Medizinische Fakultät
der Martin-Luther-Universität
Halle-Wittenberg

UKH
Universitätsklinikum
Halle (Saale)

10. International Meeting on Ageing

Cardiovascular Ageing:

From Basic Science to Translation

Heart Center of Central Germany
University Medicine Halle (Saale)
Ernst-Grube-Str. 40
06120 Halle (Saale)

Keynote Lecture
Eline Slagboom
Leiden, Netherlands

Interdisciplinary Centre on Ageing Halle (IZAH)

German National Academy of Sciences Leopoldina

DGGG - German Society of Gerontology and Geriatrics

RTG 2155: ProMoAge

From Friday,

September 3rd, 2021, 6 pm

till Sunday,

September 5th, 2021, 2 pm

Opening and Conference Site:
Steintor-Varieté
Am Steintor 10, 06112 Halle (Saale)

INTERNATIONAL SYMPOSIUM

Cardiovascular ageing:
From Basic Science to Translation

September 03rd – 05th 2021

Heart Center of Central Germany
University Medicine Halle (Saale)

in cooperation with

German National Academy of Sciences Leopoldina

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Cardiovascular ageing:
From Basic Science to Translation

- Meeting language is English -

Friday September 03rd 2021

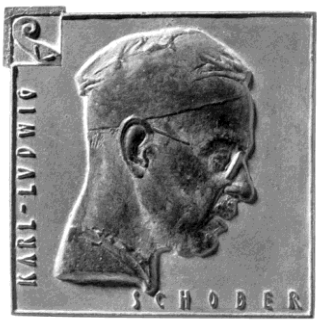
18:00 Opening

Andreas Simm

Addresses

T. Moesta, Medical Director of the University Hospital
M. Girndt, Vice Dean of the Medical Faculty

Keynote lecture and Schober Award



Laudation Eline Slagboom

by Ed Lakatta, Baltimore, USA

Keynote lecture:

Eline Slagboom
Leiden University Medical Center, Leiden, Netherlands

“Biological age, biomarkers and exceptional longevity”

20:00 Come Together (Steintor-Varieté)

Saturday September 04th 2021

08:30 – 10:00 Session 1

The elderly frail patient

Chair: Eline Slagboom, Andreas Simm

Frailty and its Roles in Ageing Research	Dhayana Dallmeier
InflammAging and frailty	Claudio Franceschi
Comprehensive risk prediction in frail cardiac surgery patients	Britt Hofmann

10:00 – 11:15 Poster talks (even numbers): one slide – one minute + Poster Session + Coffee Break

Chair: Rüdiger Horstkorte

11:15 – 12:45 Session 2

Cardiovascular Ageing: translational perspectives / biomarkers

Chair: Jojo Haendeler, Bernd Niemann

Fatty acids and the age-associated shift in inflammatory-metabolic axis	Helen Griffiths
The role of metabolic shift and metabolic stress in endothelial dysfunction and senescence	Regine Heller
Protein Glycation in Cardiovascular Aging	Andreas Simm

12:45 – 13:45 Lunch Break

13:45 – 15:15 Session 3

Functional phenotype of the aged cardiovascular system

Chair: Joachim Altschmied, Brit Hofmann

Targeting senescent cells for the treatment of lifestyle-related disease	Tohru Minamino
Cardiovascular ageing and its entanglement with frailty, dementia and gender	Ursula Müller-Werdan
Old Hearts and Arteries Operate on the Edge of Disease	Ed Lakatta

Saturday September 04th 2021

15:15 – 16:30 Poster talks (uneven numbers): one slide – one minute + Poster Session + Coffee Break
Chair: Rüdiger Horstkorte

16:30 – 18:00 Session 4

Basic mechanisms of ageing
Chair: Tamas Fülöp, Gábor Szabó

Aged-senescent cells contribute to impaired heart regeneration	Georgina Ellison
Telomerase Reverse Transcriptase – not only a nuclear weapon	Jojo Haendeler
Ageing of elastic fibers enhances the development and progression of cardiovascular diseases	Andrea Heinz

20:00 Conference-Dinner (Speiseberg)

Sunday September 05th 2021

09:00 – 11:00 Session 5

DGTHG / DGK working groups: Treatment of elderly patients
Chair: Ursula Müller-Werdan, Georgina Ellison

Cardiovascular interventions in patients with NSTEMI	Harald Rittger
Polypharmacy in old age	Christian Mahnkopf
Heart transplantation at old age	Gábor Szabó
Aortic valve therapy in frail elderly. Effects on survival through obesity and sarcopenia	Bernd Niemann

11:00 – 11:30 Poster Session + Coffee Break

11:30 – 11:45 Poster Price

11:45 – 13:45 Session 6

Is anti-aging the answer?

Chair: Georgina Ellison, Claudio Franceschi

Proteasome modulation as a strategy to battle ageing and aggregation-rtelated pathologies	Niki Chondrogianni
Is vaccination an anti-aging intervention?	Tamas Fülöp
Senolysis in the context of injury and regeneration	Mikolaj Ogrodnik
Risks and Benefits of new therapies	Alexandra Stolzing

13:45 – 14:15 Farewell

Biological age, biomarkers and exceptional longevity

P. Eline Slagboom

When we study phenotypes of biological ageing, we often explore physiological parameters mortality, multimorbidity or longevity as endpoints. Biological age could also be investigated but there is no gold standard composite marker of biological age. Biological age predictors have been generated in the past based on physiological read outs and clinical variables and the last 10 years many studies have added molecular data to this field. I will discuss especially the molecular biomarkers and the study of metabolomics in epidemiological, clinical studies and intervention studies aimed at health improvement.

Whilst age at death in the population at large has a very low heritability (~25%), longevity is transmitted across generations in families of which many members survive into extreme ages despite epidemics, wars, famines and other extreme environmental stresses of the last two centuries. It has become clear that such families display beneficial physiological characteristics, healthy ageing and compression of age-related disease. I will discuss studies into the transmission of this trait in families and genetic analyses to identify longevity mechanisms.

Frailty and its Roles in Ageing Research

Dhayana Dallmeier

The aging process shows a high degree of heterogeneity. In addition to fit older people, about 20% of older patients show signs of frailty, which can be defined as a medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiological function that increases an individual's vulnerability for many adverse health outcomes such as disability and lastly death (Morley et al., 2013). In this context frailty has evolved since its introduction as an important concept in the understanding of the process of non-healthy aging. The operationalization of frailty is quite diverse and in the field of geriatrics controversially discussed. There are now more than 60 instruments addressing the characterization of this syndrome, so that the reported prevalence will vary greatly depending on the instrument used. The Fried phenotype model, the Minitski and Rockwood deficit accumulation model, and the - in the settings of the COVID-Pandemie broadened - Clinical Frailty Scale are currently the most frequently models used in the scientific literature. Frailty, once present, may play an important role not only as a confounder, and risk factor but also as a possible effect modifier when analyzing the effects of different exposures such as biomarkers, diseases, and perhaps treatments on relevant outcomes in older adults such as falls, hospitalization, disability, institutionalization and lastly mortality. Unfortunately so far few guidelines do take frailty into account when summarizing the evidence available in the literature. Providing a good characterization with respect to frailty is becoming therefore a necessary requirement in the settings of any study involving older adults. At the end of this presentation participants should become familiar with i) frailty's definition, ii) prevalence, iii) some of the most widely used instruments for its characterization, and iv) its roles in ageing research.

InflammAging and Frailty

Claudio Franceschi

Comprehensive risk prediction in frail cardiac surgery patients

Britt Hofmann

The number of elderly patients referred for complex cardiac surgery has raised steadily over the past few decades. Currently, more than 50% of cardiac surgery procedures is performed on patients aged 70 or over. The percentage of patients over 80 years is also rising steadily and is now at 18.6%. Interestingly, postoperative mortality and morbidity have mainly remained constant due to increasingly minimally invasive surgical procedures. Furthermore, minimally invasive procedures have opened up access to surgical therapy even for multimorbid patients at an advanced age. Various studies have shown that elderly patients benefit from cardiac surgical care by improving their quality of life and alleviating or eliminating their symptoms. So far, chronological age has been considered an independent risk factor for postoperative complications and mortality. This is reflected in all established risk score systems for cardiac surgery. However, both the clinical evidence and the results of numerous studies have shown that advanced age alone is not a predictor of increased postoperative mortality and morbidity. In this respect, older patients should not be withheld from surgical treatment. To better assess the perioperative risk of older patients, it is necessary to establish preoperative evaluation processes that enable differentiation between chronological and biological age. The biological age or the frailty of the patients seems to be more relevant. Unfortunately, a gold standard of frailty assessment in clinical practice does not exist. However, a systematic review of published studies by Chainani found that reduced handgrip strength and reduced walking speed, as objective frailty markers, are associated with increased cardiovascular mortality. In addition, the Comprehensive Assessment of Frailty Score (CAF) and Fried's frailty phenotype assessment proved predictive power beyond the traditionally established scores for postoperative complications. These results and our daily practice underscore the need to develop appropriate tests to identify preoperative frail high-risk patients, clarify their expectations, and adapt the intervention/operation to the patient's specific needs.

Fatty acids and the age-associated shift in inflammatory-metabolic axis

Helen Griffiths

Diet is a well-established determinant of health and longevity. Evidence suggests that this relationship may be due to nutrient and metabolite effects on a range of physiological and molecular processes from gut dysbiosis and inflammation to mitochondrial dysfunction and oxidative stress.

We previously explored the effects of dietary enrichment with almonds in healthy older adults and observed that despite an increase in fat intake and the antioxidant micronutrient α-tocopherol, there were improvements in vascular function but not in oxidative stress markers [1]. In addition, we saw improvements in metabolic parameters. We have explored this apparent paradox between specific lipids and metabolism in healthy older adults and in people with T2D. We observed that plasma fatty acid profiles were effective predictors of metabolic capacity, vascular function and inflammatory markers in healthy older adults [2] and also in people with T2D.

The presentation will discuss our recent hypotheses [3,4] and investigations into mechanisms that underpin the relationship between diet, inflammation and ageing.

References

1. An almond-enriched diet increases plasma α-tocopherol and improves vascular function but does not affect oxidative stress markers or lipid levels. Choudhury K, Clark J, Griffiths HR. Free Radic Res. 2014 May;48(5):599-606. doi: 10.3109/10715762.2014.896458. Epub 2014 Mar 20.
2. Age-associated changes in long-chain fatty acid profile during healthy aging promote pro-inflammatory monocyte polarization via PPARγ. Pararasa C, Ikwuobe J, Shigdar S, Boukouvalas A, Nabney IT, Brown JE, Devitt A, Bailey CJ, Bennett SJ, Griffiths HR. Aging Cell. 2016 Feb;15(1):128-39. doi: 10.1111/acel.12416. Epub 2015 Nov 2.
3. Inflammation, Lipid (Per)oxidation, and Redox Regulation. Dias IHK, Milic I, Heiss C, Ademowo OS, Polidori MC, Devitt A, Griffiths HR. Antioxid Redox Signal. 2020 Jul 20;33(3):166-190. doi: 10.1089/ars.2020.8022. Epub 2020 Feb 28.
4. Lipid (per) oxidation in mitochondria: an emerging target in the ageing process? Ademowo OS, Dias HKI, Burton DGA, Griffiths HR. Biogerontology. 2017 Dec;18(6):859-879. doi: 10.1007/s10522-017-9710-z. Epub 2017 May 24.

The role of metabolic shift and metabolic stress in endothelial dysfunction and senescence

Regine Heller

Endothelial dysfunction and senescence are important contributors to ageing-induced cardiovascular diseases. Further understanding of the underlying mechanisms will therefore provide new insights into the pathogenesis of cardiovascular disorders. In this context, we focused on the characterization of cellular metabolism in senescent endothelial cells and on how metabolic stress such as dicarbonyl stress known to increase with age alters endothelial function.

To study cellular metabolism we performed Seahorse analyses, flux measurements with radiolabelled glucose, and monitored the expression of metabolic enzymes. We found that replicative senescent cells exhibit an increased glycolytic capacity but also an enhanced glucose oxidation and oxidative phosphorylation. The latter was associated with reduced protein levels of the pyruvate dehydrogenase kinase (PDHK, isoforms 1-4), resulting in an activation of the pyruvate dehydrogenase complex and enhanced tricarboxylic acid cycle activity. Increased glucose oxidation was associated with elevated mitochondrial reactive oxygen species. Of note, pharmacological inhibition of PDHK by dichloroacetate (DCA) in endothelial cells, which increased oxidative metabolism and oxidative stress, led to an induction of premature senescence.

Dicarbonyl stress is characterized by accumulation of dicarbonyls such as glyoxal, a potent glycating agent triggering carboxymethyl lysine (CML) formation of proteins. Using quantitative proteomics and a proteomic strategy to identify specific CML sites we show that glyoxal induced a complex response in endothelial cells leading to reduced cell proliferation and, in part, premature senescence. The underlying mechanisms include downregulation of processes related to proliferation and growth as well as specific CML modification of proteins in the nucleus, the cytoskeleton and the mitochondria. In particular, we show that glyoxal induces a DNA damage response, cell cycle arrest in G0/G1 and G2 and glycation of tubulin leading to impaired microtubule dynamics and inhibition of mitosis.

