THE DANISH SOCIETY FOR MATRIX BIOLOGY

Newsletter

No. 2, October, 2017

From the Chairman

Welcome to the second newsletter of Danish Society of Matrix Biology!

In May 2017 we successfully held our 2017 Danish Society of Matrix Biology (DSMB) annual meeting at BRIC, Copenhagen, which attracted over 50 researchers in attendance. Guest speakers included Prof. John Coachman (Honorary speaker) from BRIC, University of Copenhagen ”Syndecans – gatekeepers of the cell adhesion phenotype” and Prof. Michael Davies also from University of Copenhagen “Modification of the extracellular matrix of the artery wall in cardiovascular disease. Lund University was represented by Dr. Anders Aspberg “Aggrecan disease-linked mutations” and Institute of Sports Medicine was represented by post doc René Svensson “Mechanics of connective tissue at the nano scale - Advanced glycation and crosslinking”. All speakers gave intriguing and inspiring talks. A great appreciation was also given to Katja Heinemeier for her great work as a chairman for several years in DSMB. Also this year, a couple of young talented investigators (Dr. Wing Ying Chow from Berlin, Germany and Mr Tian Xia from BRIC, Copenhagen) were chosen to present their latest research. After these great talks, the attendees networked over cheese, wine and continued the scientific discussions after the general assembly.

Later this year, a seminar with invited speakers Prof. John Whitelock from Sydney, Australia (sabbatical at University of Nottingham, UK) was arranged at the Panum Institute by Dr. Christine Chuang and Professor Michael Davies. Later, a short seminar was arranged with participation of Dr. Fengying Tang “Perlecan promotes enhanced vascularisation on implanted biomaterials” from University of New South Wales, Australia and Mr Chun-Yi Ng from Westmead Hospital and University of Sydney, Australia ”Proteoglycans and the interaction with lipids: are the M2 macrophages really atheroprotective?”

In this newsletter, we present the lab and research from Dr. Chris Madsen, Lund University. Please join us and become a DSMB member (100kr) to enjoy all the membership benefits. We look forward to seeing you at our upcoming seminars, and we hope that you will also enjoy our website.

Sincerely,

Christian Couppé

Marie Kveiborg and John Couchman

Christian Couppé and Katja Heinemeier

Marie Kveiborg and John Couchman

Christian Couppé and Michael Davies

Fengying (Sally) Tang, Christine Chuang, Chun-Yi Ng

René Svensson

Group highlights

Chris D. Madsen, Division of Translational Cancer Research, Lund University, Sweden

Our objectives:
Within the tumour microenvironment; cancer cells, extracellular matrix (ECM) proteins, and cancer-associated fibroblasts (CAFs) are in constant communication with each other. This 'ménage à trois' can ultimately promote cancer progression and dissemination. The overall objective of our research is to understand this interplay during cancer dissemination, and ultimately to identify new targets of cancer metastasis.

Overview:
The devastating capacity of cancer cells to metastasise has ever since my graduate studies captured my attention. My research has brought me from single molecules *in vitro*, to the complexity of whole organ pathology *in vivo*. I began my career working on the mechanisms regulating cancer cell migration in 2D, 3D and later on within living organisms using intravital imaging. Recognizing that the metastatic spread is not only controlled by the tumour cells, I began to broaden my interest by looking at the local tumour microenvironment as well as in the entire malignant organs.

uPAR and vitronectin in cancer cell migration:
After finishing my Master's thesis at the University of Copenhagen, I decide to start my PhD in the group of Prof. Francesco Blasi, IFOM-IEO-Campus, Milano, Italy. My worked uncovered that the specific binding of urokinase receptor (uPAR) to the ECM protein, vitronectin, induces cell migration through ligand-independent activation of integrins. Our data demonstrated for the first time that changes in plasma membrane tension can activate integrins independently of their ligand binding (EMBO, 2014). It was during my PhD that I developed a great interest for applied microscopy. We performed many types of real time imaging approached using a fluorescently-tagged uPAR incl. confocal, FRAP, TIRF and FCS microscopy.

The STRIPAK complex in cancer cell migration:
I then moved to Prof. Erik Sahai's laboratory, LRI-CRUK, United Kingdom to study cancer cell migration in living animals using intravital 2-photon microscopy. My aim was to identify new regulatory mechanisms of cancer cell invasion and metastasis. I decided to exploit the parallels between cells migrating during embryogenesis and that of metastasising cancer cells. A genome-wide RNAi screen was first conducted in *Drosophila melanogaster* to identify genes involved in border cell migration and actin organization in the egg chamber. Human orthologs of these hits were then tested on human cell lines and resulted in the identification of 32 novel regulators of human epithelial cell morphology and cancer cell invasion. This screen identified the STRIPAK complex to be a key regulator of cell migration in Drosophila and of spontaneous breast cancer metastasis in mice. Importantly, this study provided conceptual advances in our understanding of how a cancer cell couples its force machinery (actomyosin) to promote cell migration through structurally different physical environments (Nature Cell Biology, 2015).

