Prevention and Intervention: from Molecular Biology to Clinical Perspectives

Heart Centre
Ernst-Grube-Str. 40
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Interdisciplinary Centre for Ageing in Halle (IZAH)

German Academy of Sciences Leopoldina

DGGG - German Society of Gerontology and Geriatrics

DGK - German Cardiac Society

DGTHG - German Society of Thoracic and Cardiovascular Surgery

Keynote Speaker
Kaisu Pitkäla
Helsinki, FIN

From Friday, September 16th, 2011, 6 pm
till Sunday, September 18th, 2011, 2:15 pm

Conference Site
Martin-Luther-University Halle-Wittenberg
Lion Building
Universitätsplatz 11
Halle (Saale)
Prevention and Intervention: from Molecular Biology to Clinical Perspectives

September 16\textsuperscript{th} – 18\textsuperscript{th} 2011

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University Hospital Halle (Saale)

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in cooperation with

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Running Program

Prevention and Intervention: from Molecular Biology to Clinical Perspectives

- Meeting language English -

Friday September 16th 2011

18:00 Opening
Andreas Simm

Address
M. Gekle, Dean of the Medical Faculty
M. Gogol, German Society of Gerontology and Geriatrics
R.-E. Silber, Director of the Department of Cardiothoracic Surgery

Keynote lecture and Schober award

Laudation Kaisu Pitkälä
by Thomas E. Johnson, Boulder, USA

Keynote lecture:
Kaisu Pitkälä, Helsinki, Finland
“Effectiveness of Preventive Interventions in Older Populations”

20:00 Come Together
Saturday September 17th 2011

08:00 – 10:00 Session 1

“Preventive Interventions in the elderly: What are our goals – and how can we measure them?”

Chair: Kaisu Pikälä, Andreas Simm

The view of a basic scientist                           Tilman Grune
The view of a sports scientist                         Nadja Schott
The view of a medical scientist                        Ursula Müller-Werdan
The view of a geriatrician                            Angelo Scuteri

10:00 – 10:30 Poster Session, Coffee Break

10:30 – 12:30 Session 2

“Malnutrition or caloric restriction: positive or negative?”

Chair: Tilman Grune, Angelo Scuteri

Nopsi: a novel RNA methyl-transferase extending life span in worm and fly and its cross-talk to nutrition   Johannes Grillari
Genetic studies on caloric restriction in the worm and in the mouse: What does it tell us?                 Thomas E. Johnson
The obesity paradox in heart failure: Benefits of being overweight?                                     Stephan von Haehling
Diets in the (oldest) old: Why?                         Cornel Sieber

12:30 – 13:30 Lunch Break
Saturday September 17th 2011

13:30 – 15:30 Session 3

“Sports or activity: what is effective in an aged population?”

Chair: Manfred Gogol, Franklin Rosenfeldt

Can you run away from aortic valve stenosis and an abdominal aortic aneurysm? Volker Adams

Aging and inactivity: Strategies for reversal LaDora Thompson

Does moderate activity positively influence biological age? A. Navarrete Santos

Effects of a standardised physical training in frail older patients with dementia: can frailty be treated? Klaus Hauer

15:30 – 16:30 Poster Session / Coffee Break

16:30 – 18:30 Session 4

“Oxidative stress and antioxidants: Re-evaluation of an old theory”

Chair: George Martin, Suresh Rattan

Mitochondrial theory of aging: dead or alive? Aleksandra Trifunovic

Growth hormone, methionine and aging Holly Brown-Borg

Epithelial stress and aging in the evolution of lung fibrosis Andreas Günther

The effects of antioxidants on lifespan and disease Flint Beal

20:00 Gala-Dinner (Moritzburg)
Sunday September 18th 2011

08:30 – 10:30 Session 5

“Preventive interventions in clinical settings”

Chair: Rolf-Edgar Silber, Ursula Müller-Werdan

Perspectives of preconditioning prior cardiac surgery – an overview  Ivar Friedrich

Preventive Implications in Cardiac Surgery of the Elderly under Gender-Specific View  Sandra Eifert

Metabolic therapy and oxidative stress in cardiac surgery and cardiovascular disease  Franklin Rosenfeldt

Ageing at heart: Too frail for intervals?  Øyvind Ellingsen

10:30 – 11:30 Poster Session / Coffee Break

11:30 – 11:45 Posterprice

11:45 – 13:45 Session 6

“Mild stress can help: The hormesis concept”

Chair: Cornel Sieber, Flint Beal

Hormesis: Its significance for toxicology, pharmacology and risk assessment  Edward Calabrese

Promoting lifespan and metabolic health by increasing oxidative stress: mitochondrial hormesis  Michael Ristow

On the quasi-stochastic distributions of major geriatric pathologies  George Martin

Applying hormesis in ageing research and interventions  Suresh Rattan

13:45 – 14:15 Farewell
Effectiveness of Preventive Interventions in Older Populations

Kaisu Pitkälä

Randomized controlled trial (RCT) is the king of the clinical study designs. This methodology is used to test effectiveness and safety of health care services, treatments, technologies and operations. However, older patients are often excluded from RCTs, especially from drug trials. Anyway, the past decade the evidence has slowly been accumulating and showing that preventive treatments, interventions and rehabilitation models are beneficial even for the oldest old. Examples can be found from primary, secondary and tertiary prevention. Examples of primary preventive interventions which are beneficial for all older people irrespective of their age or disabilities are vitamin D, exercise, social activity, cognitive training and support of self-efficacy and mastery. There is evidence for effectiveness in secondary prevention in, e.g., treatment of blood pressure, prevention of falls, etc. A-class evidence of RCTs will be dealt in this presentation.

There are, however, several pitfalls when designing a trial for older patients. One also has to think carefully about the target group of intervention: older people are heterogeneous population and not all benefit from all interventions. One also have to think carefully about the definition of risk factors (intervention targets). Geriatric giants can be either target of intervention or outcome measures (e.g. disability, cognitive decline, loneliness, falls and fractures, depression, vascular events). Similar outcome measures to younger populations (such as mortality) may not be relevant for the oldest old. Measures related to quality of life, disability or need of help may be better options when investigating the oldest old. Anyway, drop-out rate is often high and competing causes for death and disability are always present when investigating older patients. Often drop-outs are more prevalent in control groups. Thus, they dilute the effectiveness of intervention. We have hundreds of scales and measures to use among older people but when one starts to seek the ones which are good for the RCT target group and sensitive to change to show the intervention effects, there are not so many.

Money and good planning of trials is still a big issue in geriatric clinical science. Regarding how much money is spend on care and management of older patients, very little is still spent on investigating what kind of preventive interventions help older people to maintain their functioning, cognition and QOL.
The view of a basic scientist
The measurement of aging – do we need it?

Tilman Grune

The establishing of valuable biomarkers of aging is the major aim of several attempts worldwide. These attempts focus on the prediction of the aging process for individuals for a shorter or longer period of life. It is understandable that such a task is more difficult if a long-time prediction should be made. Since a multitude of factors influence the aging process, several biomarkers of aging have to be established to get information about the pacemakers of aging.

An ideal set of biomarkers should be able to predict some age-related process in an individual. Biomarkers should respond to intervention, correcting a premature biological aging. Here one has to discriminate between primary and secondary prevention and final intervention with age-related diseases.

The usage of adequate biomarkers can prolong the health-span of individuals and postpone the onset of age-related diseases.
The concept of healthy, optimal or successful aging has received increased attention due to the aging society and longer life expectancies. Multidimensional models of successful aging have become widely influential in gerontology, academic research and policy making. These models take into account cognitive, physical and social factors, and represent a clear improvement on early, simplistic theories of aging. Several studies have identified health-related life-style factors that contribute to the degree of successful aging, including involvement in physical activity.

In the last two decades there has been an increasing interest into the physical activity needs of older persons. Regular physical activity provides significant health benefits for people of all ages and abilities. Although physical activity has been promoted for children and young adults worldwide, research shows that older adults as well, benefit from physically active lifestyles. Actually, physical activity can prevent disease and promote independence and well-being for a healthier, more satisfying late life. However, despite the health benefits of physical activity, few older adults lead active lifestyles.

Comprehensive preventive health programs can lead to improvements in diverse indicators of preventive health. Prevention programs for older individuals must be based on results of scientific studies of efficacy of the intervention to reduce morbidity, disability, and mortality. The primary goal of prevention should be to maximize quality of life and active life expectancy. Empowering older individuals to know their own risk factor status and to understand the importance of screening and an active lifestyle should maximize the quality of their health.

In this talk, I will show the extent to which participating in regular physical activity can play an important role in determining whether an individual ages successfully. I will begin with a brief overview of how and why physical activity is important for older adults in the light of successful aging models. Furthermore, I will give a summary of current assessments and recommendations as well as guidelines related to physical activity program structure and content.
The view of a medical scientist

Ursula Müller-Werdan

In view of the increasing age of patients presenting with cardiovascular disease, it seems mandatory to implement geriatric expertise, particularly tools of the geriatric assessment, in the setting of cardiology.

What is the difference in cardio-vascular diseases of the elderly?

- In the elderly with acute coronary syndrome the diagnosis is frequently hampered by non-specific symptoms, these patients seek medical help often later than younger individuals. Elderly and old patients in acute coronary syndrome are still less frequently being referred to PCI than younger ones, although statistically even octogenarians profit from PCI.

- In stable coronary artery disease the focus is on treatment of risk factors.

- Therapy of systolic heart failure in the elderly is not fundamentally different from the one administered to younger individuals, and therapy is as effective. In old age diastolic heart failure is frequent.

- Risk of thrombembolic complications in atrial fibrillation increases in the elderly.

What makes the difference in cardio-vascular diseases of the elderly?

- Physiological organ ageing processes and immunosenescence provide possible explanations for the in old age frequently atypical clinical presentation of severe ailments and altered pharmacokinetics.

- Flu and pneumococci vaccinations are effective in preventing cardiovascular events.

- Multimorbidity and functional impairment has an impact on the prognosis of cardiovascular disease in a not yet determined scope.

References:


The view of a geriatrician

Bringing Prevention in Geriatric Medicine: Evidences Supporting the New Challenge

Angelo Scuteri

Aging is a dynamic and systemic process, with high inter-individual heterogeneity, likely partially adaptive.

Cardiovascular (CV) disease and hypertension are among the leading conditions causing disabilities in older subjects. Of note, the remaining lifetime risk for CV disease among subjects free of disease is similar at 40 and at 70 years of age. If, in accordance with most recent definition, prevention is any intervention before the patient receives a diagnosis, prevention is not only possible but imperative even at older age.

Additionally, disability and CV disease in the elderly may be prevented by targeting factors underlying and modulating the aging process. In such a context, the cross-talk between arterial and brain aging will be discussed as a paradigmatic clinical model fostering prevention in older subjects.
Nopsi: a novel RNA methyl-transferase extending life span in worm and fly and its cross-talk to nutrition

Johannes Grillari

Nopsi (Nop2 like SKIP interacting protein) is a protein of 55 kDa and so far uncharacterized function.
Here we show that Nopsi displays RNA-methyltransferase-activity, and localizes to the nucleolus, suggesting a role in ribosome biogenesis. Under our working hypothesis that fewer ribosomes lead to less protein synthesis and this organismal status in turn resembles calorie restriction, similarly to downregulation of translational initiation (Syntichaki et al, Nature, 2007), we tested if Nopsi knock-down influences the life span of Caenorhabditis elegans and Drosophila melanogaster. Indeed, RNAi showed a 10-15% increase in the mean and median life span of Drosophila melanogaster. In Caenorhabditis elegans we could show that the mean lifespan is increased upon knock-down by 20%. A further increase to 40% was observed in a strain harbouring a full genetic deletion within the functional domain compared to the wildtype.
Our data suggests that a reduced protein translation rate might be an evolutionarily conserved mechanism for conferring longevity.
The mechanism by which dietary restriction (DR) retards aging remains largely unknown. We have used genetic approaches to dissect the DR process, both in worms (C. elegans) and in mice (M. musculus). We analyzed mouse body weight, hair growth, tail growth, and body fat, body temperature, home-cage movement, and female fertility across these recombinant inbred (ILSXISS) strains. We have found that greater metabolic efficiency is associated with an extended lifespan. Interestingly, about half of all the mouse strains tested showed a decrease in longevity when switched to a 60% ad lib diet at about two months of age. Several QTLs achieved genome-wide statistical significance.

In C. elegans, we identified two novel genes, nlp-7 and cup-4, required for normal longevity. Nlp-7 is one of a set of neuropeptide-like protein genes; cup-4 encodes an ion-channel involved in endocytosis by coelomocytes. RNAi of nlp-7 or cup-4 significantly reduced the lifespan of the eat-2 mutant, a genetic model of dietary restriction, but had no effect on the lifespan of long-lived mutants resulting from reduced insulin/IGF-1 signaling or dysfunction of the mitochondrial electron transport chain. The lifespan extension observed in wild-type N2 worms by dietary restriction using bacterial dilution was significantly prevented in nlp-7 and cup-4 mutants. RNAi knockdown of genes encoding candidate receptors of NLP-7 and genes involved in endocytosis by coelomocytes also specifically shortens the lifespan of the eat-2 mutant. Thus two novel pathways, NLP-7 signaling and endocytosis by coelomocytes, are required for life-extension under dietary restriction in C. elegans.

(Supported by NIH RO1 AG16219, RO1 022500, and R01 AG024354)
The obesity paradox in heart failure: Benefits of being overweight?

