ERIBA

European Research Insitute
for the Biology of Ageing

2nd Molecular Biology of Ageing Meeting
Groningen, The Netherlands
8 — 11 October 2017

2nd Molecular Biology of Ageing Meeting 2017

Enquiries:
For enquiries regarding:
- Registration
- Invoicing/payments
- Accommodation/Hotels
Please contact Groningen Congres
Bureau: +31 (0)50 316 88 77
info@gbc.nl

For enquiries regarding:
- Oral and Poster presentations
- Venue
- Special requirements (dietary or other)
Please contact +31 (0)50 361 73 02
SecretariaatEriba@umcg.nl

Free wifi is available throughout the UMCG.
You can use the open network “UMCG-Guest”.
If you have a login, the secure network Eduroam is also available.

Taxis in Groningen
Taxi Groningen: +31 (0)50 5418452
Taxi Noord: +31 (0)50 5494940
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2nd Molecular Biology of Ageing Meeting 2017

www.bioageing.nl

Venue

1 University Medical Center Groningen (main entrance)
Hanzeplein 1
9713 GZ Groningen
Venue Room “De Blauwe Zaal” (follow the signs)
+31 (0)50 3616161

2 European Research Institute for the Biology of Ageing (ERIBA)
University Medical Center Groningen
Antonius Deusinglaan 1
Building 3226
9713 AV Groningen
+31 (0)50 3617300

3 Meeting Dinner October 10
(by voucher only)
Groninger Museum
Museumeiland 1
9711 ME Groningen
+31 (0)50 366 6555
(It is ~ 20 minute walk from UMCG premises)

Hotels

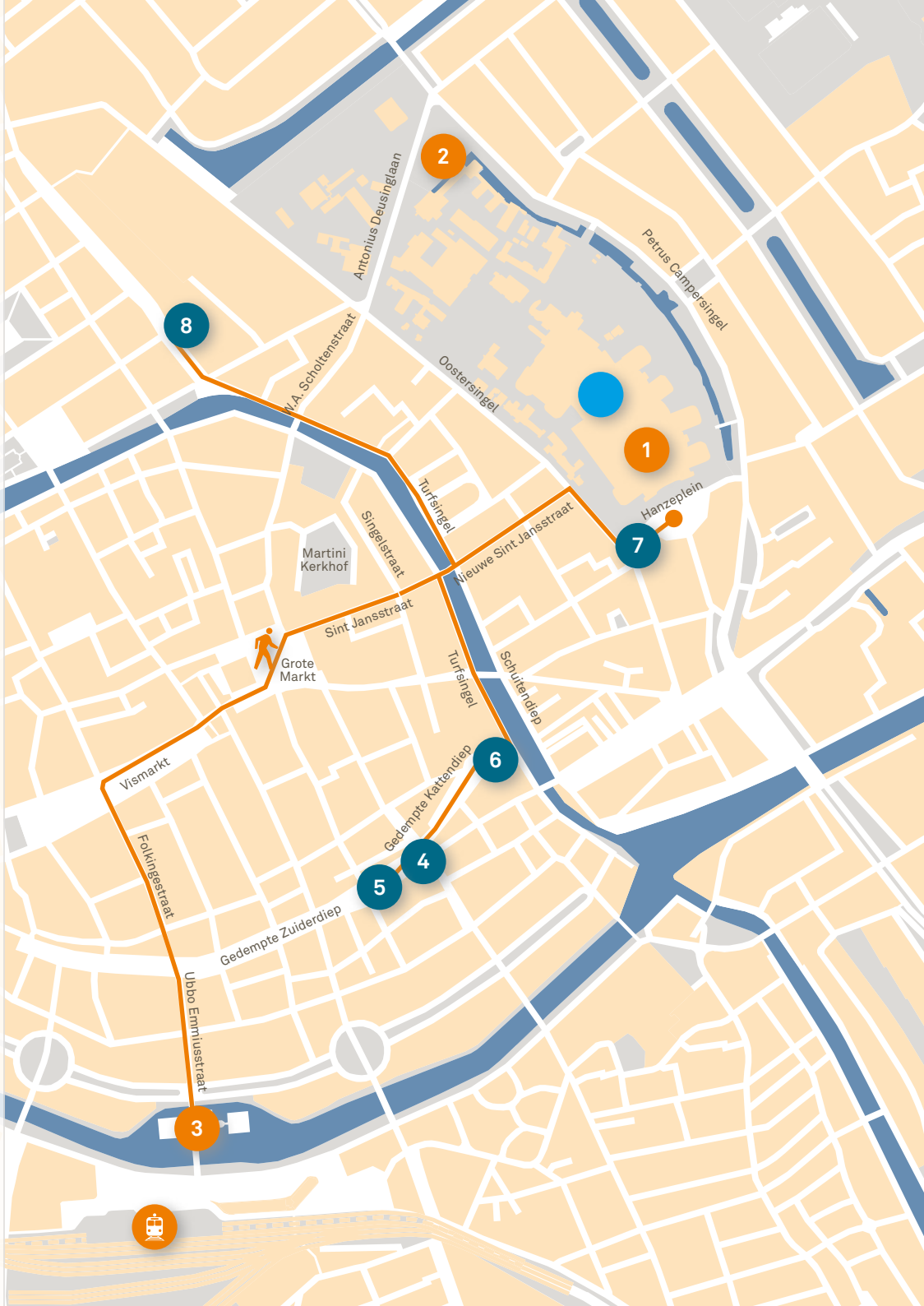
4 Bud Gett Hostel
Rademarkt 3-3A
9711 CS Groningen
+31 (0)50 5886558
From this hotel it is a 10 minute walk to the Main Entrance of the UMCG

5 Martini Hotel
Gedempte Zuiderdiep 8
9711 HG Groningen
+31 (0)50 3129919
From this hotel it is a 10 minute walk to the Main Entrance of the UMCG

6 Hampshire City Hotel
Gedempte Kattendiep 25
9711 PM Groningen
+31 (0) 50 5886565
From this hotel it is an 8 minute walk to the Main Entrance of the UMCG

7 NH Groningen Hotel
Hanzeplein 132
9713 GW Groningen
+31 (0)50 5848181
This hotel is across the street from the main entrance of the UMCG

8 Student Hotel
Boterdiep 9
9712 LH Groningen
+31 (0)50 2069161
(It is ~ 10 minute walk from UMCG premises)



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These abstracts should note be cited in bibliographies. Material herein should be treated as personal communications and should be cited as such only with the consent of the author.

Please note that recording of the oral sessions by audio, video or still photography is strictly prohibited except with the advance permission of the author(s), the organizers and the the European Research Institute for the Biology of Ageing / University Medical Center Groningen.

Organizing Committee
Gerald de Haan (Chair)
Peter Lansdorp
Michael Chang
Marco Demaria
Ellen Nollen
Katrin Paeschke

European Research Institute for the Biology of Ageing
University Medical Center Groningen — The Netherlands

Fulvio Reggiori
Ody Sibon

Department of Cell Biology — University Medical Center
Groningen — The Netherlands

Jan Hoeijmakers

Department of Genetics — Erasmus Medical Center
Rotterdam — The Netherlands

Dear colleagues and friends,

It is a great pleasure for me to welcome you to Groningen on the occasion of the 2nd Molecular Biology of Ageing Meeting. We initiated the first of such a Meeting in 2015, which was very well received by the participants, and thus encouraged us to organize the current 2017 Meeting.

The concept is the same: we have tried to bring together scientists that work on the very diverse molecular aspects of the ageing process; scientists that may not have met each other before as they cover quite distinct fields. If it is our collective goal to develop new intervention strategies to prevent and possibly reverse aspects of the ageing process, this can only be successful if we arrive to have a comprehensive insight into the multiple molecular pathways ('hallmarks') that contribute to the demise of tissue functioning during ageing. We hope and anticipate that this Meeting will contribute to achieving this goal, and will leave its participants with new ideas and insights, new collaborations, and indeed, with new friends.

The scientific programme contains a mixture of invited speakers, and speakers whose talks have been selected from submitted abstracts. The remainder of the submitted abstracts will be presented as posters, which will be up throughout the Meeting.

We also hope that you will find some opportunity to visit the historic city of Groningen. There is much to enjoy, all within easy walking distance. If you need any advice on where to go, ask any of the locals!

We are looking forward to host you, and anticipate seeing you again two years from now!

On behalf of the Organizing Committee,

Gerald de Haan
Scientific Director
European Research Institute for the Biology of Ageing
University Medical Center Groningen
The Netherlands

04:00 — 07:00 pm **Registration**

06:00 pm **Reception**

06:45 pm **Opening remarks - Welcome note**

07:10 pm Keynote Lecture by **Andrew Dillin** - Department of Molecular and Cell Biology at Berkeley
The Communication of Mitochondrial Proteotoxic Stress (The Mitokine)

08:00 — 09:30 pm **Session 1. Telomeres**
Chair **Michael Chang**
Speakers **Joachim Lingner** — École Polytechnique Fédérale de Lausanne
Telomeric chromatin analysis provides insights into damage protection
Jan Karlseder — Salk Institute for Biological Studies
Regulation of DNA Repair pathway choice in S/G2 by the NHEJ inhibitor CYREN
Miguel G. Ferreira — Institute for Research on Cancer and Aging in Nice (IRCAN)
Non-cell autonomous effects of telomere shortening in cancer and ageing
Peter Baumann — HHMI and Stowers Institute, Kansas University Medical Center
Telomerase RNA biogenesis – it takes a lot to make enough

09:00 am **Session 2. DNA repair and genome instability**
Chair **Katrin Paeschke**
Speakers **Jan Hoeijmakers** — Erasmus MC Department of Molecular Genetics
Keeping your genome intact protects you from aging and neurodegeneration
Penny Jeggo — School of Life Sciences at the University of Sussex
Maintaining Genomic Integrity in the face of DNA double strand breaks
Anne C. Meinema — ETH Zürich
DNA circles cause nuclear pore complex rearrangements during yeast aging
Jacqueline Jacobs — The Netherlands Cancer Institute
Control of DNA repair pathway choice at telomeres and DNA double strand breaks
Elsa Logarinho — IBMC-Instituto de Biologia Moleculare Celular, i3S, Porto University
Molecular basis of mitotic decline during human aging

10:50 am **Coffee break**

11:20 am **Session 3. Mitochondria and apoptosis**
Chair **Peter Lansdorp**
Speakers **Liza Pon** — Columbia University Medical Center
Reciprocal interactions between mitochondrial DNA and lifespan control in budding yeast
Marte Molenaars — Academic Medical Center Amsterdam
The Interplay between Mitochondrial Function and Protein Translation in Longevity
Vincenzo Sorrentino — École Polytechnique Fédérale de Lausanne
Enhancing mitochondrial proteostasis reduces amyloid-ß peptide proteotoxicity

12:30 pm **Lunch**

02:00 pm **Session 4. Nutrient Sensing**
Chair **Ody Sibon**
Speakers **Jens Bruening** — Max Planck Institute for Metabolism Research
Neuronal circuits in control of metabolism
Brian Kennedy — The Buck Institute for Research on Aging
Sex Differences and Aging in the mTOR Pathway
Christine Müller — European Research Institute for the Biology of Ageing, UMCG
Reduced expression of C/EBPß-LIP extends health- and lifespan in mice
Peter Tessarz — Max Planck Institute for Biology of Ageing, Cologne
Integration of metabolic and epigenetic regulation of stem cell fates in health and ageing

03:45 pm **Poster Session 1; coffee and tea will be served**
(uneven numbers: see pages 119-129)
06:00 pm **Dinner**

07:30 pm **Session 5. Autophagy and Immunity**
Chair **Fulvio Reggiori**
Speakers **David Rubinsztein** — Cambridge Institute for Medical Research
Autophagy and Neurodegeneration
Katja Simon — Oxford University
Autophagy and immune aging
Andre Nussenzweig — Center for Cancer Research, NIH
Genome Organization Drives Chromosome Fragility
Manolis Pasparakis — Institute for Genetics at the University of Cologne
Necroptosis in tissue homeostasis and inflammation

09:00 am **Session 6. (Epi)genetics and ageing**
Chair **Jan Hoeijmakers**
Speakers **Edwin Cuppen** — Center for Molecular Medicine at the UMC Utrecht
Tissue-specific mutation accumulation in human adult stem cells during life
Anne Brunet — Paul F. Glenn Laboratories for the Biology of Aging at Stanford University
Understanding and modeling aging
Mario Baumgart — Leibniz Institute on Aging - FLI
Longitudinal analysis of gene expression in the short-lived killifish Nothobranchius furzeri reveals widespread pleiotropic antagonistic actions
Bart Eggen — University Medical Center Groningen
Transcriptomic analysis of purified human cortical microglia reveals age-associated changes antagonistic actions
Markus Schosserer — University of Natural Resources and Life Sciences, Vienna
Two distinct ribosomal RNA base methylations modulate healthy lifespan

