladies and Gentlemen,

we would like to strongly encourage all of **our members to come to the international DGZ meeting in Cologne** as it provides great opportunities to catch the latest developments in cell biology and to interact, socialize and start collaborations with your cell biology colleagues within and outside of Germany.

We have assembled an exciting and diverse program brought by speakers who are at the forefront of their fields. For students and postdocs it offers exciting opportunities to not only present their own work to the broader cell biology community, but learn about other closely related fields as well as see the newest technical developments that may advance their own science. We have also assembled a prominent research career panel, who will cover different stages of a scientific career.

In short, the international DGZ meeting provides the foremost platform to interact and discuss science with your cell biology community and get the latest scientific and technical developments in the field.

We are looking forward to welcome you to Cologne!!!!!

On behalf of the local organizers and the DGZ executive board,

Carien M. Niessen
Vice president German Society for Cell Biology (DGZ) | Chair International Meeting of the German Society for Cell Biology, Cologne 2015

Plenary Sessions:

Plenary Session PS1:	Cell biology of ageing
Plenary Session PS2:	Stem cell and cell fate
Plenary Session PS3:	Signal transduction and trafficking
Plenary Session PS4:	40 Years DGZ: Past and present scientific breakthroughs in cell biology

Symposia:

Symposium S1:	Centrosomes, spindle assembly and cilia
Symposium S2:	Cellular chaperones and proteostasis
Symposium S3:	DNA repair and telomeres
Symposium S4:	Cell adhesion and mechanics
Symposium S5:	Degenerative diseases
Symposium S6:	Genome regulation
Symposium S7:	Cell Polarity – from yeast to mammals
Symposium S8:	Innate immunity in plants and animals
Symposium S9:	New functions of actin
Symposium S10:	Cell biology of mitochondria
Symposium S11:	Epithelial structure and function

Young Investigator Satellite Meetings:

Aneuploidy in health and disease
Cell biology of peroxisomes
Cell biology of lipid metabolism
Molecular mechanisms in metastasis

X-ray cryo-microscopy and other high resolution approaches for investigating cell ultrastructure

Careers in Science- Panel discussion

Local Organization Meeting Committee Cologne 2015

Prof. Dr. Carien M. Niessen (Chair)
Prof. Dr. Angelika Noegel
Dr. Sara Wickström
Prof. Dr. Thorsten Hoppe
Dr. Sandra Iden

Legal Organizer (PCO)

Conference Organization:
MCI Deutschland GmbH · Markgrafenstr. 56 · 10117 Berlin, Germany
Phone: +49 (0) 30 204 590 · Fax: +49 (0) 30 204 59 50 · E-mail: zellbiologie@mci-group.com

Conference Venue:

University of Cologne · Hörsaalgebäude · Gebäudenummer (Building No.) 105
Universitätsstraße 35 · 50931 Köln

Information/Registration: www.zellbiologie2015.de

Scientific Program

International Meeting of the German Society for Cell Biology (DGZ)

March 24–27, 2015, Cologne, Germany

Tuesday March 24, 2015

08:30 – 11:45 X-ray cryo-microscopy and other high resolution approaches for investigating cell ultrastructure

09:00 – 11:00 Young Investigator Satellite Meetings

09:00 – 11:00 Aneuploidy in health and disease
Organizer: Zuzana Storchova (Martinsried, Germany)

09:00 – 09:40 Keynote speaker: René H. Medema (Amsterdam, The Netherlands): The multiple faces of aneuploidy

09:40 – 10:05 Floris Foijer (Groningen, The Netherlands): In vivo consequences of aneuploidy

10:05 – 10:30 Jan Korbel (Heidelberg, Germany): From genomic copy number variations to molecular mechanisms

10:30 – 10:55 Zuzana Storchova (Martinsried, Germany): Aneuploidy causes proteotoxic stress

09:00 – 11:00 Cell biology of peroxisomes
Organizer: Petra Wendler (Munich, Germany)

09:00 – 09:30 Keynote speaker: Nancy Braverman (Montreal, Canada): Peroxisome biogenesis disorders, from the bedside-to-bench and back

09:30 – 10:00 Tony Rodrigues (Porto, Portugal): Dissecting the peroxisomal protein import pathway using an in vitro import/export system

10:00 – 10:30 Marc Fransen (Leuven, Belgium): PEX5, the shuttling import receptor for peroxisomal matrix proteins, functions as a stress sensor

10:30 – 11:00 Petra Wendler (Munich, Germany): Three cornered circles: molecular snapshots of the Pex1/6 AAA+ complex in action

09:00 – 11:00 Cell biology of lipid metabolism
Organizer: Mathias Beller (Duesseldorf, Germany)

09:00 – 09:45 Keynote speaker: Albert Pol (Barcelona, Spain): The many faces of caveolin in the endoplasmic reticulum: From fatty liver to neurodegeneration

09:45 – 10:10 Abdou Rachid Thiam (Paris, France): Protein crowding as a determinant mechanism of lipid droplet composition

10:10 – 10:35 Christoph Thiele (Bonn, Germany): Click-chemistry-based lipid tracing to study lipid metabolism and localisation

10:35 – 11:00 Mathias Beller (Duesseldorf, Germany): Towards a model to understand cellular lipid droplet diversification

09:00 – 11:00 Molecular mechanisms in metastasis
Organizer: Stefan Veltel (Hamburg, Germany)

09:00 – 09:45 Keynote speaker: Jim Norman (Glasgow, UK): The role of Ephrin receptor trafficking in mediating cell: cell repulsion

09:45 – 10:10 Stefan Veltel (Hamburg, Germany): Regulation of integrin trafficking on a molecular level

10:10 – 10:35 Markus Moser (Martinsried, Germany): Genetic analysis of integrin signaling in mice

10:35 – 11:00 Klaus Pantel (Hamburg, Germany): Tumor cell dissemination: emerging biological insights from the analysis of circulating tumor cells in cancer patients

11:15 – 12:15 Careers in Science- Panel discussion
- Magdalena Götz (Munich, Germany)
- Kai Kretzschmar (Utrecht, The Netherlands)
- René H. Medema (Amsterdam, The Netherlands)
- Ellen Nollen (Groningen, The Netherlands)
- Björn Schumacher (Cologne, Germany)
- Zuzana Storchova (Martinsried, Germany)

13:00 Opening words
- Prof. Carien Niessen, representing the DGZ Board and local Organizing Committee
- Prof. Ansgar Büschges, Dean of the Faculty of Mathematics and Natural Sciences of the University of Cologne
- Prof. Thomas Krieg, Dean of Faculty of Medicine of the University of Cologne

13:00 – 15:00 Plenary Session PS1: Cell biology of ageing
Chair: Thorsten Hoppe (Cologne, Germany)

13:00 – 13:30 Ellen Nollen (Groningen, The Netherlands): Modifying toxicity of aggregation-prone proteins in aging and age-related diseases

13:30 – 14:00 Martin Hetzer (La Jolla, USA): The role of nucleoporins in developmental gene regulation

14:00 – 14:30 Thomas Nyström (Göteborg, Sweden): Recognition, partitioning, and asymmetrical segregation of protein aggregates

14:30 – 15:00 Thorsten Hoppe (Cologne, Germany): Ubiquitin-dependent coordination of proteostasis and longevity

15:00 – 15:30 Coffee break

15:30 – 17:30 DGZ Awards
- **Walther Flemming Medal**
  Katrin Paeschke (Wuerzburg, Germany): Consequences of G-quadruplex structures for eukaryotic cells
- **Binder Innovation Prize**
  Holger Bastians (Goettingen, Germany): Increased microtubule dynamics triggers chromosomal instabilty and aneuploidy in human cancer cells
- **Nikon Young Scientist Award of the DGZ**
  Kai Kretzschmar (Utrecht, The Netherlands): Remodelling adult skin by epidermal β-catenin activation
- **Werner Risau Prize**
  Ayal Ben-Zvi (Jerusalem, Israel): Mfsd2a is critical for the formation and function of the blood-brain barrier

17:30 – 18:00 Coffee break

18:00 – 19:00 **Carl Zeiss Lecture**
Magdalena Götz (Munich, Germany):
Mechanisms of neurogenesis: from cell biology to neural repair

19:00 **Opening reception**

Wednesday March 25, 2015

09:00 – 12:00 **Symposia 1–4**

09:00 – 12:00 **Symposium S1: Centrosomes, spindle assembly and cilia**
Chairs: Thomas Müller-Reichert (Dresden, Germany) and Gislene Pereira (Heidelberg, Germany)

09:00 – 09:30 Jan Brugues (Dresden, Germany):
Principles of meiotic spindle organization

09:30 – 10:00 Thomas Müller-Reichert (Dresden, Germany):
Three-dimensional reconstruction of the first mitotic spindle in C. elegans reveals different populations of microtubules with distinct properties

10:00 – 10:15 Bjorn Bakker: Deletion of the Mad2 spindle assembly checkpoint gene causes chromosome instability with differential effects on liver cancer and lymphoma (short talk, A-108)

10:15 – 10:45 Coffee break

10:45 – 11:15 Jordan Raff (Oxford, UK):
How to build a centrosome during mitosis

11:15 – 11:45 Lotte Pedersen (Hillerød, Denmark):
Regulation of ciliary length and signalling by kinesin-3 motors

11:45 – 12:00 Julian Nuechel: EHD4 controls resorption of primary cilia during mitosis (short talk, A-104)

09:00 – 12:00 **Symposium S2: Cellular chaperones and proteostasis**
Chair: Jörg Höhfeld (Bonn, Germany)

09:00 – 09:30 Ulrich Hartl (Martinsried, Germany):
Chaperone mechanisms in protein folding and quality control

09:30 – 10:00 Elke Deuerling (Konstanz, Germany):
Sorting right from wrong: How ribosome-associated chaperones control protein transport processes

10:00 – 10:15 Simon Alberti:
Promiscuous interactions and protein disaggregases determine the material state of stress-inducible RNP granules (short talk, A-266)

10:15 – 10:45 Coffee break

10:45 – 11:15 Blanche Schwappach (Goettingen, Germany):
The GET pathway in proteostasis

11:15 – 11:45 Jörg Höhfeld (Bonn, Germany):
Chaperone-assisted proteostasis

11:45 – 12:00 Sebastian A. Leidel:
Misregulation of local translation rates leads to protein aggregation defects (short talk, A-183)

09:00 – 12:00 **Symposium S3: DNA repair and telomeres**
Chairs: Katrin Paeschke (Wuerzburg, Germany) and Brian Luke (Heidelberg, Germany)

09:00 – 09:30 Daniel Durocher (Toronto, Canada):
Cell cycle regulation of DNA double-strand break repair

09:30 – 10:00 Helle Ulrich (Mainz, Germany):
Dealing with DNA damage during replication

10:00 – 10:15 Amine Bouafia: p53 requires the stress sensor USF1 to direct appropriate cell fate decision (short talk, A-221)

10:15 – 10:45 Coffee break

10:45 – 11:15 Jan Karlseder (La Jolla, USA):
Telomere function in mitosis: Complex interactions determine cellular fate

11:15 – 11:45 Vincent Géli (Marseille, France): RPA prevents G4 structures at lagging strand telomeres to allow maintenance of chromosome ends

11:45 – 12:00 Brian Luke (Heidelberg, Germany): Regulation of the Mph1 helicase by Smc5/6 complex is crucial at short telomeres and RNA-DNA hybrids

09:00 – 12:00 **Symposium S4: Cell adhesion and mechanics**
Chair: Thomas Magin (Leipzig, Germany)

09:00 – 09:30 Vania Braga (London, UK): Defining functional interactions during biogenesis of epithelial junctions

09:30 – 10:00 Mechthild Hatzfeld (Halle, Germany): Functions of the desmosomal protein plakophilin 1 in cell adhesion and signaling

10:00 – 10:15 Jaap van Buul: A local VE-cadherin/Trio-based signaling complex stabilizes endothelial junctions through Rac1 (short talk, A-105)

10:15 – 10:45 Coffee break

10:45 – 11:15 Ben Fabry (Erlangen, Germany): Adhesion, contraction, or cell mechanics: which cell properties matter for cancer cell invasion?

