ISMB NEWSLETTER  
December 2009

Dear Fellow Matrix Biologists,

I hope you all had a great summer and fall.

In my previous editorial, I expressed some negative thoughts regarding the potential effects of the Stimulus Package provided by the current American Administration. I have to admit, however, that my predictions and conclusions were not so accurate. It is with a great pleasure to notice that the Stimulus Package has done some very good things. Following the tsunami of grant applications, the projected 1% success rate for the so-called Challenge Grants was indeed close to 4%, after the NIH increased the initial allocations. In other words, visionary NIH administrators funded grants that they felt were meritorious even though these proposals did not reach the 1st percentile (I applaud them). Second, the Stimulus Package has kept afloat several investigators whose grants just missed the pay line. Third, and perhaps most important, the new money supports novel research ideas, new investigators, students, technology projects and new equipment. Of course, there is still a “Sword of Damocles” hovering over our heads also translatable into a familiar theme in Greek and Roman philosophical writings as “Judge no one happy until his life is over”. The main reason for this sense of foreboding is that the new monies will be available for just two years. What will happen then? “Steady multi-year budget commitments would be better policy in the long run…” says Dr. E. Zerhouni, the former NIH Director. However, it seems obvious that this contingency plan has done some good. Now, the NIH and our universities need to plan far in advance as the best way to sustain this enhanced research body after 2011.

What has all of this to do with the ISMB? I believe that this new NIH strategy will have a significant impact on our field of matrix biology particularly because it will sustain established investigators (after all, two years of a fully oxygenated room is better than chronic hypoxia as before), and it will generate new investigators in our field of research. The various international collaborations will also benefit, as well our Matrix Biology meetings both in the USA and abroad. Relaxing visa procedures will also improve the possibility for students, visiting scholars and postdoctoral fellows to join American universities and research laboratories.

In the past few months there have been several Matrix Biology meetings focusing on various aspects of our field, including various Gordon Research Conferences on Collagen and Bone, and the FEBS Advanced Lecture Course on "Matrix Pathobiology, Signaling and Molecular Targets" which was held in sunny Patras, Greece. This was a very successful meeting which gathered over 150 researchers from several continents and a large number of young students and post-docs. Another very successful meeting was the 6th International Conference on Proteoglycans, Aix-les-Bains, France; September 13-17, 2009. The meeting was organized by Hughes Lotart-Jacob and Jacob van den Born and was located in a magnificent ancient (Roman) city, in the Savoia (or Savoie) region in south eastern France, in the Rhone Alpes. The meeting and the organization were both magnificent, and again I saw many new faces and young researchers. Another uniquely successful symposium was held in
Cologne, October 4-6, and organized under the auspices of the Klenk Family by Bjorn Olsen, Mats Paulsson, and Thomas Krieg: “25th Ernst Klenk Symposium on Extracellular Matrix in Health and Disease”. At this meeting there were only major talks by experts in the field of matrix biology, with no registration fee. This allowed many young people from underdeveloped countries to attend and actively participate in the discussions following each presentation. Photos from these conferences are at the end of the Newsletter.

I have actively participated and functioned as the ISMB photographer, a sort of paparazzo (see the collection of pictures below). By the way, I think that many of you ISMB members will likely be unaware of the etymology of the word “paparazzo”. When Federico Fellini decided to give an obnoxious name to the “annoying photographer” known now as “paparazzo”, he took the telephone book of my own native town of Catanzaro in Calabria and searched for the ugliest name he could find. He chose “paparazzo” (which mean ugly duck, and indeed does exist in multiple copies in my home town phone book........). He then used the word paparazzi to denote the obnoxious photographers in his famous movie “La dolce vita”. So I was told when I was growing up. Another version is that the name came from a southern Italian travel narrative by Victorian writer George Gissing, “By the Ionian Sea.” The book, published in 1901, gives the name of a hotel proprietor, Signor Paparazzo, according to Wikipedia.

Finally, I would like to remind you that next year we will give the Rupert Timpl Award at the FECTS meeting in Davos Switzerland (July 2010), and then we will give the Senior Investigator Award at the Biennial Meeting of the ASMB to be held in Charleston, South Carolina, October 2010. At both meetings, ISMB will have a sponsored plenary session where three ISMB travel award-winners will present short talks selected from the abstracts.