10:55 am **Coffee break**

11:25 am **Session 7A. Protein homeostasis**
Chair **Ellen Nollen**
Speakers **Mark S. Hipp** — Max Planck Institute of Biochemistry
Proteostasis impairment in protein misfolding and aggregation diseases
Alessandro Cellerino — Scuola Normale Superiore
Proteomic analysis of brain aging reveals reduction of protein/transcript correlation, loss of stoichiometry in multiple protein complexes and changes in protein thermal stability
Tobias Dansen — UMC Utrecht
Proteome-wide Changes in Protein Turnover Rates in C. elegans Models of Longevity and Age-Related Disease

12:30 pm **Lunch**

02:00 pm **Session 7B. Protein homeostasis**
Chair **Ellen Nollen**
Speakers **Giovanna Mallucci** — Department of Clinical Neurosciences, University of Cambridge
Manipulating the Unfolded Protein Response for treatment of neurodegeneration
Collin Ewald — ETH Zurich
Preferential translation of ATF-5 mediates Caenorhabditis elegans lifespan extension from reduced protein synthesis

03:00 pm **Session 8. Stem cells**
Chair **Gerald de Haan**
Speakers **Thomas Rando** — Glenn Center for the Biology of Ageing at Stanford University
Epigenetics Mechanism of stem cell aging and rejuvenation
Allison Bardin — Genetics and Developmental Biology Center at Institut Curie
Modes of genome alteration of adult stem cell during aging
Allesandro Ori — Leibniz Institute on Aging Fritz Lipmann Institute (FLI)
Age and diet affect the intestinal crypt proteome

04:30 pm **Poster session 2; coffee and tea will be served**
(even numbers: see pages 119-129)

07:00 pm **Reception and dinner at the Groningen Museum**
The Meeting's Closure Diner will take place at the Groninger Museum, one of the most iconic buildings of the city. Guests will be offered a tour to the permanent exhibition. More information about the Museum can be found here: http://www.groningermuseum.nl/en

10:00 am **Session 9. Cellular senescence**
Chair **Marco Demaria**
Speakers **Manuel Serrano** — Manuel Serrano- Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain
Integrating cellular senescence and reprogramming
Sheila A. Stewart — Department of Cell Biology and Physiology at the Washington University of St. Louis
Age-related changes in the tumor microenvironment drive tumorigenesis
Peter de Keizer — Department of Genetics, Erasmus MC Rotterdam
Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging
Peter Bruno — Harvard Medical School
Functional genetic characterization of senescence induction
Sélène Glück — École Polytechnique Fédérale de Lausanne
Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence

12:30 pm **Lunch and Departure**

Date
October 8

Time
7:10 pm

2nd Molecular Biology of Ageing

Keynote Lecture

Speaker
Andrew Dillin

Andrew Dillin

Department of Molecular and Cell Biology at Berkeley

Andrew George Dillin is a Howard Hughes Medical Investigator and the Thomas and Stacey Siebel Distinguished Chair in Stem Cell Research at the Department of Molecular and Cell Biology at Berkeley. Professor Dillin investigates the molecular pathways of aging. In particular, he focuses on how protein folding and conformations play a role in the aging process of cells and organisms and how diet can affect that link.

Title of talk

The Communication of Mitochondrial Proteotoxic Stress (The Mitokine)

Abstract

Aging is a highly coordinated process capable of eliciting recognizable and predictable changes across tissues and throughout time. The aging process is not merely determined by the events incurred toward the end of an organism's life, rather it can be shaped by experiences accumulated from the earliest stages of development, or even from the generations that came before it. An organism's perpetuations of historic cues, how its patterns of gene expression change and become cemented in response to stresses that may have occurred long in the past or in parental populations, have a significant effect on long-term health and longevity, the mechanistic details of which are only beginning to emerge. Nowhere is this concept more poignantly demonstrated than by studies on the roles of mitochondria in the aging process, which have suggested that reduced mitochondrial, function during a specific critical window of development and within specific tissues is sufficient to extend the lifespan of the organism [5-7]. The necessity for mitochondria to consolidate, interpret, and propagate information across space and time supports the predicted existence of intricate endocrine networks devoted to the dissemination of mitochondrial-derived information.

Previously, we reported that reduced mitochondrial function specifically in neurons alone was sufficient to extend the lifespan of the nematode C. elegans [6]. Mild neuronal mitochondrial stress caused an upregulation in mitochondrial stress signaling, or the UPR^{MT}, across distal tissues of the organism. Furthermore, key components of the UPR^{MT} were required for the extended lifespan of animals with reduced mitochondrial function [6, 8]. The coordinated communication of stress signaling between neuronal and peripheral tissues led us to hypothesize that mitochondrial stress within a subpopulation of neurons may elicit the creation of an endocrine-like signal (a mitokine) that becomes distributed to and acted upon by distal cells to induce the UPR^{MT}.

Date
October 8

Time
8 pm

Session 1

Session 1

Telomeres

Speakers
Joachim Lingner
Jan Karlseder
Miguel G. Ferreira
Peter Baumann

Chair
Michael Chang

Joachim Lingner

Swiss Institute for Experimental Cancer Research (ISREC)
École Polytechnique Fédérale de Lausanne

Joachim Lingner's laboratory studies the structure and function of telomeres in human cells under normal and pathological conditions. Lingner did his PhD at the Biozentrum of the University of Basel in the laboratory of Prof. Walter Keller (1989-1992) on RNA 3'end formation. For a postdoc (1993-1997) he joined the laboratory of Prof. Thomas Cech at the Howard Hughes Medical Institute, University of Colorado at Boulder working on telomerase. In 1997, he was appointed as group leader at ISREC, became associate Professor at EPFL in 2005 and full Professor in 2009. Honors include postdoctoral fellowships from EMBO and the Swiss National Science Foundation (SNSF), a START-fellowship from SNSF, the Friedrich Miescher Prize in 2002, EMBO membership in 2005, and an ERC advanced investigator grant in 2008.

Title of talk

Telomeric chromatin analysis provides insights into damage protection

Abstract

Telomeres play crucial roles in cancer, telomere syndromes and aging. Upon shortening telomeres induce DNA damage checkpoint signaling and cellular senescence. This suppresses the growth of premalignant lesions but may also limit tissue renewal and contribute to aging. Telomere shortening occurs due to the end replication problem and nucleolytic processing of chromosome ends. In addition, telomeres can shorten stochastically due to damage that occurs with oxidative stress or due to replication fork problems that occur during semiconservative DNA replication of telomeric DNA. Telomeres are difficult to replicate. Their highly repetitive nature may lead to DNA misalignments during replication. They are transcribed into the long noncoding RNA TERRA which can form R-loops.

They can form higher order structures such as t-loops and G-quadruplexes. Finally, telomere replication is unidirectional and replication problems cannot be rescued from converging replication forks. To better understand how chromosome ends are protected from damage and telomere loss, our laboratory developed a quantitative telomeric chromatin isolation protocol (QTIP) in which we analyze antibody-purified telomeric chromatin by mass spectrometry (Nature communications 4, 2848 (2013)). Thus, we are determining the chromatin composition of healthy and diseased telomeres. In addition, we coupled QTIP to iPOND for Isolation of Proteins On Nascent DNA (Genes & Development 25, 1320 (2011)) and are able to identify the proteins that are present at telomeric replication forks. I will report on employed methodologies to determine telomeric chromatin composition and insights we obtained on the functions of novel telomeric chromatin components.

Jan Karlseder

Salk Institute for Biological Studies

Jan Karlseder grew up in Tyrol, Austria, and attended the University of Vienna, where he got his Ph. D. in Molecular Biology in 1995, working on the cell cycle regulation of transcription. After a postdoc at the Rockefeller University in New York City he joined the Salk Institute for Biological Studies in 2002 and was promoted to tenured Professor in 2011. He holds the Donald and Darlene Shiley Chair for Aging Research and is currently the director of the Glenn Center for Aging Research at the Salk Institute. The Karlseder group works in the interaction of telomeres with the DNA damage and repair machinery during aging and tumorigenesis.

Title of talk

Regulation of DNA Repair pathway choice in S/G2 by the NHEJ inhibitor CYREN

Abstract

Classical non-homologous end joining (cNHEJ) and homologous recombination (HR) compete for the repair of double stranded breaks of DNA during the cell cycle. HR is inhibited in G1 phase of the cell cycle, but both pathways are active in S and G2 phases. Why cNHEJ does not always outcompete HR in S and G2 phases has been unclear. Here we show that CYREN is a cell cycle specific inhibitor of cNHEJ. CYREN suppression allows cNHEJ at telomeres and intrachromosomal breaks during S and G2 phases, while cells lacking CYREN accumulate chromosomal aberrations upon damage induction, specifically outside G1 phase. CYREN acts by binding to the Ku70/80 heterodimer and preferentially inhibits cNHEJ at breaks with overhangs by protecting them. We therefore propose that CYREN is a direct cell cycle inhibitor of cNHEJ, thereby promoting error free repair by HR in cell cycle phases where sister chromatids are present.

Miguel G. Ferreira

Institute for Research on Cancer and Aging in Nice (IRCAN)

Miguel graduated in Biology from the University of Lisbon and integrated the first edition of the Gulbenkian PhD Programme.

His PhD research focused on the cell cycle regulation of DNA replication having John Diffley as his supervisor (ICRF/Clare Hall labs). For his postdoctoral research, he joined Julie Cooper's lab as her first postdoc (first at UCHSC in Denver and later at CRUK/LIF in London) to study telomeres.

In 2006, he joined the Instituto Gulbenkian de Ciência to head the Telomere and Genome Stability Laboratory. In 2010, the lab added zebrafish to investigate the role of telomere dysfunction at the organism level. In 2017, he became Directeur de Recherche with the CNRS and he is currently at the Institute for research on Cancer and Aging of Nice, France. His research interests lie on telomeres, how they are stably inherited and, upon dysfunction, how they contribute to ageing and disease.

Title of talk

Non-cell autonomous effects of telomere shortening in cancer and ageing

Abstract

Age is the strongest carcinogen. The basis underlying this phenomenon, however, remains unclear. Telomere shortening is a recognized marker of humans aging and is correlated with many age-related diseases, including cancer. We are testing whether telomere shortening plays a causative role in tumorigenesis in zebrafish - a vertebrate model that, like humans, exhibits critically short telomeres with age.

We have been using zebrafish chimeras to disentangle cell-autonomous from non-cell autonomous effects of telomere-shortening. This system allows us to maintain mixed tissues of telomerase proficient and deficient cells throughout development and adult life. We are using second generation tert mutant zebrafish as a model for critically short telomeres. We observed that even a minor percentage of cells with critically short telomeres have a dominant effect, reducing the lifespan of otherwise wildtype zebrafish larvae.

Surprisingly, reception of signals emitted by tert mutant cells is p53 dependent. In order to directly test the non-cell-autonomous effects of telomere shortening in Cancer onset, we injected Telomerase positive Melanoma progenitor cells into tert wildtype and mutant recipient embryos.

Tumors arise from melanocyte precursors that overexpress the HRAS oncogene in adult animals with similar time of onset. However, the tert mutant environment increases tumor incidence significantly, doubling the number of cases. Our results suggest that organismal telomere shortening plays a crucial role for the age-related increased risk of cancer. With ongoing experiments we are trying to reveal the mechanisms that underlie these effects.

Peter Baumann

HHMI and Stowers Institute, Kansas University Medical Center

Peter Baumann, a native of Germany, studied at the University of Bayreuth and the University of Cambridge (UK), before completing his Ph.D. at the Imperial Cancer Research Fund (now part of Crick Institute) and University College London. He conducted postdoctoral research in the laboratory of Prof. Thomas Cech at the University of Colorado at Boulder. Since 2002, he has held academic positions at the Stowers Institute for Medical Research and the University of Kansas Medical Center in Kansas City. He is a Professor in the Department of Molecular and Integrative Physiology and an Investigator at the Howard Hughes Medical Institute and holds the Priscilla Wood Neaves Endowed Chair in the Biomedical Sciences at the Stowers Institute. Dr. Baumann has received numerous honors including the Pew Scholar in the Biomedical Sciences Award and the HHMI Early Career Scientist Award.

