American Society for Matrix Biology

President's Letter

Bill Parks

Dear Fellow Matrix Biologists,

It is mid-summer of an odd-numbered year, a time when ASMB activities tend to dip. But not this year. We have been busily putting together a new, interactive web site, including a link to Scientist Solutions, an online portal to allow a variety of interactions. Also, we have begun planning the 2010 ASMB meeting, which will be an expanded program enhanced by our growing relationship with related societies.

Our new site (which is at the same address, http://www.asmb.net) is much improved, with a variety of features designed to add value to your membership. We have increased the user friendly nature, visibility and accessibility of the site and maintained useful content such as posting for positions, meetings, and the membership directory. An interactive calendar is now highlighted and we have increased the available information of the society, such as a brief narrative of our foundation and listings of the awardees from previous meetings. In addition, we will be building databases of protocols and images – so any stunning pictures you have generated can be uploaded for all to enjoy (please, limit these to ECM-related things). Please contact Jen Holland (jholland@faseb.org) to add these files to our catalog.

Our new partnership with Scientist Solutions will offer several new opportunities to greatly improve membership interactions. This web resource provides features to allow you to seek help with protocols, find and upload protocols, chat with members, look for jobs, and much more. Please see the accompanying article in this newsletter for details, and I invite you to check out their site through our link to them from the new ASMB website.

Of course, our society's BIG event is always the biennial meeting, which will be held October 24-27, 2010, in Charleston, SC (which, in case you did not know, lies fairly north and east of Argentina). The Program Committee will be chaired by Jean Schwarzbauer, ASMB Vice President, and includes the well rounded topical program committee of Suneel Apte, David Birk, Adam Engler, Jeff Miner, Pyong Park, Amy Bradshaw and Lynn Sakai – a capable team indeed. If you have ideas on content and speakers, please send your suggestions to Jean (jschwarz@princeton.edu).

An exciting development with the 2010 meeting are new affiliate relationships we have built with the Tissue Engineering & Regenerative Medicine International Society (TERMIS: www.termis.org) and the Society of Glycobiology (SFG: www.glycobiology.org), brokered on our side by Joanne Murphy-Ullrich and Jeff Esko, respectively. The missions of both TERMIS and SFG complement well that of ASMB, and I am quite pleased that these societies have decided to join us in Charleston. We will be organizing Guest Symposia with these societies, which will be programmed the afternoon of Sunday, October 24th, 2010 just before the official start of the ASMB meeting. In addition, we will continue our close relationship with the International Society for Matrix Biology (ISMB: www.ismb.org), who will sponsor and program a plenary session at the ASMB meeting. I feel that building and fostering relationships with other research-oriented societies with overlapping and similar interests is crucial to the healthy growth of ASMB.

Finally, an important element of the biennial meeting is the recognition granted to our outstanding contributors. Our main two awards are the Senior and Junior Investigator Awards. These are prestigious awards and, as a society, we need to ensure that this biennial recognition is given to worthy members – fortunately, we have many individuals in this category. The senior awardee should be an estab-

lished, active scientist who has made seminal contributions to ECM Biology. The junior awardee should be an assistant professor-level investigator who is on an upward trajectory. You can have say in who will be considered for these awards, and an official call for nominations will be forthcoming - but in the meantime, please be thinking of names. We are also pleased to announce a re-structuring of our Student Travel award program. In the past, only onsite awards were offered to poster presenters. For 2010, we will begin a program that recognizes both outstanding abstracts selected for oral presentation at the conference (pre-selected Travel Awards) as well as the onsite selection of outstanding poster presentations. Please see the new website's section on Awards for further details and submission information.

We look forward to your feedback on the new website! Enjoy the balance of your summer and Thank You for your continued membership.

Best,

Bill Parks
ASMB President

A Message from your Executive Director

Jen Holland

I hope everyone is enjoying the summer! With 2009 being a non-meeting year, we have been working on the 2010 program but also focusing our attention on launching the new ASMB website. I hope you will visit the new site soon and take a tour of all the new features. The site has been updated on the front end both visually and functionally while the back end offers an immense change in flexibility and control.

One incredible addition is the Scientist Solutions forum link which is better described in this newsletter by Rusty Bishop's article. Rusty will be attending our meeting in 2010 and offer a special session on the extensive uses of the forum page and how it can help in your research.

