Inhalt

Deutsche Gesellschaft für Zellbiologie

Vorstand

Präsident:
Prof. Dr. Reinhard Fässler
Max-Planck-Institut für Biochemie, Martinsried

Vizepräsident:
Prof. Dr. Jürgen Wehland
Helmholtz-Zentrum für Infektionsforschung, Braunschweig

Geschäftsführer:
PD Dr. Dirk Breitkreutz
Deutsches Krebsforschungszentrum, Heidelberg

Sekretär:
Dr. Michael Sixt
Max-Planck-Institut für Biochemie, Martinsried

Sekretariat:
Sabine Reichel-Klingmann
Deutsches Krebsforschungszentrum (DKFZ)
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Beirat

Prof. Dr. Volker Gerke
Prof. Dr. Christof Hauck
Prof. Dr. Elisabeth Knust
Prof. Dr. Dietmar Vestweber
Prof. Dr. Doris Wedlich

Das **Formular „Bescheinigung der Mitgliedschaft/Bestätigung über Zuwendungen"** für Ihre Unterlagen zur Bescheinigung Ihrer Mitgliedschaft und Zahlung Ihres Mitgliedsbeitrages für das Jahr **2009** kann von den DGZ-Internetseiten www.zellbiologie.de (dort unter der Rubrik „DGZ"/Formulare) heruntergeladen und ausgedruckt werden. Eine individuell ausgestellte Bescheinigung wird Ihnen auf Wunsch aber auch künftig gerne vom Sekretariat der DGZ (dgz@dkfz.de) zugeschickt.

Titelbild: Primary mouse keratinocytes isolated from epidermal specific E-cadherin knockout mice were differentiated in high Ca2+ (1.8 mM) medium for 48 hours and stained for the tight junctional protein ZO-1 (green). Nuclei were counterstained using propidium iodide (red).
See article by Carien Niessen on p. 14-19.

Liebe Kolleginnen und Kollegen,

vom 10. bis 13. März findet unsere Jahrestagung in Regensburg statt. Anja Bosserhoff organisiert die Tagung in Regensburg und hat ein hervorragendes Programm mit hochkarätigen Sprechern zusammengestellt. Wir wollen, dass die Jahrestagung von vielen Mitgliedern besucht wird. Obwohl die Anmeldefrist für den Besuch der Jahrestagung bereits abgelaufen ist, können sich Interessierte nach wie vor bei Anja Bosserhoff anmelden.

Neben dem wissenschaftlichen Teil findet während der Tagung auch unsere Mitgliederversammlung statt, auf der ich Ihnen diesmal den neugewählten Präsidenten Harald Herrmann und sein Team vorstellen kann. Ich würde mich freuen, wenn Sie auch an dieser Versammlung zahlreich teilnehmen würden. Ihre Ideen und Anregungen und Ihre Mitarbeit sind sehr erwünscht.

Ihr
Reinhard Fässler

Einladung zur Mitgliederversammlung 2010

Hiermit laden wir alle Mitglieder der Deutschen Gesellschaft für Zellbiologie zur Mitgliederversammlung 2010 ein, die im Rahmen der Jahrestagung in Regensburg am

Donnerstag, den 11. März 2010,
um 12.30 Uhr in Hörsaal H2

stattfindet. Die Tagesordnung sieht folgende Punkte vor:

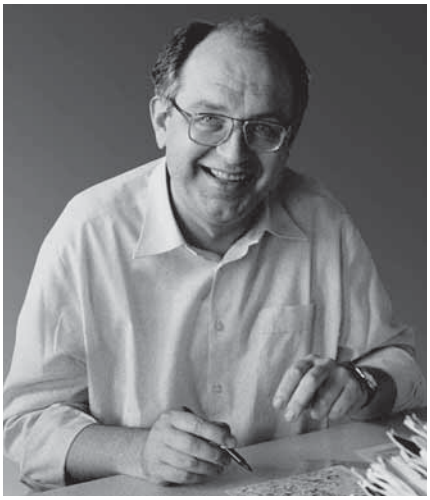
1. Bestätigung des Protokolls der letzten Mitgliederversammlung
2. Jahresbericht des Präsidenten
3. Geschäfts- und Kassenbericht
4. Bericht der Kassenprüfer
5. Entlastung des Vorstandes
6. DGZ-Wahlen, Wahl des neuen Vorstandes, Ergänzungswahl zum Beirat
   Wahl der Kassenprüfer, Ergänzungswahl zur Preisjury
7. Satzungsänderung, § 5 Die Organe der Gesellschaft (3) Der Beirat
8. Verschiedenes u.a. Mitgliedsbeitrag für emeritierte/pensionierte Mitglieder

Wir freuen uns, alle Mitglieder bei dieser Veranstaltung begrüßen zu dürfen.

Ihr DGZ-Vorstand

Die DGZ gratuliert Werner Franke

Am 31. Januar hat Werner Franke seinen 70. Geburtstag gefeiert. Zu diesem Ehrentag gratulieren ihm Vorstand und Beirat im Namen der DGZ auf das herzlichste. Werner Franke hat für die Gesellschaft und für die zellbiologische Forschung in Deutschland eine hervorragende Rolle gespielt. Und, was in Deutschland heute immer noch eine Ausnahme ist, er ist auch nach dem 65. Lebensjahr noch äußerst aktiv in der wissenschaftlichen Forschung tätig, und zwar als Helmholtz-Professor für Zellbiologie am Deutschen Krebsforschungszentrum. Diese Forschung konzentriert sich jetzt auf die „junctions", mit 10 Publikationen allein im letzten Jahr.
In Paderborn, Westfahlen, geboren hat Werner Franke, nach Ableisten des Wehrdienstes, in Heidelberg Biologie, Chemie und Physik studiert. Nach der Promotion in Heidelberg (mit 27 Jahren und summa cum laude) wurde er wissenschaftlicher Assistent an der Fakultät für Biologie an der Universität Freiburg i. Br. und habilitierte sich dort, vor Erreichen des 31. Lebensjahres, für das Fach Zellbiologie. Der Literaturdienst Pubmed verzeichnet für diese Lebensphase, 1966 bis 1971, allein 34 Publikationen, darunter die zur Universalität von Kern-Porenkomplexen, die ihn auf einen Schlag bekannt gemacht haben, und solche zu den vielfältigen Interaktionen, die Membranen mit zellulären Strukturen wie Mikrotubuli eingehen. 1973 wurde Werner Franke zum Leiter der Abteilung für Membranbiologie und Biochemie am DKFZ sowie zum Wissenschaftlichen Rat und Professor der Universität Heidelberg ernannt. Diese Position wurde zum Startpunkt für eine außerordentliche internationale Karriere, im Zentrum die Erforschung der funktionellen Architektur der Zelle. Dazu gehörten die verschiedenen Intermediärfilament-Systeme (das eigentliche Cytoskelett), die Zell-Zellverbindungen, Kernproteine sowie Aktin - auch das nukleäre (ein Cell-Paper aus dem Jahr 1984). Werner Franke hat die Ergebnisse seiner Grundlagenforschung sehr früh und konsequent für die Tumor-Diagnostik eingesetzt, wofür er 1984 den Ernst-Jung-Preis, zusammen mit seinem Weggefährten Klaus Weber (MPI für Biophysikalische Chemie, Göttingen) zugesprochen bekam. Seine Verantwortung als Wissenschaftler für die Gemeinschaft hat Werner Franke stets sehr ernst genommen, weshalb er sich als Kommissionsmitglied bei der Evaluierung der ostdeutschen Forschungsinstitute der Akademie der Wissenschaften der DDR engagierte. Und in diesem Zusammenhang war er auch sehr aktiv bei der Aufklärung der pharmakologischen Manipulationen im Sport - und zwar nicht nur dem der DDR.
Neben zahlreichen Aktivitäten als Gutachter und Editor war Werner Franke unter anderem von 1982 bis 1990 Präsident der European Cell Biology Organization (ECBO), 1984 bis 1988



Vize-Präsident der International Federation of Cell Biology und 1988 bis 1994 Generalsekretär der European Molecular Biology Conference (EMBC). Schließlich war Werner Franke von 1999 bis 2001 Präsident der DGZ und er war an der Gründung der DGZ am 26. April 1975 entscheidend beteiligt. Der 1. Vorstand setzte sich übrigens folgendermaßen zusammen: Peter Sitte (Präsident), Fritz Miller (Vizepräsident), Werner Franke (Geschäftsführer), Hanswalter Zentgraf (Sekretär). Somit hat Werner Franke auf vielen Ebenen an der Entwicklung der Strukturen entscheidend mitgearbeitet, die es uns heute ermöglichen, zellbiologisch national und international verknüpft erfolgreich zu arbeiten. Dafür danken wir ihm.

Harald Herrmann

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Wednesday, March 10, 2010

08:00 – 20:00 **Registration**

09:00 – 12:30 **Educational Session**

Session 1: Where can I get support?
Funding opportunities of the EU
Dr. S. Steiner-Lang (NKS-Lebenswissenschaften)
Funding opportunities of the German Cancer Aid
Dr. M. Serwe (Deutsche Krebshilfe)

General Discussion

Coffee break

Session 2: Scientific careers
Prof. Dr. Gunter Meister, Institute of Biochemistry I, University of Regensburg
Prof. Dr. M. Schliwa, Institute of Cell Biology, LMU Munich
Prof. Charlotte Förster, Institute of Neurobiology and Genetics, University of Wuerzburg
Dr. C. Dony, Scil Technologies GmbH, Munich

General Discussion

Time for individual questions

13:00 – 13:30 **Opening**
Reinhard Fässler (President of the DGZ)
Anja Bosserhoff (Congress chair)
Prof. Jannsen (Senatspräsident)
Armin Kurtz (Research Dean of the NWF III)
Bernhard Weber (Dean of the Medical Faculty)

13:30 – 15:40 **Symposium 1 (S1): Frontiers in cell biology**
Chairs: Reinhard Fässler (Munich), Jürgen Wehland (Braunschweig)
David Teis (Innsbruck)
Eckhard Lammert (Düsseldorf
Ohad Medalia (Beer-Sheva)

15:40 – 16:15 Coffee break

16:15 – 17:30 **DGZ Award Presentations**
Walther Flemming Medaille
Binder Innovationspreis
Werner Risau Preis

17:30 – 18:30 **Carl Zeiss Lecture**
Rudolf Grosschedl (Freiburg)

18:30 **Poster Session / Get Together**

Thursday, March 11, 2010

08:30 - 09:15 **Meet the Expert "Vesicle transport"**
Vivek Malhotra (Barcelona)

09:15 – 10:35 **Symposia 2 and 3**

09:15 **Symposium 2 (S2): Cell Signalling**
Chair: Doris Wedlich (Karlsruhe)
Doris Wedlich (Karlsruhe)
Walter Birchmeier (Berlin)
John Collard (Amsterdam)
Lukas Huber (Innsbruck)

09:15 **Symposium 3 (S3): From embryology to tumor development – what can we learn?**
Chair: Marianne Bronner-Fraser (Pasadena)
Marianne Bronner-Fraser (Pasadena)
Stefano Piccolo (Padua)
Daniel Peeper (Amsterdam)
Roberto Mayor (London)

10:35 – 11:00 Coffee break

11:00 – 12:30 **Symposia 2 and 3 cont.**

12:30 – 13:30 **Lunch / Industry Tutorials (with Lunch)**

12:30 **DGZ MEMBER MEETING**

13:30 – 14:30 **Poster Walks (topics: S2, MS2, MS3, Misc)**

14:30 – 16:30 **Minisymposia 1 – 3**

14:30 **Minisymposium 1 (MS1): Cell–cell-contacts and cell polarity**
Chair: Jürgen Behrens (Erlangen)
Ian Macara (Charlotteville)
Thomas Brabletz (Freiburg)
Olivier Gires (München)
and speakers selected from the abstracts
Sandra Iden (S2-11)
Steve Misselwitz (M1-7)

14:30 **Minisymposium 2 (MS2): Angiogenesis**
Chair: Holger Gerhardt (London)
Holger Gerhardt (London)
Stefan Schulte-Merker (Utrecht)
Hellmuth Augustin (Heidelberg)
and speakers selected from the abstracts
Sven Liebler (MS2-5)
Moritz Felcht (MS2-8)

