Friday, 06.11.2009

16:30 – 17:00 Registration and Welcome

17:00 – 17:30 ***Keynote*** **Thomas Langer (Köln)** Mitochondrial Dysfunction and Neurodegeneration

17:30 – 18:00 **Michael Ristow (Jena)** – Promoting Longevity by Increasing Oxidative Stress

18:00 – 19:00 **DNA damage and Aging**

Lenhard K. Rudolph (Ulm) – DNA damage in Stem Cell Aging

Björn Schumacher (Köln) – DNA damage in aging and longevity

Zhao Qi Wang (Jena) – DNA Damage Response Molecule MCPH1 Regulates the Neuroprogenitor Division Mode

Mark Berneburg (Tübingen) – Proteins of Nucleotide Excision Repair and Base Excision Repair Interact in Mitochondria to Protect from a Hallmark of Aging: Loss of Subcutaneous Fat

19:30 Dinner

21:00 Bar

Saturday, 07.11.2009

09:00 – 09:30 ***Keynote*** **Rudi Westendorp (Leiden, NL)** Various ways to become longlived

09:30 – 11:00 **Stress responses in Aging**

Almut Nebel (Kiel) – Fox – O – Hunting: FOXO3A, a novel longevity gene in humans

Peter Schröder (Düsseldorf) – There is More Coming from the Sun than just UV: Infrared A radiation induced signaling leads to skin aging

Alexander Bürkle (Konstanz) – Towards Identification of Biomarkers of Human Aging: The EU FP7 project MARK-AGE

Ruth Greußing (Innsbruck, A) – Mechanisms of UVB Induced Premature Senescence: A Systems Biology Approach

Thomas von Zglinicki (Newcastle, UK) – Cell Senescence in ageing mice

11:00 – 11:30 Coffee break

11:30 – 11:45 **Prof. Andreas Simm (Halle)** - News from the DGGG

11:45 – 12:00 **Dr. Simone Müller (DFG)** – Funding Opportunities in Geriatric Research and Geronotology

12:00 – 13:15 **Model Systems**

Alessandro Cellerino (Jena) – Annual Fish as a Model System to Study the Genetic Basis of Lifespan Evolution in Natural Populations

Jörg Großhans (Göttingen) – Farnesylated Nuclear Proteins Kugelkern and Laminin B Promote Aging – Like Phenotypes in Drosophila Flies

Thorsten Hoppe (Köln) – Ubiquitin Chain Editing Modulates Protein Homeostasis and Aging

Anna von Mikecz (Düsseldorf) – Nanoparticles Induce Age-Related Neural Phenotypes in Cell Culture and *Caenorhabditis elegans*

Henri Jasper (Rochester, USA) – Drosophila Intestinal Stem Cell Aging -

13:15 – 14:15 Lunch

14:15 – 14:45 ***Keynote*** **Jean Krutmann (Düsseldorf)** New Insights into the Pathogenesis of Extrinsic Skin Aging

14:45 – 15:15 ***Keynote*** **Adam Antebi (MPI – Köln)** Nuclear receptor control of life plan and life span

15:15 – 16:15 **Mitochondria**

Norbert Dencher (Darmstadt) – Changes in mitochondrial protein profile and in the supramolecular architecture of respiratory chain complexes: A clue in Ageing!?

Judith Haendeler (Düsseldorf) – Functions of Newly Discovered Proteins in the Mitochondria – Role in Senescence, Apoptosis and Migration of Endothelial Cells

Gabriele Saretzki (Newcastle, UK) – The potential role of mitochondrial telomerase for cellular survival, aging and longevity

Rudolf Wiesner (Köln) – Accumulation of mtDNA Deletions during Aging

16:15 Final Discussion and Departure

16:30 – 17:00 DGfA General Meeting

Maternushaus Köln
Kardinal-Frings-Str. 1-3
50668 Köln
E-Mail : info@maternushaus.de
Telefon : 0221 / 16 31- 0
Fax : 0221 / 16 31- 215

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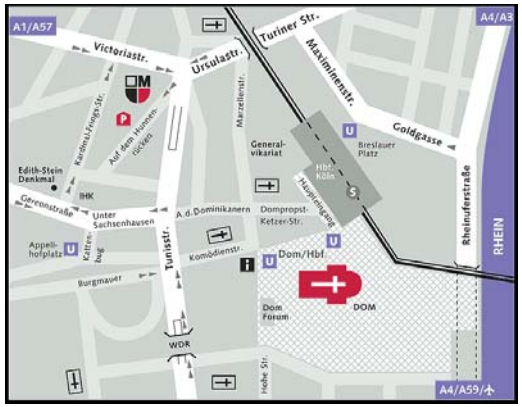
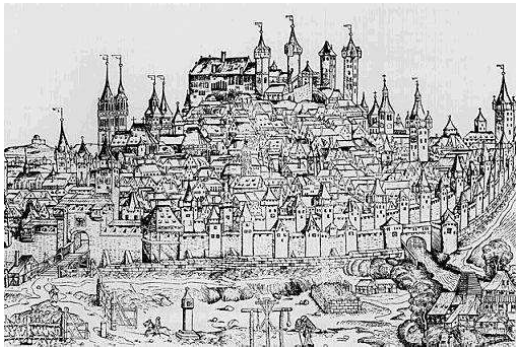


Annual Meeting of the German Association for Aging Research (DGfA)



Co – funded by the Cologne Cluster for Cellular Stress Responses in Aging-associated Diseases (CECAD Cologne)

