THE DANISH SOCIETY FOR MATRIX BIOLOGY

Newsletter

No. 3, December, 2017

From the Chairman

Welcome to our first Christmas edition of the Danish Society of Matrix Biology newsletter!

In September, we had a successful Matrix Biology PhD course at Institute of Sports Medicine Copenhagen (ISMC), Bispebjerg Hospital led by Katja Heinemeier. Professor Karl Kadler was an invited speaker DSMB was privileged that he gave a great special seminar on the circadian clock regulation of collagen homeostasis.

In late October, Prof. John Couchman held his retirement reception and said farewell at BRIC, University of Copenhagen after many years of great research (Please see the link: **http://www.bric.ku.dk/newslist/news/2017/the-matrix-man---retirement-portrait-of-john-couchman/)**. Luckily, he will continue to be active as a Professor Emeritus and also as president of the British Society of Matrix Biology for the upcoming 2018 MBE meeting at University of Manchester. Lab highlight in this newsletter is from Prof. Ulrich van dem Keller, University of Copenhagen.

Please do not forget to support and join us and become a DSMB member (100kr) to enjoy all the membership benefits. **Save the date: 2018 DSMB Annual Meeting, Monday 16th April, 2018!**

Merry Christmas and Happy New Year and we look forward to another year of exciting seminars and new matrix research in 2018.

Sincerely,

Christian Couppé

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SAVE THE DATE
2018 DSMB ANNUAL MEETING

Monday 16th April, 2018
Mærsk Tower, University of Copenhagen, Denmark

Karl Kadler's "old-school" seminar after a technical glitch!

John and Hinke's retirement reception at BRIC, KU.

Photos from PhD course - René´s teaching and workshop on how to determine mechanical properties

Group highlights

Ulrich auf dem Keller, Protease Network Degradomics, Department of Biotechnology and Biomedicine, Technical University of Denmark

Group focus

Proteases play pivotal roles in many diseases and form 5-10% of all potential drug targets. It is now clear that aberrant proteolysis results from perturbation of a complex proteolytic network rather than altered activity of a single enzyme. In particular, matrix metalloproteinases (MMPs) form such a network whose disturbance leads to severe diseases including cancer and inflammatory disorders. However, so far technical limitations prohibited a global understanding of interconnected protease activity in complex systems, contributing to devastating failures of protease inhibitors in clinical trials.

My laboratory applies and develops mass spectrometry-based proteomics workflows to identify proteases, elucidate their interactions and determine their substrates in inflammation, repair and regeneration. With a current focus on MMPs and cutaneous wound healing, we aim at elucidating interdependent proteolytic pathways and their disturbance in disease to provide a basis for the development of novel strategies for diagnostics and therapeutic intervention.

Scientific career

As a PhD student in Prof. Sabine Werner's laboratory at ETH Zurich, Switzerland, I characterized the function of the cytoprotective transcription factor Nrf2 in keratinocytes in normal skin, wounds and tumors using transgenic mouse models (*Mol Cell Biol* 2006). Thereby, we revealed a tumor-suppressive function of Nrf2 by control of oxidative stress in proliferating keratinocytes. This research laid the foundation for ongoing follow-up studies on the potential of Nrf2 as a therapeutic target in skin diseases.

In my postdoctoral research with Prof. Christopher M. Overall at University of British Columbia, Vancouver, Canada, I co-developed Terminal Amine Isotopic Labeling of Substrates (TAILS), a novel proteomics technique (*Nat Biotechnol* 2010) that we used to assess the substrate degradomes of MMPs 2 and 9 and to identify new bioactive targets linking these proteases to control of inflammation, angiogenesis and carcinogenesis (*Mol Cell Proteomics* 2010). By analysis of tissue samples, we elucidated a novel cross talk of MMP2 with serine protease activities to modulate vascular permeability and complement activation during skin inflammation (*Sci Signal* 2013) and discovered new roles for MMP12 in dampening inflammation in arthritis.

As a group leader back at ETH Zurich, I together with my co-workers extended these methods and applied them to identify novel MMP10 substrates at the epidermal-dermal interface. Many MMP10-dependent cleavage events were not direct but mediated through activation of another protease, whereby our data indicate an MMP10-MMP2 axis in fibroblast supernatants (*Mol Cell Proteomics* 2014) and activation of MMP9 by MMP10 in secretomes from keratinocytes (*Mol Cell Proteomics* 2015a). In collaborative projects with academia and industry, we demonstrated that proteolytic signatures of wound fluids obtained from a pig wound model and from trauma patients can determine critical turning points in wound progression (*Mol Cell Proteomics* 2015b, *J Invest Dermatol* 2017*)* and elucidated novel players in liver regeneration by global quantitative proteomics (*Dev Cell* 2017).

