FROM THE PRESIDENT’S DESK

Dear ISMB members,

Welcome to the 2018 Spring/Summer issue of the ISMB Newsletter.

In the last issue, I was pleased to inform you that we had reached the highest number of the ISMB members on record. With this issue, I can share yet another milestone: the Society continues to grow and currently has more than 330 members. It is my pleasure to welcome all new ISMB members hailing from Belgium, Denmark, Finland, France, Germany, Greece, Spain, Switzerland, and UK, who are listed in this issue.

As the Society grows, so do the number of travel awards that we are able to offer to junior researchers, the up-and-comers in our field. These junior researches will be participating in various matrix biology related meetings, including Matrix Biology Europe 2018 and the Gordon Research Conferences. The ISMB Council is pleased to announce the winners of the April 2018 ISMB travel award competition: Jennifer Ashworth (UK), Elena Carava (Italy), Heather Davies (France), Laura Dupont (Belgium), Andras Kiss (Hungary), Chun-Yu Lin (Sweden), Marion Marchand (France), Madalina V. Nastase (Germany), and Jazmin Ozsvar (Australia). We wish each of you a successful presentation and look forward to networking with you at the upcoming matrix meetings. Please note that the next deadline to apply for ISMB travel fellowships for graduate students and postdocs, as well as for ECM-related international meetings, is July 1st, 2018.

With the 50th Anniversary of Matrix Biology Europe taking place in July, there were fewer annual meetings of national matrix societies this spring as compared with previous years. Nevertheless, in March 2018, we had the Annual Meeting of the German and Swiss Societies for Matrix Biology in Stuttgart. Fond memories from this meeting are included in this issue. Then, in May 2018, the Dutch Society for Matrix Biology met in Lunteren,
the 24th Canadian Connective Tissue Conference was held in Toronto, and the Nordic Proteoglycan Meeting took place in Oslo.

We have a very attractive program for matrix biologists this summer and autumn. First, we will be celebrating the 50th Anniversary of Matrix Biology Europe (formerly FECTS) in Manchester from July 21-24, 2018. The ISMB is contributing to this meeting by awarding international travel grants so that young scientists may attend the meeting. In addition, we are providing ISMB member registration discounts and general meeting support. The Society is also happy to cover the Rupert Timpl awardee's costs for attendance. The Rupert Timpl award 2018, generously sponsored by Matrix Biology journal and Elsevier, will be presented during the MBE meeting to Alexandra Naba. Congratulations, Alexandra, for your achievements! Of note, during the Rupert Timpl award session, the ISMB will honor David Hulmes, current Secretary and Treasurer of the ISMB, and past President, for his service to the Society over many years. David Hulmes’s term as ISMB secretary/treasurer expires at the end of 2018. In addition to the MBE meeting, we will participate in a number Gordon Research Seminars and Conferences (on Cartilage & Disc, Proteoglycans, Musculoskeletal Biology and Bioengineering), TERMIS world Congress, as well as a FEBS Advanced Lecture Course on Extracellular Matrix. We are also very much looking forward to the ASMB meeting in Las Vegas. We have an excellent agenda and I had the pleasure to visit the extremely inviting location this spring – I'm sure you all will enjoy this meeting immensely. It will be my particular honor and pleasure to present the ISMB Distinguished Investigator award 2018 at the ASMB meeting in Las Vegas to Billy Hudson. Congratulations, Billy, for your very impressive work and important contributions to matrix biology.

In this issue, we will continue to publish useful techniques in matrix biology. Many thanks to Suneel Apte and his group for their contribution to IN FOCUS: TECHNIQUES AND TECHNICAL TIPS. If you would like to contribute to the next newsletter, please email chloe.yeung@gmail.com.

Finally, I would like to wish successful grant applications, great matrix meetings, and wonderful summer vacation to all of our members and readers. Before you leave for your well-deserved vacation, please do not forget to submit your best research to the Matrix Biology journal!

Kind regards,

Liliana Schaefer
ISMB President
COMPOSITION OF ISMB COUNCIL SUBCOMMITTEES

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Danny Chan (Hong-Kong)
Julia Etich (Germany)
Wei Kong (China)
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Meetings and travel grants
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Swiss Society of Matrix Biology - Re-founded after some years of silence
In 1986 the Swiss Society of Matrix Biology (SSMB) was founded by a number of Swiss laboratories specialized to connective tissue research as it was called then. At this time matrix biology was really in fashion. The FECST-Meeting 1986 in Manchester saw more than 700 participants and the SSMB had nearly 80 members. In parallel to the retirement of the heads of Swiss matrix laboratories, matrix biology got somehow “out of fashion”. As a result, new chairs were posted for everything, but not for matrix biology. There were still quite a bit of activities but after the 2010 FECST-Meeting in Davos, which was hosted by the German and the Swiss Society of Matrix Biology, the activities of the SSMB decreased rapidly. At the society’s 30th anniversary the number of members just dropped to two. Nothing to celebrate!
Really nothing to be mentioned? No, at this point a new generation of matrix biologist had developed in Switzerland. Their focus was not anymore purely on matrix biology, but on a wide variety of different biological questions like
- aging, repair, and regeneration, as well as cell homeostasis
- embryonal, fetal and postnatal development
- mechanobiology, tissue mechanics and physical aspects of cancer progression
- wound healing, cell-matrix adhesion and remodeling
- stem cell biology, cellular microenvironment, and engineering of biomaterials
- inherited connective tissue disorders
The matrix is coming in play, because of its large influence on these processes. Now the biological activity of the matrix is “in fashion” after many years were the (structural) components and their assembly were “in fashion”.

