北京大学定量生物学中心
CENTER FOR QUANTITATIVE BIOLOGY

Quantitative Biology 2021:

Aging and Rejuvenation

Thursday 15 July 2021 - Friday 16 July 2021

Peking University, China

Programme

Host:

Center for Quantitative Biology (CQB) at Peking University (http://cqb.pku.edu.cn)

Organization Committee:

Dr. Jing-Dong Jackie Han (Chair, CQB, Peking University, China)
Dr. Hao Li (University of California San Francisco, USA)
Dr. Chao Tang (CQB, Peking University, China)

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Venue Address:

Bldg 1#, Zhongguanyuan Global Village PKU (北京大学中关新园1号楼群英厅)

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Wednesday, July 14th

Registration 14:00-18:00 Bldg 1#, Zhongguanyuan Global Village PKU (中关新园 1 号楼大厅)

Thursday, July 15th – Bldg 1#, Zhongguanyuan Global Village PKU (中关新园 1 号楼群英厅)

Registration 7:20-8:20 Bldg 1#, Zhongguanyuan Global Village PKU (群英厅)

8:30-8:40	Opening remarks by Chao Tang (Chair: Jing-Dong Jackie Han & Hao Li)	
Session I (Chair: Hao Li)		
8:40-9:20	**Saul Villeda** University of California, San Francisco, USA	Systemic Mechanisms of Brain Rejuvenation
9:20-9:45	**Vadim Gladyshev** Harvard Institutes of Medicine, USA	Quantifying Aging and Rejuvenation
9:45-10:10	**Matt Kaeberlein** University of Washington, USA	The Dog Aging Project
10:10-10:50	Group Photo & Tea Break	
Session II (Chair: Matt Kaeberlein)		
10:50-11:15	**Hao Li** University of California, San Francisco, USA	Single Cell Aging from a Dynamic System's Perspective
11:15-11:40	**Cunyu Wang** University of California, Los Angeles, USA	Epigenetic Control of Bone-Fat Imbalance and Mesenchymal Stem Cell Exhaustion in Skeletal Aging
11:40-12:05	**Yu Sun** Shanghai Institute of Nutrition and Health, CAS, China	Epigenomic remodeling by KDM4 potentiates the senescence-associated secretory phenotype
12:05-13:30	Lunch	
Session III (Chair: Yu Sun)		
13:30-13:55	**Weiguo Zou** Center for Excellence in Molecular Cell Science, CAS, China	Conditional aging mice to study orthopedic aging diseases
13:55-14:20	**Seung-Jae Lee** Korea Advanced Institute of Science and Technology, South Korea	Promotion of healthy longevity using molecular genetics in *Caenorhabditis elegans*
14:20-14:45	**Jing-Dong Jackie Han** Peking University, China	Heterogeneity of Human Aging
14:45-15:10	**Ping Hu** Max Plank Center for Tissue Stem Cell and Regenerative Medicine, China	Human muscle stem cells are bi-potent adult stem cells
15:10-15:35	Tea Break	
Session IV (Chair: Seung-Jae Lee)		
15:35-15:45	**Qian Gao** Shanxi Medical University, China	Investigating the dose response relationship between DNA methylation age acceleration and risk of Alzheimer's disease
15:45-15:55	**Qi Liu** Peking University, China	Niche refreshment rejuvenates chronologically aged quiescent fission yeast cells
15:55-16:20	**Xianwen Ren** Peking University, China	Single-cell RNA-seq reveals new mechanisms of host immune responses against SARS-CoV-2 infection
16:20-16:45	**Evandro Fang** University of Oslo, Norway	Targeting on the NAD^+-mitophagy axis for Alzheimer's disease and healthy
16:45-17:10	**Sara Hagg** Karolinska Institute, Sweden	Human biological aging: quantifications, health predictions and interventions
17:10 -18:20	Poster session	
18:20	Reception - Shiguang Cafeteria, Zhongguanyuan Global Village (中关新园 1 号楼时光咖啡厅)	

Friday, July 16th – Bldg 1#, Zhongguanyuan Global Village PKU (中关新园 1 号楼群英厅)

Session V (Chair: Brian Kennedy)		
8:30-9:10	**Vera Gorbanova** University of Rochester, USA	SIRT6 function in longevity and rejuvenation
9:10-9:35	**Yousin Suh** Columbia University Irving Medical Center, USA	*Targeting Healthspan*: Functional Genetic Variation in Human Aging and Longevity
9:35-10:00	**Peter Adams** Burnham institute, USA	Cytoplasmic Chromatin Fragments in Senescent Cells – from Mechanisms to Healthy Aging Interventions
10:00-10:25	**Danica Chen** University of California, Berkeley, USA	Mitochondrial Metabolic Checkpoint, Stem Cell Aging and Rejuvenation
10:25-10:50	Tea Break	
Session VI (Chair: Danica Chen)		
10:50-11:15	**Brian Kennedy** National University of Singapore, Singapore	Translating Aging Discoveries to Delay Human Aging and Extend Healthspan
11:15-11:40	**Nan Hao** University of California, San Diego, USA	Divergent trajectories of single-cell aging
11:40-11:50	**Ruihuan Yu** Laurentian University, Canada	Investigate the regulatory roles of H_2S in lipid overload-induced lipotoxicity and cardiac cell senescence
11:50-12:00	**Dong-sheng Di** Huazhong University of Science and Technology, China	Life-course effects of birth weight on bone mineral density: evidence from observational and MR studies
12:05-13:30	Lunch	
Session VII (Chair: Jing Qu)		
13:30-13:55	**Alex Zhavoronkov** Insilico Medicine Hong Kong Ltd, Hong Kong, China	Deep biomarkers of aging: what can we learn about human psychological aging?
13:55-14:20	**Qiangfeng Zhang** Tsinghua University, China	RNA structure systems biology powered by big data and machine intelligence
14:20-14:45	**Weiqi Zhang** Beijing Institute of Genomics, CAS, China	Dissection of Aging Intervention at the Single-Cell Resolution
14:45-15:10	**Baohua Liu** Shenzhen University, China	Organ talks and systemic aging
15:10-15:35	Tea Break	
Session VIII (Chair: Jing-Dong Jackie Han)		
15:35-16:00	**Karsten Kristiansen** University of Copenhagen, Denmark	TBD
16:00-16:25	**Cheng Li** Peking University, China	3D genome organization and gene transcription in aneuploid embryonic stem cells
16:25-16:50	**Jing Qu** Institute of Zoology, CAS, China	Single-cell transcriptional landscape of primate aging
16:50-17:20	Poster Award & Closing Chair: Jing-Dong Jackie Han & Hao Li	