Title of talk

Telomerase RNA biogenesis – it takes a lot to make enough

Abstract

Telomerase activity levels profoundly affect replicative lifespan with high levels permitting the continued proliferation of many cancer cells, and insufficient telomerase activity linked to a spectrum of degenerative disorders that are ultimately caused by limited renewal capacity in various tissues. In recent years, mutations in telomerase components have been linked to dyskeratosis congenita and related disorders. Interestingly, mutations in PARN (poly A ribonuclease) have also been linked to premature telomere shortening and biochemical studies have linked PARN, the nuclear RNA exosome as well as other RNA processing factors to the maturation of the human telomerase RNA (hTR) subunit. These studies also demonstrated that the amount of hTR converted from the primary transcripts into the mature form is the result of a kinetic competition between RNA degradation and precise processing of the 3' end to generate the 451-nucleotide mature form. To manipulate this balance to either boost telomerase RNA levels in patients with telomeropathies or reduce hTR in cancer cells, it is critical that we understand the roles of various RNA processing factors in processing versus degradation. Using biochemical approaches, we have now characterized the processing of 3' extended, precursor and mature forms of hTR. Our study illustrates how sequence, RNA structure and RNA-protein interactions each affect processing kinetics and the choice of maturation versus degradation. In vitro reconstitution further sheds light on the specific contributions made by PARN and the RNA exosome in generating the mature 3' end of hTR.

Session 2

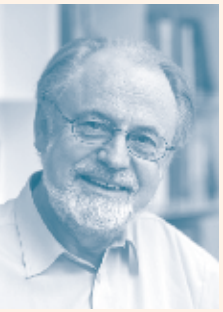
DNA repair and genome instability

Speakers
Jan Hoeijmakers
Penny Jeggo
Anne C. Meinema
Jacqueline Jacobs
Elsa Logarinho

Chair
Katrin Paeschke

Jan Hoeijmakers

Erasmus MC Department of Molecular Genetics



Education

M.Sc. Molecular Biology, Radboud University Nijmegen, 1975 (cum laude), Ph.D. University of Amsterdam, PhD work 1975-1979 (promotor Prof. Dr. Piet Borst), PhD Thesis: 'Trypanosomes: Kinetoplast DNA and Antigenic Variation' 1982 (for this work the 'Harold Quintus Bosz' Prize was awarded, 1983)

Other Positions

Associate Professor: Dept. of Genetics, Erasmus MC, Rotterdam, 1985-1993, Prof. Molecular Genetics: Dept. of Genetics, Erasmus MC, Rotterdam, since 1993, Department head 1999 -2016, Chairman of the EMC Biomedical Research Theme (6 departments, 2 cores, ~400 fte's), 2008-2016

Research Interests

Healthy aging, dna damage and repair, premature aging syndromes, mouse models, nutrition

Title of talk

Keeping your genome intact protects you from aging and neurodegeneration

Abstract

The molecular basis of aging (-related diseases) is one of the main unsolved questions in biology. Aging appears remarkably plastic: e.g. suppressing insulin signalling extends lifespan in worms, flies and mice. On the other hand, virtually all premature aging syndromes in man provide links with genome instability. We have generated mouse models which strikingly mimic human DNA repair deficiency disorders and display wide-spread accelerated aging, revealing a strong link between persisting DNA damage and many features of aging. E.g. Ercc1$^{\Delta/-}$ mice defective in ≥3 repair pathways show extensive premature multi-morbidity in post-mitotic and proliferative tissues limiting lifespan to 4-6 month. Simultaneously these mice exhibit an anti-aging 'survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR) and providing a link with the insulin signaling control of aging. Interestingly, subjecting the progeroid, dwarf mutants to actual (30%) DR tripled remaining lifespan, and drastically retarded numerous aspects of accelerated aging, with the neuronal system benefitting disproportionally. E.g. DR animals retained 50% more neurons in the neocortex and maintained full motoric function, delaying motor decline >20(!)-fold. Repair-deficient Xpg-/- mice also showing many premature aging symptoms responded similarly. The DR response in Ercc1$^{\Delta/-}$ mice resembled wt DR including (further) reduced insulin signaling. Interestingly, ad libitum Ercc1$^{\Delta/-}$ liver expression profiles showed declining expression of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. Similar aging-related transcriptional stress was discovered in human brain profiles, demonstrating relevance for normal aging in humans. DR in repair-deficient mice alleviated this decline, indicating that DR prolongs genome function. We found DR to reduce spontaneous DNA damage load, explaining the strong response of DNA repair deficient progeroid mice to DR. We will present phenotypes of conditional DNA repair models targeting aging to selected organs and connections with the unfolded protein response and proteinopathies (Alzheimer's and Parkinson diseases). Our findings strengthen the link between DNA damage and aging, establish Ercc1$^{\Delta/-}$ mice as powerful model for identifying interventions to promote healthy aging, reveal untapped potential for reducing endogenous damage, provide new venues for understanding the molecular mechanism of DR, and indicate a counterintuitive DR-like therapy for progeroid syndromes and DR-like interventions for preventing neurodegenerative diseases.

Penny Jeggo

School of Life Sciences at the University of Sussex

Penny Jeggo undertook her PhD at the National Institute for Medical Research, London in Robin Holliday's Laboratory. She subsequently undertook two postdoctoral fellowships, before establishing her own area of work in the Holliday laboratory. During her early work, Penny exploited model organisms and genetics to study DNA damage responses. Subsequently, she focused on the responses to DNA double strand breaks (DSBs) in mammalian cells, exploiting the genetic approaches used in lower organisms. Penny moved to the Cell Mutation Unit in Brighton in 1989 and in 2001 became a founding member of the Genome Damage and Stability Centre at the University of Sussex. Penny continues to elucidate the repair and signalling responses to DSBs in mammalian cells and now in stem cells. She has additional interests in radiation protection and human disorders caused by DSB repair defects.

Title of talk

Maintaining Genomic Integrity in the face of DNA double strand breaks

Abstract

DNA double strand breaks (DSBs) can arise both endogenously and from external sources such as ionising radiation (IR). Cells employ pathways of DSB repair in combination with a signal transduction pathway to maintain genomic integrity in the face of such DSBs. DNA non-homologous end-joining (NHEJ) is the major DSB repair pathway and ATM represents the signal transduction pathway responding to DSBs. Core NHEJ can take place in the absence of ATM. However, after exposure to IR, a 15-20% subset of DSBs are repaired by a sub-pathway of c-NHEJ that requires Artemis, ATM and 53BP1, which is regulated by ATM signalling. This pathway has recently been shown to be a resection-dependent process of c-NHEJ. Two aspects of the fidelity of c-NHEJ will be discussed, namely the generation of small junctional deletions and the formation of translocation events.

The slow process of c-NHEJ has been shown to have an enhanced propensity to generate translocations compared to the fast c-NHEJ process. ATM has a major role in regulating the chromatin in the DSB environment, which significantly influences the fidelity of DSB repair. Additionally, ATM regulates pathways that can prevent the proliferation of damaged cells. Such a function of ATM has been characterised in the neural SVZ compartment. In the adult SVZ, the transit amplifying progenitors (TAPS) and neuoblasts (NBs) sensitively undergo ATM-dependent apoptosis after IR exposure whilst the neural stem cells, which are predominantly quiescent, are resistant to apoptosis. However, activation of apoptosis is a feature of the cell type and not a consequence of proliferation. ATM also activates proliferation arrest and NB differentiation. After 2 Gy IR, proliferation arrest is prolonged and appears to be permanent. Collectively, these three responses (apoptosis, proliferation arrest and NB differentiation) cause neural stem cell activation. Hence following 2 Gy IR, irradiated progenitors do not proliferate and new progenitors are derived from irradiated quiescent stem cells. Significantly, in juvenile mice, which, in contrast to adult mice are sensitive to IR-induced carcinogenesis, proliferation arrest of irradiated progenitors is reduced and transient and quiescent stem cell activation is not observed. This represents an additional ATM-dependent set of responses that likely help to maintain genomic integrity in the face of DNA DSBs.

Anne C. Meinema

ETH Zürich

Anne Cornelis Meinema is interested in the changes of nuclear organization during aging. He did his PhD research at the University of Groningen in the lab of Prof. Bert Poolman and under supervision of Dr. Liesbeth Veenhoff. He studied molecular pathways for membrane protein transport into the nucleus of yeast. After his PhD, he joined the lab of Prof. Matthias Heinemann at the University of Groningen. In a collaborative effort, he analyzed the proteomic and transcriptomic changes that yeast undergoes during aging, using a systems-wide approach. Then he moved to the lab of Prof. Yves Barral at the ETH in Zürich (CH), where he currently studies the effect of aberrant DNA circles on the organization and downstream function of the nuclear pore complex during aging.

Title of talk

DNA circles cause nuclear pore complex rearrangements during yeast aging

Abstract

Saccharomyces cerevisiae confines aging factors in the mother cells during mitosis, in order to ensure the emergence of a rejuvenated and naïve daughter cell. The aging factors cause cellular dysfunction mortality. One prominent aging factor in budding yeast is the presence of noncentromeric DNA circles (1), formed by homologous recombination during DNA repair. Different studies show that DNA circles interact via SAGA with nuclear pore complexes (NPCs), causing them to stay in the mother cell during mitosis (2,3). We wondered whether DNA circle binding cause alterations in NPCs leading to loss of cell viability. We observed that NPCs having a DNA circle anchored lose the basket structure, which normally protrudes the nucleoplasm. Basket detachment, specifically Nup60, is required to anchor DNA circles to the NPC for mother cell confinement. Basketless NPCs progressively accumulated during aging. The basketless pores now fail to recruit Ulp1, preventing desumoytion of DNA-NPC interaction targets. Basket fixation to the pore prevents NPC-circle interaction and releases the circle from the mother cell. Mutations in SAGA show the same effect and are long-lived. We conclude that DNA circles require specifically basketless NPCs to be retained in the aging mother cell.

Altogether, DNA circles seem to cause an alteration of the NPC structure during aging, which is needed for their retention. Furthermore, the accumulation of modified NPCs might be a major cause of increased mortality with age. 1. Sinclair DA, Guarente L. 1997 2. Denoth-Lippuner A, et al. Elife. 2014 3. Shcheprova Z, et al. Nature. 2008

Jacqueline Jacobs

The Netherlands Cancer Institute

Dr. Jacqueline Jacobs studied Biology at the University of Nijmegen (Netherlands), specialized in Medical Biology, and received her MSc degree in 1996 cum laude. She performed her PhD studies on Polycomb-group repression of the INK4A/ARF tumor suppressor, at the Netherlands Cancer Institute (NKI) in Amsterdam with Dr. Maarten van Lohuizen. In 2000 she was awarded a cum laude PhD degree and the Antoni van Leeuwenhoek Award. After a first postdoctoral training at the NKI, she joined the lab of Prof. Dr. Titia de Lange at the Rockefeller University in New York (USA) as a Dutch Cancer Society fellow. In 2004 she returned to the NKI to continue her research independently, funded by Dutch Cancer Society and VIDI grants. In 2008 she became a junior group leader and in 2012 she obtained a tenured research group leader position, received an ERC grant and was selected as EMBO Young Investigator.

Title of talk

Control of DNA repair pathway choice at telomeres and DNA double strand breaks

Abstract

The main pathways for repair of DNA double strand breaks (DSBs) are non-homologous endjoining (NHEJ) and homology directed repair (HDR). The choice for the engagement of either one of these pathways occurs through regulation of the degree of DNA end-resection. DNA endresection is limited by 53BP1 and RIF1 to allow NHEJ, which cannot act on resected DNA, and to block HDR when an intact copy for repair by HDR is absent outside of the S/G2 phases of the cell cycle. Through functional genetic screening we recently identified the HORMA-domain protein MAD2L2 (a.k.a. REV7) as a critical contributor to the control of DNA repair activity by 53BP1/RIF1, that promotes NHEJ by inhibiting 5' end-resection downstream of RIF1, both at uncapped telomeres and at DNA DSBs. This inhibition of end-resection by 53BP1/RIF1/MAD2L2 is released in S/G2 to allow error-free HDR once a sister-chromatid is present. We now further investigated how MAD2L2 operates at DNA DSBs by looking into its recruitment and protein-complex formation upon DNA damage. Furthermore, we addressed how cells ensure that during S-phase, when NHEJ and HDR pathways are both active and both un-replicated and replicated DNA regions coexist, HDR only operates on replicated regions of the genome. We found that the replication status of the DNA locally ensures the engagement of the correct DNA repair pathway, through epigenetics. More specifically, replication-associated dilution of H4K20me2 distinguishes prereplicative from post-replicative chromatin to locally direct the NHEJ-promoting 53BP1/RIF1 complex to pre-replicative chromatin and the HDR-promoting BRCA1 protein to post-replicative chromatin.