In February 2017 the Swiss Society of Matrix Biology was officially re-founded and the first annual meeting after many years of silence was held in Bern. We are now about 40 members and the 2018 annual meeting took place as a very successful joint meeting with the German Society of Matrix Biology. We, as a society are looking forward to future activities like our annual meetings and, very important, to the ECMATRIX summer school “New Frontiers in Extracellular Matrix Research” which is organized jointly by labs of the ETH Zürich and the EPFL in Lausanne. The school will take place at Balgrist University Hospital in Zurich September 9-13, 2018 and will focus on four main areas which are believed to shape the future of ECM biology, namely mechano-, immuno-, regenerative, and responsive-matrix (https://ecmatrix.epfl.ch/about-the-school/, deadline, July 1st, 2018).

Johannes Schittny, Institute of Anatomy, University of Bern (Switzerland)
MEETING REPORT

The annual scientific meeting of the German and Swiss Societies for Matrix Biology was held between the 22nd and 24th March in Stuttgart, the centre of Germany’s thriving southwestern industrial area and was organized by Katja Schenke-Layland from the German Society for Matrix Biology.

A total of 114 researchers from 11 countries joined the conference to share and discuss the latest advances in the field of matrix biology. This enabled us to touch upon a broad range of subtopics in matrix biology, ranging from sessions devoted to ECM in development and ageing, all the way to ECM in tissue engineering and regenerative medicine. The conference organisation was most pleased to have Matthias Lutolf as speaker in the opening ceremony, and Michael Sherratt, Laurent Debelle, Antonella Viola, Ankur Singh, and Dimitrios Zeugolis as session keynote speakers.

For the second time, the meeting was preceded by a Young Investigators Session aimed at pre- and postdoctoral scientists on March 21st and 22nd, which created a unique forum for young scientists to present and exchange novel findings.

Thanks to our sponsors, Renishaw GmbH and Greiner Bio-One GmbH, the University Women’s Hospital Tuebingen, as well as the German and Swiss Societies for Matrix Biology, we were able to present 8 poster prizes as well as a Young Investigator Award. Among the young scientists, Björn Bluhm was awarded the Young Investigator Award for his exciting research of miRNAs and how they modulate cellular and extracellular cartilage compartments. Poster awards were awarded to Eva Brauchle, Melanie Föll, Stefanie Heumüller, Mugdha Sawant, Oliver Schneider, Herimela Solomon-Degefa, Kaori Sugiyama, and Louise Tzung-Harn Hsieh. A more detailed overview of the awarded posters can be found on the website of the German Society for Matrix Biology: www.matrixbiologie.de. Moreover, it is our great pleasure to introduce current members of the German Society for Matrix Biology Council (re- or newly elected at this conference): Julia Etich (president), Gerhard Sengle (treasurer), Rita Dreier (secretary), Susanne Grässel, Katja Schenke-Layland, Alexander Nyström, Dominique Muschter (representative of junior scientists). The new council thanked Liliana Schaefer for her remarkable term as president of the DGMB and her devoted commitment within the last eight years to successfully promote the DGMB at the national and international level and support young investigators.

In retrospect, the conference was very worthwhile, as many new impressions were gained, ideas generated and precious contacts made. We are already looking forward to the next conference 2019 in Regensburg, Germany.

1. EPFL, Switzerland
2. The University of Manchester, UK
3. University Reims Champagne-Ardenne, France
4. University of Padua, Italy
5. Cornell University, USA
6. NUI Galway, Ireland
7. University of Cologne, Germany
8. University of Tuebingen, Germany
9. University of Freiburg, Germany
10. University of Stuttgart, Germany
11. University of Tsukuba, Japan
12. Goethe University Frankfurt
13. University of Muenster, Germany
14. University of Regensburg, Germany
The annual scientific meeting of the German and Swiss Societies for Matrix Biology
March 22-24, 2008, Stuttgart (Germany)

POSITIONS AVAILABLE

on ISMB website (http://ismb.org/career/)
Gene expression analysis by RNA in situ hybridization in matrix biology

**Applications:** RNA in situ hybridization (ISH) has an important place in matrix biology, as the only method that allows in situ discrimination of the precise sites of gene expression in space and time. Whereas immunohistochemistry shows where a matrix protein localizes, ISH identifies the cell of origin; thus, these methods provide complementary information for insights on the life cycle of a matrix molecule. ISH has been widely used for analysis of embryonic development, both as a whole mount and section method, and for sections of normal and diseased adult tissue. For decades, one of two methods has prevailed, radioactive ISH with continuously labeled cRNA probes or oligonucleotides, and ISH with continuously labeled digoxigenin-labeled (DIG) probes. Both methods take at least a couple of days and have been regarded as somewhat specialized, requiring skill and “touch”. Use of radioisotopes presents a definite hazard as well.

**RNAscope- A new commercial method:** In this method, specific probes can be purchased from Advanced Cell Diagnostics that are synthesized with labeled oligonucleotides for either fluorescent or enzymatic detection. They are bought as user-ready probes and the ISH experiment can be completed in a single day. The method is highly sensitive, quantitative and permits multiplexing. It is quite easy for novices to become expert in this technique. We use it extensively and have mapped the expression of at least two dozen matrix-related genes using this method, mostly members of the ADAMTS protein family.