Systemic Mechanisms of Brain Rejuvenation

Saul Villeda

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Aging drives cognitive impairments in the adult brain. It is imperative to gain insight into what drives aging phenotypes in the brain in order to maintain, and even restore, functional integrity in the elderly. We, and others, have shown that systemic manipulations - such as heterochronic parabiosis (in which a young and old circulatory system are joined) and administration of young blood plasma - can reverse age-related impairments in regenerative and synaptic processes, as well as rescue cognitive faculties in the aged brain. More recently, my lab demonstrated that administration of exercise-induced blood factors can likewise partially reverse age-related loss of plasticity in the aged brain. As a consequence, we can now consider reactivating latent plasticity dormant in the aged brain as a means to rejuvenate regenerative, synaptic and cognitive functions late in life. The goal of my research program is to elucidate cellular and molecular mechanisms that can be targeted to halt the aging process or promote rejuvenation in the old brain. Understanding how to reverse aging in the brain could enable us to sidestep the effects of aging that promote vulnerability to neurodegenerative diseases altogether, providing a unique therapeutic approach.

Quantifying Aging and Rejuvenation

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DNA methylation of a defined set of CpG dinucleotides emerged as a critical and precise biomarker of the aging process. Multi-variate machine learning models, known as epigenetic clocks, can exploit quantitative changes in the methylome to predict the age of bulk tissue with remarkable accuracy. We have developed several types of aging clocks and applied them to assess the effect of interventions that extend lifespan as well as the effect of treatments that support rejuvenation. Our recent studies will be presented at the meeting to show how clocks can provide insights into the aging and rejuvenation processes. Intrinsic sparsity and digitized methylation in individual cells have so far precluded the assessment of aging in single cell data. For this, we developed scAge, a probabilistic approach to determine the epigenetic age of single cells. The data suggest that while tissues age in a coordinated fashion, some cells age more or less rapidly than others. We found that embryonic stem cells exhibit an age close to zero and that certain adult stem cells show a reduced age compared to their chronological age. Excitingly, we discovered that early embryogenesis is associated with the reduction of epigenetic age, followed by aging. This finding supports the idea of a natural rejuvenation event during embryogenesis.

The Dog Aging Project

Matt Kaeberlein

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Age is the greatest risk factor for most major causes of death and disability in developed nations. Although many aspects of aging are shared, the rate and order of various functional declines and onset of disease can vary greatly among individuals. The mechanisms underlying individual trajectories of aging are influenced by a complex combination of genes, environment and lifestyle that remains poorly understood. Most of what we know about the biology of aging comes from laboratory studies of inbred, lab-adapted species--yeast, worms, flies, and mice. While these laboratory models have facilitated rapid progress in identifying conserved mechanisms of aging, translation has been limited by the challenge of identifying causal determinants of aging in the real world. To better understand how genes and environment shape aging outside of the lab, we have turned to the companion dog as a powerful animal model that ages rapidly and shares the human environment. Here, I will describe the Dog Aging Project (DAP), an Open Science long-term longitudinal study of aging in tens of thousands of companion dogs. The objectives of this study are to identify the genetic, environmental, and lifestyle factors that influence aging in dogs, to discover the underlying molecular mechanisms by which they do so, and to test potential ways to increase the duration of healthy lifespan in dogs and people.

Single Cell Aging from a Dynamic System's Perspective

Hao Li

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Yeast replicative aging is a classical model for aging research. Genetic analyses have identified ~200 genes whose deletion extends lifespan, yet we still cannot put together a global mechanistic picture and answer the basic question why do mother cells age and die. We attempted to tackle this problem by employing a novel strategy that combines a dynamic system's approach with genetic and device engineering. From a dynamic system's perspective, replicative aging can be viewed as loss of homeostasis caused by a drift of the cell cycle trajectory in the state space; correcting that drift could potentially lead to rejuvenation. I will describe a number of new technologies we developed that may help us to achieve a comprehensive and quantitative description of how the dynamic cellular state evolves with age and to identify key targets for intervention.

Epigenetic Control of Bone-Fat Imbalance and Mesenchymal Stem Cell Exhaustion in Skeletal Aging

Cun-Yu Wang

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Skeletal aging is a complex process, characterized by a decrease in bone formation, an increase in marrow fat, and stem cell exhaustion. Loss of H3K9me3, a heterochromatin mark, has been proposed to be associated with aging. On the contrary, some studies suggest that senescence-associated heterochromatin foci (SAHF; heterochromatin gain) are associated with cell aging, but most of studies focus on oncogenic transformation. These two models are controversy in the field of aging, and there is very little genetic evidence which proves or disproves these models. Here, we show that loss of KDM4B in mesenchymal stem/stromal cells (MSCs) exacerbates skeletal aging and osteoporosis by reducing bone formation and increasing marrow adiposity by increasing H3K9me3. KDM4B epigenetically coordinates β-catenin/Smad-mediated transcription by removing repressive H3K9me3. Importantly, loss of KDM4B impairs MSC self-renewal and promotes MSC exhaustion with aging by inducing SAHF formation, providing a mechanistic explanation for stem cell exhaustion with aging. Moreover, while KDM4B is required for parathyroid hormone-mediated bone anabolism, KDM4B depletion accelerates bone loss and marrow adiposity induced by high fat diet. Our results suggest that the epigenetic rejuvenation and reversing bone-fat imbalance might be new strategies for preventing and treating skeletal aging and osteoporosis by activating KDM4B in MSCs.