I hope you all have a fantastic holiday season.

Warmest regards to all,

Renato V. Iozzo, M.D.
President ISMB

From the ISMB Secretary

This is the last Newsletter of 2009. It is time to take a look at what the New Year 2010 will bring us. In conjunction with the ISMB, the German and Swiss Societies for Matrix Biology will organise the XXIIth FECTS (Federation of European Connective Tissue Societies) meeting. The location of the meeting is the Congress Centre in Davos, Switzerland, where the (in) famous World Economic Forum has taken place during the past decades. FECTS meetings are major international conferences in matrix biology, held biannually, and since 2004 with the ISMB. Together with the memories of the high scientific standard and the recreational and networking value of the last FECTS meeting in Davos in 1992, this should already be plenty of incentive to attend.

Typically, 600 participants convene from all over the world and the programme features high profile scientists, some of them also from other fields to help to broaden the scope. I rarely go to other meetings where the international flavour is as prominent as in the FECTS meetings. One of the highlights of the last few FECTS meetings has been the Rupert Timpl Award that has been given to young and very promising colleagues having published outstanding articles in the field of extracellular matrix biology during the two preceding years (see Awards). The laureate will give a lecture on the subject of his award during the 2010 FECTS meeting in Davos. Preliminary information on the 2010 FECTS meeting has just become available on the internet (http://www.fects.eu). Have a look and get a first impression - I am sure that you will enjoy this meeting.

Unfortunately, the date (July 3-7, 2010) partially coincides with the basement membrane conference foreseen to be held in Nashville (July 7-9, 2010). Time constraints appear to make this necessary although ISMB has tried its best to avoid the clash. The upside is that you will have the choice between two major events in matrix biology that take place next year, the second one geared to invigorate once again the interest in basement membranes. Other meetings in matrix biology have received their due attention elsewhere in this Newsletter.

I have another “last call” in this last Newsletter of 2009. This is your last opportunity to settle your open account with ISMB. You won’t believe it but I still do not seem to have convinced all members of the necessity to do this. All information is available under http://www.ismb.org should you be one of those few who still need to do this. Your loyalty to the international cause of matrix biology will be highly appreciated.

Peter Bruckner, ISMB Secretary and Treasurer (for the ISMB Council)
Awards

The year 2009 is nearing its end and I hope that your great scientific success met your well-founded expectations. A lot of excellent papers have appeared during the past two years. The ISMB awards the Rupert Timpl Prize to the principal author of the best paper in the field of matrix biology which has appeared in the two years preceding the FECTS / ISMB-meetings. The prize is given to an excellent young matrix biologist. The next meeting takes place in Davos in July 2010 (July 3 -7; see also announcement in this Newsletter issue). The award ceremony includes the Rupert Timpl lecture delivered by the recipient. The prize is named after Rupert Timpl (1936 – 2003), an outstanding matrix biologist and the discoverer of “laminin”. The previous recipients have been Claus Franzke (2004), Elizabeth Canty (2006), and Adam Engler (2008). The task now at hand is to find the next laureate.

As a member of ISMB you are encouraged to make nominations of scientists qualifying for this prestigious prize. Your nominee(s) should have made a decisive contribution, usually as the first author, to an outstanding paper with a publication date in 2008 or 2009 and dealing with a subject in matrix biology. In general, your nominee(s) should be less than 40 years old. If the person is older, you should include your written nomination good reasons why you believe that the candidate still qualifies. Please send your nominations by e-mail to peter.bruckner@uni-muenster.de. Include short CVs of your candidate(s) and, of course, the papers in question, along with a short appraisal why you think that they are worthy of a Rupert Timpl prize. The deadline for nominations is January 31, 2010. The Council of ISMB will then select the prize winner and invite the laureate to the FECTS-/ISMB-meeting in Davos, expecting her / him to be available during the entire meeting. The prize will also include costs accommodation and travel (economy class) as well as the registration fee of the meeting. Doesn’t this look like a major honour for your candidate and wouldn’t you be proud to have named the successful contender? I look forward to your responses.