November 6th to 7th, 2009

Maternushaus, Cologne, Germany

CECAD COLOGNE Excellent in Aging Research – Exzellent in Alternsforschung

Proteins of nucleotide excision repair and base excision repair interact in mitochondria to protect from a hallmark of aging: loss of subcutaneous fat

York Kamenisch[1*], Maria Fousteri[2*], Jennifer Knoch[1], Anna-Katharina von Thaler[1] Birgit Fehrenbacher[1], Hiroki Kato[3], Thomas Becker[4], Martijn Dolle[5], Raoul Kuiper[5], Marc Majora[6], Martin Schaller[1], Gijsbertus van der Horst[7], Harry van Steeg [5], Martin Röcken[1], Doron Rapaport[3], Jean Krutmann[6*], Leon H. Mullenders[2*] and Mark Berneburg[1]

[1]Department of Dermatology, Eberhard Karls University, Liebermeisterstrasse 25, D-72076 Tuebingen, Germany, email: Mark.Berneburg@med.uni-tuebingen.de

[2]MGC-Department of Radiation Genetics and Chemical Mutagenesis, Leiden University Medical Center, Wassenaarseweg 72, 2333 AL, Leiden, The Netherlands; email: L.Mullenders@lumc.nl

[3]Interfakultary Institute for Biochemistry, Tübingen, Germany

[4]Institute for Biochemistry and Molecular Biology, Freiburg, Germany

[5]MGO, RIVM, Utrecht, Netherlands

[6]Institut für Umweltmedizinische Forschung IUF, Auf´m Hennekamp 40, D-40225 Düsseldorf, Germany

[7]Erasmus University, Rotterdam, Netherlands

Defects in the DNA repair mechanism nucleotide excision repair (NER) may lead to tumors in Xeroderma pigmentosum (XP) or to premature aging with loss of subcutaneous fat in Cockayne syndrome (CS). Mutations of mitochondrial (mt)DNA play a role in aging, but a link between the NER-associated CS proteins and base excision repair (BER)-associated proteins in mitochondrial aging remains enigmatic. We show functional increase of CSA and CSB inside mitochondria and complex

formation with mtDNA, human 8-oxoguanine glycosylase (mtOGG)-1 and mt single-stranded DNA binding protein (SSBP)-1 upon oxidative stress. MtDNA mutations are highly increased in cells from CS patients and in subcutaneous fat of aged *Csb*$^{m/m}$- and *Csa*$^{-/-}$-mice. Thus, the NER-proteins CSA and CSB localize to mitochondria and directly interact with BER-associated mtOGG-1 to protect from aging- and stress-induced mtDNA mutations and apoptosis-mediated loss of subcutaneous fat, a hallmark of aging found in animal models, human progeroid syndromes like Cockayne syndrome and in normal human aging.

Towards Identification of Biomarkers of Human Ageing: The EU FP7 project MARK-AGE

Alexander Bürkle (on behalf of the MARK-AGE Consortium), Dept of Biology, University of Konstanz, D-78457 Konstanz, Germany, Email: alexander.buerkle@uni-konstanz.de

The Large-Scale Integrating Project MARK-AGE ("European Study to Establish Biomarkers of Human Ageing"; www.mark-age.eu) was launched in April 2008 and is carried out by 26 research groups from academia, SMEs and industry. The scientific background is the following: The rate of ageing in humans is not uniform, due to genetic heterogeneity and the influence of environmental factors. Age-related changes in body function or composition that could serve as a measure of "biological" age and predict the onset of age-related diseases and/or residual lifetime are termed "biomarkers of ageing". Many candidate biomarkers have been proposed but their variability in cross-sectional studies is considerable and no single measurement has so far proven to yield a useful biomarker of ageing on its own. Within the MARK-AGE project, we are conducting a population study (3,700 subjects) in order to identify a set of biomarkers of ageing which, as a combination of parameters with appropriate weighting, would measure biological age better than any marker in isolation. The range of candidate biomarkers being tested includes (a) "classical" ones for which data from several smaller studies have been published; (b) "new" ones, based on recent preliminary data, as well as (c) "novel" ones, based on recent research on mechanistic aspects of ageing, conducted by project participants. Bioinformatics will be used in order to extract a robust set of biomarkers of human ageing from the large amounts of data to be generated and to derive a model for healthy ageing.

Annual fish as a model system to study the genetic basis of lifespan evolution in natural populations.

E.Terzibasi[1*], J. Kirschner[2*], K.Reichwald[2], D.Valenzano[4], A.Dorn[1], A. Brunet[4], C.Englert[3], M.Platzer[2], **A.Cellerino**[1].

[1]Biology of Aging,[2]Genome Analysis,[3]Molecular Genetics, Leibniz Institute for Age Research - Fritz Lipmann Institute, 07745 Jena[4] Dept. of Genetics, Stanford University [4]

[*]denotes equal contribution

Genetic manipulations in model systems have identified a number of genes which can prolong lifespan when artificially manipulated. At present, very little is known as of the natural genetic variation which is responsible for inter- and intraspecific variation of lifespan in natural populations.

Annual fish of the genus *Nothobranchius* are a group of teleosts found in ephemeral bodies of water which form during the monsoon season in eastern and southern Africa. All adults die when the habitat dries out and their maximum natural lifespan is limited to few or several months, making them among the shortest-lived vertebrates. In particularly, the species *Nothobranchius furzeri* has a median lifespan of 11-28 weeks depending on strain and expresses a series of *bona fidae* aging markers. These strains interbreed and give rise to fertile F_1 hybrids and therefore are ideal for quantitative trait loci (QTL) analysis of longevity. To prove that genetic analysis is possible in *N.furzeri*, a linkage map was generated and used to identify the loci linked to sex and tail color.