**Limitations:** RNAscope can be applied only to sections, so the DIG-method is still necessary for whole mount ISH. The probes and the necessary reagent kits are expensive, but the time saved and reproducibility may in the long run mitigate the material cost. It requires a specialized hybridization oven supplied by the manufacturer that is costly. However, the oven could be purchased by a core facility or as a shared instrument to reduce capital costs for an individual laboratory.

**Tips:** Like most ISH protocols, it is imperative to follow the protocol to the letter. The user should follow the timing of each step precisely. From start to finish, the experiment takes approximately eight hours. If the user wants to finish this experiment in one day, as we recommend (and how could you wait until tomorrow to see the result?), planning ahead and having all solutions ready is a must. It is crucial that paraffin-embedded tissues be sectioned and used within 24 hours, and preferably cut immediately prior to hybridization otherwise the target RNA is lost, and signal is reduced. Be certain to use the recommended hydrophobic barrier pen to ensure the section does not dry out during incubations. Be sure to use the probes when they are fresh as they do have a shelf life and use after expiration date results in reduced signal. We suggest to take pictures shortly after mounting, but certainly within a few days, before staining fades. Scanning the whole slide is recommended for long-term use.

Contributed by Tim Mead and Suneel Apte, Cleveland Clinic Lerner Research Institute (OH, USA). Neither author has any relationship with Advanced Cell Diagnostics or other relevant conflict.
NEWS FROM MATRIX BIOLOGY

Dear Fellow Matrix Biologists,

I would like to give you an update on our journal Matrix Biology.

Matrix Biology is now the number one journal in our field with an impressive impact factor of 7.4 and a Cite Score of 6.33 for 2016. We are in the top quartile and we are #30 out of 353 journals in Biochemistry, Genetics and Molecular Biology.

The current Cite Score is 6.45 with still a month to go before the final Cite Score for 2017. More importantly, we have received over 170 new submissions in the first quarter of 2018, a nearly 400% increase since 2012. I triage about 90% of the new submissions. The main reason is not the quality of the research, which is very high, but rather the descriptive nature of it. We search for mechanisms of diseases related to matrix biology. Even an attempt to find a mechanism is better than a highly sophisticated description of two phenotypes, or experimental conditions etc.

We have completed a great Special Issue on Fibrosis edited by Liliana Schaefer which will be published in the next large triple volume encompassing 40 papers, many of which are highly translational and written by leaders in their field. The next Special Issue on Extracellular Matrix-Driven Diseases edited by myself will be published thereafter.

I hope you support the journal by citing articles published in it and also by submitting your best research. I remind you that there are neither page nor color charges.

I wish you all a great Spring/Summer and hope to see many of you at the matrix meetings this summer and fall.

All the best,

Renato Iozzo,
Editor-In-Chief
Matrix Biology
It is my great pleasure to announce that a Special Issue of Matrix Biology exploring "Fibrosis – Mechanisms and Translational Aspects" will be published in volumes 68-70 of the journal.

Fibrosis, a complex process of abnormal tissue healing which inevitably leads to loss of physiological organ structure and function, is a world-wide leading cause of death. Despite a large body of research over the last two decades, antifibrotic approaches are mainly limited to organ replacement therapy generating high costs of medical care. In this translational issue, a unique group of basic and clinical researchers provide meaningful answers to a desperate call of society for effective antifibrotic treatments. Fortunately, a plethora of novel fibrogenic factors and biomarkers has been identified. Noninvasive diagnostic methods and drug delivery systems have been recently developed for the management of fibrosis. Consequently, a large number of exciting clinical trials addressing comprehensive, organ and stage-specific mechanisms of fibrogenesis are ongoing. By critically addressing previously unsuccessful and novel promising therapeutic strategies, we aim to spread hope for future treatments of the various forms of organ fibrosis.

This issue was brought to fruition by the close collaboration between basic researchers and clinical scientists. The contribution of all 149 authors involved in the 40 manuscripts included in this issue is highly appreciated. All contributors are leading specialists in the field of fibrosis and they have undertaken great efforts to transfer knowledge from bench to bedside. I would like to express my gratitude to the Editor in Chief of Matrix Biology, Dr. Renato V. Iozzo. We are all grateful to Elsevier, the publisher of Matrix Biology, in particular to Valerie M. Teng-Broug for her unwavering support for this project and for promoting publicity in the extracellular matrix community. The attractive cover of this special issue has been designed by Roman Strazanec, photographer and graphic designer (Vienna and London).

ISMB NEWSLETTER May 2018

RECENT PAPERS


Abstract: Resistance to antiangiogenic drugs limits their applicability in cancer therapy. Here, we show that revascularization and progression of pancreatic neuroendocrine tumors (PNETs) under extended vascular-endothelial growth factor A (VEGFA) blockade are dependent on periostin (POSTN), a matricellular protein expressed by stromal cells. Genetic deletion of Postn in RIP1-Tag2 mice blunted tumor rebounds of M2-like macrophages and αSMA+ stromal cells in response to prolonged VEGFA inhibition and suppressed PNET revascularization and progression on therapy. POSTN deficiency also impeded the upregulation of basic fibroblast growth factor (FGF2), an adaptive mechanism previously implicated in PNET evasion from antiangiogenic therapy. Higher POSTN expression correlated with markers of M2-like macrophages in human PNETs, and depleting macrophages with a colony-stimulating factor 1 receptor (CSF1R) antibody inhibited PNET revascularization and progression under VEGFA blockade despite continued POSTN production. These findings suggest a role for POSTN in orchestrating resistance to anti-VEGFA therapy in PNETs.