Epigenomic remodeling by KDM4 potentiates the senescence-associated secretory phenotype

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Cellular senescence restrains the expansion of neoplastic cells through several layers of regulation, including epigenetic decoration of chromatin structure and functional modulation of bioactive components. Here we report that expression of the histone H3-specific demethylase KDM4 is upregulated in human stromal cells upon cellular senescence. In clinical oncology, upregulated KDM4 and diminished H3K9/H3K36 methylation are correlated with adverse survival of cancer patients post-chemotherapy. Global chromatin accessibility mapping via ATAC-seq and expression profiling through RNA-seq reveal extensive reorganization of chromosomes and spatiotemporal reprogramming of the transcriptomic landscape, events responsible for development of the senescence-associated secretory phenotype (SASP). Selectively targeting KDM4 dampens the SASP of senescent stromal cells and enhances the apoptotic index of cancer cells in the treatment-damaged tumor microenvironment (TME), together prolonging overall survival of experimental animals. Our study supports the dynamic change of H3K9/H3K36 methylation marks during cellular senescence, identifies an unusually permissive chromatin state, unmasks KDM4 as a key modulator of the SASP, and presents a novel therapeutic avenue to manipulate cellular senescence and curtail age-related pathologies. It is essential to further understand the role of the extensive senescence-associated 3D genome reorganization and generate genome-wide chromatin interaction maps by integrating data from multi-omics for target mining to advance precision geriatric medicine.

Conditional aging mice to study orthopedic aging diseases

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In an aging society, orthopedic aging-related diseases, including osteoporosis and osteoarthritis, are highly prevalent. We used a mouse model of progeria to construct conditional aging mice to study the pathological mechanisms of osteoporosis and osteoarthritis. We found that aging of Col2-cre positive chondrocytes can induce osteoarthritis and Prx1-cre positive mesenchymal cells can cause osteoporosis. Using single-cell RNA sequencing, we found that the proportion of growth plate-resident subpopulations (gpSSCs) and periosteal resident subpopulations (pSSCs) was decreased in a premature aging model. These two subpopulations are responsible for lifelong production of trabecular and periosteal osteoblasts, respectively. Finally, by integrating chromatin and transcriptional analysis, we showed that both SSCs subpopulations increased p53-mediated DNA damage and lost extracellular matrix (ECM).

Promotion of healthy longevity using molecular genetics in Caenorhabditis *elegans*

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Many environmental and genetic factors that influence lifespan have been identified for the last three decades. My laboratory aims to elucidate molecular mechanisms by which intrinsic and extrinsic factors regulate lifespan by using molecular genetics of the roundworm Caenorhabditis elegans. In this talk, I will present our latest work on signaling pathways that mediate the effects of internal and external factors on lifespan and aging. In particular, I will talk about our findings regarding a novel longevity-promoting protein kinase VRK-1, which activates the master cellular energy sensor AMPK via phosphorylation. In addition, I will present our work regarding how PTEN, a key phosphatase acting in insulin/IGF-1 signaling, uncouples healthy longevity from impaired fitness in C. elegans. Because many findings on aging regulation in C. elegans have been shown to be evolutionarily conserved, homologous mechanisms may exist in mammals including humans.

Heterogeneity of Human Aging

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Aging is a systems level process and needs systems level models to quantify. After searching for quantitative aging biomarkers and models at the epigenomic and transcriptomic levels, we have recently focused our attention on 3D facial images. Based on a small cohort, we generated the first comprehensive mapping of the aging human facial phenome, and found quantitative facial features, such as eye slope and forehead size, highly associated with age. Even based on this small cohort, linear age predictors identified slow- and fast-agers that are significantly supported by health. By extending the study to a large Northern Chinese cohort of 5,000 people we can now use deep learning AI models trained on either chronological age or perceived age of the 3D facial images to more precisely estimate individuals' aging status. These models achieve an average difference between chronological or perceived age and predicted age of ±2.8 years. We further profile blood transcriptomes from 280 individuals and infer the molecular regulators mediating the impact of lifestyles on facial aging speed through a causal inference model. Overall, we find that humans age with different rates both in the blood and in the face, but coherently, with heterogeneity peaking at middle age. Our study provides an example how artificial intelligence can be leveraged to determine perceived age of humans as marker of biological age, no longer relying on prediction errors to chronological age, and to estimate the heterogeneity of aging rates within a population. I will also share some of our newest results on the oral microbiota and blood metabolome aging rate associations and ethnic group differences on facial aging rate.

Human muscle stem cells are bi-potent adult stem cells

Ping Hu

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Tendon injury occurs at high frequency and is difficult to repair. Identification human stem cells being able to regenerate tendon will greatly facilitate the development of regenerative medicine for tendon injury. We identified human muscle stem/progenitor cells having tendon differentiation potential both in vitro and in vivo. Interestingly, the tendon differentiation potential is not present in mouse muscle stem cells. These findings reveal that human muscle stem cells are bi-potential adult stem cells and can serve as a new source for tendon regeneration.

Investigating the dose-response relationship between DNA methylation age acceleration and risk of Alzheimer's disease

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Abstract

Background: DNA methylation age (DNAm age) is widely used as a biomarker for aging. Difference between DNAm age and chronological age is often referred to as DNAm age acceleration and indicates the degree of aging. Previous studies have demonstrated an association between accelerated DNAm age and risk factors for Alzheimer's disease (AD), AD related neuropathological markers, and AD related cognitive decline. Therefore, we hypothesized that DNA methylation-based measures of accelerated ageing might be a risk factor for AD, and aimed to test this hypothesis by estimating the dose-response curve.

Methods: Seven DNA methylation datasets covering four brain regions were downloaded from GEO database. DNAm age was calculated using cortical DNAm age classifier [1]. To sufficiently control the confounding of chronological age, we regressed DNAm age on chronological age and chronological age-square. The residual was defined as DNAm age acceleration [1]. Within each brain region, generalized propensity score method was performed to assess dose-response relationship between DNA methylation age acceleration and risk of AD [2]. Finally, we meta-analyzed the dose-response relationship for each brain region.