Peter Bruckner, ISMB secretary / treasurer

Meeting Announcements

8th International Conference on Hyaluronan
June 6-11, 2010, Kyoto, Japan
http://www.ishas.org/

Gordon Research Conference on:
Signal Transduction By Engineered Extracellular Matrices
Gordon-Kenan Research Seminar
June 26-27, 2010, University of New England, Biddeford, ME
Chairs: Jennifer L. Leight and Wesley R. Legant

The German and Swiss Societies of Matrix Biology
we invite you to the  XXII FECTS meeting
Davos (Switzerland) July 3rd -7th, 2010

Topics include: The role of the extracellular matrix in acquired and genetic diseases, cell therapy, stem cell research, biomaterials and biomechanics, inflammation and angiogenesis, tissue engineering and regenerative medicine. The meeting includes plenary lectures, workshops with short talks selected from submitted abstracts, and poster sessions for individual scientific discussions.

Invited speakers include: Attila Aszodi, Gorg Duda, Martin Humphries, Renato V. Iozzo, Cay Kielty, Magareta Müller, Gillian Murphy, David Ornitz, Wiltrud Richter, Markus Ruegg, Lydia Sorokin, Rocky Tuan, Fiona Watt, and Sabine Werner

Registration and abstract submission opens January 1st, 2010
The deadline for abstract submission will be April 6th, 2010
Detailed information is provided on the FECTS – homepage (http://www.fects.eu/)

Chairs: PD Dr. Susanne Grässel Prof. Dr. Johannes C. Schittny
See poster at the end of the Newsletter for more details.
Symposium on Basement Membranes in Tissue Development and Regeneration
July 7-9, 2010, Vanderbilt University, Nashville, TN
Registration opens January 1, 2010
http://www.mc.vanderbilt.edu/cmb/ (see attached flyer)

Gordon Research Conference on:
Proteoglycans - Development, Disease And Therapeutics
July 11-16, 2010, Proctor Academy, Andover, NH
Chair: Marian F. Young and Robert J. Linhardt

Gordon Research Conference on:
Transglutaminases In Human Disease Processes
July 18-23, 2010. Davidson College, Davidson, NC
Chaired by: Richard Eckert and Kapil Mehta

Thrombospondins and Other Matricellular Proteins in Tissue Organization and Homeostasis
18 July-23 July 2010, Snowmass Village, Colorado, USA
Conference Organizers: David D. Roberts, NIH, and Joanne E. Murphy-Ullrich, UAB
Contact: Julie Levin, jlevin@faseb.org

Matricellular proteins are non-structural proteins of the connective tissue that modulate cell functions through regulation of cell adhesion, growth factor activity, and signaling networks. Matricellular proteins, including thrombospondins, tenascins, SPARC, and the CCN family, have been implicated in a number of disease and developmental processes and represent novel therapeutic targets for major diseases. The program will include presentations by leading investigators, poster sessions, and short talks selected from the submitted abstracts. Major themes and session chairs:

Structural biology and genetics of matricellular proteins
Deane F. Mosher University of Wisconsin

Matricellular proteins in fibrosis and tissue remodeling
Joanne E. Murphy-Ullrich University of Alabama at Birmingham

Neurobiology and developmental biology
Richard P. Tucker University of California at Davis

Roles in injury and stress responses
David D. Roberts NIH

Functions in musculoskeletal development and disease
Jacqueline T. Hecht University of Texas Medical School

Roles in metabolic regulation
Olga I. Stenina Cleveland Clinic

Carcinogenesis and tumor progression
Jack Lawler Harvard Medical School

Cardiovascular disease and angiogenesis
William A Frazier Washington University St Louis

Immunity and inflammation
Ruth Chiquet-Ehrismann Friedrich Miescher Institute

Gordon Research Conference on:
Biomineralization
August 15-20, 2010, Colby-Sawyer College, New London, NH
Chair: Lia Addadi and Peter Fratzl

Biennial Meeting of the American Society for Matrix Biology.
Celebrating 10 years of ECM Connections! The meeting is set for October 24–27, 2010 in beautiful Charleston, SC. The Francis Marion Hotel will be providing the accommodations and meeting space and we are certain you will enjoy the charm of this prime location. Our Meeting Chair, Jean Schwarzbauer, has put together an amazing program committee and they are busily working on program topics and speakers. They have already identified a wonderful keynote speaker, Elaine Fuchs, from The Rockefeller University presenting “Stem Cells, Extracellular Matrix, Tissue Morphogenesis and
Cancer in Skin*. We will also have Satellite symposiums presented by guest societies TERMIS, SFG and ISMB. More details will be forthcoming. Please check back regularly for updates on the website (www.asmb.net)