Other new and improved features include:

- An improved online historical record of ASMB's origins, meetings, awards etc.
- Easy access to connect with ASMB Council Members
- Improved online membership processing with welcome letters to new members, subscription only options for members and better membership record tracking
- Increased award information and online applications
- Improved member searches including interest area focus
- Expanded career opportunities and other meeting listings with links and online submissions
- Online newsletter archive and online article submission
- Improved Matrix Biology linkage and online subscription instructions
- Expanded resource links for partnering societies and organizations
- Member Photo Gallery with scientific image archives
- Event calendar with links

Please take a moment and see how ASMB is working to improve your membership benefits with the new website! I look forward to hearing your feedback and am open to your ideas for other features to include. We especially want our members to start taking advantage of the photo gallery and welcome all photo submissions. What better way to reach out and collaborate with your fellow Matrix Biologists! Just email your attachments to jholland@faseb.org.

As the fall of 2009 quickly approaches, so does our gearing up for the 2010 Meeting in Charleston, SC (October 24-27, 2010). Check the new website regularly for updated information on the program, abstract submission and ASMB's new award structure which further helps our junior scientists on their research path.

As always, I value your membership with ASMB and welcome your input anytime!

Best regards,

Jen Holland
jholland@faseb.org

ASMB Image Gallery

Have images to contribute to our new image gallery? Send them to asmb@asmb.net! We welcome your submission of scientific images to include in our new image gallery. Help us build our home page slideshow and take a front seat on the new website!

Join us for ASMB's 10 Year Anniversary at the 2010 Biennial Meeting. October, 2010 Charleston, South Carolina

Mark your calendars and save the date. The ASMB national meeting will be held October 24-27, 2010 at the Francis Marion in Charleston, SC, USA. The keynote speaker will be Dr. Elaine Fuchs from the Laboratory of Mammalian Cell Biology and Development, Rockefeller University. The title of her presentation is: "Stem Cells, Extracellular Matrix, TIssue Morphogenesis, and Cancer in Skin".

We are pleased to announce a partnership with TERMIS and The Society for Glycobiology as well as our continuing relationship with ISMB who will be presenting special symposia at the meeting.

ASMB Partners with Scientist Solutions online

Professional societies, like the ASMB, exist to help a specific group of individuals improve themselves. The goal of any society is to provide a venue for its members to share ideas, improve one another's science, provide a forum for publication of these ideas, and to form professional connections. Traditionally this type of communication occurs at national meetings, which never fail to send everyone home more excited about their science and with a notebook full of ideas. The question has become; how as a society can you continue this conversation throughout the rest of the year and the in between year?

Enter Scientist Solutions.com.

ScientistSolutions.com is an open access internet site developed for scientists by scientists. The website was established in 2004, and the company is comprised over 75 scientist volunteers. The main focus of ScientistSolutions.com is the discussion boards, which feature user generated discussions in major categories spanning the life sciences. The site has 15,000 registered scientists and services 150,000 scientist visits per month.

ScientistSolutions.com aims to provide solutions to common laboratory problems (troubleshooting experiments), disseminate high quality information (meetings, jobs, protocols, publications, funding opportunities, etc.), and promote discussion amongst scientists throughout the world. In a nut shell, we help each other get passed the little things that take scientists months to figure out through shared knowledge.

Scientist Solutions has worked with the ASMB to create specialized discussion board for your society members to be jointly hosted on the Society's new website and ScientistSolutions.com. The ASMB section will provide Society members with areas to discuss upcoming society events, post announcements, share information regarding local Matrix Biology events, forums to give and receive advice to other scientists, and much more. By interacting as a society within Scientist Solutions you will be joining a larger community of scientists online. We feel this will provide an excellent venue for you to continue your conversations during the roughly 103 weeks between annual meetings. Furthermore, it will place the ASMB within an existing community of scientists that allows you to share your enthusiasm and expertise more broadly and to receive advice from new and diverse perspectives.

You can visit the main site of Scientist Solutions at www.scientistsolutions.com or directly access your ASMB forums from the new ASMB website upon launch. I encourage you to post your questions, ideas, and to take a minute to suggest an answer to some of the 1000s of questions posted to the site.

If you have any questions about how the site works or would be interested in lending your expertise to help other scientists as a moderator, you can contact Rusty Bishop (former post-doc in Jeff Esko's lab) at rusty@scientistsolutions.com.