Elsa Logarinho

IBMC-Instituto de Biologia Molecular e Celular, i3S, Porto University

E. Logarinho completed her PhD at the University of Porto in 2002. Her PhD research in the lab of Prof. Claudio Sunkel focused in cell division mechanisms, using Drosophila as model system, and major findings were the discovery of Polo/Plk1 localization at kinetochores and the characterization of the first spindle assembly checkpoint mutant in higher eukaryotes. After her PhD, E. Logarinho embraced a full-time academic career in the Health Sciences University (2002-2006) and the Medical School in Minho University (2007-2009), and pursued her research on the spindle assembly checkpoint. In 2009, E. Logarinho returned to a full-time research activity, and joined lab of Prof. Helder Maiato at IBMC/University of Porto, where she acquired solid expertise in live cell imaging and uncovered alternative mechanisms of mitotic spindle multipolarity (Pfizer Prize 2011, SPGH Prize 2013). In 2013, E. Logarinho started her own research group focusing on the positive feedback loop between ageing and aneuploidy and the modulation of mitotic fidelity as a potential means to ameliorate healthy lifespan. E. Logarinho presently holds an FCT Investigator grant from the National Foundation for Science and leads the Aging and Aneuploidy Group at the i3S consortium of Porto University.

Title of talk

Molecular basis of mitotic decline during human aging

Abstract

Aneuploidy, an abnormal chromosome number, has been linked to aging and age-associated diseases, but the underlying molecular mechanisms remain unknown. Supported by direct live-cell imaging of young, middle-aged and old-aged primary human dermal fibroblasts, we found that aneuploidy increases with aging due to general dysfunction of the mitotic machinery. Increased chromosome segregation defects in elderly mitotic cells correlated with an early senescenceassociated secretory phenotype (SASP) and repression of Forkhead box M1 (FoxM1), the transcription factor that drives expression of most G2/M genes. By restoring FoxM1 levels in elderly and Hutchison-Gilford Progeria Syndrome fibroblasts we prevented aneuploidy and, importantly, ameliorated cellular phenotypes associated with aging. Moreover, senescent fibroblasts isolated from elderly donors' cultures were mostly aneuploid, suggesting that aneuploidy is a key player in the progression into full senescence phenotypes. Based on this feedback loop between cellular aging and aneuploidy, we propose modulation of mitotic efficiency through FoxM1 as a potential strategy against aging and progeria syndromes.

Session 3

Mitochondria and apoptosis

Speakers
Liza Pon
Marte Molenaars
Vincenzo Sorrentino

Chair
Peter Lansdorp

Liza Pon

Columbia University Medical Center

Liza Pon studied mitochondrial function in steroid hormone biosynthesis as a pre-doctoral student in the laboratory of N.R. Orme-Johnson at Tufts University (1982-1987). As an NRSA Postdoctoral Fellow with Gottfried Schatz at the University of Basel, she studied protein import into mitochondria (1987-1990). Dr. Pon established her own laboratory in 1990 at Columbia University, where she is currently Professor of Pathology and Cell Biology and the Institute of Human Nutrition, and Director of the Confocal and Specialized Microscopy Shared Resource. The focal point of her research is organelle interactions and how they affect mitochondrial dynamics and function in cellular fitness and lifespan control.

Title of talk

Reciprocal interactions between mitochondrial DNA and lifespan control in budding yeast

Abstract

Mitochondrial DNA (mtDNA) encodes subunits of the electron transport chain and ATP synthase, as well as components required for mitochondrial protein synthesis. For example, mtDNA of the budding yeast Saccharomyces cerevisiae encodes protein subunits of respiratory chain complexes III, IV and V as well as rRNAs and tRNAs. mtDNA also affects processes beyond mitochondrial respiratory activity, including genome stability, iron-sulfur cluster formation and cell cycle progression. While it is clear that mtDNA is essential for normal cellular functions, links between mtDNA and lifespan control are not well understood. An increase in mtDNA mutations with age has been observed in yeast and mammalian cells. Moreover, early studies revealed that mutations in the proofreading activity of mtDNA polymerase gamma can result in premature aging in mouse models. However, it is not clear that the aging observed in the mtDNA mutator mice reflects normal aging. Studies in yeast have yielded apparently conflicting evidence on the effect of mtDNA on lifespan: loss of mtDNA can extend, reduce or have no effect on yeast replicative lifespan. Revisiting this question with advanced imaging techniques and methods for isolating old cells, we observe reciprocal interactions between mtDNA and lifespan in budding yeast. We detect age-associated changes in the organization of mtDNA. Conversely, we find that cells respond to the loss of mtDNA by altering expression of numerous loci, including genes linked to aging. Furthermore, we find that cells that adapt to mtDNA loss show increased replicative lifespan.

Marte Molenaars

Academic Medical Center Amsterdam

Marte Molenaars received her MSc degree in biomedical sciences from the University of Amsterdam in 2016. Following internships in the fields of metabolism and circadian rhythms first in the Academic Medical Center Amsterdam (AMC) and later at the University of Zurich (Switzerland), she came back to the AMC where she is currently doing her PhD under supervision of dr. Riekelt Houtkooper and dr. Alyson MacInnes. Now her research is focusing on metabolism and aging and she would like to find out how (dys)functional mitochondria communicate with the rest of the cell in a way that ultimately slows down cytoplasmic protein translation and extends lifespan.

Title of talk

The Interplay between Mitochondrial Function and Protein Translation in Longevity

Abstract

Several key pathways are involved in the lifespan of C. elegans, including mitochondrial function and protein translation. Many reports have demonstrated that reducing mitochondrial respiration or down-regulating factors involved in protein translation (such as ribosomal proteins or elongation factors) result in lifespan extension. Energy is produced in the mitochondria, and more than 50% of this energy is utilized for ribosome biogenesis and protein translation. Therefore, we hypothesize that there are unexplored regulatory links between these two pathways contributing to lifespan extension.

Here, we use polysome profiling to investigate the precise role of protein translation in C. elegans with altered mitochondrial function. In addition to providing a global overview of protein translation rates, this allows us to specifically isolate RNAs associated with ribosomes and compare them with total RNA.

Polysome profiles of long-lived mitochondrial Clk-1-mutants, reveal strong repression of monosomal and polysomal peaks, suggesting global repression of protein translation. Additionally we profiled worms where mitochondrial protein translation was inhibited, either by mrps-5 knockdown or doxycycline treatment, both known to extend lifespan. In contrast these worms reveal a shift from polysomes to monosomes, suggesting that more mRNAs are being translated by only a single ribosome.

To obtain an unbiased readout of precisely which RNAs are being translated in these different populations, we are performing RNA-seq of total RNA and polysomal RNA. The results will provide insight into how these distinct methods of dysfunctional mitochondria communicate with the cytoplasmic protein translation machinery in a way that ultimately slows down translation and extends lifespan.

Vincenzo Sorrentino

École Polytechnique Fédérale de Lausanne

Dr. Vincenzo Sorrentino obtained his Master's Degree in Biotechnological Sciences, at the University of Naples, Italy, in 2009. Afterwards, he undertook his Ph.D. studies in the lab of Prof. Noam Zelcer at the Academic Medical Center of Amsterdam, the Netherlands, where he focused on the regulation of LDL-cholesterol metabolism by the E3–ubiquitin ligase IDOL. He obtained his Ph.D. cum laude in 2014, and subsequently joined the lab of Prof. Johan Auwerx at EPFL, Switzerland, to investigate the role of mitochondria and mitochondrial proteostasis in aging and disease.

Title of talk

Enhancing mitochondrial proteostasis reduces amyloid-ß peptide proteotoxicity

Abstract

Amyloid-ß peptide (Aß) diseases, typified by Alzheimer's disease (AD) and inclusion body myopathy (IBM), are common and devastating, yet we know relatively little about their underlying molecular mechanisms or how to treat them effectively. Here, we provide evidence of a mitochondrial stress response signature that is conserved in AD in human, mouse and C. elegans, and that involves the UPRmt and mitophagy pathways. Using a worm model of Aß proteotoxicity, the GMC101 strain, we recapitulated mitochondrial features and confirmed the induction of this mitochondrial stress response as key to maintain mitochondrial proteostasis and health.

Importantly, boosting mitochondrial proteostasis by pharmacologically and genetically targeting mitochondrial translation, biogenesis, and mitophagy increases fitness and lifespan of GMC101 worms and reduces the levels of Aß aggregation. Our data support the relevance of enhancing mitochondrial proteostasis to delay Aß proteotoxic diseases, such as AD and IBM.

Session 4

Nutrient Sensing

Speakers
Jens Bruening
Brian Kennedy
Christine Müller
Peter Tessarz

Chair
Ody Sibon

Jens Bruening

Jens C. Bruening, MPI Metabolism Research, Cologne Germany

Dr. Jens Brüning is Director of the Max Planck Institute for Metabolism Research in Cologne and Director at the Policlinic for Endocrinology, Diabetes and Preventive Medicine at the University Hospital in Cologne.

His research focusses on elucidating the CNS-dependent regulation of energy and glucose metabolism. These studies revealed a previously unappreciated role for insulin action in the central nervous system (CNS) to control organismal glucose homeostasis and insulin sensitivty. His group has defined distinct Agouti-related peptide (AgRP)-expressing neurons in the hypothalamus as critical mediators of insulin's metabolic actions, revealed the molecular mechanisms of insulin action in these neurons as well as their alterations in obesity. More recently, through the use of neurocircuitry mapping techniques his group defined the projections of these AgRP-neurons within the CNS, which govern insulin-dependent control of systemic insulin sensitivty via the regulation of autonomic innervation.

Title of talk

Neuronal circuits in control of metabolism

Abstract

The Central Nervous System (CNS) is constantly instructed about the energy state of the organism via hormonal and nutritional signals. It then coordinately regulates a wide array of behavioral and autonomic responses to adapt energy intake, energy expenditure, and nutrient flux across different organs, as well as higher cognitive functions according to energy availability of the organism. Dysregulation of these homeostatic circuits causes prevalent diseases, such as obesity and type-2 diabetes mellitus, which are on an epidemic rise in industrialized societies. The presentation will focus on the fundamental regulatory principles of how neurons sense nutritional cues and on the neurocircuitry responsible for the coordinated adaptation of behavioral and autonomic outputs. Moreover, the underlying cellular and molecular mechanisms for alterations in these pathways during the development of obesity and type-2 diabetes mellitus will be discussed.

Brian Kennedy

The Buck Institute for Research on Aging

Dr. Brian Kennedy is internationally recognized for his research in the basic biology of aging and is a visionary committed to translating research discoveries into new ways of delaying, detecting, preventing and treating age-related conditions. He was the President and CEO of the Buck Institute for Research on Aging from 2010 to 2016 and remains a professor at the Institute. During his tenure as head of the Buck, and in conjunction with the University of Southern California, he also launched the nation's first PhD Program in the Biology of Aging. In addition, he is an Adjunct Professor in the Davis School of Gerontology at the University of Southern California and an Affiliate Professor in the Department of Biochemistry at the University of Washington.

Dr. Kennedy's current work involves nutrient signaling pathways linked to dietary restriction, particularly the TOR pathway, which generated excitement in the age research field when it was shown recently that the drug rapamycin can extend mouse lifespan. One of the goals of his research is to determine whether pathways like TOR can be regulated to treat the diseases of aging. Specifically, Dr. Kennedy's lab focuses on cardiovascular disease and metabolic syndromes like type II diabetes. Dr. Kennedy also studies the genetic mutations underlying diseases such as dilated cardiomyopathy, muscular dystrophy and Hutchinson-Gilford Progeria Syndrome, which resembles premature aging.

More recently, Dr. Kennedy has become active in the Biotechnology and Pharmaceutical arena, serving as a consultant for several companies. He is currently on the Board of Directors of three companies, including acting as Board Chair of Mt. Tam Pharmaceuticals. He has also completed research projects for several Biotechnology companies. The primary focus of his efforts are to identify interventions that extend human health span, and to accelerate paths for their testing and implementation in humans.

Title of talk Sex Differences and Aging in the mTOR Pathway

Abstract

A working hypothesis in our laboratory is that aging leads to aberrant upregulation in the mTOR pathway in specific tissues. This findings intersects with studies in a wide range of diseases that also show elevated mTOR activation. We have developed models to explore how enhanced mTORC1 activity contributes to pathology in various contexts and believe the mechanisms are overlapping, depending on tissue, specific pathology and the age of the animal. Interestingly, we have discovered that two major substrates downstream of mTORC1, S6 Kinase and 4EBP are differentially regulated in males and females during aging, or high fat diet exposure in young animals. In females, elevated activation of S6 kinase is the predominant differences, whereas in males loss of expression of 4EBP1 is the predominant change. The latter effect is likely mediated by inflammation, which is known to be higher in male mice. I will discuss these findings in detail and describe how the findings might be used to interpret sex-specific effects of interventions that extend lifespan. Understanding how males and females age differently will be an essential step toward defining which interventions will extend lifespan and health span in humans and is an early step toward personalized aging strategies.