Stephan von Haehling

Data are accumulating for more than a decade to suggest that patients with heart failure may benefit from a higher body mass index (BMI) compared to patients with a “normal” BMI in terms of a decreased risk of death and hospitalisation. In 1996, Ellis et al. were among the first to study this phenomenon systematically in patients undergoing percutaneous coronary interventions (Ellis et al., 1996). These authors concluded that both low-normal or high BMI are a “newly described and powerful risk factor for in-hospital death after percutaneous coronary intervention”. This so-called “obesity paradox” in heart failure has been a matter of ongoing research in recent years (von Haehling and Anker 2010, Davos et al., 2003, Horwich et al., 2001). These studies showed that obesity may have a protective role in heart failure. One study described a cohort of patients with advanced systolic disease (Horwich et al., 2001). In this study, overweight and obese patients were found to be more likely to present with hypertension, diabetes, and high cholesterol, but their renal function and pulmonary wedge pressure were not altered compared to other patients with heart failure. Since then, a large number of analyses have drawn attention to this surprising finding (Lavie et al., 2003). The “obesity paradox”, is part of a series of surprising findings that has been called “reverse epidemiology” (Horwich and Fonarow, 2007). Indeed, not only higher BMI, but also higher serum cholesterol values and the presence of hypertension are associated with better survival in patients with CHF (Rauchhaus et al., 2003). These relationships, like the obesity paradox, persisted even after extensive adjustment. Such phenomena may be present in several chronic diseases such as chronic kidney disease or rheumatoid arthritis.

References

Diets in the (oldest) old: Why?

Cornel Sieber

Many diseases affecting adults in Western societies are linked to overnutrition and obesity. The metabolic syndrome as it is still coined these days, is therefore of paramount importance in adults. Nevertheless, recent data depict a paradigmatic shift when it comes to (oldest) old persons. Not just an increased body mass index (BMI), especially the body composition determines functional decline, morbidity and mortality in this age-group. The pathophysiological background of this frailty syndrome is sarcopenia.

The aim of this talk is to define sarcopenia (new definitions) and its implication on physical activity, nutritional intake in both prevention and treatment of sarcopenia/frailty. Diets in old age are in this respect most often not indicated, but even dangerous for people at stake. If ever started, they have to be accompanied with physical activity programs, as well as a balanced protein-rich diet also rich in anti-oxidative agents.
Can you run away from aortic valve stenosis and an abdominal aortic aneurysm?

Volker Adams

Currently, no effective therapy to prevent calcified aortic valve (AV) disease exists. Calcified AV disease confers significant morbidity and mortality as the severity of disease progresses. Thus adverse events can be avoided or delayed if it becomes possible to prevent the progression of AV disease at an earlier time point, before the presentation of severe valve calcification (eg, AV sclerosis). Accumulated evidence suggests that degenerative calcified AV disease and atherosclerosis share similar mechanisms such as clinical risk factors (eg, physical inactivity) and histopathological features (eg, valvular/vascular endothelial disruption, oxidative stress, calcification). We and others could demonstrate that exercise training prevents the progression of atherosclerotic cardiovascular disease by modulating important mechanisms all of which may be expected to improve degenerative AV disease. During the talk, we will discuss new results from animal studies showing that exercise training as primary prevention but not in the setting of secondary prevention has a positive impact on the development/progression of aortic valve sclerosis. In addition a molecular working model will be discussed.

The development of an abdominal aortic aneurysm (AAA) depends on an increased oxidative stress followed by activation of MMPs and the subsequent destruction of the vascular wall. In the second half of the talk, we will discuss the impact of exercise training in the setting of primary prevention on the development of an AAA and the molecular mechanisms in an animal model.
Aging and Inactivity: Strategies for Reversal

LaDora V. Thompson

The deleterious changes associated with inactivity (e.g., imposed bed rest) are greatly compounded in the older adult due to the presence of age-induced sarcopenia. Studies have shown that when adverse changes of inactivity are superimposed on age-induced sarcopenia there is further physiological deconditioning. To date, there is little information or evidence regarding the effectiveness of therapeutic exercise as an intervention during periods of inactivity to preserve skeletal muscle function, especially in the elderly. Consequently, the objective of this study was to test the hypothesis that a clinically-based therapeutic exercise would prevent the deterioration in muscle power output in single muscle fibers associated with inactivity for adult, middle-age and very old rats. Adult (5-12 months), middle age (24-31 months) and very old (>31 months) F344BNF1 rats were randomly assigned to one of the following experimental groups: sedentary-control, hindlimb unweighted for 14 days, or hindlimb unweighted for 14 days and exercised on a treadmill for approximately 15 min four times daily. The contractile properties [peak power output, peak force, contraction velocity] of single myosin heavy chain type I fibers from the soleus muscle were determined and analyzed with a 2-way ANOVA. Peak power output is a physiological measurement of maximum work and is a function of force X velocity. Two weeks of inactivity reduced peak power output and peak force in all three age groups, whereas contraction velocity did not change. With therapeutic exercise, peak power output was completely recovered in the middle age group, partially rescued in the adult group, and remained reduced in the old age group. Peak force remained reduced with exercise, whereas contraction velocity increased in the adult and middle age groups. In contrast, contraction velocity decreased in the old age group with exercise. Collectively, the results of the current study support the use of mild treadmill therapeutic exercise for the adult and middle-age groups, which showed the most dramatic attenuation of inactivity-induced reduction in muscle peak power output. However, in old rats, treadmill exercise did not improve muscle peak power. Taken together, therapeutic exercise recommendations for individuals who are hospitalized require consideration of the patient's age.
Does moderate activity positively influence biological age?

Alexander Navarrete Santos

The human lifespan is very heterogeneous and unpredictable. Biomarkers of aging should help to characterize the biological age of individuals and may be used to identify individuals at high risk of developing age-associated diseases. Formation of AGEs (advanced glycation endproducts) is one of the major faults whose lifelong accumulation causes ageing. Whereas it is well known that physical activity positively modulate the lifespan, it is still unclear whether this can be monitored by biomarkers. AGE associated skin fluorescence is a marker for the accumulation of AGEs in the tissue and positively correlate with age. Thus, the skin fluorescence may act as a biomarker of ageing. Here we analyzed the effect of 6 weeks moderate sport / training on parameters of health, physical fitness as well as on AGE-associated skin fluorescence on 146 nonathletic subjects. As expected, strength as well as endurance of the subjects was significantly increased. Blood pressure as well as heart rate as parameters of health improved, whereas the body mass index was only changed, if training was combined with a diet. The self-reported quality of life (SF-12) increased as well. Interestingly, the skin fluorescence significantly decreased by 4.2%, which indicate that the biological age can be modified by moderate sport. This improvement could be detected independently on the age of the subjects. In conclusion our data show that biological age can positively be influenced even by a short time exercise intervention, reflected by a reduction in skin fluorescence.
Effects of a standardised physical training in frail older patients with dementia: can frailty be treated?

Klaus Hauer

The concept of frailty has been developed as a distinct phenomenon in contrast to effects of morbidity and disability. Apart from molecular markers, frailty has been conceptualised by different assessment models, partly based on subjective general ratings, mathematical models based on cumulative incidence of somatic deficits and phenotypes based on clinical symptoms.

Worldwide the best established phenotype of frailty has been developed by Linda Fried et al based on clinical markers related to catabolic metabolism or insufficient energy production as leading symptoms of the ageing process. Assessment items relate to loss of weight (cachexia/ sarcopenia), strength, functional performance, physical activity and perception of fatigue.

This Phenotype has repeatedly been modified as the concept has been used to retrospectively analyse longitudinal data of large ageing studies. Modifications related to exchange of assessment issues as well as to cut-off values, which heavily depend on the studied sample or the scoring. Interestingly, the predictive value of the phenotype remained valid.

Frailty models have so far mainly been used in epidemiological research demonstrating convincing evidence for predictive validity for a number of high impact outcomes in older persons such as loss of independence, morbidity and mortality.

Such associative data lead to the research question whether frailty – or at least the phenotype as assessed according to valid assessment models- can be modified in interventional studies. Apart from this heuristic question methodological issues have to be solved as the scoring of the Fried phenotype in it’s original form allows analysis in large ageing study samples but has severe limitations in interventional studies with much smaller sample sizes.

Although some studies mainly focusing on motor interventions showed successful training approaches with respect to motor parameters as used in the Fried phenotype, the proof of modifying the frailty phenotype is still missing to our knowledge.

A large intervention trail on motor training in frail, multimorbid geriatric patients at the Bethanien hospital in Heidelberg showed significant effects on most of the items used in the Fried model, as well as in the total scoring according to Fried’s phenotype. Issues used in the Phenotype showed varying responsiveness to the training approach including progressive strength and functional training.
Mitochondrial theory of ageing: dead or alive?

Aleksandra Trifunovic

Although mitochondria have long been anticipated as a perpetrator of aging, there was little experimental evidence to link these changes directly with the cellular pathology of aging. MtDNA mutator mouse was the first model showing that collective amount of somatic mtDNA mutation could cause ageing in experimental animals. Before this mtDNA mutations and especially random mtDNA point mutations were seen more as a consequence than the driving force of ageing. The mtDNA mutator mice have high levels of point mutations and linear deletions of mtDNA causing a progressive respiratory chain dysfunction and a premature ageing phenotype. Surprisingly, we showed that increased levels of mtDNA mutations were not associated with increased oxidative stress in mtDNA mutator mice. In agreement with this, we now show that mtDNA mutator produce significantly less net ROS than WT mitochondria, when energized by an optimal mixture of substrates that allow maximal oxidative capacity. We hypothesized that normal or even decreased net ROS production in mtDNA mutator mice might be a consequence of increased uncoupling due to high upregulation of uncoupling protein 2 (UCP2) in different tissues of mtDNA mutator mice. The UCP2 upregulation might also lead to decreased ATP production and thus explain higher energy expenditure observed in mtDNA mutator mice. In order to elucidate the role of UCP2 in conditions of severe mitochondrial dysfunction we have created the UCP2 deficient mtDNA mutator mice. Surprisingly, the UCP2 upregulation did not affect ROS production, membrane potential or respiration in the mtDNA mutator mitochondria. However, UCP2 deficiency in mtDNA mutator mice decreases circulating glucose levels and lead to lactic acidosis. Our results indicate that UCP2 upregulation in mtDNA mutator mice represent a protective mechanism allowing metabolic shift toward fatty acid utilization in the conditions of mitochondrial dysfunction.
Growth hormone, methionine and aging

Holly Brown-Borg

Growth hormone mutant mice are diminutive in size, exhibit enhanced antioxidative capacity and extended longevity when compared to their growth hormone sufficient counterparts. Many physiologic mechanisms appear to be altered in these mice that may contribute to these differences including aspects of glutathione and methionine metabolism. The atypical methionine metabolism in the Ames dwarf mice leads to differential expression of DNA methylation enzymes (Dnmt) and differential methylation. Gene expression of the Dnmt enzymes (Dnmt1, Dnmt3a and Dnmt3b) is greater in Ames dwarf mice in comparison to age-matched wild type mice (p<0.05). However, protein levels of Dnmt1 are lower while levels of Dnmt3a protein tend to be higher in dwarf compared to wild type mice. Dnmt enzyme activity levels also differ by genotype and age and may be responsible for the differences in methylation observed in an earlier array experiment. In addition to the enhanced ability to counter oxidative stress, these epigenetic changes may be contribute to altered gene expression and the overall extension of health span and lifespan enjoyed by these mice.
Epithelial stress and aging in the evolution of lung fibrosis

Andreas Günther

Idiopathic Pulmonary Fibrosis (IPF) is a life-threatening disease affecting ~ 160,000 – 250,000 in the EU/US. Patients experience a cancer-like disease, with a median survival time of less than 3y. The precise mechanism of IPF is still not fully understood but chronic injury of alveolar type II cells (AEC2) is increasingly accepted as key event. In my talk I will review misfolding or disturbed processing/transport of surfactant proteins and impaired DNA repair as underlying reasons for development of a maladaptive endoplasmic reticulum (ER) stress response, increased ROS production and/or DNA damage. As a result, excessive AEC2 apoptosis occurs and causes a permanent perturbation of the alveolar epithelial homeostasis. I will also discuss the role of secondary exogenous hits (e.g. smoking, respiratory infections), which seem to aggravate the disease and may contribute to an increased turnover rate of the epithelium, thereby exhausting the regenerative capacity of the progenitors. As a consequence, the delicate epithelial-mesenchymal interaction is profoundly disturbed: epithelial cells do not adequately produce and release prostacyclin E2 (PGE2), but instead release large amounts of developmental signalling factors belonging to the Wnt and the Notch pathway. As I will discuss, these factors may, in parallel, promote fibroblast proliferation and transdifferentiation. On the contrary, fibroblasts show reduced expression and activation of HGF and FGF-7, two key epithelial-protective factors, thus favouring epithelial cell death. In addition, epithelial-mesenchymal transition has been proven to occur in appropriately designed animal models of lung fibrosis and in response to ER-stress and circulating fibrocytes have been identified as important source of lung fibroblasts. Treatment modalities aiming to attenuate epithelial injury are currently developed, but novel drugs acting on highly activated fibroblasts may still be needed.
The effects of antioxidants on lifespan and disease

Flint Beal

There is substantial evidence which implicates mitochondrial dysfunction and oxidative damage in both normal aging and neurodegenerative diseases. We showed that there are age-dependent exponential increases in oxidative damage to DNA with normal aging, and that mitochondrial-DNA (mt-DNA) damage was much greater than nuclear DNA damage. There was a significant further 3-fold increase in oxidative damage to mt-DNA in Alzheimer’s Disease (AD) postmortem tissue. Dietary restriction is one of the few treatments which extends life span, and it is associated with reduced oxidative damage to DNA. In Drosophila, increases in the antioxidant enzymes MnSOD and methionine sulfoxide reductase A extend life span. In both Huntington’s Disease (HD) and Parkinson’s Disease (PD), there is extensive evidence of increased oxidative damage to DNA, proteins and lipids.