Related Meetings Announcements

6th International Conference on Proteoglycans

September 13-17, 2009 Aix-les-Bains, France

Conference co-organizers:
H. Lortat-Jacob (Grenoble, France)
J. Van den Born (Gronigen, The Netherlands)
Contact: contact.pg2009@ibs.fr

For details please visit: http://pg2009-france.ibs.fr/

Annual Meeting of the Society for Glycobiology

November 12-15, 2009, San Diego, CA

Contacts: Dr. Tom Oeltmann, President;
president@glycobiology.org AND
Dr. Kelley Moremen, Secretary; moremen@uga.edu
For details, please visit::http://www.glycobiology.org

2009 Matrix Metalloproteinases Gordon Research Conference

The 2009 MMP Gordon Research Conference will be held Aug 30-Sept 4, 2009 at Les Diablerets Conference Center in Les Diablerets, Switzerland. Conference Chair: Carl Blobel, Co-Chair Rafael Fridman. The Program and online application can be found on the Gordon Conference website using the following link: http://www.grc.org

Thrombospondins and other Matricellular Proteins in Tissue Organization and Homeostasis

July 18-23, 2010 Snowmass, Colorado

2010 FASEB Summer Research Conference. Organizers: David D. Roberts, Chair; Joanne Murphy-Ullrich, Co-Chair

Hyaluronan 2010

June 6-11, 2010 Kyoto, Japan

International Society for Hyaluronan Sciences
8th International Conference, Kyoto, Japan
Conference organizers:
Koji Kimata (Aichi Medical University)
Masaki Yanagishita (Tokyo Medical & Dental University)
Bryan Toole (Medical University of South Carolina)
For details, please visit: http://www.ishas.org

2010 Proteoglycan Gordon Research Conference

The 2010 Proteoglycan Gordon Research Conference will be held July 16-17, 2010 at Proctor Academy in Andover, NH. Conference Chair: Marian Young, Co-Chair Robert Lindhardt. http://www.grc.org

Aortic Disease Summit

Sept 22-23, 2009 Hyatt Regency Baltimore on the Inner Harbor

The Aortic Disease Summit is being held to consolidate and disseminate current information regarding disease pathogenesis, progression, and treatment of aortic disease and to identify future directions. The meeting is being sponsored by the NHLBI's GenTAC Registry, the Office of Rare Diseases and the National Marfan Foundation. The National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) was initiated in 2006 by NHLBI and NIAMS with the goal of collecting clinical data and biologic samples from 3000 patients with diverse conditions that predispose to thoracic aortic aneurysm.

Meeting Sessions to Include
- New insights into the pathogenesis of aortic aneurysm from disease genes and animal models
- Advances in the imaging and biomarkers of aortic disease
- Gaps in the natural history of aortic disease
- Controversies and opportunities in the surgical management of aortic disease
- Novel medical therapeutic strategies in the treatment of aortic disease

To register or to see the full meeting agenda, go to: http://www.regonline.com/aortic.

25th Ernst Klenk Symposium in Molecular Medicine

4-6 October 2009 Cologne, Germany

The 25th Ernst Klenk Symposium in Molecular Medicine on **Extracellular Matrix in Health and Disease** will be held from 04 - 06 October, 2009, in the Main Lecture Hall of the Medical Faculty of the University of Cologne, Germany.

The program can be found on the following webpage:
http://www.zmmk.uni-koeln.de/klenk-symposium-2009/program
Please note that the participation is free of charge. For free registration please visit:
http://www.zmmk.uni-koeln.de/klenk-symposium-2009/registration

Prof. Bjorn R. Olsen (Department of Developmental Biology, Harvard School of Dental Medicine, Boston, USA) has been substantially involved in the scientific coordination. Prof. Olsen will also present the Ernst Klenk Lecture on "Translational Cell and Matrix Biology of Vascular Disease" on Monday, 05 Oct. The list of speakers includes internationally leading researchers who will speak on a variety of pertinent subjects including extracellular matrix proteins, their processing, their cellular receptors and their role in development and in disease.

The Klenk Symposium - organized by the "Zentrum für Molekulare Medizin der Universität zu Köln (ZMMK)" - intends to provide a forum for discussion of state-of-the-art research in these fields for interested scientists and students from academia and industry. The symposium starts on Sunday, 04. Oct. 2009, at 1.00 p.m. and ends on Tuesday, 06. Oct. 2009, at around 12.30 p.m.

Due to the Cologne Marathon on 04 October, overnight accommodation will be extremely limited. We pre-reserved several hotels that are only available for the participants of the Symposium. Please visit the following link for further information:
http://www.zmmk.uni-koeln.de/content/common/klenk_hotelliste_2009.pdf

We expect lively and fruitful discussions and look forward to welcoming you to the 25th Ernst Klenk Symposium in Cologne.