11:15 – 11:30 Antje Schaefer: Actin-binding proteins differentially control endothelial cell stiffness to drive function of the β2 integrin ligand ICAM-1 and neutrophil transmigration (short talk, A-102)

11:30 – 12:00 Manuel Thery (Paris, France):
Force scaling in stress fibers

12:00 – 13:00 **Lunch**

12:00 – 13:00 **Lunch Symposium 1: Carl Zeiss Microscopy GmbH – München**
The New ZEISS LSM 8 Family:
Revolutionize Your Confocal Imaging
Referent: Dr. Sebastian Wiesner

13:00 – 15:00 **Poster Session 1**

15:00 – 18:00 **Plenary Session 2: Stem cells and cell fate**
together with the Dutch Society for Cell Biology
Chairs: Jacco van Rheenen (Utrecht, The Netherlands) and Carien Niessen (Cologne, Germany)

15:00 – 15:30 Hans Clevers (Utrecht, The Netherlands):
Wnt signaling, Lgr5 stem cells and cancer

15:30 – 16:00 Timm Schroeder (Basel, Switzerland): Long-term single cell quantification: New tools for old questions

16:00 – 16:30 Cristina Lo Celso (London, UK):
Plastic interactions between normal and malignant haematopoietic cells and their bone marrow niches

16:30 – 17:00 Coffee break

17:00 – 17:30 Eileen Furlong (Heidelberg, Germany):
Three-dimensional properties of enhancer interactions during embryonic development

17:30 – 18:00 Jacco van Rheenen (Utrecht, The Netherlands):
Intravital microscopy of epithelial stem cells and cancer

Thursday, March 26, 2015

09:00 – 12:00 Symposia 5–8

09:00 – 12:00 Symposium S5: Degenerative diseases
Chair: Eva-Maria Mandelkow (Bonn, Germany)

09:00 – 09:30 Joachim Herz (Dallas, USA): ApoE, ApoE receptors and Alzheimer's Disease

09:30 – 09:45 Gültekin Tamgüney:
Brain homogenates from patients with multiple system atrophy and aged control subjects without neurological disorder cause neuropathology in transgenic mice expressing human wild-type (short talk, A-239)

09:45 – 10:15 Eva-Maria Mandelkow (Bonn, Germany):
Tau toxicity and rescue in animal models of Tau pathology

10:15 – 10:45 Coffee break

10:45 – 11:15 Peter St. George-Hyslop (Toronto, Canada):
Amyloid, presenilin, and inflammation in Alzheimer disease

11:15 – 11:30 Simon Alberti:
The ALS-associated protein FUS forms liquid compartments, whose biophysical properties correlate with disease (short talk, A-264)

11:30 – 12:00 Sandrine Humbert (Grenoble, France):
Huntington's disease: from corticogenesis to neurodegeneration

09:00 – 12:00 Symposium S6: Genome regulation
Chair: Ana Pombo (Berlin, Germany)

09:00 – 09:30 Josée Dostie (Montreal, Canada):
Linking chromatin architecture to RNA

09:30 – 10:00 Musa Mhlanga (Pretoria, South Africa):
A new enhancer-like noncoding RNA influencing genome organization and the transcription cycle in the immune response

10:00 – 10:15 Kurt Engeland:
Genome-wide analysis of transcription suggests a pathway for p53-dependent cell cycle regulation (short talk, A-281)

10:15 – 10:45 Coffee break

10:45 – 11:00 Marina Lusic:
Nuclear architecture dictates HIV-1 integration site selection (short talk, A-180)

11:00 – 11:30 Francois Spitz (Heidelberg, Germany):
Function and regulation of long-distance chromosomal interactions

11:30 – 12:00 Ana Pombo (Berlin, Germany):
Novel, ligation-free method for identifying chromatin interactions genome-wide

09:00 – 12:00 Symposium S7: Cell Polarity – from yeast to mammals
Chair: Sandra Iden (Cologne, Germany)

09:00 – 09:30 Roland Wedlich-Söldner (Muenster, Germany):
Yeast polarity – a paradigm for mesoscale systems biology

09:30 – 10:00 Marta Shahbazi (Cambridge, UK):
The making of an epithelium from embryonic stem cells: architectural and transcriptional patterns

10:00 – 10:15 Mike Boxem:
Unraveling the C. elegans interactome underlying cell polarity (short talk, A-285)

10:15 – 10:45 Coffee break

10:45 – 11:15 Patrick Humbert (East Melbourne, Australia):
Cell polarity, tissue organisation and the regulation of cancer progression

11:15 – 11:45 Sandra Iden (Cologne, Germany):
The different faces of the Par3 polarity complex in skin cancer

11:45 – 12:00 Mirka Uhlirova:
Atf3 bridges the gap between cell polarity and the nucleus (short talk, A-276)

09:00 – 12:00 Symposium S8: Innate immunity in plants and animals
Chair: Jane Parker (Cologne, Germany)

09:00 – 09:30 Jane Parker (Cologne, Germany):
Evolutionary and molecular dynamics of plant innate immunity

09:30 – 10:00 Marie-Cécile Caillaud (Lyon, France):
Probing plant cellular immunity with pathogen virulence factors

10:00 – 10:15 Kamlesh Pawar:
Mycobacteria escape autophagy by counter regulating long non-coding RNA MEG3 (short talk, A-118)

10:15 – 10:45 Coffee break

10:45 – 11:15 Manolis Pasparakis (Cologne, Germany):
Cell death in immunity and inflammation

11:15 – 11:30 Deblina Chakraborty:
Expression and role of S100A8/A9 in acute lung injury (short talk, A-263)

11:30 – 12:00 Thomas Bosch (Kiel, Germany):
The molecular logic of Hydra´s immune system

12:00 – 13:00 Lunch

13:00 – 14:00 DGZ Member Meeting

13:00 – 15:00 Poster Session 2

15:00 – 18:00 Plenary Session PS3: Signal transduction and trafficking
Chair: Philippe Bastiaens (Dortmund, Germany)

15:00 – 15:30 Alexander Sorkin (Pittsburgh, USA):
Regulation of EGF receptor by endocytosis

15:30 – 16:00 Bruno Goud (Paris, France):
Spatiotemporal selection of downstream partners of phosphoinositide-binding proteins through phosphoinositide clustering

16:00 – 16:30 Marko Kaksonen (Heidelberg, Germany):
Visualizing the dynamic architecture of the endocytic machinery

16:30 – 17:00 Coffee break

17:00 – 17:30 Philippe Bastiaens (Dortmund, Germany):
RTK trafficking switches from a cyclic safeguard to a finite signaling mode

17:30 – 18:00 Peter Devreotes (Baltimore, USA):
The cell's compass: How cells move and know where to move

18:00 – 19:00 Frontiers in Science Lecture
Joseph Penninger (Vienna, Austria):
Forward and reverse genetics using haploid stem cells

19:00 Posters and Party

Friday, March 27, 2015

09:00 – 11:00 Plenary Session PS4: 40 Years DGZ: Past and present scientific breakthroughs in cell biology
Chaired by the DGZ Board

09:00 – 09:30 Harald Herrmann (Heidelberg, Germany): Electrons and photons: From electron microscopy to super-resolution techniques and back

09:30 – 10:00 Jan Ellenberg (Heidelberg, Germany): Systems biology of the human cell using light microscopy

10:00 – 10:30 Jennifer Lippincott-Schwartz (Bethesda, USA): Cell survival under starvation: crosstalk between mitochondria, lipid droplets and autophagy

10.30 – 11:00 Matthias Mann (Martinsried, Germany): High throughput proteomics and it application to insulin signaling

11:00 – 12:00 Coffee break with lunch

12:00 – 15:00 Symposia 9–11

12:00 – 15:00 Symposium S9: New functions of actin
Chair: Robert Grosse (Marburg, Germany)

12:00 – 12:30 Gregg Gundersen (New York, USA):
LINCing actin cables to the nuclear envelope for nuclear movement

12:30 – 13:00 Peter Lénárt (Heidelberg, Germany):
An Arp2/3 nucleated F-actin shell fragments nuclear membranes at nuclear envelope breakdown

13:00 – 13:15 Sven Bogdan: Shaping cells into organs – The WAVE regulatory complex (WRC) acts through FAT2 to control Drosophila egg chamber elongation (short talk, A-107)

13:15 – 13:45 Coffee break

13:45 – 14:15 Maria Vartiainen (Helsinki, Finland):
Regulation of nuclear actin - from dynamics to function

14:15 – 14:45 Robert Grosse (Marburg, Germany):
Actin dynamics during entotic cell-in-cell invasion

14:45 – 15:00 Marco Rust:
A novel function of ADF/cofilin-dependent actin dynamics in neurotransmitter release and behavior (short talk, A-225)

12:00 – 15:00 Symposium S10: Cell biology of mitochondria
Chair: Elena Rugarli (Cologne, Germany)

12:00 – 12:30 Benedikt Westermann (Bayreuth, Germany):
Mitochondrial inheritance and dynamics in yeast

12:30 – 12:45 Timothy Wai:
Metabolic intervention rescues heart failure caused by unbalanced mitochondrial dynamics (short talk, A-297)

12:45 – 13:15 Heidi McBride (Montreal, Canada):
Establishing the function of mitochondrial vesicle transport

13:15 – 13:45 Coffee break

13:45 – 14:15 Janet M. Shaw (Salt Lake City, USA):
Cellular and physiological roles for mitochondrial motility

14:15 – 14:45 Elena Rugarli (Cologne, Germany):
Cluh and regulation of mitochondrial biogenesis

14:45 – 15:00 Sven Thoms:
Functional translational readthrough enables protein import into organelles (short talk, A-201)

12:00 – 15:00 Symposium S11: Epithelial structure and function
Chair: Inke Näthke (Dundee, Scotland/UK)

12:00 – 12:30 Lindsay Hinck (Santa Cruz, USA):
The role of SLIT/ROBO signaling in mammary stem cell self-renewal

12:30 – 13:00 Marija Plodinec (Basel, Switzerland):
An in vitro epithelium that bears the mechanobiological hallmarks of living tissue with the implications for cancer progression

13:00 – 13:15 Vanessa Weichselberger:
Interface mechanics between transcriptionally divergent cell groups cause epithelial cyst formation (short talk, A-237)

13:15 – 13:45 Coffee break

13:45 – 14:15 Helen McNeill (Toronto, Canada):
Regulation of epithelial structure and branching morphogenesis in the developing mouse kidney

14:15 – 14:45 Inke Näthke (Dundee, Scotland/UK):
Gut epithelial tissue changes during early transformation

14:45 – 15:00 David Schneider:
Cellular mechanics in keratinocyte differentiation and epidermal stratification (short talk, A-158)

15:00 – 15:30 End of the meeting

www.zellbiologie2015.de

Sensing of pathogen-induced F-actin perturbations – a new paradigm in innate immunity?

Angelika Hausser, Kornelia Ellwanger & Thomas Kufer

Summary

The F-actin cytoskeleton plays pivotal roles in cell shape, cell migration and signaling. Many bacterial pathogens subvert the actin regulatory machinery to assure pathogenicity. Recent evidence now suggests that mammalian host cells are able to sense pathogen induced perturbations in their F-actin network. Here we provide a brief summary of our current understanding of this emerging concept focusing on key molecules that are supposed to be involved in sensing of pathogen-induced host F-actin remodeling.

Introduction

Mammals evolved to respond to pathogen by means of immune reactions. An immediate response towards invading pathogens is provided by the innate immune system. Virtually any cell in the body expresses particular receptors that are able to detect conserved microbial structures. Triggering of these receptors leads to the release of chemokines and cytokines to attract cells of the adaptive immune system and to instruct adaptive immune responses, but also to the release of antimicrobial peptides that can counteract microbial action at the site of invasion (Akira et al., 2006).

Within the recent decades many of these, so called pattern-recognition-receptors (PRRs) have been identified and we know in most cases the respective microbial ligand, termed microbe-associated molecular pattern (MAMP) of these receptors. PRRs exist as transmembrane proteins residing in the cell membrane and in the endocytic compartments, but also in the cytoplasm. Prominent examples of membrane bound PRRs are the Toll-like receptors (TLRs), including the lipopolysaccharide receptor TLR4, that is critically involved in septicemia (Kawai and Akira, 2011). Cytosolic PRRs were recognized more recently and include the family of Nod-like receptors (NLRs). In particular the NLR proteins NOD1 and NOD2 are well established PRRs for cytosolic bacterial peptidoglycan (PGN). Activation of NOD1 and NOD2 leads to stimulation of the NF-κB and MAPK pathways, resulting in transcriptional reprogramming and expression of pro-inflammatory proteins (Kufer, 2008).

Recent work now suggests that PRR signaling is intimately linked to F-actin and that changes in the activity of actin regulatory proteins e.g. the Arp2/3 complex and the actin depolymerization factor cofilin, profoundly affects PRR mediated immune responses. Moreover, it emerges that PRR signaling might be used by the mammalian cell to sense perturbations of F-actin by pathogenic bacteria that hijack the actin machinery to assure their pathogenicity.

Here we will briefly summarize these novel functions of the actin cytoskeleton in innate immunity.