14:30 **Minisymposium 3 (MS3): Vesicle transport**
Chair: Volker Gerke (Münster)
Volker Gerke (Münster)
Vivek Malhotra (Barcelona)
Miguel Seabra (London)
and speakers selected from the abstracts
Christian Schuberth (MS3-5)
Anne Spang (MS3-9)

16:30 – 17:00 Coffee break

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17:00 – 19:00 **Minisymposia 4 – 6**

17:00 **Minisymposium 4 (MS4): Best posters**
Chair: Anja Bosserhoff (Regensburg)
Speakers selected from the abstracts
Sarah Wickström (MS3-19)
Julia von Blume (MS3-23)
Oliver Gruss (MS14-10)
Sarah Schmidt (MS10-11)
Evelyne Frijns (MS10-5)
Margarete Goppelt-Struebe (S2-15)

17:00 **Minisymposium 5 (MS5): Cellular metabolism**
Chair: Peter Oefner (Regensburg)
Jacques Pouyssegur (Nice)
Alexander Pfeifer (Bonn)
Tobias Walther (Martinsried)
and speakers selected from the abstracts
Markus Marniak (MS5-7)
Christina Warnecke (MS5-11)

17:00 **Minisymposium 6 (MS6): Protein modification**
Chair: Helle Ulrich (London)
Helle Ulrich (London)
Ramin Massoumi (Malmö)
Jürgen Dohmen (Köln)
and speakers selected from the abstracts
Thorsten Pflanzner (MS6-1)

Friday, March 12, 2010

08:30 – 09:15 **Meet the Expert "Stem cells and cancer stem cells"**
Andreas Trumpp (Heidelberg)

09:15 – 10:35 **Symposia 4 and 5**

09:15 **Symposium 4 (S4): miRNA /TUFs (transcripts of unknown function)**
Chair: Gunter Meister (Regensburg)
Gunter Meister (Regensburg)
Carlo Croce (Boston)
Anders Lund (Copenhagen)
Sven Diederichs (Heidelberg)

09:15 **Symposium 5 (S5): Stem cells and cancer stem cells**
Chair: Christoph Klein (Regensburg)
Lenhardt Rudolph (Ulm)
Andreas Trumpp (Heidelberg)
Markus Frank (Boston)
Christoph Klein (Regensburg)

10:35 – 11:00 Coffee break

11:00 – 12:30 **Symposia 4 and 5 cont.**

12:30 – 13:30 **Lunch / Industry Tutorials (with Lunch)**

13:30 – 14:30 **Poster Walks**
(topics: S3+5; S4+MS6+MS12; MS5; MS7+MS9)

14:30 – 16:30 **Minisymposia 7 – 9**

14:30 **Minisymposium 7 (MS7): Cytoskeleton**
Chair: Eugen Kerkhoff (Regensburg)
Robert Grosse (Heidelberg)
David Kovar (Chicago)
Eugen Kerkhoff (Regensburg)
and speakers selected from the abstracts
Jennifer Block (MS7-6)
Kathrin Schloen (S2-4)

14:30 **Minisymposium 8 (MS8): Molecular basis of tumor therapy**
Chairs: Jürgen Becker (Würzburg), Manfred Kunz (Lübeck)
Freddy Radtke (Epalinges)
Ze'ev Ronai (La Jolla)
Ashani Weeraratna (Baltimore)
and speakers selected from the abstracts
Grit Ebert (MISC-11)
Robert Besch (S3-4)

14:30 **Minisymposium 9 (MS9): Nuclear transport**
Chair: Katja Strässer (München)
Katja Strässer (München)
Dirk Görlich (Göttingen)
Yuh Min Chook (Dallas)
and speakers selected from the abstracts
Ralph Kehlenbach (MS9-1)

16:30 – 17:00 Coffee break

17:00 – 19:00 **Minisymposia 10 – 12**

17:00 **Minisymposium 10 (MS10): Cell-Matrix-Adhesion**
Chair: Arnoud Sonnenberg (Amsterdam)
Jim Norman (Glasgow)
Marc Ginsberg (La Jolla)
Arnoud Sonnenberg (Amsterdam)
and speakers selected from the abstracts
Claudia Mierke (S7-4)
Philipp Peterburs (S7-9)

17:00 **Minisymposium 11 (MS11): New players in melanoma development and progression**
Chairs: Cornelia Mauch (Köln), Birgit Schittek (Tübingen)
Keith Hoek (Zürich)
Maria Soengas (Madrid)
Richard Marais (London)
and speakers selected from the abstracts
Daniel Müller (S4-2)
Ngum Abety (MS11-4)

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17:00 **Minisymposium 12 (MS12): New methods in cell biology**
Chair: Frank Buchholz (Dresden)
Frank Buchholz (Dresdren)
Petra Schwille (Dresden)
Morgan Maeder (Boston)
and speakers selected from the abstracts
Dagmar Salber (MS12-1)
Regina Kleinhans (MS12-5)

19:00 **Get Together**

Saturday, March 13, 2010

08:30 – 09:15 **Meet the Expert "miRNA"**
Carlo Croce (Boston)

09:15 – 10:35 **Symposia 6 and 7**

09:15 **Symposium 6 (S6): Epigenetics**
Chair: Michael Rehli (Regensburg)
Juerg Müller (Heidelberg)
Christoph Plass (Heidelberg)
Gernot Längst (Regensburg)
Peter Becker (München)

09:15 **Symposium 7 (S7): Cytoskeletal dynamics**
Chair: Jochen Wittbrodt (Heidelberg)
Christiana Ruhrberg (London)
Jochen Wittbrodt (Heidelberg)
Darren Gilmour (Heidelberg):
Erez Raz (Münster)

10:35 – 11:00 Coffee break

11:00 – 12:30 **Symposia 6 and 7 cont.**

12:30 – 13:00 Lunch

13:00 – 14:00 **Poster Walks (topics: S7+MS1; MS8+MS11; MS10; MS13+MS14)**
with Coffee

14:00 – 16:00 **Minisymposia 13 – 15**

14:00 **Minisymposium 13 (MS13): Apoptosis**
Chair: Jürgen Eberle (Berlin)
Andreas Villunger (Innsbruck)
Peter Krammer (Heidelberg)
Gerry Melino (Rome)
and speakers selected from the abstracts
Sven Horke (MS13-1)
Anja Berger (MS13-3)

14:00 **Minisymposium 14 (MS14): Cell division and cell cycle regulation**
Chair: Rolf Jessberger (Dresden)
Rolf Jessberger (Dresden)
Olaf Stemmann (Bayreuth)
Ingrid Hoffmann (Heidelberg)
and speakers selected from the abstracts
Zuzana Storchova (MS14-3)
Lea Arnold (MS14-2)

14:00 **Minisymposium 15 (MS15): Bioinformatics and systems biology**
Chair: Rainer Spang (Regensburg)
Nikolaus Rajewski (Berlin)
Martin Vingron (Berlin)
Kay Hofmann (Bergisch-Gladbach)
and speakers selected from the abstracts
Theresa Niederberger (München)

16:00 **Poster Awards**

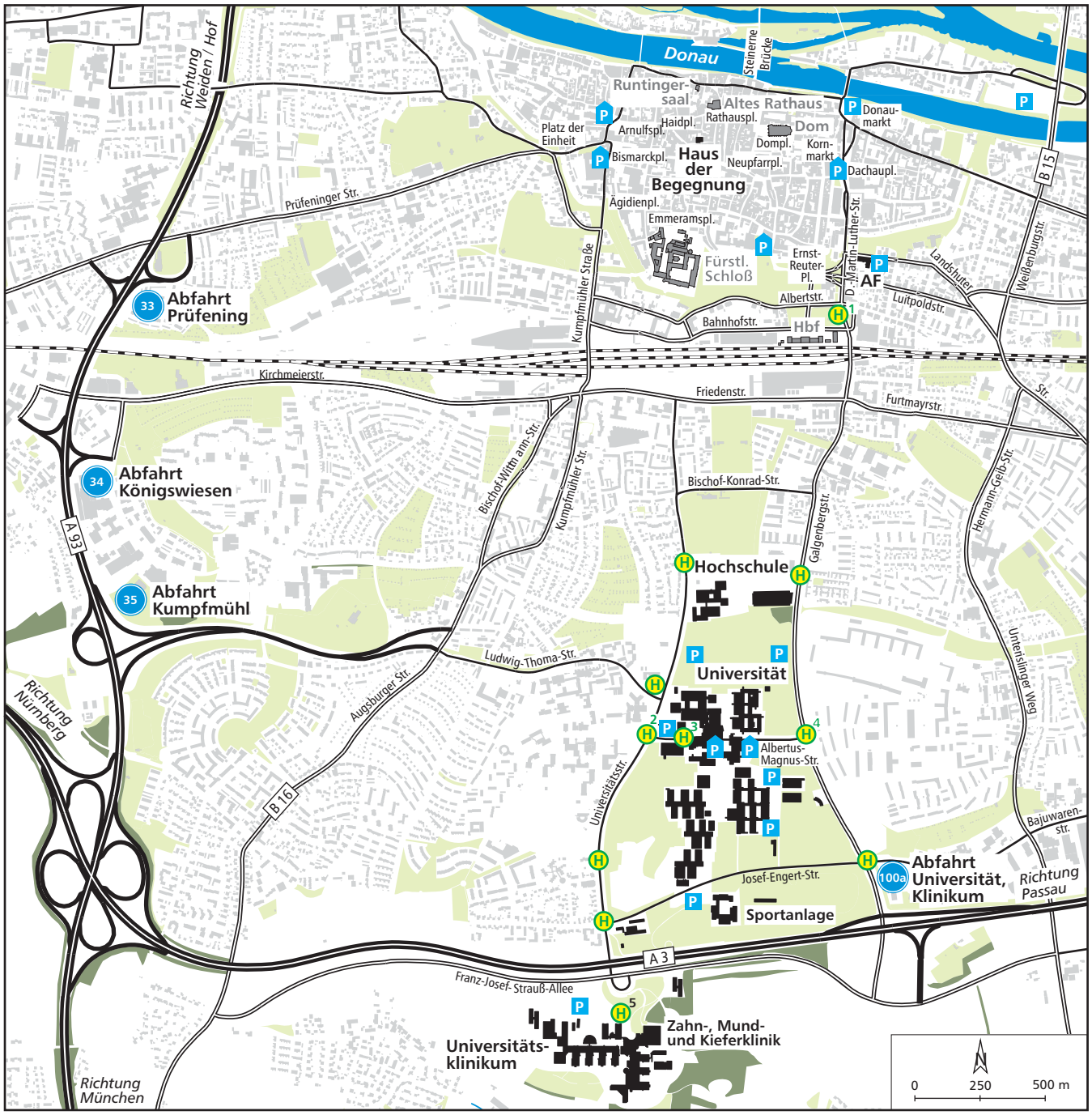
End of DGZ Meeting and Frontiers in Melanoma Research

Fare Well

Das ausführliche Programm mit Vortragstiteln und aktuelle Informationen zur Jahrestagung finden Sie auf den Internetseiten

www.zellbiologie2010.de

Universität Regensburg - Anfahrtsplan



Entwurf und Bearbeitung Grundkarte: S. Fischer, Univ. Regensburg - Lst. f. Wirtschaftsgeogr. 2008 ; Kartengrundlage: Stadt Regensburg, Amt für Stadtentwicklung 2007.

- Parkhaus/Tiefgarage
- Parkplatz
- Bushaltestelle
- Bundesautobahn, -auffahrt
- Bundes- und Hauptverkehrsstraße
- Ausgewählte sonstige Straße
- Bahngleis
- Gebäude der Universität und des Klinikums
- Wichtiges Gebäude
- Grünfläche
- Waldfläche

Busverbindungen (Hauptbahnhof - Universität/Klinikum):

(Fahrtdauer ca. 7 Min./13 Min., zusätzlich Fußweg Hbf - Bustreff ca. 5 Min.)

Linie 6 (Wernerwerkstraße - Klinikum):

Abfahrt: Bustreff Albertstraße/D.-Martin-Luther-Straße (1)

Haltestellen: Otto-Hahn-Straße (4),
Universität Mensa (3),
Universität Haupteingang (2),
Klinikum (5)

Linie 11 (Roter Brachweg - Sophie-Scholl-Straße/Burgweinting)

Abfahrt: Bustreff Albertstraße/D.-Martin-Luther-Straße (1)

Haltestellen: Universität Haupteingang (2),
Universität Mensa (3),
Otto-Hahn-Straße (4)

Zu den Stoßzeiten fahren Sonderlinien zwischen Hauptbahnhof und Universität (Linie 11S) bzw. Klinikum (Linie 19).