Christine Müller

Research Associate at the Laboratory of Gene regulation in Ageing and Age-related diseases, European Research Institute for the Biology of Ageing at the University Medical Center Groningen

Dr. Christine Müller studied biology at the Universities of Bonn and Heidelberg in Germany and received her PhD from the Humboldt-University of Berlin in 1996. Between 1996 and 2004 she was a postdoctoral fellow in the Lab of Dr. A. Leutz at the Max Delbrück Center for Molecular Medicine (MDC) in Berlin. In 2005 she joint the Lab of Dr. C. Calkhoven at the Leibniz Institute for Age Research - Fritz Lipmann Institute (FLI) in Jena, Germany and moved in 2013 together with the Calkhoven Lab to the European Research Institute for the Biology of Ageing (ERIBA) at the University Medical Center Groningen. Her research interests include the post-transcriptional control and function of C/EBP transcription factors and in particular their involvement in ageing, metabolism and cancer.

Title of talk

Reduced expression of C/EBPß-LIP extends health- and lifespan in mice

Abstract

Aging is associated with physical decline and the development of age-related diseases including metabolic disorders and cancer; conditions that can be attenuated by calorie restriction (CR). Understanding the molecular mechanisms that act downstream of CR may reveal novel therapeutic strategies to defeat aging-associated decline and diseases. We have shown earlier that translation of the C/EBPß-mRNA into the metabolic transcription factor isoform C/EBPß-LIP is stimulated by the nutrient and energy-sensitive mTORC1 pathway, which critically depends on a short upstream open reading frame (uORF) within the C/EBPß-mRNA sequence. Mice that are deficient in LIP expression through ablation of the uORF (C/EBPßΔuORF mice) display CR-like metabolic improvements, including enhanced fatty acid oxidation and lack of steatosis, improved insulin sensitivity and glucose tolerance and higher adiponectin levels (Zidek et al., 2015 EMBO Rep. DOI 10.15252/embr.201439837).

Now we present that these C/EBPßΔuORF mice show improvements in a broad spectrum of aging parameters, including cancer incidence, motor coordination, glucose tolerance and memory/naïve T-cell ratio. Moreover, liver transcriptome analysis revealed that old C/EBPßΔuORF mice show less inter-individual variation in expression of particularly metabolic genes compared to old wt mice, indicating a delay in aging-associated heterogeneity in gene expression in C/EBPßΔuORF mice. Finally, we show that female C/EBPßΔuORF mice display an extended median lifespan of 20.6% and an increase in maximum lifespan of 9%. Our data demonstrate an important role of C/EBPß in the aging process and suggest that restriction of LIP expression sustains health and fitness during aging.

Peter Tessarz

Max Planck Institute for Biology of Ageing, Cologne

Peter Tessarz obtained his PhD from the University of Heidelberg, Germany for his work on the role of AAA+ proteins in the heat shock response in S. cerevisiae. He then joined the lab of Tony Kouzarides at the Gurdon Institute of the University of Cambridge, UK where he worked on a new type of histone modification that specifically depends on RNA Pol I transcription. In 2014 he was appointed as a group leader at the Max Planck Institute for Biology of Ageing where he set up his independent lab. The research interests of his lab are the interplay between chromatin architecture and transcription and the regulation of chromatin structure by metabolism.

Title of talk

Integration of metabolic and epigenetic regulation of stem cell fates in health and ageing

Abstract

Stem cells reside in niches, in which specific extracellular matrix components, growth factors, assisting cells and oxygen levels provide the very specific environments that preserve their stem cell phenotype and help maintain their pool. Mesenchymal stem cells (MSCs) are adult multipotent stem cells, able to differentiate into adipocytes, osteoblasts or chondroblasts. MSCs reside in the endosteum of the bones, where oxygen levels range from 1.8 to 2.9%. In this hypoxic niche, low oxygen levels promote glycolysisdependent energy metabolism, which is associated with quiescent, undifferentiated cellular states. Epigenetic enzymes deposit or remove chromatin methylation, acetylation and other marks, regulating transcription and hence cellular phenotypes. These enzymes require co-factors and/or substrates: metabolites, whose cellular levels are tightly tied to the cell‘s energy metabolism.

Here, we investigate how the hypoxic niche preserves stem cell state through the regulation of metabolism and its connection to the epigenome. We use changes in oxygen tension to address this question. We will discuss ongoing experiments that aim at unraveling the crosstalk between niche, metabolism and epigenetics.

Session 5

Autophagy and Immunity

Speakers
David Rubinsztein
Katja Simon
Andre Nussenzweig
Manolis Pasparakis

Chair
Fulvio Reggiori

David Rubinsztein

Cambridge Institute for Medical Research, Cambridge, United Kingdom

David Rubinsztein did a BSc(Med) Hons and PhD at the University of Cape Town after his basic medical training and housejobs. He came to Cambridge in 1993 as a senior registrar in Genetic Pathology. He is currently deputy director of the Cambridge Institute for Medical Research and Academic Lead of the Alzheimer's Research UK Cambridge Drug Discovery Institute.

Rubinsztein has published more than 350 papers, which have an h index of 107 and >50,000 citations (Google Scholar), and was selected as a Thomson Reuters' Highly Cited Researcher. He was elected as a Fellow of the Academy of Medical Sciences (2004), Professor of Molecular Neurogenetics (University of Cambridge, personal chair (2005)), as an EMBO member (2011) and a Fellow of the Royal Society (2017). He was awarded the Graham Bull Prize for Clinical Science (Royal College of Physicians, 2007) and the 2017 Thudichum Medal (Biochemical Society) for outstanding contributions to neuroscience.

Title of talk

Autophagy and neurodegeneration

Abstract

Intracellular protein aggregation is a feature of many late-onset neurodegenerative diseases, including Parkinson's disease, tauopathies, and polyglutamine expansion diseases (like Huntington's disease (HD)). Many of these mutant proteins, like that causing HD, cause disease via toxic gain-of-function mechanisms. Therefore, the factors regulating their clearance are crucial for understanding disease pathogenesis and for developing rational therapeutic strategies.

The two major intracellular protein degradation pathways are the ubiquitin-proteasome system and (macro)autophagy. Autophagy is initiated by double-membraned structures, which engulf portions of cytoplasm. The resulting autophagosomes ultimately fuse with lysosomes, where their contents are degraded.

I will briefly describe the basic biology of autophagy before outlining its roles in neurodegeneration. We showed that the autophagy inducer, rapamycin, reduced the levels of mutant huntingtin and attenuated its toxicity in cells, and in Drosophila and mouse HD models. We have extended the range of intracellular proteinopathy substrates that are cleared by autophagy to other related neurodegenerative disease targets, like Parkinson's disease. While autophagy induction is protective in models of various neurodegenerative diseases, certain other conditions are associated with compromised autophagy. I will discuss how genetic variants in Parkinson's disease and Alzheimer's disease impact on autophagosome biogenesis and then focus on recent work describing the roles of polyglutamine stretches in autophagy regulation.

Katja Simon

Kennedy Institute of Rheumatology
Oxford University

Katja Simon is Professor at Oxford University (UK) and principal investigator at the Kennedy Institute of Rheumatology, studying autophagy in immunity and hematopoiesis. She trained as an Immunologist at the DRFZ Berlin and found excessive TH1 cytokines in the human autoimmune disease rheumatoid arthritis in her PhD (EULAR Award). As a postdoc at the CIML Marseille, she discovered distinct transcription factors regulate thymic cell death. During her second postdoc in Oxford she pursued her interest in cell fate, studying cell death molecules in thymic selection, inflammation and tumour immunity. Her independent line of enquiry as a principal investigator focuses on autophagy in the hemato-immune system. Her group discovered that autophagy, the main conserved cellular bulk degradation pathway improves healthy cellular differentiation, maintains stem cells and memory T cells. She found that autophagy is key for the prevention of ageing of the hematopoietic system. She is a Wellcome Trust investigator.

Title of talk

Autophagy and immune ageing

Abstract

With extension of the average lifespan, ageing has become a heavy burden in society. Immune senescence is a key risk factor for many age-related diseases such as cancer, neurodegeneration and increased infections in the elderly, and hence, has elicited much attention in recent years. As our body's guardian, the immune system maintains systemic health through removal of pathogens and damage. Autophagy is an important cellular "clearance" process by which a cell internally delivers damaged organelles and macromolecules to lysosomes for degradation. Here, we discuss the most current knowledge of how impaired autophagy can lead to cellular and immune senescence.
We will provide an overview, with examples, of the clinical potential of exploiting autophagy to delay immune senescence and/or rejuvenate immunity to treat various age-related diseases.

Andre Nussenzweig

Center for Cancer Research, NIH

Dr. Andre Nussenzweig's research program is in the Laboratory of Genome Integrity at the National Institutes of Health, where he has been a tenured investigator for the past 14 years and Laboratory Chief for the past six. The Nussenzweig lab is focused on the exploration of the causes and consequences of genomic instability, mechanisms of DNA repair and the study of DNA repair breakdown as an initiating or protective event in aging and cancer. Dr. Nussenzweig's program has historically emphasized a mechanistic understanding of the pathways that maintain genomic integrity and how these pathways intersect with normal cellular physiology and cancer. His program is continually mindful that the primary application of these insights should lead to the development of new therapeutic strategies in cancer treatment.

Dr. Nussenzweig's record of career-high achievements in the study of DNA damage/repair has led to his recently designated title of "NIH Distinguished Investigator".

Title of talk

Genome Organization Drives Chromosome Fragility

Abstract

We show that evolutionarily conserved chromosome loop anchors bound by CTCF and cohesin are vulnerable to DNA double strand breaks (DSBs) mediated by topoisomerase 2B (TOP2B). Polymorphisms in the genome that redistribute CTCF/cohesin occupancy concomitantly rewire DNA cleavage sites to novel loop anchors. While transcription- and replication-coupled genomic rearrangements have been well documented, we demonstrate that DSBs at loop anchors are largely transcription-, replication-, and cell type- independent. DSBs are continuously formed throughout interphase, are enriched on both sides of strong topological domain borders, and frequently occur at breakpoint clusters commonly translocated in acute leukemias and prostate cancers. Thus, loop anchors serve as preferred and promiscuous fragile sites that generate DSBs and chromosomal rearrangements.

Manolis Pasparakis

Institute for Genetics at the CECAD University of Cologne

Manolis Pasparakis received his bachelor's and Ph.D. degrees in biology from the University of Athens, Greece. After postdoctoral training in the Institute for Genetics of the University of Cologne he started his independent research as a group leader at the Mouse Biology Programme of EMBL in Monterotondo, Italy. He became a faculty member at the Institute for Genetics of the University of Cologne in 2005, where he works since then. His research aims to understand the mechanisms regulating inflammation and the pathogenesis of inflammatory diseases and cancer. Topics of particular interest in the Pasparakis' lab include TNF receptor signaling and biology, the IKK/NF-κB pathway and its function in tissue homeostasis and disease, as well as RIP kinases and their role in cell death and inflammation.

Title of talk

Necroptosis in tissue homeostasis and inflammation

Abstract

Chronic inflammation contributes to the pathogenesis of a number of ageing associated diseases. Cell death was recognized since many years as a feature of inflamed tissues, but until recently it was considered a consequence of the ongoing immune response. Recent studies provided experimental evidence that cell death is a potent trigger of inflammation and plays a causative role in the pathogenesis of inflammatory diseases. Necroptosis, a type of necrotic cell death regulated by RIPK3 and its substrate MLKL, has been identified as a highly inflammatory cell death process. Different mechanisms have been proposed for necroptosis-driven inflammation, including the release of danger signals (DAMPs) from dying cells but also the breach of epithelial barriers. We showed previously that necroptosis of epithelial cells in the skin and the intestine resulted in severe chronic inflammatory diseases in these tissues.

Our results revealed that the interplay between IKK/NF-κB and RIPK1 signalling is critical for the regulation of necroptosis and the maintenance of tissue homeostasis. RIPK1 is modified by phosphorylation and ubiquitination and these modifications are believed to control its biological function. In particular, enzymes controlling the presence of K63- and M1-linked ubiquitin chains on RIPK1, including the E3 ligases cIAP1/2 and LUBAC and the deubiquitinating enzymes A20, CYLD and Otulin, have a critical role in regulating RIPK1 function. Our studies on the mechanisms that regulate RIPK1 function and are critical for the maintenance of tissue homeostasis and the pathogenesis of chronic inflammatory diseases will be discussed.

Session 6

(Epi) genetics and ageing

Speakers
Edwin Cuppen
Anne Brunet
Mario Baumgart
Bart Eggen
Markus Schosserer

Chair
Jan Hoeijmakers

Edwin Cuppen

Center for Molecular Medicine, University Medical Center Utrecht

Edwin Cuppen is professor of Human Genetics and runs his research lab at the Center for Molecular Medicine, University Medical Center Utrecht. Furthermore, he is director of a national sequencing center, the Hartwig Medical Foundation, in Amsterdam, which aims for the stratification of cancer patients towards targeted treatments based on whole genome measurements of the tumor and to bring these developments to all relevant cancer patients in The Netherlands in a timely and responsible manner.