Thomas Krieg
Vice Chairmann - CMMC & Department of Dermatology

Mats Paulsson
Executive Bord Member - CMMC & Institute for Biochemistry

Check out the New and Improved ASMB Website

www.asmb.net

Website Features

- Society information, including bylaws, history, Council members, etc.
- Complete ASMB awards information including criteria, applications and history
- Historical information about past ASMB meetings
- Career opportunities as posted on our new forum site with Scientist Solutions
- Other meetings listings
- Links to other resources such as partnering societies
- Newsletter archive
- Image Gallery

ASMB business

- Join/Renew your membership
- Manage and update your ASMB record
- Search our member database
- Link to Scientist Solutions forums
- Post related meetings
- Post job opportunities (under forums)
- Manage your *Matrix Biology* journal subscription

Need help navigating the new website?
Email asmb@asmb.net and we'll be happy to assist!

Don't Forget to Renew!

Your participation in our Society is the most important contribution you can make to helping increase awareness of research and opportunities in extracellular matrix biology.

With the help of your membership dues, we have added professional management of the society and provided students and postdoctoral fellows with travel awards to our national meeting. In the coming year, your dues will be at work to improve our website. We urge you to pay your dues so we can continue to add programs that benefit matrix biology.

The 2009 Annual Dues are $90 for regular membership and $50 for students/postdoctoral fellows. Dues can be paid any time via the ASMB website: http://www.asmb.net/

Alternatively, checks can be sent to the administrative office: ASMB, 9650 Rockville Pike, Bethesda, MD 20814.

Advantages of Membership:

- Discounts on *Matrix Biology* subscriptions (print and online)
- Discounts on Biennial Meeting registration
- Access to online forums and image galleries
- Receive society newsletters with article reviews and summaries
- Partner links to numerous other societies and valuable scientific resources
- Opportunities to submit abstracts for biennial meeting presentations
- Biennial meeting award eligibility
- Eligibility to run for Council positions and help direct the Society
- Access to list and view career opportunities within the community
- Make valuable professional connections with junior and senior researchers

JOB OPENINGS

Thomas Jefferson University, Philadelphia, PA

POSTDOCTORAL POSITIONS IN PROTEOGLYCAN RESEARCH, CANCER AND ANGIOGENESIS

Two postdoctoral positions are available to investigate the biology of perlecan and decorin in cancer and angiogenesis. The candidates will join a multi-disciplinary team of researchers involved in investigating the molecular mechanisms through which these two proteoglycans affect tumor biology, EGFR and Met receptor signaling, growth and angiogenesis, both in vitro and in vivo (J. Cell Biol. **166**:97-109, 2004; J. Biol. Chem. **280**:32468-32479, 2005; Nature Rev. Mol. Cell. Biol. **6**:646-656, 2005; J. Natl. Cancer Inst. **15**: 1634-1646, 2006; Blood **109**: 3745-3749, 2007; J. Biol.Chem. **283**:2335-2344, 2008; J. Cell Biol. **181**:381-394, 2008.; Biochemistry **47**:11174-11183, 2008; Am. J. Pathol. **173**:844-855. 2008; J. Cell Biol. **185**:743-754, 2009).

Requirements include a Ph.D. or an M.D./Ph.D. in biochemistry or cell biology. A molecular biology background is highly desirable. Send resume and three letters of reference to:

Renato V. Iozzo, M.D.
Department of Pathology, Anatomy & Cell Biology
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Philadelphia, PA 19107-6799, U.S.A.
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Email: Iozzo@mail.jci.tju.edu

IECB

UNIVERSITÉ DE BORDEAUX

Instituts thématiques Inserm

Institut national de la santé et de la recherche médicale

Pre-Doctoral Fellowship in Molecular and Cellular Biology (Bordeaux, France)

Job Description:

An EU-FP7 Marie-Curie-supported **pre-doctoral training fellowship** is available for three years at an INSERM (Institut National de la Santé et de la recherche Médicale) laboratory. This project is a component of the Tissue Transmigration Training Network, **T3Net**. This Network aims to promote excellence in training in the fields of cell adhesion and cell migration, concentrating on the cellular structures mediating tissue invasion, known as podosomes and invadopodia.

Signaling and cellular features
regulated by TGFbeta in arterial endothelial cells

Backgroud : TGFbeta plays an essential role in vascular homeostasis and alterations in TGFbeta biodisponibility is likely contribute to common (atherosclerosis) and rare (HHT, MFS, LDS) vascular diseases. We have discovered that TGFbeta causes formation of podosomes in endothelial cells. These are actin-based and integrin-enriched punctate adhesion microdomains localized at the plasma membrane. These structures recruit metalloproteases that are instrumental in the degradation of extracellular matrix. Our working hypothesis is that podosomes contribute to vessel repair.