There is evidence that the transcriptional coactivator PGC-1alpha is deficient in both HD and PD and that PGC-1alpha attenuates oxidative damage. Most attempts to slow aging or treat neurodegenerative disease with antioxidants have been unsuccessful. More recently, we and others tested triterpenoids, which are selective activators of the Nrf2/ARE pathway. These compounds transcriptionally activate glutathione synthesis and they increase expression of antioxidant enzymes, heme oxygenase 1 and heat shock proteins. Triterpenoids showed efficacy in the MPTP model of PD and 3-nitropropionic acid (3-NP) toxin model of HD. They also were effective in transgenic mouse models of AD, HD and ALS. We showed that triterpenoids attenuate immunoreactivity for 8-OhdG, 3-nitrotyrosine and malondialdehyde modified protein, as well as levels of isoprostanes and malondialdehyde in these mice.

Activation of transcriptional pathways which control antioxidant genes, is therefore, efficacious in multiple transgenic mouse models of neurodegenerative diseases.

Similarly, treatment with the antioxidant CoQ10 shows neuroprotective effects in transgenic mouse models of HD and AD, and in the MPTP model of PD. Antioxidants, therefore, have great promise for the treatment of both normal aging and neurodegenerative diseases.
Perspectives of preconditioning prior cardiac surgery – an overview

Ivar Friedrich

The value of physical and psychological pre-treatment in patients awaiting cardiac surgery is still unclear. In particular, elderly patients with multiple comorbidities may benefit from pre-surgical treatment. Frailty is a significant risk factor for unfavorable outcome following cardiac surgery. These older patients are more likely to suffer from anxiety disorders and depression, which are not only predictors of morbidity and mortality, but also of postoperative quality of life as an independent risk factor. Mental stress reduction and psychological cognitive behavioral therapy have been shown to improve postoperative outcome. Nevertheless, little is known about the impact of specific physical pre-treatment. In frail patients, a low, 6 minute walking test has demonstrated the best predictive value for long term survival. Extended preoperative physical training regimes may have a significant impact on recovery following cardiac surgery. Targets for clinical improvement include lung function and breathing, grip strength and 6 minute walking. The presentation will focus on the discussion of the available data and will provide a framework for future studies which may shed some light on a field which world appear to lend itself to further detailed investigation.
Preventive Implications in Cardiac Surgery of the Elderly under Gender-Specific View

Sandra Eifert

Coronary vascular disease (CVD) is the leading cause of death among patients in every major developed country; therefore, there is strong rationale to sustain efforts to control CVD risk factors with or without surgical treatment to apply evidence-based preventive approaches. Based on general preventive strategies more recently special perspectives and therapies in women based on the Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women – 2011 Update was clinically focussed.

The major evolution from previous guidelines to the 2011 update is that effectiveness (benefits and risks observed in clinical practice) of preventive therapies was strongly considered and recommendations were not limited to evidence that documents efficacy (benefits observed in clinical research).

Therefore, we want to report about the major classical risk factors such as smoking and diabetes depending on age and gender as well comorbidities such as preexisting COPD. In women risk classification remains the cornerstone of prevention. In terms of CVD risk, women may be classified as: high risk, at risk, or at ideal cardiovascular health specifically at higher age. Previous pregnancy complications like preeclampsia, gestational diabetes, or pregnancy-induced hypertension, and systemic autoimmune diseases are criteria to specifically classify women as at risk for CVD mandating different prevention and treatment strategies.

The presentation will focus on differences in pharmacological treatment depending on age. We also want to show surgical differences in outcomes depending on age and gender including conventional and OPCAB techniques, followed by the introduction of the German off-pump study in elderlies (older than 75 years).

Furthermore, on the prospect of minimally invasive mitral valve repair we report a propensity score-adjusted retrospective comparison of early and mid-term results after mitral valve repair versus replacement in octogenarians and a comparison of minimally invasive versus conventional approach for MVR.

With the development of percutaneous valve implantation, an increasing amount of interest is being expressed in outcomes of conventional aortic valve replacement (AVR) in elderly patients. We evaluated characteristics and outcomes of elderly patients undergoing isolated AVR with a particular focus on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) risk stratification.
Metabolic therapy and oxidative stress in cardiac surgery and cardiovascular disease

Franklin Rosenfeldt

Introduction  Ageing, major surgery and cardiac disease cause metabolic and oxidative stresses. Identification and quantification of these stresses can provide a guide to targeted therapy and enable the efficacy of such therapy to be assessed.

Metabolic and antioxidant therapy  An increasing proportion of patients presenting for cardiac surgery in the present era are elderly, with a high incidence of co-morbidities such as diabetes, heart failure, previous myocardial infarction and renal impairment. Advanced age and significant co-morbidities are associated at a biochemical level with an enhanced degree of oxidative stress and clinically with high rates of postoperative complications and an increased length of hospital stay. We postulated that by the perioperative use of metabolic agents we could favourably influence metabolism and improve clinical outcomes. We used 2 months preoperative: coenzyme Q10, lipoic acid, selenium, magnesium orotate, and omega-3 polyunsaturated fatty acids in a prospective randomised clinical trial in patients having elective cardiac surgery. We found that preoperative metabolic therapy was associated with improved redox status, reduced myocardial damage, shortened length of postoperative hospital stay and reduced hospital costs1.

The Cardiac Wellness Program  We assessed the preoperative efficacy of a holistic programme of mental stress reduction and physical exercise2 and then developed an expanded regimen of metabolic therapy combined with adjunctive therapies in the peri-operative period including instruction in healthy lifestyles and introduction to postoperative rehabilitation programmes. We have recently added postoperative massage therapy to our wellness programme. In a prospective randomised trial, massage, compared to bed rest, reduced postoperative pain by 52%. The Cardiac Wellness program was associated with a 46% increased participation in cardiac rehabilitation; clinical outcomes are currently being evaluated.

Conclusions  It is possible to assess oxidative stress preoperatively and to introduce metabolic and holistic perioperative programmes to improve postoperative recovery. These programmes may prove particularly useful in elderly patients undergoing major surgery.
Ageing at heart: Too frail for intervals?

Øyvind Ellingsen

The level of physical activity and aerobic fitness, measured as maximal oxygen uptake VO$_{2\text{max}}$, are powerful prognostic markers of good health, well-being and survival across age and morbidity groups. Although there is significant genetic variation, exercise training is one of the best proven non-pharmacological interventions to prevent, delay and reverse age-related disease and loss of function. In contrast to its large potential to improve the health of Europe’s ageing population, lack of physical activity is an important cause of morbidity and mortality related to lifestyle. An important task is therefore how to develop evidence-based programs for defined health conditions including ageing.

A number of recent experimental and small clinical studies have demonstrated significantly larger effects on aerobic fitness compared to the same amount of exercise performed at moderate intensity. Patients typically participated in 12-weeks interval training programs comprising 2-3 weekly supervised sessions of 4x4 minutes exercise at 85-90% of VO$_{2\text{max}}$, interspersed with 3 minutes active breaks at low intensity or continuous exercise at 70%. These results applied to several conditions that are prevalent in ageing populations, including chronic heart failure, coronary artery disease, peripheral artery disease and metabolic syndrome. Mean age were 75, 62, 65 and 50 years, respectively, indicating a significant proportion of ageing or elderly participants. High intensity exercise also induced significantly larger beneficial effects on some functional and structural outcomes, including left ventricular remodeling, arterial endothelial function and skeletal mitochondrial biogenesis.

Although no excess of adverse effects have been detected with high intensity exercise, the number of patients in these early studies is too small to assess safety and long-term clinical outcomes. In healthy individuals, however, epidemiological evidence seems sufficient to recommend increasing intensity to maximize health benefits.
Hormesis: Its significance for toxicology, pharmacology and risk assessment

Edward Calabrese

This presentation provides an assessment of hormesis, a dose-response concept that is characterized by a low-dose stimulation and a high-dose inhibition. It will trace the historical foundations of hormesis, its quantitative features and mechanistic foundations, and its risk assessment implications. It will be argued that the hormetic dose response is the most fundamental dose response, significantly outcompeting other leading dose-response models in large-scale, head-to-head evaluations used by regulatory agencies such as the EPA and FDA. The hormetic dose response is highly generalizable, being independent of biological model, endpoint measured, chemical class, physical agent (e.g., radiation) and interindividual variability. Hormesis also provides a framework for the study and assessment of chemical mixtures, incorporating the concept of additivity and synergism. Because the hormetic biphasic dose response represents a general pattern of biological responsiveness, it is expected that it will become progressively more significant within toxicological evaluation and risk assessment practices as well as having numerous biomedical applications, some of which will be emphasized in this presentation.
Promoting lifespan and metabolic health by increasing oxidative stress: mitochondrial hormesis

Michael Ristow

Recent evidence suggests that calorie restriction and specifically reduced glucose metabolism induces mitochondrial metabolism to extend life span in various model organisms, including S. cerevisiae, D. melanogaster, C. elegans and possibly mice. In conflict with Harman’s free radical theory of aging (FRTA), these effects may be due to increased formation of reactive oxygen species (ROS) within the mitochondria causing an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. This type of retrograde response has been named mitochondrial hormesis or mitohormesis, and may in addition be applicable to the health-promoting effects of physical exercise in humans and, hypothetically, impaired insulin/IGF1-signaling in model organisms. Consistently, abrogation of this mitochondrial ROS signal by antioxidant supplements impairs the lifespan-extending and health-promoting capabilities of glucose restriction and physical exercise, respectively. In summary, the findings discussed in this review indicate that ROS are essential signaling molecules which are required to promote health and longevity. Hence, the concept of mitohormesis provides a common mechanistic denominator for the physiological effects of physical exercise, reduced calorie uptake, glucose restriction, and possibly beyond.

For details see: Exp Gerontol, 45, 410-8 [2010], PubMedID 20350594
On the quasi-stochastic distributions of major geriatric pathologies

George Martin

This presentation is a follow up of my 2009 Halle conference presentation on “Epigenetic Gambling and Epigenetic Drift as an Antagonistic Pleiotropic Mechanism of Aging: Outline of a New Theory of Aging & Some of its Predictions” (GM Martin, Aging Cell 8: 761, 2009). We have begun to establish baseline statistics on the coefficients of variation of cell-to-cell variegations for several nuclear protein markers using semi-quantitative immunohistochemical methods in a line of normal diploid human fibroblasts immortalized with hTERT. These lines have been exposed to EMS mutagenesis in an effort to isolate stable variants of cell-to-cell variegations that are either excessive (“high stakes gamblers”) or constrained (“low stakes gamblers”). The major focus of this presentation, however, will be on the proposition that epigenetic gambling and drift may explain the striking quasi-stochastic distributions of a wide range of geriatric human pathologies, including Alzheimer’s disease, Parkinson’s disease, atherosclerosis, sarcopenia, non-ischemic congestive heart failure, osteoarthritis, benign prostatic hyperplasia, and numerous types of benign and malignant neoplasms. It is proposed that the loss of proliferative homeostasis, with concomitant multi-focal atrophies and hyperplasias, are the first steps towards the genesis of the many cancers associated with aging. Some evidence in support of that proposition comes from a study that revealed clonal expansions of cells bearing neutral mutations immediately surrounding adenocarcinomas of the colon (JJ Salk et al., PNAS 106, 20871, 2009).
Applying hormesis in ageing research and interventions

Suresh Rattan

Ageing occurs not due to any specific gerontogenes but due to imperfect maintenance and repair pathways. The focus of ageing interventionary research is to find ways for preventing the failure of maintenance and slowing down ageing. A promising and powerful approach is that of mild stress-induced hormesis for strengthening the homeodynamic ability of self-maintenance. Hormesis in ageing is characterized by the beneficial effects that result from cellular responses to mild stress. Hormetic response to the stressor defends the organism not only against that particular stress, but also it overshoots, facilitates the removal of other molecular damages in cells and tissues, and improves the overall homeodynamic ability. Our studies have shown that repeated mild heat stress (RMHS) has ageing-modulatory effects on growth and on various other cellular and biochemical characteristics of normal human cells undergoing ageing in vitro. RMHS increased the basal levels of various chaperones, reduced the accumulation of oxidatively and glycoxidatively damaged proteins, stimulated proteasomal activities for the degradation of abnormal proteins, improved cellular resistance to ethanol, hydrogenperoxide and UV-B rays, enhanced the levels of various antioxidant enzymes, and increased the phosphorylation-mediated activities of stress kinases. Hormesis-inducing conditions or agents are termed as hormetins, and are divided in three categories: (i) nutritional hormetins, (ii) physical hormetins, and (iii) mental hormetins. Various nutritional components, including spices, flavanoids, polyphenols and micronutrients are potential hormetins. Intracellular network of stress-response pathways can be the basis for discovering novel nutritional hormetins, which can be used as nutritional supplements and ageing modulators.
Posters
(in alphabetical order)

Sunday 18th of September of 11:30 to 11:45

The Poster Award Ceremony

1st Place 1,000 €

2nd Place 500 €

3rd Place 250 €
Unhealthy diet and air pollution compromise human cardiovascular cell functions – induction of a “cardiovascular aging phenotype”?