Abstract: Focal adhesions anchor cells to extracellular matrix (ECM) and direct assembly of a pre-stressed actin cytoskeleton. They act as a cellular sensor and regulator, linking ECM to the nucleus. Here, we identify proteolytic turnover of the anti-adhesive proteoglycan versican as a requirement for maintenance of smooth muscle cell (SMC) focal adhesions. Using conditional deletion in mice, we show that ADAMTS9, a secreted metalloprotease, is required for myometrial activation during late gestation and for parturition. Through knockdown of ADAMTS9 in uterine SMC, and manipulation of pericellular versican via knockdown or proteolysis, we demonstrate that regulated pericellular matrix dynamics is essential for focal adhesion maintenance. By influencing focal adhesion formation, pericellular versican acts upstream of cytoskeletal assembly and SMC differentiation. Thus, pericellular versican proteolysis by ADAMTS9 balances pro- and anti-adhesive forces to maintain an SMC phenotype, providing a concrete example of the dynamic reciprocity of cells and their ECM.


Abstract: Heterotopic ossification (HO) is a significant clinical problem with incompletely resolved mechanisms. Here, the secreted metalloproteinases ADAMTS7 and ADAMTS12 are shown to comprise a unique proteoglycan class that protects against a tendency toward HO in mouse hindlimb tendons, menisci, and ligaments. Adamts7 and Adamts12 mRNAs were sparsely expressed in murine forelimbs but strongly coexpressed in hindlimb tendons, skeletal muscle, ligaments, and meniscal fibrocartilage. Adamts7-/- Adamts12-/- mice, but not corresponding single-gene mutants, which demonstrated compensatory upregulation of the intact homolog mRNA, developed progressive HO in these tissues after 4 months of age. Adamts7-/- Adamts12-/- tendons had abnormal collagen fibrils, accompanied by reduced levels of the small leucine-rich proteoglycans (SLRPs) biglycan, fibromodulin, and decorin, which regulate collagen fibrillogenesis. Bgn-/0 Fmod-/ mice are known to have a strikingly similar hindlimb HO to that of Adamts7-/- Adamts12-/- mice, implicating fibromodulin and biglycan reduction as a likely mechanism underlying HO in Adamts7-/- Adamts12-/- mice. Interestingly, degenerated human biceps tendons had reduced
ADAMTS7 mRNA compared with healthy biceps tendons, which expressed both ADAMTS7 and ADAMTS12. These results suggest that ADAMTS7 and ADAMTS12 drive an innate pathway protective against hindlimb HO in mice and may be essential for human tendon health.


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Abstract: Proteoglycan accumulation is a hallmark of medial degeneration in thoracic aortic aneurysm and dissection (TAAD). Here, we defined the aortic proteoglycanome using mass spectrometry, and based on the findings, investigated the large aggregating proteoglycans aggrecan and versican in human ascending TAAD and a mouse model of severe Marfan syndrome. The aortic proteoglycanome comprises 20 proteoglycans including aggrecan and versican. Antibodies against these proteoglycans intensely stained medial degeneration lesions in TAAD, contrasting with modest intralamellar staining in controls. Aggrecan, but not versican, was increased in longitudinal analysis of Fbn1mgR/mgR aortas. TAAD and Fbn1mgR/mgR aortas had increased aggrecan and versican mRNAs, and reduced expression of a key proteoglycanase gene, ADAMTS5, was seen in TAAD. Fbn1mgR/mgR mice with ascending aortic dissection and/or rupture had dramatically increased aggrecan staining compared with mice without these complications. Thus, aggrecan and versican accumulation in ascending TAAD occurs via increased synthesis and/or reduced proteolytic turnover, and correlates with aortic dissection/rupture in Fbn1mgR/mgR mice. Tissue swelling imposed by aggrecan and versican is proposed to be profoundly deleterious to aortic wall mechanics and smooth muscle cell homeostasis, predisposing to type-A dissections. These proteoglycans provide potential biomarkers for refined risk stratification and timing of elective aortic aneurysm repair.


Corresponding author: aptes@ccf.org

Abstract: Secreted and cell-surface proteases are major mediators of extracellular matrix (ECM) turnover, but their mechanisms and regulatory impact are poorly understood. We developed a mass spectrometry approach using a cell-free ECM produced in vitro to identify fibronectin (FN) as a novel substrate of the secreted metalloprotease ADAMTS16. ADAMTS16 cleaves FN between its (I)5 and (I)6 modules, releasing the N-terminal 30 kDa heparin-binding domain essential for FN self-assembly. ADAMTS16 impairs FN fibrillogenesis as well as fibrillin-1 and tenascin-C assembly, thus inhibiting formation of a mature ECM by cultured fibroblasts. Furthermore ADAMTS16 has a marked morphogenetic impact on spheroid formation by renal tubule-derived MDCKI cells. The N-terminal FN domain released by ADAMTS16 upregulates MMP3, which cleaves the (I)5-(I)6 linker of FN similar to ADAMTS16, therefore creating a proteolytic feed-forward mechanism. Thus, FN proteolysis not only regulates FN turnover, but also FN assembly, with potential long-term consequences for ECM assembly and morphogenesis.