Regulation of host actin dynamics by the cofilin signaling network

In eukaryotic cells the actin cytoskeleton responds to external cues by a dramatic rearrangement that, for example, is observed in migrating cells. Actin filaments are composed of monomeric actin molecules that associate via non-covalent interactions. Actin polymerization is a steady state process mainly driven from the so-called barbed end of F-actin, by association of ATP-loaded actin monomers. At the opposite end – the pointed end – ADP-loaded actin monomers are released, and after exchange of ADP for ATP these free actin monomers refill the monomeric actin pool available to the actin polymerization cycle (reviewed in (Pollard, 1990)). Actin polymerization requires nucleation, which includes the formation of actin dimers and trimers and is an energetically unfavorable process until actin tetramers are formed. Actin nucleation is promoted by the so called nucleators, which reduce the energy barrier for the formation of actin dimers or trimers (Sept and McCammon, 2001). In general, F-actin is either organized as linear cables or branched networks. Branched F-actin is generated at membrane protrusions such as lamellipodia and invadopodia through the action of the actin nucleator Arp2/3 complex, which binds to the sides of pre-existing filaments enabling the growth of new filaments at these sites (reviewed in (Rotty et al., 2013) and (Mullins, 2000)). Actin-binding proteins belonging to the ADF/cofilin family regulate the disassembly of F-actin. These proteins are essential in all eukaryotes and can be found in three different isoforms in mammals: ADF, cofilin-1 and cofilin-2 (reviewed in (Bamburg, 1999; Bernstein and Bamburg, 2010)). Cofilin-1 is the main isoform in nonmuscle tissue whereas cofilin-2 is predominantly expressed in muscle cells. Here we will focus on cofilin-1 and refer thus to it as cofilin. Cofilin severs F-actin filaments and thus increases the number of free barbed ends, which serve as starting points for further actin polymerization. In addition, the interaction between cofilin and F-actin increases the rate of actin dissocia-

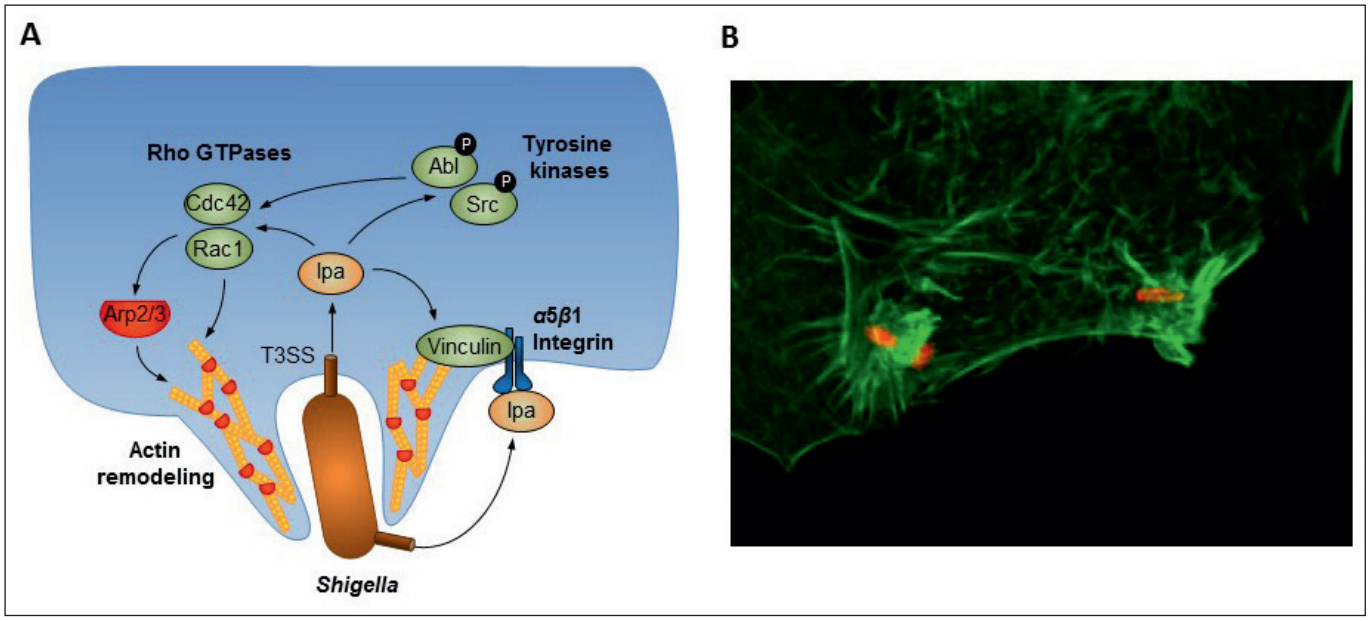


Figure 1: (A) Effector mediated targeting of host cell signaling pathways regulating F-actin dynamics. The pathogen (e.g. *Shigella*) delivers invasion plasmid antigen (Ipa) proteins that induce host cytoskeletal rearrangements on different levels and finally drive bacterial uptake. Ipa proteins activate the Rho GTPases Rac1 and Cdc42 and promote F-actin remodeling via the Arp2/3 complex. Vinculin is either directly or indirectly targeted by Ipa proteins and promotes F-actin reorganization. Tyrosine kinases Abl and Src are activated upon pathogen infection and lead to further F-actin rearrangements. (B) Immunofluorescence micrograph showing F-actin (green) in a HeLa cell that is invaded by *S. flexneri* (red).

tion from pointed ends, thus providing fresh G-actin molecules to the actin pool (reviewed in (Mizuno, 2013)). Because cofilin has emerged as a central player in actin filament turnover and the generation of free barbed ends in various cell lines and organisms its activity needs to be tightly controlled. Several control mechanism such as the intracellular pH, phosphoinositides and the phosphorylation state of serine 3 have been identified (reviewed in (Mizuno, 2013)). Especially the phosphorylation-dependent regulation of cofilin is well understood and involves the balanced action of several kinases and phosphatases. Phosphorylation of cofilin at serine 3 by the LIM kinase (LIMK) family (LIMK1 and LIMK2) and the related testicular protein (TES) kinases turns off the actin-binding activity of cofilin and thus leads to inactivation. On the other hand, dephosphorylation by slingshot (SSH1, SSH2, SSH3) as well as chronophin phosphatases results in reactivation of the actin binding activity of cofilin (reviewed in (Mizuno, 2013)). Accordingly, the level and activity of cofilin kinases and phosphatases are tightly regulated as well by a variety of proteins. Among those is the Rho family of small GTPases. In humans, more than 20 Rho proteins have been identified with RhoA, Rac1 and Cdc42 being the best characterized members (Bos et al., 2007). Rho GTPases are key regulators of the actin and microtubule cytoskeleton, thereby controlling different steps of cell migration, adhesion and polarity, and vesicular trafficking (Hall, 2012). Rho protein activity is tightly controlled in a spatial and temporal manner by three classes of regulators: Firstly, guanine exchange factors (GEFs) promote the exchange of bound GDP for GTP, leading to activation of the Rho GTPase and subsequent binding of downstream effectors. Activated Rho GTPases are targeted to cell membranes by their C-terminal prenyl groups serving as lipid anchors. Secondly, GTPase activating proteins (GAPs) enhance the low intrinsic GTPase function of the Rho proteins thereby leading to their inactivation. Lastly, binding of guanine nucleotide dissociation inhibitors (GDIs) keeps Rho GTPases in the inactive state by preventing the release of GDP or by masking the prenyl group thereby sequestering Rho GTPases in the cytoplasm (Bos et al., 2007).

Rho GTPases and the cofilin signaling network are connected on multiple levels: For example, the Rho effector kinase ROCK directly phosphorylates and activates LIMK on a conserved threonine residue in the activation loop of the kinase domain. In addition, the Cdc42 effector kinase MRCKα acts on both, LIMK1 and 2, whereas the Cdc42 and Rac effector kinases PAK1 and PAK4 exclusively phosphorylate and activate LIMK1 (Scott and Olson, 2007). Other key players in the cofilin signaling network are the three members of the protein kinase D (PKD) family, PKD1, PKD2 and PKD3. The three isoforms are central regulators of vesicular trafficking but also directed cell migration and invasion by controlling F-actin dynamics. PKD is activated downstream of Rho but also Rac and, by direct phosphorylation, impacting its substrates PAK4 and SSH1 in a positive and a negative manner, respectively, the consequence of which is the inactivation of cofilin (Olayioye et al., 2013). Because SSH1 has been recently identified to be a central regulator of NOD1-mediated signaling (Bielig et al., 2014) it is intriguing to speculate that PKD contributes to innate immunity responses as well. This assumption is supported by studies in *C. elegans* showing that animals who have lost DKF-2, a *C. elegans* PKD, were hypersensitive to killing by bacterial pathogens (Ren et al., 2009).

Subversion of actin dynamic by bacterial pathogens

As discussed above, F-actin plays pivotal roles in the regulation of cell shape, polarization and cellular trafficking. Many invasive bacterial pathogens have evolved to subvert these functions for their own benefit (Figure 1). This is most often mediated by secreted virulence proteins (invasion plasmid antigen (Ipa) proteins) from these bacteria that are released by particular secretion apparatuses (T3SS, type 3 secretion system) into the host cell. Targets of bacterial subversion of actin dynamics are among others tyrosine kinases, vinculin and predominantly small GTPases of the Rho family (Figure 1A). Bacteria mainly modify the activity of these enzymes by physical interaction and by chemical modification to induce profound alterations in F-actin that in the case of enteroinvasive bacteria such as *Shigella flexneri* can induce the uptake of the pathogen by epithelial cells (Valencia-Gallardo et al., 2015) (Figure 1B). A long list of examples for both cases is known (for a recent review see (Baxt et al., 2013)) including the SopE2 effector from *Salmonella* that acts as a GEF (Rudolph et al., 1999; Friebel et al., 2001; Schlumberger and Hardt, 2005), YopE from *Yersina pseudotuberculosis* that acts as a GAP (reviewed in (Aepfelbacher et al., 2011)) and C3 exoenzyme of *Clostridium botulinum* that confers ADP-ribosylation of Rho GTPases (reviewed in (Aktories, 2011)), just to name some prominent cases.

The action of all these virulence factors ultimately results in altered actin dynamics that supports the attachment, uptake, cellular movement and cell to cell spread of the pathogens. A promising strategy for the host to detect pathogen invasion thus is to sense perturbations in GTPase controlled cellular processes and changes in F-actin dynamics. Importantly, this pathogen sensing is independent of MAMPs, which can be regulated by pathogens to a certain extent for their own benefit. Such a concept is rather new in the field of mammalian innate immunity which still is mainly based on the view that foreign structures on pathogens are sensed in a more or less direct manner by host receptors. However, in plants it has been supposed that the cytosolic receptors involved in plant immune responses can function as sentinels of perturbations of cellular pathways, and thus act as "guards" for cellular pathways (Dangl et al., 2013). Interestingly, these plant cytosolic receptors share homology to mammalian NLR proteins (Maekawa et al., 2011).

Molecular dissection of the function of mammalian NLR- and related proteins in the context of bacterial infection now recently brought up new exiting findings that suggest that similar principles exist in mammalian cells.

It is known that perturbation of F-actin by depolymerizing drugs affects pro-inflammatory signaling in myeloid cells (Kustermans et al., 2008a; Kustermans et al., 2008b), however we could show that actin depolymerization specifically affects NOD1 and NOD2 signaling (Legrand-Poels et al., 2007; Kufer et al., 2008; Bielig et al., 2014). Moreover, evidence accumulates that Rho GTPase activity also severely affects the outcome of PRR-mediated inflammatory responses. This was shown for TLR2- (Arbibe et al., 2000), NOD1- and NOD2- (Legrand-Poels et al., 2007; Eitel et al., 2008; Fukazawa et al., 2008; Keestra et al., 2013) and NLRP3-mediated (Eitel et al., 2012) responses. The underlying molecular

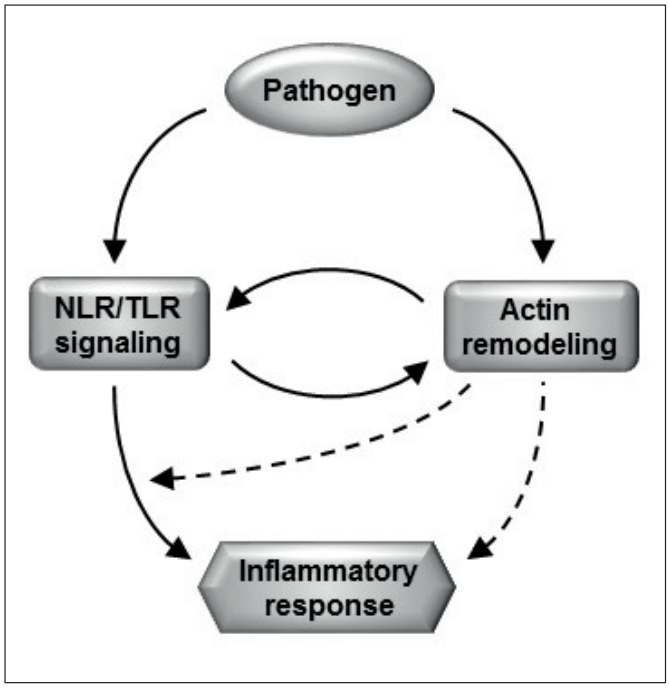


Figure 2: Interplay of NLR/TLR signaling and actin remodeling in pathogen induced inflammatory responses. During infection, innate immune responses are triggered upon recognition of PAMPs by PRRs like NLR or TLR. In parallel, pathogens provoke reorganization of the host actin cytoskeleton, e.g. to enable bacterial uptake. Besides, PRRs directly sense changes in actin remodeling and integrate pathogen induced actin perturbations into innate immune responses.

details of these interconnections still remain largely elusive. A protein that was recently recognized to be able to react towards bacterial induced perturbations of GTPase functions is NOD1. NOD1 is a bona fide PRR and the best described function of NOD1 is the sensing of bacterial peptidoglycan in the cytosol that induces cell-autonomous innate immune responses, which is of particular importance for immune responses towards enteroinvasive bacterial pathogens. These bacteria, such as *Salmonella* and *Shigella* enter epithelial cells by induced uptake upon contact to host cells and delivery of type III effectors to the host cell cytoplasm that induce profound changes in the cortical F-actin network (Figure 1). For invasion of *S. flexneri*, it was reported that GEF-H1, a GEF for RhoA plays an important role in this process. Moreover, NOD1 localizes at F-actin rich structures at the cell cortex and at the site of bacterial invasion (Kufer et al., 2008). Recent evidence now links GEF-H1 to NOD1-mediated detection of the *Shigella* effector proteins (Fukazawa et al., 2008). Notably, induction of inflammatory responses by this pathway requires RhoA mediated activation of Rho-associated protein kinases (ROCKs) (Fukazawa et al., 2008). This would suggest that NOD1 can monitor small Rho GTPase activity in the host cell and translates pathogen induced perturbations into inflammatory responses by activation of NF-κB downstream of NOD1. Evidence for such a function of NOD1 is provided by a study that recently showed that the Rho GEF *Salmonella* SopE can activate NOD1 (Keestra et al., 2013). We recently identified another key component of the F-actin regulatory network, the phosphatase SSH1 as critical component of NOD1-mediated responses (Bielig et al., 2014). Our studies strongly suggest a role of SSH1 in NOD1 signaling as knockdown of cofilin mimicked the effect of SSH1 depletion (Bielig et al., 2014). Furthermore, we showed that modulation of ROCK activity equally resulted in altered NOD1-mediated inflammatory responses (Bielig et al., 2014).