1) Niloofar Ale-Agha, Nicole Büchner, Ulrich Sydlik, Klaus Unfried, Joachim Altschmied, Judith Haendeler

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Environmental factors like diet and industrial or consumer derived pollution are known to affect “healthy cardiovascular aging”. The molecular consequences of the permanent burden for aging of the cardiovascular system are unknown, since they have never been examined in primary, adult human cells. Therefore, the following study investigates the impact of unhealthy diet on aging-related signaling pathways of human primary cardiovascular cells and of airborne ultrafine particles on human primary endothelial cells. Several studies demonstrated that ultrafine particles can enter the circulation and thus may interact with endothelial cells directly. Nutrition health reports have shown that the diet in industrialized countries contains more than 100 mg/dl low density lipoprotein (LDL) and a too high fraction of monosaccharides, especially fructose, which is metabolized insulin-independently. Both components have been shown to increase the risk for cardiovascular diseases. To simulate unhealthy diet we supplemented cell culture media of human, primary endothelial cells (EC), smooth muscle cells (SMC) and cardiomyocytes (CM) with 100 mg/dl LDL and replaced one third of the glucose with fructose for one week. This treatment did not induce cell death in any of the cell types. However, we observed increased senescence, loss of endothelial nitric oxide synthase and increased nuclear localization of Foxo3 in EC, increased proliferation in SMC and hypertrophy in CM. With respect to pollution we have used ultrafine carbon black particles (ufCB), one of the major constituents of industrial and exhaust emissions, in concentrations our vessels are constantly exposed to. These concentrations of ufCB are non-toxic and non-inflammatory for EC. Despite the absence of these immediate effects, ufCB dramatically reduced the S-NO content, a marker for NO-bioavailability in EC and increased reactive oxygen species formation. As a consequence, ufCB dramatically increased senescence of EC after two weeks.

Thus, unhealthy diet and a long term exposition to ultrafine carbon black nanoparticles seem to induce a “cardiovascular aging” phenotype which can lead to severe cardiovascular diseases.
Differentiation of patient specific mRNA IPS cells into fibroblasts

2) Antje Arnold, Jörn Wiegand, Alexandra Stolzing
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Introduction:
The generation of induced pluripotent stem cells (iPS) has enormous potential for the development of patient-specific regenerative medicine. IPS cells developed with mRNA-transfections are without genetic modifications and therefore they could be used in clinical translation. The aim of this study was to analyze the characteristics of fibroblasts derived from iPS cells compared to the donor fibroblasts regarding some aging aspects. Recent publications show controversial data about premature aging signs of cells derived from iPS cells.

Methods:
Fibroblasts derived from iPS cells were identified using two fibroblast specific marker expressions (e.g. D7Fib, Vimentin). Donor fibroblasts and fibroblasts derived from mRNA IPS cells were analysed regarding doubling times and levels of senescent cells using β-galactosidase staining. Telomere length was determined using qPCR. DNA damage level and repair capacity after oxidative stress was measured using the Comet Assay. Resistance to H$_2$O$_2$ induced apoptosis was measured using FACS.

Results:
Fibroblasts derived from mRNA iPS cells showed lower frequency of β-galactosidase positive cells compared to the donor fibroblasts on the same passage levels. P53 and p21 expression were increasing faster in fibroblasts derived from emo compared to donor fibroblasts. The expression levels of anti-oxidant defence markers (GpX and SOD1) were also determined on the same passage levels in both cell types. Gpx1 expression decreased faster during expansion (3 passages) in fibroblasts derived from iPS compared to the donor fibroblasts. The same trend was found for the level of apoptotic and necrotic cells after treatment with H$_2$O$_2$.

Conclusion:
With respect to our and published data it seems that the question if iPS cells do show signs of premature senescence is still controversial. It might depend on the cell line analysed or the donor material used for reprogramming. More in depth analysis and comparison of many different lines are necessary to find a conclusive answer.
Advanced glycation end-products impair the non-small cell lung carcinoma progression

3) B. Bartling, H.-S. Hofmann*, A. Sohst, Y. Hatzky, V. Somoza#, R.-E. Silber, A. Simm

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Non-small cell lung carcinoma (NSCLC) is an age-related disease and, therefore, it occurs simultaneously with other age-related changes including the accumulation of advanced glycation end-products (AGEs) in the human body. Although many age-related changes might contribute to the NSCLC development, our clinical and experimental studies indicate an anti-tumorigenic effect of circulating and extracellular matrix-bound AGEs. This has been demonstrated in a clinical study showing that NSCLC patients with high AGE-related plasma fluorescence were characterized by a later reoccurrence of the tumor after curative surgery and a higher long-term survival rate compared to patients with low AGE fluorescence (25% vs. 47% 60-month-survival, \( P = 0.011 \)). Moreover, another clinical study showed a better mid-term (20-month) survival of NSCLC patients with diabetes mellitus, which is associated with AGE increase, compared to patients without diabetes (76% vs. 59%, \( P = 0.048 \)). To confirm the impact of circulating and matrix-bound AGEs on the NSCLC progression, we studied the \textit{in vivo} NSCLC growth in mice of whom elevated circulating AGE level were induced by AGE-enriched nutrition and the \textit{in vitro} NSCLC cell migration through collagen matrix increasingly modified with AGEs, respectively. The \textit{in vivo} tumorigenicity assay demonstrated that mice with higher levels of circulating AGES developed smaller tumors than mice with normal AGE levels, and the \textit{in vitro} assay showed a reduced invasive cell migration through AGE-modified collagen matrix than non-modified collagen. Moreover, we found an inverse correlation between the \textit{in vitro} NSCLC spheroid growth in plasma/serum of patients/mice and the plasma/serum AGE levels. In summary, our clinical and experimental studies indicate a protective effect of AGES on the NSCLC progression.
Reverse crosstalk between β-catenin/T cell factor-4 and estrogen receptor α in MCF7 cells

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Institut für Biochemie II, Universitätsklinikum Jena

The Wnt- and estrogen-signalling cascades represent important regulatory systems controlling various biological processes such as differentiation, proliferation and migration. Recent observations in different model systems indicate a convergence of these pathways at different levels. Both estrogen- and Wnt-signalling have been implicated in development and progression of versatile diseases including cancer and myocardial hypertrophy. Here, we report that estrogen receptor α (ERα) associates with β-catenin/TCF-4 complexes and is able to directly bind to β-catenin upon activation by 17β-estradiol in the human breast adenocarcinoma cell line MCF7. In binding to the β-catenin N- and C-terminal domains, ERα represses transcription of target genes such as Axin2 and CyclinD1. Two-step ChIP experiments revealed binding of β-catenin/ERα complexes to promoters in a 17β-estradiol-dependent manner. Ectopic expression of ERα in ER negative HEK293 cells supported these observations. Vice versa β-catenin/TCF-4 overexpression enhanced transcriptional activity of ERα in MCF7 cells. In summary our observations revealed a gene- and context-specific crosstalk between β-catenin and ER signalling which may be involved in sex-specific differences in target gene expression and development of disease.
Comparison of the telomerase deletion response between two budding yeasts

Caroline Machlitt⁹, Dalit Fischer⁸, Yehuda Tzfatib and 5) Karin D. Breuniga

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Cellular senescence is associated with marked changes in gene expression. In Saccharomyces cerevisiae senescence induced by telomerase depletion results in altered expression of many genes and metabolic reprogramming (1). To identify evolutionarily conserved signaling components of the telomerase deletion response (TDR) we have compared the TDR of S. cerevisiae with that of the budding yeast Kluyveromyces lactis. The latter has diverged from the Saccharomyces lineage before the whole genome duplication and displays a higher preference for respiratory metabolism. K. lactis tlc1 mutants show marked changes in colony morphology immediately after telomerase depletion induced by loss of the wild-type TLC1 gene. Its endogenous beta-galactosidase gene located at a subtelomeric position is frequently lost in senescent cells revealing a remarkable degree of genetic instability. We have focused on the Snf1/AMPK signaling network, which is central to energy homeostasis. We report that among others SIP4, a gene that is highly upregulated in the TDR of S. cerevisiae, is transiently downregulated in K. lactis immediately after loss of the TCL1 gene. SIP4 encodes a Snf1 controlled transcription factor, which functions redundantly with Cat8 in S. cerevisiae but not in K. lactis. We propose that SIP4 regulation might reflect changes in the activity of Snf1 kinase activity, in response to telomere depletion, a hypothesis that currently under investigation. An influence of telomere status on this key regulator might also contribute to metabolic reprogramming in senescent cells of higher organism.
Effects of ambient air pollution on endothelial cells

6) Nicole Büchner, Niloofer Ale-Agha, Ulrich Sydlik, Klaus Unfried, Joachim Altschmied, Judith Haendeler

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Particulate matter (PM) pollution imparts a burden to the public health. One would think that PM causes a health risk mostly to the lung, however, the overall evidence indicates that the majority of the PM effects are upon the cardiovascular system. Several studies demonstrated that ultrafine particles can directly enter the circulation and thus may interact with endothelial cells. However, molecular mechanisms using non-cytotoxic, in vivo relevant concentrations of particles have not been investigated in endothelial cells in vitro and in vivo. Therefore, this research project aims for the first time to analyze the effects of ultrafine and fine particles of different materials in non-toxic concentrations on endothelial cells. First, we incubated primary human endothelial cells with ultrafine and fine Carbon Black (ufCB and fCB) particles as well as Titaniumdioxide (ufTiO2 and fTiO2) and determined the non-toxic concentrations. MTT measurements revealed that 0.1 µg/cm² and 1 µg/cm² did not reduce endothelial cell viability. To test whether these concentrations influence endothelial cell function, we measured nitric oxide (NO) bioavailability, which is important for vessel function. Only ultrafine particles (ufCB and ufTiO2) reduced S-NO content in endothelial cells, whereas fCB and fTiO2 had no effect at the same concentrations. Interestingly, the effects of ufCB and ufTiO2 were more pronounced than with known reducers of NO bioavailability, TNFα and H₂O₂, suggesting that ultrafine particles dramatically reduce endothelial function also in vivo. We previously demonstrated that NO increased Telomerase Reverse Transcriptase (TERT) activation, an enzyme essential for telomere maintenance. TERT activation is required for endothelial cell function and is inactivated by the Src kinase under conditions of oxidative stress. Therefore, we investigated the effects of ufCB and ufTiO2 on TERT and Src activation. ufCB and ufTiO2 significantly reduced TERT activation and increased Src kinase activity further supporting the concept that ultrafine particles indeed impair endothelial function. Thus, a high burden of ultrafine nanoparticles seems to induce an aging-like cardiovascular phenotype and can lead to severe cardiovascular diseases.
Cellular stress response is a crucial factor in maintaining efficient homeodynamics for survival, health and longevity. Both the immediate and delayed responses to external and internal stressors effectively determine the molecular biochemical and physiological homeostasis in a dynamic and interactive manner.

There are three main aspects of stress responses: (i) immediate stress response involving extra- and intra-cellular signaling during the period of disturbance and exposure to the stressors; (ii) delayed stress response involving sensors and modulators in the presence of stressors or after the removal of the stressors; and (iii) down-stream effectors for counteracting the effects of disturbance and for re-establishing homeodynamics. At the present it is not known how these three steps are maintained interactively in terms of kinetics and intensity, and how these may alter during growth, development and ageing.

Our aim is to define and establish the immediate and delayed stress profiles of normal human skin fibroblasts undergoing ageing in vitro. This is done efficiently by using various cellular, molecular and antibody-based detection methods, combined with functional assays, such as wound healing in vitro by fibroblasts, and induction of differentiation of stem cells. Furthermore immediate and delayed stress profiles need to be established at several age points during the replicative senescence of cells in culture, which can then be the basis for testing potential protectors and stimulators of homeodynamics, and create a kind of “gold-standard” for monitoring the efficacy of other potential anti-ageing and pro-survival natural and synthetic compounds.

We have so far standardized an effective method for detecting one of the seven stress response pathways, namely autophagy, by measuring the protein LC-3 and by determining the turnover of mitochondria by JC-1 fluorescence. The kinetics of autophagy is further elucidated by the turnover of LC-3, using lysosomal hydrogenases inhibitors, pepstatin A and E64d.
Aging-research on vertebrates is hampered by the lack of short-lived model-organisms. The annual killifish *Nothobranchius furzeri* has a very short lifespan. The inbred line from the terra-typica (GRZ) can reach an age of 3.5 months and the wild-derived strain MZM-04/10 reaches up to 10 months of age. Both strains can be kept and bred under lab-conditions and are useable as a short-lived vertebrate-models in aging-research.

Lifespan of this fish-species can be modulated by administration of certain pharmaceuticals.

Everolimus is an orally active analogue of rapamycin and it is tested for its effects on lifespan and learning behaviour in *Nothobranchius furzeri* by administration through the food. This compound inhibits TOR-activity which can be detected by measuring the phosphorylation of p70 S6 Kinase and S6 ribosomal protein.

In a learning-based test treated fish perform worse than untreated individuals.

The life-span of treated fish compared to controls is also reduced.

(Immunohisto)microscopy demonstrates that normal tissue shows a higher S6-protein activity than tissue of tumors.