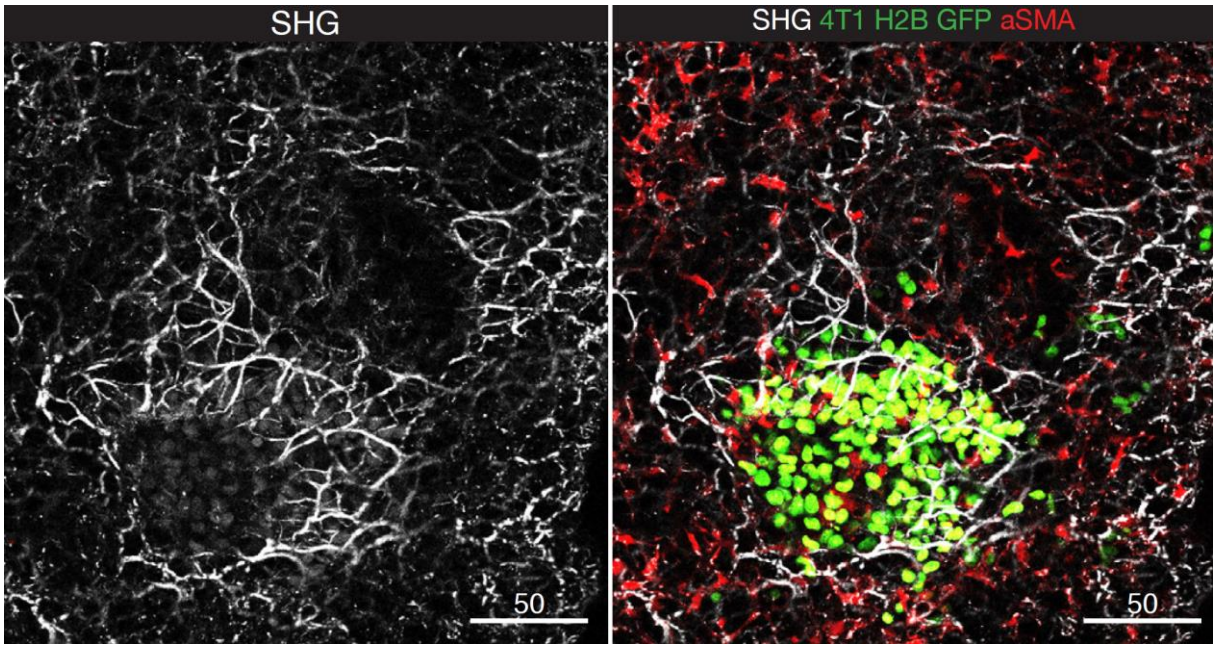
Remodelling of the cancer ECM niche:
During my time in the United Kingdom, I also discovered that cancer-associated fibroblasts (CAFs) lose their ability to remodel their surrounding matrix when cultured in low oxygen (hypoxia). I moved to Prof. Janine Erler's laboratory, University of Copenhagen, Denmark, to further investigate this question. We went on to demonstrate that sustained hypoxia or loss of the oxygen sensing protein, prolyl hydroxylase domain-containing protein 2 (PHD2), leads to the de-activation

of CAFs and loss of contractile force. As a result, loss of PHD2 results in reduced ECM stiffening of the primary tumour and as a consequent fewer spontaneous metastasis to lungs and liver (EMBO Report 2015).

I then began to exploit the advantage of 2-photon imaging and second harmonic generation (SHG) to visualise topographical changes in the ECM. Together with members of Prof. Janine Erler's group (Alejandro Mayorca Guiliani and Thomas R. Cox), we developed a new platform to map the ECM topography of any healthy and malignant organ in 3D. This platform combines, whole organ decellularisation *in situ*, quantitative mass spectrometry, and high resolution 2-photon microscopy. This platform has given us astonishing information about the pathological changes occurring in cancer, and we believe this imaging platform will move the structural ECM biology to an entire new dimension (Nature Medicine 2017).

Group leader at Lund University.