Our data suggest that (1) a shift to oxidative metabolism may promote senescence in endothelial cells and that (2) dicarbonyl stress may induce endothelial dysfunction and premature senescence by alterations of the proteome and by specific CML modifications of cellular proteins.

Protein Glycation in Cardiovascular Aging

Andreas Simm

Advanced Glycation End Products (AGEs) seem to be involved in aging as well as in the development of diseases such as cardiovascular diseases, diabetes mellitus, and renal failure. During aging, AGEs can accumulate in intra- and extracellular proteins. During protein glycation, reactive carbohydrates or dicarbonyls react with amino groups from lysines and arginines. As histones are rich in lysines and arginines and are regulated by acetylation or methylation of these amino acids, it is of interest to investigate the possible glycation of these sites. Indeed, we identified hot spots of glycation in all four histones, H2A, H2B, H3, and H4. Against our prediction, we do not see an accumulation of AGEs in histones with aging.

Beside intracellular proteins, AGEs can accumulate in extracellular matrix proteins like collagen. We analyzed the AGE modifications in the collagens extracted from residual bypass graft material and cardiac tissue. Collagen types I and III (pepsin digestible collagen-, collagenase digestible collagen- and insoluble collagen fractions) were isolated, quantified by 4-hydroxyproline assay, and AGEs by the AGE intrinsic fluorescence. The collagen AGE auto-fluorescence in patient material increased with patient's age and in diabetes mellitus. AGE-associated skin auto fluorescence (SaF) provided the best predictive value in identifying patients with major morbidity risks after cardiac surgery (OR=3.13; 95%CI 2.16–4.54).

Conclusion: These findings suggest that glycation may play an essential role in cardiovascular aging. AGEs within histones may modify epigenetic regulation, whereas SaF is a promising biomarker candidate to assess the perioperative risk of patients in cardiac surgery.

Targeting senescent cells for the treatment of lifestyle-related disease

Tohru Minamino

Epidemiological studies have shown that age is the dominant risk factor for lifestyle-related diseases. The incidence and the prevalence of diabetes, heart failure, coronary heart disease and hypertension increase with advancing age. However, the molecular mechanisms underlying the increased risk of such diseases that is conferred by aging remain unclear. Cellular senescence is originally described as the finite replicative lifespan of human somatic cells in culture. Cellular senescence is accompanied by a specific set of phenotypic changes in morphology and gene expression including negative regulators of the cell cycle such as p53. Primary cultured cells from patients with premature aging syndromes are known to have a shorter lifespan than cells from age-matched healthy persons. It is also reported that the number of senescent cells increases in various tissues with advancing age. Interestingly, such accumulation of senescent cells in aged animals is attenuated by caloric restriction that regulates the lifespan regulatory system and delays age-associate phenotypes. I therefore hypothesize that cellular senescence in vivo contributes to the pathogenesis of age-associated disease and have shown a critical role of cellular senescence in age-related pathologies. However, a direct inhibition of cellular aging signaling would lead to the increased incidence of cancer, so we need to develop anti-senescent therapy without cancer development. Here I will show our recent data on a novel strategy of anti-senescent therapy for lifestyle-related disease by targeting cellular senescence (Seno-antigens, Seno-metabolites, SASP), which would not promote tumorigenesis.

Cardiovascular ageing and its entanglement with frailty, dementia and gender

Ursula Müller-Werdan

The cardiovascular continuum, as proposed by Braunwald and Dzau, emphasizes the lifelong progression of deficit accumulation within the cardiovascular system, while medical taxonomy – required for practical purposes in research and patient management – sets cesuras within this continuum essentially arbitrarily. Cardiovascular ageing moreover is intertwined with deterioration of both mobility/skeletal muscle function and cognitive function: both physical and cognitive frailty may consequently be regarded as being annexed to the cardiovascular continuum. Cardiovascular risk factors may even be looked upon as driving force for frailty and dementia. In search of a common denominator for ageing and disease in the cardiovascular system, the striking differences between men and women – particular with regard to cardiovascular pathology – deserve special attention and may help identify biomarkers of and key mediators of ageing. Sexual dimorphism of the immune system gives rise to different paces in immunosenescence between women and men. Our group (Herpich et al. 2021) e.g. found sex differences between associations of GDF15 (growth differentiation factor 15, a member of the transforming growth factor ß superfamily involved in inflammatory and apoptotic pathways and associated with all-cause mortality in humans) with muscle mass and strength parameters in a cohort of older hospital patients.

Reference:
Herpich C, Franz K, Ost M, Otten L, Coleman V, Klaus S, Müller-Werdan U, Norman K. Associations Between Serum GDF15 Concentrations, Muscle Mass, and Strength Show Sex-Specific Differences in Older Hospital Patients. Rejuvenation Res. 2021 Feb;24(1):14-19. doi: 10.1089/rej.2020.2308.

Old Hearts and Arteries Operate on the Edge of Disease

Ed Lakatta

Aging is a manifestation of progressive, time-dependent failure of molecular mechanisms that create disorder within a system of DNA and its environment (nuclear, cytosolic, tissue, organ, organism, other organisms, society, terra firma, atmosphere, universe). Continuous signaling, transmitted with different kinetics across each of these environments, confers a "mutual enslavement" that creates ordered functions among the components within the system. Accrual of age-associated molecular disorder over time, i.e., during aging, causes progressive changes in the structure and function of the heart and arteries that are quite similar in humans, non-human primates, rabbits and rats that compromise cardiovascular reserve function, and confer a marked risk for incident cardiovascular disease. Nearly all aspects of signaling within the DNA environment system within the heart and arteries become disordered with advancing age: Signals change, as does sensing of the signals, transmission of signals and responses to signals, impaired cell renewal, changes in the proteome due to alterations in genomic transcription, mRNA translation, and proteostasis. The density of some molecules becomes reduced, and post translational modifications, e.g., oxidation and nitration phosphorylation, lead to altered misfolding and disordered molecular interactions. The stoichiometry and kinetics of enzymatic and those reactions which underlie crucial cardiac and vascular cell functions and robust reserve mechanisms that remove damaged organelles and proteins deteriorate. Aging cells generate an inflammatory defense in an attempt to limit the molecular disorder. The resultant proinflammatory milieu is not executed by "professional" inflammatory cells (i.e., white blood cells), however, but by activation of renin-angiotensin-aldosterone endothelin signaling cascades that leads to endothelial and vascular smooth muscle and cardiac cells' phenotype shifts, resulting in production of inflammatory cytokines. Progressive molecular disorder within the heart and arteries over time leads to an excessive allostatic load on the cardiovascular (CV) system, that results in an increase and "overshoot" in the inflammatory defense signaling. This age associated molecular disorder-induced inflammation that accrues in the heart and arteries does not, itself, cause overt clinical signs or symptoms of CV disease (CVD). But an emerging school of thought is that accelerated age-associated alterations within the heart and arteries, per se, ought to be considered to be a type of CVD, because the molecular disorder and the inflammatory milieu that accrues within the heart and arteries with advancing age are the roots of the pathophysiology of major CVDs, e.g., atherosclerosis and hypertension. Because many effects of aging on the CV system can be delayed or attenuated by changes in lifestyle, e.g., diet and exercise, or by presently available drugs, e.g., those that suppress Ang II signaling, CV aging is a promising frontier in preventive cardiology that is not only ripe for, but also in dire need of attention! But, sadly, the reality of the age-associated molecular disorder within the heart and arteries has, for the most part, been kept outside of mainstream clinical medicine

Aged-senescent cells contribute to impaired heart regeneration

Georgina M. Ellison-Hughes

Mammalian ageing is defined as a gradual loss of the capacity to maintain tissue homeostasis or to repair tissues after injury/stress. The adult heart is considered a post-mitotic organ, having a low cardiomyocyte turnover rate over the course of human lifespan, which decreases further with ageing. Accumulation of senescent cells in tissues, including the heart, with ageing and at etiological sites in multiple chronic diseases is detrimental, contributing to pathophysiology and deterioration.

The adult myocardium, including human, harbours a rare population of resident multi-potent cardiac stem and progenitor cells (CPCs). CPCs, positive for stem cell markers (i.e. c-kit, Sca-1, PDGFRα) and negative for hematopoietic and endothelial lineage (i.e. CD45, CD34 and CD31) and mast cells (i.e. tryptase), exhibit properties of stem cells; being clonogenic, self-renewing and multipotent, both *in vitro* and *in vivo* (Smith et al. 2014, Nat Protoc; Vicinanza et al. 2017, Cell Death & Diff; Aquila et al. 2019, Cell Death Dis). When tested in an injury model that simulates muscle wear-and-tear with a small dropout of LV cardiomyocytes (~8%), and in the presence of a patent coronary circulation, CPCs have true intrinsic regenerative capacity (Ellison et al. 2013, Cell). Manipulation of CPCs ex-vivo and in situ has opened new therapeutic avenues for myocardial repair and regeneration. Regulation of cell senescence will impact the efficacy of regenerative therapies, especially if the majority of patients in need of it are of advanced age as occurs with heart diease and failure.

My talk will focus on the impact of ageing and senescence on human CPCs, and how this influences their myocardial regenerative potential (Lewis-McDougall et al. 2019, Aging Cell). I will show how by pharmacologically eliminating senescent cells using senolytic agents, the regenerative capacity of the aged heart can be rejuvenated. Finally, I will present new data determining the effects of senencence and the senolytic agents, Dasatinib+Quercetin, on human cardiomyocyte and endothelial cell survival and proliferation.

Telomerase Reverse Transcriptase – not only a nuclear weapon

Jojo Haendeler

Telomerase has originally been described as a nuclear ribonucleoprotein counteracting telomere erosion, which occurs during every cell division. However, it has been demonstrated that at least its catalytic subunit, Telomerase Reverse Transcriptase (TERT) is not only present in the cell nucleus, but also in mitochondria. Interestingly, TERT is upregulated upon injury or after exercise in the heart, which consists to a large part of post-mitotic, non-dividing cells, suggesting that in this organ TERT has other functions than telomere protection. We could show that mitochondrial TERT exerts protective functions in the cardiovascular system *ex vivo* and, using a new mouse model containing TERT exclusively in the mitochondria, *in vivo*. Furthermore, an increase in mitochondrial TERT levels led to improved outcomes in various cell types and in myocardial infarction. Therefore, an elevation in mitochondrial TERT content could have therapeutic potential in aging and age-related cardiovascular diseases

Ageing of elastic fibers enhances the development and progression of cardiovascular diseases

Andrea Heinz

Elastic fibers are essential constituents of the extracellular matrix of higher vertebrates and confer elasticity and resilience to several tissues and organs including lungs, skin and blood vessels. During the human lifespan, elastic fibers are exposed to a variety of enzymatic, chemical and biophysical influences, and accumulate damage due to their low turnover. Ageing of elastin and elastic fibers involves enzymatic degradation, oxidative damage, glycation, calcification, aspartic acid racemization, binding of lipids and lipid peroxidation products, carbamylation and mechanical fatigue. These processes may result in an impaired elastic fiber function, a reduced tissue elasticity or even a loss of function of organs and tissues such as the cardiopulmonary system, which considerably increases morbidity and mortality. The presentation gives an overview on the molecular mechanisms of elastic fiber ageing and its connection to cardiovascular diseases such as atherosclerosis and aortic aneurysms.

Cardiovascular interventions in patients with NSTEMI

Harald Rittger

Presumably due to the fear of complications and in combination with an uncertainty about the possible success of such an intervention, the use of invasive diagnostic and therapeutic procedures decreases with increasing age. In the light of the existing data, older patients presenting with an acute coronary syndrome (ACS) in general have a broader spectrum of clinical presentation and higher complication rates when undergoing treatment, either interventionally or conservatively.

These patients should not be treated differently from younger patients, since they gain the greatest benefit from interventional treatment. However, more caution evaluating benefits and risks of usual therapies should be applied. The consideration of remaining life expectancy, quality of life and patient preferences and values is more important for clinical decision making than in younger patients.

Polypharmacy in old age

Christian Mahnkopf

Polypharmacy is common among elderly and very old patients due to the need to treat the various diseases that develop with age. Many studies have found that various numbers of medications are associated with negative health outcomes, even if more research is needed to further delineate the consequences associated with unnecessary drug use in elderly patients. The literature review found that polypharmacy continues to increase and is a known risk factor for morbidity and mortality in elderly and very old patients. There are a few rigorously designed intervention studies that have been shown to reduce unnecessary polypharmacy in older adults. Evaluation of polypharmacy is of important concern in every elderly patient to avoid all possible adverse effects. Therefore, comprehensive medication review and risk assessment should be carried out by interdisciplinary team to identify the polypharmacy and its adverse effects. Various rules, e.g. the frequency of use, the number of medications, etc., must be followed very urgently when prescribing medication for elderly and very old patients. In this lecture we will explain the peculiarities in the daily handling of this very vulnerable patient group.