Matrix Research Update

Papers in press or recently published

Extracellular and cell surface proteases in wound healing: new players are still emerging.
Moali C, Hulmes DJS

Tissue remodelling results from the concerted action of numerous extracellular and cell surface proteases. These act to synchronize the synthesis and degradation of the extracellular matrix with the control of cytokine activity and cell signalling in order to create appropriate environments for cell proliferation, migration and differentiation. Wound healing is a complex example of tissue remodelling that includes several steps occurring either concomitantly or successively during the process of repair: haemostasis, inflammation, angiogenesis, re-epithelialisation, granulation tissue formation, wound contraction and matrix remodelling. The main extracellular and cell surface proteases involved in wound healing are serine proteases, especially plasmin, and metalloproteases of the metzincin family (MMPs, ADAM(TS)s, tolloids, meprins, pappalysins) with cysteine proteases playing less prominent roles. Several regulatory proteins and hundreds of substrates have been identified for these proteases, either in vitro or in vivo. The aim of this review is not to present an exhaustive list of proteases and related molecules but to give an overview of the proteolytic events that are potentially relevant during tissue repair. New developments aimed at approaching a more integrative view of all the molecular events involved in tissue remodelling are also discussed.

Strong cooperativity and loose geometry between CUB domains are the basis for procollagen C-proteinase enhancer activity.

Procollagen C-proteinase enhancers (PCPE-1 and -2) specifically activate bone morphogenetic protein-1 (BMP-1) and other members of the tolloid protease family during C-terminal processing of fibrillar collagen precursors. PCPEs consist of two CUB domains (CUB1 and CUB2) and one NTR domain separated by one short and one long linker. It was previously shown that PCPEs can strongly interact with procollagen molecules but the exact mechanism by which they enhance BMP-1 activity remains largely unknown. Here, we used a series of deletion mutants of PCPE-1 and two chimeric constructs with repetitions of the same CUB domain to study the role of each domain and linker. Out of all the forms tested, only those containing both CUB1 and CUB2 were capable of enhancing BMP-1 activity and binding to a mini-procollagen substrate with nanomolar affinity. Both these properties were lost by individual CUB domains which had dissociation constants at least three orders of magnitude higher. In addition, none of the constructs tested could inhibit PCPE activity, though CUB-2CUB2NTR was found to modulate BMP-1 activity through direct complex formation with the enzyme, resulting in a decreased rate of substrate processing. Finally, increasing the length of the short linker between CUB1 and CUB2 was without detrimental effect on both activity and substrate binding. These data support the conclusion that CUB1 and CUB2 bind to the procollagen substrate in a cooperative manner, involving the short linker that provides a flexible tether linking the two binding regions.

**TGF-β enhances the integrin α2β1-mediated attachment of mesenchymal stem cells to type I collagen.**
Katrin Warstat, Diana Meckbach, Michaela Weis-Klemm, Anita Hack, Gerd Klein, Peter deZwart, and Wilhelm K. Aicher.
*Stem Cells and Development,* epub Oct 14