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Abstract: The proteome and N-terminome of the human odontoblast cell layer were identified for the first time by shotgun proteomic and terminal amine isotopic labeling of substrates (TAILS) N-terminomic analyses, respectively, and compared with that of human dental pulp stroma from 26 third molar teeth. After reverse-phase liquid chromatography-tandem mass spectrometry, >170,000 spectra from the shotgun and TAILS analyses were matched
by 4 search engines to 4,888 and 12,063 peptides in the odontoblast cell layer and pulp stroma, respectively. Within these peptide groups, 1,543 and 5,841 protein N-termini, as well as 895 and 2,423 unique proteins, were identified with a false discovery rate of ≤1%. Thus, the human dental pulp proteome was expanded by 974 proteins not previously identified among the 4,123 proteins in our 2015 dental pulp study. Further, 222 proteins of the odontoblast cell layer were not found in the pulp stroma, suggesting many of these proteins are synthesized only by odontoblasts. When comparing the proteomes of older and younger donors, differences were more apparent in the odontoblast cell layer than in the dental pulp stroma. In the odontoblast cell layer proteome, we found proteomic evidence for dentin sialophosphoprotein, which is cleaved into dentin sialoprotein and dentin phosphoprotein. By exploring the proteome of the odontoblast cell layer and expanding the known dental pulp proteome, we found distinct proteome differences compared with each other and with dentin. Moreover, between 61% and 66% of proteins also occurred as proteoforms commencing with a neo-N-terminus not annotated in UniProt. Hence, TAILS increased proteome coverage and revealed considerable proteolytic processing, by identifying stable proteoforms in these dynamic dental tissues. All mass spectrometry raw data have been deposited to ProteomeXchange with the identifier <PXD006557>, with the accompanying metadata at Mendeley Data (https://data.mendeley.com/datasets/b57zf6wmy/1).


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Abstract: The natural aging process and various pathologies correlate with alterations in the composition and the structural and mechanical integrity of the connective tissue. Collagens represent the most abundant matrix proteins and provide for the overall stiffness and resilience of tissues. The structural changes of collagens and their susceptibility to degradation are associated with skin wrinkling, bone and cartilage deterioration, as well as cardiovascular and respiratory malfunctions. Here, matrix metalloproteinases (MMPs) are major contributors to tissue remodeling and collagen degradation. During aging, collagens are modified by mineralization, accumulation of advanced glycation end-products (AGEs), and the depletion of glycosaminoglycans (GAGs), which affect fiber stability and their susceptibility to MMP-mediated degradation. We found a reduced collagenolysis in mineralized and AGE-modified collagen fibers when compared to native fibrillar collagen. GAGs had no effect on MMP-mediated degradation of collagen. In general, MMP digestion led to a reduction in the mechanical strength of native and modified collagen fibers. Successive fiber degradation with MMPs and the cysteine-dependent collagenase, cathepsin K (CatK), resulted in their complete degradation. In contrast, MMP-generated fragments were not or only poorly cleaved by non-collagenolytic cathepsins such as cathepsin V (CatV). In conclusion, our data indicate that aging and disease-associated collagen modifications reduce tissue remodeling by MMPs and decrease the structural and mechanic integrity of collagen fibers, which both may exacerbate extracellular matrix pathology.


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Abstract: The cellular microenvironment, characterized by an extracellular matrix (ECM), played an essential role in the transition from unicellularity to multicellularity in animals (metazoans), and in the subsequent evolution of diverse animal tissues and organs. A major ECM component are members of the collagen superfamily -comprising 28 types in vertebrates - that exist in diverse supramolecular assemblies ranging from networks to fibrils. Each assembly is characterized by a hallmark feature, a protein structure called a triple helix. A current gap in knowledge is understanding the mechanisms of how the triple helix encodes and utilizes information in building scaffolds on the outside of cells. Type IV collagen, recently revealed as the evolutionarily most ancient member of the collagen superfamily, serves as an archetype for a fresh view of fundamental structural features of a triple helix that underlie the diversity of biological activities of collagens. In this Opinion, we argue that the triple helix is a protein structure
of fundamental importance in building the extracellular matrix, which enabled animal multicellularity and tissue evolution.

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Abstract: Background. Human type IV collagenopathy is associated with mutations within the COL4A1 and to a less extent the COL4A2 genes. The proteins encoded by these genes form heterotrimers and are the highest molar ratio components of the ubiquitous basement membrane. The clinical manifestations of the COL4A1/A2 mutations are systemic affecting many tissues and organs among these kidneys. In order to uncover the cellular and biochemical alterations associated with aberrant type IV collagen, we have explored the phenotype of the Malpighian tubules, the secretory organ and insect kidney model, in col4a1 collagen gene mutants of the fruit fly Drosophila melanogaster. In Malpighian epithelial cells of col4a1 mutants, robust mitochondrial fusion indicated mutation-induced stress. Immunohistochemistry detected proteins nitrated by peroxynitrite that localized to the enlarged mitochondria and increased level of membrane peroxidation, assessed by the amount of proteins alkylated by 4-hydroxy-2-nonenal that similarly localized to the fused mitochondria. Nuclei within the Malpighian epithelium showed TUNEL-positivity suggesting cell degradation. The results demonstrated that col4a1 mutations affect the epithelia and, consequently, secretory function of the Malpighian tubules and provide mechanistic insight into col4a1 mutation-associated functional impairments not yet reported in human patients and in mouse models with mutant COL4A1.