Objectives: To find out under what conditions podosomes are formed in vitro, in vascular segments (ex-vivo) and in genetically engineered animals models (in vivo) and to study their role in vascular remodeling. These studies should provide important information about the role of TGFbeta in vascular physiology and pathology.

Profile : French scientist are not eligible for this fellowship unless they have been working in France for less than a year. Applicants should have an M.Sc. degree in molecular and cellular biology, biochemistry or related sciences. We seek an individual with a strong interest in advanced microscopic techniques as applied to biomedical research, and the ability to work in a research team and willing to move for extended intervals to our T3Net partner laboratories within Europe and possibly Canada (Toronto). A good command of the English language is mandatory.

Location : The laboratory is located at the European Institute of Chemistry and Biology near Bordeaux. This new institution provides an exceptional scientific environment, at the interface of different disciplines with first class scientific programs in physical-chemistry, chemistry and biology (http://www.iecb.u-bordeaux.fr/,

Monthly salary 2100 € net + travel allowance

Deadline for application: September 30 th 2009, Starting date autumn 2009

Further enquiries and application

Contact Dr Elisabeth GENOT
Please send : (1) a curriculum vitae; (2) name and contact details of two potential referees (3) a cover letter outlining your background experience and why you are interested in this position: e.genot@iecb.u-bordeaux.fr
our website http://www.iecb.u-bordeaux.fr/fileadmin/IECB/HTML/POLE4/GENOT/index.htm

THE INVADOSOME CONSORTIUM

MARIE CURIE ACTIONS

Interesting Science

Decorin is a Novel Antagonistic Ligand of the Met Receptor

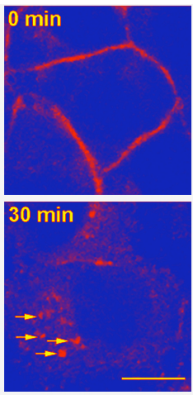
Silvia Goldoni, Ashley Humphries, Alexander Myström, Sampurna Sattar, Rick. T. Owens, David J. McQuillan, Keith Ireton, and Renato V. Iozzo

J. Cell Biol. 185:743-754, 2009

http://www.f1000biology.com/article/id/1159659/evaluation

Decorin, a member of the small leucine-rich proteoglycan gene family, regulates tumor cell growth by downregulating the epidermal growth factor receptor. Due to the complex binding repertoire of decorin, we predicted that decorin would modulate the bioactivity of other tyrosine kinase receptors. We discovered that decorin binds directly and with high affinity (K_d~2 nM) to Met, the receptor for hepatocyte growth factor (HGF). Binding of decorin to Met was efficiently displaced by HGF, and less efficiently by internalin B, a bacterial leucine-rich protein that binds to Met with similar affinities. Interaction of decorin with Met induced transient activation of the receptor, recruitment of the E3 ubiquitin ligase c-Cbl, followed by rapid intracellular degradation of Met ($T_{1/2}$~6 min). Decorin suppressed intracellular levels of b-catenin, a known downstream Met effector, and inhibited cell migration and growth via Met receptor-mediated events. These findings indicate that decorin exerts its cytostatic activity by antagonistically targeting multiple tyrosine kinase receptors, thereby contributing to reduction in primary tumor growth and metastastic spreading.

Contributed by Renato Iozzo



Confocal fluorescence images of HeLa cells (blue pseudocolor) immunostained for Met receptor (red) before or after a 30-min incubation with decorin core. Notice the rapid loss of cell surface Met and its translocation into endosomal degradative vesicles (arrows). Bar = 10 μm.

Cadherin adhesion, tissue tension, and noncanonical Wnt signaling regulate fibronectin matrix organization.

Dzamba, B.J., Jakab, K. R., Marsden, M., Schwartz, M. A., and DeSimone, D. W.