The heterodimeric integrins are important receptors for the attachment of cells to their extracellular matrix. Here, we studied the attachment of human mesenchymal stem cells (MSC) to type I collagen, which is part of the extracellular matrix in bone, skin and connective tissues. Furthermore, we examined how TGF-β influences the integrin expression and attachment of MSC. Using flow cytometry, immunoblot and RT-PCR, we report that MSC express several integrin subunits, including the α2β1 integrin (VLA-2, CD49b/CD29). TGF-β increases the expression of integrin subunits α2, α6 and β1 in MSC, thereby enhancing the attachment of MSC to type I collagen. The TGF-β mediated up-regulation of the expression of the integrin subunits α2 and α6 is mainly mediated in MSC by Smad2.
The role of endogenous inducers of inflammation is poorly understood. To produce the proinflammatory master cytokine IL-1α, macrophages need double stimulation with ligands to both Toll-like receptors (TLR) for IL-1α gene transcription and nucleotide-binding oligomerization domain-(NOD)-like receptors for activation of the inflammasome. It is particularly intriguing to define how this complex regulation is mediated in the absence of an infectious trigger. Biglycan, an ubiquitous leucine-rich repeat (LRR) proteoglycan of the extracellular matrix, interacts with TLR2/4 on macrophages. Objective of this study was to define the role of biglycan in the synthesis and activation of IL-1α. Here we show that in macrophages soluble biglycan induces the NLRP3/ASC inflammasome, activating caspase-1 and releasing mature IL-1β without need for additional costimulatory factors. This is brought about by the interaction of biglycan with TLR2/4 and purinergic P2X4/ P2X7 receptors, which induces receptor cooperativity. Furthermore, reactive oxygen species (ROS) formation is involved in biglycan-mediated activation of the inflammasome. By signaling through TLR2/4 biglycan stimulates the expression of NLRP3 and pro-IL-1b mRNA. Both in a model of non-infectious inflammatory renal injury (unilateral ureteral obstruction) and in LPS-induced sepsis biglycan-deficient mice displayed lower levels of active caspase-1 and mature IL-1β in the kidney, lung and circulation. Our results provide evidence for direct activation of the NLRP3 inflammasome by biglycan and describe a fundamental paradigm of how tissue stress or injury is monitored by innate immune receptors detecting the release of the extracellular matrix components and turning such a signal into a robust inflammatory response.

**Enzymatic processing of α-dystroglycan recombinant ectodomain by MMP-9: identification of the main cleavage site**

Manuela BOZZI, Rosanna INZITARI, Diego SBARDELLA, Susanna MONACO, Ernesto PAVONI, Magda GIOIA, Stefano MARINI, Simona MORLACCHI, Francesca SCIANDRA, Massimo CASTAGNOLA, Bruno GIARDINA, Andrea BRANCACIO, and Massimo COLETTA

*IUBMB Life* 61(12):1143-52

Dystroglycan (DG) is a membrane receptor belonging to the complex of glycoproteins associated to dystrophin. DG is formed by two subunits, α-DG, a highly glycosylated extracellular matrix protein, and α-DG, a transmembrane protein. The two DG subunits interact through the C-terminal domain of α-DG and the N-terminal extracellular domain of α-DG in a noncovalent way. Such interaction is crucial to maintain the integrity of the plasma membrane. In some pathological conditions, the interaction between the two DG subunits may be disrupted by the proteolytic activity of gelatinases (i.e. MMP-9 and/or MMP-2) that removes a portion or the whole α-DG ectodomain producing a 30 kDa truncated form of β-DG. However, the molecular mechanism underlying this event is still unknown. In this study, we carried out proteolysis of the recombinant extracellular domain of α-DG, α-DG(654–750) with human MMP-9, characterizing the catalytic parameters of its cleavage. Furthermore, using a combined approach based on SDS-PAGE, MALDI-TOF and HPLC-ESI-IT mass spectrometry, we were able to identify one main MMP-9 cleavage site that is localized between the amino acids His-715 and Leu-716 of α-DG, and we analysed the proteolytic fragments of α-DG(654–750) produced by MMP-9 enzymatic activity.

**Journal of Cell Communication and Signaling**

Contents of a themed issue on matricellular proteins - December 2009

1) Overview (Bornstein)
2) The role of matricellular proteins in nervous system development and function (Eroglu)
3) The effects of thrombospondins on extracellular matrix structure (Lawler and Tan)
4) Thrombospondins function as regulators of angiogenesis (Bornstein)
5) Thrombospondins in the heart: potential functions in cardiac remodeling (Schellings et al.)
6) The role of thrombospondins in wound healing, ischemia, and the foreign body reaction (Kyriakides and MacLauchlan)
7) Thrombospondin-2 and SPARC regulate skeletal growth and remodeling (Hankenson and Delany)
8) The role of SPARC in extra matrix assembly (Bradshaw)
9) The role of SPARC in adipocyte differentiation (Nie and Sage)
10) SPARC as a regulator of tumor progression (Arnold and Brekken)
11) The many facets of the protein periostin during cardiac development, remodeling, and pathophysiology (Norris et al.)
12) The role of tenascin-C in tissue injury and tumorigenesis Midwood and Orend)
13) The role of osteopontin in inflammatory processes (Lund et al.)
14) The matricellular properties of small leucine-rich proteoglycans (Merline et al.)
15) Fibulin 5, an integrin-binding matricellular protein, modulates cellular behavior and function (Yanagisawa, Brekenk)
POSTDOCTORAL SCIENTIST (E13; 4 year position)
Available immediately at the University of Muenster, Germany.
Work focuses on murine stroke models and the role of the ECM in CNS vessel structural and functional integrity. This scientist will be part of the EUSTROKE network (see www.europeanstrokenetwork.eu).
Please send applications and at least 2 references to: Prof. Lydia Sorokin, Inst. Physiological Chem. & Pathobiochem., University of Muenster, sorokin@uni-muenster.de. See www.sorokinlab.uni-muenster.de for further information on the work carried out in the Sorokin lab.