I was recently so fortunate to open my own laboratory at Lund University, Sweden. Here, my lab will continue to dissect the mechanisms by which cancer cells metastasise and how they take advantage of 'migratory plasticity' to circumvent the physical obstacles (adhesion, rigidity, confinement and topology) they encounter on their way through the body. While the intrinsic mechanisms behind cell migration are relatively well studied, the challenge now is to understand how the extracellular environment regulates this machinery to maintain efficient movement. Our research aims to provide ground-breaking insight into how cancer cells navigate anatomical distinct tissues (soft tissue, stiff tissue, vessel walls, and basement membranes). We will test new strategies to prevent metastasis that hopefully can be translated into the clinic to benefit cancer patients. We take a multidisciplinary approach with specific emphasis on real time imaging in 2D, 3D and animals including 2-photon microscopy (see figure).



Breast cancer metastasis in the lung. The micrometastasis (green) induces linearization of fibrillar collagen (white) surrounding the core of the micrometastasis. The metastasis is also surrounded by cancer-associated fibroblasts (red). SHG - second harmomic generation of fibrillar collagen (white). 4T1 tumour cells (green). aSMA-positive fibroblasts (red).

Our research also aims at preventing the fibrotic conversion of malignant cancer tissue by targeting CAFs. We believe that targeting these cells can normalise the subtle, but critical, imbalances occurring in the tumour microenvironment, and as a result halt the spread of cancer and in the same time render the primary tumour more susceptible to cytotoxic drugs. Being on the same wavelength, we recently bought the first hybrid tomographic optoacoustic / ultrasound imaging system (MSOT inVision 512-echo) in Europe for whole animal imaging. This system is unique among its kind, and will permit us to measure drug delivery and penetrance in real time, as well as studying changes in tissue elasticity during disease progression. We believe this will give us a unique possibility to monitor the efficacy of combining conventional cytotoxic drugs with anti-stromal therapy in longitudinal studies.

References

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2. *Madsen CD, Hooper S, Tozluoglu M, Bruckbauer A, Fletcher G, Erler JT, Bates PA, Thompson B, Sahai E. STRIPAK components determine mode of cancer cell migration and metastasis. Nature Cell Biology. 2015 Jan;17(1):68-80.*
3. *#Madsen CD, Pedersen JT, Venning F, Singh LB, Moeendarbary E, Charras G, Cox TR, Sahai E, Erler JT. Hypoxia and loss of PHD2 inactivate stromal fibroblasts to decrease tumour stiffness and metastasis. EMBO Report. 2015 Nov; 16(10): 1394-1408. # Corresponding author*
4. **Mayorca-Guiliani A, *Madsen CD, *Cox TR, Horton ER, Venning FA, Erler JT. ISDoT: In Situ Decellularisation of Tissues for high-resolution imaging and proteomic analysis of native extracellular matrix. Nature Medicine. 2017 Jul; 23(7):890-898. *Shared first authorship.*

Links

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http://ragnarsoderbergsstiftelse.se/chris-madsen
https://vimeo.com/149126294
http://portal.research.lu.se/portal/en/persons/chris-madsen(53192ae1-4bc5-4f83-b80b-6fa8655518b3).html#Overview

Membership

This year, we would like to be able to expand the membership benefits to allow members to be eligible for travel grants, to help young scientists attend various local and international matrix biology meetings including the 2018 Matrix Biology Europe (Manchester, UK) and future, BSMB, GRS/GRC meetings.

Therefore, we need your continued support by becoming and/or renew your DSMB membership for only 100 dkr per annum. We also appreciate any extra donation and will acknowledge your contribution in our next newsletter. You can pay by:

*1) Transferring via MobilePay to **46151** (Danish Society for Matrix Biology) and WRITE "DSMB, NAME AND EMAIL ADDRESS".*

OR

*2) Transferring to the DSMB bank account: Reg: 1551 Account: 1227130 (Danske bank). Please indicate "**DSMB membership**" on your bank transfer and write an email to our treasurer Abbas Jafari (ajafari@sund.ku.dk) to let him know who you are and that you have paid the membership fee.*

Upcoming meetings

3rd Matrix Biology Europe – Celebrating 50 years of FECTS
21st-24th July, 2018, Manchester, UK
http://www.confercare.manchester.ac.uk/events/mbe2018/

33rd Ernst Klenk Symposium in Molecular Medicine: Tissue regeneration, wound healing and fibrosis
15th-17th Oct., Cologne, Germany
http://www.cmmc-uni-koeln.de/events/ernst-klenk-symposium/ernst-klenk-symposium-2017/

Collagen in all its Forms – Scientific day in honour of David Hulmes
9th Nov., En Lyon, France
http://www.sfbmec.fr/?page_id=2530

2017 Annual MBSANZ meeting:
17th Nov, Melbourne, Australia
http://www.mbsanz.org/Home/Meetings#annual

4th Annual Matrix Biology Ireland meeting:
Learning from Development to Engineering Therapeutics
30th Nov-1st Dec., Dublin, Ireland
http://www.mbi.ie/meeting-2017/home