Dev. Cell 16:421-431 (2009)

2-D cell culture experiments have previously shown fibronectin (FN) fibrillogenesis to be dependent upon tension, generated via cytoskeletal anchoring at focal adhesions and transmitted to FN dimers by integrin receptors. Dzamba et al. have now examined this paradigm in an organismal context, the Xenopus embryo, focusing on cells of the blastocoel roof (BCR), which assemble FN fibrillar matrix at the onset of gastrulation. As both FN matrix and Wnt signaling are known regulators of convergence and extension movement of cells, such as those that occur in gastrulation, the authors examined whether Wnt signaling might affect FN fibrillogenesis in vivo. They, in fact show FN fibrillogenesis to depend upon the noncanonical Wnt planar cell polarity (PCP) pathway, but not canonical Wnt signaling, also showing the small GTPase Rac, downstream of Disheveled in the PCP pathway, to be critical to FN assembly. Traction force microscopy suggests that cell-cell adhesion via cadherins, rather than cell adhesion to FN, is altered in cells in which Wnt signaling is inhibited, while imaging showed FN fibrillogenesis to coincide with maturation of cadherin-containing adherens junctions, at gastrulation onset. Moreover, cadherin overexpression led to precocious FN fibril assembly, while expression of a dominant-negative cadherin inhibited FN fibril formation, consistent with the conclusion that cadherin adhesion is required for FN assembly. Inhibition of Rac inhibited both FN fibrillogenesis and formation of the actin-containing cytoskeleton, while the authors showed Pak, a downstream effecter of Rac, to be important in cytoskeleton formation, FN fibrillogenesis and convergent extension. Direct mechanical application of tension to the BCR led to precocious FN fibril formation, whereas mechanical decrease in tension inhibited FN fibrillogenesis. These studies have thus refined the model of FN fibrillogenesis, gleaned from many 2-D culture experiments, in the context of a specific in vivo system. In this new system, it is Wnt/PCP signaling-induced cadherin-mediated cell-cell adhesion, rather than the focal adhesions of culture dishes, that, together with cytoskeleton formation, leads to increased cell tension, changes in integrin-FN traction, FN conformational changes, and fibril assembly. These occurrences are also shown to be co-stimuli in driving cell movements at gastrulation.

Contributed by Dan Greenspan

Thrombospondin-1 and CD47 Regulate Blood Pressure and Cardiovascular Responses to Vasoactive Stress

Isenberg, J.S., Qin, Y., Despres, D., Bandle, R.W., Schnermann, J., Frazier, W.A., and Roberts, D.D.

Matrix Biol. 28:110-119, 2009

Extracellular matrix components play important structural roles in blood vessels to maintain their integrity and enable elastic responses to pulsatile changes in blood flow. Consequently, mutations in several vascular matrix genes have been linked to cardiovascular disease. In addition to these major structural components of vascular matrix, a polymorphism in the secreted protein thrombospondin-1 was previously linked to increased risk of early cardiovascular disease. Thrombospondin-1 is not a structural component of extracellular matrix, but its presence at low levels in matrix can modulate cell behavior by engaging specific cell surface receptors. The major previously known function of thrombospondin-1 in the cardiovascular system was to

inhibit angiogenesis, so its effects on cardiovascular health were thought to involve long term effects on vascular remodeling. However, a new study reveals that thrombospondin-1 also has acute systemic effects on regulation of blood pressure and cardiac function (Isenberg et al, 2009). This study revealed that the low levels of endogenous thrombospondin-1 in the vessel wall exert a hypertensive activity by engaging its receptor CD47. This results in inhibition of the nitric oxide-activated enzyme soluble guanylate cyclase and decreases levels of the second messenger cGMP in vascular smooth muscle. Consequently, thrombospondin-1 null mice have a decreased pulse pressure and exaggerated hypotensive responses to vasodilators. These studies reveal an important physiological function of thrombospondin-1 in maintaining normal blood pressure by opposing the hypotensive activity of nitric oxide. However, previous reports of elevated thrombospondin-1 in atherosclerotic blood vessels, in diabetics, and with aging suggest that thrombospondin-1 may also contribute to the pathogenesis of these diseases by acutely limiting the beneficial effects of nitric oxide to limit blood pressure and improve flow. Thus, drugs that inhibit the interaction of thrombospondin-1 with its receptor CD47 could be beneficial in these diseases.

Contributed by David Roberts

Fibrillin assembly requires fibronectin

Sabatier, L., Chen, D., Fagotto-Kaufmann, C., Hubmacher, D., McKee, M.D., Annis, D.S., Mosher, D.F., and Reinhardt, D.P.