In contrast to data suggesting that NOD1 senses actin perturbation by directly sensing Rho activity, our data rather argue that NOD1 activation by MAMPs results in activation of cofilin, which is a prerequisite of downstream signaling to inflammatory pathways. This on the other hand would offer an opportunity for the host to integrate changes in the F-actin network induced by bacterial effector proteins into pro-inflammatory signaling.

More studies are needed to validate this hypothesis and to bring forward the involved players. However strong support for such a scenario comes from two very recent publications: NLRC4 was shown to induce actin polymerization upon activation and this process was found to be essential for downstream activation of caspase-1 but also for containing intracellular pathogens, as shown for *Salmonella* (Man et al., 2014). Moreover, cofilin was recently found to be a key player in the integration of TLR-mediated and B cell receptor (BCR) signals in B cells (Freeman et al., 2015).

Conclusion

Many bacterial pathogens, including also non-invasive bacteria, such as enteropathogenic *Escherichia coli* induce profound alterations of the cortical F-actin network. We assume that sensing of such perturbations of host cell F-actin could be involved in most innate immune reactions induced by bacterial pathogens (Figure 2) and suggest cofilin as a key player of these responses. Future research will address if and how the members of the cofilin signaling network are regulated upon pathogen invasion to impinge on cofilin activity. This research will also help to answer the critical question in the field that is still controversially discussed: Do pattern-recognition receptors sense changes in Rho GTPase activity directly or integrate pathogen induced responses into innate immune responses by the use of F-actin as a hub to link to inflammatory pathways?

References

Aepfelbacher, M., Roppenser, B., Hentschke, M., and Ruckdeschel, K. (2011). Activity modulation of the bacterial Rho GAP YopE: an inspiration for the investigation of mammalian Rho GAPs. European journal of cell biology 90, 951-954.

Akira, S., Uematsu, S., and Takeuchi, O. (2006). Pathogen recognition and innate immunity. Cell 124, 783-801.

Aktories, K. (2011). Bacterial protein toxins that modify host regulatory GTPases. Nat Rev Microbiol 9, 487-498.

Arbibe, L., Mira, J.P., Teusch, N., Kline, L., Guha, M., Mackman, N., Godowski, P.J., Ulevitch, R.J., and Knaus, U.G. (2000). Toll-like receptor 2-mediated NF-kappa B activation requires a Rac1-dependent pathway. Nat Immunol 1, 533-540.

Bamburg, J.R. (1999). Proteins of the ADF/cofilin family: essential regulators of actin dynamics. Annual review of cell and developmental biology 15, 185-230.

Baxt, L.A., Garza-Mayers, A.C., and Goldberg, M.B. (2013). Bacterial subversion of host innate immune pathways. Science 340, 697-701.

Bernstein, B.W., and Bamburg, J.R. (2010). ADF/cofilin: a functional node in cell biology. Trends in cell biology 20, 187-195.

Bielig, H., Lautz, K., Braun, P.R., Menning, M., Machuy, N., Brugmann, C., Barisic, S., Eisler, S.A., Andree, M., Zurek, B., Kashkar, H., Sansonetti, P.J., Hausser, A., Meyer, T.F., and Kufer, T.A. (2014). The Cofilin Phosphatase Slingshot Homolog 1 (SSH1) Links NOD1 Signaling to Actin

Remodeling. PLoS pathogens 10, e1004351.
Bos, J.L., Rehmann, H., and Wittinghofer, A. (2007). GEFs and GAPs: critical elements in the control of small G proteins. Cell 129, 865-877.
Dangl, J.L., Horvath, D.M., and Staskawicz, B.J. (2013). Pivoting the plant immune system from dissection to deployment. Science 341, 746-751.
Eitel, J., Krull, M., Hocke, A.C., N'Guessan, P.D., Zahlten, J., Schmeck, B., Slevogt, H., Hippenstiel, S., Suttorp, N., and Opitz, B. (2008). Beta-PIX and Rac1 GTPase mediate trafficking and negative regulation of NOD2. J Immunol 181, 2664-2671.
Eitel, J., Meixenberger, K., van Laak, C., Orlovski, C., Hocke, A., Schmeck, B., Hippenstiel, S., N'Guessan, P.D., Suttorp, N., and Opitz, B. (2012). Rac1 regulates the NLRP3 inflammasome which mediates IL-1beta production in Chlamydophila pneumoniae infected human mononuclear cells. PloS one 7, e30379.
Freeman, S.A., Jaumouille, V., Choi, K., Hsu, B.E., Wong, H.S., Abraham, L., Graves, M.L., Coombs, D., Roskelley, C.D., Das, R., Grinstein, S., and Gold, M.R. (2015). Toll-like receptor ligands sensitize B-cell receptor signalling by reducing actin-dependent spatial confinement of the receptor. Nature communications 6, 6168.
Friebel, A., Ilchmann, H., Aepfelbacher, M., Ehrbar, K., Machleidt, W., and Hardt, W.D. (2001). SopE and SopE2 from Salmonella typhimurium activate different sets of RhoGTPases of the host cell. The Journal of biological chemistry 276, 34035-34040.
Fukazawa, A., Alonso, C., Kurachi, K., Gupta, S., Lesser, C.F., McCormick, B.A., and Reinecker, H.C. (2008). GEF-H1 mediated control of NOD1 dependent NF-kappaB activation by Shigella effectors. PLoS pathogens 4, e1000228.
Hall, A. (2012). Rho family GTPases. Biochemical Society transactions 40, 1378-1382.
Kawai, T., and Akira, S. (2011). Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity 34, 637-650.
Keestra, A.M., Winter, M.G., Auburger, J.J., Frassle, S.P., Xavier, M.N., Winter, S.E., Kim, A., Poon, V., Ravesloot, M.M., Waldenmaier, J.F., Tsolis, R.M., Eigenheer, R.A., and Baumler, A.J. (2013). Manipulation of small Rho GTPases is a pathogen-induced process detected by NOD1. Nature 496, 233-237.
Kufer, T.A. (2008). Signal transduction pathways used by NLR-type innate immune receptors. Mol Biosyst 4, 380-386.
Kufer, T.A., Kremmer, E., Adam, A.C., Philpott, D.J., and Sansonetti, P.J. (2008). The pattern-recognition molecule Nod1 is localized at the plasma membrane at sites of bacterial interaction. Cellular microbiology 10, 477-486.
Kustermans, G., El Mjiyad, N., Horion, J., Jacobs, N., Piette, J., and Legrand-Poels, S. (2008a). Actin cytoskeleton differentially modulates NF-kappaB-mediated IL-8 expression in myelomonocytic cells. Biochemical pharmacology 76, 1214-1228.
Kustermans, G., Piette, J., and Legrand-Poels, S. (2008b). Actin-targeting natural compounds as tools to study the role of actin cytoskeleton in signal transduction. Biochemical pharmacology 76, 1310-1322.
Legrand-Poels, S., Kustermans, G., Bex, F., Kremmer, E., Kufer, T.A., and Piette, J. (2007). Modulation of Nod2-dependent NF-kappaB signaling by the actin cytoskeleton. Journal of cell science 120, 1299-1310.
Maekawa, T., Kufer, T.A., and Schulze-Lefert, P. (2011). NLR functions in plant and animal immune systems: so far and yet so close. Nature immunology 12, 817-826.
Man, S.M., Ekpenyong, A., Tourlomousis, P., Achouri, S., Cammarota, E., Hughes, K., Rizzo, A., Ng, G., Wright, J.A., Cicuta, P., Guck, J.R., and Bryant, C.E. (2014). Actin polymerization as a key innate immune effector mechanism to control Salmonella infection. Proceedings of the National Academy of Sciences of the United States of America.
Mizuno, K. (2013). Signaling mechanisms and functional roles of cofilin phosphorylation and dephosphorylation. Cellular signalling 25, 457-469.
Mullins, R.D. (2000). How WASP-family proteins and the Arp2/3 complex convert intracellular signals into cytoskeletal structures. Current opinion in cell biology 12, 91-96.
Olayioye, M.A., Barisic, S., and Hausser, A. (2013). Multi-level control of actin dynamics by protein kinase D. Cellular signalling 25, 1739-1747.
Pollard, T.D. (1990). Actin. Current opinion in cell biology 2, 33-40.
Ren, M., Feng, H., Fu, Y., Land, M., and Rubin, C.S. (2009). Protein kinase D is an essential regulator of C. elegans innate immunity. Immunity 30, 521-532.
Rotty, J.D., Wu, C., and Bear, J.E. (2013). New insights into the regulation and cellular functions of the ARP2/3 complex. Nature reviews. Molecular cell biology 14, 7-12.
Rudolph, M.G., Weise, C., Mirold, S., Hillenbrand, B., Bader, B., Wittinghofer, A., and Hardt, W.D. (1999). Biochemical analysis of SopE from Salmonella typhimurium, a highly efficient guanosine nucleotide exchange factor for RhoGTPases. The Journal of biological chemistry 274, 30501-30509.
Schlumberger, M.C., and Hardt, W.D. (2005). Triggered phagocytosis by Salmonella: bacterial molecular mimicry of RhoGTPase activation/deactivation. Curr Top Microbiol Immunol 291, 29-42.
Scott, R.W., and Olson, M.F. (2007). LIM kinases: function, regulation and association with human disease. Journal of molecular medicine 85, 555-568.
Sept, D., and McCammon, J.A. (2001). Thermodynamics and kinetics of actin filament nucleation. Biophysical journal 81, 667-674.
Valencia-Gallardo, C.M., Carayol, N., and Tran Van Nhieu, G. (2015). Cytoskeletal mechanics during Shigella invasion and dissemination in epithelial cells. Cellular microbiology 17, 174-182.

Authors

Angelika Hausser
studied technical Biology at the University of Stuttgart. She did her PhD with Klaus Pfizenmaier at the Institute of Cell Biology and Immunology in Stuttgart working on the role of protein kinase D at the Golgi compartment and continued with these studies during her postdoc. Since 2003 she leads the PKD signaling group at the Institute of Cell Biology and Immunology, University of Stuttgart.

Kornelia Ellwanger
studied technical Biology at the University of Stuttgart. For her PhD thesis and postdoc, she joined the Lab of Angelika Hausser in 2004 where she works on *in vivo* models to study protein kinase D function.
From April 2015 she will join the group of Thomas Kufer, Department of Immunology at the University of Hohenheim.

Thomas Kufer
studied Biology in Ludwig-Maximilian University in Munich. He did his PhD with Erich Nigg at the MPI in Martinsried working on mitotic kinases. For his postdoc he went to the Institut Pasteur in Paris, France where he worked with Dana Philipott and Philippe Sansonetti on NOD1 and NOD2. He was then an Independent Junior Group Leader within the SFB670 at the Institute for Medical Microbiology, Immunology and Hygiene at the University of Cologne. Since October 2014 he heads the department of Immunology at the University Hohenheim.
Universität Hohenheim, Institut für Ernährungsmedizin,
Fg. Immunologie, Fruwirth Str. 12, 70593 Stuttgart,
thomas.kufer@uni-hohenheim.de

Cellular force generation in focal adhesion maturation and extracellular matrix remodeling

Jessica Morgner[1] and Sara A. Wickström[1, 2]
[1]Paul Gerson Unna Group 'Skin Homeostasis and Ageing', Max Planck Institute for Biology of Ageing, Joseph-Stelzmann Strasse 9b, 50931 Cologne, Germany
[2]CECAD Cologne Excellent in Aging Research, Joseph-Stelzmann Strasse 26, 50931 Cologne, Germany

Abstract
The extracellular matrix (ECM) functions as a structural scaffold for tissues, but it also drives intracellular signaling by interacting with specific receptors and by regulating the bioavailability of growth factors. This unique combination of functions makes the ECM an important regulator of organ development and maintenance. The deposition and remodeling of the ECM into a precise configuration is a cell-dependent process that requires integrin adhesion receptors as well as generation of cellular forces. Integrin-linked kinase (ILK) is an essential adaptor protein that binds to β1- and β3-integrin cytoplasmic tails and links them to the actin cytoskeleton. Our work has uncovered functions of ILK in cellular force transduction and ECM remodeling and the role of these processes in cell fate regulation.

Interactions between cells with their neighbors and the environment not only provide tissues their shape and proper architecture, but also regulate fate decisions of individual cells. Cell-matrix interactions have the potential to propagate signals that regulate proliferation, differentiation, and migration, which ensure coordinated cell behaviors during development and tissue homeostasis (Wickström et al., 2011). Cells further actively remodel the extracellular matrix (ECM) thereby engaging in dynamic crosstalk with their environment (Daley and Yamada, 2013).