Everolimus might increase spontaneous tumorigenesis in the short-lived vertebrate *Nothobranchius furzeri* which could also be an explanation of the shortened life-span of treated fish vs. controls.
Association of Thioredoxin-1 with Caspase 3: A new anti-apoptotic function of Thioredoxin-1

9) Anna Eckers, Tim-Christian Zschauer, Joachim Altschmied, Judith Haendeler

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Defense against oxidative stress as well as inhibition of apoptosis in the endothelium is mediated by thioredoxin-1 (Trx-1). Trx-1 protein levels are reduced in aged endothelial cells (EC) \textit{in vitro} and \textit{in vivo}. In EC, not only the active site cysteines 32 and 35 are responsible for anti-apoptotic action of Trx-1, but also cysteine 69. Several interaction partners of Trx-1 have been described to date, but the mechanisms underlying protection against apoptosis by Trx-1 in EC are not completely understood. Therefore, the aim of this study was to investigate whether Trx-1 interacts with Caspase 3, the most important apoptosis executor protein in EC, and thereby modulates Caspase 3 function. Communoprecipitation experiments revealed an interaction between both proteins only under non-reducing conditions, indicating involvement of a disulfide bridge. To analyze whether Trx-1 directly interacts with the active subunit of Caspase 3, p17, we coexpressed p17 and Trx-1 in EC. Indeed, Trx-1 associated with p17. Analysis of Trx-1 mutants demonstrated that this interaction depends on cysteine 32 and/or 69 in Trx-1. To assess the functional relevance of the Trx-1 p17 interaction in EC, we induced apoptosis by overexpressing p17 and investigated the effects of Trx-1 wildtype (wt) and mutants, in which single or multiple cysteine residues were replaced by serines thereby preventing disulfide bridge formation. Apoptosis induction by p17 was significantly reduced by Trx-1 wt (p17+\textit{lacZ} 16.99\pm1.35\% vs. p17+Trxwt 8.60\pm1.31\% apoptotic cells). Interestingly, overexpression of Trx-1 with mutations of cysteines 32 and 69 enhanced apoptosis induction by Caspase 3 p17 (23.42\pm2.84\% apoptotic cells). On the contrary, no increase in apoptosis was observed when only cysteine 32 or 69 were mutated, suggesting that both residues can scavenge p17 via disulfide bridge formation thereby preventing its association with the second Caspase 3 subunit p12 and thus activation of the enzyme. The data of the present study suggest that Trx-1 has a new anti-apoptotic function by binding the apoptosis executing Caspase 3 and its loss in senescent EC accounts for the increased apoptosis sensitivity.
Androgen effects on the adipogenic differentiation of mesenchymal stem cells

10) Thomas Greither1, Matthias Kraus1, Daniela Bräuer2, Hermann M. Behre1

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The physiological impact of an excessive amount of visceral body fat in the etiology of type 2 diabetes and cardiovascular diseases is important, especially in the context of the epidemic spread of obesity in the developed countries. Thus, the molecular factors facilitating the adipogenic differentiation of mesenchymal stem cells and the genesis of adipose tissue are of great interest.

In many men a significant decrease of serum testosterone levels occurs during ageing, frequently in combination with clinical symptoms of a hypogonadism. This syndrome is designated as late-onset hypogonadism and combines symptoms of primary, secondary and compensated hypogonadism (Tajar et al., 2010). A low serum testosterone level is a significant independent risk factor for the development of a metabolic syndrome including consequential diseases like type 2 diabetes and cardiovascular diseases (Laaksonen et al., 2004). In general, a further symptom of late-onset hypogonadism is a significant increase of visceral fat tissue, which can be reverted by a testosterone replacement therapy (Allan et al., 2008). Thus it can be assumed, that a decrease in serum testosterone level is a cause of increased adipogenic differentiation of visceral mesenchymal progenitor cells.

We evaluated the microRNA expression of mesenchymal stem cells during adipogenic differentiation with and without the addition of the androgen dihydrotestosterone (DHT) after 24 hours using microArrays. With the addition of DHT to medium, 18 microRNAs were upregulated more than 2 fold, while 3 microRNAs were downregulated more than 2 fold. Intriguingly, two downregulated microRNAs were described to be associated to adipogenic differentiation in the literature recently, namely microRNA miR-210 and miR-143. Both microRNAs are predicted to regulate several target genes promoting adipogenic differentiation, including Tcf7l2 (miR-210; Qin et al., 2010) or insulin-like growth factor binding protein 5 (IGFBP5) and insulin-like growth factor 1 receptor IGF1R (miR-143).

Summarizing, in this work we present microRNAs as new targets of androgen-induced suppression of adipogenesis and putative novel targets for the therapy of adverse effects caused by the decrease of the serum testosterone levels during male ageing.
Among vertebrates that can be kept in captivity the annual fish *Nothobranchius furzeri* possesses the shortest known lifespan. It also shows typical signs of ageing and is therefore an ideal model to assess the role of different physiological and environmental parameters on ageing and lifespan determination. Here we used *Nothobranchius furzeri* to study whether ageing is associated with mitochondrial DNA (mtDNA) alterations and changes of mitochondrial function. We sequenced the complete mitochondrial genome of *N. furzeri* and found an extended control region. Large-scale mtDNA deletions have been frequently described to accumulate in other organisms with age, but there was no evidence for the presence of detectable age-related mtDNA deletions in *N. furzeri*. However, mtDNA copy number significantly decreased with age in skeletal muscle, brain, liver, skin and dorsal fin. Consistent with this finding, expression of *Pgc-1α*, that encodes a transcriptional co-activator of mitochondrial biogenesis and expression of *Tlam* and *mtSsbp* both encoding mtDNA binding factors was down-regulated with age. The investigation of possible changes in mitochondrial function revealed that the content of respiratory chain complexes III and IV was reduced in skeletal muscle with age. In addition, ADP-stimulated and succinate-dependent respiration was decreased in mitochondria of old fish. These findings suggest that despite the short lifespan, ageing in *N. furzeri* is associated with a decline in mtDNA copy number, the down-regulation of mtDNA-associated genes, and an impairment of mitochondrial function.
Influence of Systemic Normo- or Hypothermia on Myocardial Oxygen Tension during Extracorporeal Circulation

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Objectives: Controlled hypothermia is a common method of myocardial protection during extracorporeal circulation (ECC). Although the beneficial aspects of hypothermia on myocardial metabolism have been widely demonstrated the effect of hypothermia on the oxygen tension of the myocardium (pO2myo) is unclear.

Methods: In an experimental study the influence of systemic normo- (n=10 pigs; strain: german landrace) and mild hypothermia of 32°C (n=6 pigs) on the pO2myo of the beating heart was analyzed during ECC. pO2myo was assessed by using flexible pO2 microprobes.

Results: During normothermal ECC in an unloaded beating heart a continuous increase of pO2myo from 36.5±15.8 mmHg to 52.6±27.2 mmHg (+43.9%) after 1400 sec was observed (p=0.02). In case of mild hypothermia, a continuous decrease of the pO2myo occurred. On average the pO2myo dropped significantly (p<0.0001) from initially 46.9±17.5 mmHg to a minimum of 28.9±9.9 mmHg (-38.4%). After reaching a stable temperature of 32°C the pO2myo levelled at 36.7±20.8 mmHg (p<0.01). There were no signs of ischemia or arrhythmia during normo- and hypothermal ECC.

Conclusion: It seems obvious that the effect of mild hypothermia on reducing the oxygen transport to myocardial cells (oxygen transfer) outweighs the reduction of myocardial metabolism (oxygen consumption). Oxygen supply to the heart remained in mild hypothermia of 32° C sufficient for normal myocardial function.
Age-dependent disparities of Monocytes in patients with coronary heart disease

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Introduction: The effects of aging on innate immune responses are incompletely understood. Monocytes may be differentiated into phenotypically and functionally distinct cell types by the presence or absence of the lipopolysaccharide receptor CD14 and the Fcγ-receptor CD16. Recent studies have found conflicting results regarding an association between subtypes of monocytes as defined by the expression of these two surface markers to atherosclerosis. We hypothesized that subgroups of monocytes are different in dependence on age in patients with coronary heart disease.

Methods: We investigated subtypes of monocytes by using flow cytometry in 745 patients with angiographically documented coronary heart disease, submitted to the Department of Medicine III and the Department of Cardiothoracic Surgery of the University Clinics, Martin Luther-University Halle-Wittenberg. We compared two subgroups of a dissimilar age with each other, Patients with an age ≥75 years (n=205) and younger Patients (n=540).

Results: In the subgroup of the elder patients the relative lymphocyte counts were significantly decreased {21.5±8.8% age ≥75 years vs. 24.4± 7.6% age < 75 years (p<0.001)}. Moreover, elder patients had significantly higher total numbers of circulating CD14++CD16+ monocytes as compared to younger patients {248.8±195.8 cells/µl age ≥75 years vs. 189.1± 151.4 cells/µl age <75 years (p<0.001)}. Furthermore the group of Patients ≥75 years showed higher counts of CD14+CD16+ monocytes {162.7±150.6 cells/µl age ≥75 years vs. 139.9± 89.2 cells/µl age <75 years (p=0.011)}. CD14++CD16- monocytes and the percentage of total monocytes were not different in both patient groups.

Conclusion: Our study showed that there is an increase in CD14++CD16+ monocytes and a decrease of lymphocytes dependent on age in patients suffering from coronary heart disease. This might contribute to the well-known cardiovascular vulnerability of the elderly patient.
Biochemical characterization of the M712T-mutation of the UDP-N-acetylglucosamine 2-epimerase/N-acetyl-Mannosaminekinase in hereditary inclusion body myopathy

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Hereditary inclusion body myopathy is a neuromuscular disorder characterized by muscle weakness with a late onset and slow progression. It is caused by mutations of the gene encoding UDP-N-acetylglucosamine-2-epimerase/N-acetylmannosamine kinase (GNE). One of the most frequent mutations is an exchange of methionine to threonine at position 712 (M712T). Here we analyzed wildtype (wt) and M712T-mutated (M712T) GNE. We identified threonine 712 as an additional possible phosphorylation site and found by two-dimensional gel-electrophoresis a lower isoelectric point compared to wt-GNE. This lower isoelectric point could be reversed back to the wildtype isoelectric point after treatment with protein phosphatase. Furthermore, in contrast to wt-GNE, a significant fraction of M712T-GNE was in the insoluble fraction. Finally, by using bimolecular fluorescence complementation we demonstrate that the M712T mutation is not involved in formation of GNE-oligomers.
Advanced glycation end products (AGEs) seem to be involved in the development of diseases such as diabetes mellitus, renal failure and Alzheimer's disease. During ageing, the AGEs accumulate in matrix proteins like collagen and fibronectin. Bypass operations are the most common intervention in patients suffering from coronary heart disease. However as the majority of the patients are older than 60, the graft material (vein or artery) of these patients is probably enriched on AGE-modifications. To which extension these modifications may affect the quality of the bypass operation is unknown. In this study we analyzed the AGE-modifications in the collagen of veins and arteries used as graft material in bypass operations. Two fractions of collagen (soluble [AGE-unmodified] and insoluble [AGE-modified]) were isolated. As expected, the insoluble collagen fraction showed a higher amount of AGE-modifications in comparison to the soluble fraction as detected by slot blot and by the measurement of the AGE intrinsic fluorescence. The amount of AGE-modifications in the insoluble collagen is positive correlated with the age of the patients. AGE-modifications were also measured in the heart muscle and atrium collagen. The possible role of the AGE-modifications in the graft material and heart muscle is discussed.
Eukaryotic elongation factor-2 (eEF-2) catalyses the motion of the growing peptide chain relative to the mRNA at the ribosomes during protein synthesis. Mother Nature gives us a hint to the vital importance of this highly conserved G-protein by making it the specific target of two lethal bacterial toxins, Pseudomonas aeruginosa exotoxin A and diphtheria toxin. These toxins exert their detrimental action by ADP-ribosylating a biologically unique posttranslationally modified histidine residue (diphthamide$^{715}$) within eEF-2, thus inactivating the enzyme. Diphthamide$^{715}$ is also the target of endogenous (mono) ADP-ribosyl transferase activity. Here we report the first known activator of endogenous ADP-ribosylation of eEF-2, interleukin-1β (IL-1β). Thereby systemic inflammatory processes, as encountered in the ageing process, may link to protein synthesis regulation.
Caffeine is one of the most widely used drugs in the world. In the past decades caffeine was hypothesized to increase the risk of cardiovascular diseases. Recent studies have shown a protective effect of caffeine on the cardiovascular system. High concentrations of caffeine mobilize calcium from intracellular stores. In contrast, we have shown that concentrations of caffeine measured after moderate coffee consumption (50 µM) enhanced the migratory capacity of endothelial cells (EC) independent of intracellular calcium levels. As EC migration is critically dependent on energy provision by mitochondria we wanted to identify the molecular link between caffeine, mitochondrial energy metabolism and migration. Surprisingly, we found that caffeine induces the translocation of p27/Kip1 (p27), originally identified as a cell cycle inhibitor, into the mitochondria. Reducing p27 levels with siRNA inhibited caffeine- as well as vascular endothelial growth factor-induced migration, demonstrating a general role for p27 in the migratory process in EC. Overexpression of mitochondrial, but not nuclear targeted p27 led to increased EC migration, enhanced mitochondrial ATP production mitochondrial membrane potential, both of which are necessary for the migratory capacity of cells. Along the same lines, only mitochondrial p27, but not nuclear p27, rescued the complete loss of migratory capacity induced by the knockdown of p27. To identify the domains in p27 responsible for EC migration and ATP production, we created a set of mitochondrial targeted deletion mutants. ATP production required the C-terminus of the protein, whereas the pro-migratory effect is relayed by both the N- and the C-terminus of p27. To investigate the connection of caffeine and p27 also in vivo, we performed microarray analysis of hearts from wildtype and p27-deficient mice treated with caffeine (0.1 % = 50 µM serum concentration) in their drinking water for 10 days to exclude central nervous system effects. Caffeine induced expression of several genes involved in mitochondrial biogenesis and mitochondrial energy metabolism only in wildtype mice demonstrating a crucial role for p27 in enhanced mitochondrial function. Therefore, caffeine seems to have a dual function, a short term translocation of p27 to the mitochondria improving their function and in the long run a change in gene expression leading to mitochondrial biogenesis.
NOX 4 is a member of the family of NADPH Oxidases whose only purpose known to date is the production of ‘reactive oxygen species’ (ROS) which are considered to be the source of mutagenesis and gross cellular damage. Deregulation of Nox4 and altered levels of ROS have been related to various forms of cancer and other diseases, especially in the field of hypertension and vascular diseases but also to diabetic nephropathy, Alzheimer’s disease and Parkinson’s disease.