Fußweg (Hauptbahnhof - Galgenbergstraße - Universität) ca. 25 Min.

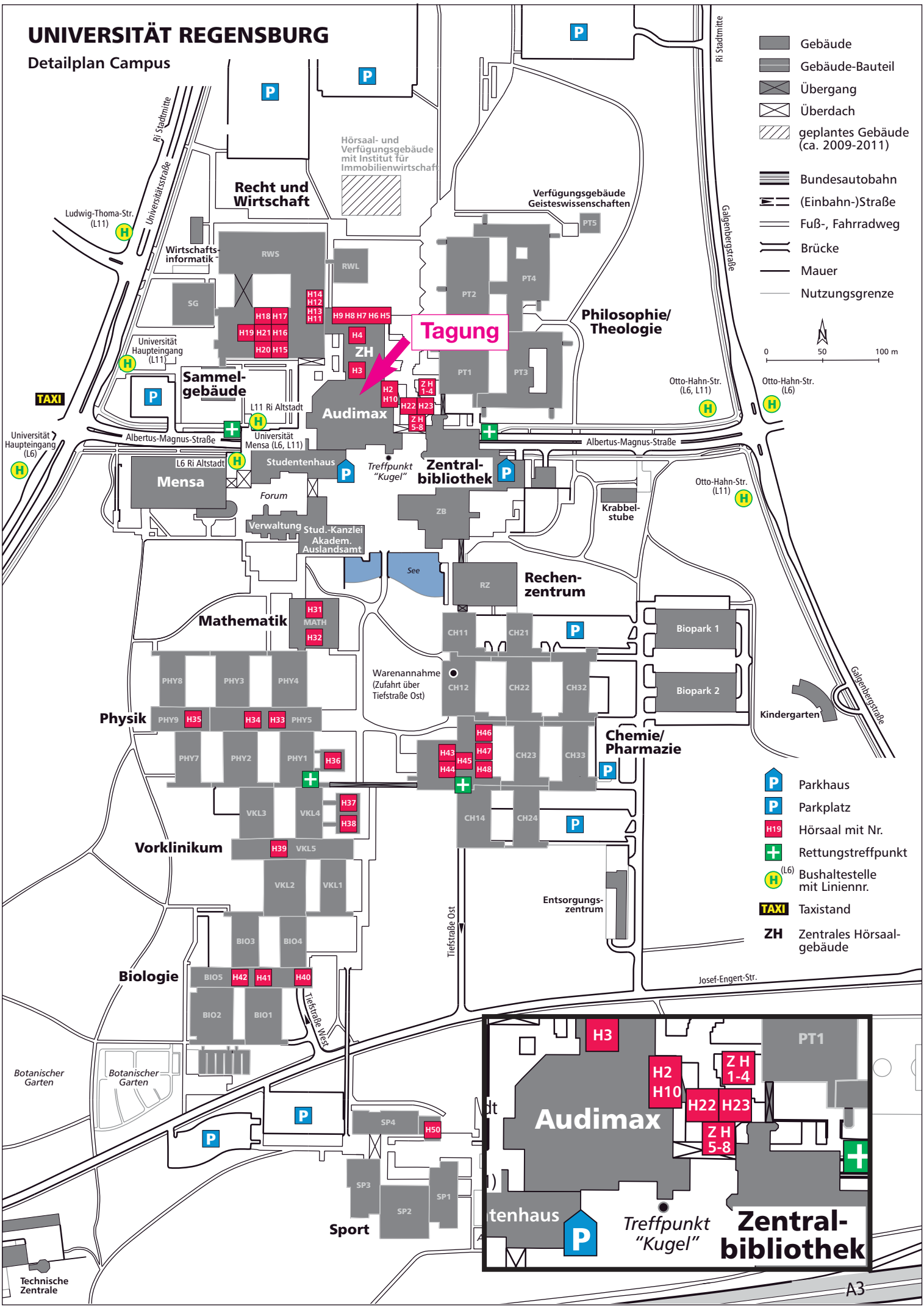
Adressen:

Universität
Universitätsstraße 31, 93053 Regensburg

Universitätsklinikum
Franz-Josef-Strauß-Allee 11, 93053 Regensburg

Standort "Altes Finanzamt" (AF)
Landshuter Straße 4, 93047 Regensburg

Haus der Begegnung
Hinter der Grieb 8, 93047 Regensburg



Entwurf und Bearbeitung Grundkarte: S. Fischer, Univ. Regensburg - Lst. f. Wirtschaftsgeogr., 2008; Kartengrundlagen: Digitale Daten vom Staatl. Bauamt Regensburg - Hochschulbau.

Primary cilia and polycystic kidney disease

Karin Babinger and Ralph Witzgall

Situs inversus and polycystic kidney disease converge at primary cilia

Although at first glance our body looks symmetrical, our internal organs obviously are arranged asymmetrically. It goes without saying that the heart is located on the left side and the liver on the right side yet such a seemingly trivial fact poses a very difficult biological question: How is the arrangement of the internal organs, the *situs*, regulated? Development of the organism starts with the fertilized oocyte, a round structure with no obvious asymmetry. At some point during development, however, axis formation occurs: A dorsal-ventral, an anterior-posterior and a left-right axis are established. Defects in left-right axis formation have been observed and are compatible with life, the patients suffer from *situs inversus*, i.e. their heart is located on the right side and the liver is located on the left side. As in many other circumstances, evidence obtained in the mouse has led to important insight into how the left-right axis may be formed. One mouse mutant, the *inv* mouse, not only presents with *situs inversus* but also with polycystic kidneys. At the time of its first description it posed a puzzle why both symptoms were present in the same mouse mutant.

Polycystic kidneys are characterized by the continuous formation of cysts, fluid-filled cavities lined by an epithelium. The disease is found in almost 10% of patients suffering from end-stage renal disease, so far no curative therapy is known and many patients finally require dialysis or a kidney transplant (Anonymous, 1991, 1998; European Dialysis and Transplant Association Registry, 1986; Lowrie and Hampers, 1981; Torra et al., 1995). At a prevalence of at least 1:1,000 autosomal-dominant polycystic kidney disease, one of the forms of polycystic kidney disease, belongs to the most common monogenetic diseases affecting patients (Davies et al., 1991; Higashihara et al., 1998). In 1994 mutations in the first gene responsible for autosomal-dominant polycystic kidney disease, *PKD1*, were published (European Polycystic Kidney Disease Consortium, 1994). *PKD1* codes for polycystin-1, a 4,302 amino acid long integral membrane protein with 11 membrane-spanning domains (Hughes et al., 1995; Nims et al., 2003). The NH_2-terminus of polycystin-1 represents the largest portion of the protein and extends into the extracellular space. It contains many characteristic motifs and is speculated to mediate cell-cell and/or cell-matrix contacts but so far the function of polycystin-1 remains enigmatic. Mutations in the second gene, *PKD2*, were published two years later (Mochizuki et al., 1996). Whereas *PKD1* is mutated in ~85% of the patients, the remaining ~15% suffer from mutations in the *PKD2* gene (Peters and Sandkuijl, 1992; Roscoe et al., 1993; Torra et al., 1996; Wright et al., 1993). Polycystin-2 (Figure 1) also is an integral membrane protein but with 968 amino acids it is much smaller than polycystin-1. It contains the characteristic features of cation channels (Delmas et al., 2004; Koulen et al., 2002). Polycystin-2 traverses the membrane 6 times, the ion-conducting pore is located between the 5th and 6th membrane-spanning domain, and the NH_2- and COOH-terminus both extend into the cytoplasm. The phenotype of the *Pkd1* and *Pkd2* knock-out mice confirmed that both genes are responsible for the development of polycystic kidneys. One additional, surprising finding in the *Pkd2* [but not in the *Pkd1* (Karcher et al., 2005)] knock-out mice was *situs inversus* (Pennekamp et al., 2002). The connection between polycystic kidneys and situs inversus became immediately clear once it was recognized that polycystin-2 is a component of the primary cilium, a hair-like extension of epithelial and many other cell types. Primary cilia are not only found on epithelial cells lining the kidney tubules but also on cells of the primitive node which is suspected to play a central role in breaking left-right symmetry.

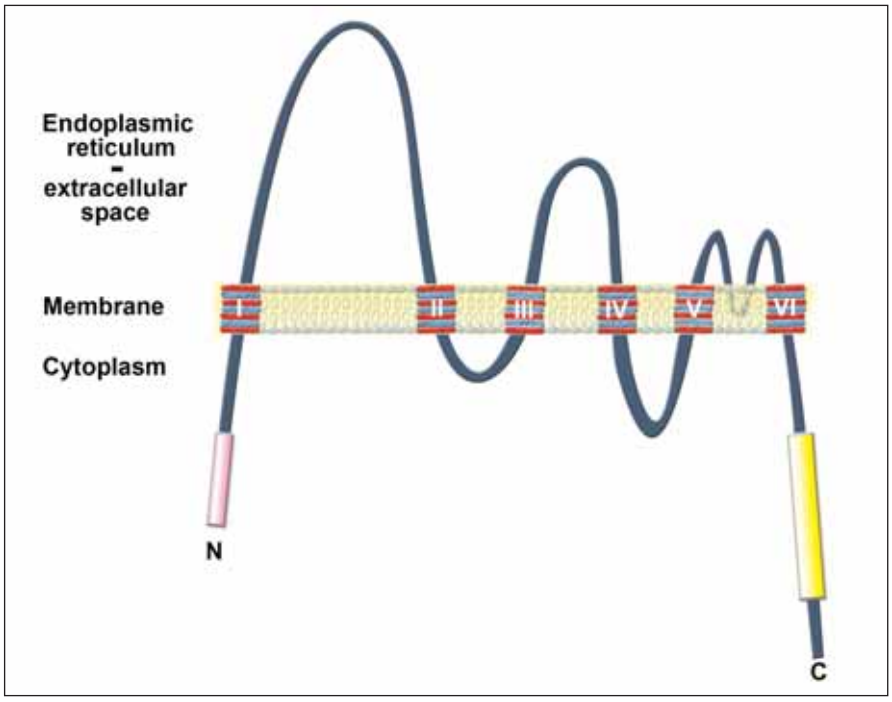


Figure 1. Structure of polycystin-2. *The human polycystin-2 protein is 968 amino acids long and contains 6 transmembrane domains (I-VI), the ion-conducting pore is located between the 5th and 6th transmembrane domain. Both its NH2- and COOH-terminus extend into the cytoplasm. Depending on whether polycystin-2 is retained in the endoplasmic reticulum or reaches the ciliary plasma membrane, loops 1, 3 and 5 extend into the lumen of the endoplasmic reticulum or into the extracellular space. A ciliary targeting motif was found at the extreme NH2-terminus (pink box, Geng et al., 2006), and a retention signal for the endoplasmic reticulum was identified in the COOH-terminus (yellow box, Cai et al., 1999).*

Primary cilia, long-neglected organelles

Primary cilia (Figure 2) were documented for the first time in 1898 by Zimmermann (Zimmermann, 1898) but their more precise characterization was not possible until the arrival of the electron microscope and improved techniques for preparing ultra thin sections (Barnes, 1961; Currie and Wheatley, 1966).

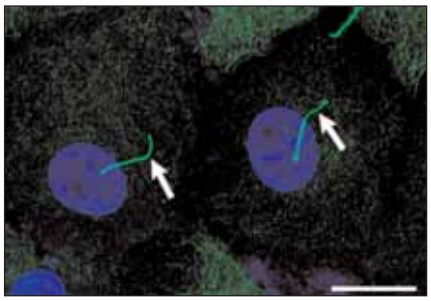


Figure 2. Primary cilia on renal epithelial LLC-PK1 cells. *Primary cilia (arrows) were visualized with a primary antibody directed against acetylated tubulin and a FITC-conjugated secondary antibody. Nuclei are shown in blue. Bar, 15 µm.*

Although experimental work on primary cilia began at the end of the 1970s (Wheatley, 2005) they were often viewed as rudimentary cell appendages with no function. The primary cilium is found on many different cell types in the mammalian body [(Wheatley et al., 1996), and http://www.bowserlab.org/primarycilia/cilialist.html] and occurs as a solitary, non-motile (with the exception of nodal cilia, see below), hair-like cell appendix extending from the basal body. In contrast to motile kinocilia with their 9 peripheral microtubule doublets and one central pair of microtubules, primary cilia lack the central pair of microtubules, the dynein arms, nexin and radial spokes (Figure 3). The plasma membrane of the cell body and of the primary cilium appear to be seamlessly connected, yet a barrier has to exist between them because some proteins can only be found in the primary cilium and not in the surrounding somatic plasma membrane.