Results: The number of datasets contained in different brain regions ranged from 3 to 5. More than 80% observations aged over 65. Univariate analysis showed statistically significant accelerations in AD for DNA methylation-based measures of ageing. However, after controlling for potential confounders, there were no significant dose-response relationships between aging acceleration and risk of AD in any brain regions.

Conclusions: There is no evidence revealed a causal dose-response relationship between increased DNAm age acceleration and AD risk. One potential explanation is that the clinical diagnosis AD is only an incomplete measure of the underlying neuropathology. Therefore, further studies are required to investigate the dose-response between the severity of AD (as estimated by cognitive decline or neuropathology) and methylation-based measures of accelerated ageing.

Keywords: DNA methylation age; aging acceleration; Alzheimer's disease; dose-response.

References

[1] Recalibrating the epigenetic clock: implications for assessing biological age in the human cortex

[2] High-dimensional generalized propensity score with application to omics data

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Niche refreshment rejuvenates chronologically aged quiescent fission yeast cells

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Abstract

Recovery ability constitutes the most essential property of quiescent cells. During prolonged quiescence state, both the survivability and recovery activity of quiescent cells are declining with chronological age. This process is generally recognized as the cellular chronological aging. While it is widely accepted that the chronological aging is irreversible for multicellular individuals, it remains largely unknown whether it still holds true for single cells. By quantitatively measuring the recovery time of quiescent fission yeast cells from nitrogen starvation with different chronological age and without or with niche refreshment which still maintains nitrogen starvation, we found that niche refreshment can greatly improve the both recovery activity and survivability of chronologically aged quiescent cells. Surprisingly, the exacerbated chronological ageing by excessive glucose can also be rescued by niche refreshment. Furthermore, we found the extent of improvement depends on the energetics and chronological age of quiescent cells. The possible mechanisms of rejuvenation by niche refreshment will be discussed.

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Single-cell RNA-seq reveals new mechanisms of host immune responses against SARS-CoV-2 infection

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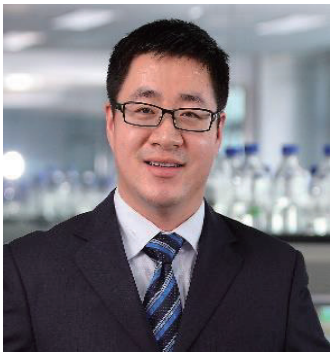

COVID-19 has resulted in deep impacts on the global society, yet detailed understanding of host immune response is incomplete. We applied single-cell RNA sequencing to 284 samples from 196 COVID-19 patients and controls and created a comprehensive immune landscape with 1.46 million cells. The large dataset enabled us to identify that different peripheral immune subtype changes are associated with distinct clinical features, including age, sex, severity, and disease stages of COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA was found in diverse epithelial and immune cell types, accompanied by dramatic transcriptomic changes within virus-positive cells. Systemic upregulation of S100A8/A9, mainly by megakaryocytes and monocytes in the peripheral blood, may contribute to the cytokine storms frequently observed in severe patients. Our data provide a rich resource for understanding the pathogenesis of and developing effective therapeutic strategies for COVID-19.

Targeting on the NAD+-mitophagy axis for Alzheimer's disease and healthy longevity

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There were 962 million elderly (60+) globally in 2017, and this number will rise to 2.1 billion in 2050, bringing formidable healthcare and socio-economic challenges. Ageing is arguably the highest risk factor for numerous human diseases, thus understanding the molecular mechanisms of human aging holds the promise to develop interventional and therapeutic strategies for many diseases all simultaneously, promoting healthy longevity. Accumulation of damaged mitochondria is a hallmark of aging and age-related neurodegeneration, including Alzheimer's disease (AD). However, the molecular mechanisms of the impaired mitochondrial homeostasis and their relationship to AD are still elusive. Mitophagy is a cellular self-clearing process of damaged and superfluous mitochondria, thereby plays a fundamental role in maintaining neuronal function and survival. We hypothesize that age-susceptible defective mitophagy causes accumulation of damaged mitochondria, which further in combination with the two AD-defining pathologies, Aβ plaques and tau tangles, to exacerbate AD progression. Restoration of mitophagy through upregulation of cellular NAD+, a primary molecule in human health and life, and genetic approaches, forestalls pathology and cognitive decline in C. elegans and three mouse models of AD and improves mitochondrial function in the AD iPSC neurons. In view of the physiological feature of NAD+ in human, our study suggests immediate interventional/therapeutic potential for both normal ageing and age-related memory loss.

Human biological aging: quantifications, health predictions and interventions

Sara Hagg

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Human biological age can be assessed using a biomarker (e.g., telomere length), combined score (e.g., epigenetic clock) or other metric (e.g., frailty index) associated with age. Molecular-based biological ages in epidemiological cohorts are commonly done on samples from whole blood, but other tissues may be useful as well such as skeletal muscle, skin, saliva and brain. For other biological ages, physiological tests (e.g., blood pressure), functional ability (e.g., grip strength) and brain aging (e.g., neuroimaging) could be used.
Some of the different biological age metrics are correlated with each other, but often they reflect varying parts of the aging process. Common to all metrics is the fact that they predict health outcomes and mortality beyond chronological age.
In my talk, I will give an overview of the current know-how on human biological aging. I will describe how the biological age assessments are developed and which is currently the most useful predictor. I will briefly mention their ability to predict diseases. Finally, I will discuss some intervention studies and how biological age assessments may be used in future clinical trials.