Knockdown of NOX 4 has been shown to extend the lifespan of HUVEC in our group. All inhibitors currently available are either not fully characterised, not proven to inhibit NOX 4 directly, or toxic. None of the inhibitors on hand has reached the state of clinical trial. To date nothing is known about the mechanism of Nox4 inhibition, therefore the search for potent NOX 4 inhibitors is an important task to learn about the role of NOX 4 in the cell.

We identified some novel inhibitors by screening a variety of food plant compounds that could possibly reveal activity in NOX 4 inhibition thereby reducing potential toxic effects in the first place. In line with a suggestion from literature we set up a system of different assays on living cells to screen for, identify and characterise potential Nox4 inhibitors. This includes assays for Nox4 activity, ROS scavenging, Nox2 and Nox5 activity as well as a broken cell assay to further investigate the mechanism of inhibition. The data on hand has been used to perform a virtual screening to improve and complement the set of compounds to be tested in these assays. Also some inhibitors only recently discovered have been included in the characterisation and are compared to our hits.

We plan to further investigate the mechanism of Nox4 inhibition by NMR spectroscopy of the purified Nox4-dehydrogenase-domain, continually improve the set of data for the virtual screening and provide information for a molecular modelling approach of the inhibitor binding site and possibly the dehydrogenase domain.
RAGE and age related changes in heart function

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Introduction: Advanced glycation end-products (AGEs) are involved in mediating the effects of hyperglycemia in diabetes and aging. It is suggested that AGEs either directly or via their interaction with RAGE play a pivotal role in the development and acceleration of atherosclerotic cardiovascular disease. We therefore investigated the effect of the expression level on heart function during aging.

Methods: Wild type Bl6 (WT) as well as RAGE knock-out (KO) and cardiac specific RAGE overexpressing transgenic (TR) mice were investigated by ultrasound at 3 and 24 month of age. To test if activity (started at old age) leads to increased cardiovascular function, a group of mice had a possibility to voluntary wheel running.

Results: In young mice, we observed altered heart function, dependent on RAGE expression. RAGE KO mice had a left ventricular ejection fraction (LEF, in %) of 64 +/- 0.85, WT mice 61 +/- 1.28 and TR mice 56 +/- 2.07. The left ventricular systolic as well as diastolic diameter increased with increased RAGE expression. The same trend can be seen in old mice. Interestingly, in all genotypes, female mice had better cardiac parameters than male mice independent of age. Regarding age, we observed a reduction of the heart function. Interestingly, young TR mice had nearly the same heart function values as old WT mice. Starting an activity program at old age had no benefit on heart function.

Conclusion: RAGE expression is negatively correlated with heart function. It is still unknown if this is dependent on receptor activation. Regarding the possibility to positively influence heart function by voluntary activity, we did not see an enhancement in the active group in comparison to the sedentary group.
Grainyhead-like 3 plays an essential role in key endothelial functions compromised in senescence

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Endothelial dysfunction is involved in the healthy aging process and the development of cardiovascular diseases. The dysfunction is characterized by a reduced nitric oxide (NO) bioavailability, decreased migratory capacity and apoptosis sensitivity of human endothelial cells (EC) and an increase in Src kinase activation. Recently we have identified the transcription factor grainyhead-like 3 (GRHL3) as a pro-migratory factor in EC. This, together with the reduced expression of GRHL3 in senescent EC suggested that GRHL3 might control EC functions impaired during aging. Therefore, we wanted to investigate the regulation of GRHL3 by NO and Src kinase and GRHL3 effects on NO-bioavailability, apoptosis and migration. We treated EC either with physiological concentrations of NO or the Src kinase inhibitor PP2. In both cases GRHL3 expression was increased (3.75 fold and 4.50 fold, respectively). In addition, both treatments induced migration and inhibited apoptosis. Furthermore, overexpression of GRHL3 activated endothelial nitric oxide synthase (eNOS), its upstream regulator Akt and subsequently increased the S-NO protein content of EC. This demonstrates that GRHL3 enhances NO-bioavailability in EC, which is inseparably tied to apoptosis protection and migration. Along this line, GRHL3 overexpression reduced apoptosis of EC (1.89 fold reduction of basal apoptosis vs. empty vector transfected cells). Interestingly, this anti-apoptotic effect was dependent on eNOS activity, since the eNOS inhibitor L-NMMA completely abrogated the protective effect of GRHL3. Having demonstrated a pro-migratory effect of GRHL3, we wanted to know whether this effect is mediated by induction of vascular endothelial growth factor (VEGF) expression. Surprisingly, GRHL3 overexpression did not change VEGF protein levels. On the other hand, we wanted to exclude a bystander effect of GRHL3 in EC migration. Therefore we knocked down GRHL3 expression with shRNA. Downregulation of GRHL3 mRNA levels reduced basal and NO-induced EC migration (scr: 76 +/- 10 migrated cells; shGRHL3: 26 +/- 7 migrated cells; scr+NO: 145 +/- 26 migrated cells; shGRHL3+NO: 30 +/- 5 migrated cells) demonstrating an essential role for GRHL3 in this process.

Taken together, the downregulation of GRHL3 in aged EC seems to compromise vital functions of the endothelium suggesting that maintenance of GRHL3 expression may result in prolonged endothelial monolayer integrity.
Two isoforms of the transcription factor Sister-of-Mammalian Grainyhead have opposing effects in endothelial cells and in vivo

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One feature of aged blood vessels is a decline in endothelial cell functions characterized by increased apoptosis and reduced migratory capacity of human endothelial cells (EC). Among other cytokines, TNFalpha has been described as one apoptotic stimulus, which is increased during cardiovascular aging. Furthermore, recent findings support the hypothesis that TNFalpha can induce survival genes before committing cells to apoptosis. In a screen for anti-apoptotic genes regulated by TNFalpha we have identified the transcription factor sister-of mammalian grainyhead/grainyhead-like 3 (SOM/GRHL3). In humans two RNAs are transcribed from the gene, one of which is alternatively spliced, yielding the protein isoforms SOM1 and SOM3, the latter being an N-terminally truncated version. We have found that both isoforms are expressed in EC. Because nothing is known about the functions of these proteins in EC, we investigated their functional properties and role in migration and apoptosis. To analyze their transcription factor activity we established a SOM-dependent reporter system by inserting tandem SOM binding sites and corresponding mutants upstream of a minimal promoter driving luciferase expression. To assess transcriptional activation by SOM1 and SOM3 we cotransfected these reporters with expression vectors for both proteins. In contrast to previously published work, in which isolated SOM domains fused to a Gal4 DNA binding domain were used, we found that both full length proteins are active transcription factors. We next examined the influence of SOM1 and SOM3 on EC functions. Surprisingly, overexpression of isoform 1 induced migration and inhibited apoptosis, whereas isoform 3 had opposite effects. Along the same lines, SOM1, but not SOM3 activated endothelial nitric oxide synthase (eNOS) and protein kinase B (Akt). To investigate whether these isoforms have different functions also in vivo, we overexpressed them in zebrafish embryos. SOM3 but not SOM1 overexpression led to increased lethality, a strong reduction in normal phenotype and a 10 fold higher frequency in heavy deformations. The fact that both SOM1 and SOM3 are transcriptional activators and their opposing effects on EC migration and apoptosis as well as on zebrafish development suggest that these isoforms activate different sets of target genes, which we are currently identifying by microarray analysis.
Upregulation Of The High Mobility AT-Hook 2 Gene In Acute Aortic Dissection

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Introduction: Acute aortic dissection (AAD) is a lethal injury of the aorta. We studied the expression of the high mobility group AT-hook 2 gene (HMGA2) in AAD tissue, since the HMGA2 protein is known to participate in epithelial mesenchymal transition, a process during which epithelial cells are reorganized to migratory mesenchymal cells. The transition of endothelial cells is a special form of EMT called endothelial mesenchymal transition (EndMT).

Methods and Results: Aortic specimens were collected from 51 patients including 19 with acute aortic dissection, 26 with aortic aneurysm, two with Marfan syndrome and four aortic valves. Quantitative real-time-polymerase chain reaction was carried out for HMGA2 and immunohistochemical analyses were performed for HMGA2, SNAI1, CD34, MKI-67 and TGFB1. The expression of let-7d microRNA, which is assumed to play a role in the regulation of HMGA2, was also quantified. Quantitative PCR revealed a significantly higher HMGA2 expression in AAD compared to the control group (193.1 vs. 8.1 fold normalized to calibrator, \( P < 0.001 \)). The immunohistochemical investigation showed that HMGA2 and SNAI1 proteins were mainly detected in the endothelial cells of the vasa vasorum.

Conclusion: The HMGA2 gene is upregulated in acute aortic dissection. This is the first report describing a link between HMGA2 and AAD. Since the HMGA2 protein is known to participate in the regulation of EndMT and the EndMT-marker SNAI1 is also expressed, the transition of aortic vasa vasorum endothelial cells to mesenchymal cells during AAD seems possible. The expression of HMGA2 seems to be independent of regulatory miRNA let-7d and occurs mainly in the vasa vasorum.
Adipose tissue has been shown to contain high numbers of mesenchymal stem cells (ADSC), which can be utilized for therapeutic applications in regenerative medicine. ADSC have shown very close characteristic to bone marrow-derived MSC (BM-MSC) however there are strong reasons to believe that like BM-MSC, the properties and thus the functionality of ADSC may change with age. Analysis of cellular signaling, WNT pathway, reveal the involvement of Wnt proteins in proliferation, migration/invasion, differentiation and self-renewal of MSC indicating a pivotal role of WNT in MSC functions. Therefore it is crucial to characterize age induced changes in ADSC, in order to contribute to a higher pace concerning the development of cell-based therapies.

ADSC derived from subcutaneous tissue show variations in WNT gene expression according to gender. A dramatic decrease in gene expression has been detected for ADSC-derived from females at the age of 40-60 years. Genes involved in the cell cycle have shown a slight decline during ageing and cell differentiation markers indicate spontaneous differentiation among the ADSC cultures. On the other hand, gene expression analysis from ADSC derived from liposuction resulted in absence of nearly all WNT genes analyzed and different pattern of cell cycle genes and differentiation markers.

Ageing of ADSC has an effect on WNT cellular signaling especially on the female population. This drastic effect was not evident for cell cycle and differentiation markers. Further study of these differences may lead to important discoveries in the mechanisms WNT signaling in the cells from different niches and regeneration capacity of MSC.
Age and obesity-associated changes in AMPK signaling in human right atrial tissue

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Background: Obesity is associated with an increased incidence of left ventricular hypertrophy, heart failure, and premature cardiac ageing. Activation of the AMP-dependent protein kinase (AMPK) has been shown to be involved in the cellular response to diverse stresses. In the heart, intrinsic AMPK activation plays a pivotal role in the stress response to ischemia and hypertrophy. The purpose of the present study was to investigate the influence of obesity and ageing on the AMPK signaling pathway.

Methods: 60 male cardiac surgery patients were included in the study according to their body mass index (18.5-25: normal weight or 30-35: obese) and age (<55 years: young or >70: old) and divided into 4 groups (old normal-weight:ON; old obese: OO; young normal-weight: YN, Young obese: YO) with 15 patients each. Right atrial tissue (RA) was analyzed for the expression of the AMPK upstream kinases CAMKK beta and LKB1, activation AMPK as well as the phosphorylation of the AMPK downstream targets ACC, eEF2, mTOR and eNOS. Adipose tissue was analyzed for the expression of the endogenous AMPK activator adiponectin. The metabolic state of all patients was further characterized in fasting blood samples.

Results: Old patients (ON, OO) and young obese subjects displayed higher fasting glucose, insulin and leptin plasma levels compared to the young, normal weight group, although below the threshold required for the diagnosis of type 2 diabetes. Plasma adiponectin as well as total adiponectin protein expression in visceral adipose tissue were decreased in these three groups. Analyses of adiponectin isoforms by native gel electrophoresis revealed significant differences in the high molecular weight isoforms between the groups. Despite the low plasma adiponectin and the unchanged expression of the AMPK upstream kinases CAMKK beta and LKB1, AMPK activation was high in the RA of obese patients (JO, OO).