Mol. Biol. Cell 20:846-858 (2009)

Microfibrils play essential roles in diverse tissues from blood vessels to bone and are associated with a family of diseases termed fibrillinopathies. They act as structural scaffolds for deposition of elastic fibers, and they regulate TGF-β/BMP signaling through interactions with latent TGF-β binding proteins (LTBP). Electron microscopic analyses show a characteristic bead-on-a-string organization of microfibrils but how individual fibrillin subunits are put together to form multimeric assemblies is not well understood. Reinhardt and his colleagues now provide new insights into the assembly of microfibrils. Using siRNA knockdown experiments, they show that fibrillin assembly by human dermal fibroblasts is dependent on the presence of a fibronectin matrix. Inhibition of fibronectin fibril assembly ablates fibrillin deposition into the matrix. Fibrillin and fibronectin co-localize by immunofluorescence staining but, importantly, also by immunogold transmission electron microscopic analyses. While some evidence was available prior to this study to suggest co-localization of fibrillin and fibronectin, Sabatier et al. have gone further in identifying a potential mechanism for this assembly process. Using recombinant fragments of these proteins, they map the binding sites to the C-terminal half of fibrillin and the gelatin-binding domain of fibronectin. Notably, the C-terminal fibrillin fragments form multimers, and gel filtration followed by solid phase binding assays showed that these multimers are the functional form for fibronectin binding. This group has previously shown dependence on C-terminal multimerization for high affinity interactions between N- and C-terminal fibrillin fragments. Evidence that the multimerization occurs early in the fibrillin assembly pathway suggests that these multimers act as intermediates that ultimately depend on fibronectin matrix for organization into microfibrils.

Contributed by Jean Schwarzbauer

One-dimensional topography underlies three-dimensional fibrillar cell migration

Andrew D. Doyle, Francis, W. Wang, Kazue Matsumoto, and Kenneth M. Yamada

J. Cell Biol. 184:481-490 (2009)

Much of what we know about cell migration comes from studies of cells moving on planar surfaces, such as a glass slide or culture dish. However, with exception of epithelial (and endothelial) cells migrating across a denuded matrix during wound closure, essentially all other cells move through 3-dimensional spaces, such as EMT at gastrulation, vasculogenesis, trafficking of leukocytes, the spread of metastatic cells, axon guidance, and much more. Does surface dimension matter in how a cell migrates? The compelling data in this February 2009 JCB paper by Ken Yamada and coworkers demonstrates it clearly does. They found that cells migrating on 1D matrices (basically, 1-2 μm wide lines of fibronectin, vitronectin, or type IV collagen) migrated significantly faster, had much tighter coordinated forward protrusion:rear retraction cycles, and altered polarity compared to cells on 2D matrices. Importantly, with about everything they measured, cells on 1D matrices looked and behaved just like cells in 3D matrices. In contrast, cells on 2D matrices were a different bird altogether. I really liked this paper, and I think it provides a rare example of a publication suggesting rather strongly that a way of studying something (in this case, cell migration on 2D surfaces) needs to be reconsidered. I am not suggesting that all the knowledge gleaned from cells moving on 2D substratum be tossed out, but I do think that with the publication of this paper, future studies on cell migration will need to what the cells are moving on or in.

Contributed by Bill Parks

Canonical Wnts function as potent regulators of osteogenesis by human mesenchymal stem cells

Guizhong Liu, Sapna Vijayakumar, Luca Grumolato, Randy Arroyave, HuiFang Qiao, Gal Akiri and Stuart Aaronson

J. Cell Biol. 185:67-75 (2009)

This paper has provided both in vitro and in vivo data toward further elucidating the roles of canonical Wnts as regulators of osteogenesis by adult human mesenchymal stem cells (hMSCs). The major findings in this study have led to a working hypothesis in which a gradient of Wnt activity levels plays an important role in stimulating self-renewal and expansion of hMSCs / progenitors (high Wnt Activity) as well as induction of osteoblast differentiation (low Wnt activity). With respect to tissue engineering research, these studies have significance toward determining appropriate strategies to enhance the therapeutic value of hMSCs for the restoration of bone defects.

In the canonical pathway, Wnt ligands signal through frizzled and LRP5/6 co-receptors, leading to the inactivation of the axin-GSK-3β complex. As a result, stabilized β-catenin translocates to the nucleus and forms a complex with T cell factor (TCF)/ lymphoid enhancer-binding factor transcription factors to activate Wnt target genes. Adult human mesenchymal stem cells (hMSCs) are multipotent and are an attractive source of cells for tissue engineering with respect to bone, cartilage and muscle. The in vitro effects of Wnt signaling on osteogenic differentiation of hMSCs are controversial whereby both inhibitory and stimulatory effects have been reported. Therefore, the present study was undertaken in an effort to better define how Wnts influence hMSC commitment along the osteoblast lineage, as well as the adipogenic lineage, and the mechanisms involved.