SIRT6 function in longevity and rejuvenation

Vera Gorbunova

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Species of mammals differ dramatically in their maximum lifespan and cancer susceptibility. We investigate mammalian species that naturally evolved long lifespan and cancer resistance with the goal of understanding molecular mechanisms of longevity and cancer resistance and then applying them to benefit human health. Remarkably, long-lived animal species, in general, have more efficient DNA double-strand break repair. Recent study from our group, showed that the protein responsible for more efficient DNA repair in long-lived species is SIRT6. In long-lived rodents SIRT6 has higher biochemical activities. We identified centenarian variant of SIRT6 that is better at stimulating DNA repair than the wild type SIRT6, and is also more active as a tumor suppressor. We propose that specific SIRT6 activators may be developed for cancer prevention and lifespan extension.

Targeting Healthspan: Functional Genetic Variation in Human Aging and Longevity

Yousin Suh

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Aging is a major risk factor for all chronic human diseases. The discovery of evolutionarily conserved pathways with major impact on lifespan and health span in animal models has suggested a potential to identify therapeutic targets for interventions that could favorably influence age-related outcomes in humans. Identification of gene variants that protect humans against, or increase risk of, crippling diseases at old age is likely to help find novel strategies for prevention and therapy. With the advent of novel high-throughput genomic technologies, discovery of functional pathways that influence lifespan or health span in humans is now feasible through identification of genetic variants associated with these outcomes. We have been conducting systematic multidisciplinary studies to discover functional gene variants associated with longevity or diseases of aging in the conserved pathways of aging using functional genomics approach. To understand molecular mechanisms underlying the association with longevity, functional consequences of gene variants on age-related parameters are assessed in cell culture and in vivo animal models. The results may open up the possibility of targeted and personalized intervention strategies, ultimately leading to improved quality of life of the elderly population.

Cytoplasmic Chromatin Fragments in Senescent Cells – from Mechanisms to Healthy Aging Interventions

Peter Adams

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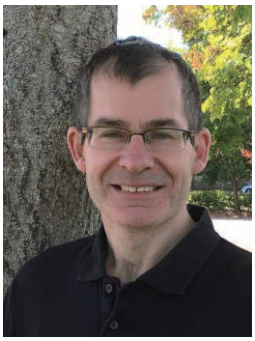

Recent studies from our lab and collaborators have shown that senescent cells expel fragments of chromatin from the nucleus into the cytoplasm (Cytoplasmic Chromatin Fragments, CCF) by a specialized form of nuclear autophagy. Once in the cytoplasm these CCF activate the cytoplasmic DNA sensing cGAS/STING pathway to drive the pro-inflammatory and pro-aging Senescence Associated Secretory Phenotype (SASP). Recent published and unpublished studies investigating the mechanism of formation and function of CCF, and targeting CCF for healthy aging interventions, will be presented.

Mitochondrial Metabolic Checkpoint, Stem Cell Aging and Rejuvenation

Danica Chen

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Cell cycle checkpoints are surveillance mechanisms in eukaryotic cells that monitor the condition of the cell, repair cellular damages, and allow the cell to progress through the various phases of the cell cycle when conditions become favorable. Recent advances in stem cell biology highlight a mitochondrial metabolic checkpoint that is essential for stem cells to return to the quiescent state. As quiescent stem cells enter the cell cycle, mitochondrial biogenesis is induced and mitochondrial stress is increased. Mitochondrial unfolded protein response and mitochondrial oxidative stress response are activated to alleviate stresses and allow stem cells to exit the cell cycle and return to quiescence. These processes are critically regulated by several sirtuin family members. Because loss of stem cell quiescence results in the depletion of the stem cell pool and compromised tissue regeneration, deciphering the molecular mechanisms that regulate the mitochondrial metabolic checkpoint in stem cells will increase our understanding of tissue homeostasis and how it becomes dysregulated under pathological conditions and during aging. More broadly, this knowledge is instrumental for understanding the maintenance of cells that convert between quiescence and proliferation to support their physiological functions.

Translating Aging Discoveries to Delay Human Aging and Extend Healthspan

Brian Kennedy

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Abstract: TBD.

Website:
https://medicine.nus.edu.sg/bch/faculty/brian-kennedy/

Research Interest

Research in the Kennedy lab is directed at understanding the biology of ageing and translating research discoveries into new ways of delaying, detecting, preventing and treating human ageing and associated diseases.

Current Research Projects

Several research strategies are employed to understand the biology of human ageing and to develop translational approaches. We use multiple model organisms and systems for these purposes, relying on non-vertebrates for discovery-based approaches to generate hypotheses regarding ageing mechanisms and studies in mammals to test hypotheses and to develop translational strategies. Specific projects include: 1) Systems biology strategies to understand ageing, 2) Murine longevity and studies and disease models

Divergent trajectories of single-cell aging

Nan Hao
Section of Molecular Biology, Division of Biological Sciences, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

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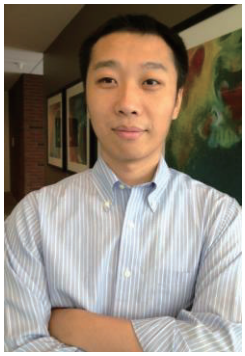

Cellular aging is a complex process that involves many interwoven molecular processes. Studies in model organisms have identified many individual genes and factors that have profound effects on lifespan. However, how these genes and factors interact and function collectively to drive the aging process remains unclear. We investigated single-cell aging dynamics throughout the replicative lifespans of S. cerevisiae, and found that isogenic cells diverge towards two aging paths, with distinct phenotypic changes and death forms. We further identified specific molecular pathways driving each aging fate and revealed that these pathways interact and operate dynamically to enable an early-life switch that governs the aging fate decision and the progression towards death. Our work uncovers the interconnected molecular pathways that drives the aging process and opens up the possibility of designing interventions that simultaneously target multiple network nodes, instead of single genes, to more effectively extend the healthspan.