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Abstract: We present a computational model of the Vascular Endothelial Growth Factor (VEGF), an important regulator of blood vessels formation, which function is affected by its heparin interactions. Although structures of a receptor binding (RBD) and a heparin binding domain (HBD) of VEGF are known, there are structural data neither on the 12 amino acids interdomain linker nor on its complexes with heparin. We apply molecular docking and molecular dynamics techniques combined with circular dichroism spectroscopy to model the full structure of the dimeric VEGF and to propose putative molecular mechanisms underlying the function of VEGF/VEGF receptors/heparin system. We show that both the conformational flexibility of the linker and the formation of HBD-heparin-HBD sandwich-like structures regulate the mutual disposition of HBDs and so affect the VEGF-mediated signalling.

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Abstract: Sterile inflammation is a therapeutic target in many diseases where it represents an important initiator of disease progression. However, the detailed mechanisms underlying its evolution and biological relevance are not yet completely elucidated. Biglycan, a prototype extracellular matrix-derived damage-associated molecular pattern, mediates sterile inflammation in macrophages through Toll-like receptor (TLR) 2 and/or TLR4-dependent signaling pathways. Here we discovered that soluble biglycan is a novel high-affinity ligand for CD14 in macrophages. Matrix Biol doi:10.1016/j.matbio.2018.05.006
Corresponding author: schaefer@med.uni-frankfurt.de

Abstract: We present a computational model of the Vascular Endothelial Growth Factor (VEGF), an important regulator of blood vessels formation, which function is affected by its heparin interactions. Although structures of a receptor binding (RBD) and a heparin binding domain (HBD) of VEGF are known, there are structural data neither on the 12 amino acids interdomain linker nor on its complexes with heparin. We apply molecular docking and molecular dynamics techniques combined with circular dichroism spectroscopy to model the full structure of the dimeric VEGF and to propose putative molecular mechanisms underlying the function of VEGF/VEGF receptors/heparin system. We show that both the conformational flexibility of the linker and the formation of HBD-heparin-HBD sandwich-like structures regulate the mutual disposition of HBDs and so affect the VEGF-mediated signalling.
and subsequent nuclear translocation of p38, p44/42, and NF-κB, and these effects were due to a specific, high-affinity interaction between biglycan protein core and CD14. Finally, we provide proof-of-principle for the requirement of CD14, by transiently overexpressing biglycan in a mouse model of renal ischemia/reperfusion injury performed in Cd14−/− mice. Lack of Cd14 prevented biglycan-mediated cytokine expression, recruitment of macrophages, M1 macrophage polarization as well as mitigated the tubular damage and serum creatinine levels, thereby improving renal function. Thus, CD14 inhibition could lead to the reduction in the activation of biglycan-TLR2/4 signaling pathways and could be a novel therapeutic approach in inflammatory kidney diseases.


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Abstract: Proteins destined for secretion move from the endoplasmic reticulum (ER, the site of synthesis) to Golgi cisternae then to the cell surface in transport vesicles. Although the mechanism of anterograde and retrograde transport via vesicles is well understood the temporal coordination of transport between organelles has not been studied. Here we show that the extracellular levels of collagen-I (the most abundant secreted protein in vertebrates) are rhythmic over a 24-hour cycle in tendon, the tissue richest in collagen-I. Rhythmicity is the result of circadian clock control of the secretory pathway via ER-ribosome docking, Tango1-dependent ER export, phosphodiesterase-dependent Golgi-ER retrograde transport of Hsp47 (a collagen molecular chaperone), and Vps33b-dependent post Golgi export. These mechanisms pause collagen-I transport at each node of the pathway over a 24-hour cycle. Thus, the circadian clock is a master logistic operator of the secretory pathway in mammalian cells.


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Abstract: Fibrillar collagens of the extracellular matrix are critical for tissue structure and physiology; however, excessive or abnormal deposition of collagens is a defining feature of fibrosis. Regulatory mechanisms that act on collagen fibril assembly potentially offer new targets for antifibrotic treatments. Tissue weakening, altered collagen fibril morphologies, or both, are shared phenotypes of mice lacking matricellular thrombospondins. Thrombospondin-1 (TSP1) plays an indirect role in collagen homeostasis through interactions with matrix metalloproteinases and transforming growth factor–β1 (TGF-β1). We found that TSP1 also affects collagen fibril formation directly. Compared to skin from wild-type mice, skin from Thbs1−/− mice had reduced collagen cross-linking and reduced prolysyl oxidase (proLOX) abundance with increased conversion to catalytically active LOX. In vitro, TSP1 bound to both the C-propeptide domain of collagen I and the highly conserved KGHR sequences of the collagen triple-helical domain that participate in cross-linking. TSP1 also bound to proLOX and inhibited proLOX processing by bone morphogenetic protein-1. In human dermal fibroblasts (HDFs), TSP1 and collagen I colocalized in intracellular vesicles and on extracellular collagen fibrils, whereas TSP1 and proLOX localized only in intracellular vesicles. Inhibition of LOX-mediated collagen cross-linking did not prevent the extracellular association between collagen and TSP1; however, treatment of HDFs with KGHR-containing, TSP1-binding, triple-helical peptides disrupted the collagen-TSP1 association, perturbed the collagen extracellular matrix, and increased myofibroblastic differentiation in a manner that depended on TGF-β receptor 1. Thus, the extracellular KGHR-dependent interaction of TSP1 with fibrillar collagens contributes to fibroblast homeostasis.
ISMB NEWSLETTER May 2018

ISMB MEMBERSHIP: BECOME A MEMBER OF ISMB!