Duration of the wet season, hence maximum natural lifespan, varies greatly over the *Nothobranchius* distribution range and some variation is observed even within the distribution range of *N. furzeri*. The large-scale differences in captive lifespan (11 vs. 28 weeks) of different laboratory strains of *N. furzeri* may simply be the results of captive history and inbreeding, but may also, in part, reflect an evolutionary response of natural populations to different durations of the wet season. To test this hypothesis, we have studied several independent strains (for a total of 10 strains) for two pairs of sister species of *Nothobranchius*: *N.furzeri*/*N.kuhntae* and *N.sp.*"black"/*N.rachovii*. For each, pair, one species originates from a semi-arid inland region (400-600 mm/year rain) and the other from a coastal wet region (> 1200 mm/year rain). In both cases, the species originating from the arid habitat showed faster aging rate and expression of age markers when contrasted with the sister species originating from the more humid habitat. This result demonstrate parallel evolution of lifespan in response to climate along distinct lineages of *Nothobranchius*.

In summary, our results demonstrate that annual fish of the genus *Nothobranchius* are a unique model system where large-scale natural variations in lifespan exist between closely-related populations/species and that these differences are, at least in part, an evolutionary response to differences in extrinsic mortality. *Nothobranchius* can therefore represent a tractable genetic system to study evolution of lifespan in vertebrates.

Changes in mitochondrial protein profile and in the supramolecular architecture of respiratory chain complexes: A clue in ageing !?

Norbert A. Dencher, Monika Frenzel, Frank Krause, Eva R. Schäfer, Michiru Sugawa[#], Tetyana Syzonenko, Sandra Thilmany, Diksha Dani

Physical Biochemistry, Department of Chemistry, Technische Universität Darmstadt, Petersenstrasse 22, D-64287 Darmstadt, Germany.
[#]Charité – Universitätsmedizin Berlin, D-14050 Berlin, Germany.

Analysis of the protein profile of organisms and its age-dependent variation is a promising approach to unravel mechanisms involved in ageing and age-related diseases. Our studies focus on the mammalian mitochondrial membrane proteome, especially of the inner mitochondrial membrane with the respiratory chain complexes and other proteins possibly involved in life span control and ageing. Variations of the mitochondrial proteome during ageing, with the emphasis on the abundance, composition, structure, post-translational modifications and activity of membrane proteins, are examined in various rat tissues by native polyacrylamide gel electrophoresis techniques in combination with mass spectrometry.
In rat brain, age-modulated differences in the abundance of various non-mitochondrial and mitochondrial proteins are detected. The age-related alterations in the abundance and oligomerisation of the MF_oF_1 ATP synthase observed by us in rat cortex might be one clue for understanding the link between respiration and longevity. Also, the abundance of OxPos (Oxidative Phosphorylation) supercomplexes, the natural assemblies of the respiratory complexes I, III, and IV into supramolecular stoichiometric entities such as $I_1III_2IV_{0-4}$, differs in young and aged cortex tissue. The mitochondrial proteome profile of the cortex is compared with that of hippocampus and striatum. Investigation of the influence of life-long and short-term calorie restriction (CR) on the mitochondrial liver protein profile will be discussed in relation to the observed anti-ageing and pro-ageing effects of CR. The combination of blue-native (BN) gel system with fluorescence difference gel electrophoresis (DIGE) favoures an efficient and highly sensitive quantitative analysis. Alterations in the level of reactive oxygen species (ROS), in anti-oxidative status and lipid composition are considered. The data discussed and methodologies described are also of high relevance for elucidating the molecular basis of age-related diseases such as Alzheimer's and Parkinson's Disease.
Supported by the European Community, EC FP6 contract number LSHM-CT-2004-512020, MiMage, and the Deutsche Forschungsgemeinschaft, grant SFB 472, to N.A.D.

Norbert A. Dencher
Phone: + 49 (0)6151 165275
Fax: + 49 (0)6151 164171
E-mail: nad@hrzpub.tu-darmstadt.de

Amyloidogenic Degeneration of the Protein Homeostasis

in Ageing and Age-Related Diseases

Marcus Fändrich

The function of proteins normally depends on their ability to adopt specific, and well-defined, three-dimensional states, termed globular proteins. However, the chemical structure of polypeptide chains allows the formation of an alternative and fundamentally different arrangement, termed amyloid aggregate (Fändrich et al., 2001). The degeneration of proteins into amyloid aggregates occurs inside the body either in the course of ageing or associated with several diseases (Dobson, 2003). For example, amyloid aggregates occur as secondary complications of atherosclerosis or type II diabetes. In Alzheimer's disease and AL amyloidosis, amyloid aggregates are thought to present the primary disease agent.

Our group has been studying the structure of amyloid aggregates and the mechanisms of their formation. We have been involved in establishing techniques to reconstruct the structure of amyloid fibrils with cryo electron microscopy. In case of amyloid fibrils from Alzheimer's Aβ peptide, we could obtain a structural resolution of better than 10 Å (Sachse et al., 2008) which revealed the fundamental structural arrangement of the fibril. We devised methods for the generation of antibody domains that bind to specific amyloid states (Habicht et al., 2007). These antibody domains have enabled us to explore the mechanism of amyloid formation and to provide potential tools for the amyloid interference (immunotherapy). Recently, we could show that amyloid plaque formation in cell culture is a cell-dependent process (Friedrich et al., submitted) that involves the internalization of amyloid precursors and the intravesicular extension of amyloid fibril bundles.