Seminal experiments in the nematode *Caenorhabditis elegans* and with renal epithelial cells have finally attributed chemo- and mechanosensory roles to primary cilia. *C. elegans* has a highly developed chemosensory system to find food and to detect mates. The sensory transduction molecules in the worm's chemosensory neurons are located in the sensory cilium which has a structure very similar to that of a primary cilium (Ward et al., 1975; Ware et al., 1975). Barr and Sternberg showed that LOV-1 and PKD-2, the likely orthologues of polycystin-1 and polycystin-2 in *C. elegans*, respectively, are both present in sensory neurons of adult males. PKD-2 is believed to regulate the ability of adult male worms to respond to mating cues that likely involve both chemosensory and mechanosensory components (Barr et al., 2001; Barr and Sternberg, 1999). Mutant worms with defects in LOV-1 and PKD-2 present with the same sensory defects in mating behaviors which argues for a functional connection between the two proteins. Indeed it has been demonstrated by various approaches that polycystin-1 and polycystin-2 also interact biochemically (Casuscelli et al., 2009; Qian et al., 1997; Tsiokas et al., 1997).

Around the same time Praetorius and Spring investigated how MDCK (Madin-Darby canine kidney) renal epithelial cells respond to flow. They produced good evidence that primary cilia act as a flow sensor. When they bent the cilium, the intracellular calcium concentration increased, probably due to the influx of Ca^{2+} ions through mechanosensitive channels in the shaft or at the base of the primary cilium. Following the influx of extracellular Ca^{2+} ions, Ca^{2+} becomes released from inositoltriphosphate (IP_3)-sensitive stores (Praetorius and Spring, 2001). When the cilia were removed, a flow-induced Ca^{2+} response was no longer observed (Praetorius and Spring, 2003). Subsequent experiments by the group of Jing Zhou showed the involvement of polycystin-1 and polycystin-2 in sensing flow (Nauli et al., 2003). The authors suggest that polycystin-1, possibly through the PKD domains in its long extracellular NH_2-terminus, acts as a mechanosensor and transduces the flow-induced bending of the primary cilium into a molecular signal. Through its interaction with polycystin-2 a local Ca^{2+} influx in the primary cilium would ensue which would be amplified through Ca^{2+}-induced Ca^{2+} release via ryanodine receptors. The changes in intracellular Ca^{2+} concentrations may modulate various cellular functions such as gene expression, growth, differentiation and apoptosis. Loss or dysfunction of polycystin-1 and polycystin-2 may therefore lead to polycystic kidney disease as a result of the inability of the cells to sense mechanical stimuli that normally regulate tissue morphogenesis.

An exception to the rule that primary cilia are immotile are the nodal cilia in the primitive node, a crucial structure during embryonic development. Just like normal primary cilia they lack a central pair of microtubules but they contain radial spokes and dynein arms. Nodal cilia are capable of a characteristic counterclockwise rotation which occurs for only a few hours during development. This movement is responsible for a fluid flow from right to left across the node which in turn is essential for left-right axis formation (Nonaka et al., 2002; Nonaka et al., 1998). Accordingly the randomization of left-right axis specification has been observed in mice lacking the ciliary transport proteins Kif3a (Marszalek et al., 1999; Takeda et al., 1999) and Kif3b (Nonaka et al., 1998). But how does nodal flow determine the left-right axis in the embryo? One model is based on the observation that two forms of nodal cilia exist – in addition to cilia with their rotating motion also immotile primary cilia can be found. The immotile primary

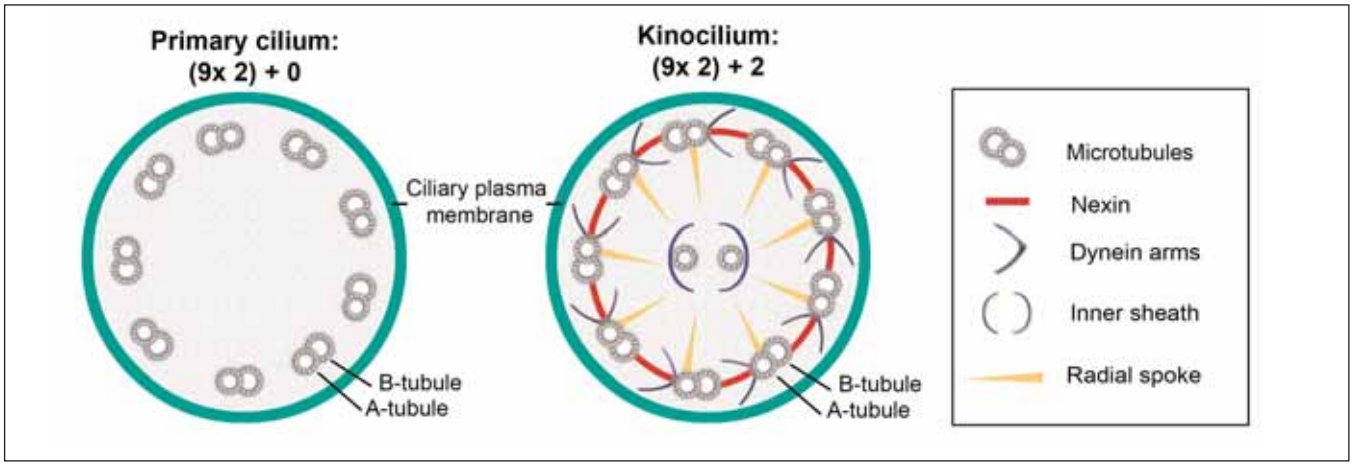


Figure 3. Structure of primary cilia and kinocilia. *Primary cilia only contain 9 peripheral doublets of microtubules whereas kinocilia also contain a central pair of microtubules and additional structural features such as dynein arms and nexin between neighboring microtubules.*

cilia sense the presence of a yet to be identified morphogen whose asymmetric concentration results from the flow produced by the motile nodal cilia (McGrath and Brueckner, 2003; McGrath et al., 2003). Such a scenario is supported by the observation that the intracellular Ca^{2+} concentration is higher on the left side of the node (McGrath and Brueckner, 2003). Some cilia-associated proteins like polycystin-2 (Pennekamp et al., 2002), polaris (Moyer et al., 1994; Murcia et al., 2000) and the already mentioned inversin (the protein mutated in the *inv* mouse mutant) (Morgan et al., 1998) obviously are important both during embryonic development in the node and for tubulogenesis in the kidney because their inactivation results in *situs inversus* and polycystic kidneys.

Polycystin-2, a non-selective cation channel of the primary cilium

Although it was speculated early on that polycystin-2 acts as an ion channel (Mochizuki et al., 1996), it took several years before formal proof was obtained. Meanwhile it has been firmly established that polycystin-2 belongs to the TRP family of cation channels. It is permeable for mono- and divalent cation and exhibits a large conductivity (Delmas et al., 2004; Koulen et al., 2002). Small concentrations of Ca^{2+} activate the channel whereas high concentrations of Ca^{2+} inactivate it. The structural analysis of the COOH-terminus of polycystin-2 has demonstrated the presence of 2 Ca^{2+}-binding sites, one with a low and the other one with a high affinity (Schumann et al., 2009). In the absence of Ca^{2+} polycystin-2 forms higher-order complexes, possibly trimers, whereas in its presence the complex dissociates. It therefore seems possible that the assembly state of polycystin-2 determines the activity of the channel: In the presence of high Ca^{2+} concentrations the protein complex disassembles and polycystin-2 no longer functions as a channel.

Many interacting proteins have been identified for polycystin-2 which may modulate its activity. For example, Kif3a (Li et al., 2006), α-actinin (Li et al., 2005) and fibrocystin (Wang et al., 2007) interact with the NH_2-terminus of polycystin-2, and more than 20 proteins such as polycystin-1 (Qian et al., 1997; Tsiokas et al., 1997), polycystin-2 itself (Tsiokas et al., 1997), PIGEA-14 (Hidaka et al., 2004), Kif3a (Li et al., 2006) and Kif3b (Wu et al., 2006) interact with the COOH-terminus of polycystin-2. Some of the interacting proteins influence the intracellular location of polycystin-2, a controversially discussed topic in the field (Witzgall, 2005). Exogenous polycystin-2 produced in HEK 293 cells (a human embryonic kidney cell line), MDCK cells, LLC-PK1 cells (a porcine kidney epithelial cell line) and HeLa cells (a human cervical carcinoma cell line) is found in a reticular pattern, consistent with its location in the endoplasmic reticulum (Cai et al., 1999; Koulen et al., 2002). The immunofluorescence findings were confirmed biochemically. On their way to the plasma membrane the sugar residues of *N*-glycosylated proteins become modified in the Golgi apparatus in such a way that they cannot be removed by endoglycosidase H any longer. Indeed exogenous polycystin-2 is *N*-glycosylated and still sensitive to endoglycosidase H (Cai et al., 1999; Hidaka et al., 2004). Results from density gradient centrifugations and cell surface biotinylations also support the notion that polycystin-2 is located in the endoplasmic reticulum. An explanation for the intracellular location of polycystin-2 is the presence of a retention signal for the endoplasmic reticulum in the COOH-terminus of the protein (Cai et al., 1999). The findings in the various cell lines have been confirmed with human and murine kidney tissues (Cai et al., 1999; Koulen et al., 2002). It should also be mentioned, however, that evidence for the presence of endogenous polycystin-2 in the plasma membrane has been presented (Luo et al., 2003; Scheffers et al., 2002). Whatever the final outcome will be, it is generally accepted that a small portion of polycystin-2 escapes from the endoplasmic reticulum and reaches the primary cilium.

Protein transport to and in the primary cilium

Little is known how integral membrane proteins such as polycystin-2 reach the primary cilium and are transported in the primary cilium. We believe that most of polycystin-2 is located in the endoplasmic reticulum from where it is transported in a COPII-dependent fashion to the cis-side of the Golgi apparatus. The majority of polycystin-2 is transported back to the endoplasmic reticulum due to a 34-amino acid retention signal in its COOH-terminus (Cai et al., 1999) but a small percentage of the protein escapes and is transported to the base of the primary cilium with the aid of a ciliary trafficking motif at its NH_2-termi-

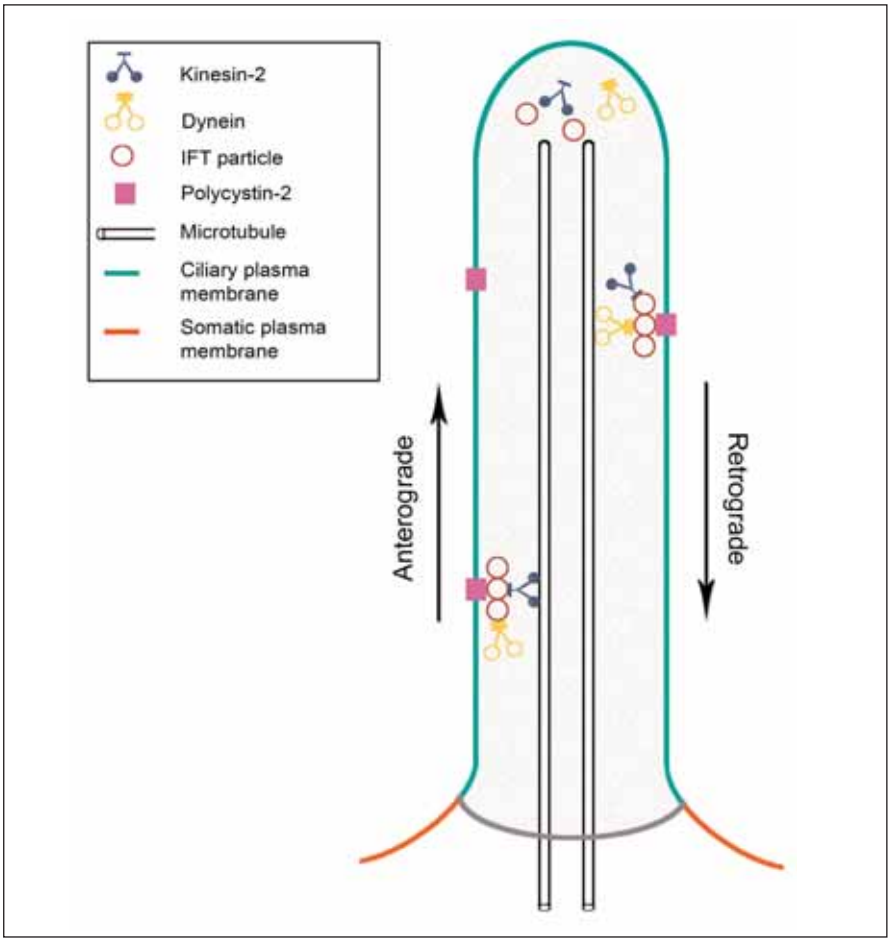


Figure 4. Intraflagellar transport. *Many proteins, including integral membrane proteins, are actively transported in primary cilia. Transport to the tip of the cilium is mediated by kinesin-2, retrograde transport by dynein. The switch at the tip of the cilium is not understood, furthermore the nature of the barrier at the base of the cilium is unknown.*

nus (Geng et al., 2006). The docking of transport vesicles at the base of the primary cilium probably depends on Rab8a, a monomeric G-protein, and on the BBSome, a complex of proteins which are mutated in patients suffering from Bardet-Biedl syndrome (Nachury et al., 2007; Yoshimura et al., 2007).