The ECM and integrins
The ECM is a complex non-cellular network composed mainly of fibrous proteins and proteoglycans that determine the biochemical and mechanical properties of the tissue. It serves as a physical scaffold, but also as a platform for intercellular communication and as a reservoir for growth factors. Therefore the composition and organization of the ECM needs to be tightly controlled (Frantz et al., 2010; Watt and Fujiwara, 2011; Gattazzo et al., 2014).
Integrins are the major ECM receptors in all metazoans. Accordingly, their main task is to facilitate the adhesion of cells to the ECM. In addition, intracellular coupling of integrins to the actin and intermediate filament cytoskeletons allows generation of traction forces and regulation of cell shape and mechanics. Finally, integrins are able to assemble large intracellular signaling platforms termed focal adhesions (FAs) that activate signaling cascades. These unique features make integrins essential for a large number of cellular processes (Legate et al., 2009; Wickström et al., 2011).
Integrins comprise of 18 α and 8 β subunits that assemble non-covalently into 24 distinct heterodimers (Hynes, 2002). The specific subunit combination determines their binding affinity and ligand specificity. A hallmark of integrin receptors is their ability to mediate bi-directional signaling. "Inside-out" signaling regulates the ligand binding properties of integrins and is induced by

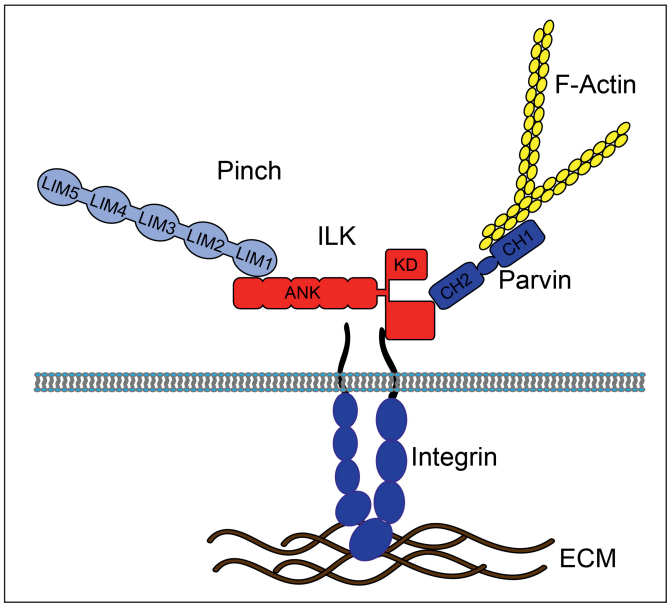


Figure 1: Integrin-linked kinase and its main binding partners
Integrin-linked kinase (ILK) is composed of two domains that are connected by a short linker: the N-terminal ankyrin repeat domain (ARD) and a C-terminal kinase domain (KD). The ARD binds to the LIM1 domain of particularly interesting Cys-His-rich protein (PINCH). The KD of ILK is a protein-protein interaction domain that binds among others to the CH2 domain of parvins and the cytoplasmic tails of β integrins. Parvins are capable of binding F-actin, thereby facilitating a direct link between integrins and the actin cytoskeleton. It is not clear, however, whether ILK binds β integrins directly in vivo and whether parvins can bind actin while bound to ILK (modified from Ghatak et al., 2013).

non-integrin mediated signaling pathways such as growth factor signaling. "Outside-in" signaling regulates cellular responses induced by ligand binding to integrin receptors that regulate cell spreading, migration and proliferation (Hynes, 2002). Upon ligand binding, integrins cluster at the plasma membrane and various integrin-binding proteins are recruited to their cytoplasmic tails to form FAs. These core FA components subsequently recruit a large number of actin-modulatory proteins and signaling molecules allowing actin stress fiber formation, FA maturation, and propagation of intracellular signaling cascades (Legate et al., 2009; Wickström et al., 2011).

Integrin-linked kinase – a pseudokinase with adaptor function

ILK is a central component of β1- and possibly also of β3-integrin adhesion complexes. It is ubiquitously expressed, consists of 452 amino acids, and has a molecular weight of 52 kDa. ILK was originally identified in a yeast two-hybrid screen as a direct binding partner of β1-integrin (Hannigan et al., 1996). Due to its sequence homology to protein kinases as well as in vitro observations showing that ILK is capable of phosphorylating substrates such as GSK-3β and PKB/AKT and β1-integrin, it was initially reported to be a serine/threonine kinase (Hannigan et al., 1996).

ILK is composed of five N-terminal ankyrin repeat (ANK) domains, followed by a pleckstrin homology (PH)-like sequence and an N-terminal kinase domain (KD). Together the five ANK domains form a superhelical spiral that serves as a binding domain for PINCH, another important integrin adaptor (Chiswell et al., 2008). The PH-like sequence of ILK is integrated into the ILK-KD and is in fact not capable of binding the second messenger phosphatidylinositol 3-phosphate (PIP3). The KD of ILK functions as a protein-protein interaction domain that binds among others the calponin homology 2 (CH2) domain of parvin (Fukuda et al., 2009; Stiegler et al., 2013). In cells, ILK, PINCH and parvin are mostly present in a ternary complex within FAs (Fig. 1).
Despite initial in vitro observations of kinase activity, inspection of the KD sequence already raised doubts about its catalytic activity. During phosphotransfer, the DFG (Asp-Phe-Gly) motif that is conserved in most eukaryotic kinases mediates the alignment of the γ-phosphate, but in ILK this motif is replaced by DVK (Asp-Val-Lys). Phosphotransfer further requires the proton acceptance from the hydroxyl group catalyzed by the aspartate residue in the HRD (His-Arg-Asp) motif that is also lacking in ILK (Wickström et al., 2010a). It is generally presumed that the presence of both DFG and HRD motif is required for kinase activity, and no kinase with reported activity lacks both of the motifs (Boudeau et al., 2006).

Definitive proof for the lack of catalytic activity was provided by the crystal structure of the ILK-KD bound to the CH2 domain of α-parvin, one of the 3 mammalian parvin isoforms. It revealed that ILK-KD folds into a typical bilobial kinase structure but it has a dramatically degenerated catalytic core compared to known kinases. The P-loop structure that is essential for ATP-binding contains a non-flexible motif in ILK, which is unable to receive non-transferable phosphates of ATP. Due to the unusual DVK motif the γ-phosphate is abnormally aligned and lies far away from the putative catalytic site. Hence, bound ATP remains in an unhydrolyzed state (Fukuda et al., 2009). It was further demonstrated that kinase activity can be detected in impure protein preparations of recombinant ILK, but this activity is lost upon further purifications steps (Fukuda et al., 2009; Fukuda et al., 2011).

Genetic studies provided further evidence for ILK being a pseudokinase with adaptor function. Deletion of ILK in D. melanogaster leads to embryonic lethality with failure in muscle attachment. Expression of ILK containing a mutation in the kinase domain (E359K) (a reported kinase dead mutant ILK), in ILK-deficient flies completely rescues the phenotype, indicating that ILK fulfills its function independent of kinase activity (Zervas et al., 2001). Similarly, the knockout of pat-4 (paralyzed, arrested elongation at two-fold; C. elegans homolog of ILK) in C. elegans impairs actin and myosin filament recruitment in embryonic muscle, and this can be rescued by the expression of a kinase dead ILK (Mackinnon et al., 2002).

The constitutive deletion of ILK in mice is embryonic lethal (Sakai et al., 2003b). The embryos succumb during peri-implantation due to a failure in epiblast polarization. This is caused by impaired F-actin rearrangement and basement membrane remodeling (Sakai et al., 2003b). In stark contrast, knock-in mice that carry either a R211A mutation within the PH-domain leading to a kinase-dead ILK, or specific mutations within the putative autophosphorylation site leading to a kinase-dead (S343A) or hyperactive (S343D) ILK are viable and healthy and show no differences in phosphorylation of the reported ILK substrates AKT or GSK-3β (Lange et al., 2009), supporting the kinase-independent function of ILK. Knock-in mice with mutations in the ATP-binding site, K220A or K220M, die shortly after birth due to renal dysgenesis (Lange et al., 2009). This mutation in ILK destabilizes the KD and thereby interferes with its ability to bind to α-parvin, demonstrating that ILK-α-parvin interaction is crucial for the function of ILK. α-parvin knockout mice develop similar kidney phenotype as that observed in ILK K220A/M mutants (Lange et al., 2009). Together, all these studies confirm the non-catalytic, adaptor function of ILK.

ILK regulates force generation, adhesion maturation, and actin dynamics

The assembly and remodeling of integrin adhesion complexes is a highly dynamic process that requires the recruitment of adaptor proteins and myosin II-containing actin networks to adhesion sites (Vicente-Manzanares and Horwitz, 2011). Upon cell attachment, integrins bind to the underlying substrate and focal complexes (FCs; also termed nascent adhesions) assemble at the contact site of the cell with the ECM. The maturation of small FCs (~100 nm in size) into large FAs (~1 μm) is driven by active myosin II that enables further recruitment of adhesion-associated proteins with actin-binding or modulatory activity, such as vinculin or paxillin, along polymerizing actin. The integrin-actin connection is subsequently strengthened leading to formation of stress fibers, antiparallel myosin II-containing actin bundles (Zamir and Geiger, 2001; Vicente-Manzanares and Horwitz, 2011).

A large number of studies implicate that the central cellular function of ILK is to regulate adhesion maturation and to establish and maintain the integrin-actin linkage. Mammalian cells lacking ILK display defects in actin reorganization and FA maturation (Sakai et al., 2003b). ILK itself lacks actin-binding properties and the precise molecular details of how ILK regulates actin engagement at FAs are not clear. A possible adaptor linking ILK to actin is parvin that was shown to bind actin through its two in-tandem CH-domains (Olski et al., 2001) (Fig. 1). ILK has also been reported to impact the activity of small GTPases such as RhoA and Rac that modulate actin dynamics but the detailed molecular mechanism of this regulation is not known (Boulter et al., 2006; Kogata et al., 2009; Blumbach et al., 2010). Interestingly, ILK also regulates the architecture and stability of the microtubule network, which might have implications on intracellular signaling as well as on the regulation of GTPase activity (Wickström et al., 2010b).

During FA maturation, the connection between integrin ligands and the actin cytoskeleton is strengthened and myosin II-dependent actin stress fiber formation facilitates cell contraction (Schiller and Fässler, 2013). ILK-deficient fibroblasts display large FAs at the cell edges but absence of nascent FCs and fibrillar adhesions (FBs), a specialized type of adhesion involved in ECM remodeling (Stanchi et al., 2009; Radovanac et al., 2013) (Fig. 2A). It has been proposed that ILK collaborates with α-parvin to segregate α5β1 integrins from FAs, thus allowing the recruitment of tensin and maturation of FBs (Stanchi et al., 2009). Furthermore, the actin cytoskeleton of ILK-deficient fibroblasts is disorganized and poorly linked to the abnormal FAs (Sakai et al., 2003b). As a consequence, these cells are severely compromised in their ability to generate traction forces and to exert force on the underlying ECM (Radovanac et al., 2013) (Fig. 2B, C). Collectively these data indicate that ILK is important for adhesion maturation by acting as an adaptor to establish and maintain the integrin-actin linkage.

ILK is essential for ECM remodeling

During FA maturation fibronectin (FN)-bound integrins such as α5β1 are segregated along the actin cytoskeleton. The subsequent generation of cellular forces and recruitment of additional adaptor proteins such as tensin induces FB formation (Pankov et al., 2000). The cellular force that is applied on FN leads to its conformational changes and self-assembly, resulting in FN fibrillogenesis (Zamir et al., 2000; Ohashi et al., 2002). FB maturation is a prerequisite for subsequent FN fibrillogenesis. Although the expression of FN in ILK-deficient fibroblasts is unaltered compared to controls, FN fibrillogenesis is absent (Radovanac et al., 2013) (Fig. 2D). As the affinity of integrin α5β1 to its ligand FN

is not altered in ILK-deficient cells (Vouret-Craviari et al., 2004), the defect in matrix assembly most likely results from the impairment in force generation and the failure to form FBs.

Interestingly, it was recently shown that the recruitment of most proteins to adhesion sites is dependent on myosin II activity (Schiller and Fässler, 2013). However, ILK recruitment to FA sites occurs independent of myosin II activity (Schiller and Fässler, 2013), suggesting that ILK might act upstream and be involved in myosin II-dependent recruitment of other FA components. Our finding that ILK is required for the generation of traction forces provides further functional evidence for this notion (Fig. 2B). This inability to generate force is very likely to affect further recruitment of FB-associated proteins, leading to the observed failure in ECM remodeling in ILK-deficient fibroblasts (Fig. 2D). Besides driving α5β1 integrin segregation along the actin cytoskeleton, ILK could additionally be involved in mediating force-dependent conformational changes in α5β1 integrins, which occur during fibrillogenesis (Clark et al., 2005).

Although α5β1 integrin is the primary FN receptor (Huveneers et al., 2008), integrin αvβ3 (Wennerberg et al., 1996), α4β1 (Sechler et al., 2000) and αIIbβ3 (Olorundare et al., 2001) have been shown to be involved in FN fibrillogenesis in vitro. Knockout studies in mice suggest overlapping as well as independent functions for α5- and αv-class integrins in this process and only the double knockout of α5- and αv- integrins in mice results in loss of fibrillogenesis (Yang et al., 1999). It is tempting to speculate that ILK, through its ability to bind both to β1- and β3-integrins, might be involved in their differential engagement and thereby in fine-tuning the forces required for FN fibrillogenesis.