References

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Fändrich M, Fletcher MA, Dobson CM. Nature 2001, 410, 165-166

Friedrich RP, Tepper K, Rönicke R, Westermann M, Reymann K, Kaether C, Fändrich M. submitted

Habicht G, Haupt C, Friedrich RP, Hortschansky P, Sachse C, Meinhardt J, Wieligmann K, Gellermann GP, Brodhun M, Götz J, Halbhuber KJ, Röcken C, Horn U, Fändrich M. Proc. Natl. Acad. Sci. U.S.A. 2007, 104, 19232–19237

Sachse C, Fändrich M, Grigorieff N. Proc. Natl. Acad. Sci. U.S.A. 2008, 105, 7462–7466

Reactive oxygen species are involved in senescence of human cells independently from irradiation exposure

Monika Frenzel[1], Sebastian Zahnreich[2], Claudia Fournier[2], Sylvia Ritter[2] und Norbert A. Dencher[1]
[1]Physical Biochemistry, TU Darmstadt, Petersenstraße 22, 64287 Darmstadt, Germany
[2]Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany
E-mail: monika.frenzel@web.de

To date it is assumed that during ageing reactive oxygen species (ROS) accumulate in cells and trigger ageing. Upon X-ray or heavy ion irradiation, cells undergo senescence earlier compared to the non-irradiated controls. Irradiation induces a transient increase in the intracellular level of ROS up to 14 days after exposure. To assess whether ROS accumulation leads to genetic instability and alterations in the protein pattern in progeny of irradiated human fibroblasts, several cell strains of different origin were irradiated with X-rays and carbon ions. Currently we are studying the ageing process and the effect of oxidative stress in various cell-lines. Besides cell-line specific differences, also the effect of X-rays compared to heavy ions will be discussed.
Confluent NHDF (normal human dermal fibroblasts) have been irradiated with X-rays (8 Gy) and subcultured until 222 days after exposure. At different time points (early, intermediate, late) cells were harvested and the ROS-level, chromosomal aberrations and changes in the mitochondrial proteome in progeny of irradiated cells and controls were analysed. X-ray irradiation increases the ROS-level until 6 days after exposure. To study the long-term effects, ROS-levels were measured after 66 and 151 days. No significant differences were observed in progeny of irradiated cells compared to the control. Comparison of non-irradiated young as well as of irradiated and non-irradiated long-time subcultured NHDF cells demonstrate that there is a senescence-related increase of ROS-level independently of irradiation exposure.
We are analysing the effect of irradiation and/or senescence on the nuclear DNA and the mitochondrial proteome, especially of the inner membrane with the oxidative phosphorylation complexes and other proteins possibly involved in senescence or irradiation induced cellular responses. Besides alterations in the total abundance of individual proteins or protein complexes like HSP60 or ATP-synthase also variations in protein-protein interactions, such as respiratory chain complexes, supercomplexes, oligomerisation of ATP-synthase will be discussed.

(Supported by the EC, FP6-2003-LifeSciHealth, Integrated Project MiMage: “Role of Mitochondria in Conserved Mechanisms of Ageing” to NAD and by BMBF, grant 02S8497.)

Mechanisms of UVB induced premature senescence: a systems biology approach

Ruth Greussing[1], Hermann Unterluggauer[1], Hans-Peter Deigner[2], Johannes Grillari[3], Edith Hofer[4], Zlatko Trajanoski[4] and Pidder Jansen-Dürr[1,5]

[1]*Institute for Biomedical Aging Research of the Austrian Academy of Sciences, Innsbruck, Austria*
[2]*Biocrates Life Sciences AG, Innsbruck, Austria*
[3]*Institute of Applied Microbiology, University of Natural Resources and Applied Life Sciences, Vienna, Austria*
[4]*Institute for Genomics and Bioinformatics, University of Technology, Graz, Austria*
[5]*Tyrolean Cancer Research Institute, Innsbruck, Austria*

Ultraviolet B light (UVB, 280-320 nm) is an essential component of sunlight and has a profound effect on extrinsic skin aging. In this study we adopted an in vitro model for UVB-induced premature senescence of human diploid fibroblasts, applying a series of 8 sublethal exposures to UVB at 400 mJ/cm². Using time-resolved and genome-wide Affymetrix RNA profiling, we found considerable changes in gene expression which revealed the activation of several transcriptional programs leading to premature senescence. To validate and extend these results, we performed low-density arrays and immunoblots for selected target genes/proteins. The role of specific microRNAs in the regulation of key senescence target genes is studied using genome-wide microRNA expression analysis. Finally, concentrations of selected metabolites are determined and integrated with the gene expression data to provide a comprehensive analysis of the series of events triggered by mild UVB irradiation, and to understand their contribution to the senescent phenotype. With this study we want to gain new insight into the mechanisms of UVB induced premature senescence via transcriptomics, proteomics and metabolomics, with the ultimate goal to identify new targets for intervention in extrinsic skin aging.

M.Polychronidou, J. Großhans.

Zentrum Biochemie und Molekulare Zellbiologie, Universitätsmedizin, Universität Göttingen.

Farnesylated nuclear proteins Kugelkern and Lamin B promote ageing-like phenotypes in Drosophila flies

Changes in nuclear morphology are observed in cells from old human individuals and ageing nematodes and flies as well as in cells from patients with the Hutchinson-Gilford progeria syndrome. We address the role of nuclear morphology for chromatin organisation and stability and organismal ageing by studying the activity and function of the farnesylated nuclear proteins, Dm-Lamin B (lamDm0) and Kugelkern in cultured cells and adult Drosophila flies.