While the phosphorylation of the AMPK downstream targets mTOR and ACC were not altered, eEF2 and eNOS were lower in old patients (ON, OO) and young obese subjects. This was associated with a higher protein phosphatase type-2A (PP2A) activity.

Conclusion: These data indicate that obesity and ageing result in significant changes in the myocardial AMPK signaling pathway.
Identification of the active advanced glycation endproduct compounds in the bread crust


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The non-enzymatic glycation of proteins leads to the formation of advanced glycation endproducts (AGEs) which are usually formed endogenously but can also be present in food or beverages. On one hand the endogenous formation of AGEs is linked to age- and diabetes-related chronic inflammation, such as atherosclerosis, uremia and cataract. On the other hand nutritive AGEs have the ability to induce the antioxidative capacity on the cellular level. To determine the antioxidative capacity of food derived AGEs, our group used bread crust (BC) as source of an AGE-rich diet. The effect of BC was studied using the mouse fibroblast cell line AKR-2B as well as a mouse cardiac fibroblast cell line. We showed that BC protected cells against oxidative stress by mechanisms including NFkB-activation. However until now it is unclear, which AGE-compound was responsible for the BC effect. Using HPLC analysis and the intrinsic AGE-fluorescence, different AGE-containing fractions have been isolated. The presence of AGE-modification in the fractions was confirmed by western blot using antibodies against arg-pyrimidine, imidazolone, pentosidine and carboxymethyllysine. Furthermore the fractions have been tested in cell culture. The identification of the different biological active AGEs in the fractions is still in progress.
The extracellular matrix (ECM) has many functions in tissues, including anchorage of cells, regulation of cell behavior and sequestration of growth factors. Therefore, an altered expression, proteolysis and/or modification of the ECM can influence numerous biological processes. As fibrillar collagens (COLI, COLIII) and the basement membrane collagen (COLIV) are important ECM components in lung, we studied the effect of aging on their expression (mRNA, protein) and modification with advanced glycation end-products (AGE) in lung tissue from young (3-8 month) and old (25-34 month) mice. The mRNA level was measured by real-time PCR and gene microarray. For protein analysis collagen was extracted from lung by high salt precipitation with subsequent proteolytic digestion (1. pepsin, 2. collagenase, 3. hydrochloric acid hydrolysis of the final fraction) and measured by hydroxyprolin assay. AGE modifications were estimated by detecting the AGE-related fluorescence ($E_{360\ nm}/E_{440\ nm}$). The mRNA level of all collagens (COLI$\alpha_1$, COLI$\alpha_2$; COL3$\alpha_1$; COLIV$\alpha_1$) was reduced in lung from old compared to young mice. Moreover, the total amount of collagen protein was reduced by age (18.9 vs. 17.4 µg/mg wet lung tissue, p<0.01). Although the protein amount of collagen was not different in the collagenase-digestible fraction of old compared to young mice (4.9 vs. 5.3 µg/mg; p>0.1), collagen was age-dependently reduced in the pepsin-digestible fraction (1.9 vs. 0.3 µg/mg; p<0.001) and final fraction (12.2 vs. 11.9 µg/mg; p<0.001). The AGE-related fluorescence of collagen was increased in both the pepsin-digestible fraction and final fraction but not in the collagenase-digestible fraction. Analysis of in vitro generated AGE-collagen and control collagen did not show an impact of AGE modifications on the collagen proteolysis by pepsin, collagenase or hydrochloric acid. In summary, our study suggests a reduced amount of collagen in aging mouse lung associated with an increased AGE modification of lung collagen.
Upregulation of NOS1 – Putative trigger for NADPH oxidase-dependent oxidative stress in aged cardiomyocytes

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We analyzed contractile function of ventricular myocytes derived from young (2-4 months) and aged (24-26 months) wild-type and NOS1-/- mice. Contractions (sarcomere shortening, MyoCam system), calcium transients (Indo-1 fluorescence) and myofilament ATPase activity (blebbistatin-sensitive phosphate generation) were evaluated. Expression of NOS isoforms and NADPH oxidase subunits were quantified (real-time PCR, Western blots).

Calcium decay and shortening/relengthening were slowed in aged wild-type ventricular myocytes. Despite increased calcium transient amplitude in aged myocytes, fractional shortening was unchanged. As expected, calcium sensitivity of myofilament ATPase activity was reduced in aged wild-type myocytes. Oxidative stress was responsible for these age-dependent alterations, because application of Tiron (superoxide scavenger) normalized all of them. Interestingly, calcium transients, myofilament ATPase activity and contractile function were not compromised in myocytes from aged NOS1-/- mice. Therefore, we hypothesized that NOS1 might contribute to increased oxidative stress in aged mouse hearts.

Therefore, we analyzed NOS isoform expression. In contrast to NOS3, NOS1 was upregulated in aged hearts of wild-type mice. Additionally, expression of core subunits of cardiac NADPH oxidases (NOX2/NOX4) that are a major source of cardiac superoxide formation was induced and NADPH oxidase activity was increased. However, these changes in NADPH oxidase expression and activity were not detectable in hearts of aged NOS1-/- mice.

In agreement with these data, we found an increased expression of NOX2 and NOX4 in hearts of transgenic mice with an inducible, cardiomyocyte-specific overexpression of NOS1.

We conclude that upregulation of NOS1 contributes to oxidative stress in aged myocytes via induction of NADPH oxidase-dependent superoxide formation that in turn interferes with the contractile function of aged murine ventricular myocytes.
Insulin-dependent diabetes mellitus (IDDM) negatively affects pregnancy by causing miscarriage and poorer pregnancy outcomes in humans. Prior to implantation embryo development is regulated by maternal and embryonic factors, interacting at the cellular level independent from placental interference. The production and release of maternal factors like insulin, insulin like growth factors (IGFs) and glucose play a major role in maintaining cell viability and survival of the embryo. We used the rabbit as a model for diabetes mellitus in pregnancy. This model allows studying the influence of IDDM on maternal reproductive organs and their endocrine regulation on one side and on blastocyst development and molecular adaptation on the other.

Maternal diabetes mellitus reduced the number of blastocysts per female by 40%. Blastocyst development and gastrulation were delayed. The uterine secretions of diabetic females contain less insulin and a 3fold higher glucose concentration, demonstrating that embryos in diabetic mothers grow up in hypoinsulinaemic and hyperglycaemic conditions. These changes in the uterine environment necessitate metabolic adjustments by the embryo. Compensatory adjustments are the increased expression of uterine and embryonic IGFs and of adiponectin, indicating that the embryo is able to counterbalance insulin deficiency. We demonstrate that these molecular adaptations are sensed and regulated by the transcription factor cAMP responsive element binding protein (CREB). Blastocysts from diabetic females showed a significantly reduced CREB phosphorylation and an increased adiponectin expression, compensating the model lack of maternal insulin in order to maintain the embryonic glucose homeostasis.

Supported by the German Research Council (DFG; NA 418/4-2) and the Wilhelm Roux Programme of the MLU Faculty of Medicine
Aging of canine brains as a model for human Alzheimer`s disease

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Background:
In Germany are about 1,3 million dementia patients – 700.000 of them have Alzheimer`s Disease (AD) and that this number will duplicate until 2050. Despite many ongoing studies, the underlying course of the disease is still under discussion and not fully understood. Dogs naturally develop an age related cognitive dysfunction syndrome with several aspects which resemble Alzheimer's in humans.

Introduction:
The accumulation of β-pleated amyloid (Aß) and neurofibrillary tangles (NFT) in and around neurons are markers for AD. Dogs develop an early form of plaques consisting of β-pleated amyloid. The canine app has a 98% similarity to the human counterpart while the Aß42 peptide is 100% identical to the human peptide. Dogs also show an age related cognitive dysfunctions and might be considered an early stage AD model. Most Alzheimer related studies were performed with beagles leaving many other breeds out. The aim of this project is to compare different breeds in relation to plaque accumulation and microglia activation.

Material and methods:
Our experimental groups consist of large breeds (>8 years) and small breeds (>12 years) and younger control groups. The brain is cut sagitally and fixed with 4% formalin for least 48 hours. The brains are stained with Nissl for the overall neuronal structure. Activated microglia, astrocytes and amyloid plaques are stained and counted using sterology. Thioflavin is performed to identify dense core neuritic plaques. Tau accumulation will be analysed using proteomic.

Outlook:
It is the intention of the project to gain further information of structural changes in aged dogs and want to correlate the Aß pathology in different breeds and it’s consequences for neurodegeneration.
Mortality after percutaneous coronary intervention with stent implantation – Differences between the old and young

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Background: Identification of cardiovascular risk factors (CVRFs) is derived from studies with younger patients and these may not be valid for the elderly. Aim of our study was to investigate factors influencing mortality after percutaneous coronary intervention (PCI) in patients aged 75 years or older in comparison to younger patients.

Methods: We assessed patients who had undergone PCI with stent implantation. Kaplan-Meier-analyses were performed on three predefined models concerning the primary endpoint of all-cause mortality. Model 1 was an univariate analysis of the influence of age dichotomized by age on the primary endpoint. Model 2 included age and other classical CVRFs (body-mass-index (BMI), smoking, diabetes, hypertension, dyslipidemia and family history of CHD). Model 3 consisted of age, classical CVRFs and other factors (medication, hemoglobin-, CRP-, low density lipoprotein cholesterol (LDL)-, creatinine-levels, left ventricular ejection fraction (LVEF)).

Results: Age was significantly related to mortality in univariate (HR 1.068, p<.001) and multivariate models (model 2: HR 1.062, p<.001, model 3: HR 1.035, p=.037). Furthermore, in model 3, stroke, peripheral arterial disease (PAD), diabetes, elevated creatinine and LDL were related to elevated mortality risk, whereas hemoglobin levels and LVEF in normal range were associated with decreased mortality. In patients <75 years (n=1,390) same predictors for death were found in the multivariate model 3 as seen in all patients. In patients ≥75 years (n=419) different results were found: arterial hypertension was related with poor outcome, previous anti-platelet therapy was a predictor for reduced mortality in model 3 (HR 0.098, p = 0.039), all other variables were not significantly related to outcome. For younger patients anti-platelet drugs did not show superiority in mortality (HR 0.95, p=0.893).

Conclusion: Age is an independent predictor for all-cause mortality after PCI. Known risk factors were predictors for death in all patients and in younger patients. In the elderly only arterial hypertension increased, treatment with platelet inhibitors decreased mortality.
Age, body mass index and uric acid are independent predictors for an elevated TNF-alpha plasma level in a complex risk model

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BACKGROUND: Tumor necrosis factor-alpha (TNF-alpha) has been implicated in the pathogenesis of numerous complex diseases. The plasma level of this pro-inflammatory cytokine is associated with a variety of different risk factors, but little is known about the genetic background and the complex interactions.

METHODS: in this clinical study, correlations were studied between plasma levels of circulating TNF-alpha protein (ELISA), its mRNA expression in monocytes (RT-PCR) and genetic variants of TNF-alpha gene (SSCP), with several diseases, including obesity, atherosclerosis, diabetes mellitus, hypertension, as well as risk factors such as age, gender, inflammatory markers, the coagulation/fibrinolysis balance, and lipid metabolism. One hundred and ninety four clinically and biochemically well-characterized patients were enrolled.

RESULTS: At the transcriptional level, measured in monocytes, no association with any clinical or biochemical parameter investigated was found, including TNF-alpha protein level. Investigating the influence of genetic variants of the TNF-alpha gene on mRNA and protein levels, only one promoter polymorphism, namely c.-238G > A, was shown to be associated with transcriptional but not with translational expression. However, at the translational level, significant positive, but weak associations were determined for obesity (P -/+ 0.037), age (P -/+ 0.038), uric acid (P < 0.001), body mass index (P -/+ 0.01), plasminogen (P -/+ 0.013), and fibrinogen (P -/+ 0.002) in bivariate regression analyses, whereas HDL-cholesterol (P -/+ 0.005) was shown to be negatively correlated. However, investigating confounding effects in stepwise multivariate regression analysis, body mass index (P -/+ 0.009), uric acid (P -/+ 0.026) and age (P -/+ 0.037) turned out to be significantly associated with plasma levels of circulating TNF-alpha (adjusted R(2) -/+ 0.117; SE: 0.688).
Analysis of skin, nails and hairs as non-invasive markers of the biological age

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Introduction: The lifespan in individual humans is very heterogeneous. There are attempts to analyse this individual age, the so called biological age, in comparison to the chronological age. Biomarkers of ageing should help to characterise the biological age of individual persons by monitoring a basic process that underlies the ageing process. Based on the accumulation of advanced glycation endproducts (AGEs), we tested if skin, nails or hairs can be used as the material for the non-invasive age analysis.

Methods: 30 subjects (below 20, 30-50, over 60 years) were analyzed. Proteins from nails and hairs were extracted, Carboxymethyllysine (CML) tested by Dot-Blot and overall AGEs by fluorescence analysis. AGE associated skin auto fluorescence was analyzed using the AGE-Reader (Diagnoptics, Groningen).

Results: There is a good, gender independent, correlation of the AGE-associated skin auto fluorescence with age (Pearson R=0.65). Whereas the CML levels of the nails did not correlate with age, there is a slight correlation of the 330/405 (ex./em.) fluorescence with age (Pearson R=0.3). The 360/440 fluorescence do not correlate with age but show a significant gender difference (women versus men: 31985 +/- 7134 versus 14210 +/- 2506 , p=0.03). The CML levels of the hair-proteins correlate with age (Pearson R=0.34). None of the fluorescence measurements of hair proteins show any significant correlation with age or gender.