It has been proposed that the assembly state of FN fibers plays an important role in regulating cell behavior by acting as a checkpoint signal for subsequent ECM remodeling (Schwarzbauer and DeSimone, 2011). For instance, only the precise ratio of FN fibril assembly ensures epithelial branching morphogenesis during cleft formation (Sakai et al., 2003a). Furthermore, FN fibrillogenesis regulates fibrillin-1 microfibril assembly (Kinsey et al., 2008) and could thereby impact the ability of these

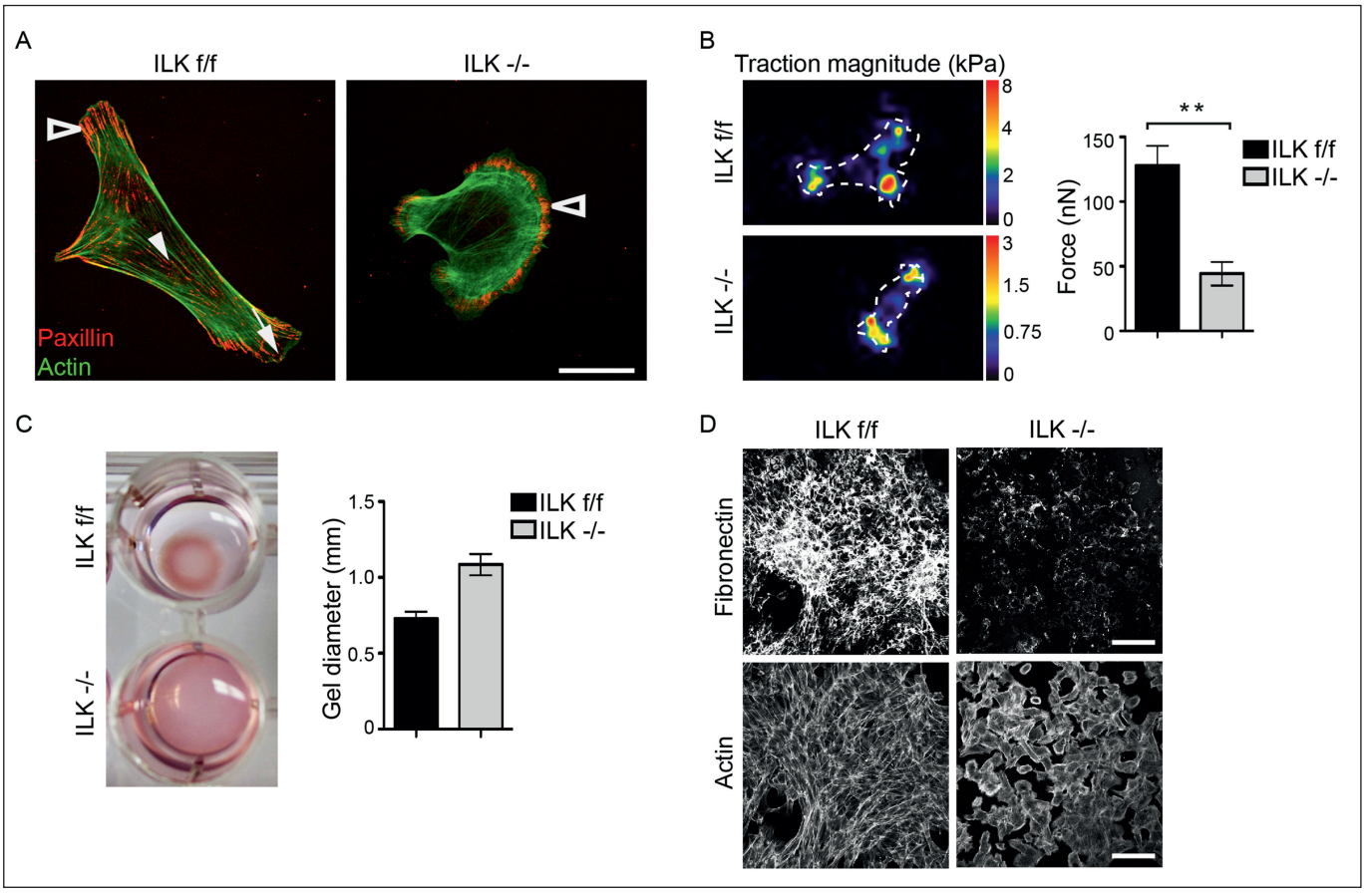


Figure 2: Integrin-linked kinase is required for focal adhesion maturation, cellular force generation and extracellular matrix deposition
A. Immunofluorescence analysis of paxillin as a marker for focal adhesions and F-actin in fibroblasts. Wild type fibroblasts display small focal complexes (arrow), focal adhesions (open arrowhead), and fibrillar adhesions (arrowhead), which are tightly connected to the actin cytoskeleton. Note lack of focal complexes and fibrillar adhesions, reduced amount of actin stress fibers, and accumulation of large peripheral focal adhesions (open arrowhead) in ILK-deficient cells. Scale bar 25 µm. B. Left panel shows a heat-scale map of traction stress magnitudes obtained using traction force microscopy. The color code indicates local traction in kPa. Cell outlines are indicated by dotted lines. Right panel shows the quantification of total cellular traction forces (mean ± SEM, n>30, **p=0.0011). Deletion of ILK severely compromises the ability of fibroblasts to generate traction forces. C. Collagen gel contraction assay with ILK f/f and -/- fibroblasts. Deletion of ILK impairs the ability of fibroblasts to contract collagen gels. D. Immunofluorescence staining of the fibronectin matrix and the actin cytoskeleton (phalloidin) to visualize cell area. Note decreased matrix deposition in ILK -/- cells. Scale bar 100 µm (modified from Radovanac et al., 2013).

structures to bind and regulate growth factor bioavailability. Therefore it is becoming clear that the ECM-remodeling function of ILK is central to its role as an essential regulator of cell and tissue behavior. It will be of great interest to evaluate how force-induced fibril assembly driven by ILK impacts these processes and what is the role of ECM remodeling in the various phenotypes of ILK-deficient mice.

ILK in dermal tissue repair and fibrosis

ECM deposition is an indispensible, but transient and reversible process during wound healing. When disturbed, it can convert tissue repair into a progressive and irreversible fibrotic response, leading to hypertrophic scarring, keloids or fibrosis. This results in destruction of normal tissue architecture and compromised organ function (Gabrielli et al., 2009; Hunzelmann and Krieg, 2010; Wynn and Ramalingam, 2012). ILK has important functions both during physiological tissue repair as well as in fibrosis. Deletion of ILK in dermal fibroblasts in mice results in impaired myofibroblast generation during wound healing, compromising matrix remodeling and subsequently tissue repair (Blumbach et al., 2010; Vi et al., 2011).

Interestingly, ILK, due to its kinase fold, is a substrate of the chaperone Heat shock protein 90 (Hsp90) that is required to stabilize ILK. Inhibition of Hsp90 activity in fibroblasts therefore leads to degradation and subsequent depletion of ILK protein, inducing a cellular phenotype closely resembling ILK-deficient cells (Radovanac et al., 2013). Consequently, blocking Hsp90 activity severely attenuates myofibroblast generation and the development of skin fibrosis in mice (Radovanac et al., 2013). This might provide a potential therapeutic strategy to treat fibrotic disease.

Interestingly, rigidity and mechanical stability of the matrix, in conjunction with the key profibrotic mediator transforming growth factor β1 (TGFβ1), act as the primary stimulus for myofibroblast differentiation and persistence (Tomasek et al., 2002; Nakamura-Wakatsuki et al., 2012). Furthermore, myofibroblasts can activate latent TGFβ1 that is bound to the ECM using integrin-mediated contraction, suggesting that activation of TGFβ1 is driven by a mechanical mode of action. In this respect it is interesting to note that ILK-deficient fibroblasts show impaired differentiation into myofibroblasts, and decreased release of TGFβ1 (Blumbach et al., 2010; Vi et al., 2011; Radovanac et al., 2013).

Concluding remarks

To conclude, recent work from our lab and others has identified mechanisms by which integrins, through adaptors such as ILK, transduce traction forces that are central to adhesion maturation, regulation of cell shape and migration as well as ECM remodeling. In addition, this work has revealed exciting new mechanisms by which kinase domains can be utilized as specific protein-protein interaction domains by pseudokinases. An important aim for future work is to understand the precise mechanisms by which cellular behavior is regulated by the dynamic crosstalk between cells and their immediate ECM microenvironment.

Acknowledgements

The ILK work in the Wickström lab is supported by the Max Planck Society and by the DFG (SFB 829, WI 4177/2).

References

Blumbach, K., Zweers, M.C., Brunner, G., Peters, A.S., Schmitz, M., Schulz, J.N., Schild, A., Denton, C.P., Sakai, T., Fassler, R., Krieg, T., and Eckes, B. (2010). Defective granulation tissue formation in mice with specific ablation of integrin-linked kinase in fibroblasts - role of TGFbeta1 levels and RhoA activity. Journal of cell science 123, 3872-3883.

Boudeau, J., Miranda-Saavedra, D., Barton, G.J., and Alessi, D.R. (2006). Emerging roles of pseudokinases. Trends Cell Biol 16, 443-452.

Boulter, E., Grall, D., Cagnol, S., and Van Obberghen-Schilling, E. (2006). Regulation of cell-matrix adhesion dynamics and Rac-1 by integrin linked kinase. FASEB journal : official publication of the Federation of American Societies for Experimental Biology 20, 1489-1491.

Chiswell, B.P., Zhang, R., Murphy, J.W., Boggon, T.J., and Calderwood, D.A. (2008). The structural basis of integrin-linked kinase-PINCH interactions. Proc Natl Acad Sci U S A 105, 20677-20682.

Clark, K., Pankov, R., Travis, M.A., Askari, J.A., Mould, A.P., Craig, S.E., Newham, P., Yamada, K.M., and Humphries, M.J. (2005). A specific alpha5beta1-integrin conformation promotes directional integrin translocation and fibronectin matrix formation. Journal of cell science 118, 291-300.

Daley, W.P., and Yamada, K.M. (2013). ECM-modulated cellular dynamics as a driving force for tissue morphogenesis. Current opinion in genetics & development 23, 408-414.

Frantz, C., Stewart, K.M., and Weaver, V.M. (2010). The extracellular matrix at a glance. Journal of cell science 123, 4195-4200.

Fukuda, K., Gupta, S., Chen, K., Wu, C., and Qin, J. (2009). The pseudoactive site of ILK is essential for its binding to alpha-Parvin and localization to focal adhesions. Mol Cell 36, 819-830.

Fukuda, K., Knight, J.D., Piszczek, G., Kothary, R., and Qin, J. (2011). Biochemical, proteomic, structural, and thermodynamic characterizations of integrin-linked kinase (ILK): cross-validation of the pseudokinase. J Biol Chem 286, 21886-21895.

Gabrielli, A., Avvedimento, E.V., and Krieg, T. (2009). Scleroderma. N Engl J Med 360, 1989-2003.

Gattazzo, F., Urciuolo, A., and Bonaldo, P. (2014). Extracellular matrix: a dynamic microenvironment for stem cell niche. Biochim Biophys Acta 1840, 2506-2519.

Hannigan, G.E., Leung-Hagesteijn, C., Fitz-Gibbon, L., Coppolino, M.G., Radeva, G., Filmus, J., Bell, J.C., and Dedhar, S. (1996). Regulation of cell adhesion and anchorage-dependent growth by a new beta 1-integrin-linked protein kinase. Nature 379, 91-96.

Hunzelmann, N., and Krieg, T. (2010). Scleroderma: from pathophysiology to novel therapeutic approaches. Exp Dermatol 19, 393-400.

Huveneers, S., Truong, H., Fassler, R., Sonnenberg, A., and Danen, E.H. (2008). Binding of soluble fibronectin to integrin alpha5 beta1 - link to focal adhesion redistribution and contractile shape. Journal of cell science 121, 2452-2462.

Hynes, R.O. (2002). Integrins: bidirectional, allosteric signaling machines. Cell 110, 673-687.

Kinsey, R., Williamson, M.R., Chaudhry, S., Mellody, K.T., McGovern, A., Takahashi, S., Shuttleworth, C.A., and Kielty, C.M. (2008). Fibrillin-1 microfibril deposition is dependent on fibronectin assembly. Journal of cell science 121, 2696-2704.

Kogata, N., Tribe, R.M., Fassler, R., Way, M., and Adams, R.H. (2009). Integrin-linked kinase controls vascular wall formation by negatively regulating Rho/ROCK-mediated vascular smooth muscle cell contraction. Genes Dev 23, 2278-2283.

Lange, A., Wickström, S.A., Jakobson, M., Zent, R., Sainio, K., and Fässler, R. (2009). Integrin-linked kinase is an adaptor with essential functions during mouse development. Nature 461, 1002-1006.

Legate, K.R., Wickström, S.A., and Fässler, R. (2009). Genetic and cell biological analysis of integrin outside-in signaling. Genes Dev 23, 397-418.

Mackinnon, A.C., Qadota, H., Norman, K.R., Moerman, D.G., and Williams, B.D. (2002). C. elegans PAT-4/ILK functions as an adaptor protein within integrin adhesion complexes. Current biology 12, 787-797.

Nakamura-Wakatsuki, T., Oyama, N., and Yamamoto, T. (2012). Local injection of latency-associated peptide, a linker propeptide specific for active form of transforming growth factor-beta1, inhibits dermal sclerosis in bleomycin-induced murine scleroderma. Exp Dermatology 21, 189-194.