Novo Nordisk Foundation Young Investigator Award – Technical University of Denmark

With help of a Novo Nordisk Foundation Young Investiogator Award, I am currently establishing my research program on proteolytic networks in skin inflammation and repair within the Department of Biotechnology and Biomedicine at Technical University of Denmark. In this program, we exploit our newly developed proteomics technologies to map MMP and kallikrein (KLK) activation networks in inflamed tissues and hyperproliferative epithelia using the skin as model system (Figure). Targeted degradomics assays discriminate pro- from active proteases, and our next-generation positional proteomics workflow allows analyzing small sample amounts from cells and tissues obtained from animal models and patient biopsies. In a second line of research, we monitor and functionally characterize substrate cleavages as net outcomes of complex proteolytic activities in healing impairments, a common complication in elderly people and patients suffering from diabetes. In collaboration with clinical researchers, we apply our approach that we have implemented using a clinically relevant pig wound model to the analysis of wound fluids from patients with normal and delayed healing.

In the future, these subnets will be extended to ultimately map the entire protease web in protease-related disorders and to build predictive models that allow evaluating proteases as diagnostic indicators and therapeutic targets within the scope of personalized medicine.

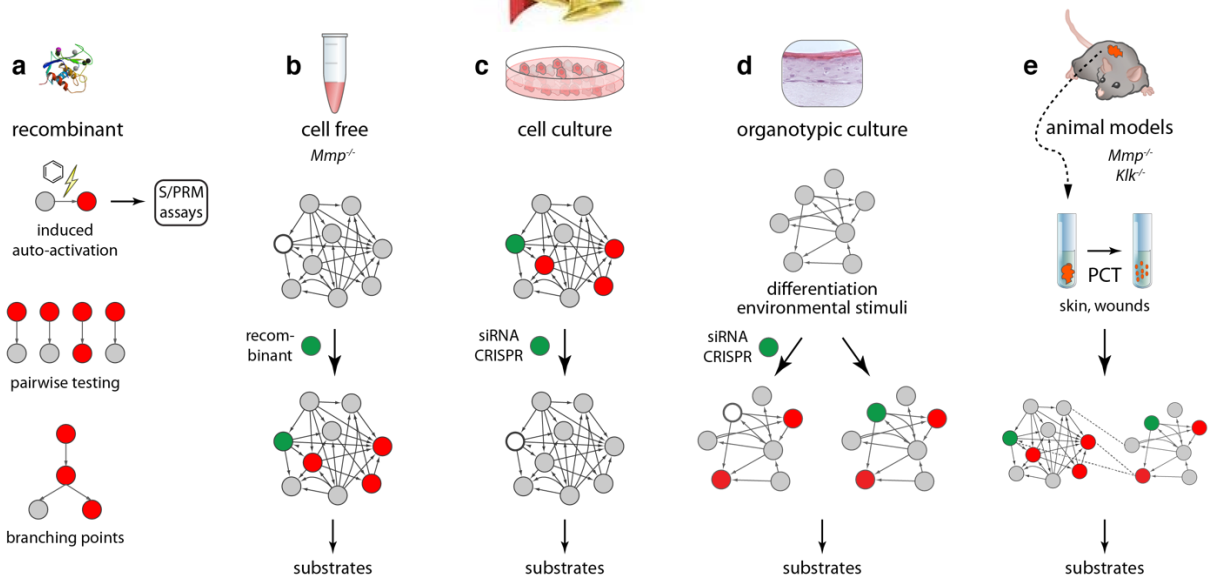

Figure: Mapping of interconnected protease activation networks in the skin. We develop and apply targeted Selected/Parallel Reaction Monitoring assays (S/PRM) to map protease activation networks on the levels of **a** recombinant proteases and upon perturbation of **b** cell free, **c** cell-based, **d** organotypic and **e** *in vivo* skin systems. Pressure cycling technology (PCT) helps in preparing mass spectrometry-compatible protein lysates from very small tissue specimens.

References

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5 Schlage, P. *et al.* Time-resolved analysis of the matrix metalloproteinase 10 substrate degradome. *Mol. Cell. Proteomics* **13**, 580-593, doi:10.1074/mcp.M113.035139 (2014).

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9 Bachofner, M. *et al.* Large-Scale Quantitative Proteomics Identifies the Ubiquitin Ligase Nedd4-1 as n Essential Regulator of Liver Regeneration. *Dev. Cell* **42**, 616-625 e618, doi:10.1016/j.devcel.2017.07.025 (2017).

Links

http://www.researcherid.com/rid/G-6004-2012
http://novonordiskfonden.dk/en/content/leading-edge-protein-researcher-moving-denmark
http://www.bioengineering.dtu.dk/english/researchny/research-groups/protease-network-degradomics

Membership

Please join us 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 either:

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

*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

2018 Danish Society for Matrix Biology Annual Meeting
16th April 2018, University of Copenhagen, Copenhagen, Denmark
https://www.dsmb.dk/

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

2018 GRS and GRC on Proteoglycans
Proteoglycans in Homeostasis and Disease: Cracking the PG Code
7th-13th July 2018, Proctor Academy, Andover, NH, USA
https://www.grc.org/proteoglycans-grs-conference/2018/
https://www.grc.org/proteoglycans-conference/2018/

2018 American Society of Matrix Biology Biennial Meeting
ECM Microenvironments in Disease, Aging and Regeneration
14th-18th October 2018, Red Rock Casino, Las Vegas, NV, USA
http://www.asmb.net/current-meeting