Conclusion: Whereas skin auto fluorescence is a good marker for the age of a subject, it seems to be difficult to use nails or hairs as sample probes which can be due to chemical modifications like hair coloration or nail varnish.
Vitamin D status and cardiovascular health

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Vitamin D deficiency has a dramatic high prevalence in Germany and is a major health problem in all age groups, especially in the elderly. Evolving data indicate that vitamin D deficiency does not only deteriorate bone health, but may play also a role in development of cardiovascular diseases. However, epidemiologic data from the German population and mechanistic studies that investigated the role of vitamin D in the development of cardiovascular risk factors and atherogenesis are scarce.

First studies that investigated the role of vitamin D for cardiovascular health in a BMBF-supported joint project have started. A pilot study with a nested case-control design was conducted in EPIC-Potsdam. Therefore, 100 participants who had suffered a myocardial infarction during ~8 years of follow-up and 200 controls who remained free of cardiovascular diseases were selected. Incident cases of myocardial infarction had a 1.4 ng/ml lower mean plasma 25(OH)D₃ concentrations than controls (95% confidence interval -3.1, 0.3 ng/ml). Compared to those in the lowest quartile of 25(OH)D₃, the odds of myocardial infarction in the second, third, and highest quartile were 5, 30, and 59% lower, respectively, after adjusting for age, sex, and season of blood draw. On a continuous scale, the odds ratio per 1 ng/ml increase in 25(OH)D₃ was 0.95 (95% confidence interval 0.90, 1.00).

Additionally, an experiment with LDL receptor knockout mice as an atherosclerosis model was conducted. Three groups of mice received diets with either low, adequate and high amounts of vitamin D₃ for 4 months. Intake of varying vitamin D amounts were reflected by conspicuous differences in plasma concentrations of 25(OH)D₃ (low vitamin D₃ group: 5.3 ± 1.6 ng/ml; adequate vitamin D₃ group: 26.0 ± 3.3 ng/ml, high vitamin D₃ group: 52.4 ± 8.1 ng/ml). Mice fed adequate and high amounts of vitamin D had less aortic calcification than mice fed the low vitamin D-diet. Mean atherosclerotic lesion size, proportions of collagen, lipids, smooth muscle cells and macrophages were not influenced by the vitamin D supply. Follow-up studies are necessary to elucidate whether differences in calcification may explain the higher rates of cardiovascular outcomes.
The role of 1,25 Dihydroxyvitamin D in corneal wound healing

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The cornea is a transparent, avascular connective tissue that acts as important structural barrier of the eye against the ingestion of bacteria and other infections. The human cornea consists of five layers; the outermost first layer is the epithelium. The epithelium can be damaged by chemical burns, chronic ulcers or severe diseases such as Stevens-Johnson syndrome. If wound healing is impaired, as in diabetic or elderly patients corneal injuries may result in complete loss of vision. For such patients, an effective therapy to promote fast reepithelialisation is still absent.

1,25 dihydroxyvitamin D (D3) is the most potent biologically active form of vitamin D. Its effects are mediated by the vitamin D receptor. Besides its well known activities on phosphate and calcium homoeostasis as a systemic hormone, it has pronounced effects on cell differentiation, inflammation and proliferation. Therefore, we have studied the effect of D3 in an in vitro corneal wound healing system employing an immortalized human corneal cell line (HCE). These cells expressed the vitamin D receptor (VDR) and its partner, the retinoid X receptor (RXR) and were able to respond to D3 by i. e. activation of cyp24 expression.

In in-vitro wound healing assays, D3 accelerated closure of simulated wounds within 24 h by 36%. Furthermore, we have found that D3 had effects on shape and size of the cells. D3 exposed cells changed from a flattened to a more rounded morphology. We also demonstrated in cell migration assays that 1,25 dihydroxyvitamin D accelerated the migration of HCE cells, but no effect on proliferation was observed.

In conclusion, our data suggest that supplementation of D3 might be useful in cases of impaired wound healing of the cornea.
Comparison of body fat measurements by waist circumference, body impedance analysis (BIA) and dual energy x-ray absorptionimetry in subjects of the Berlin Aging Study (BASE-II) – which method is better to detect visceral obesity?

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Background: Obesity and visceral adiposity have become an increasing problem in present times. Especially in old people body fat is often underestimated because of weight loss due to malnutrition and sarcopenia. BIA and DEXA are popular methods in estimating body composition and are well investigated in middle-aged people but not in the elderly. In the cross- and also longitudinal sectional Berlin Aging Study II (BASE-II) there is a cohort of old and a cohort of young subjects. Due to this fact a good possibility is given to compare these two methods and to examine if there are differences between the two cohorts.

Methods: A total of 498 subjects were analyzed (w=331; m=167) including 114 (w=67; m=47) in the young cohort (22-35 y) and 384 (w =264; m=120) in the old cohort (62-83 y). BIA measuring was performed by using the multifrequent tetrapolar Nutriguard M-2000 from Data Input. DEXA was done by using Discovery from Hologic. Besides anthropological data like weight, height and body circumferences also blood samples were taken to compare the measured body fat with blood lipid levels.

Results: First preliminary results show that 22,0% (BMI AV=22,9; SD= ± 3,39) of the young and 65,1% (BMI AV=26,9; SD= ± 4,03) of the older cohort were overweight (BMI>25) which is unexpected for geriatrics. An elevated waist circumference (WC) (m>102 cm; w>88cm) was detected in 12,3 % young and 56,8% old subjects. Focusing on the old cohort statistically significantly more women belonged to the elevated WC-group (w=42,2%; m=14,6%; p<0,05). Body fat measured by BIA was significantly below those of DEXA (AV BIA= 26,5% SD= ±8,3; AV DEXA= 34,5% SD= ± 7,9; p<0,01; r=0,85).

We will show the full results with multivariate analysis and implications for clinical practice.
Advices based on clinical pharmacological aspects to meet the specific requirements of the elderly patient in accident surgery

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Increasing age is partly related to - thus associated with - polypharmacy. As a result the elderly patient (eP) > 64 years of age being submitted to hospital for surgical intervention is on a broad spectrum of medicaments that might even have contributed to the accident. Potentially inadequate drugs for the elderly are listed, yet there is urgent demand to meet analogous requirements in clinical practise.

We stepwise focus on 4 aspects taking into regard the clinical diagnosis of the individual eP:
1. Which drugs the patient is on can or should be avoided?
2. What does the patient need for the acute surgical situation?
3. Individual list of resulting medicaments ☞ What kind of adverse effects (AEs) and drug-drug interactions must we have to take into account and take care of?
4. Presumption of an adapted list of drugs on the P’s discharge as a preventative contribution.

Further algorithm from our pharmacological advices is based on preliminary findings resulting from clinical visitation at regular intervals. First impressions predominantly call attention to drug dose with AEs and interactions in the eP. Altered pharmacokinetics and dynamics are major factors to consider.

E.g. HMG-CoA reductase inhibitors require dose adjustment in severe renal and hepatic impairment and avoidance of interacting medicaments via inhibition of the cytochrome P450 (CYP)3A4 system with the risk of myoglobinemia and rhabdomyolysis. We even would postulate to be careful with statins perioperatively because of concomitantly increased musculoskeletal injury. To fine-tune the dose esp. in antibiotics and to avoid nephrotoxic agents in preexisting renal impairment is recommended. Substitution for hypothyreoidism must be very cautious in the eP because of cardiovascular risks with hypertension and arrythmias, e.g. atrial fibrillation. Yet it may cause depression, hyperlipidemia and thus requires careful therapy. Anemia is not an uncommon finding and not always related to the surgical intervention. Thus it should be diagnosed and drug-relations must be excluded. The same is true for severe hyponatremia resulting from longlasting therapy with various agents. The absolute benefit of treatment of urinary incontinence with anticholinergic drugs with antimuscarinic effects over placebo is small, and esp. in older P with dementia the risks of these drugs, e.g. tachycardia, drowsiness and decreased cognitive function outweigh the benefits. The concomitant use of aspirin and NSAIDs has to be avoided partly because ibuprofen antagonizes the cardioprotective effect of aspirin by competitively inhibiting aspirin binding platelets. The favourite analgetic combination of metamizol, tramadol and metoclopramide (“Würzburger Schmerztropf”) needs being adapted in the eP. Haloperidol is known to be associated with fall and hip fracture. Metformin should not be administered if the creatinine clearance is <60 mg/dl. Co-dispensing with SSRIs is critical in a broad spectrum of drugs.

Constant review of medication list is essential for safe and minimized polypharmacy. The potential of drug interactions rises to 38% with 4 drugs and is as high as 100% with 8 drugs per day. Awareness and vigilance for AEs should be maintained to enable improved patient care.
Inhibition of p53 in the setting of acute infarction in mice: mechanisms of disturbed early remodeling

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Introduction: The activation of p53 during myocardial ischemia can provoke apoptosis of cardiomyocytes so that the inhibition of p53 might be considered a hypothetical therapeutic target. In previous experiments we have shown that administration of the synthetic p53-inhibitor pifithrin-α (PFTa) indeed reduces the percentage of apoptotic cardiomyocytes in a model of acute MI in mice but in parallel leads to an increase of left ventricular rupture because of destabilization of the forming scar. With the experiments presented here we tried to unveil the mechanisms responsible for this early occurring disturbance of cardiac remodeling.

Methods and results: Administration of PFTa for 6 days starting 24h after LAD-ligation leads to a significant reduced number of apoptotic cardiomyocytes as expected. However, PFTa increases lethality of the animals after MI which can be explained by ventricular rupture as seen from autopsy. Additionally, 7 days after LAD-ligation PFTa-treated animals show significant larger infarcts than seen in sham-treated controls (MI without PFTa; 62.0 ± 3.1 % vs. 51.3 ± 3.3 %; p < 0.05). Histological analysis reveals a reduced deposition of collagen in the area of the forming scar after PFTa-treatment (34 ± 7 % vs. 57 ± 5 %; p < 0.05). This finding can be explained by an increased activity of matrix metalloproteinase 2 (MMP2) as well as by the reduced number of proliferating fibroblasts (see figure). However, the immigration of CD45-expressing neutrophils (26 vs. 28 per microscopic field; n.s) or Mac3-expressing macrophages (15 vs. 19 per microscopic field; n.s) is not changed by PFTa. Studies with homozygous p53-knock out mice show that the effects induced by PFTa are indeed the result of the specific inhibition of p53 as in p53−/− mice the administration of PFTa neither increases the likelihood of ventricular rupture nor the activity of MMP2 (see figure).

Discussion: Although the targeted inhibition of p53 induced by PFTa inhibits the apoptosis of cardiomyocytes after acute MI this effect is counteracted by a severe disturbance of early cardiac remodeling caused by an elevation of MMP2 activity and reduced proliferation of fibroblasts finally leading to reduced collagen deposition in the forming scar and subsequent ventricular rupture.
Thioredoxin-1 and γ-actin interact together to protect endothelial cells from stress fiber formation, Thioredoxin-1 degradation and apoptosis induction

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Thioredoxin-1 (Trx-1) is one of the major antioxidative enzymes in endothelial cells (EC). It is downregulated during the process of cardiovascular aging and is required for apoptosis protection of EC. Apoptosis induction is dependent on cytoskeletal changes resulting in formation of stress fibers, thick bundles of actin. Thus, the aim of this project was to elucidate whether there is an interaction between Trx-1 and actin. First, we immunoprecipitated Trx-1 out of human primary EC, and γ-actin was identified as a new binding partner using a mass spectrometric approach. This interaction was confirmed by co-immunoprecipitation experiments. To investigate whether Trx-1 interacts with non-polymerized or polymerized actin, we first performed immunohistochemical analysis and could observe a co-immunostaining predominantly in areas with non-polymerized actin. To further strengthen this observation we incubated EC with cytochalasin D, a known interruptor of actin polymerization. Immunohistochemical and immunoprecipitation experiments indeed showed an increased association of Trx-1 with actin in cells treated with cytochalasin D. Since the phosphorylation and thereby activation of the Focal Adhesion Kinase (FAK) is an upstream event in stress fiber assembly, inhibition of FAK phosphorylation at tyrosine 397 with PF-573228, a known FAK inhibitor, reduced H₂O₂-induced formation of stress fibers after preincubation for 6h. Interestingly, preincubation with exogenous Trx-1 for 6 h also inhibited phosphorylation of FAK and stress fiber formation. However, we did not find an additive effect of PF-573228 and exogenous Trx-1, suggesting a common signaling pathway. To further investigate whether stress fiber formation is indeed required for H₂O₂-induced apoptosis, we treated EC with H₂O₂ for 18 h. Increased phosphorylation of FAK, induced stress fiber formation, reduced Trx-1 protein levels and increased apoptosis were observed. Preincubation with PF-573228 for 6h inhibited phosphorylation of FAK, reduction of Trx-1 protein levels and apoptosis induction. On the contrary, incubation with PF-573228 1h after H₂O₂ treatment did not inhibit formation of stress fibers and degradation of Trx-1 protein and, thus, did not abrogate apoptosis induction by H₂O₂. These data demonstrate that stress fiber formation is a prerequisite for apoptosis induction in endothelial cells. Furthermore, the interaction of Trx-1 and γ-actin protects Trx-1 from degradation, which occurs during endothelial cell death and induction of senescence.
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