Ohashi, T., Kiehart, D.P., and Erickson, H.P. (2002). Dual labeling of the fibronectin matrix and actin cytoskeleton with green fluorescent protein variants. Journal of cell science 115, 1221-1229.

Olorundare, O.E., Peyruchaud, O., Albrecht, R.M., and Mosher, D.F. (2001). Assembly of a fibronectin matrix by adherent platelets stimulated by lysophosphatidic acid and other agonists. Blood 98, 117-124.

Olski, T.M., Noegel, A.A., and Korenbaum, E. (2001). Parvin, a 42 kDa focal adhesion protein, related to the alpha-actinin superfamily. Journal of cell science 114, 525-538.

Pankov, R., Cukierman, E., Katz, B.Z., Matsumoto, K., Lin, D.C., Lin, S., Hahn, C., and Yamada, K.M. (2000). Integrin dynamics and matrix assembly: tensin-dependent translocation of

alpha(5)beta(1) integrins promotes early fibronectin fibrillogenesis. J Cell Biol 148, 1075-1090.
Radovanac, K., Morgner, J., Schulz, J.N., Blumbach, K., Patterson, C., Geiger, T., Mann, M., Krieg, T., Eckes, B., Fässler, R., and Wickström, S.A. (2013). Stabilization of integrin-linked kinase by the Hsp90-CHIP axis impacts cellular force generation, migration and the fibrotic response. EMBO J 32, 1409-1424.
Sakai, T., Larsen, M., and Yamada, K.M. (2003a). Fibronectin requirement in branching morphogenesis. Nature 423, 876-881.
Sakai, T., Li, S., Docheva, D., Grashoff, C., Sakai, K., Kostka, G., Braun, A., Pfeifer, A., Yurchenco, P.D., and Fässler, R. (2003b). Integrin-linked kinase (ILK) is required for polarizing the epiblast, cell adhesion, and controlling actin accumulation. Genes Dev 17, 926-940.
Schiller, H.B., and Fässler, R. (2013). Mechanosensitivity and compositional dynamics of cell-matrix adhesions. EMBO reports 14, 509-519.
Schwarzbauer, J.E., and DeSimone, D.W. (2011). Fibronectins, their fibrillogenesis, and in vivo functions. Cold Spring Harb Perspect Biol 3.
Sechler, J.L., Cumiskey, A.M., Gazzola, D.M., and Schwarzbauer, J.E. (2000). A novel RGD-independent fibronectin assembly pathway initiated by alpha4beta1 integrin binding to the alternatively spliced V region. Journal of cell science 113, 1491-1498.
Stanchi, F., Grashoff, C., Nguemeni Yonga, C.F., Grall, D., Fässler, R., and Van Obberghen-Schilling, E. (2009). Molecular dissection of the ILK-PINCH-parvin triad reveals a fundamental role for the ILK kinase domain in the late stages of focal-adhesion maturation. Journal of cell science 122, 1800-1811.
Stiegler, A.L., Grant, T.D., Luft, J.R., Calderwood, D.A., Snell, E.H., and Boggon, T.J. (2013). Purification and SAXS analysis of the integrin linked kinase, PINCH, parvin (IPP) heterotrimeric complex. PLoS One 8, e55591.
Tomasek, J.J., Gabbiani, G., Hinz, B., Chaponnier, C., and Brown, R.A. (2002). Myofibroblasts and mechano-regulation of connective tissue remodelling. Nature reviews. Molecular cell biology 3, 349-363.
Vi, L., de Lasa, C., DiGuglielmo, G.M., and Dagnino, L. (2011). Integrin-linked kinase is required for TGF-beta1 induction of dermal myofibroblast differentiation. J Invest Dermatol 131, 586-593.
Vicente-Manzanares, M., and Horwitz, A.R. (2011). Adhesion dynamics at a glance. Journal of cell science 124, 3923-3927.
Vouret-Craviari, V., Boulter, E., Grall, D., Matthews, C., and Van Obberghen-Schilling, E. (2004). ILK is required for the assembly of matrix-forming adhesions and capillary morphogenesis in endothelial cells. Journal of cell science 117, 4559-4569.
Watt, F.M., and Fujiwara, H. (2011). Cell-extracellular matrix interactions in normal and diseased skin. Cold Spring Harb Perspect Biol 3.
Wennerberg, K., Lohikangas, L., Gullberg, D., Pfaff, M., Johansson, S., and Fassler, R. (1996). Beta 1 integrin-dependent and -independent polymerization of fibronectin. J Cell Biol 132, 227-238.
Wickström, S.A., Lange, A., Hess, M.W., Polleux, J., Spatz, J.P., Kruger, M., Pfaller, K., Lambacher, A., Bloch, W., Mann, M., Huber, L.A., and Fässler, R. (2010b). Integrin-linked kinase controls microtubule dynamics required for plasma membrane targeting of caveolae. Dev Cell 19, 574-588.
Wickström, S.A., Lange, A., Montanez, E., and Fässler, R. (2010a). The ILK/PINCH/parvin complex: the kinase is dead, long live the pseudokinase! EMBO J 29, 281-291.
Wickström, S.A., Radovanac, K., and Fässler, R. (2011). Genetic analyses of integrin signaling. Cold Spring Harb Perspect Biol 3.
Wynn, T.A., and Ramalingam, T.R. (2012). Mechanisms of fibrosis: therapeutic translation for fibrotic disease. Nature Medicine 18, 1028-1040.
Yang, J.T., Bader, B.L., Kreidberg, J.A., Ullman-Cullere, M., Trevithick, J.E., and Hynes, R.O. (1999). Overlapping and independent functions of fibronectin receptor integrins in early mesodermal development. Developmental biology 215, 264-277.
Zamir, E., and Geiger, B. (2001). Molecular complexity and dynamics of cell-matrix adhesions. Journal of cell science 114, 3583-3590.
Zamir, E., Katz, M., Posen, Y., Erez, N., Yamada, K.M., Katz, B.Z., Lin, S., Lin, D.C., Bershadsky, A., Kam, Z., and Geiger, B. (2000). Dynamics and segregation of cell-matrix adhesions in cultured fibroblasts. Nature cell biology 2, 191-196.
Zervas, C.G., Gregory, S.L., and Brown, N.H. (2001). Drosophila integrin-linked kinase is required at sites of integrin adhesion to link the cytoskeleton to the plasma membrane. J Cell Biol 152, 1007-1018.

5th Annual Symposium "Physics of Cancer",

This 5th Annual Symposium "Physics of Cancer", October 2nd to 5th, was special in many ways: Scientifically excellent, it was demanding their German participants to give up on a German holiday and therefore a long weekend. This holiday was the 3rd of October, the day celebrating the German reunification. However, where is a better place to remember this event than directly in Leipzig?

And we chose a special way to celebrate such an important event for Germany: By looking forward, forward to future, forward to science. By assembling international scientists of 14 different countries – with PIs and students coming places as far as from New Zealand! – and by discussing the latest concepts in understanding and treatment of cancer. However, this was not a 'conventional' cancer meeting but in this notable gathering of scientists from all disciplines, physicists to physicians, provided a special way of looking at cancer! And of course the physical view dominated. So questions asked – and sometimes answered – were not which medication is changing this or that molecular event, but how it might change the physical properties of the tissue, the cancer cells or the surrounding materials. Physical properties are for example the stiffness of cells, but also their refractive index, their migration speed or migration persistence. Mechanical properties of cancer cells are specifically interesting for the physicist and many of the participants work on such problems. We therefore had even two sessions on this topic, ranging from the idea of applying pressure to cancer tissue in order to stop it growing (Giovanni Cappello) up to the question how cancerous transformed cells sense the stiffness of their environment compared to healthy cells (Paul Janmey).

Furthermore, the technical aspect how physical tools can be used in order to shed new light on cancer was investigated. Here, we had a whole session on microtools which are used for cancer research, such a small, artificial channels to investigate the migration of cancer cells (Ben Fabry, Matthieu Piel) or how to hold a huge number of single floating cells so that we can investigate them further (Dino Di Carlo). Since mechanical properties of cells are closely related to the cytoskeleton, the cortex and the membrane, one session was dedicated to such issues: Patricia Bassereau reported on the way of pulling tubes out of membranes. The role of actin and microtubules in cancer were discussed by many of the participants. And even theoretical physicists joined us and presented models about how we could understand changed cellular reactions in cancer, such as an altered migration (Raphael Voituriez and Claudia Fischbach-Teschl).

However, we were happy that we had the possibility not only to listen to the long standing principle investigators, which can always give excellent presentations within a large context, but who are not the ones actually doing the experiments anymore. Those are the PhD students and the Postdocs, who are working for months on small problems that are so important in order to understand the big picture. Hence, we were lucky to listen to nine chosen presentations of junior scientists ranging from the mechanics of human cancer tissue (Anatol Fritsch) up to the movement of cancerous cell pairs on circular patterns (Felix Jakob Segerer). Since we were not able to give all junior scientists a platform presentation, we then enjoyed a whole evening with the discussion of 36 excellent posters.

After all this exciting science, we did not turn away our faces from history and tradition, not at all. In the evening of the 3rd of October, all participants enjoyed a mess at the famous Thomas church and together visited a museum dedicated to the German reunification (Zeitgeschichtliches Forum).

The conference was a great success and many participants stayed in contact afterwards, working on new or already on-going collaborations. We hope the next symposium of this conference cycle, again in Leipzig, 7th – 9th of September 2015, will bring parts of us together once more in order to pick up the discussions. Of course we hope further that we will attract new people, with new ideas and new methods to communicate, so that we can face this big cancer concern together – in a physical but integrative approach!

Franziska Lautenschläger

The 6th Symposium Physics of Cancer

will take place in Leipzig from September 7 to 9th 2015.

In continuation to the previous successful meetings, we will bring together researchers from the worldwide pioneering groups that are concerned with investigating the physical mechanisms underlying cancer progression.

Topics

- Biomechanics - Biopolymers, Networks, Rheology, Cytoskeleton, Cell Shape, Extracellular Matrix
- Forces, Motion, Adhesion - Cell Motility, Assembly, Molecular Motors, Cell Division
- Oncology
- Imaging

Organizing Committee

Franziska Lautenschläger, University of Saarbrücken

Darius Köster, National Centre for Biological Sciences ,Bangalore

Harald Herrmann, German Cancer Research Center, Heidelberg

Joachim Spatz, MPI for Intelligent Systems, Stuttgart

Josef Käs, University of Leipzig

PoC

www.uni-leipzig.de/poc/

Meeting report of the DGZ study group 'Signal Transduction' and its participation in the 18th Joint Meeting "Signal Transduction – Receptors, Mediators and Genes"

Katharina Kubatzky, Frank Entschladen, Klaudia Giehl, Ottmar Janssen and Ralf Hass

As in the previous years, the annual Joint Meeting "Signal Transduction – Receptors, Mediators and Genes" again took place in Weimar (November 5-7 2014). This 18th meeting was organized by the Signal Transduction Society (STS) and the signaling study groups of the German Societies for Cell Biology (DGZ), for Biochemistry and Molecular Biology (GBM) as well as two study groups of the German Society for Immunology (DGfI) on "Signal Transduction" and on the "Biology of B Cells". Since 2013 the German Society for Pharmacology (DGP) also supports this meeting by organising a workshop on G Proteins and GPCRs. Other financial and scientific contributions were made by the SFB 854 from Magdeburg on the "Molecular Organisation of Cellular Communication in the Immune System" (B. Schraven, Magdeburg) and the BMBF e:Bio network T-Sys (R. Baumgrass, Berlin). The conference organisation was performed by the STS council together with the chairpersons of the study groups and members of the STS Advisory Board.

The special focus of the 2014 meeting was 'Signaling in Immune Cells' with a number of exciting keynote lectures. Joachim Schultze (Bonn), Andreas Radbruch (Berlin), Thomas Höfer (Heidelberg) covered aspects of signalling in the innate adaptive immune system and the possibilities of computational analysis of such molecular networks, while Gottfried Baier (Innsbruck, Austria) put emphasis on Bench to Clinic approaches and Vigo Heissmeyer (München) focussed on the post-transcriptional regulation of T cell differentiation. The many other facets of signal transduction were addressed in workshops on "G Proteins and GPCRs" with a keynote lecture by Silvano Sozzani (Brescia, Italy), "Pathogens and Disease" with a keynote talk by Frank Kirchhoff (Ulm), and the session on "Differentiation, Stress, and Death" which was introduced in a presentation by Henning Walczak (London, UK). Moreover, Lucia Kucerova (Bratislava, Slovakia) presented a keynote lecture in the DGZ-sponsored workshop "Tumor Biology" which was organized by the signaling study group of the DGZ. By introducing several cellular models, Dr. Kucerova focused on the role of mesenchymal stroma/stem cells (MSC) during tumor development, particularly breast cancer. She demonstrated stimulation of tumor growth as well as inhibitory effects by MSC depending on a variety of different interactions between MSC and breast cancer cells which may similarly take place in vivo.

The STS/CCS honorary medal 2014 was awarded to Nobel laureate Jules Hoffmann by the CCS Editor-in-Chief and members of the STS and STS council (from left to right: Frank Entschladen, Ralf Hass, Dieter Kabelitz, Jules Hoffmann, Stephan Feller, Klaudia Giehl, Ottmar Janssen).

All keynote lectures were followed by a number of short talks selected from the submitted abstracts. Here, the mixture of presentations given by group leaders, post-doctoral fellows and also a number of PhD students was highly appreciated as a unique feature of the STS meetings.