POSTDOCTORAL FELLOW POSITION
Postdoctoral fellow position available in the laboratory of Dr. Alexander G. Marneros. Cutaneous Biology Research Center, Department of Dermatology, Massachusetts General Hospital/Harvard Medical School, Boston.

The main focus of research for this project is on chemical and genetic targeting of Hedgehog-signaling in non-melanoma skin cancer, hair growth and epidermal functions. In vivo and in vitro assays will be used to determine physiological and disease-related functions of Hedgehog-signaling components. For more information see: http://www.mgh.harvard.edu/cbrc/research/researchlab.aspx?id=1076

Required profile: M.D. or Ph.D. with strong background in molecular biology, experience in working with mice absolutely required, ability to work independently within a dynamic team. Interested candidates should send the CV and references to Alexander G. Marneros, M.D., Ph.D., email: alexander_marneros@yahoo.com

The MGH/Harvard Cutaneous Biology Research Center is a committed Equal Opportunity/Affirmative Action Employer. Minorities, women, handicapped and veterans are encouraged to apply.
on behalf of the German and Swiss Societies of Matrix Biology

we invite you to the

**XXII FECTS-Meeting**

Davos (Switzerland) July 3rd - 7th, 2010

**Topics**

Role of the *extracellular matrix* in acquired and genetic diseases, cell therapy, stem cell research, biomaterials and biomechanics, inflammation and angiogenesis, tissue engineering and regenerative medicine

**Invited speakers**

Attila Aszodi, Georg Duda, Martin Humphries, Renato V. Iozzo, Cay Kielty, Magareta Müller, Gillian Murphy, David Ornitz, Wiltrud Richter, Markus Ruegg, Lydia Sorokin, Rocky Tuan, Fiona Watt, and Sabine Werner

The meeting includes plenary lectures, workshops with short talks selected from submitted abstracts, and poster sessions for individual scientific discussions.

Registration and abstract submission opens **January 1st, 2010**

The deadline for abstract submission will be **April 6th, 2010**

Detailed information is provided on the FECTS – homepage


We look forward to welcome you at the XXII FECTS-Meeting in Davos!

---

**PD Dr. Susanne Grässel**  
Experimental Orthopedics, University of Regensburg  
ZMB / BioPark 1, Josef-Engert-Str. 9  
D-93053 Regensburg, Germany  
Phone +49 941 943-5065, FAX -5066  
susanne.graessel@klinik.uni-regensburg.de

**Prof. Dr. Johannes C. Schittny**  
Institute of Anatomy, University of Bern  
Baltzerstrasse 2,  
CH-3012 Bern, Switzerland  
Phone +41 31 631-4635, FAX -3807  
schittny@ana.unibe.ch
Vanderbilt University Medical Center
Center for Matrix Biology
presents a
Symposium on Basement Membranes in Tissue Development and Regeneration

July 7-9, 2010
at
Vanderbilt University, Nashville

Registration opens January 1, 2010
http://www.mc.vanderbilt.edu/cmb/
Registration and meals $250

Topics
Macromolecular Components
Development, Tissue Morphogenesis and Stem Cells
BMs in Disease
Use of Model Organisms