How is the movement of proteins in the primary cilium regulated? For the assembly and maintenance of the primary cilium a coordinated process called intraflagellar transport (IFT, Figure 4) is necessary (Pazour et al., 2000; Pazour and Rosenbaum, 2002). In *C. elegans* IFT appears to be dispensable for the movement of the polycystin-2 orthologue PKD-2 inside the cilium (Bae et al., 2006; Qin et al., 2005). However, in the flagella of *Chlamydomonas reinhardtii* the retrograde (but not the anterograde) transport component of IFT is essential for the trafficking of the polycystin-2 orthologue CrPKD2. But also in this organism the anterograde IFT component plays no role in the movement of CrPKD2 (Huang et al., 2007). Our own studies with LLC-PK$_1$ cells suggest that the situation is different yet again in mammalian cells.

Perspectives

Many novel results on primary cilia and polycystic kidney disease were obtained during the last decade. The intracellular transport of polycystin-2 and other integral membrane proteins from the endoplasmic reticulum to the primary cilium represents a fascinating cell biological problem with many unanswered questions. Where and how does polycystin-2 leave the Golgi compartment? How does it reach the base of the primary cilium? How does it enter the primary cilium? What is the barrier between the ciliary membrane compartment and the surrounding plasma membrane? Answers to these questions promise to provide intriguing insight into fundamental cell biological problems.

Acknowledgement

We are thankful for the superb design and arrangement of the figures by Antje Zenker. Financial support from the German Research Council through SFB 699 is gratefully acknowledged.

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Classical cadherin function in the epidermis

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Introduction

An important requirement for tissue structure and function is the ability of neighbouring cells to connect to each other through intercellular intercellular adhesive interactions. Classical cadherins are Ca^{2+}-dependent adhesion molecules that mediate these adhesive interactions and play fundamental roles in the establishment and maintenance of tissue architecture. Cadherins form the molecular backbone of of adherens junctions, dynamic intercellular structures that not only connect intercellular adhesion to the actin cytoskeleton but also function as signal platforms that regulate cytoskeletal dynamics and cell polarity. As such, cadherins regulate a diverse range of other cellular processes next to adhesion, such as cell shape, division, growth, apoptosis and barrier function. Therefore, understanding how cadherin adhesive complexes are formed and maintained is not only important to recognize how cells adhere to each other but also provides important insights into how these junctions regulate cell communication, thereby contributing to tissue homeostasis. Most knowledge on the function of classical cadherins in epithelial morphogenesis comes from studies with simple epithelia. In my group we study how classical cadherins regulate the formation and maintenance of the largest barrier of the organism, the stratifying epithelium of the skin, the epidermis. Here I provide a selective overview of classical cadherins and their role in epidermis.

Classical cadherin/catenin complex

Cadherins

Classical cadherins are type I single span transmembrane proteins that belong to the cadherin super family (Nollet et al., 2000). This family contains more than 80 proteins and is characterized by the presence of a calcium-binding motif, the so-called cadherin repeat (EC repeat) in their extracellular domain, which range in number from 4 to 34. Classical cadherins have 5 EC repeats in their extracellular domain and provide cells with Ca^{2+}-dependent intercellular adhesion properties. E-cadherin is the most intensively characterized classical cadherin. Other well-known examples are N-cadherin, P-cadherin and VE-cadherin.

Classical cadherins form a basic complex with the catenins, α, β, and p120 catenin (Fig.1) (Niessen and Gottardi, 2008). Two conserved regions in the cadherin cytoplasmic domains bind p120 and β-catenin, respectively, whereas α-catenin interacts indirectly through binding to β-catenin. Even though the extracellular domain contains the basic information for engagement of other cadherins on opposite cells, the interaction of the cadherin with the catenins is absolutely essential for full adhesive function.

Classical cadherins are considered homophilic (homotypic) adhesion molecules such that one cadherin only can bind to the same cadherin expressed on a neighbouring cell (e.g. E-cadherin only binds E-cadherin). These homophilic adhesion properties were thought to be the driving force behind sorting of cells. This is important during development e.g. when mesoderm induction leads to a switch from E-cadherin to N-cadherin expression and thereby segregates from the ectoderm. Similar E- to N-cadherin switching is observed in many carcinomas and directly contributes to the acquisition of invasive properties. However, recent data indicate that binding can be more promiscuous and that classical type I cadherins also can interact in a heterophilic fashion (Duguay et al., 2003; Niessen and Gumbiner, 2002). These findings then implicate that as yet not clearly identified other mechanisms than simple homophilic recognition regulate cell sorting, tissue segregation and migratory properties.

β-catenin

The cytoplasmic protein β-catenin not only binds the cadherin but also serves as a central player in the Wnt signaling pathway, which regulates cell fate decisions (MacDonald et al., 2009). β-catenin belongs to the armadillo repeat (arm repeat) protein family, characterized by the presence of varying copies of this repeat. The 12 armadillo repeats of β-catenin not only bind to the cadherin cytoplasmic domain (Huber and Weis, 2001) but is also used for binding to different partners important in transduction of the β-catenin dependent Wnt signal regulation. In the absence of Wnts, non-cadherin associated β-catenin interacts with and is phosphorylated by the APC/Axin phospho-destruction complex, thereby targeting it for ubiquitylation and proteasome mediated degradation. Wnt activation inactivates the phospho-destruction complex, resulting in β-catenin stabilization and subsequent translocation to the nucleus where it binds to TCF/LEF transcription family members to regulate gene expression . The N-terminus

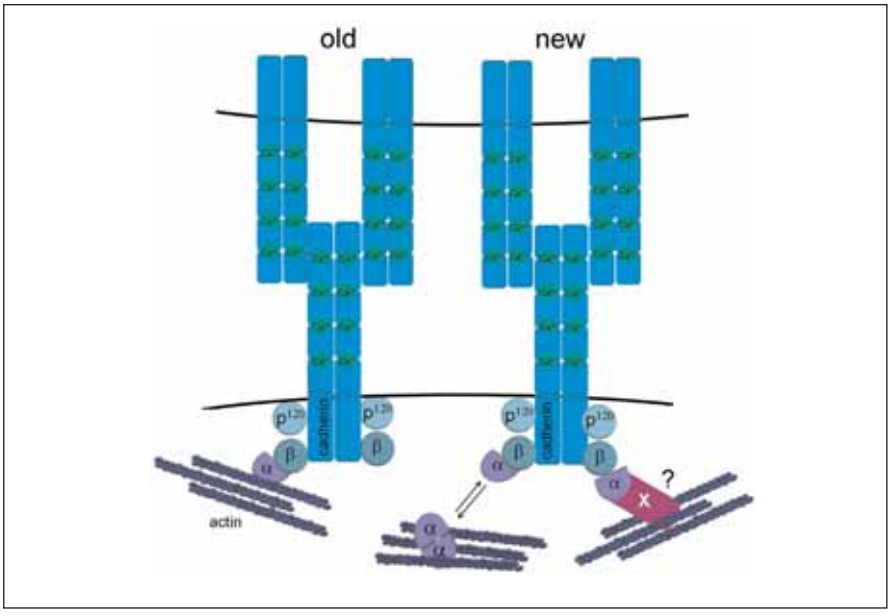

Figure 1: The Cadherin/catenin complex
In the text book model (old) the cadherin complex was directly bound to actin via α-catenin. In the recently proposed models, actin binding either takes place in the vicinity of adherens junctions through dynamic exchange of α-catenin and/or binding is through other actin binding proteins that link α-catenin to actin.

of β-catenin binds α-catenin and contains the phosphorylation dependent destruction sequence, whereas the C-terminus binds to various proteins that can modulate the adhesive or transcriptional activity of β-catenin.
Binding of β-catenin to the cadherin serves several crucial functions: it (1) protects the unstructured cadherin domain from degradation (2) promotes efficient transport from the ER to the cell surface (3) recruits a-catenin to the complex, a necessary step for full adhesive function and (4) protects β-catenin from binding to the destruction complex. Together these functions render β-catenin an excellent candidate to mediate signal-induced changes in cadherin adhesive contacts (Nelson and Nusse, 2004).

α-catenin

The actin binding protein α-catenin is homologous to the actin binding protein vinculin and characterized by three vinculin homology domains (VH1-3). VH1 binds in a mutually exclusive manner to either β-catenin or another α-catenin molecule, thereby forming a homodimer. VH2 is involved in binding to the actin binding proteins afadin, vinculin and α-actinin whereas VH3 can directly bind actin, the tight junctional protein ZO-1 or the actin binding protein Eplin (Pokutta et al., 2008). Loss of α-catenin results in strongly reduced intercellular adhesion, despite the presence of cadherin/β-catenin complexes on the cell surface, indicating that the link to α-catenin is absolutely essential for productive adhesion. Since the C-terminus of α-catenin can bind actin whereas the N-terminus was shown to bind β-catenin, it was assumed that α-catenin directly connected the cadherin complex to actin. As such, this model is presented in every textbook of cell biology (Fig.1). However, *in vitro* binding studies using isolated proteins were unable to detect the existence of a ternary cadherin-β-α-catenin-actin complex. More importantly, since the α-catenin dimer formation that binds actin is mutually exclusive with monomer binding to β-catenin, this strongly suggests the absence of a direct connection through α-catenin. Nevertheless, both genetic and cell biological data strongly indicate that α-catenin dependent regulation of actin polymerization does take place at or in close vicinity of the adherens junctions (Gates and Peifer, 2005; Scott and Yap, 2006). This has led to the proposal of new models (Fig.1b), in which dynamic exchange of α-catenin and the formation of dimers and binding to actin takes place close to the adherens junction (Nelson, 2008) and/or α-catenin regulates actin dynamics through binding of other actin interacting proteins .

p120ctn

P120 catenin (p120ctn) was initially identified as one of the major substrates of the cytoplasmic tyrosine kinase Src and only later it was recognized that p120^{ctn} was a core component of the cadherin adhesive complex (Reynolds, 2007). P120ctn belongs to a sub-family of Armadillo repeat containing proteins, which also include δ-catenin, ARCVF and p0071 (McCrea and Park, 2007). P120ctn consists of 10 armadillo repeats that, similar to β-catenin, are necessary for binding to the cadherin and relatively long N-terminus and short C-terminus subject to ser/thr phosphorylation. These are subject to extensive tyrosine and serine/threonine phosphorylation with most of the phosphorylation sites contained in a short segment in the N-terminus close to the arm repeats, suggesting that this region may play a role as a regulatory domain (Alema and Salvatore, 2007). Unlike α- and β-catenin, which are stabilized by expression and binding to cadherins, p120ctn stability is not increased by cadherin expression. Instead, cadherins are necessary and sufficient to translocate p120ctn from the cytoplasm to the membrane to sites of cell-cell adhesion. Moreover, unlike β-catenin, many p120ctn variants exist that arise from a combination of alternative use of translation initiation sites and alternative splicing. Differential expression of these variants may confer cells with different functions. For example, the p120 long variant 1 provides cells with migratory properties and is associated with a mesenchymal phenotype whereas the shorter variant 3 provides cells with stationary properties and is found in epithelial cells. Like β-catenin, p120ctn is found in the nucleus and regulates gene expression, through binding to a transcription factor, the POZ/Zinc finger family member Kaiso. P120ctn binding to Kaiso relieves Kaiso mediated transcriptional repression of target genes (Daniel, 2007).
Over the last decade p120ctn has emerged as a master regulator of cadherin cell surface stability and turnover by regulating access to the endocytic machinery (Reynolds, 2007). Loss of p120ctn results in increased cadherin turnover, and, as a consequence, a reduction in α- and β-catenin. Binding of p120 to cadherins inhibits their endocytosis whereas mutations in the p120 binding site of cadherins increase cadherin endocytosis. In addition, p120ctn serves as a master regulator of the Rho subfamily of GTPases by inhibiting Rho activity and, to a lesser extent, promoting Rac activity. Although these activities were initially identified in the context of cytoplasmic overexpression of p120ctn, it is now clear that inhibition of Rho under certain conditions requires binding of p120ctn to the cadherin.