Since 2010, the STS honors an outstanding scientist in the field of signal transduction research to conclude the workshop program with a "Honorary Medal Lecture". The STS/CCS Honorary Medal was introduced by the STS in cooperation with the open access journal

STS stipends are awarded to 10 young scientists by STS council members Klaudia Giehl (right) and Ralf Hass (left)

"Cell Communication and Signaling" (CCS). Following Tony Pawson in 2010, Tony Hunter in 2011, Carl-Henrik Heldin in 2012, and Klaus Rajewsky in 2013, the Nobel prize winner Jules Hoffmann from Strasbourg (France) received this year's STS/CCS Honorary medal. The laudatio was given by Dieter Kabelitz (Kiel). In his award lecture entitled "Innate Immunity – from Flies to Humans", Jules Hoffmann described his discovery of similarities of genes and signaling pathways between mammals and insects, leading to the description of the Toll pathway that controls the response of the host organism to a challenge by microorganisms. The audience of the STS conference was taken in by his charismatic presentation and he received a well-deserved long-lasting applause for his presentation.

Another important aspect of the STS joint meeting has always been the support of young scientists. This year, as many as 10 Bachelor/Master or MD/PhD students received travel grants of 2,500.-- € in total to support their meeting attendance. All poster presenters again had the chance to attract the audience to their posters during the well-known 'one minute – one transparency' session which was again a great success. Moreover, five poster prizes were selected from the more than 60 poster presentations and rewarded with a total of 750.-- € of prize money.

STS Science Award 2014 ceremony sponsored by BIOMOL GmbH (from left to right: Klaudia Giehl, Andreas Linkermann, Ralf Hass, Edgar Lipsius)

This year's STS Science Award of 1,000.-- €, sponsored again by BIOMOL GmbH (**www.biomol.de/company_pressemappe.html**) was received by Andreas Linkermann (Kiel), who presented data on a new tightly-regulated cell death program which contributes to organ failure, predominantly renal function collapse.

All in all, the 2014 Meeting 'Signal Transduction' was again a great success. The preparations for the 19th Joint meeting with a special focus on "Tumor Biology" have already started. The meeting is scheduled for November 2nd to 4th, 2015 and will again take place at the Leonardo Hotel in the historical city of Weimar. Details and updated information will be available at **www.sigtrans.de**

Report of the Workshop "Cell Biology of Viral Infections"

Steeve Boulant and Claudia Claus

Dr. Steeve Boulant (Heidelberg) and Dr. Claudia Claus (Leipzig) took on the task of organizing the 13th annual workshop on "Cell Biology of Viral Infection". This year's conference was no longer held at the traditional site of Ketschauer Hof in Deidesheim but was moved to the Kloster Schöntal in Schöntal, Germany. The participants were all very enthusiastic about the location change and enjoyed being able to stay directly at the conference site, and having evening gatherings and wine tasting in the cellar. The very active, lively and interested participations of the attendees during the seminar sessions had a very positive impact on the course of this year's meeting, which, from the beginning to the end, was a real success for us.

The theme of this year's workshop was "Mimicking Organ Physiology: Impact of Stem Cells and Tissue Engineering on Virology". This topic was chosen to help advance the current classical culture systems used by virologist. The workshop was held from the 19th-21st of November and we were very happy to have four keynote lecturers, which are leaders in the field of stem cell biology. The workshop was opened with a fantastic lecture by Dr. Micha Drukker on the "Fate Choice of Pluripotent Stem Cells". Dr. Drukker is the head of the research group "Human Pluripotent Stem Cell Lineage Choice Research" at the Institute for Stem Cell Research at the Helmholtz Zentrum München. Since most participants were from a virology background, Dr. Drukker gave a nice introduction to the field of pluripotent stem cells. He also showed exciting data from his lab demonstrating the post-transcriptional changes of transcription factors, which leads to exiting a pluripotent state and how they were able to identify surface markers to differentiate stem cells subtypes. Finally, he described the recently unraveled phenomenon of paraspeckles, which marks cells that have undergone differentiation.

The following day, two fabulous lectures from Prof. Petra Boukamp and Prof. Catherine Verfaillie gave us detailed examples to obtain specific organ cultures close to physiology from stem cells. First, Prof. Petra Boukamp from the German Cancer Research Center (DKFZ) discussed "Goodbye Flat Biology: the Role of the Microenvironment in Normal Human Skin and Skin Cancer". She described beautifully the years of work from her lab showing the development of a 3D human skin cell model. They found that mice are unable to substitute as a model due to their drastically different tissue organization. Additionally, she showed that a 2D culture system is also not sufficient and a 3D structure is essential for the skin growth because a layered organization is needed. This layered structure allows for the expression of growth factors in the proper time and space. This elegant model has then been used to answer questions about skin regeneration, and how cancer can develop and vascularize in skin tissue. Next, Prof. Catherine Verfaillie of the Stem Cell Institute of the University of Leuven in Belgium discussed "Creating and Engineering Hepatocytes from Pluripotent Stem Cells". Prof. Verfaille's research group is using many state-of the art techniques to genetically modify and visualize stem cells. This has allowed for the generation of a hepatocyte culture model from stem cells, which was of particular interest to many hepatitis virologist in the audience. The final day was concluded with a lecture from Prof. Ian Chambers from the MRC Centre for Regenerative Medicine at the University of Edinburgh on "Transcription Control of Pluripotent Cell States". His group was the first to discover Nanog, which is a key factor for the maintenance of stem cell pluripotency. He discussed the impressive work from his lab in unraveling the expression patterns of proteins, which regulate the process of self-renewal and cell differentiation.

This year's workshop was attended by 32 participants coming from most regions in Germany and also from Bordeaux, France. The majority of participants were virology students and post-doctoral fellows. The participants gave presentations on three virology themes: "Virus-Host Interactions", "Virus in 3D Culture Model" and "Virus Assembly and Replication". These presentations covered a large variety of RNA and DNA viruses and discussed topics from virus entry, and replication to

sensing by the innate immune system. There were also talks on using 3D cell culture systems to study viral infection and using viruses as models for drug delivery design. This year Sarah Hofmann from the group of Dr. Eva Herker at Heinrich-Pette-Institute in Hamburg was awarded a prize for the best student presentation with the title "HCV's interaction with host lipid metabolism". Sarah discussed how she has performed lipid profiling to determine how lipids change during hepatitis C virus infection. Her award will allow for her to attend next year's workshop for free.

The workshop would like to thank the German Society for Cell Biology (DGZ), the Society for Virology (GfV) and the company Reblikon for their years of both financial and administrative support of the workshop. Additionally, this workshop would not have been possible without the generous sponsorship of the Chica and Heinz Schaller (CHS) Foundation and Peprotech. We would like to thank all the keynote speakers for their exciting presentations on stem cell biology and participants for the lively discussion and great atmostphere.

The 14th annual workshop will be held again at the Kloster Schöntal from September 30th–October 2nd 2015. This year's theme will be "Regulation of cell fate: Balance between death and survival pathways". Additional information and updates can be found at our website **www.gfv-cellviro.de**.

3rd International Meeting of the German Society for Cell Biology (DGZ) on

Actin Dynamics

May 2nd - 5th, 2015
Regensburg, Germany

Organizers:

Eugen Kerkhoff (University of Regensburg, Germany)

Klemens Rottner (Technical University Braunschweig, Germany)

Theresia Stradal (Helmholtz Centre for Infection Research)

Further information and contact: **www.actindynamics.org**

DGZ DFG SP P 1464 BayGene Bayerisches Genomforschungsnetzwerk

Image courtesy of Jan Müller and Vic Small (Müller et al., 2014, PLoS Biol **12**(1): e1001765)

Keynote Speakers:

Gaudenz Danuser, Dallas, USA

Benjamin Geiger, Rehovot, Israel

Michael Rosen, Dallas, USA

Speakers:

Hervé Agaisse, Yale, USA

Inés Antón, Madrid, Spain

Steffen Backert, Erlangen, DE

Mary Beckerle, Salt Lake City, USA

Daniel Billadeau, Rochester, USA

Vania Braga, London, UK

John Brumell, Toronto, Canada

Ken Campellone, Connecticut, USA

Philippe Chavrier, Paris, France

Petra Dersch, Braunschweig, DE

Paul Forscher, Yale, USA

Margaret Frame, Edinburgh, UK

Lukas Huber, Innsbruck, Austria

Kinneret Keren, Haifa, Israel

Vassilis Koronakis, Cambridge, UK

Michael Sixt, Klosterneuburg, Austria

Theresia Stradal, Braunschweig, DE

Gaia Tavosanis, Bonn, DE

Alpha Yap, Queensland, Australia

James Zheng, Atlanta, USA

Impressum

Publisher:
Deutsche Gesellschaft für Zellbiologie e.V. (DGZ)
(German Society for Cell Biology)

Editor-in-Chief:
Prof. Dr. Ralph Gräf
(Universität Potsdam)

Editors:
Prof. Dr. Ludwig Eichinger
(Universität zu Köln)
PD Dr. Oliver Gruss
(Universität Heidelberg)
Prof. Dr. Eugen Kerkhoff
(Universität Regensburg)
Prof. Dr. Friedemann Kiefer
(MPI Molecular Biomedicine, Münster)
Prof. Dr. Thomas Magin
(Universität Leipzig)
Prof. Dr. Carien Niessen
(Universität zu Köln)
Prof. Dr. Klemens Rottner
(Techn. Universität Braunschweig)

Editorial Office Manuscripts/Advertisements:
Sabine Reichel-Klingmann
Office of the German Society for Cell Biology
c/o German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Tel.: 06221/42-3451
Fax: 06221/42-3452
E-mail: dgz@dkfz.de
Internet: www.zellbiologie.de

Production:
abcdruck GmbH
Waldhofer Str. 19 · 69123 Heidelberg
info@abcdruck.de · www.abcdruck.de

Media Creation:
Anna Wagner · a.wagner@abcdruck.de

Full electronic version

Frequency of publication:
4 issues yearly

If you are interested in advertising, please contact the DGZ office (dgz@dkfz.de)

Missing members:

We have no valid address from the members listed below. If anybody can help us in this respect, please send a message to the DGZ office at dgz@dkfz.de.

A
Stephan Adelt
Marwan Al Falah
Kirstin Albers
Jens Altrichter
Dorit Arlt

B
Jennifer Baltes
Tanja Barendziak
Friederike Bathe
Manuel Bauer
Wolfgang Bielke
Jessica Blume
Peter Brandt
Theo Brigge
Andreas Brown
Julia Bubeck
Winfried Busch

C
Stacy Carl-McGrath
Rüdiger Cerff
Miguel Coelho

D
Philip Dannhauser
Susanne Dietrich
Georgi Dimchev
Ulrich Drews

E
Hans-Georg Eckert
Fouzi El Magraoui

F
Danai Feida
Michael Fredrich
Jürgen Frey

G
Christiane Gerlach

H
Horst Hameister
Kristina Hartmann
Detlev Herbst
Michael Hilker
Anna-Lena Hillje
Christoph Hinzen
Christa Hochhuth
Christine Hoffmann
Eggehard Holler
Jan Hönnemann

J
Thomas Jarchau

K
Günter Kahl
Dieter Kaufmann
Tore Kempf
Antje Kettelhake
Erich Knop
Karl-Hermann Korfsmeier
Martina Kralewski
Bernd Krüger
Ralf Kuchenbecker
Christian Kutzleb

L
Stefan Lakämper
Philipp Lange
Gilbert Lauter
Friederike Lehmann
Lasse Lehnert
Joern Linkner
Anneke Loos
Madeleine Lupke

M
Sabine März
Anne Meinzinger
Gottfried Mieskes
Elena Motrescu
Günter Müller
Jens Müller

N
Thomas Noll

O
Adaling Ogilvie
Tobias Ölschläger

P
Andrea Pauli
Gerd Paulus
Stephan Peter
Kirsten Peters
Winfried Peters
Alexander Petrovitch
Johannes Pohlner

R
Jürgen Rauterberg
Eduard Resch
Filomena Ricciardi
Astrid Riehl
Josef Rüschoff

S
Klaus-Dieter Scharf
Raphaela Schwappacher
Gerd Schwarz
Sarah Schwarz G. Henriques
Kyrill Schwarz-Herion
Udo Seedorf
Klaus Seidl
Andrea Sokoll
Karsten Spring

T
Michael F. Trendelenburg

U
Nadime Ünver

V
Jürgen Voigt

W
Wibke Wagner
Horst Waldvogel
Diego J. Walther
Shuoshuo Wang
Carolin Weise
Christiane Weydig
Stefan Winheim

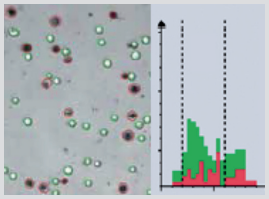
Put a Spark in your research!

Accelerate your research with the new Spark™ 10M multimode microplate reader

Discover a revolutionary platform that brings together the advanced capabilities of a multimode reader, incubator, cell counter and dispenser, all in a single, high performance, upgradable instrument offering exceptional flexibility and ease of use.

The new Spark 10M multimode reader from Tecan optimizes cell-based and biochemical assays with cutting-edge features and capabilities.

To see how changing your plate reader could change your lab life, visit **www.tecan.com/ignite** and put a Spark in your research.



Label-free cell counting and live analysis

Remote access and management

Call: The Americas: +1 919 361 5200 Europe: +49 79 5194 170 Asia: +81 44 556 7311
info@tecan.com

TECAN.