He is an expert in whole genome sequence analysis and in his scientific work he combines experimental methods, including next-generation DNA sequencing and other -omics techniques, with patient cohort and cellular model systems and integrative bioinformatic approaches to understand the causes and consequences of genetic variation under normal and disease conditions like cancer and congenital disease. Edwin is a pioneer in personalized genomics, carrying his genome not only in his own cells, but also on his iPad.

Title of talk

Tissue-specific mutation accumulation in human adult stem cells during life

Abstract

The gradual accumulation of genetic mutations in human adult stem cells (ASCs) during life is associated with various age-related diseases, including cancer. Extreme variation in cancer risk across tissues was recently proposed to depend on the lifetime number of ASC divisions, owing to unavoidable random mutations that arise during DNA replication. However, the rates and patterns of mutations in normal ASCs remain unknown. We determined genome-wide mutation patterns in >50 ASCs of the small intestine, colon and liver of human donors with ages ranging from 3 to 87 years by whole genome sequencing of clonal organoid cultures derived from primary multipotent cells. Our results show that mutations accumulate steadily over time in all of the assessed tissue types, at a rate of approximately 40 novel mutations per year, despite the large variation in cancer incidence among these tissues.

Liver ASCs, however, have different mutation spectra compared to those of the colon and small intestine. Mutational signature analysis reveals that this difference can be attributed to spontaneous deamination of methylated cytosine residues in the colon and small intestine, probably reflecting their high ASC division rate. In liver, a signature with an as-yet-unknown underlying mechanism is predominant. Interestingly, mutation spectra of driver genes in cancer show high similarity to the tissue-specific ASC mutation spectra, suggesting that intrinsic mutational processes in ASCs can initiate tumorigenesis. Notably, the inter-individual variation in mutation rate and spectra are low, suggesting tissue-specific activity of common mutational processes throughout life.

Anne Brunet

Paul F. Glenn Laboratories for the Biology of Aging at Stanford University

Anne Brunet is the Michele and Timothy Barakett Professor of Genetics at Stanford University. Dr. Brunet obtained her BSc from the Ecole Normale Supérieure in Paris, France and her PhD from the University of Nice, France. She did her postdoctoral training in Dr. Michael Greenberg's lab at Harvard Medical School. Dr. Brunet is interested in the mechanisms of aging and longevity, with a particular emphasis on the nervous system. Her lab studies the genetic and epigenetic regulation of aging. She is particularly interested in neural stem cells aging. Another goal of the Brunet lab is to discover new genes and processes that regulate longevity using short-lived systems, the nematode C. elegans and the naturally short-lived African killifish. Dr. Brunet has received several grants from the National Institute on Aging. She has published over 80 peer-reviewed papers, reviews, and book chapters. She has received a number of awards, including the Pfizer/AFAR Innovations in Aging Research Award, an Ellison Medical Foundation Senior Scholar Award, and the Vincent Cristofalo Rising Star Award in Aging Research. She was awarded a Pioneer Award from the NIH Director's fund, which supports scientists of exceptional creativity.

Title of talk

Understanding and modeling aging

Abstract

Age is the greatest risk factor for most diseases, including neurodegenerative diseases, cardiovascular diseases, cancer, metabolic disorders, diabetes, and autoimmune diseases. However, our understanding of aging is still rudimentary because aging is an extraordinarily complex process that defies many conventional rules in biology. My lab aims to discover new, fundamental principles of aging regulation that can ultimately be translated to humans. We have broken new ground by pioneering the naturally short-lived African killifish as a new model to study aging and diseases in the context of aging in vertebrates.

This new model has allowed us to generate a high throughput platform to not only model diseases by also screen for the impact of genetic pathways and chemical compounds on disease. In addition to developing this fish, my lab is also using <i>C. elegans</i> and mice, as well as cells from mice and humans, to identify genetic and epigenetic mechanisms involved in the regulation of lifespan and understand their mode of action. This approach has already generated new insights on the epigenetic regulation of aging. Our work has the promise to transform our understanding of why aging is at the heart of so many human diseases.

Mario Baumgart

Leibniz Institute on Aging - FLI

Mario Baumgart received his Ph.D. in Biology in 2009 at the University of Kassel, Germany. From 2009 he worked as a postdoc in the group of Alessandro Cellerino at the Leibniz Institute on Aging - Fritz-Lipmann-Institute (FLI) in Jena, Germany, exploring the biology of aging of the short-lived Killifish N. furzeri. In 2015 he received a Temporary Positions for Principal Investigators Grant from the German Research Foundation (DFG) and is continuing his work with A. Cellerino on N. furzeri at the FLI since then.

The main current projects of the group investigate transcriptomic and proteomic changes in the aging brain, aging synapses, aging of neural stem cells and the effect on adult neurogenesis. Further projects are focused on the identification of early markers for longevity, the functional analysis of novel aging-related genes and identification of genes under positive selection.

Title of talk

Longitudinal analysis of gene expression in the short-lived killifish Nothobranchius furzeri reveals widespread pleiotropic antagonistic actions

Abstract

Mutations and genetic variability affect gene expression and lifespan, but the impact of variations in gene expression within individuals on their aging-related mortality is poorly understood. In this study, we performed a longitudinal study of genome-wide gene expression in the short-lived killifish N. furzeri by obtaining fin biopsies at two time points during early adult life and correlated variations in transcript abundance with age at death. Our aim was to assess transcriptomic predictors of lifespan at two different ages. We calculated for each gene whether its expression is a risk factor (higher expression is correlated with higher mortality) or if it is a protective factor (higher expression is correlated with lower mortality), using cox-regression analysis, separately at ages 10 and 20 weeks (corresponding to ~ 15% and ~ 30% of maximum life span). We compared this results with gene expression profiling during aging, obtained by a cross sectional study, using 5 time points covering the entire life span, and with differences in gene expression between a short and a long-lived strain at the onset of sexual maturity (5 weeks).

For the majority of genes, we found, they are either a risk factor in younger age and a protective factor in the older or vice versa. Those genes, protective at younger age, with increasing expression levels during aging and those genes, protective at older age, with decreasing expression levels during aging, are causative for aging. In conclusion, our data delivers empirical support for the antagonistic pleiotropic theory of aging.

Bart Eggen

University Medical Centre Groningen

Bart Eggen received his MSc (1989) and PhD (1995) from the University of Utrecht working on the regulation of B-50/GAP-43 gene expression. He obtained a Human Frontiers Science Program fellowship to work with Gail Mandel, HHMI, Stony Brook, New York and later with Ali Hemmati-Brivanlou, Rockefeller University, New York on the transcriptional repressor REST/NRSF. In 2000, he joined the Dept. of Developmental Genetics at the University of Groningen working on (epi)genetic regulation of ES cell pluripotency. In 2010, he moved to the Dept. of Neuroscience at the UMCG and currently serves as head of the Medical Physiology section. There his main research focus is the (epi)genetic regulation of microglia identity and function in the context of the normal brain, during aging and under neuroinflammatory or neurodegenerative conditions such as multiple sclerosis and Alzheimer's disease.

Title of talk

Transcriptomic analysis of purified human cortical microglia reveals age-associated changes

Abstract

Microglia are essential for central nervous system (CNS) homeostasis and innate neuroimmune function, and play important roles in neurodegeneration and brain aging. Here, we present gene expression profiles of purified microglia isolated at autopsy from the parietal cortex of 39 human subjects with intact cognition. Overall, genes expressed by human microglia are similar to those in mouse, including established microglia genes CX3CR1, P2YR12, and ITGAM/CD11B. However, a number of immune genes, not identified as part of the mouse microglial signature, were abundantly expressed in human microglia, including TLR, Fcg, and SIGLEC receptors, as well as TAL1 and IFI16, regulators of proliferation and cell cycle. Age-associated changes in human microglia were enriched for genes involved in cell adhesion, axonal guidance, cell surface receptor expression, and actin (dis)assembly. Limited overlap was observed in microglial genes regulated during aging between mice and humans, indicating that human and mouse microglia age differently. Nature Neuroscience, in press.

Markus Schosserer

University of Natural Resources and Life Sciences, Vienna

Markus Schosserer is postdoc/lecturer at University of Natural Resources and Life Sciences, Vienna, Department of Biotechnology, Vienna, Austria since 2012. He received his PhD in Biotechnology from the same university in 2012.

His research interests lie in the areas of biogerontology and RNA biology, with special emphasis on ribosomes and protein translation. Markus Schosserer is also interested in advanced microscopy techniques, including Raman and STED. His teaching activities include courses on Biology of Aging, Animal Cell Culture, Microscopy and Flow Cytometry.

Markus Schosserer co-authored 12 papers (August 2017) and presented his work at several national and international conferences. He won three poster prizes, two best talk awards and collaborates actively with researchers in several other disciplines of aging research and RNA/ribosome biology.

Title of talk

Two distinct ribosomal RNA base methylations modulate healthy lifespan

Abstract

The ribosome has been seen for decades as a static machine that translates mRNAs into proteins. However, over the last few years it became clear that it rather represents a highly dynamic structure that responds to various stimuli by adapting its structure and, as a consequence, its function. Such structurally distinct ribosomes are postulated to be “specialized ribosomes” comprising peculiar functional properties and are thus considered to be engaged in translating specific subsets of cellular messages. Although ribosomal RNA is heavily modified by methylations and pseudouridinylations, the functional roles of such modifications in regulating translation are not understood.

We recently reported that lack of a single, conserved C5-methylation at 25S ribosomal RNA residue C2278 alters ribosomal structure and thus translational fidelity in yeast, resulting in a ‘reprogramming’ of the ribosome towards translation of mRNAs involved in cellular stressresponse. Importantly, we showed that lack of this methylation by deletion of NSUN5 extends the lifespan and stress resistance of yeast, worms and flies (Schosserer et al., 2015). Interestingly, reduced expression of other ribosomal RNA methyltransferases in addition to nsun-5, such T07A9.8, were implicated in regulating the lifespan of Caenorhabditis elegans as well. Thus, methylation of ribosomal RNA might represent an important regulator of organismal aging, but the precise molecular mechanisms underlying this lifespan modulation have not been investigated so far. We will here present a characterization of these RNA methlytransferases regarding RNA substrate, their regulation and effects on translation. We furthermore show that their depletion improves life- and healthspan.

Session 7A

Protein homeostasis

Speakers
Mark S. Hipp
Alessandro Cellerino
Tobias Dansen

Chair
Ellen Nollen

Mark S. Hipp

Max Planck Institute of Biochemistry

Mark S. Hipp is a Group Leader in the Department of Cellular Biochemistry, headed by Prof. F. Ulrich Hartl, at the Max Planck Institute of Biochemistry in Martinsried near Munich. He studies the basic mechanisms of aggregate toxicity and tries to understand how aberrant protein folding is linked with neurodegenerative diseases, like Huntington's Disease.

Mark Hipp, studied Biochemistry in Tübingen, and previously worked as a postdoctoral fellow in the Department of Biology at Stanford University in the laboratory of Prof. Ron R. Kopito, and as graduate student at the University of Konstanz under Prof. Marcus Groettrup.

Title of talk

Proteostasis impairment in protein misfolding and aggregation diseases

Abstract

Cells possess an extensive network of components to safeguard proteome integrity and maintain protein homeostasis (proteostasis). When this proteostasis network (PN) declines in performance, as may be the case during aging, newly-synthesized proteins are no longer able to fold efficiently and metastable proteins lose their functionally active conformations, particularly under conditions of cell stress. Apart from loss-of-function effects, a critical consequence of PN deficiency is the accumulation of cytotoxic protein aggregates, which are also associated with many age-dependent neurodegenerative diseases and other medical disorders. Chronic production of aberrantly folded and aggregated proteins in these diseases is harmful by overtaxing PN capacity, setting in motion a vicious cycle of increasing proteome imbalance that eventually leads to PN collapse and cell death.

We investigated the basic mechanisms by which aggregates exert cytotoxicity in a compartment-specific manner, and analyzed the interactions between these proteins and components of the PN. To do this we used authentic disease proteins and artificial beta-sheet proteins known to form prefibrillar and fibrillar aggregates, and directed them to different cellular compartments. Expression of otherwise identical protein resulted in clearly distinguishable aggregate species that interacted with distinct subsets of the PN, which lead to large differences in aggregation mediated toxicity.

Alessandro Cellerino

Scuola Normale Superiore

Alessandro Cellerino is assistant professor of Physiology at Scuola Normale Superiore, Pisa, Italy and head of a cooperation group at the Leibniz Institute on Aging, Jena Germany.