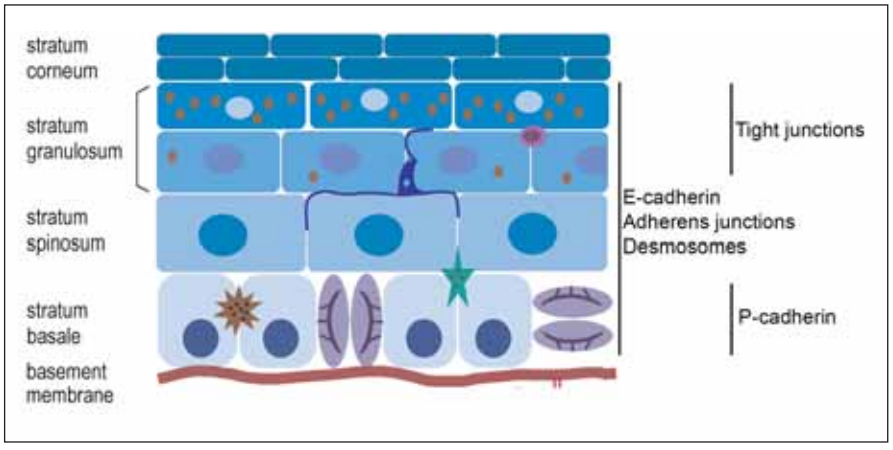

Figure 2: Schematic model of the epidermis
Shown are the different layers of the epidermis, the expression of classical cadherins and the appearance of junctions in the layers. Symmetric and asymmetric divisions occur in the basal layer to drive self renewal and differentiation.

Cadherin/catenin complex and signaling

Cadherin cytoplasmic domains or catenins have no enzymatic activity and are therefore unable to intrinsically mediate signaling upon changes in adhesion. However, these adhesion complexes directly and indirectly interact with several different classes of proteins that have enzymatic activity and/or are involved in the regulation of different signaling cascades. These include members of the Rho and Rap subfamily of GTPases and their regulators (Braga and Yap, 2005; Pannekoek et al., 2009), several cytoplasmic tyrosine and serine/threonine kinases and phosphatases, receptor tyrosine kinases (Perez-Moreno et al., 2003) and lipid kinases, such as PI3-kinase (Rivard, 2009). Such interactions provide cadherins with the

potential to transfer signals into the cell. Vice versa, these signals may also regulate adhesive capacity by regulating processes such as cadherin clustering, association of the complex, or interactions with the cytoskeleton. In addition, the cadherin cytoplasmic domain contains sequences that regulate its trafficking to the surface as well as internalization by interacting with regulators of these processes.

Cadherins and the regulation of polarity

The establishment and maintenance of cell polarity, which is the asymmetric distribution of proteins or subcellular structures in a cell, is crucial for cell morphology and function. Cadherins have emerged as important contributors to different polarization processes. The formation of intercellular junctions is functionally coupled to the acquisition of apicobasolateral polarity in simple epithelial cells and loss of cadherin disturbs polarization. Apicobasolateral polarity is the establishment of differential apical and basolateral membrane domains with respect to both lipid and protein composition and this allows for the formation of epithelial barriers. This requires a coordinated interaction of the secretory pathway, the cytoskeleton, polarity protein complexes and adhesion. Initial engagement of cadherins provides an early polarity cue by targeting the basolateral vesicle adaptor machinery to sites of cell-cell contact (Nejsum and Nelson, 2009). Cadherins have also been implicated in the regulation of stem cell positioning and differentiation. The cadherin complex provides a polarity cue for spindle positioning during the process of asymmetric cell division (Le Borgne et al., 2002; Lechler and Fuchs, 2005) and is essential to mediate interactions of the stem cell with its local niche (Song et al., 2002). Asymmetric cell division results in two daughter cells with differential cell fate and is used as a mechanism by several stem cell populations to self renew while simultaneously producing a more differentiated cell population. This process is also thought to play a role in the selfrenewal and differentiation of the epidermis.

The epidermis

The stratifying epidermis of the skin separates the organisms from its environment and serves as its first line structural and functional defense against dehydration, chemical substances and micro-organisms. Epidermal keratinocytes balance life long self-renewal with a spatiotemporally strictly regulated terminal differentiation program, which ultimately leads to the formation of a dead, cornified and water impermeable cell layer (Fuchs, 2007; Koster et al., 2002, Candi et al., 2006). This differentiation program generates four functionally different layers, each of which is characterized by a specific expression repertoire of intracellular and cell surface associated proteins (Fig.2): (i) the basal layer or stratum basale consists of undifferentiated, proliferating cells firmly attached to the underlying basement mebrane. (ii) the spinous layer or stratum spinosum contains the cells that either have withdrawn from the cell cycle, migrated up from the basal layer while committing to differentiation or of cells that divided asymmetrically with the spindle perpendicular to the basement membrane. These cells also have switched keratin subtypes to synthesize a mechanically more stable keratin network. (iii) the granular layer or stratum granulosum, dedicated to producing the majority of proteins, lipids and enzymes for formation of (iv) the stratum corneum. This layer, also known as the cornified layer, consists of corneocytes composed of an insoluble cross-linked protein structure, the cornified envelope that serves as a scaffold for specialized lipids that form the intercellular lamina, thereby providing the epidermis with a water impermeable barrier.

An important aspect in the formation and maintenance of the barrier is the tight but dynamic intercellular adhesion between keratinocytes to form strong cohesive sheets through intercellular junctions like adherens junctions and desmosomes. This results in the formation of strong cohesive cell sheets. Desmosomes mediate adhesion through other members of the cadherin superfamily, the desmosomal cadherins. Tight junctions form a second barrier in the most viable suprabasal layer, as recently shown. For keratinizing epithelia, it was originally thought that the secretion and deposition of this cross-linked protein-lipid barrier obviated the need for a tight junction barrier in such tissues.

Classical cadherins and the epidermis

Two types of classical cadherins are expressed in the epidermis: P-cadherin, expressed in the basal layer mainly around and in hair follicles, and E-cadherin found in all layers of the epidermis (Figure 2). It was recently reported that human E-cadherin is a target of auto-antibodies in pemphigus, a skin blistering disease. Mutations in human P-cadherin are associated with a hair disorder, hypotrichosis with juvenile macular dystrophy, and with ectodermal dysplasia associated with extrodactyly and macular dystrophy (EED) (Lai-Cheong et al., 2007).

Epidermal inactivation in mice revealed overlapping and specific functions for the cadherin associated catenins (Perez-Moreno and Fuchs, 2006). Loss of β-catenin in the epidermis confirmed its importance in the Wnt signaling pathway and its role in hair follicle morphogenesis and stem cell regulation (Huelsken et al. 2001). However, no obvious defects in intercellular adhesion and junction formation were observed, most likely because plakoglobin substituted for α-catenin in the cadherin complex. Inactivation of $p120^{ctn}$ in the epidermis resulted in reduced adherens junctions and skin inflammation associated with activation of NfκB. Epidermal deletion of α-catenin An almost complete loss of adherens junctions, reduced desmosomes and subsequent skin blistering was observed when α-catenin was

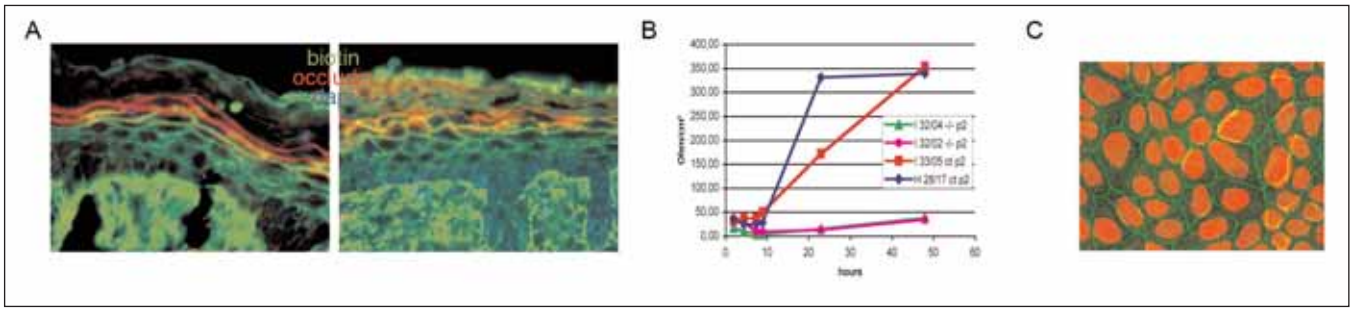

Figure 3: Loss of E-cadherin impairs epidermal tight junctional barrier function.
(A) Impaired inside-out barrier in E-cadherin$^{epi-/-}$ mice. (B) TER measurements of differentiating (hours after Ca^{2+}-switch) primary keratinocytes showing impaired tight junctional ion barrier in E-cad$^{-/-}$ keratinocytes. (C) Normal recruitment of ZO-1 to the membrane in E-cad$^{-/-}$ keratinocytes.

deleted from the epidermis (Radice et al., 1997). However, P-cadherin inactivation did not reveal any obvious skin phenotypes. Since both P-cadherin and E-cadherin interact with the three catenins, these results suggested that loss of a single cadherin may be insufficient to phenocopy the deletion of either α-catenin or p120ctn. Alternatively, each catenin may have other functions, similar to β-catenin, that are independent of the cadherin complex.

Classical cadherins; key regulators of intercellular junction formation

To examine the role of E-cadherin in stratifying epithelia, such as the epidermis and to address if loss of E-cadherin contributes to the phenotypes observed in the absence of one of the catenins we used Cre-LoxP to delete E-cadherin in all layers of the epidermis. Surprisingly, mice with epidermal loss of E-cadherin show no blistering but did have a red wrinkly skin and died due to enhanced epidermal water loss. Inactivation of E-cadherin in the epidermis later during development results in hair loss (Tinkle et al., 2004; Young et al., 2004). The most obvious explanation was a disturbed stratum corneum barrier function. However, lucifer yellow penetration assays failed to detect breaches in the "outside-in" stratum corneum barrier and toluidine blue dye penetration assays revealed no difference in the functional development of the stratum corneum barrier (Tunggal et al., 2005)). These results resembled observations for the claudin-1 knockout mice, which showed a normal outside-in barrier function but disturbed inside-out barrier function (Furuse et al., 2002). Indeed, dermally injected biotin diffused past the stratum granulosum in the E-cadherin$^{epi-/-}$, whereas control mice showed restricted flow indicating impairment of the tight junction inside-out barrier (Fig.3A). In vitro analysis further showed that both the ion and size barrier of the tight junctions is disturbed in E-cadherin$^{-/-}$ keratinocytes, using trans epithelial resistance measurements (TER) and differential sized dye penetration assays (Fig.3B). Interestingly, unlike in simple epithelial cell cultures, TJ dysfunction does not alter the localization of claudin-1, occludin and ZO-1 (Fig.3C), suggesting that E-cadherin regulates a late step in the functional formation of tight junctions. Functional tight junctions are restricted to the uppermost viable layers, where E-cadherin is also expressed whereas P-cadherin is only found in basal layers. In addition, knockdown of P-cadherin in keratinocytes did not alter either the size or ion barrier function of tight junctions. This suggested a specific role for E-cadherin in the formation of functional tight junctions. However, the tight junctional barrier defect was rescued either by P-cadherin or E-cadherin, thus showing that cadherin levels and not cadherin specificity is important to establish tight junctions.