Heart transplantation at old age

Gabór Szabó

The incidence of heart failure is continuously growing in the elderly population, and became a leading cause of cardiovascular mortality. Despite of the development novel, medical and device therapies, the prognosis remains very poor comparable to lung cancer. The gold standard of the treatment of terminal heart insufficiency still remains cardiac transplantation. However; donor shortage remains a major limitation of this therapeutic option. Under these circumstances ageing becomes a significant factor also in the context of cardiac transplantation in different ways. On one hand more and more older donors are considered as potential cardiac donors. On the other hand, cardiac transplantation seems to be a realistic therapeutic option also in the elderly population. The present paper provides a short state-of-the art review of cardiac transplantation in the context of ageing.

Aortic valve therapy in frail elderly.
Effects on Survival through obesity and sarcopenia

Bernd Niemann

The obesity paradox describes a prognostic benefit due to mild and high overweight in chronically ill patients. Clinicians often misapply this definition often to chronic and non-chronic courses of a disease.

On the other hand, effects of cachexia have to be clearly divided from obesity. Nevertheless, an “obesity paradox” is often stated but seems to originate from a misunderstanding of these two pathologies. In adults, obesity, defined by a body mass index (BMI) 30 kg/m^2, is associated with an increased risk for death. Obesity has become a global epidemic and is now recognized as a risk factor for multiple chronic diseases, including cardiac diseases. Mitochondrial dysfunction, including mitochondrial loss and the production of reactive oxygen species (ROS), was suggested to be involved in the development of insulin resistance and the progression of aging. Consequently, many of the observed phenotypic changes and pathomechanisms in obesity are also present in the aging heart. The mitochondrial respiratory chain is generally assumed to be the main source of ROS. Subsequently, increasing damage to deoxyribonucleic acid (DNA), proteins, or lipids accumulates with age progression, and as a consequence, an impairment of cellular function may result. Respiratory chain function decreases with age, while oxidative damage and mutations of mitochondrial DNA (mtDNA) increase during human ageing. This effects might have impact on an increasing cardiac vulnerability in elderly patients.

In Western society, cardiac surgeons are facing increasingly obese and old patients displaying elevated perioperative risk. However clinical routine lacks a clear definition of obesity, acopenia or – moreover important obese sarcopenia. Therefore, the need for strategies for risk analysis and risk reduction in these patients is evident. The influence of overweight or underweight is controversially discussed and not implemented in clinical scoring systems for the estimation of risk-adjusted surgical outcomes, except for the Parsonnet score. Adverse cardiac effects of obesity include left ventricular (LV) hypertrophy, chronic volume overload, systolic and diastolic dysfunction, left atrial enlargement with atrial fibrillation, and coronary artery disease. Reduction in body weight, in contrast, has been shown to improve blood pressure, insulin sensitivity, and inflammatory parameters, including the release of protective adipocytokines.

In different cardiovascular morbidities the existence of an obesity paradox has been questioned so far[1]. In cardiac surgery, mild overweight is proven to be associated with an improved perioperative and long-term outcome. However, both - cachexia and morbid obesity increase peri- and postoperative morbidity and mortality. Furthermore, after adjustment for confounders[6], an obesity paradox is absent in bigger cohorts of CHF patients. While general weight reduction in international guidelines for CHF is not recommended or might be harmful, benefits have been estimated by reducing overall fat mass and inflammatory-over activation in heart failure

While sparsely but emerging data describe an obesity paradox to be evident in TAVR patients, little data is available on the effects and influence of different fat tissue compartments on the periprocedural course and long-term outcome of these patients during and after TAVR. We speculate that benefits addicted to obesity in TAVR patients compared to lean or lowest weight subjects might only be a consequence of a higher prevalence of cachectic and risk louden patients in TAVR cohorts analyzed so far. Effects of dysbalanced tissue distribution patterns even in “normosome” individuals might as well modulate outcome data beside unobtrusive BMI-calculation.

The purpose of our investigation is to analyze for the impact of epicardial fat tissue, visceral abdominal fat tissue and subcutaneous fat tissue on the short- and longterm mortality in elderly undergoing cardiac treatment. We speculate that morbid obesity and cachexia / sarcopenia are rather propagators of perioperative and intermediate term risk than a paradox drivers.

Proteasome modulation as a strategy to battle ageing and aggregation-related pathologies

Niki Chondrogianni

Proteasomes are constituents of the cellular proteolytic network that maintain protein homeostasis through regulated proteolysis of normal and abnormal (in any way) proteins. Proteasome activation in cell lines and Caenorhabditis elegans resulted in cellular and organismal lifespan extension and in deceleration of protein aggregation in Alzheimer's (AD) and Huntington's (HD) nematode models. The potential of proteasome modulation as an anti-ageing and anti-aggregation strategy will be discussed along with the involved molecular mechanisms. Results on natural-occurring or chemically-synthesized compounds with proteasome activating properties will be presented.

Acknowledgements We acknowledge funding by the European Union and Greek national funds through the Operational Program Competitiveness, Entrepreneurship and Innovation under the Program "Special Actions Aquaculture – Industrial Materials – Open Innovation in Culture" (project ALGOSMETIC, Τ6ΥΒΠ-00474)

Is vaccination an anti-aging intervention?

Tamas Fülöp

Aging is a complex process still very ill defined. From this lack of consensus arises the debate whether aging can be considered a disease. This concept is very important as it determines our approach for treatment of aging per se, rather than treatment of aging-related diseases. A majority of the gerontology community (and even WHO) nowadays consider aging as a disease which should be treated. This treatment in view of Geroscience would decrease the occurrence of the abovementioned age-related diseases. The science behind this view is the definition of the nine pillars of aging. The clinical science implementing this view is called anti-aging medicine. There is already a myriad of anti-aging treatments, claimed to be affecting the aging process. The most important are the rapalogues, the senolytics and the immunomodulators. It is of note that most of our knowledge translated to humans comes from experiments in laboratory animal models. We aim in this presentation to discuss how the aging process can be conceptualized (considering its numerous definitions), whether aging is a disease or not, and how aging is implicated in age-related disease. Finally, we will present how benefits of vaccination can be defined in the complex systems biology of aging, but certainly not as an anti-aging intervention.

Senolysis in the context of injury and regeneration

Mikolaj Ogrodnik

The term "cellular senescence" is defined as an irreversible cell cycle arrest that is accompanied by changes in morphology, intracellular signaling, damage content and secretory profile, among others. Broadly speaking, conditions that are known to relate to an accumulation of damage and/or an increase in pro-growth stimuli, such as development, aging, obesity and regeneration, all show an increase in the quantity of senescent cells. Importantly, while the etiology of the accumulation of senescent cells in those highly distinct conditions is unclear, the persistence of senescent cells have been proven to contribute to the pathology of age-related diseases and other detrimental conditions. In fact, therapeutics selectively eliminating senescent cells, such as senolytic drugs, which induce apoptosis specifically in senescent cells delay or even prevent age associated diseases. However, it is unclear, how senolytic interventions would affect conditions, which are characterized by potentially beneficial functions of cellular senescence, for example during wound healing. The presentation aims at outlining the etiology of cellular senescence in vivo, summarizing the concept of senolysis and showing the conceptual basis for its influence on skin injury and regeneration.

Is anti-ageing the answer?

Alexandra Stolzing

An emerging consensus has identified a defined number of ‘hallmarks of aging’ making the prospect of combinatorial therapies to delay or even reverse, age-related functional decline plausible. This has sparked increased research and investment into translating insights from basic biogerontology towards clinical applications, including in cardiology. However, as I will show using the example of cellular senescence, these novel ‘anti-aging’ concepts face various challenges: interventions in basic metabolic processes need to be carefully calibrated and pathways for funding and assessing clinical trials in this sector are in their infancy. I argue that ‘anti ageing’ is not the goal of biogerontology - informed regenerative medicine but instead its necessary side effect.

Posters

(in alphabetical order)

Sunday 05th of September from 11:30 to 11:45

The Poster Award Ceremony

(1) Alzheimer-Associated Risk Genes in the Context of Disturbed Blood-Brain Barrier Function and Microglia-Mediated Inflammation

Chaudhry Luqman Abid
Martin-Luther-Universität Halle-Wittenberg, Institute for Physiological Chemistry

Alzheimer's disease (AD) is the leading cause of dementia. The two histopathological markers of AD are amyloid plaques composed of the amyloid-β (Aβ) peptide, and neurofibrillary tangles of aggregated, abnormally hyper-phosphorylated tau protein. The majority of AD cases are late-onset, after the age of 65, where a clear cause is still unknown. However, there are different multifactorial contributors including age, environment, biology and genetics, which can increase risk for the disease. Genetic factors such as rare variants of TREM2 (triggering receptor expressed on myeloid cells-2), ABCA7, and CD33 strongly increase the risk of developing AD, confirming the role of microglia in AD pathogenesis. Rare variants in the ABCA7 gene recommend the analysis of disturbed blood-brain barrier function in AD patients. Therefore, we developed and characterised a blood-brain barrier model and microglia-like cell model from patient-derived induced pluripotent stem cells harbouring the risk genes for AD. These models can further be used to study the pathology of AD and the contribution of risk variants to the disease.

(2) The impact of mitochondrial Telomerase Reverse Transcriptase on myocardial ischemia / reperfusion injury

Niloofar Ale-Agha[1], Philipp Jakobs[1], Christine Goy[1], Florian von Ameln[1], Andre Heinen[2], Axel Gödecke[2], Yogi Altschmied[1], Jojo Haendeler[1]
[1] Environmentally induced cardiovascular degeneration, Institute of Clinical Chemistry and Laboratory Diagnostics;
[2] Institute for Cardiovascular Physiology, University Hospital and Heinrich-Heine-University Düsseldorf

Background: Mitochondrial dysfunction due to aging is associated with cardiovascular disorders. The catalytic subunit of Telomerase, Telomerase Reverse Transcriptase (TERT) is a dual-targeted protein found in the nucleus and in mitochondria. TERT has a protective function in the cardiovascular system and the absence of TERT impairs mitochondrial respiration. Since the exact roles of mitochondrial TERT in cardiovascular aging and disease processes have not been clarified, we created two mice models containing TERT exclusively either in the mitochondria (mitoTERT mice) or in the nucleus (nucTERT mice).

Results: Both, mitoTERT and nucTERT mice were phenotypically normal and did not show differences in the basal cardiac function compared to wildtype and knockout mice. However, cardiac mitochondria from nucTERT mice, similar to TERT-deficient animals, exhibited reduced complex I respiration, while respiration was improved in cardiac mitochondria from mitoTERT mice. After ischemia/reperfusion, infarct and scar sizes were larger in TERT knockout and nucTERT mice than in wildtype animals, whereas mitoTERT mice had smaller infarcts and scars. Moreover, mitochondrial TERT attenuated the decrease in ejection fraction observed in the other genotypes and improved vascularization after myocardial infarction. In addition, serial echocardiography over 28 days after myocardial infarction demonstrated a left ventricular dilation, which was significantly reduced in mitoTERT mice compared to TERT-deficient mice. Furthermore, after 28 days, stroke volume was increased even over wildtype animals.

Conclusion: We could show for the first time a compartment-specific function of TERT in the cardiovascular system *in vivo* by demonstrating that mitochondrial, but not nuclear TERT, is crucial for cardioprotection after myocardial infarction.

(3) Characterization of the APOE Knockout Rabbit as a Model of Metabolic Ageing in Female Reproduction

Maximilian Buske, Maria Schindler, Juliane Thoma, Johanna de Nivelle, Juliane-Susanne Jung, Elisabeth Halbauer, Alicia Toto Nienguesso and Anne Navarrete Santos
Department of Anatomy and Cell Biology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany

The laboratory rabbit (*Oryctolagus cuniculus*) is widely used as a reproductive model, which shares similar characteristics to humans, in preimplantation development and lipid metabolism. One molecular factor for lipoprotein clearance is the glycoprotein Apolipoprotein E (APOE). APOE knockout rabbits (APOE (-/-)) have an altered lipid metabolism, resulting in elevated levels of plasma cholesterol and triglycerides (1). The working hypothesis is that the APOE gene knockout leads to an early ageing in female reproductive organs. Advanced maternal age and metabolic diseases are associated with decreased female fertility.

We obtained preimplantation embryos, female reproductive tract organs and liver samples from APOE (-/-) and old rabbits (>108 weeks) as well as from young rabbits (16 weeks, control group). Using quantitative RT-PCR, Western Blot and Simple Western Blot Sally Sue we investigated the expression of marker genes involved in cholesterol- and fatty acid metabolism and genes associated with cellular ageing and development.

In APOE (-/-) and old rabbits the transcript amounts of the metabolic markers Srebp 2 (liver) as well as VLDLR and LDLR (liver, ovary, endometrium) were upregulated while HMGCR (liver, fallopian tube) was downregulated compared to young controls. Furthermore, CPT1 B, which is involved in the beta oxidation, was upregulated in the liver and ovary in old and APOE (-/-), while pACC and FASN were downregulated. FASN is decreased in the endometrium of old rabbits too. Moreover, the insulin-like growth factor 2 (IGF2) expression was reduced in the APOE (-/-) and old rabbits.