A commercial source of bone marrow-derived hMSCs (from three donors) as well as standard adipogenic and osteogenic differentiation medium (from Lonza) was used in this study. Under binary differentiation conditions, they found differential sensitivities of hMSCs to Wnt inhibition of osteogenesis versus adipogenesis. These results suggest that sensitivity to Wnt inhibition may alter the equilibrium and shift the commitment from adipocytes toward osteoblasts. Clearly there is a fine balance between osteogenesis and adipogenesis given the well-described observations of a decrease in bone-forming ostoblasts and an increase in marrow adipocytes that occurs with ageing, for example.

The mechanism of action of Wnt-induced inhibition of osteogenesis by hMSCs was then investigated. It was found that expression of osteoblast transcription factors (Runx2, Osx andDlx5) was down-regulated and activation of c-Jun terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) was inhibited.

Since canonical Wnt signaling has been implicated in stem/progenitor cell maintenance in several adult tissues (*Reya & Clevers, 2005), Liu et al investigated the endogenous Wnt signaling activity in hMSCs. They confirmed endogenous activity using a TCF luciferase reporter system and also noted that activity was hetereogenous where only ~5% of hMSCs were shown to exhibit high activity. Further experiments led to the proposal that endogenous Wnt signaling plays an important role in maintaining hMSCs in a relatively undifferentiated state. In one such experiment, they showed that endogenous Wnt activity decreased during osteogenic differentiation as was expression of Axin2, a known β-catenin target gene. In the same system, the expression of the Wnt antagonist Dkk1 was markedly increased during osteogenesis suggesting a role of Wnt inhibitors in controlling differentiation too. In another experiment, dnTCF4 was over-expressed in order to inhibit complex formation with β-catenin. In other words, this approach inhibited the downstream effects of endogenous Wnt activity. As a result, osteogenesis (and adipogenesis) was increased. Together, these in vitro results suggest that lower Wnt activity favors osteoblast differentiation of hMSCs while higher levels may act to inhibit osteogenesis or at least maintain the hMSCs in a less differentiated state.

To translate their in vitro findings to bone formation in vivo, an established ectopic bone formation model in immunodeficient mice was used. Consistent with the in vitro studies, they found that Wnt1-expressing hMSCs exhibited little to no ectopic bone formation compared to controls. They then carried out a series of clever experiments using a mixture Wnt1-expressing hMSCs and empty vector-expressing hMSCs. This was done in order to recapitulate the heterogenous endogenous Wnt activity that was found in vitro. This resulted in a significant increase in ectopic bone formation. They labeled the non-Wnt1-expressing hMSCs with LacZ and found that more efficient bone formation was induced when predominantly LacZ staining cells were present. Also, Wnt1 immunostaining was observed in dense cell clusters surrounding bone structures, strongly suggesting that Wnt-1 expressing hMSCs act primarily to stimulate osteogenesis by acting on Wnt1-negative hMSCs. They then localized cytoplasmic β-catenin in the mixed cell implants of both LacZ-positive as well as hMSC-Wnt1 cells, but not in the osteocytes within the bone. These results suggest that cells with low Wnt signaling activity are capable of differentiating to osteocytes. An increase in cell proliferation was also found in the mixed cell implants suggesting that Wnt1 can stimulate proliferation of hMSCs in vivo in both autocrine and paracrine manner, thereby increasing the population of naïve hMSCs capable of undergoing osteogenesis under low or undetectable Wnt signaling. Finally, Liu et al determined if the effects on bone formation and proliferation in the mixed cell implants was due specifically to Wnt1 and not other factors induced by β-catenin signaling. Here they expressed a stabilized mutant form of β-catenin in hMSCs and created mixed cell implants with LacZ-expressing hMSCs. Although cell proliferation was induced, there was no indication of bone formation in vivo. It would have been interesting if the group had carried out Oil Red O staining in these in vivo ectopic bone formation assays to determine if adipocyte differentiation was induced in these experimental conditions. In any case, these results established that canonical Wnt ligands act in a cell nonautonomous manner and, under the appropriate conditions, are required for enhanced bone formation.

This group has made a bold and thorough attempt at deciphering the mode of action of canonical Wnts in hMSC osteogenic differentiation in vitro and in vivo. It is clearly a complex area and it is apparent that we now need to think about hMSC cell numbers and levels of Wnt activity that will maximize the generation of new bone tissue in vivo. In this case it would seem that "less is more" in terms of inducing osteoblast generation. In addition, these studies also provide a rationale to investigate the role of Wnt inhibitors as another mechanism of controlling bone formation using hMSCs.

Contributed by Audrey McAlinden

* Reya, T & Clevers, H. 2005. Wnt signaling in stem cells and cancer. Nature. 434:843-850