Investigate the regulatory roles of H_2S in lipid overload-induced lipotoxicity and cardiac cell senescence

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Abstract

Hydrogen sulfide (H_2S) is now recognized as a third gaseous mediator along with nitric oxide and carbon monoxide. H_2S can be endogenously produced from cysteine in our body, and cystathionine gamma- lyase (CSE) acts as a major H_2S -generating enzyme in the cardiovascular system. Increasing evidence has demonstrated that disturbed H_2S production is relevant to heart disorders. Obesity is a leading risk factor for heart dysfunctions by interrupting lipid metabolism. This study investigated the regulatory roles of CSE/ H_2S system on lipid overload-induced lipotoxicity and cardiac senescence. Here, it was found that incubation of H9C2 (rat cardiomyocyte cells) with lipid mix inhibited cell viability and promoted the cellular accumulation of lipid, generation of reactive oxygen species (ROS), mitochondrial dysfunctions, and lipid peroxidation, all of which could be reversed by incubation with exogenously applied NaHS (an H_2S donor). Further data revealed that H_2S protected H9C2 cells from lipid overload-induced senescence by altering the expressions of lipid metabolism-related genes and inhibiting the generation of acetyl-CoA and the level of global protein acetylation. In vivo, knockout of the CSE gene strengthened cardiac lipid accumulation, protein acetylation, and cellular aging in high fat diet-fed mice. Taken together, the CSE/ H_2S system is essential for maintaining lipid homeostasis and cellular senescence in heart cells under lipid overload. Besides, the CSE/ H_2S system would serve as a target for preventing and treating obesity and age-related heart diseases.

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Life-course effects of birth weight on bone mineral density: evidence from observational and MR studies

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Abstract

Objective: The influence of birth weight on bone mineral density later in life is unclear. This study aimed to evaluate the life-course effects of birth weight on bone mineral density in adolescent and elderly individuals.

Methods: Data from five rounds of the U.S. NHANES (2007-2016) were analyzed for the cross-sectional association between birth weight (BW) and bone mineral density (BMD) among children averagely aged 13.56 (SD: 0.028) years (n = 2,171). Based on the genome-wide association study summary statistics for the BW (n = 153,781)[1] and total body BMD (n = 66,628)[2] of European ethnic populations, a two-sample MR study was performed to explore the causality of the BW-BMD association.

Results: In the cross-sectional study, no BW-BMD associations achieved significance. Corresponding standardized β coefficients (95% CI) were -0.13×10^{-5} (-1.98×10^{-5}, 1.72×10^{-5}), 0.59×10^{-5} (-1.02×10^{-5}, 2.20×10^{-5}), and 0.26×10^{-5} (-1.18×10^{-5}, 1.69×10^{-5}) for BMDs at spine, femur, and total body, respectively, controlling for all involved covariates. The MR study revealed significantly negative BW-BMD associations with standardized β coefficients (95% CI) of -0.204 g/cm^2 (-0.380, -0.027) in those aged 31-45 years, -0.190 g/cm^2 (-0.351, -0.029) in those aged 46-60 years, -0.171 g/cm^2 (-0.326, -0.015) in those aged over 60, and -0.151 g/cm^2 (-0.258, -0.044) in all participants. However, the BW-BMD associations did not achieve significance among those either aged 0-15 years (β=-0.076; 95% CI: -0.230, 0.077) or 16-30 years (β=-0.088; 95% CI: -0.332, 0.156).

Conclusions: Birth weight associated with BMD negatively in adults aged over 30 years. The BW-BMD association did not show significance during childhood and youth. Future studies are still needed to elucidate the underlying mechanism for the life-course effect of birth weight on bone mineral density later in life.

Keywords: Birth weight; Bone mineral density; Mendelian randomization; Osteoporosis.

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Deep biomarkers of aging: what can we learn about human psychological aging from longitudinal data analysis?

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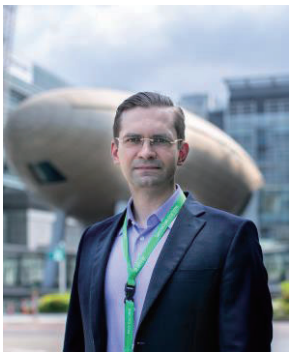

Aging clocks that accurately predict human age based on various biodata types are among the most important recent advances in biogerontology. Since 2016 multiple deep learning solutions have been created to interpret facial photos, omics data, and clinical blood parameters in the context of aging. Some of them have been patented to be used in commercial settings. However, psychological changes occurring throughout the human lifespan have been overlooked in the field of "deep aging clocks". Unlike other animals, humans are conscious of their age, physiological decline, and eminent death and evolved to adjust to biological and chronological age. In this talk we will present two deep learning predictors trained on social and behavioral data from Midlife in the United States (MIDUS) study: (a) PsychoAge, which predicts chronological age, and (b) SubjAge, which describes personal aging rate perception. Using 50 distinct features from the MIDUS dataset these models have achieved a mean absolute error of 6.7 years for chronological age and 7.3 years for subjective age. We also show that both PsychoAge and SubjAge are predictive of all-cause mortality risk, with SubjAge being a more significant risk factor. Both clocks contain actionable features that can be modified using social and behavioral interventions, which enables a variety of aging-related psychology experiment designs. The features used in these clocks are interpretable by human experts and may prove to be useful in shifting personal perception of aging towards a mindset that promotes productive and healthy behaviors.

RNA structure systems biology powered by big data and machine intelligence

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To date, SARS-CoV-2 has infected more than 140 million people with more than 3 million deaths, causing tremendous damage to the global human society. SARS-CoV-2 is a single-stranded RNA virus, and its viral RNA is a key component in regulating host infection: the tiny SARS-CoV-2 genome (and the limited proteome it encodes) relies heavily on interactions with proteins in host cells—the so-called "host factors"—to complete the viral lifecycle. Thus, understanding the molecular structure of SARS-CoV-2 RNA and identifying the host factors that interact with it can support the development of efficacious drugs to treat COVID-19.

We recently resolved the SARS-CoV-2 RNA genome structure in infected human cells. This in vivo structural data informed a deep learning Artificial Intelligence tool to predict binding of host factor proteins on SARS-CoV-2 RNA. We experimentally confirmed that several of these predicted host proteins are vulnerable to chemical inhibition of some already approved FDA-approved drugs. That is, these re-purposed drugs disrupt the capacity of the SARS-CoV-2 infections. These scientific, technological, and medical advances together shed new light on coronaviruses and have revealed multiple candidate therapeutics for COVID-19 treatment.