Our results show that a loss of APOE leads to alterations in metabolic pathways in the reproductive tract organs. The downregulation of IGF2 hints at alterations in early pregnancy development. The APOE (-/-) rabbit produced significantly lower amounts of embryos (Mean±SD: 7.1±2.3 vs. 10.2±3.7), demonstrating the loss in fertility at preimplantation stage. Since old rabbits show comparable results, APOE might be a crucial factor for fertility at higher maternal age.

This study was supported by the German Research Council (DFG; ProMoAge GRK 2155)

1: Niimi, M., et al. (2016). ApoE knockout rabbits: A novel model for the study of human hyperlipidemia. Atherosclerosis **245**: 187-193.

(4) Effects of curcumin on endothelial cells

Fiona Cox[1,2], Jan Greulich[1], Philipp Jakobs[1], Niloofar Ale-Agha[1], Maria Grandoch[2], Yogi Altschmied[1], Jojo Haendeler[1]

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Background: The natural bioactive compound curcumin, a polyphenolic compound extracted from the rhizome of the turmeric plant, has been ascribed beneficial effects in aged individuals. In particular, curcumin increases lifespan and has anti-aging effects in several animal models. Moreover, it improves endothelial functionality in elderly humans. Besides others, these effects are related to changes in the transcriptome. Several plant compounds have been suggested to activate or inactivate the transcription factors aryl hydrocarbon receptor (AhR) and nuclear factor (erythroid-derived 2)-like 2 (Nrf2), which have opposing effects in the cardiovascular system. While AhR expression is negatively correlated with cardiovascular functionality, Nrf2 has been shown to be beneficial.

Results: We could show that 7.5 µM curcumin increases migration of EC, one readout for proper EC function, independently of AhR levels. Moreover, curcumin did neither induce nuclear translocation of AhR nor did it increase the transcript level of *cyp1a1, a bona fide* AhR target gene excluding AhR as a direct mediator of curcumin effects in EC. In contrast, curcumin treatment resulted in an increase in Nrf2 levels and promoted its nuclear translocation, which was mirrored in the upregulation of the Nrf2 target *sod2* on the transcript and protein level. Thus, activation of Nrf2 is likely one of the primary effects of curcumin in EC. Since several studies have already shown a link between Nrf2 and AhR, we examined if an interaction between these two signaling pathways exists with respect to the response to curcumin. We could show that the activation of Nrf2 by curcumin was not affected by the downregulation of AhR via RNA interference.

Conclusion: The mechanism of action of curcumin, and therefore its protective effects in the endothelium are mainly based on activation of the transcription factor.

(5) Mechanistic insights into functions of mitochondrial Telomerase Reverse Transcriptase in the heart

Nadine Dyballa-Rukes[1, 2], Philipp Jakobs[1], Christine Goy[1], Sabine Metzger[2], Yogi Altschmied[1], Jojo Haendeler[1]

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[2] MS-Platform, Cluster of Excellence on Plant Sciences, Botanical Institute, University of Cologne

Background: Aging is one major risk factor for cardiovascular diseases. The enzyme Telomerase Reverse Transcriptase (TERT) designated as an anti-aging enzyme is not only expressed in stem cells and highly proliferating cells but also in non-proliferating tissues like the heart and vasculature. Interestingly, the protein is also present in mitochondria. To delineate the molecular functions of mitochondrial TERT in the cardiovascular system we performed proteomic studies.

Results: Comparative analyses of the mitochondrial proteome showed that the protein Prohibitin is present in higher levels in heart mitochondria of TERT-deficient mice compared to wildtype animals, but shows a lower mitochondrial content in so-called mitoTERT mice which contain TERT exclusively in the mitochondria of all cells. This finding was corroborated in cardiac fibroblasts from the respective mice. Prohibitin is known to sequester matrix arm subunits of complex I from the respiratory chain, thereby impairing complex I functionality. Along this line, we demonstrated improved stoichiometry of complex I matrix arm and membrane subunits in cardiac fibroblasts from mitoTERT mice. On the cellular level, we showed that complex I activity is required for differentiation of cardiac fibroblasts into myofibroblasts, a cell type required in the early phase after myocardial infarction. While TERT-deficient cardiac fibroblasts were incapable of myofibroblast differentiation, this process was improved in cells from mitoTERT mice.

Conclusion: Exclusively mitochondrial-localized TERT is critical for mitochondrial respiration, by improving complex I subunit composition and enhances myofibroblast differentiation.

(6) Mineralocorticoid Receptor-regulated Genes in Cardiovascular Aging

Yekaterina Gadasheva, Alexander Nolze, Nicole Straetz, Claudia Grossmann
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One of the risk factors for the development of cardiovascular diseases is aging. The mineralocorticoid receptor (MR) is a transcription factor with aldosterone (aldo) as endogenous ligand. Classical epithelial MR effects are sodium, and water reabsorption as well as proton and potassium secretion in the kidney. The MR is also expressed in the cardiovascular system, where it supports endothelial dysfunction, fibrosis, hypertrophy and inflammation. MR antagonists provide effective treatment for patients with heart failure with reduced ejection fraction, reducing morbidity and mortality. There is significant evidence of increased MR activity during aging in the vasculature wall without correlating changes of its ligand aldo, possibly through posttranslational modifications of the MR. Our aim was the identification and characterization of MR-regulated genes that play a role in cardiovascular aging. To assess aldo-regulated genes, RNA-seq experiments were performed in an inducible, MR overexpressing HEK cell system. Among highly regulated, novel genes, three are involved in energy homeostasis (PRKAB2, MAP3K6, and PDK4). As deregulated nutrient sensing and mitochondrial dysfunction belong to the hallmarks of cardiovascular aging, we focused on PDK4, a major regulator of metabolic flexibility in mammals. In our RNA-seq data only one upregulated isoform of PDK was detected, which was validated by qRT-PCR and Western blot. PDK4 activity was assessed by analyzing phosphorylation of the downstream target PDHA1. The p(S293)-PDHA1/PDHA1 ratio was increased in aldo-stimulated cells compared with control group, which correlates with elevated PDK4 mRNA levels. To investigate the functional consequences, glucose consumption, lactate production and cell death (apoptosis and necrosis) were measured. We saw an increase in glucose consumption, lactate production as well as elevated caspase and LDH levels as indicators of apoptosis and necrosis. Concurrently, we found a reduction in protein content in aldo-stimulated cell lysates. Overall, we saw that activated MR leads to augmented PDK4 expression and activity with increased glucose consumption and lactate production as well as increased apoptosis and necrosis with reduced protein content. These results suggest that MR through modulating PDK4 expression may lead to metabolic changes that have an effect on cardiovascular energy homeostasis and aging.

(7) The transcription factor Grainyhead-like 3 exerts extra-nuclear functions in the endothelium by interaction with endothelial nitric oxide synthase

Jan Greulich[1], Annika Vierkant[1], Kirsten Jander[1], Niloofar Ale-Agha[1], Philipp Jakobs[1], Corina Marziano[2], Swapnil K. Sonkusare[2], Jojo Haendeler[1], Yogi Altschmied[1]
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[2] Robert M. Berne Cardiovascular Research Center, University of Virginia, Charlottesville, VA, USA

Background: Aging is accompanied by a decline in vascular functionality. Important hallmarks are reduced expression of endothelial nitric oxide synthase (eNOS) resulting in decreased bioavailability of nitric oxide (NO), impaired migratory capacity and increased apoptosis sensitivity of endothelial cells (EC). The transcription factor Grainyhead-like 3 (GRHL3) is expressed in primary human EC, where it inhibits apoptosis and increases migratory capacity as well as NO bioavailability. However, the underlying mechanisms are not completely understood.

Results: Using *en face* preparations of arteries from different vascular beds of mice we showed that GRHL3 is also localized outside the nucleus in myo-endothelial projections. The presence of GRHL3 in these protrusions of endothelial cells directly contacting the adjacent smooth muscle cell layer suggests that GRHL3 might have extra-nuclear functions. After generating a GRHL3 variant that cannot enter the nucleus anymore, we demonstrated that this protein is still capable of inhibiting EC apoptosis and promoting migration. In line with the notion that both processes depend on NO, we showed that extra-nuclear GRHL3 induces activation of eNOS and increases the cellular S-NO content. Interestingly, extra-nuclear GRHL3 more potently improved those cellular processes than the unaltered GRHL3. Mechanistically, we found that GRHL3 interacts with eNOS in a proximity ligation assay. This interaction was more pronounced with extra-nuclear GRHL3. Moreover, the close proximity between GRHL3 and eNOS was also found in arteries of mice *in vivo.*

Conclusion: One extra-nuclear function of GRHL3 is its interaction with eNOS in the endothelium. In the future this might be useful in devising strategies to delay endothelial dysfunction and thus, the age-associated loss of vascular functionality.

(8) BioSALSA: Biomarkers of Healthy Ageing in Saxony-Anhalt

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Since 2002, citizens of Halle (Saale) contribute to answering scientific questions in the CARdiovascular disease, Living and Ageing in Halle (CARLA) Study. The study originated from the scientific interest in the prevalence and risk factors of cardiovascular diseases, thus covering diverse cardiovascular parameters and tests.

From 2007 to 2010 and in 2013, two follow-ups already took place, and currently, the third follow-up (FU-3) is implemented to investigate healthy aging in the average population of Halle (Saale).

Participants are undergoing a thorough examination to characterize their aging, including functional tests and parameters, an interview and questionnaires, and an echocardiogram. Additionally, blood parameters are analyzed, and blood and urine samples are collected for further analysis. Furthermore, peripheral white blood cells are isolated and also stored for future research.

We pursue both longitudinal and cross-sectional approaches for biomarker analysis. For example, in baseline and FU-3 samples, a panel of blood biomarkers including ferritin, PSA and DHEAS is measured, as well as a panel of advanced glycation endproducts(AGE)-related markers like soluble receptor for AGEs, AGE-autoantibodies, and AGE-fluorescence. Furthermore, cross-sectional analyses are carried out within FU-3 to evaluate, for example, the immune senescence of the cohort.

Due to the duration of the CARLA-cohort, we have the rare opportunity to carry out longitudinal biomarker and outcome analysis on data and samples spanning nearly 20 years of the participants' lives. Thus, despite the small cohort size, we believe that BioSALSA will uncover new aspects of healthy aging. Final results can be expected in 2022.

(9) The Aryl Hydrocarbon Receptor: a Novel Receptor for Advanced Glycation End Products?

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For over 20 years, the receptor of advanced glycation end products (RAGE) is under investigation for its binding of advanced glycation end products (AGEs) and triggered downstream signaling cascades. However, studies, especially when utilizing complex AGE-mixtures or RAGE-knock-out models, describe changes that cannot be explained by RAGE as the only involved receptor.

Thus, we hypothesize that a currently unknown receptor can mediate those effects following activation of active components in mixtures of AGEs. Literature research revealed one receptor, the aryl hydrocarbon receptor (AhR), with a strikingly similar downstream repertoire and first hints towards an activation by AGEs or related modifications.

To follow up on this hypothesis, we utilized two reporter-cell lines of AhR-activity and stimulated them by a water-soluble extract of bread crust (BCE) containing a wide variety of AGE- and oxidative modifications. Further biochemical analyses were also carried out to describe AhR-activation by BCE in the reporter cell lines and non-reporter cell lines with low RAGE content.

Indeed, both reporter cell lines displayed an activation following BCE-stimulation, which could be omitted by AhR-inhibitors but was not influenced by a RAGE-inhibitor. Expression of downstream targets could also be confirmed in non-reporter cell lines via qRT-PCR. Apart from this nuclear AhR-signaling, analyses of receptor-degradation hinted towards the presence of non-classical, kinase-based AhR-signal transduction taking place in nearly all cell lines.

In summary, the conducted analyses suggest that the aryl hydrocarbon receptor is activated by modifications in AGE-rich extracts and could account for RAGE-independent effects seen in previous studies. Thus, the AhR might be a novel receptor of AGEs or related oxidative modifications and should be considered a novel target in the research of AGE effects.

(10) N-octanoyl dopamine is associated with alterations in gene expression and reduced oxidative stress when administered to the brain-dead donor rats

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[4] Department of Medicine V (Nephrology/Endocrinology/Rheumatology), University Medical Centre Mannheim, Mannheim, Germany.

Objectives Hearts of brain-dead (BD) donors still constitute the primary source of heart transplantation. We previously demonstrated that N-octanoyl-dopamine (NOD) administration in donors after the onset of brain death improves cardiac function. To further identify the molecular mechanisms and the pathway linked to the beneficial effects of NOD, in this study, we analysed the expression of 96 genes and investigated oxidative as well as nitro-oxidative damage in donors after brain death.

Methods Male Lewis rats were either subjected to sham operation or brain death, followed by a continuous intravenous infusion of either NOD (0.882 mg/kg/h, BD+NOD group) or a physiological saline vehicle (BD group) for 5.5h. *In vivo* left-ventricular (LV) cardiac function was assessed with a Millar pressure-volume (PV) conductance catheter system. The expression of 96 genes and immunohistochemical staining of 4-hydroxy-2-nonenal (HNE) and nitrotyrosine were performed.