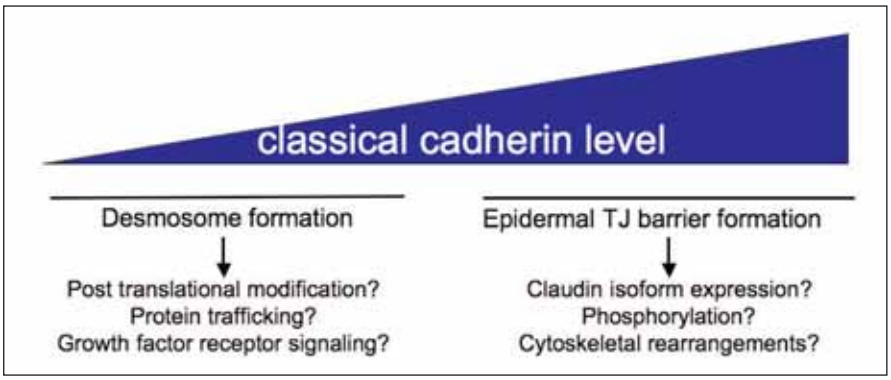

Figure 4: Different levels of classical cadherins are required for desmosome or tight junction formation. The tight junctional barrier is more sensitive to reduced classical cadherin levels whereas desmosome formation is only impaired when the level of classical cadherins is strongly reduced. Possible explanations for how classical cadherins regulate tight junctions and desmosmes are also provided.

The mechanisms that restrict the assembly of a tight junction barrier to the uppermost layers of stratifying epithelia are unclear. Since many tight junction components are expressed throughout the epidermal layers, it is possible that a local signal in the granular layer triggers TJ formation. We speculate that the dead cell/keratin layer may initiate this signal, similar to other simple epithelia, which secrete and are polarized by an apical matrix (e.g., such as follicular epithelia in flies that secrete an apical cuticle). Alternatively, TJ formation in the lower layers may be actively inhibited by the presence of an overlying viable cell layer. Either mechanism suggests that the restriction of tight junctions to the apical most layer in stratifying epidermis or apical region of simple epithelia may be conserved. Indeed, our data discussed here and others support this argument: E-cadherin is required for tight junction formation in both simple and stratifying epithelia. Blocking E-cadherin *in vitro* inhibits tight junctions in simple epithelia as does genetic loss of epidermal E-cadherin. The latter is associated with loss of active aPKC from sites of cell-cell contact (Tunggal et al., 2005). We and others have shown that aPKC inhibition interferes with tight junctions in both simple and stratifying epithelia (Suzuki et al., 2001; Mertens et al., 2005; Helfrich et al., 2007). Thus, junctional and polarity proteins required in simple epithelia are also turning out to be critical for epidermal barrier function, suggesting these processes may be mechanistically related.

In vitro studies in simple epithelial cells have indicated that E-cadherin regulates not only the formation of adherens junctions but also desmosomes and tight junctions. Surprisingly, in vivo intercellular contacts were not obviously disturbed in the E-cadherin$^{epi-/-}$ mice and ultrastructural analysis revealed the presence of abundant desmosomes. This was in agreement with antibody blocking studies in keratinocytes that indicated a cooperative role for E- and P-cadherin (Lewis et al., 1994). These results then raised the question whether classical cadherins are dispensable for desmosome formation or whether the other classical cadherin in the epidermis, P-cadherin, can functionally compensate for the loss of E-cadherin.

To examine this, E-cadherin$^{-/-}$ keratinocytes were transduced with lentiviral hairpin RNAs to knockdown P-cadherin. Loss of both classical cadherin almost completely prevented the formation of intercellular contacts and, on the ultrastructural level, desmosomes were no longer observed. Reexpression of either E-cadherin or P-cadherin was sufficient to restore adherens junctions and desmosome formation, indicating that, as for tight junctions, classical cadherin levels but not specificity regulate intercellular junction formation (Michels et al., 2009b), as was also recently shown in another study (Tinkle et al., 2008). An important question remains why despite their intrinsic capacity to mediate Ca^{2+}-dependent adhesion desmosomal cadherins are unable to establish productive adhesive structures in the absence of classical cadherins. Our initial experiments indicate that classical cadherin engagement restricts tyrosine kinase activity thereby allowing the stabilization of desmosomal cadherins on the surface (Fig.4).

In conclusion, the data show that classical cadherin engagement regulates not only the formation of adherens junctions but also that of tight junctions and desmosomes. Interestingly, there seem to be different requirements for classical cadherins in tight junction forma-

tion and desmosome formation since tight junctions are impaired on the functional level but not structurally and are more sensitive to a reduction in levels of cadherins than desmosomes, which require very little cadherin expression for their formation (Fig.4). Thus, mutations or dysfunction of classical cadherins in human disease may also affect pathogenesis indirectly, by affecting the tight junctions and desmosomes. An important future goal is to decipher the mechanisms by which classical cadherins regulate desmosomes and tight junctions.

Acknowledgements

Work in my laboratory is supported by the DFG, SFB829 and SFB832, CECAD, MPG and the Deutsche Krebshilfe. I would like to thank the members of my laboratory, especially Christian Michels, and other colleagues that contributed to the projects and for discussion.

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Laboratory of Dr. B.M. Gumbiner, Cellular Biochemistry & Biophysics Program

Principle Investigator
2002-2008
Junior Research Group Leader, Center for Molecular Medicine Cologne, University of Cologne, Germany
2008-present
Professor in Dermato-oncology, Department of Dermatology, Center for Molecular Medicine Cologne, University of Cologne

Honors and awards
Dutch Cancer Society Fellow, 1997-1998
Charles A. Dana Fellow, 1999-2001
ROSA "Skin Dryness" award 2006

12th DGZ Young Scientist Meeting "Actin Dynamics"

September 15 – 18, 2010, Jena

Organizers:
Eugen Kerkhoff, Theresia Stradal, Klemens Rottner

Further information:
www.zellbiologie.de · dgz@dkfz.de

Personalien

Die DGZ begrüßt folgende neue Mitglieder:

Emmanuel AMPOFO, PD Dr. Alexandr BAZHIN, PD Dr. Ingrid BOCKHOFF, Volker BUCK, Dr. Claudia GEY, Prof. Dr. Margarete GOPPELT-STRÜBE, Lilia HAFNER, Dr. Carsten HÖGE, Dr. Sandra IDEN, Oliver KUHNERT, Verena LORENZ, Sarah OPPENHEIMER, Nadin PLETZ, Zheng QU, Susann RÄTH, Björn RÖDER, Norman SACHS, Dr. Frank SCHNORRER, Nora STAUBACH, Vivica STOKES, Carina TROJAHN

Wer kann uns helfen? Von den unten aufgeführten Mitgliedern fehlen uns die aktuellen Adressen. Wenn jemand uns diesbezüglich weiterhelfen kann, bitten wir um Mitteilung an unser Sekretariat. Wir sind für jeden Hinweis dankbar. Vielen Dank für Ihre Mithilfe!

Adelt Stephan, **Adjogble** Koku Zikpi, **Alev** Cantas, **Bajbouj** Khuloud, **Barendziak** Tanja, **Baur** Tina, **Behrendt** Marc, **Bichelmeier** Ulrike, **Blume** Jessica, **Boshart** Michael, **Brandt** Peter, **Brigge** Theo, **Buchner** Klaus, **Bumann** Johann, **Carl-McGrath** Stacy, **Cerff** Rüdiger, **Conradi** Anne, **Dannhauser** Philip, **Dressler** Cathrin, **Eckert** Hans-Georg, **Eichstaedt** Stefanie, **Friedrich** Eckhard, **Geßner** Reinhard, **Grabenbauer** Markus, **Grimme** Susanne, **Gruner** Karl Reinhold, **Gunzer** Matthias, **Hameister** Horst, **Hartmann** Kristina, **Hartwig** Benedikt, **Herbst** Detlev, **Hesse** Michael, **Hilker** Michael, **Hillje** Anna-Lena, **Hinz** Giselbert, **Hochhuth** Christa, **Hofmann** Wilma, **Huff** Thomas, **Jarchau** Thomas, **Kalbas** Matthias, **Kessels** Michael M., **Kettelhake** Antje, **Klebig** Christiane, **Knoll** Gerhard, **Koch** Dennis, **Korfsmeier** Karl-Hermann, **Kralewski** Martina, **Kröger** Stephan, **Krüger** Bernd, **Kuchenbecker** Ralf, **Küchler** Michael, **Lahm** Harald, **Lange** Philipp, **Lehmann** Friederike, **Lehnert** Lasse, **Lucka** Lothar, **Michel** Caroline, **Moodt** Susanne, **Motrescu** R. Elena, **Müller** Jens, **Murk** Kai, **Nalbant** Perihan, **Oberbäumer-Wesch** Ilse, **Pauli** Andrea, **Paulus** Gerd, **Peschke** Matthias, **Peters** Kirsten, **Peters** Winfried, **Petrovitch** Alexander, **Pohlner** Johannes, **Riehl** Astrid, **Röser** Kerstin, **Rudel** Thomas, **Schenk** Hainfried, **Schmidt** Annette, **Schreiber** Daniela, **Schwarz** Gerd, **Seedorf** Udo, **Seidl** Klaus, **Siemon** Marén, **Smolenová** Eva, **Sprick** Martin, **Spring** Karsten, **Traub** Otto, **Von der Ahe** Dietmar, **Wacker-Schröder** Irene, **Walch-Solimena** Christiane, **Waldvogel** Horst, **Wolters** Hanno, **Zimmer** Klaus-Peter.

Mitglieder werben Mitglieder

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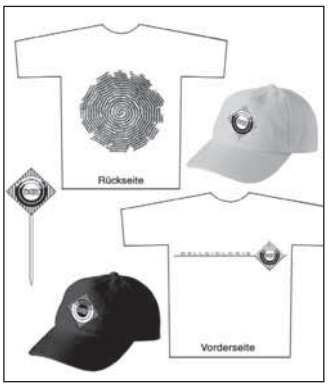
- Reduzierte Registrationsgebühren bei den DGZ-Jahrestagungen
- Möglichkeit einer Reisekostenunterstützung bei den DGZ-Jahrestagungen für junge Wissenschaftler/innen in unbezahlter oder teilbezahlter Stellung
- Möglichkeit der aktiven Mitarbeit bei den DGZ-Tagungsgestaltungen
- Freier Bezug der Mitgliederzeitschrift Zellbiologie aktuell (3 Ausgaben pro Jahr)

Information: dgz@dkfz.de, www.zellbiologie.de



Das **Formular für Beitrittserklärung und Mitgliedsdaten** kann von der Homepage der DGZ **www.zellbiologie.de** (unter „DGZ"/Formulare) heruntergeladen werden.