Dissection of Aging Intervention at the Single-Cell Resolution

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Aging causes a functional decline in tissues throughout the body that may be delayed by caloric restriction (CR). However, the cellular profiles and signatures of aging, as well as those ameliorated by CR, remain unclear. Here, we built comprehensive single-cell and single-nucleus transcriptomic atlases across various rat tissues undergoing aging and CR. CR attenuated aging-related change in cell type composition, gene expression, and core transcriptional regulatory networks. Immune cells were increased during aging, and CR favorably reversed the aging-disturbed immune ecosystem. Computational prediction revealed that the abnormal cell-cell communication patterns observed during aging, including the excessive proinflammatory ligand-receptor interplay, were reversed by CR. Our work provides multi-tissue single-cell transcriptional landscapes associated with aging and CR in a mammal, enhances our understanding of the robustness of CR as a geroprotective intervention, and uncovers how metabolic intervention can act upon the immune system to modify the process of aging.

Organ talks and systemic aging

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Aging population are great burdens for society and individuals. Many of the life-threatening age-related diseases are tissue/organ specific, e.g., cardiovascular diseases and dementia, for most of which the specific tissue/organ aging and/or degeneration are the common cause. Thus, understanding the mechanisms of tissue/organ aging would benefit the early diagnosis, the prevention, and the treatment of age-related diseases.

Aging is time-dependent and different tissue/organs age with different rate, making it difficult to study which is the trigger of systemic aging and how it happens. Using a progeria mouse model, we showed that vascular endothelium (VE) specific dysfunction is enough to accelerate aging in multiple tissues/organs and shorten lifespan, mediated by systemic inflammation. VE-targeted gene therapy with NAD+-dependent deacetylase SIRT7 rescues aging features and extends lifespan. Moreover, the number and/or function of endothelial progenitor cells (EPCs) declines with premature and physiological aging, and the replenishment with young and wild-type EPCs promotes health and longevity in progeria and physiologically aged mice. Similarly, adipocyte-specific expression of progerin, the causal mutation of progeria, causes multiple aging features and a shortened lifespan. Mechanistically, compromised expansion of white adipose tissue (WAT) results in chronic cold stress which upregulates cyclooxygenase-2 (COX2). Pharmacologic inhibition of COX2 with celecoxib ameliorates aging features and promotes lifespan. Our data revealed VE and WAT as important tissues that are essential for systemic aging and identified SIRT7 and COX2 as two important mediators of organ(tissue) talks and potential therapeutic targets of anti-aging and age-related diseases.

3D genome organization and gene transcription in aneuploid embryonic stem cells

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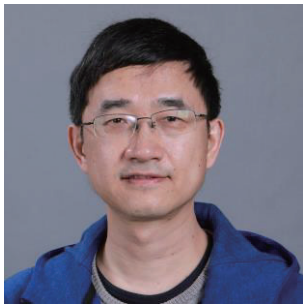

Aneuploidy frequently occurs in cancer and developmental diseases such as Down syndrome, with its functional consequences implicated in dosage effects on gene expression and global perturbation of stress response and cell proliferation pathways. However, how aneuploidy affects spatial genome organization and through which disturbs gene transcription is less understood. In this study, we applied Hi-C, RNA-seq, chromosome painting and nascent RNA imaging to study the 3D genome structures and gene transcription of isogenic wild-type and trisomic mouse embryonic stem cells (mESCs). We observed chromosome-wide transcriptional up-regulation of trisomic chromosomes and shared dysregulated pathways across different trisomic mESC lines. However, there exists chromosome-wide dosage compensation of gene expression of trisomic chromosomes, which coincides with contracted chromosome volume and weakened transcriptional activity for trisomic chromosomes. We also found that inter-chromosomal interactions are associated with chromatin regions with high gene density and active histone modifications and high transcription levels, which is confirmed by imaging. Our integrative approach can be applied to many other diseases affected by aneuploidy, which may reveal potential therapeutic targets from the angle of aneuploidy and chromatin structures.

Single-cell transcriptional landscape of primate aging

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The study of aging is complicated as aging is a heterogeneous process in which disorder is increased to varying degrees in individual cells and thereby drives a heterogeneous functional decline in organs and tissues. Emerging single-cell transcriptomic methods allow for molecular profiling of cells, probing of regulatory states and cell-fate determination, thus providing promising tools for unravelling the heterogeneous process of aging and making it amenable to intervention. Toward this goal, we captured the aging landscapes of multi organs in non-human primate, including arteries, pancreatic islets, ovaries, hearts and lungs based on the single-cell RNA sequencing strategy. For primate ovaries, a disturbance in antioxidant signaling was recognized as a main aging feature; moreover, genes involved in redox regulation were identified as potential diagnostic biomarkers for human ovarian aging. For pancreatic islets, ER stress and expression of ER stress related genes, including HSP90B1, were observed to be increased in aging beta cells, and HSP90B1 upregulation in beta cells may mediate the aging-related glucose tolerance. For arteries, by gene network analyses we characterized FOXO3A, a longevity-associated transcription factor, as a master regulator gene that was downregulated in six subtypes of monkey vascular cells during aging, which provided a critical resource for understanding the principles underlying primate arterial aging and contributes important clues to future treatment of age-associated vascular disorder. Overall, our studies illustrated the cell-type-specific transcriptomic alterations for multi-organ aging in primate, providing indications of promising new lines of human aging research.