Results NOD treatment significantly improved cardiac parameters in the BD group (stroke work: 5688±561 vs 1933±459 mmHg*µl; the slope E_{max} of the end-systolic PV relationship: 4.04±0.51 vs 2.1±0.4 mmHg/µl; maximum rate of fall of LV pressure dP/dt_{min} -6349±1110 vs -2822±580 mmHg/s, $p \lessdot 0.05$). BD significantly altered the expression of 14 genes compared to control (Birc3, Nos2, Nox4, Ccl3, Ccl4, Ccl11, Ccl12, Cxcr4, Il6, Sele, Tnf, Bcl2l1, Ptgs1, and Ccl20). When comparing BD and BD+NOD groups to control, NOD downregulated Nox4 and upregulated Hmox1. Furthermore, NOD treatment decreased immunoreactivities of HNE (1.5±0.1 vs 2.4±0.2, $p<0.05$) and nitrotyrosine (1.8±0.2 vs 2.2±0.1, $p=0.29$) compared to BD group.

Conclusions N-octanoyl dopamine is associated with alterations in gene expression and reduced oxidative stress when administered to the brain-dead donor rats.

SKI and GS contributed equally

(11) Functional characterization of the murine aorta considering location, sex, and age

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Objectives: The regulation of the vascular tone is involved in many physiological and pathophysiological processes. However, a comprehensive characterization of the vasomotor function considering sex, age, and location has not been described yet.

Methods: Proximal and distal segments of the descending thoracic aorta of young male and young female, each 3-4 mo, as well as old male and old female, each 18-19 mo, C57BL/6J mice (N=6/group) were cut into rings and mounted in organ bath chambers. We investigated maximal vasoconstriction by potassium chloride (KCl), endothelial integrity using phenylephrine (PE), and endothelial-dependent vasorelaxation using acetylcholine (ACh).

Results: Maximal vasoconstriction to KCl and PE was significantly stronger in old compared to young mice (KCl: 1.72±0.03 vs. 1.19±0.06 g; $p<0.001$; PE: 1.17±0.10 vs. 0.67±0.06 g; $p<0.001$). Relaxation to ACh was not significantly different between young and old mice. We observed no statistical differences between male and female mice regarding KCl, PE and ACh. Maximal vasoconstriction to PE was significantly stronger in proximal compared to distal rings (1.04±0.09 vs. 0.74±0.07 g; $p<0.05$). Distal rings showed a significantly higher maximal endothelial-dependent relaxation to ACh than proximal segments (83.05±1.78 vs. 77.97±1.35%; $p<0.05$). Maximal vasoconstriction to KCl did not show significant differences between proximal and distal rings. We will show subgroup comparisons of young male and female as well as old male and female mice considering location in the meeting presentation.

Conclusion: The preliminary results of the research series suggest that first, maximal vasoconstriction is dependent on age, that second, endothelial integrity is dependent on age and location, and that third, endothelium-dependent vasorelaxation is dependent on location. The conclusions might be adapted when all experiments are finished.

(12) Skeletal muscle mitochondrial dysfunction is associated with life expectancy in rats with high or low intrinsic exercise capacity and is sex specific

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Aging is associated with decreasing exercise capacity and increasing incidence of diseases. Mitochondrial function is central in ageing and is associated with exercise capacity. In rats with genetically determined (inherited) high (HCR) or low (LCR) exercise capacity, LCR present with 1/3 lower life expectancy and we aimed to assess, if this is related to mitochondrial dysfunction.

Adult (15 weeks) and old (100 weeks) HCR and LCR as well as senescent (130 weeks) HCR were tested for exercise capacity and cardiac function. Mitochondria from cardiac and skeletal muscle were functionally assessed.

Independent of age, exercise capacity was lower in LCR. Cardiac function decreased with age but was comparable in male HCR and LCR whereas contractile function was higher in old LCR compared to old HCR in females. In skeletal muscle, mitochondrial mass decreased in old males whereas respiratory capacity decreased in old females. Both effects were stronger in LCR compared to HCR. Senescent HCR showed an additional impairment of mitochondrial mass in males and mitochondrial respiratory capacity in females leading to the same low levels as found in old LCR.

Impairment in skeletal muscle mitochondrial function is associated with approaching end of life but the type of impairment differs between sexes independent of inherited exercise capacity.

(13) NIT1 acts as a repressor of FoxO3a-dependent stress resistance

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FoxO3a (Fork-head box O3a) is a transcription factor that regulates various cellular processes such as stress resistance, metabolism, cell-cycle arrest, and apoptosis. Of these, modulation of the cellular stress response by FoxO3a was shown to contribute to longevity in model organisms, such as *C. elegans*. In order to analyze the regulation of FoxO3a in response to oxidative stress we assessed the interaction of FoxO3a with the metabolite repair enzyme NIT1 (Nitrilase1). We not only found that NIT1 interacts with FoxO3a, but that this interaction is altered upon exposure to varying concentrations of hydrogen peroxide (H_2O_2). Moreover, we show that FoxO3a transcriptionally regulates NIT1 expression, suggesting a feedback regulatory mechanism. Akt-dependent phosphorylation of FoxO3a appears to be involved in the regulatory mechanism, as demonstrated using a dominant active FoxO3a mutant with all Akt target sites mutated (T32A, S253A, S315A). Furthermore, NIT1 repressed the expression of FoxO3a target genes, such as those encoding mitochondrial superoxide dismutase (SOD2) and catalase. In line with these cell culture data, we observed that Nit-Fhit (Nft)-deficient *C. elegans* have a longer lifespan than wild-type worms, suggesting a repressive role of NIT1 on the stress resistance elicited by FoxO3a.

(14) Reversing endothelial cell aging by partial reprogramming strategy

Katrin Kalies[1], Kai Knöpp[1], Leonie Wurmbrand[1], Magdalena Baier[1], Max Rieckmann[1], Jochen Dutzmann[1], Daniel Sedding[1]
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Background and purpose: Senescent endothelial cells (EC) are key players in the pathophysiology of cardiovascular diseases. They are characterized by a reduced angiogenic and regenerative potential and an enhanced inflammatory phenotype. Therefore, reversing EC senescence might represent a promising therapeutic strategy to restore vascular function and increase health and lifespan. Here, we show a reversal of EC senescence following the application of a pharmacological, non-genetic, partial reprogramming strategy to induce a timely restricted induction of the Yamanaka-factors Oct3/4, Sox2, Klf4 and c-Myc (OSKM).

Methods: Methods to characterize the effects of pharmacological reprogramming included the quantification of gene expression, Western Blot analysis, immunofluorescence staining's as well as the analysis of EC function by proliferation, tube formation and sprouting assays *in vitro*.

Results: The application of a pharmacological cocktail to senescent EC resulted in a robust but timely restricted induction of OSKM. This was associated with a significantly reduced expression of senescence markers such as p16ink4a and p14arf on mRNA expression level. Additionally, telomere length was stabilized. We also observed enhanced functional properties of senescent EC, such as proliferation, migration, sprouting and tube formation. Secretion of cytokines as TNF-α and IL1- β was reduced compared to senescent untreated cells.

Conclusion: In summary, we demonstrate that a short induction of OSKM via a pharmacological cocktail of FDA approved drugs holds the potential to reverse senescence in EC *in vitro* and thus might enhance endothelial regenerative capacity *in vivo*.

(15) Cellular and molecular impact of nuclear protein glycation

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Ageing is a complex process of genetic and environmental components, which leads to degenerative diseases, and ultimately ends with death. Posttranslational modifications (PTMs) of proteins play an important role in the ageing process. PTMs include enzymatically controlled modifications as well as reversible and irreversible non-enzymatic reactions. Glycation is a non-enzymatic reaction between reducing sugars or other α-dicarbonyl compounds and amino groups of proteins, lipids, and nucleic acids, resulting in Advanced Glycated End Products (AGEs). Histones are rich in lysine and arginine, and therefore they are prone to glycation. The nucleosome core is formed of H2A-H2B dimers and an H3-H4 tetramer. We aim to investigate posttranslational modification (PTM) of histones and their possible impact on function during aging.

Site-directed mutagenesis was applied to create wild type (wt) and mutant type (mt) histones by exchanging lysine/arginine with glutamine/tyrosine, thereby mimicking AGE modifications. Protein purification was done by using ion-exchange chromatography followed by the gel filtration chromatography technique. After purification of all core histones in wt and mt, salt dialysis technique and SDS gel separation were applied to study the nucleosome assembly and histone-histone interaction.

In previous work performed by Arina Urazova, we observed that senescent cells tend towards lower level of AGE-modifications on histones and towards less abundancy of the H2BK43CML and H3K79CEL modifications. Furthermore, in our recent study, we found out that H2AK95Q and H2BK43Q do not affect histone octamer formation, whereas H2BK43Q decreases nucleosome stability. In the current study, we are focusing on wt and mt four core histones (mimicking protein glycation). The impact of histone glycation on the protein structure and protein-protein or protein-DNA interaction at the molecular level will be investigated.

(16) Physical activity trajectories at older age and all-cause mortality: a cohort study

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Background

A physically active lifestyle is recognized as a precondition of healthy aging. However, the majority of studies exploring its association with mortality in cohorts of adults used single-time physical activity (PA) estimate, which do not consider its dynamic nature with changes that occur with aging. The aim of the present study is to explore the presence of different PA trajectories in a population-based cohort and their association with mortality.

Methods

We used data of the population based cohort study CARLA and included 1041 elderly subjects (45-83 years at baseline) with self-reported physical activity at baseline (2002-2006), first follow-up (2007-2010) and second follow-up (2013). Trajectories were identified using growth mixture modelling. Cox proportional hazard models were used to assess the association between trajectories of PA and all-cause mortality during ~6 years since the second follow-up after adjusting for age, sex, lifestyle factors and comorbidities.

Results

Three PA trajectories (categorized as consistently low, consistently moderate, and high at baseline but strongly decreasing PA across time) were identified, and 121 deaths due to all causes occurred. Compared with participants who had consistently low PA-levels throughout the follow-up period, participants who maintained moderate PA-levels were at a lower risk of all-cause mortality (hazard ratio [HR], 0.50; 95%CI, 0.30-0.70). Participants with high PA-levels at baseline but strongly decreasing PA across time, had similar mortality risk compared to the participants with consistently low PA-levels (hazard ratio [HR], 0.89; 95%CI, 0.50-1.70).

Conclusions

Our results suggest that, compared to those who had consistently low PA levels, those who maintained a moderate level of PA showed a protective effect in terms of their mortality risk but not those who displayed a decline from high PA levels.

(17) A novel preservation solution for cardiac and vascular grafts in aged rats: mesenchymal stem cell-derived conditioned medium

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Objectives: Heart transplantation is the standard therapy in end-stage heart failure. A shortage of donor hearts forced transplant programs to accept older donors. Furthermore, in patients undergoing coronary artery bypass grafting (CABG) ischemia/reperfusion injury (IRI) is the main contributor to organ dysfunction. Ageing-induced vascular damage may be further aggravated during CABG. Favourable effects of conditioned medium (CM) from mesenchymal stem cells (MSCs) have been suggested against IRI. We hypothesized that preservation of donor hearts (*Study 1*) or vascular conduits (*Study 2*) with a CM protects the graft from IRI in 15-month-old rats.

Methods: CM from rat MSCs indicates the presence of 28 factors involved in apoptosis, inflammation, and oxidative stress. *Study 1*: Hearts from aged donor Lewis rats were explanted and continuously perfused for 5h with oxygenated, 4°C cardioplegic solution, supplemented with either cell culture medium vehicle or CM. Then, the hearts were heterotopically transplanted. We evaluated 1.5h after transplantation *in vivo* left-ventricular (LV) graft function. *Study 2*: Thoracic aortic rings from aged Lewis rats were explanted and immediately mounted in organ bath chambers (aged group) or underwent 24h of cold ischemic preservation in saline-supplemented either with cell culture medium (aged-IR group) or CM (aged-IR+CM group), prior to mounting. Three month-old rats were used as control young animals.

Results: *Study 1*: LV contractility and relaxation parameters were significantly reduced in aged rats compared to young ones. After transplantation, systolic function (dP/dt_{max}: 1197 ± 94 vs. 1825 ± 279 mmHg/s at 140 µl, $p < 0.05$) and diastolic function (dP/dt_{min}: 737 ± 168 vs. 1200 ± 166 mmHg/s at 140 µl, $p < 0.05$) were significantly improved in the CM group compared to controls. Among the 120 surveyed genes, the expression of 66 were altered. Genes of proinflammatory cytokines and interleukins were down-regulated, while the expression of antioxidant gene superoxide dismutase-2 was up-regulated in the CM-treated grafts compared to controls. *Study 2*: Ageing was associated with an increase in intima-to-media thickness, an increase in collagen-content, higher caspase-12 mRNA-levels and immunoreactivity compared to young rats. Impaired endothelium-dependent vasorelaxation to acetylcholine in the aged-IR group compared to the aged rings was improved by CM (aged 61 ± 2% vs aged-IR 38 ± 2% vs aged-IR+CM 50 ± 3%, $p < 0.05$).