Alessandro Cellerino has discovered the shortest-lived vertebrate that can be bred in captivity: the annual fish Nothobranchius furzeri and proposed it as a novel model organism for aging. Over the last 15 years he has studied the aging process of this novel model organism with particular emphasis on evolution of aging, brain aging, adult neuronal stem cells and regulation of longevity. More recently, he focussed his activity on high-through put technologies and transgenesis to identify novel genetic mechanisms controlling aging.

Title of talk

Proteomic analysis of brain aging reveals reduction of protein/transcript correlation, loss of stoichiometry in multiple protein complexes and changes in protein thermal stability

Abstract

A large number of studies investigated the effects of aging on transcript regulation but how these changes translate into protein levels is unclear. Here, we used the short-lived killifish N. furzeri as model system, and combined high-resolution mass spectrometry-based proteomics with RNAsequencing and a novel approach for high-throughput measurement of protein stability to characterize proteome dynamics during brain aging. This is the first study of this kind in the context of vertebrate aging.

The main results of the study are: Proteome changes during brain aging are widespread. Correlation between protein abundance and transcript level is reduced during aging and there are many cases of protein down regulation despite transcript up regulation. These “discordant” proteins are highly enriched for functions related to biosynthesis of macromolecules such as RNA processing and translationSeveral protein complexes, such as the ribosome, loose their stoichiometry during aging with some subunits being up regulated and others down regulatedAging is associated with changes in protein thermal stability that may underlie age-dependent protein aggregation or changes in post-translational modification Finally, by comparing a short-lived and a longer-lived strain, we find that age-related proteome changes are anticipated in the short-lived strain providing evidence for the fact that these proteomic changes are lifespan associated. In summary, our work defines a subset of protein networks that are affected during aging as a consequence of failure in proteostasis systems. These networks are likely to have a central role in the decline of cognitive function and neurodegenerative processes during aging.

Tobias Dansen

UMC Utrecht

Tobias Dansen studied Chemistry at Utrecht University (NL) and has ever since been fascinated by the molecular mechanisms underlying protein function, as well as how these molecular mechanisms subsequently determine life and death of a cell and eventually the organism. After his PhD (Biochemistry, Utrecht University) he decided that he wanted to continue working at the boundary between chemistry and biology and to learn more about the latter he worked as a post-doc in the lab of Gerard Evan (tumor biology) at the Comprehensive Cancer Center of the University of California at San Francisco. After a second post-doc in the group of Boudewijn Burgering (FOXO transcription factors) he started his own independent research line on the role of Redox Signaling in the biology of cancer and aging at the University Medical Centre Utrecht. What characterizes his research is a multidisciplinary approach using a wide range of techniques and model systems.

Title of talk

Proteome-wide Changes in Protein Turnover Rates in C. elegans Models of Longevity and Age-Related Disease

Abstract

The balance between protein synthesis and protein breakdown is a major determinant of protein homeostasis, and loss of protein homeostasis is one of the hallmarks of aging. Here we describe pulsed SILAC-based experiments to estimate proteome-wide turnover rates of individual proteins. We applied this method to determine protein turnover rates in Caenorhabditis elegans models of longevity and Parkinson's disease, using both developing and adult animals.

Whereas protein turnover in developing, long-lived daf-2(e1370) worms is about 30% slower than in controls, the opposite was observed in day 5 adult worms, in which protein turnover in the daf-2(e1370) mutant is twice as fast as in controls. In the Parkinson's model, protein turnover is reduced proportionally over the entire proteome, suggesting that the protein homeostasis network has a strong ability to adapt. The findings shed light on the relationship between protein turnover and healthy aging.
We are currently extending the pulsed-SILAC method to colorectal cancer organoids to study how proteostasis is altered in light of aneuploid genomes.

Session 7B

Protein homeostasis

Speakers
Giovanna Mallucci
Collin Ewald

Chair
Ellen Nollen

Giovanna Mallucci

Department of Clinical Neurosciences, university of Cambridge

Giovanna Mallucci is Professor of Clinical Neurosciences at the University of Cambridge Her undergraduate degrees were in Physiological Sciences and Medicine from the University of Oxford, with clinical training at University College, London. She obtained her PhD from London University in Neurogenetics, for which she generated the first adult-onset mouse model of prion protein knockout that paved the way to her discoveries about reversibility of early neurodegeneration and underlying mechanisms. Since her PhD she has combined clinical work and basic research and led groups in the MRC Prion Unit (2001-2008) and the MRC Toxicology Unit, where she is Head of Neurobiology (2008-present), before moving to Cambridge. Her lab is pioneering interventions targeting common pathways for treatment of dementia. She has received numerous national and international awards for her work, including a SciAm50 award for leadership in research as one of the top 50 scientific innovators worldwide, and has given many plenary and keynote talks at international conferences. She is an ERC Consolidator Fellow and a Fellow of the Academy of Medical Sciences. In March 2017, she was selected as Associate Director of the UK Dementia Research Institute at the University of Cambridge, where she will be Scientific Director. She is an Honorary Consultant Neurologist at Addenbrooke's Hospital and a practicing clinician, specialising in Dementia.

Title of talk

Manipulating the Unfolded Protein Response for treatment of neurodegeneration

Abstract

My lab focuses on the identification of common pathways across the spectrum of neurodegenerative disorders (which include Alzheimer's and related diseases) relevant for both mechanistic insights and therapy. I will focus on our work modulating the Unfolded Protein Response pharmacologically in mouse models, including and the recent discovery of repurposed drugs ready for clinical trials.

Collin Ewald

ETH Zurich

Collin Ewald completed his PhD in Neuroscience in New York working on Alzheimer's disease. Collin did his post-doctoral training with Keith Blackwell at Harvard Medical School discovering how insulin/IGF-1 signalling prolongs extracellular matrix maintenance (Ewald et al., Nature 2015). After a short junior faculty position at the Joslin Diabetes Center and as an Instructor in Medicine at Harvard Medical School working on how NADPH-oxidase-mediated ROS production affects aging (Ewald et al., eLife 2017), Collin returned to Switzerland to join the Institute for Translational Medicine (ITM) as an assistant professor at ETH Zurich focusing his research on the role of the extracellular matrix during aging (www.ewaldlab.com). Collin is the co-founder and currently the president of the Swiss Society for Aging Research (www.ssfar.ch). Collin has received multiple awards, including the DeLill Nasser Award, the Ellison Medical Foundation and American Federation for Aging Research fellowship and the Swiss National Science Foundation professorship.

Title of talk

Preferential translation of ATF-5 mediates Caenorhabditis elegans lifespan extension from reduced protein synthesis

Abstract

Organisms respond to stress by reducing overall protein synthesis. Decreasing the level of protein synthesis per se is sufficient to increase the lifespan of yeast, fruit flies, and C. elegans. Here, we show that lifespan extension from reduced translation in C. elegans is mediated through activation of the bZIP transcription factor ATF-5. ATF-5 is the orthologue of yeast GCN4 and mammalian ATF4, which are important in the unfolded protein response. When protein translation is reduced globally in C. elegans, ATF-5 is translated preferentially.

Inhibition of translation increases C. elegans lifespan in an atf-5-dependent manner, and ATF-5 overexpression is sufficient to increase lifespan. Interestingly, preferential translation of ATF-5 is required for lifespan extension when either the mTORC1 or mTORC2 kinase complexes is inhibited. To gain insights into downstream mechanisms that are activated when ATF-5 is preferentially translated, we compared the expression profile of long-lived ATF-5 overexpression animals to wild type and found an upregulation of a very narrow subset of genes that included extracellular matrix genes and small heat-shock chaperones. Consistent with this, RNAi knockdown of small heat shock chaperones or of the heat shock transcription factor (HSF-1) blunts the ATF-5 overexpression-mediated longevity. Our results identify activation of ATF-5 and the heat shock response as essential protective mechanisms that promote longevity when global protein translation is reduced. Furthermore, several long-lived mice models also show higher ATF4 protein levels indicating that in mammals a similar mechanism might be conserved.

Date
October 10

Time
3:00 pm

Session 8

Stem cells

Speakers
Thomas Rando
Allison Bardin
Allesandro Ori

Chair
Gerald de Haan

Thomas Rando

Stanford Centre on Longevity

Thomas A. Rando, MD, PhD is Professor of Neurology and Neurological Sciences and Director of the Glenn Laboratories for the Biology of Aging at Stanford University School of Medicine. Research in the Rando laboratory concerns the basic biology of stem cells, how stem cells function in adult tissue homeostasis, and how their function is altered in degenerative diseases and during aging. Groundbreaking work from his laboratory, using heterochronic parabiosis, showed that the age-related decline in stem cell function is due to influences of the aged environmental. Dr. Rando has received numerous awards, including a Paul Beeson Physician Faculty Scholar in Aging, a Senior Scholar Award from the Ellison Medical Foundation, and a “Breakthroughs in Gerontology” Award from the American Federation for Aging Research. He is a recipient of the received the prestigious NIH Director’s Pioneer Award for his work at the interface between stem cell biology and the biology of aging, and he received a Transformative Research Award from the NIH for studies of the mechanisms of the enhancement of cognitive function by physical activity and changes that occur in this “muscle-brain axis” that occur during aging. Dr. Rando is an elected member of the National Academy of Medicine.

Title of talk

Epigenetics Mechanism of stem cell aging and rejuvenation

Abstract

There is an age-dependent decline in stem cell functionality in many tissues. Many molecular, biochemical, and functional features of stem cells have been characterized, and these changes have been assumed to be largely irreversible and inevitable accompaniments of aging. Supported by data from studies of heterochronic parabiotic pairings of mice, it is clear that the aged phenotype can be modified when aged cells are exposed to a youthful systemic milieu. These findings raise the question as to what extent, the aged phenotype is epigenetically determined. We have found changes in patterns of chromatin modification that occur during the aging of quiescent stem cells.

In particular, there is a marked increase in the enrichment of the repressive mark, H3K27me3, at transcription sites along the genome, a change that we also observed as quiescent stem cells activate and enter the cell cycle. We have sought to correlate these epigenetic changes with both transcriptional changes and higher order chromatin structure to better define cellular age at a molecular level. Elucidating the underlying epigenetic features of aged stem cells will provide a framework for understand the fundamental molecular mechanisms of aging and the mechanisms by which environmental influences can reverse the aged phenotype.

Allison Bardin

Genetics and Developmental Biology Center at Institute Curie

Allison Bardin received a B.A. in Biochemistry from the University of California, Berkeley and a Ph.D. in Biology from the Massachussetts Institute of Technology, where she did doctoral work on cell cycle regulation in budding yeast with Dr. Angelika Amon. For her post-doctoral work, she went abroad to the lab of Dr. Francois Schweisguth in Paris, France. There, using the Drosophila model system, she investigated mechanisms of Notch signaling and cell fate control. Since late 2010, she has directed a research group at the Institut Curie focusing on regulation of cell fate and genome stability of Drosophila adult intestinal stem cells. Studies from the team demonstrated frequent genome alteration of stem cells through mitotic recombination, gene deletion and large-scale genome rearrangement leading to selection of neoplastic cells. The lab is currently exploring the nature and consequences of genome-instability in stem cells during aging.

Title of talk

Modes of genome alteration of adult stem cell during aging

Abstract

During development and aging, mistakes are made, leading to genome alteration and somatic mosaicism within adult tissues. What are they nature of these mistakes? How do they affect the resulting tissue? Our recently published work (Siudeja, Cell Stem Cell, 2015) used genetic assays and whole-genome sequencing to demonstrate that mutations arise frequently in adult Drosophila intestinal stem cells. Our ongoing studies to understand somatic stem cell mutation will be presented.

Allesandro Ori

Leibniz Institute on Aging – Fritz Lipmann Institute (FLI)

Dr. Alessandro Ori earned a master degree in medical biotechnology from the University of Bologna and a PhD in biochemistry from the University of Liverpool. Dr. Ori was a postdoctoral fellow at the European Molecular Biology Laboratory in Heidelberg in the laboratory of Martin Beck. During his postdoc, he applied mass spectrometry based proteomics to answer fundamental questions in the fields of structural and systems biology. Dr. Ori has pioneered the integration of genomic and proteomic data to study the impact of aging on the mammalian proteome. He joined the Leibniz Institute on Aging – Fritz Lipmann Institute (FLI) in Jena in September 2015 where he is heading a junior research group. His current research aims at the identification of molecular networks altered by aging with a particular focus on adult stem cells and their interaction with the niche.