ISMB is dedicated to promoting matrix biology research on a global scale and to facilitating communication among matrix-related organizations and researchers from different countries. Members are eligible for discounted registration fees at matrix meetings supported by ISMB. The Society sends out newsletters highlighting recent research advances, descriptions of matrix biology resources, new appointments and awards, together with announcements of relevant meetings.

Every two years, the Society presents the Rupert Timpl Award to a young scientist (<40 years old) for the best paper related to matrix biology published in the previous two years and gives the Distinguished Investigator Award for lifetime achievement in the field of matrix biology. ISMB sponsors travel grants for young scientists to attend international matrix meetings. If you work in the matrix biology area, consider becoming a member of ISMB to support the international matrix community and give your input on ways to improve interactions and communication. See the website www.ismb.org to join, and for recent job postings and newsletters.

Welcome to new members of ISMB since February 2018

**PhD students**
- Devadarssen Murdamoothoo: Mol. Immunorheumatology, Strasbourg, France
- Antonios Giannipoulos: Inst. For Sports Medicine, Copenhagen, Denmark
- Cheng Zhang: Inst. for Sports Medicine, Copenhagen, Denmark
- Marion Marchand: CIRB - Collège de France, Paris, France
- Theodoros Karalis: University of Patras, Patras, Greece
- Georgios Efthymiou: Institute of Biology Valrose, Nice, France
- Konstantina Karamanou: University of Patras, Patras, Greece
- Yasmene Alanazi: University of Manchester, Manchester, UK

**Post-docs**
- Laura Dupont: University of Liege, Liège, Belgium
- Madalina Nastase: Inst. General Pharmacology and Toxicology, Frankfurt, Germany
- Eva-Maria Brauchle: Institute for Womens' Health, Tübingen, Germany
- Nikolaos Kouvatsos: University of Manchester, Manchester, UK
- Joan Chang: University of Manchester, Manchester, UK
- Goncalo Barreto: Tissue Engineering and Biofabrication, Zurich, Switzerland
- Ioanna Kalograiaki: Biological Research Center, CSIC, Madrid, Spain

**Senior scientists**
- Hervé Emonard, CNRS Researcher: CNRS/University of Reims, Reims, France
- Stéphane Brezillon, CNRS Researcher: CNRS/University of Reims, Reims, France
- Ellen van Obberghen-Schilling, Research Director: Institute of Biologie Valrose, Nice, France
- Valerio Izzi, Senior Researcher: Biochemistry and Molecular Biology, Oulu, Finland
OBITUARY

Adèle BOSKEY
Reprinted from https://www.hss.edu/research-staff_boskey-adele.asp

“It is with great sadness that we share with you the news that Adele Boskey, PhD, Starr Chair in Mineralized Tissue Research, passed away after a long illness. Her passing is a loss for all at HSS and for the entire field of musculoskeletal research. Dr. Boskey was a leader and trailblazer in bone disease research, not just at HSS, but worldwide. Her impact on the countless scientists and surgeons she mentored is immeasurable. Without Dr. Boskey, HSS Research would not be what it is today. An important member of the HSS family for more than 40 years, Dr. Boskey worked as a Senior Scientist and Program Director of the Musculoskeletal Integrity Program. For nearly five decades, she studied how bone structure, composition and mineral formation influence bone strength and fracture risk, with major grants from the National Institutes of Health supporting her research. Her work contributed to the understanding of a number of musculoskeletal diseases, including osteoarthritis and osteoporosis.

Todd Albert, MD, Surgeon-in-Chief
Lionel Ivashkiv, MD, Chief Scientific Officer
Lou Shapiro, President & CEO”

MATRIX MEETING ANNOUNCEMENTS

MATRIX BIOLOGY EUROPE 2018
Celebrating 50 years of FECTS Meetings
The University of Manchester, 21st - 24th July 2018

A list of plenary and workshop speakers together with the preliminary programme are available on the web site http://www.confercare.manchester.ac.uk/events/mbe2018/

It is our great pleasure to invite you to attend MBE2018 in Manchester. The meeting is organised by the British Society for Matrix Biology together with the Wellcome Trust Centre for Cell-Matrix Research and will be hosted at The University of Manchester. We are grateful for support from both the ISMB and ASMB and all our other sponsors.

The MBE2018 meeting in Manchester will mark, almost to the day, 50 years since the very first conference of European matrix biology societies in Cambridge (30th June-2nd July 1968). At MBE2018, we will continue this emphasis on young career researchers.