Conclusion: Perfusion of donor hearts or preservation of vascular grafts with CM protects against IRI in 15-month-old rats.

(18) Non-Contact Measurement of Heart Rate Variability and the importance of a potential geriatric biomarker for frailty

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Frailty is a central geriatric syndrome and comprises increased physiological vulnerability. Heart rate variability (HRV) is also described to be compromised by frailty, which – vice versa - might therefore serve as a surrogate parameter (Katayama: Cardiac autonomic modulation in non-frail, pre-frail and frail elderly women: a pilot study, 2015). HRV is typically acquired by an ECG, which may not be tolerated especially by older patients suffering from dementia and/or delirium. Against this background, we sought to measure HRV in a non-contact and unobtrusive way through photoplethysmography imaging (PPGI). The objective of this pilot-study was therefore to determine whether PPGI could reveal 1) HRV differences between frail and non-frail individuals and 2) the influences of early geriatric rehabilitation on HRV.

For our pilot-study we included 10 frail geriatric patients undergoing early geriatric rehabilitation (EGR) versus 10 healthy community-dwelling older adults aged 70 years and older. We assessed frailty according to the Fried's criteria. The HRV of the frail patients were measured both at the beginning and at the end of their hospital stay (EGR). HRV in terms of LF/HF ratio was analysed both for intra-individual changes during the EGR and differences between frail geriatric patients and non-frail community-dwelling individuals.

Among all frail geriatric patients, the median LF/HF ratio obtained with PPGI was found to be reduced during EGR. The frail patients also revealed a higher LF/HF ratio than their community-dwelling counterparts. Both observations in PPGI-based HRV were confirmed by the reference measurements employing a conventional ECG with obstrusive electrodes.

In conclusion, our pilot study shows that PPGI as non-obstrusive measurement is capable of detecting HRV changes and trends in this age group. While the tracking of intra-individual HRV changes is also possible, its reliability needs further improvement. In our study, we demonstrated that the non-contact measurement principle of PPGI emphasise its potential for application in geriatric medicine.

(19) Heterogeneity of senescent endothelial cells

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Cardiovascular diseases (CVDs) are a major cause of death worldwide, and ageing is a relevant risk factor. During ageing, senescent cells accumulate in different tissues. Endothelial cell senescence within blood vessels might have an impact on age-related CVDs. Senescent cells differ from younger proliferating cells by their phenotype and their gene expression. Although common markers for cellular senescence exist, specific markers for potential subgroups of senescent endothelial cells have not been described yet.

This study is aimed to find senescence-specific surface markers for subgroups of senescent endothelial cells and compare them to common senescence markers regarding their sensitivity and specificity. For this purpose, cultured human umbilical vein endothelial cells (HUVEC) will be sorted by fluorescence-activated cell sorting into senescent and young proliferating cells after induction of cellular senescence by passaging/oxidative stress.

By single-cell transcriptome analysis, the expression of senescence-associated genes in young and old cells will be examined. The transcriptome examination includes the expression analysis of common senescence markers, such as cyclin-dependent kinase inhibitor p16INK4a, and surface markers which showed an altered expression in cellular senescence. Potential subgroups of endothelial cells should be identified by the bioinformatics analysis of the transcriptomic data sets.

Further, the identified surface markers will be tested on primary endothelial cells, isolated from graft material of CVD patients.

(20) Landscape of protein post-translational modifications in the aging brain: dysregulation, cross-talk and site competition

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Cell proteostasis can be defined as the dynamic process that ensures correct folding and assembly of newly synthesized polypeptide chains, and the rapid degradation of damaged, mislocalized, or unfolded proteins. The main pathways involved in the maintenance of proteostasis are the ubiquitin-proteasome system, lysosome/autophagy, and several chaperons collectively defined as the quality control system [1,2]. All of these processes are regulated by protein posttranslational modifications (PTMs). Therefore, perturbation of PTMs dynamics can be an indication of proteostasis maintenance decline. How the whole PTMs landscape changes during aging and how this can contribute to the increased vulnerability of aged cells to disease is still not completely elucidated. To investigate age-related changes of PTMs, we initially focused on the mice brain ubiquitinylome, since accumulation of ubiquitin positive protein aggregates is an established hallmark of aging and neurodegeneration. Using a K-GG remnant motif enrichment[3] coupled with mass spectrometry, we were able to quantify more than 3000 modified ubiquitination sites in young and old brains. By normalizing the changes in ubiquitin modified peptides levels with the changes in the whole proteome abundance, we identified several proteins that are targeted by altered ubiquitination in aging without being affected in their total protein level. Moreover, in a previous study[4], we identified carboxymethyl-lysine (CML), an advanced glycation end-product, to occur on ubiquitin and other components of the UPS. We found in our data that CML modifies several lysines on ubiquitin, including the residues K6, K27, K33, and K63 that are generally used for the assembly of poly-ubiquitin chains[5,6]. This suggests a potential interference of non-enzymatic PTMs on ubiquitin chain assembly by direct competition for the same lysine residues. In the future, we plan to expand our analysis to other PTMs including phosphorylation and acetylation, in order to gain further insights into how different PTMs interact and compete with each other in the context of aging.

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(21) Protective effect of SELENOT in LPS-induced endothelial dysfunction

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Background: The incidence and mortality of sepsis increases dramatically with age. Sepsis is an exaggerated immune response upon infection with lipopolysaccharide (LPS) as the main causative agent. LPS-induced activation and apoptosis of endothelial cells (EC) can lead to organ dysfunction and finally organ failure. We have previously demonstrated that the first twenty amino acids of the Apurinic/Apyrimidinic Endodeoxyribonuclease 1 (APEX1) are sufficient to inhibit EC apoptosis.

Results: To identify genes whose regulation by LPS is affected by the N-terminal APEX1 peptide, EC were transduced with an expression vector for the APEX1 peptide or an empty control vector and treated with LPS. Following RNA deep sequencing, genes upregulated in LPS-treated EC expressing the APEX1 peptide were identified bioinformatically. Selected candidates were validated by semi-quantitative real time PCR, a promising one was Selenoprotein T (SELENOT). For functional analyses, two expression vectors for SELENOT were generated. One contains – besides the coding sequence – a part of the 3'-untranslated region of the SELENOT gene with a selenocysteine insertion sequence (SECIS), which is necessary for selenocysteine incorporation at an internal UGA stop codon. The second one lacks the SECIS such that translation terminates at this UGA resulting in a truncated protein. To study the effect of SELENOT expression on LPS-induced EC activation and apoptosis these vectors were transfected in EC. Immunostaining showed that both proteins were expressed and localized in the ER. EC transfected with the SECIS-containing plasmid showed no activation and reduced apoptosis induced by LPS. No such or even opposite effects were observed when the truncated SELENOT protein was expressed.

Conclusion: SELENOT can protect EC against LPS-induced activation and apoptosis and could provide a new therapeutic approach in the treatment of sepsis.

(22) Expression and posttranslational modification of methyltransferase EZH2 in adipose tissue-derived stem cells (ASC) from young and old donors

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Posttranslational modifications (PTM) made to histones can affect gene expression by altering chromatin structure or recruiting histone modifiers. Acetylation and methylation of lysine residues in the tails of nucleosomal core histones have a crucial role in chromatin packaging and gene expression. The histone-modification process changes with cell age. A possible mechanism for “histone ageing” can be alterations in enzymatic modification process. The enzyme enhancer of zeste homolog 2 (EZH2) catalyses the di- and trimethylation of histone H3 at lysine 27 (K27) to form H3K27me2/3. Recently Chu and co-workers identified the cross talk of two important PTMs- histone methylation and methyltransferase activation by O-GlcNAcylation in tumour cells [1]. The hypothesis is that specific EZH2 modifications as O- GlcNAcylation regulate stem cell properties and provides a new approach for cellular ageing in adult stem cells.

We successfully established rabbit adipose tissue-derived stem cell (ASC) cultures from young and old donors which represent an in vitro model for studying the mechanisms of stem cell ageing [2]. In ASCs, obtained from old female rabbits the stem cell plasticity decreased with age of the donor. In ASCs from old rabbits, the level of H3K27 acetylation (ac) increased, indicating for a more open and accessible chromatin state. Furthermore, the increase of H3K27ac correlated inversely with EZH2 expression levels in ASCs from old donors. In addition to expression changes, the crucial factor for EZH2 functionality and stability is the O-GlcNAcylation of specific Ser/Thr moieties as Ser76 and Ser729 [1,3]. In ASCs the mRNA levels of EZH2 seem to be reduced with age. The overall O-GlcNAcylation was analysed as well as mitochondrial respiration to observe possible changes in metabolic functions in adult mesenchymal stem cells in old and young ASCs. Our data indicate that the alteration of EZH2 expression and modification is a potential reason for mesenchymal stem cell ageing in adipose tissue.

This study was supported by the German Research Council (DFG; ProMoAge GRK 2155)

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(23) Effects of lipofuscin on cardiomyocyte function and autophagy

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Background: Aging is a multifactorial process affecting the physiological and functional capacity of all organs and cells of the organism. One important hallmark of the aging process is the accumulation of modified proteins, caused by impaired proteostasis. Failure of protein quality control can reinforce an accumulation of highly oxidized and cross-linked protein aggregates such as lipofuscin (LF) with age. Particularly in postmitotic cells as cardiomyocytes, LF can rapidly accumulate and impact cell function. Thus, we aimed to investigate whether protein aggregates, exemplified by artificial LF, can directly reduce function and autophagy of cardiomyocytes.

Methods: To investigate the impact of LF on cardiomyocyte function, we isolated cardiomyocytes from 5-months old C57Bl/6J mice and treated the cells up to 18 h with artificial LF. To determine the physiological consequences of LF on the cardiomyocytes, changes in contractility and calcium release were measured using the Myocyte Calcium and Contractility System of IonOptix. In parallel, effects of LF on autophagy were determined by immunoblot analysis of autophagy maker LC3 and p62.

Results: After 18 h incubation with LF a significant decrease in the contraction and calcium amplitude of the cardiomyocytes, in comparison to the control, was measured. Similar effects were obtained for the contraction and relaxation velocities. Further, LF can affect autophagy of isolated cardiomyocytes.

Conclusion: Artificial LF can reduce contractility and calcium release of isolated cardiomyocytes. Future experiments with LF in combination with autophagy inducer rapamycin, which was able to compensate the effects of LF on cardiomyocytes contractility, can help to understand the underlying mechanisms.

(24) The GID-ubiquitin ligase complex regulates metabolism via AMPK and influences life-span

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AMP-activated protein kinase (AMPK) is the key regulator of cellular energy homeostasis and influences organismal lifespan. AMPK is composed of a catalytic α-subunit, a regulatory β- and an adenosyl nucleotide-binding γ-subunit. It is activated under energy-deprived conditions, when ATP is depleted and AMP levels are increased. Among many AMPK-substrates, phosphorylation of RPTOR (regulatory-associated protein of mTOR, RAPTOR) and TCS2 (Tuberous Sclerosis Complex 2, Tuberin) inhibit mTOR signaling and regulate many other processes including autophagy, fatty acid and amino acid metabolism, mitogenesis and mitophagy.

Posttranslational modification of proteins with ubiquitin orchestrates a vast number of biological processes, including targeted protein degradation by the ubiquitin proteasome system (UPS), lysosomal/vacuolar protein degradation, endocytosis, intracellular trafficking, regulation of the secretory pathway and transcriptional regulation. Ubiquitination requires a sequential and hierarchical reaction of three enzyme classes, the ubiquitin-activating enzyme (E1), the ubiquitin-conjugating enzyme (E2) and the substrate specific ubiquitin ligase (E3). The GID-protein complex is a highly conserved ubiquitin-ligase complex that regulates the metabolic switch from gluconeogenesis to glycolysis in *Saccharomyces cerevisiae* by targeting key enzymes of gluconeogenesis for 26S proteasomal degradation. Individual subunits of the yeast GID-complex are conserved throughout the eukaryotic kingdom and Gid1p, Gid2p, Gid4p, Gid5p, Gid7p, Gid8p and Gid9p have their closest human orthologs in RANBP9/10, RMND5A/B, GID4, ARMC8, MKLN1/TWA2 (or WDR26), GID8/TWA1 and MAEA/EMP, respectively.

Our recent data reveal that the GID-complex regulates metabolism via AMPK. Loss of GID-function results in a shift from anabolic to catabolic metabolism and several pathways regulated by AMPK are affected. Here we show that the GID-complex regulates AMPK activity by ubiquitination and that loss of this modification results in aberrant AMPK activation and prolongs life-span.

(25) Characterization of selenium-binding proteins, pro-aging factors in *C. elegans*

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Selenium-binding protein 1 (SELENBP1) was recently identified as a methanethiol oxidase (MTO), catalyzing the conversion of methanethiol to hydrogen sulphide (H_2S), hydrogen peroxide (H_2O_2) and formaldehyde. *Caenorhabditis elegans* is frequently used as a model organism to study the impact of metabolism on aging processes. We previously demonstrated that the proposed *C. elegans* protein and SELENBP1 ortholog Y37A1B.5 is a pro-aging factor that confers selenite resistance (1). Here, we tested whether this protein also has MTO activity and therefore constitutes a novel potential source of hydrogen sulphide in *C. elegans*.