Title of talk

Age and diet affect the intestinal crypt proteome

Abstract

The small intestine is responsible for nutrient sensing and absorption, and it is one of the most important interfaces between the environment and our body. During aging, deregulation of intestinal stem cell (ISC) activity leads to loss of epithelial barrier function, food malabsorption and dysbiosis of commensal bacteria. In order to investigate both cell intrinsic and extrinsic factors influencing ISC aging, we isolated crypts and stem cells from the small intestine of mice and D. melanogaster midgut. We compared proteomic profiles of tissues and cells from different age groups using state-of-the-art mass spectrometry. We found proteome signatures in the intestinal epithelium, which indicate that aging affects metabolic networks, stem cell proliferation, and epithelial immune responses.

Of note, some of these aging-associated alterations (e.g., immune modulatory responses) are reverted by dietary restriction (DR), a health span extending intervention conserved across species. In particular, we found that both aging and DR influence the expression of a key enzyme in ketone body metabolism, and demonstrate that perturbation of its activity as well as the exogenous supplementation of ketone bodies can influence ISC regeneration in organoid cultures. Our data demonstrate how aging and dietary intervention can modulate metabolic networks and influence stem cell activity by altering the concentration of metabolites in the niche.

Session 9

Cellular senescence

Speakers
Manuel Serrano
Sheila A. Stewart
Peter de Keizer
Peter Bruno
Sélène Glück

Chair
Marco Demaria

Manuel Serrano

Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain

Manuel Serrano is a researcher at the Spanish National Cancer Research Centre (CNIO), in Madrid, and Director of the Molecular Oncology Program of the CNIO. Manuel Serrano performed his PhD in Madrid, in the Centre of Molecular Biology (CBM), under the supervision of Margarita Salas. Manuel Serrano joined the laboratory of David Beach, at Cold Spring Harbor Laboratory, NY, USA, as postdoctoral fellow from 1992 to 1996. During this time, Manuel Serrano made two of his most important contributions, namely, the discovery of the tumor suppressor p16, and the characterization of the cell response known as oncogene-induced senescence. In 1997, Manuel Serrano established his research group in Madrid, first in the National Centre of Biotechnology (CNB), and since 2003 in the Spanish National Cancer Research Centre (CNIO). The main contributions of the Serrano´s laboratory are related to the concept of senescence and the anti-aging activity of tumor suppressors. More recently, Serrano´s group has worked on the connection between tumor suppressors and metabolism, and it has demonstrated the feasibility of embryonic reprogramming within live adult organisms (this last discovery was considered “Advance of the Year 2013 by Nature Medicine”).

Title of talk

Integrating cellular senescence and reprogramming

Abstract

Reprogramming of differentiated cells into pluripotent cells can occur in vivo, but essentially nothing is known about the mechanisms, processes, and mediators involved. We have generated mice where we can induce ubiquitous expression of the four Yamanaka reprogramming factors. These factors, when expressed continuously during 1 week, produce widespread de-differentiation in multiple tissues. Upon switching off the reprogramming factors, de-differentiated tissues re-differentiate and homeostasis is restored. We have found that senescence participates in the process of in vivo reprogramming. Senescence is a cellular response to damage characterized by an abundant production of cytokines and other extracellular factors, which recruit inflammatory cells and can orchestrate tissue remodeling. I will present an integrated view of tissue repair whereby tissue injury, through senescence, primes surviving cells to undergo partial reprogramming and initiate tissue repair.

Sheila A. Stewart

Department of Cell biology and Physiology at the Washington University of St. Louis

Dr. Stewart is a Professor in the Department of Cell Biology and Physiology and Medicine at Washington University in St. Louis and is the Associate Director for Basic Science at the Siteman Cancer Center. She received her Ph.D. in Microbiology and Immunology from UCLA in 1997, and completed her postdoctoral fellowship in Cancer Biology at the Whitehead Institute at MIT in Robert Weinberg's laboratory. Dr. Stewart is an American Cancer Society Scholar and research is focused on understanding how age-related changes in the tumor microenvironment impact tumorigenesis. Her laboratory has shown that aged stromal cells, similar to cancer associated fibroblasts express a plethora of pro-tumorigenic factors, many of which are subject to post-transcriptional stabilization. Importantly Dr. Stewart is now targeting this stabilization mechanism in preclinical models of breast cancer. In addition, recent focus in the laboratory is examining how age-related changes in the premetastatic niche facilitate tumor cell seeding and outgrowth in the bone and how these changes alter the local immune response to facilitate tumor cell proliferation as well as tumor cell dormancy.In addition, using the BubR1 progeroid model, the van Deursen lab was the first to show an in vivo link between p16-induced cellular senescence and the development of age-related pathologies. Then, in collaboration with several laboratories in the Kogod Center on Aging, including the Kirkland and the LeBrasseur labs, his lab went on to show that clearance of p16-positive senescent cells from BubR1 progeroid mice delays the onset of age-related disease, further confirming the causal link between senescence and aging and demonstrating that removal of senescent cells can prevent or delay tissue dysfunction and extend healthspan.

Title of talk

Age-related changes in the tumor microenvironment drive tumorigenesis

Abstract

Age is a significant risk factor for the development of cancer. The mechanisms that drive this risk are complex and involve both the accumulation of cell autonomous mutations within incipient tumor cells as well as pro-tumorigenic changes in the tumor microenvironment. Investigation into the impact of an aging microenvironment on tumorigenesis has revealed that senescent stromal cells can directly stimulate preneoplastic and neoplastic growth. Because senescent cells accumulate with age, these observations raise the possibility that senescent cells are an important contributor to age-related increases in tumorigenesis. To understand how senescent stromal cells contribute to tumorigenesis, we developed the FASST mouse (Fibroblasts Accelerate Stromal-Supported Tumorigenesis) that allows us to control the spatial and temporal activation of senescence in mesenchymal cells.

Using this mouse, we found that senescent cells impact tumorigenesis by directly altering the local microenvironment. Indeed, reactive stromal cells within the bone drove localized increases in osteoclastogenesis, which facilitated tumor cell seeding to the bone. In addition, senescent stromal cells modulate the immune response creating localized areas of immune suppression that shelter incipient tumor cells and allows their outgrowth. This is in contrast to what is described for senescent tumor cells, which elicit immune cell mediated tumor cell clearance. These findings underscore the importance of context: where, when and to what extent senescence is invoked can drastically alter its impact on tumorigenesis. Mechanisms that drive these local changes will be discussed. These findings suggest that senescent stromal cells, which accumulate in a tissue with age, contribute to tumorigenesis by altering the local microenvironment.

Peter de Keizer

Department of Genetics, Erasmus MC Rotterdam

Peter de Keizer received his PhD from Utrecht University Medical Center in 2009 for his work on FOXO transcription factors in tumor suppression. He received his postdoctoral training at the Buck Institute for Research on Aging in Novato, CA, USA on the molecular hallmarks of cellular senescence. His research focusses on the role of senescence in aging and cancer. Senescence has been causally linked to age-related diseases, but not therapeutic methods exist to remove senescent cells from an organism. His goal is to develop these, something which he dubbed TASC (Targeted Apoptosis of Senescent Cells). His second focus lies on targeting chemoresistance in metastatic cancer. He found certain senescence-associated proteins to be associated with therapy resistance and developed methods to overcome this. In 2010 he was elected as a fellow of the Dutch Cancer Society (KWF) and in 2014, he was awarded the prestigious “Talent Extraordinary Award” from the Erasmus University Medical Center.

Title of talk

Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging

Abstract

Senescent cells accumulate with age and are thought to impair tissue function by permanently arresting their neighboring cells in a chronic state of stemness. Genetic clearance of senescent cells delays features of aging and identifying how senescent cells avoid apoptosis would allow for the prospective design of anti-senescence compounds to address whether homeostasis can also be restored. We identified FOXO4 as a pivot in senescent cell viability and designed a D-Retro-Inversed FOXO4 peptide, FOXO4-DRI, which selectively perturbs the FOXO4 interaction with p53. In senescent cells, this selectively causes p53 nuclear exclusion and cell-intrinsic apoptosis. Excitingly, under conditions where it was well tolerated in vivo, FOXO4-DRI neutralized Doxorubicin-induced chemotoxicity. Moreover, it restored fitness, fur density and renal function in both fast aging XpdTTD/TTD and naturally aged mice. Thus, therapeutic targeting of senescent cells is feasible under conditions where loss of health has already occurred and in doing so tissue homeostasis can effectively be restored. Current research is focused on better understanding the potential long-term dangers of senescence-clearance and the molecular mechanisms that dictate sensitivity or resistance to the FOXO4-DRI.

Peter Bruno

Harvard Medical School

Dr. Peter Bruno is an HHMI Fellow of The Jane Coffin Childs Memorial Fund for Medical Research studying senescence and DNA damage in the laboratory of Dr. Stephen Elledge. He completed his Ph.D. in the laboratory of Dr. Michael Hemann at the Massachusetts Institute of Technology in 2016 where he used functional genetics to evaluate chemotherapy mechanisms of action and resistance. He graduated summa cum laude from University of California, San Diego in 2010 with a B.S. in Molecular Biology.

Title of talk

Functional genetic characterization of senescence induction

Abstract

Senescence is an irreversible cell state characterized by permanent exit from the cell cycle that occurs in response to cellular stresses such as shortened telomeres and DNA damage. Thus, senescent cells accumulate as an organism ages. Senescence is accompanied by the senescence associated secretory phenotype (SASP), in which the secreted factors can impart dramatic changes to the microenvironment. Importantly, it has been shown that elimination of senescent cells in old mice extends healthy lifespan. Therefore, achieving a better understanding of the genetic underpinnings of senescence can lead to improved prevention and treatment of aging-related diseases.

It's currently thought that senescence is mediated by three distinct pathways, characterized by their primary facilitators: p53, p16, and GATA4. However, few unbiased genome-scale approaches have been employed to study senescence. To examine senescence induction, we have taken advantage of a senescence reporter, miR146a-GFP, to isolate GFP-expressing senescent IMR90 fibroblasts after introduction of genome-scale ORF libraries. This has identified genes whose expression is sufficient to mediate induction of senescence. Furthermore, we are examining the relationship between the newly identified genes and the previously characterized senescence pathways. We're doing this by testing induction of senescence via expression of the newly identified genes after CRISPR-Cas9 mediated knockout of each of the primary senescence facilitators, and after inhibition of ATM/ATR function. Independence of these pathways would suggest a role for a novel fourth branch of senescence induction. Discovery of novel mediators of senescence will deepen our understanding of ageing and open new avenues for the development of therapeutics.

Sélène Glück

École Polytechnique Fédérale de Lausanne

Selene Glück obtained her Master degree in Virology at the University of Zurich (Switzerland) under the supervision of Catherine Eichwald and Mathias Ackermann. She studied the cell cycle during the rotavirus infection. Afterwards, she worked as a research scientist in the Center of Experimental Rheumatology in Zurich (Switzerland) where she studied the epigenetic modifications in rheumatoid arthritis. In 2015, she joined the group of Andrea Ablasser at the EPFL (Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland) to do her PhD.

Her major research are the innate immune sensing of endogenous DNA and the function of the Cgassting pathway during senescence. She observed that cGAS promotes senescence through sensing of cytosolic chromatin fragments. Her work has recently been published in July 2017 in Nature Cell Biology (Glück et al., 2017).

Title of talk

Innate immune sensing of cytosolic chromatin fragments through cGAS promotes senescence

Abstract

Cellular senescence is triggered by various distinct stresses and characterized by a permanent cell cycle arrest. Senescent cells secrete a variety of inflammatory factors, collectively referred to as the senescence-associated secretory phenotype (SASP). The mechanism(s) underlying the regulation of the SASP remains incompletely understood. Here we define a role for innate DNA sensing in the regulation of senescence and the SASP. We find that cyclic GMP-AMP synthase (cGAS) recognizes cytosolic chromatin fragments (CCFs) in senescent cells. The activation of cGAS, in turn triggers the production of SASP factors via Stimulator of interferon genes (STING), thereby promoting paracrine senescence. We demonstrate that diverse stimuli of cellular senescence engage the cGAS-STING pathway in vitro and we show cGAS-dependent regulation of senescence upon irradiation and oncogene activation in vivo. Our findings provide insights into the mechanisms underlying cellular senescence by establishing the cGAS-STING pathway as a crucial regulator of senescence and the SASP.

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Y

Yang, Daozheng — European Research Institute for the Biology of Ageing, UMCG — Poster 81
Epigenetic alterations in histone modifications of murine young and old hematopoietic stem cells

Yu, Wei-hsuan - National Taiwan University, College of Medicine — Poster 95
Proteolytic Nucleus envelope protein, lamin B1 fragments translocating into mitochondria involved in the EGFR axes modulate mitochondria proliferation

Z

Zaini, Mohamad Amr — European Research Institute for the Biology of Ageing, UMCG — Poster 6
A p300 and SIRT1 regulated acetylation switch of C/EBPa controls mitochondrial function

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