On the cellular level we find that induced expression of Kuk or LaminDmO leads to reduced heterochromatin staining, higher levels of DNA damage and more nuclear pore staining. These observations are similar to the phenotype of cells from HGPS patients or cells transfected with progerin-encoding constructs (hu-laminA-delta50). Our data show that HGPS-like phenotypes can also be induced by farnesylated nuclear proteins other than lamin and that changes in nuclear morphology and lamina structure may be causally related to the observed defects in genome organisation and stability. Currently we are investigating molecular interactions of Kugelkern and the role of lamina components for the peripheral localisation of the hyperactivated X-chromosome in male cells.

Furthermore we investigated the activity of LaminB and Kugelkern on the organismal level in adult flies. We have shown previously that induced expression of Lamin or Kugelkern leads to nuclear shape changes in young flies and causes a 50% reduction in life span together with a premature appearance of ageing-related behaviour. The accelerated ageing-like phenotype is due to farnesylated protein, since it can be suppressed by a farnesyl-transferase inhibitor. The life-span of wild-type flies is not extended by the FT inhibitor, however. To define the cellular basis for the ageing-like phenotypes, we are investigating changes in nuclear morphology in post-mitotic muscle cells as well as stem cells and differentiated cells in the gut.

Functions of newly discovered proteins in the mitochondria – Role in senescence, apoptosis and migration of endothelial cells

Judith Haendeler

Molecular Aging Research, IUF, at Heinrich-Heine-University Düsseldorf gGmbH, 40225 Düsseldorf, Germany

Every cell in our body contains mitochondria, organelles that produce the energy, but have also been suggested to be one origin of signalling events. Recently, 150 proteins were identified in mitochondria, which had never been associated with mitochondria before. Taken into account that mitochondria act as signalling organelles and that mitochondrial energy metabolism is associated with aging, apoptosis, reactive oxygen species formation and migratory capacity of cells, in particular endothelial cells, the aim of this study was to identify whether molecular links exist between mitochondrial energy metabolism, protein translocation and cellular function. First, we identified telomerase reverse transcriptase (TERT), a protein which has been demonstrated to be important for endothelial cell aging, in the mitochondria of endothelial cells. TERT is imported into the mitochondria via the translocase of outer membrane 20 and the translocase of inner membrane 23. TERT binds to mitochondrial DNA specifically at the coding region for ND1 and ND2. Binding of TERT to mitochondrial DNA protects against UV light induced damage. Functionally, TERT increased respiratory chain activity and mitochondrially targeted TERT protects from H_2O_2-induced apoptosis in endothelial cells. Secondly, we identified that VEGF-induced migration critically depends on mitochondrial function and on the mitochondrial translocation of p27/kip1 (p27), originally discovered as cell cycle inhibitory protein. Reducing p27 levels by siRNA abrogated basal and VEGF-induced migration. Targeted expression of p27 to the mitochondria stimulated mitochondrial ATP biosynthesis and increased the mitochondrial membrane potential. Of note, only mitochondrial, but not nuclear p27 rescued the impaired migratory capacity after siRNA-mediated suppression of endogenous p27 protein expression.

In conclusion, these findings clearly indicate that the mitochondria have a central role in the life and death of cells and determine the functional capacity of cells. Thus, elucidating how a mitochondrion remodels in response to changes in energy demands and in disease states will importantly contribute to our understanding of cellular processes and may provide new avenues for drug development.

Ubiquitin Chain Editing Modulates Protein Homeostasis and Aging.

Kirsten Kuhlbrodt[1,3], Philipp Christoph Janiesch[1,3], Eva Kevei[2], Alexandra Segref[2], Roja Barikbin[1], and Thorsten Hoppe[2 *]
[1] Centre for Molecular Neurobiology (ZMNH), University of Hamburg, Falkenried 94, 20251 Hamburg, Germany.
[2] Institute for Genetics and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, 50674 Cologne, Germany
[3] These authors contributed equally to this work
[*] Correspondence should be addressed to: Thorsten.Hoppe@uni-koeln.de

Protein ubiquitylation turned out to be a key posttranslational control mechanism providing different fates of targeted substrates in diverse cellular processes such as protein quality control, cell-cycle progression, signal transduction and development. Therefore, it is not surprising that recent studies have identified a role for ubiquitin in the regulation of longevity. Polyubiquitylation of protein substrates required for proteasomal degradation involves ubiquitin-activating E1 enzymes, ubiquitin-conjugating E2 enzymes, ubiquitin protein E3 ligases, and sometimes polyubiquitylation factors (E4 enzymes). Work over the past 20 years identified genetic programs regulating aging. Among those pathways, the best understood regulators are the insulin/insulin-like growth factor signaling (IIS) and the dietary restriction (DR) pathways. So far, two E3 ligases have been identified to influence the IIS-pathway, whereas a recent study describes the first link between ubiquitylation and DR. However, since the targets critical for longevity have not been identified yet, the role of ubiquitylation is thus completely unclear.

Here, we identified a novel unanticipated function of the ubiquitin-selective chaperone CDC-48 in age-related processes. Together with a ubiquitin hydrolase that deubiquitylates Lys48-linked polyubiquitin chains, CDC-48 regulates life span in *C. elegans*. Moreover, life span extension of the corresponding double mutant depends on the conserved Insulin/IGF signaling pathway. Thus, our data suggest that protein degradation and life span regulation are specifically linked by editing the ubiquitylation status of certain protein substrates.