First, we developed an MTO activity assay that can be used on isolated proteins and on cell and *C. elegans* lysates. The assay is based on *in situ*-generation of methanethiol from methionine as catalyzed by a bacterial recombinant L-methionine gamma-lyase (MGL), followed by detection of two of the three methanethiol oxidation products, H_2S and H_2O_2 (2).

We isolated recombinant Y37A1B.5 protein, followed by MTO activity analysis and found that it is active as a methanethiol oxidase, similar to recombinant human SELENBP1.

We then sought to test for MTO activity of the protein in its natural environment and tested *C. elegans* lysates for MTO activity. To assess the overall contribution of Y37A1B.5 to any *C. elegans* MTO activity, we also used a newly generated Y37A1B.5-deficient *C. elegans* mutant strain. Whereas MTO activity was easily detected in wildtype *C. elegans* lysates, no MTO activity was detected in the mutant strain, suggesting that the Y37A1B.5 protein is the major *C. elegans* MTO. Moreover, life span analysis revealed that the mutant strain had an extended lifespan, similar to the previously reported wildtype worms exposed to Y37A1B.5-specific RNAi (1). Two of the three MTO reaction products, hydrogen sulphide and hydrogen peroxide, have been reported to modulate lifespan*,* through interaction with signal pathways and cell respiration in *C. elegans.* To which extend MTO-activity or its reaction products contribute to the observed pro-aging effects or the modulation to oxidative stress remains elusive and requires further research.

In summary, the Y37A1B.5 protein is a novel methanethiol oxidase and therefore a novel potential source of hydrogen sulphide in *C. elegans*. It is also a factor apparently shortening lifespan. Based on its homology to human selenium-binding protein 1, we renamed it SEMO-1 (SELENBP1 ortholog with MTO activity).

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This study was supported by the German Research Foundation (DFG, Bonn, Germany), through research training grant #RTG 2155/2 “ProMoAge”.

(26) Biodistribution of liposomes as an immunomodulator of myocardial inflammation

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Since increasing age is correlated with cardiovascular pathologies, e.g. myocardial infarction, a therapeutic agent of the common causal mechanisms is of interest in an aging society. The phenomena of senescence include "inflammaging", a systemically increased inflammatory baseline and breakdown of tolerogenic mechanisms. It leads to increased inflammatory autoaggression and defective healing, causing heart failure and fibrosis after myocardial infarction. A protagonist herein are myeloid cells. As a central part of the mononuclear phagocyte system, monocytes and macrophages are modifiable by liposomes, nanomedical vesicles influencing innate immune pathways of phagocytosis- and toll-like-receptors and effectively changing gene expression to a pro-healing phenotype.

Herein, we differentially characterize the pharmakokinetics of i.v. injected PEGylation-coated liposomes, containing different surface loads of therapeutic phospholipids, both in healthy and infarcted mice. Produced liposomes showed diameters below 150 nm, narrow size distributions and composition-dependent surface charges. Using fluorescence imaging, we traced the labelled liposomes non-invasively over 48 hours, and measured their systemic distribution *ex vivo* at single organ resolution.

While our control phospholipid S100 circulated over days, phosphatidylserine(PS)- and phosphatidylglycerol(PG)-liposomes accumulated withing 15-45 minutes in liver and spleen. Repetitive injections lead to a cumulating total dose, while single injection led to a stable signal intensity over 2-3 days. The distribution profile of healthy and infarcted mice was comparable, with the exception of S100-liposomes accumulating in the infarct area.

Investigations of therapeutic effects and mechanisms are ongoing.

Taken together, liposomes offer a safe and relevant therapeutic possibility of interfering with post-infarction inflammatory responses.

(27) Clonal hematopoiesis in experimental induced colitis

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Introduction/ Background: Clonal hematopoiesis (CH) describes the expansion of individual blood cells in the circulatory system and in peripheral, functional tissues, that is associated with the occurrence of a somatic DNA mutation. The development of such a cell mosaic is a natural aging process and is connected with a higher risk of malignant hematological diseases. Besides changes in the blood cells themselves, also changes in the bone marrow niche might be involved in this process. Rising evidence indicates a general connection between conditions with chronic inflammation and an increased selection pressure for the development of CH.

Aim/Method: Purpose of this study is (i) to analyze alterations in the bone marrow (BM) microenvironment with effects on inflammatory processes and (ii) to assess a mutual influence of CH and inflammatory bowel disease (IBD). For the development of experimental colitis, male Apolipoprotein E (*Apoe)*-deficient mice receive 1,5% dextran sodium sulfate (Dss) via drinking water in five cycle feeds. Alterations in BM composition were examined using MRI (magnet resonance imaging) and histological staining. Circulating immune cells and BM resident leukocytes and stem cells were analyzed by flow cytometry analysis. DNA single nucleotide polymorphism mutations (SNPs) from BM derived neutrophils and monocytes were evaluated by Sanger sequencing.

Results: Experimental induced colitis reduces survival, causes decreased weight gain and leads to morphological changes in the intestine and spleen. Further, a chronic inflammatory response including neutrophilia and monocytosis in cardiac blood and BM is observed, as well as an increased number of various stem cell populations. First preliminary data from *Ppm1d*-sequencing of neutrophils and monocytes shows no occurrence of SNPs within mice with colitis phenotype.

(28) Potential impact for the elderly: Coagulation of satellite veins during skeletonized internal mammary artery harvesting affects the sternal microcirculation

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Objectives: The population of coronary artery bypass grafting (CABG) patients became older within the last decades. Elderly patients are more likely to develop wound healing complications. A preserved microcirculation is of significant importance to prevent wound healing complications. The effect of coagulation of the satellite veins during skeletonized harvesting of the internal thoracic artery (ITA) on sternal microcirculation has not been investigated yet.

Methods: In a pig model, we measured sternal microcirculation (sLDP) with an invasive laser doppler perfusion (LDP) needle probe during skeletonized harvesting of the ITA with or without coagulation of the satellite veins (N=8/groups). In a sham-operated group (N=8), we ligated the ITA with a clip to show the effect of total avoidance of any surgical manipulation on sLDP.

Results: After skeletonized harvesting of the ITA, sLDP was reduced significantly to 71±9% ($P<0.001$). Coagulation of the satellite veins resulted in a significantly exacerbated reduction of sLDP (56±11% vs. 71±9%; $P<0.05$) compared to non-coagulated satellite veins. ITA clipping reduced sLDP significantly to 71±8% ($P < 0.001$) in the sham-operated group.

Conclusion: ITA harvesting markedly impairs microcirculation of the sternum but remains unavoidable when coronary artery bypass grafting should be performed. Nevertheless, coagulation of the satellite veins should be avoided to minimize the risk of deep sternal wound healing complications, especially in the elderly.

(29) Aging is not related to increased mitochondrial ROS production in a rat model of genetically determined high or low exercise capacity

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High exercise capacity is associated with lower risk for cardiovascular diseases and better outcome in disease and surgical interventions. Aging is associated with decreasing exercise capacity and increasing oxidative stress, originating to a great part from mitochondrial ROS production. In the model of rats with inherited high (HCR) or low (LCR) intrinsic exercise capacity, LCR present with 1/3 lower life expectancy and we aimed to assess, if this is related to increased oxidative stress.

Female adult (15 weeks) and old (100 weeks) HCR and LCR were tested for exercise capacity and cardiac function. ROS production from cardiac and skeletal muscle mitochondria was assessed and oxidative stress determined.

Cardiac contractile function decreased with age and was higher in old LCR compared to old HCR. Exercise capacity decreased with age in HCR only, but remained at a higher level than in LCR. Both, cardiac and skeletal muscle showed a decrease of mitochondrial ROS production with age. In parallel, antioxidative capacity of catalase was increased with age which was more pronounced in LCR in the heart and in HCR in skeletal muscle. However, oxidative protein damage increased to the same extent in old HCR and LCR.

The Increase in oxidative stress with aging was found independent of genetically determined exercise capacity. It seems to be associated with non-mitochondrial ROS production.

(30) Skeletal muscle but not cardiac mitochondria as mediator for a shorter lifespan in rats with lower intrinsic exercise capacity

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With increasing life expectancy healthy aging is gaining relevance. Low exercise capacity is the best predictor for earlier mortality and higher morbidity. The intrinsic (inherited) and extrinsic (acquired) part of exercise capacity cannot be distinguished in humans. However, in a rat model of high (HCR) and low (LCR) intrinsic exercise capacity, LCR show a reduced lifespan.

We aimed to assess if the differences in lifespan are associated with mitochondrial content and the activity of mitochondrial respiratory chain complexes.

Therefore, we measured citrate synthase activity in homogenate and complex activities in isolated mitochondria of heart and gastrocnemius muscle of 20, 100 and 130 weeks old HCR and 20 and 100 weeks old LCR male rats photometrically.

In skeletal muscle mitochondria of adult HCR, complex activities were higher than in adult LCR (CII activity (µM/min/g prot) HCR vs. LCR: 15,6±2,8 vs. 4,1±1,2). Complex activities decreased from adult to old in HCR only (CIII 20 vs. 100 w: 2408±388 vs. 1202±148). Thus, complex activities of old HCR and LCR were comparable. There was no further decrease from old to senescent HCR in complex activities. Citrate synthase activity was higher in adult HCR compared to adult LCR and decreased with age in both phenotypes, reaching comparable activities in senescent HCR and old LCR. Considering both, mitochondrial content and complex activities, senescent HCR and old LCR were comparable.

Complex activities of cardiac mitochondria were higher in adult HCR compared to adult LCR. Complex activities decreased from adult to old in HCR only. Thus, complex activities of old HCR and LCR were comparable. Citrate synthase activity of HCR and LCR were comparable and decreased with age in both phenotypes. The further decrease of citrate synthase activity in senescent HCR was compensated by increased complex activities.

Shorter lifespan in LCR was associated with lower respiratory chain complex activity and lower mitochondrial content of skeletal but not heart muscle.

(31) Characterisation of murine pancreatic islets to clarify the impact of senescence on beta cell functionality

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Ageing is considered as a continuous cellular functional and regenerative decline, whereas senescence, a state of permanent cell cycle arrest, is considered an important hallmark of ageing. During the progression of ageing pancreatic islets undergo morphological and metabolic changes. Possible age-related limitations in the functionality of insulin-producing pancreatic beta cells are assumed to affect the progression of type-2-diabetes. Though, changes of pancreatic islets during ageing under non-pathological conditions are poorly investigated.

Previous work by our group showed that the number of senescent $p16^{ink4a}$-positive beta cells increased significantly in pancreatic islets of C57BL/6J wildtype mice, starting from 10 months of age. Interestingly, blood glucose and plasma insulin levels remain unchanged in all age groups. Furthermore, islets from aged mice, show downregulated beta cell identity markers, as well as increased expression of specific senescence markers. As the number of senescent cells increase with age, investigating single beta cell gene expression patterns, senescence associated secretory phenotype development and the impact of senolysis at different age groups, is of great interest. Furthermore, characterisation of senescent beta cells may lead to a better understanding on the role of ageing in beta cell dysfunction and elucidate new drug targets for treatment of T2D. In this poster we show first results on the characterisation upon beta cell heterogeneity of murine pancreatic islets in healthy aged C57Bl/6J mice, encouraging us to further study the potential effect of induced metabolic stress in the ageing mouse model.

(32) Alternative oxidase expression impairs long-term adaptive remodeling following cardiac ischemia

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Objectives: Cardiac ischemia and reperfusion (I/R) causes heart muscle injuries, which induce organ remodeling eventually leading to contractile failure. Much of the muscle damage occurring in the course of ischemia and reperfusion has been attributed to mitochondrial respiratory dysfunction and the concomitant production of reactive oxygen species (ROS).

Alternative oxidase (AOX) is a respiratory enzyme that restores respiratory chain function when impaired thereby blunting ROS production. Hence, AOX was proposed to be a natural rescue mechanism from ischemia and reperfusion injuries and contractile dysfunction.

Methods and Results: To test this assumption, wild-type (WT) and AOX transgenic mice (AOX^{Rosa26}) underwent transient left anterior descending coronary artery ligation (LAD) at approximately 12-weeks and were followed-up for 3 or 9 weeks. Cardiac contractile function was studied using a Langendorff-perfused heart model, mitochondrial respiratory capacity was measured using high-resolution (O2k) respirometry and adaptive organ remodeling was studied using RT-PCR and tissue proteomics. Our data revealed that AOX attenuated mitochondrial ROS load and preserved mitochondrial respiration in post-ischemic tissue. Yet, presence of AOX blunted the gene expression of presumingly stress response genes such as atrial natriuretic peptide (*Anp*) whilst pro-fibrotic and pro-apoptotic genes were up-regulated. Finally, tissue proteome analysis indicated altered expression of proteins involved in extracellular matrix remodeling best exemplified for periostin. Periostin was up-regulated almost 5-fold in post- ischemic AOX hearts at 3 weeks, and 17-fold at 9 weeks, whilst the increase in the corresponding WT hearts was less than 2- and nearly 7-fold after 3 and 9 weeks, respectively.