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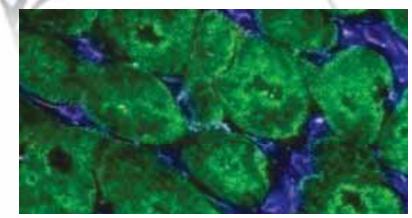
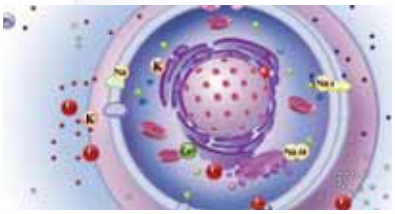
cells in focus



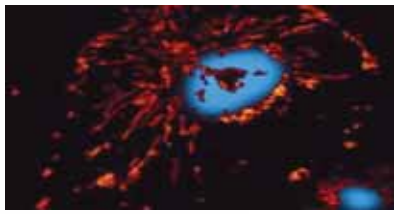
Cardiovascular assays

- Metabolic state of cardiomyocytes
- Cellular ATP demand



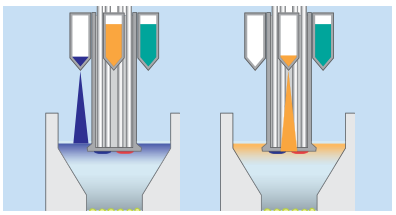
Obesity/Diabetes

- Fatty acid/glucose oxidation
- Bioenergetics in primary cells



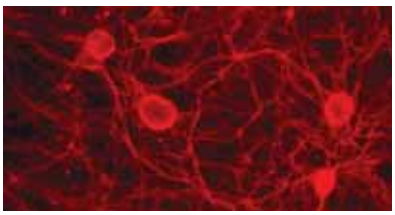
in vitro toxicity

- Drug & metabolite studies
- Multiple assays on cellular metabolism



Compound screening

- Non invasive, real time measurements
- Drug development



Neurodegenerative Disease

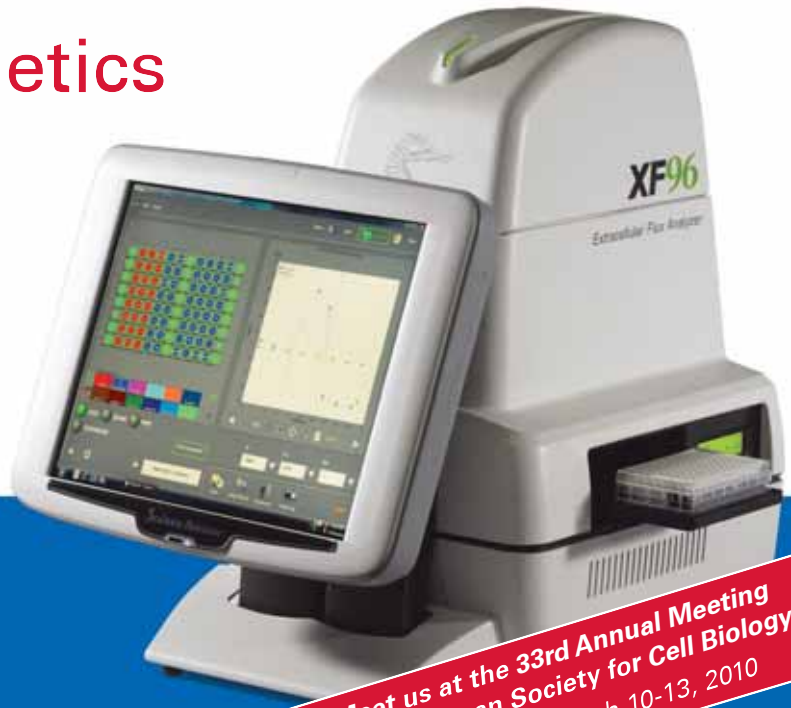
- Mitochondrial dysfunction and ATP turnover
- *in vitro* oxygen consumption

Cancer

- Anaerobic versus aerobic metabolism
- Lactate production/glycolysis

Cellular Bioenergetics in a Microplate

Determine aerobic respiration and glycolysis



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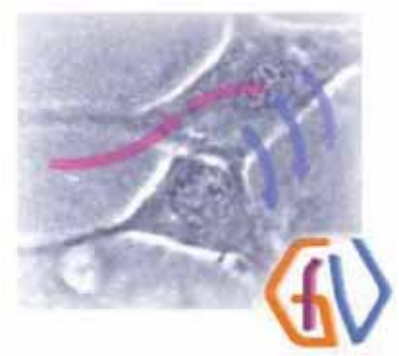
Meet us at the 33rd Annual Meeting of the German Society for Cell Biology
Regensburg, March 10-13, 2010

2010 / 01

The viruses' view of the cell – cell biology using viruses as probes

Meeting Report on the 8th Workshop ‚Cell Biology of Viral Infections' of the German Society of Virology (GfV) in Deidesheim, October 5th-7th 2009.

By Kay Grünewald[1] and Mario Schelhaas[2].



Viruses are not living organisms in a strict sense, but are obligatorily dependent on cells to replicate and to fulfil their 'life cycles'. Towards this end, viruses exploit a large variety of basic cellular processes such as endocytosis, nuclear import, transcription, replication, and exocytosis. Early cell biological studies made use of viruses as they provided a simple, limited component system that could be easily followed by the molecular biological, biochemical, and morphological techniques available. With the technological advances made over the decades, cell biologists expanded their model systems and toolkits, and pathogens ceased to be a major tool to study cellular biology. However, this field at the crossroad between cell biology and infection biology has re-emerged with new vigour particularly in membrane traffic [1-4], for overviews refer to [5-8].

To foster exchange and research at the crossroads of cell biology and virology, the German Society of Virology established the study group ‚Cell Biology of Viral Infections'. The main purpose of this study group is to bring together researchers of the allegedly divided fields by means of informal workshops. Held again on the estates of the famous winery Basserman-Jordan (Deidesheim) in the palatinate region, last year's 8th annual workshop was again generously co-sponsored by the German Society of Cell Biology. Four cell biological keynote speakers gave exciting insights into their particular research efforts.

Mark Marsh from the MRC-Laboratory of Molecular Cell Biology at the University College London re-visited lentivirus assembly focusing on fidelity and pathogenesis. He described the involvement of the cellular ESCRT machinery, the specific role of its different components in the viral assembly process, and he made the comparison to their genuine cellular function. He pointed out the similarity in membrane topologies for the structures budding away from the cytosol in the formation of multivesicular bodies and retrovirus budding. His presentation, moreover, summarized the importance of following membrane continuities over long distances to reveal the nature of a compartment that on a first look might appear endosomal but was revealed to be a complex invagination of the plasma membrane.

Volker Haucke (FU Berlin) talked about the regulation of adaptor-mediated membrane dynamics with a focus on clathrin-mediated endocytosis. This regulation is highly complex and involves the crosstalk of various cellular signalling pathways. Additionally, he emphasized the differences between clathrin coats on the plasma membrane and those on other intracellular compartments. Throughout his talk, he summarized the contribution of a wide range of methodological approaches that have contributed to our current understanding of the processes involved.

Jonathon Howard from the MPI of Molecular Cell Biology and Genetics (Dresden) gave an entertaining and insightful talk on the motor protein family of kinesins and their interaction with the cytoskeleton. He clearly laid out the many uses of these engines. This covered the mechanisms by which the proteins convert chemical energy derived from the hydrolysis of ATP into mechanical work, how this is used to move along microtubules but also to depolymerize microtubules. The dynamic properties of this system required the combination of several dedicated techniques - single-molecule fluorescence, optical tweezers, image processing, modelling, molecular biology, nanofabrication and nanofluidics, and electron microscopy. Integrating the results helped to understand the self-organization of molecules into organelles and interactions that constitute a form of mechanical signalling.

Finally, *Marius Lemberg* from the ZMBH, Heidelberg highlighted the mechanism and function of intramembrane proteases. While cytosolic or secreted proteases are rather well understood and most biologists are aware of their basic functions, intramembrane proteases as the name suggests act within membranes and such have more specific functions. Given that many signalling pathways receive their signals from a membrane surface and such the majority of the elements of a signalling cascade are integral or proximal to this membrane, these proteases have an import role in the regulation of cellular functions by cutting proteins within the lipid bilayer. At the same time, these proteases have to be regulated themselves. The presentation, again covering results stemming from a wide range of approaches, provided valuable insights into these complex

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networks and crosstalks. The following discussion visualized the challenges that a virus faces when successfully hijacking and modulating this complexity.

Besides the invited speakers, the participants displayed in a number of talks the wide variety of cell biological features of viral infections. The four sessions 'Organelles, membranes and membrane traffic', Cytoskeleton', 'All around the nucleus', and 'Cells and tissues' covered topics ranging from molecular details of single open membrane sheet generation during vaccinia virus assembly, analysis of virus induced and modulated signalling (Influenza A, Adenovirus, HIV) to modulation of host cell tissue changing e.g. polarity and barrier functions (Adeno- and Herpesviruses) - just to name a few. That for the first time a dedicated session on tissues was included, certainly provided the meeting with a wider scope. The talks also represented a wide expertise in techniques covering a range from specialized life cell imaging at cutting edge speed and sensitivity, small molecule techniques, RNAi screens, proteomics and electron microscopy, with the latter spanning from advanced immunolabelling, tomography to high resolution cryo electron microscopy.

The meeting proved again to be a platform that stimulated interdisciplinary discussions, provided valuable feedback and served as a nucleation point for a number of new collaborations. Among the presentations there were a number of studies that had emerged during discussions at earlier meetings. This year, we explored the source of the excellent Riesling in a guided vineyard walk followed by a wine tasting – this social event served once again as a stimulant for the scientific discussions. We hope this year´s 9th workshop will be similarly successful – and in order to make it happen, we would like to emphasize and explicitly extend our invitation to all researchers in fields of cell biology as well as pathogen-modulated host cell behaviour to join us from 29th September to 1st October 2010, again in Deidesheim. We take the committed participation in the discussions by the cell biological keynote speakers as clear sign that the covered aspects are by far not just of interest to virologists. Notably, among the best-received and –discussed talks was one by Miriam Stoeber from the Helenius lab at the ETH Zurich covering a pure cell biological topic. We are sure that this series of workshops will continue to stimulate interactions between researchers, both, with cell biological and virological interest.

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8. Galan JE, Cossart P (2005) Host-pathogen interactions: a diversity of themes, a variety of molecular machines. *Curr Opin Microbiol* 8: 1-3.

Termine

33. Jahrestagung der DGZ
10. – 13. März 2010, Regensburg
Information: www.zellbiologie2010.de, info@zellbiologie2010.de

3. Gemeinsame Tagung der Deutschen Gesellschaft für Hygiene und Mikrobiologie (DGHM) e.V. und der Vereinigung für Allgemeine und Angewandte Mikrobiologie (VAAM)
28. – 31. März 2010,
Information: www.vaam-dghm2010.de, vaam-dghm2010@conventus.de

REGMEDINVEST 2010: 2nd GRM Investors Conference of the German Society for Regenerative Medicine
9. April 2010, Frankfurt/Main
Information: www.regmedinvest.com

International Workshop "Role of various types of ubiquitin chains in membrane trafficking"
20. – 21. Mai 2010, Paris
Information: https://www.eurtd.com/rubicon-workshop/

3rd European Workshop on Lipid Mediators
3. – 4. Juni 2010, Pasteur Institute Paris
Information: http://workshop-lipid.eu

DGZ-Nachwuchswissenschaftler-Tagung „Actin Dynamics"
15. – 18. September 2010, Jena
Information: www.zellbiologie.de, dgz@dkfz.de

13. Jahreskongress der Deutschen Gesellschaft für Wundheilung und Wundbehandlung e.V.
17. - 19. Juni 2010, Freiburg
Information: www.wunde-wissen.de

EMBO Workshop on Chromosome Segregation and Aneuploidy
19. – 23. Juni 2010, Edinburgh
Information: http://aneuploidy2010.bio.ed.ac.uk

5. Kongress der Mitteldeutschen Chirurgen
23. – 25. September 2010, Magdeburg
Information: www.conventus.de/mdcv2010/

40. Jahrestagung der Deutschen Gesellschaft für Immunologie
22. – 25. September 2010, Leipzig
Information: www.immunologie2010.de

5. Jahrestagung der Deutschen Gesellschaft für Stammzellforschung (GSZ)
30. September – 2. Oktober 2010, Lübeck
Information: www.conventus.de/gsz2010

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Impressum

Zellbiologie *aktuell*

Herausgeber:
Deutsche Gesellschaft für Zellbiologie e.V. (DGZ)

Verantwortlicher Schriftleiter:
PD Dr. Dirk Breitkreutz, Geschäftsführer

Redaktion/Anzeigen:
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Manuskripte:
Erbeten an das Sekretariat der DGZ

Anzeigen:
Vorlagen an das Sekretariat der DGZ

Produktion:
abcdruck GmbH
Waldhofer Str. 19
69123 Heidelberg
Tel.: 06221/8446-19
Fax: 06221/8406-00
Gestaltung: Heike Fischer

Auflage:
1800 Exemplare

Erscheinungsweise:
3 Ausgaben jährlich

Bezug:
Für Mitglieder der DGZ kostenlos