Kuhlbrodt K, Mouysset J, Hoppe T. (2005). Orchestra for assembly and fate of polyubiquitin chains. *Essays Biochem.* 2005;41:1-14.
Janiesch PC, Kim J, Mouysset J, Barikbin R, Lochmüller H, Cassata G, Krause S, Hoppe T. (2007). The ubiquitin-selective chaperone CDC-48/p97 links myosin assembly to human myopathy. *Nat Cell Biol.* 4, 379-90.

Nanoparticles induce age-related neural phenotypes in cell culture and *Caenorhabditis elegans*

Anna von Mikecz, Min Chen, Adam Pluskota, Andrea Scharf, Lena Singer

Institut für umweltmedizinische Forschung an der Heinrich-Heine-Universität Düsseldorf gGmbH, Auf'm Hennekamp 50, D-40225 Düsseldorf, Germany

In aging societies neurodegenerative aggregation diseases increase, while pathological mechanisms are largely unknown. Triplet repeat diseases are characterized by protein aggregates and nuclear inclusions containing components of the ubiquitin-proteasome system, expanded polyglutamine proteins and transcriptional activators. We recently reported that silica-nanoparticles (silica-NPs) induce formation of nuclear protein aggregation that exactly recapitulates the protein composition and biochemical properties of nuclear inclusions which occur in neurodegenerative aggregation disorders such as Huntington's disease (1). In cells treated with silica-NPs inhibition of nuclear processes such as replication, and transcription induces a significant reduction of cell proliferation, whereas cell viability remains unaffected. Thus, silica-NPs enable cell culture-based models for both, protein aggregation in the cell nucleus and cellular aging processes.

In order to transfer our knowledge about the effects of nanoparticles to the *in vivo* situation, we currently use the nematode *C. elegans* because of it's accessibility to microscopic analysis, short lifespan and well described nervous system. Treatment with silica-NPs results in decreased progeny production and higher incidence of the egg-laying phenotype "bag-of-worms" (BOW), which is characterized by internally hatched progeny in the parent hermaphrodite. This phenotype occurs at a low level in aged WT hermaphrodites, and in mutant worms with egg-laying deficiency. Since developmental and intrinsic muscular effects can be excluded, we propose that silica-NPs act via neural pathways of *C. elegans* (2).

References

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2. Pluskota, A., Horzowski, E., Bossinger, O., and von Mikecz, A. (2009) In *Caenorhabditis elegans* Nanoparticle-Bio-Interactions Become Transparent: Silica-Nanoparticles Induce Reproductive Senescence. *PLoS One* 4: e6622

Fox-O Hunting:
FOXO3A, a novel longevity gene in humans

Almut Nebel
Institute of Clinical Molecular Biology, Christian-Albrechts-University, Schittenhelmstr. 12, 24105 Kiel, Germany
Phone: + 49 (0)431 597 1373
Fax: + 49 (0)431 597 2196
E-mail: a.nebel@mucosa.de

Human longevity is influenced by multiple genetic, epigenetic and environmental factors. The genetic component to this phenotype is estimated at 25-32%. Until recently, only variation in the apolipoprotein E gene (*APOE*) was found to be consistently associated with longevity in diverse populations. Although numerous case-control candidate gene studies have been performed and associations of the longevity phenotype with biologically plausible genes have been described, results from these experiments have proven difficult to validate. In September 2008, Willcox et al. published a study describing the association of variation in the forkhead box O3A (*FOXO3A*) gene with human longevity[1]. *FOXO3A* is an evolutionarily conserved key regulator of the insulin-IGF1 signalling pathway. The important role of this "master regulator" in diverse biological pathways including stress resistance, apoptosis, immune regulation and inflammation renders *FOXO3A* a very convincing candidate. However, the Willcox' results were tentative as they had not been replicated in an independent population. Therefore, we have investigated 16 known *FOXO3A* single nucleotide polymorphisms (SNPs) in our collection of 1762 German centenarians/nonagenarians and younger controls. Our results provide conclusive evidence that polymorphisms in this gene are indeed associated with the ability to attain exceptional old age[2]. Furthermore, we observed that the *FOXO3A* association was considerably stronger in centenarians than in nonagenarians, highlighting the importance of the oldest old for genetic longevity research. In a subsequent study, Anselmi et al. additionally validated the *FOXO3A* association in a sample of centenarians from Southern Italy[3]. However, so far no functional SNPs in *FOXO3A* have been reported that are known to influence the longevity phenotype. A strategy for the identification of causative variants in the gene (rare and/or common) will be presented and discussed.

[1] Willcox et al. 2008, Proc Natl Acad Sci USA 105:13987–13992
[2] Flachsbart et al. 2009, Proc Natl Acad Sci USA 106: 2700-2705
[3] Anselmi et al. 2009, Rejuvenation Res 12: 95-104

p53 deletion impairs clearance of chromosomal instable stem cells compromising integrity of the intestine in aging telomere dysfunctional mice

Begus-Nahrmann Y, Lechel A, Obenauf A, Nalapareddy K, Peit E, Hoffmann E, Schlaudraff F, Liss B, Schirmacher P, Kestler H, Danenberg E, Barker N, Clevers H, Speicher M, Rudolph KL.