Conclusion: Our data identified mitochondrial ROS originating from a dysfunctional respiratory chain as a possible effector for post-ischemic heart remodeling and preservation of contractility.

(33) Regulation of the vasoprotective transcription factor Grainyhead-like 3 by plant derived agents in endothelial cells

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Background: Vascular aging and diseases are accompanied by a loss of nitric oxide, a disturbed redox balance and decreased mitochondrial functionality, which all contribute to induction of cellular senescence. Among others, one important aspect of endothelial dysfunction, a hallmark of aged vessels, is the increasing number of senescent endothelial cells (EC). The plant derived agents curcumin and caffeine have been shown to exert vasoprotective functions, especially in the endothelium. The transcription factor Grainyhead-like 3 (GRHL3) is expressed in EC. It increases NO bioavailability, reduces apoptosis and increases migratory capacity of EC. However, its regulation in cellular senescence and by curcumin and caffeine has not been investigated.

Results: A well-established model of stress-induced senescence in human EC is treatment over two weeks with low dose H_2O_2 every second day. This treatment results in increased senescence markers like senescence-associated beta-Galactosidase and the cell cycle inhibitor p21 and decreased endothelial NO Synthase (eNOS). Similar to the reduced eNOS protein levels, GRHL3 was also diminished in stress-induced endothelial cell senescence. To determine whether curcumin and caffeine have per se an effect on GRHL3 expression, we first performed short-term experiments and treated EC for 24 hours with curcumin and caffeine. Curcumin as well as caffeine - in concentrations improving migratory capacity - induce GRHL3 levels. Having demonstrated that, we next investigated the role of caffeine and curcumin in stress-induced senescence. Interestingly, caffeine and curcumin inhibited senescence and increased GRHL3 levels.

Conclusion: The upregulation of GRHL3 is a new mode of action for caffeine and curcumin in EC. Thus, administration of caffeine and/or curcumin could reduce the incidence of senescent endothelial cells by increasing GRHL3.

(34) Defining the mode of action of caffeine in the cardiovascular system

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Background: Cardiovascular functionality decreases with age. Interestingly, recent studies have shown a protective effect of caffeine on the cardiovascular system also in the elderly. We demonstrated that concentrations of caffeine detectable in serum after moderate coffee consumption enhance the migratory capacity of endothelial cells (EC), which critically depends on mitochondrial function. Therefore, we wanted to identify the molecular link between caffeine, mitochondrial energy metabolism and migration.

Results: First, we found that caffeine induces the translocation of p27/Kip1 (p27) - known as nuclear cell cycle inhibitor - into the mitochondria. Reducing p27 levels with siRNA inhibited caffeine induced migration. To investigate the effects of p27 localization on mitochondrial energy metabolism and migration, we expressed mitochondrial and nuclear targeted p27 (mito p27/nuc p27) in EC. While expression of nuc p27 decreased basal migration, mito p27 increased migration. Only mito p27, but not nuc p27, rescued the complete loss of migratory capacity induced by knockdown of endogenous p27. Moreover, mitochondrial p27 improved mitochondrial membrane potential, increased ATP content, and is required for the pro-migratory effect of caffeine. Domain mapping of p27 revealed that the N-terminus and C-terminus are needed for improved energy metabolism and migratory capacity. Further analysis of those regions revealed that the translocation of p27 into the mitochondria and its pro-migratory activity depend on serine 10 and threonine 187.

The link between caffeine, p27 and aging, was also found in mice. Old mice (22 months) as well as p27-deficient animals (6 months) showed reduced complex I respiration in heart mitochondria. Strikingly, caffeine did not increase respiration in p27-deficient animals, whereas improved complex I respiration was found in old mice, which is accompanied by increased translocation of p27 into mitochondria.

Conclusion: The enhanced mitochondrial translocation of p27 defines the new mode of action of caffeine in the cardiovascular system.

(35) Bakery products as functional food

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Advanced glycation end products (AGEs) are the result of a non-enzymatic reaction of proteins with reactive carbohydrates. Heat-processed food like bread contains high amounts of AGEs. Numerous previous studies suggest an antioxidative and cardioprotective potential of extracts from the bread crust (BCE). The activation of NF-κB signaling pathway by BCE is well understood. However, it is largely unknown whether NRF2, the master regulator of oxidative stress resistance in mammalian cells, is affected by BCE. Understanding the molecular mechanism of BCE action is an important prerequisite to establish BCE as a functional food product. Therefore, we developed a cell culture model to elucidate the effect of different bread crust extracts on NRF2 activation in an endothelial reporter cell line (NRF2-mCherry). An increased nuclear translocation of NRF2 in these cells results in elevated mCherry expression, which was analyzed by flow cytometry. Our data showed for the first time, that soluble extracts from bread crust are capable to stimulate NRF2 signaling pathways in endothelial cells. Furthermore, NRF2 pathway activation was confirmed by microarray analyses. QRT-PCR measurements and Western-Blot analyses indicated an induction of antioxidative genes like HMOX1, GCLM and NQO1 upon BCE treatment. Moreover, BCE pretreated cells had a survival advantage compared to control cells, when cells are exposed to oxidative stress. In a survey of different crop-extracts (wheat-, rye-, spelt-, oat- and barley-crust), which were incubated with cells, strongest induction of HMOX1 was observed with wheat- and rye-crust. Furthermore, comparison of bright versus dark baked bread resulted in stronger stimulation of NRF2-transcripts after treatment of cells with dark bread crust extracts. In view of these results feeding studies in NF-κB and NRF2 reporter mice are ongoing. First results will be presented on the meeting poster.

In continuative studies we want to optimize and enhance the action of BCE by changing the baking conditions and ingredients.

(36) Regulation of protein *O*-GlcNAcylation during endothelial senescence

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Background and aim: The enzymatic addition of *O*-linked β-N-acetylglucosamine (*O*-GlcNAcylation) to serine/threonine residues of proteins is a posttranslational modification, which regulates protein and cellular functions. It is involved in the aetiology of many age-related diseases, in particular metabolic disorders and their vascular complications as a consequence of endothelial dysfunctions. However, mechanistic links between ageing, *O*-GlcNAcylation and metabolically triggered endothelial dysfunction remain elusive. Here, we investigate the regulation of *O*-GlcNAcylation in senescent endothelial cells.

Results: In a replicative senescence model, in which primary human endothelial cells were cultured up to passage 20, several proteins showed decreased *O*-GlcNAcylation as determined by immunoblotting using an anti-O-GlcNAc antibody. In parallel, protein levels of glutamine:fructose-6-phosphate amidotransferase 1 (GFAT1), a rate-limiting enzyme of the *O*-GlcNAc machinery, were reduced. Moreover, mass spectrometry (MS)-based proteomics indicates a reduction in the abundance of *O*-GlcNAc transferase (OGT, an enzyme which adds *O*-GlcNAc to proteins) and an increase in levels of *O*-GlcNAcase (OGA, an enzyme that cleaves *O*-GlcNAc from proteins). Supporting these trends, we observed an even more pronounced reduction of GFAT1 (with unchanged OGT and OGA) and consequently *O*-GlcNAc levels in endothelial cells, in which premature senescence was induced by oxidative stress (H_2O_2). Based on our initial data, we expect numerous *O*-GlcNAc-driven functional rearrangements in the course of endothelial cell senescence. To disentangle them in more detail, we are currently establishing a streamlined MS workflow for the analysis of the endothelial cell *O*-GlcNAcome, utilizing advanced fragmentation techniques and ion mobility separation.

Conclusions: In the present study we observed decreased *O*-GlcNAcylation in senescent endothelial cells as a consequence of altered protein levels of key components involved in the regulation of *O*-GlcNAcylation (GFAT1, OGT and OGA) suggesting a functional role of this largely understudied PTM in ageing of endothelial cells.

(37) Gender-specific drop of cardiac function driven by chronic RAGE overexpression associated with reduced FHL2

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An overexpression of the receptor for advanced-glycation endproducts (RAGE) in cardiac tissue is well-known in the elderly, in diabetes mellitus and after acute cardiac infarction or ischemia/reperfusion injuries. RAGE and binding partners affect the clinical outcome of heart failure and may play an important role by accelerating cardiovascular age-decline. Therefore, hearts of wild type (WT) C57black6/N and cardiac-specific RAGE-overexpressing transgenic (TR) mice were investigated for function by ultrasound at young (4-5 months) and old (22-23 months) ages. Omics were performed to detect molecular candidates contributing to the encountered elderly-like phenotype, followed by target validation of ATP production and protein expression. Transgenic mice exhibit significantly increased systolic (LVD-sy) as well as diastolic (LVD-di) diameters. The left ventricular ejection fraction (EF) is significantly reduced in young TR male mice. Overexpression of RAGE did not result in activation of inflammation but altered energy-associated pathways in transcriptomics and proteomics. Indeed, the mitochondrial energy allocation was diminished in TR animals. Gender differences might be influenced by an altered expression of the four and a half LIM domains protein 2 (FHL2). Geriatric associated RAGE-overexpression contribute to cardiac EF decrease by energy reduction and may help to understand sex differences in the development of cardiovascular diseases.

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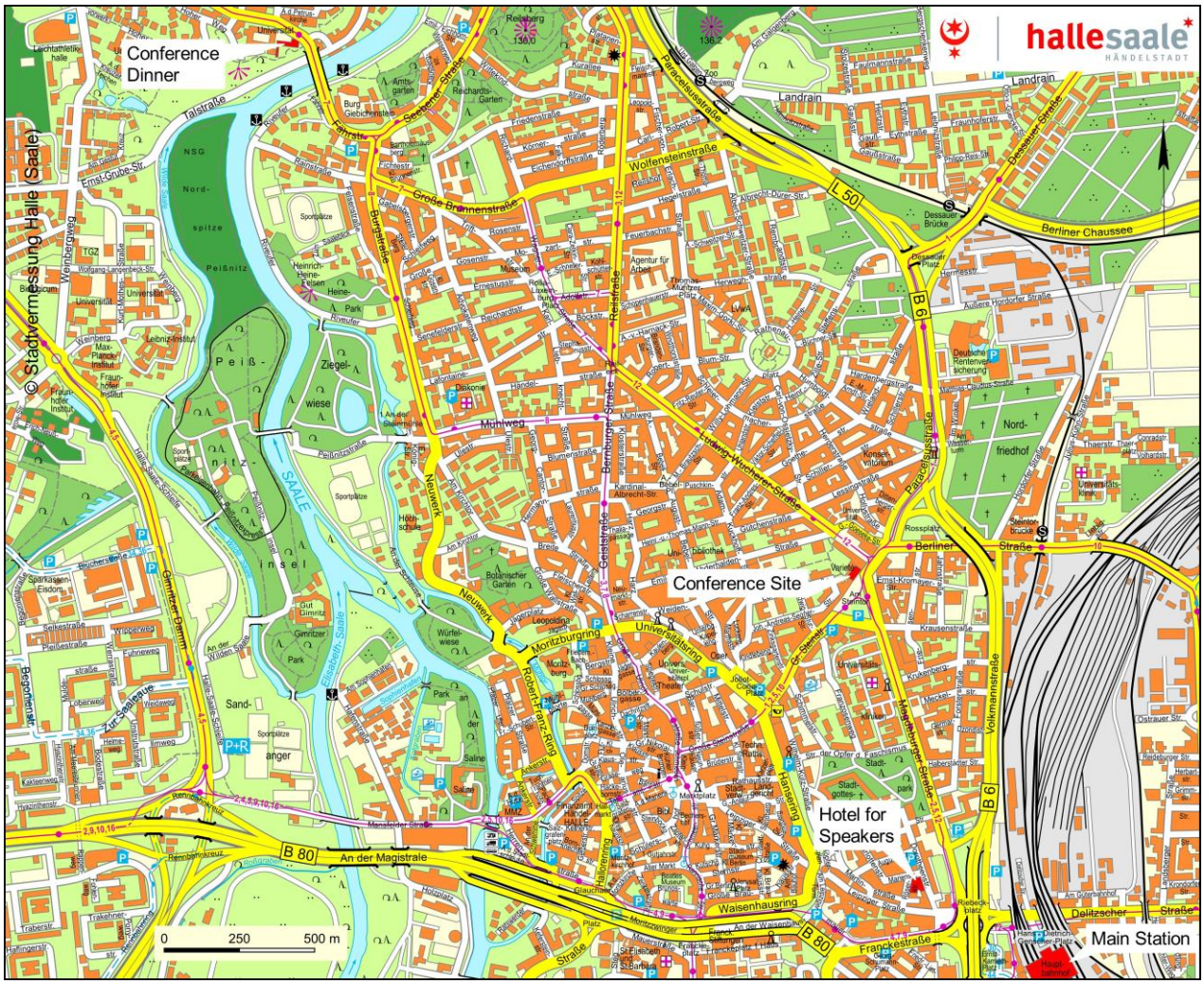

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