Poster Abstracts Welcome

Invited Speakers
Hans Peter Bächinger
Nick Brown
Eri Arikawa-Hirasawa
Reinhard Fässler
Laura Feltri
Billy Hudson
James Kramer
Jeff Miner
Jim Patton
Brent Polk
Susan Richardson
Kiyo Sekeiguchi
Arnoud Sonnenberg
Lydia Sorokin
David Sherwood
Jouni Uitto
Yujia Xu
Pampee Young
Peter Yurchenco
ISMB Members in action, International Conference on Proteoglycans, Aix-les-Bains, France, Sept. 13-17

Liliana Schaefer  Marianna Cappuro  Enrique Brandan  Jacob van den Born  Vince Hascall  Daniela Seidler

Nick Shworak  Tim Hardingham  Hideaki Nagase  Barbara Mulloy  John Whitelock

A moment of reflection......  A moment of ..................ectasy  No John.........it’s not Cannabis

Cay Kiely  Cathy Merry  Sally Stringer  Ariane De Agostini

Renato Iozzo  Tim Hardingham  “The ESKOs”  Ulf
The beauties of Aix-Les-Bains: water, flowers, history good music and excellent food

Abbaye d'Hautecombe

Aix derives from the latin Aqua, water, and was a bath during the Roman Empire
ISMB members in action at the Klenk Symposium, Cologne, October 4-6 2009

Monique Aumailley
Peter Bruckner
Lydia Sorokin
Dick Heinegård
Kathy Cheah
Renato
Mats Paulisson

Bjorn Olsen receives an award and a T-shirt from Tom Krieg

Hal Dietz
Renato Iozzo
Bjorn Olsen
Bjorn again
Dwayne Stupack
Kathy and Benoit
Ken Yamada

Gerard Karsenty
Leena Bruckner-Tuderman
Reinhard Fässler
From the Editor’s Desk

When primary cilia fail

Dear readers of Matrix Biology,

In previous editorials (Olsen, 2005, 2007) I have discussed recent work that has catapulted primary cilia, the single non-motile flagellar organelle present on nearly all interphase cells in vertebrates, from a position of obscurity and neglect to center stage in cell biology. As a result of this work, primary cilia are now celebrated as sensory organelles for detection and transmission of mechanical and chemical information from the extracellular environment of cells (Gerdes et al., 2009; Olsen, 2005). Cilia are also important for cell differentiation and polarity and regulation of the cell cycle. Primary cilia are dismantled as cells enter the cell cycle and they are reassembled during interphase. Ciliary growth and maintenance depend on activities of microtubule-based transport processes that bring cargo into the cilium from the apical cytoplasmic region in a kinesin II-dependent manner (antegrade intraflagellar transport, IFT) and out of the cilium in a dynein-dependent manner (retrograde IFT) (Scholey, 2008).

These transport processes are responsible for localizing receptors and components of several signaling pathways in primary cilia. For example, PDGF-Rα is localized to primary cilia (Schoenfeld et al., 2006) and activation of this receptor by serum-derived PDGF appears to be a key factor in triggering ciliary disassembly when cells enter the cell cycle. Of interest to matrix biologists is the localization of β1 integrin to primary cilia (Praetorius et al., 2004) and the demonstration that laminin-511 and its primary receptor β1 integrin are required for primary cilia formation in the condensed region of mesenchymal cells. The dermal papilla of developing hair: Laminin-511 is the primary laminin of epithelial cells in early developing hair follicles and Li et al. (2003) reported that absence of this laminin in mice results in defects that include arrested development of hair and deficient expression of Sonic hedgehog in epithelial cells of hair follicles. In a more recent study, Gao et al. (2008) found that dermal papilla cells from laminin-511-deficient mice failed to express the BMP inhibitor Noggin and exhibited a dramatic decrease in primary cilium formation. Primary cilia were significantly restored when dermal papilla mesenchymal cells from laminin-511-deficient mice were incubated with purified laminin-511, but not with laminin-111. Furthermore, when dermal papilla cells from wild-type mice were incubated with blocking antibodies against β1 integrin, primary cilia were dramatically decreased; blocking antibody against β3 integrin had no effect. Also disrupted was the ability of embryonic skin, treated with β1 integrin blocking antibody, to support hair formation on grafted onto the backs of nude mice.