Deletion of components of the DNA-damage signaling pathway can rescue the maintenance and the function of stem cells in aging telomere dysfunctional mice (Choudhury et al; Schätzlein et al.). p53 is activated in response to DNA damage leading to induction of apoptosis or p21-dependent cell cycle arrest. Depletion of intestinal stem cells and crypt atrophy represent major phenotypes in aging telomere dysfunctional mice. To analyze the in vivo role of p53 in this context, *Terc*$^{-/-}$ mice were crossed to conditional, intestine-specific *Trp*53-knock out mice. In aging IF1 *Terc*$^{+/-}$ *Trp*53 deletion did not induce an obvious intestinal phenotype until 18 months. In contrast *Trp53* deletion significantly shortened the lifespan of iG4 *Terc*$^{-/-}$ *Trp53*$^{-/-}$ animals compared to iG4 *Terc*$^{-/-}$ *Trp53*$^{+/+}$. This reduction correlated with earlier appearance of crypt atrophy and weight loss but was not associated with tumor formation. Deletion of the *Trp5*3 gene resulted in complete abrogation of p21 activation, accumulation of DNA damage and an increase in apoptosis in the intestinal epithelium of these mice. Moreover this correlated with an accumulation of intestinal stem cells carrying high levels of DNA damage. Our results provide first experimental evidence that p53 induction has a protective role preventing accumulation of damaged stem cells and organ degeneration induced bin aging in the context of telomere dysfunction.

The potential role of mitochondrial telomerase for cellular survival, ageing and longevity

Gabriele Saretzki
Crucible Lab, Institute for Ageing and Health, Newcastle University, UK

Telomerase plays an important role for telomere maintenance and cellular immortalisation. Recently it has been shown that the catalytic subunit of telomerase, TERT has telomere-independent functions as well. These include the increase of resistance against DNA damaging agents and apoptosis, interference with gene expression and subcellular shuttling. We and others have demonstrated that a mitochondrial localisation of telomerase decreases cellular oxidative stress and improves mitochondrial function.

3 independent groups have shown that telomerase translocates from the nucleus to mitochondria upon oxidative stress but different cellular outcomes have been reportet. After demonstrating subcellular shuttling in a model of telomerase overexpressing cells recently it has been demonstrated that this process also takes part in cancer cells and stem cells, including embryonic and adult stem cells. In addition it seems that regular subcellular shuttling is not only occur as a result of increased oxidative stress but could be a cellular defense mechanism that prevents and /or repairs DNA damage due to exogenous treatment with components such as hydrogen peroxide or chemotherapeutic drugs.

We hypothesis that an active shuttling of telomerase could be an active mechanism for cellular survival. This process could play a role for the increased resistance of cancer stem cells against drug treatment and irradiation as well as a natural defense mechanism in adult stem cells that could contribute to organismal and tissue ageing. Little is known about properties of oxidative stress, telomerase expression and telomere shortening in these cells.

Persistent transcription-blocking DNA damage in aging and longevity

Björn Schumacher

Cologne Excellence Cluster for Cellular Stress Responses in Aging Associated Diseases (CECAD)
Zülpicher Str. 47, 50674 Cologne, Germany
bjoern.schumacher@uni-koeln.de

Keywords: Premature aging, longevity, hormesis, somatotropic axis, IGF-1 receptor, transcription-coupled repair

Accumulation of stochastic DNA damage throughout organisms' lifespan is thought to contribute to aging. Conversely, aging appears phenotypically reproducible and regulated through genetic pathways such as insulin-like growth factor-1 receptor (IGF-1R) and growth hormone receptor (GHR), which are central regulators of the somatic growth axis. Attenuation of the somatotropic axis leads to lifespan extension. Rapid accumulation of DNA damage as a result of defects in genome maintenance systems leads to accelerated aging.

In a comparative transcriptome analysis we uncovered genome-wide correlations between mouse models of accelerated aging and mice with extended longevity. Strikingly, premature aging and naturally aged animals, like mice with extended longevity, showed attenuation of the somatotropic axis. We next asked whether age-related gene expression changes might comprise response programs to DNA damage accumulation in aging. We show that low levels of persistent DNA damage in primary cells elicits similar changes in global gene expression as those occurring in various organs of naturally aged animals. We further demonstrate that, as in aging animals, IGF-1R and GHR expression is attenuated resulting in cellular IGF-1 resistance. This cell-autonomous attenuation is specifically induced by persistent lesions leading to RNA polymerase II stalling, in proliferating, quiescent and terminally differentiated cells, is exacerbated and prolonged in cells from progeroid mice and confers resistance to oxidative stress. Our findings suggest that DNA damage accumulation in transcribed genes in most if not all tissues, contributes to the aging-associated shift from growth to somatic maintenance that triggers stress resistance and is thought to antagonize tumorigenesis and promote longevity. We propose that RNA polymerase II dependent damage sensing constitute a mechanistic basis for hormetic effects of low levels of DNA damage.