The conference will include 6 plenary sessions and 8 workshops each centred on a specific theme of Matrix Biology, plus the BSMB Fell-Muir Award Lecture, the ISMB Rupert Timpl Award Lecture and the Dick Heinegård Young Investigator Award Session plus talks from selected abstracts and posters galore (6 poster prizes). Early Bird registration deadline is on 15th June (Save £40 for full members and £30 for students). The deadline
for abstract submission to be considered for an oral presentation has passed. However, there are still opportunities for posters (till 15th June).

Welcome Reception will take place at the Living World Gallery of the Manchester Museum. Time for you to reengage with colleagues and friends by the polar bears and tigers, with drinks, food and a string quartet.

The MBE Conference Dinner takes place at the Manchester United Football Club (the Old Trafford Stadium- “the Theatre of Dreams”) in a pitch-viewing functional suite. Admiring the glory of one of the most successful clubs in English football history? Missed the FA Cup Final? Here is your chance to catch up. Coaches to and from the venue have been arranged. Due to the size limitations of the Suite, dinner numbers will be limited to first come first served and we would recommend you book early to avoid disappointment. Prior to the Dinner reception, we are also arranging for tours of the stadium to take place. Transport will be provided at an earlier time for those booking the stadium tour.

Transport: with over 225 non-stop flight routes, Manchester Airport offers flights to more destinations than any other UK airport. The airport is situated just 10 miles (16 km) from Manchester city centre and is connected by direct trains which run every 10 minutes to Piccadilly train station.

Airport to city centre by train: 10 miles / 15 minutes / c. £3.50
Airport to city centre by taxi: 10 miles / 20-25 minutes / c. £20.00
INTERNATIONAL SYMPOSIUM ON THE EHLERS-DANLOS SYNDROMES
September 26-29, 2018, Ghent, Belgium
The International Symposium on the Ehlers-Danlos Syndromes (EDS) is a state-of-the-art meeting in which new research on clinical advances and the molecular and pathogenic mechanisms underlying EDS and related syndromes is discussed. We offer a high quality scientific program with the general theme: “Interaction and signaling: recurrent themes in the molecular mechanisms of EDS.” The meeting brings together an international panel of clinicians, clinical and basic scientists and representatives of patients support groups to foster constructive discussions and multidisciplinary debates that focus on the multiple aspects of the Ehlers-Danlos syndromes and associated pathologies. These include the molecular etiology of these disorders, the biochemical abnormalities produced by the underlying mutations affecting genes involved in connective tissue homeostasis, the clinical consequences of these mutations, the latest advances in therapies and management (medical, surgical and physiotherapeutic) and the effects of these interventions on the natural history of the disease. We strongly encourage clinicians and researchers with an interest in the Ehlers-Danlos syndromes to attend this meeting. We expect 250 delegates and key opinion leaders in the field from around the world to attend. The multidisciplinary nature of the conference provides an opportunity to talk to specialists from many different fields including basic scientists, geneticists, internists, orthopedic and vascular surgeons, dentists, pediatricians, physiotherapists, genetic counselors, nurses, representatives of patient support groups, and many others working with Ehlers-Danlos syndromes.

FEBS ADVANCED LECTURE COURSE EXTRACELLULAR MATRIX: CELL REGULATION, EPIGENETICS AND MODELING
27 September - 2 October, 2018, Patras, Greece
Extracellular matrix: cell regulation, epigenetics and modeling
https://extracellularmatrix.febsevents.org/
Organizer: Nikos K. Karamanos
This Advanced Lecture Course will cover a wide range of topics, from basic and applied science to clinical applications. The course will focus on recent highlights in the fields of matrix biology, biochemistry, structural biology, epigenetics, pharmacology and medicine to present PhD students and postdoctoral scientists, as well as academic and institute research fellows, with novel aspects of modeling, design and pharmaceutical targeting. Plenary lectures, poster sessions, panel discussions, flash presentations and speaker’s corner/meet-the-experts sessions will encourage the interaction of young scientists with the invited experts in discussions about science and career development.
Deadline for applications: YTFs, May 15, 2018; Registration and Abstract submission, May 31, 2018
Important note: A pilot FEBS Network room to support the extracellular matrix (ECM) research community and in particular an upcoming FEBS ALC on the ECM. Once delegates are selected for the event, the plan is for the room to become a private delegates-only space to support further discussion, learning and interaction around the event. Register and post your comments, papers, discussions:
ASMB Biennial Meeting, October 14-17, 2018, Las Vegas, NV (USA)

• Abstract submission is now open (www.asmb.net) Early bird registration, abstract submission, and award submission deadline is June 25, 2018
• ISMB Members get a special discount on registration
• ISMB sponsors an award lecture at this ASMB meeting. Billy Hudson will receive the ISMB Distinguished Investigator Award and will present a lecture on Tuesday, October 16.
• Travel awards from ASMB, the Histochemical Society, and the Alport Syndrome Foundation, are available for students and post-docs. Apply for travel awards during abstract submission.
• Guest Society participation by Matrix Biology Ireland, the Histochemical Society, TERMIS, and the Alport Syndrome Foundation
• Trainee-led Special Interest Sessions and Mentoring breakfasts
• Las Vegas has a wonderful climate in October and beautiful vistas year round!
FASEB SCIENCE RESEARCH CONFERENCE ON MATRICELLULAR PROTEINS 2019
Chairs: Olga Stenina-Adognravi and Joanne Murphy-Ulrich
July 14-19, 2019, Lisbon, Portugal