These data, in conjunction with the evidence that primary cilia are required for all aspects of the hedgehog signaling pathway (Caspari et al., 2007; Corbit et al., 2005; Gerdes et al., 2009; Huangfu and Anderson, 2005; Rohatgi et al., 2007) provide the basis for a mechanistic model in which epithelial-derived laminin-511 binds to β1 integrin in mesenchymal cells, stimulates Noggin expression and primary cilia formation in the mesenchyme; in turn, this induces hedgehog expression in the epithelium and allows ciliary-based hedgehog signaling to occur in mesenchymal cells (Gao et al., 2008). Strong support for this mechanism comes from a recent study of Lehman et al. (2009), who demonstrate that Cre-mediated disruption of primary cilia in the dermis of mice results in severe lack of hair in affected areas.

With the flood of evidence for the ciliary association of multiple important cellular processes has also come the realization that a large group of inherited human disorders, now called ciliopathies, are consequences of ciliary abnormalities. Among the best characterized of ciliopathies are different forms of Bardet–Biedl syndrome (BBS) caused by mutations in various proteins that regulate ciliary assembly and function (Gerdes et al., 2009). The clinical features of BBS syndromes are quite variable but include renal abnormalities, retinal dystrophy, obesity, anosmia, skeletal defects (polydactyly/syndactyly/brachydactyly), and mental retardation.

Identification and characterization of the genes responsible for the different forms of BBS are providing important clues about the cilia-related functions of their protein products. Recent studies of two BBS-like syndromes also provide an excellent example of how human genetic analyses help expand the already long list of signaling processes that are associated with primary cilia. The two syndromes are Joubert syndrome (De Haene, 1955; Joubert et al., 1990), characterized by midbrain–hindbrain malformation, retinal dystrophy, renal defects, liver fibrosis and polydactyly, and a syndrome known as the Morquio syndrome, characterized by mental retardation, truncal obesity, congenital nonprogressive retinal dystrophy and microphthalmia in males (Hampshire et al., 2006). In affected members of seven families with Joubert syndrome, Bielas et al. (2009) identified 5 different homozygous missense mutations within the phosphatase domain of the gene encoding inositol polyphosphate-5-phosphatase E, INPP5E. The enzyme, which hydrolyzes the 5-phosphate of phosphatidylinositol (PtdIns) (3,4,5) P3 and PtdIns(4,5) P2, was found to be localized to the primary cilium in cells of the midbrain that are affected in patients with Joubert syndrome. The mutations severely decreased the phosphatase activity of the enzyme, resulting in altered homeostatic ratios of PtdIns in cells. The mutations also resulted in impaired ciliary stability and abnormal cell cycle dynamics. Complementing the studies of Bielas et al. (2009), Jacoby et al. (2009) discovered a single nucleotide change in the terminal exon of the INPP5E gene, resulting in a premature stop and loss of the last 18 amino acid residues of the enzyme protein, in affected members of a family with Morquio syndrome. The loss of the terminal residues did not affect the phosphatase activity of the enzyme. However, when tagged wild-type and mutant proteins were expressed in cells, the wild-type protein was found distributed along the ciliary axoneme. In contrast, mutant protein was largely localized in the extremity of the
cilia. Interestingly, the mutation also affected the ability of INPP5E to interact with 14-3-3 proteins when overexpressed in cells. In strong support of the conclusion that INPP5E plays an important role in primary ciliary function, Jacoby et al. (2009) further reported that mice deficient for Inpp5e develop defects in several organs (eyes, kidneys, brain, skeleton, palate) and die soon after birth. Primary cilia of cells in the affected organs were sparse and appeared dilated. Comparison of embryonic fibroblasts from wild-type and mutant mice showed that Inpp5e is not required for cilia formation in serum-starved cells, but is essential for maintaining cilia when cells are stimulated with serum. Finally, using a tamoxifen-inducible Cre strategy to inactivate Inpp5e in adult mice Jacoby et al. (2009) found that loss of the phosphatase at that stage had no effect on survival, but resulted in obesity, severe retinal dystrophy and cystic renal abnormalities. These are among the features that are characteristic of patients with Joubert/MORM syndromes.

Further work is needed to fully characterize the role(s) of Ptlin5 signaling in primary cilia, but the studies of Bielas et al. (2009) and Jacoby et al. (2009) have opened the door wide open to future important discoveries. Stay tuned.

References


Olen, B.R. 2007. From the Editor's Desk "And the winner is...". Matrix Biol 26, 583-586.