Abstract for the DGfA Meeting
6th - 7th November 2009 in Cologne

DNA methylation is regulated upon long-term culture and aging of human mesenchymal stromal cells

Wolfgang Wagner, Simone Bork, Patrick Horn, Hendrik Witt, Bernhard Korn, Anthony D. Ho, Stefan Pfister

The regenerative potential diminishes with age and this has been ascribed to functional impairments of adult stem cells. We have addressed the impact of long-term culture on mesenchymal stromal cells (MSC) from human bone marrow. Within two to three months of cultivation MSC demonstrated morphological abnormalities, enlargement, attenuated expression of specific surface markers, and ultimately proliferation arrest. Adipogenic differentiation potential decreased whereas the propensity for osteogenic differentiation increased. Microarray analysis revealed continuous changes in the global gene expression profile upon long-term culture (PLoS ONE 2008). Furthermore, we have analyzed effects of aging on gene expression profiles of MSC (21 to 92 year old donors). It was striking that several age-related gene expression changes in MSC were also differentially expressed upon replicative senescence *in vitro* (PLoS ONE 2009). In continuation of this work we have now analyzed DNA methylation changes using the HumanMethylation27 BeadChip assessing 27,578 unique CpG sites. Overall, the methylation pattern was maintained throughout both long-term culture and aging but highly significant differences were observed at specific CpG sites. Many of these differences were observed in homeobox genes and genes involved in cell differentiation. Methylation changes were verified by pyrosequencing after bisulfite conversion and compared to gene expression data. Notably, also the methylation changes in MSC were related in long-term culture and aging *in vivo*. This supports the notion that replicative senescence and aging represent developmental processes that are regulated by specific epigenetic modifications.

DNA damage response molecule MCPH1 regulates the neuroprogenitor division mode

Ralph Gruber[1], Mikhail Sukchev[1], Zhongwei Zhou[1], Pierre-Olivier Frappart[2] and Zhao-Qi Wang[1,3]

1. Leibniz Institute for Age Research - Fritz Lipmann Institute, Jena, Germany;
2. Institute of Molecular Cell Biology, Center for Molecular Biomedicine (CMB), Friedrich-Schiller University of Jena;
3. Faculty of Biology and Pharmacy, Friedrich-Schiller-University, Jena, Germany.

MCPH1/microcephalin is proposed to function in ATM- and ATR-mediated DNA damage response (DDR), and controls cell cycle progression. After ionizing and UV irradiation MCPH1 colocalizes with several key components of DDR, including 53BP1, MDC1, NBS1, RPA, Chk1 and BRCA1. Mutations of the MCPH1 gene cause the neurodevelopmental disorder Primary Microcephaly (MCPH), characterized by great reduction in brain size and mental retardation, and the premature chromosome condensation (PCC) in cells, which is probably due to disturbed G2-M transition of the cell cycle. To investigate how MCPH1 controls brain size, we dirupted the *Mcph1* gene in mice. Mutant mice exhibit microcephaly due to neocortical developmental defects. Deletion of *Mcph1* increases apoptosis in the ventricular and subventricular zones of the neocortex. *Mcph1*-deficient neuroprogenitors contain hypercondensed chromosomes, reminiscent of PCC. *Mcph1* deletion causes hypophosphorylation of Chk1-Cdk1 and thus compromises the G2-M checkpoint. However, *Mcph1*-deficiency does not affect ATM-mediated DNA damage response. While *Mcph1*-mutant neural progenitors proliferate normally, they show a severely constraint self-renewal capacity, which leads to a premature cell cycle exit. Further, deletion of *Mcph1* affects the division mode of neuroprogenitors by promoting asymmetric cell division and neuronal fate. Altogether, our study demonstrates that MCPH1 functions in regulating the neuroprogenitor division mode and thus maintains the neuroprogenitor pools during mammalian brain development.

Accumulation of mtDNA deletions during aging

J. Neuhaus, O. Baris, J.-C.von Kleist-Retzow[1], N. Moser[2], H-J. Schroeder[2] & R.J. Wiesner

Institute of Vegetative Physiology, Childrens Clinic[1] and Department II of Anatomy[2], Medical Faculty, University of Köln, Germany

Many studies have reported an accumulation of mtDNA deletions during normal aging as well as in several age related pathologies, but little is known about the molecular mechanisms involved in their generation and their clonal expansion over time. In particular, it is unclear why some tissues seem to preferentially accumulate these DNA alterations. One striking example are dopaminergic neurons in the substantia nigra of humans, where a drastic increase in deleted mtDNA molecules has been observed in Parkinsonism and during normal aging, conditions where these neurons degenerate.

To test the hypothesis that dopamine metabolism and/or accumulation of neuromelanin, the black pigment of substantia nigra, is involved, we analyzed various mouse brain tissues for three different mtDNA deletions, using qPCR and long range PCR, allowing the detection of both known and unknown deletions, respectively. Deletions were not found in 12 week old mice, but at week 50 and increased with age. Interestingly, we found strong similarities in the deletion accumulation pattern reported recently for humans, even though S. nigra of mice does not display any neuromelanin, which thus can be excluded as causative. Deletions were most prominent in S. nigra, followed by striatum, cerebellum and cortex. In addition, in the adrenal gland, the percentage of deleted molecules was about 5fold higher than in S. nigra, supporting our hypothesis that a high turnover of catecholamines stimulates the generation and/or clonal expansion of mtDNA deletions. A different pattern of deletions was found in adrenal gland compared to the brain regions, where their ratio was rather similar, indicating that additional, cell type specific factors involved in mtDNA replication, divergent metabolic profiles, turnover etc. may be responsible for the individual patterns. Since different deletions will have different consequences, namely lack of rRNAs, tRNAs, subunits of respiratory chain complexes, truncated proteins or even fusion proteins, a wide range of pathomechanisms can be postulated leading to neurodegeneration. Using cultures of dopaminergic neurons in which the generation of deletions can be induced, these mechanisms will be analysed.

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2	Altschmied, Joachim	Düsseldorf		Yogi-altschmied@uni-duesseldorf.de
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4	Baniahmad, Aria	Jena		aban@mti.uni-jena.de
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58	Schneider, Jennifer	Köln		Jennifer.schneider@uni-koeln.de

59	Wolters, Stefanie	Köln		wolterss@uni-koeln.de