An aging-associated lncRNA, PK3, regulates cellular senescence

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Abstract

Aging is an inevitable process during life span, and leads to loss of genomic stability, epigenetic alterations, proteostasis, deficient nutrient signaling, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and deviant intercellular communication [1]. What's more, it leads to immunodeficiency and inflammaging, thus accelerates pathologies and major reasons of human frailty and mortality, such as cardiovascular disease, obesity, neurodegenerative disorders and cancer. Recently, ENCODE project reveals that the noncoding genome has biochemical activity with transcription, transcription factor bindings, chromatin structure and histone modification. How the noncoding transcripts including long noncoding RNAs regulate the aging process still have many unknown. Previously, we found out that aging-assciated lncRNAs are evolutionary conserved and the age-up regulated lncRNAs participate in NFκB pathway [2]. How the age-down regulated lncRNAs regulate the aging process still remains to investigate. Here we found that PK3, which is age-down regulated lncRNAs, is also reduced expression level in senescent cells, can regulate cellular senescence process.

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Age-dependent decline in stress response capacity revealed by proteins dynamics analysis

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Abstract

The aging process is regarded as the progressive loss of physiological integrity, leading to impaired biological functions and the increased vulnerability to death. Among various biological functions, stress response capacity enables cells to alter gene expression patterns and survive when facing internal and external stresses. Here, we explored changes in stress response capacity during the replicative aging of *Saccharomyces cerevisiae*. To this end, we used a high-throughput microfluidic device to deliver intermittent pulses of osmotic stress and tracked the dynamic changes in the production of downstream stress-responsive proteins, in a large number of individual aging cells. Cells showed a gradual decline in stress response capacity of these osmotic-related downstream proteins during the aging process after the first 5 generations. Among the downstream stress-responsive genes and unrelated genes tested, the residual level of response capacity of Trehalose-6-Phosphate Synthase (TPS2) showed the best correlation with the cell remaining lifespan. By monitor dynamics of the upstream transcription factors and mRNA of *Tps2*, it was suggested that the decline in downstream stress response capacity was caused by the decline of translational rate of these proteins during aging.

Moreover, when the response capacity decreased to a critical value, which we assumed was the internal noise level, the cell soon died. To survive, the response capacity should be, at minimum, sufficiently strong to resist intracellular noise. Thus, we conjecture that lifespan might be extended by enhancing stress response capacity

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Osmotic stress extends *Caenorhabditis elegans* lifespan

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Abstract
Aging is characterized by extensive metabolic reprogramming. Here, to identify metabolic pathways of osmotic stressed *C.elegans* associated with aging, we analyzed the changes of metabolic pathways in *C.elegans* subjected to osmotic stress. We found that with osmotic stress T metabolic pathway is associated with aging. Knock down the levels of enzymes in the T pathway, which can block the effect of osmotic stress. And by RNAi screening assay, We generally determined the direction of D degradation affected *C.elegans* lifespan under osmotic stress.

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Contribution of MSB3 in replicative aging regulation of Saccharomyces cerevisiae

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Abstract

MSB3, a Ypt/Rab-specific Rab GTPase-activating protein, was predicted as a core gene organizing genetic regulatory network of yeast replicative aging by our lifespan prediction model. Moreover, we found that knockout of MSB3 extended yeast lifespan by 33%. To dissect MSB3 centralized regulator network underlying lifespan extension, we compared the transcriptomics of MSB3 deletion strain with wild-type strain. We found that the differential expressed genes are divided into two major biological process terms. One term is associated with glycometabolism. Particularly, multiple genes participating in glycogen and trehalose biosynthesis are increased simultaneously in MSB3 deletion strain. Our results are in agreement with the concepts that glucose restriction and trehalose-induced autophagy promotes lifespan extension. Another term is linked to the glutathione related genes, including reductase and transferase. As an antioxidant, glutathione helps counteract free radicals and alleviate aging. We found that in MSB3 knockout strain, a large number of glutathione genes is up-regulated, suggesting that MSB3 deficient might promotes cellular antioxidative activity to resist aging. Our findings provide novel insights on MSB3 for aging, but the details remain to be further confirmed.

Key words

GTPase-activating protein, MSB3, RLS, Glycometabolism, Glutathione system, Yeast

This work was supported by grant from the National Science Foundation of China NSFC81673338.

Microbial metabolites as anti-aging ingredients

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Abstract

Aging, together with its associated diseases such as Alzheimer's disease (AD), constitutes a huge burden to the modern society[1]. Discovery and development of drugs to antagonize aging and AD remain far from achieved to date. Gut microbiota, various microbes colonizing the digestive tracks, are continuously producing numerous intermediate metabolites. Correlations have been found between these metabolites and age-related cognitive impairment[2], suggesting that microbial biosynthesis represents a novel tool in manufacturing anti-aging chemicals. In the purpose of systematic identification of these metabolites in regulating aging processes, we utilized a model system of the nematode *Caenorhabditis elegans*. Taking advantages of their short life cycle as well as single and lab-controlled microbiota[3], we have identified several bacteria-derived compounds showing efficacy in prolonging lifespan and alleviating AD pathologies. The most potent one obtained so far was designated as FD12. When supplemented with FD12, both wild-type and a human amyloid-β transgenic *C. elegans* strains exhibit remarkably extended survival. We further tested effects of FD12 in the fruit flies. As a result, FD12 similarly prolongs *Drosophila* lifespan and postpones proliferation of intestinal epithelial cells caused by dedifferentiation, a specific sign of aging. More intriguingly, FD12 is capable of lowering mitochondrial ROS production in mammalian cells, and our testing of FD12 effectiveness in the mouse AD models is ongoing. Based on our preliminary efforts, searching for longevity-promoting chemicals, as examplified by FD12, is highly promising and displays enormous translational potential.

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Adipose-derived stem cells secreted peptide affects skin fibroblasts function *in vitro*

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Abstract

Adipose-derived stem cells (ADSCs) are considered promising cells for skin rejuvenation. Recently, peptide drugs have shown great value in clinical applications. In this study, we used liquid chromatography-tandem mass spectrometry to identify differentially expressed peptides in adipose-derived stem cells-conditioned medium (ADSCs-CM) at different time points (24 h, 48 h, 72 h). A total of 1108 peptides were detected in ADSCs-CM at 48 h. Further bioinformatics analysis (Gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway analysis) indicated that precursor proteins of these peptides correlate with protein binding, organic cyclic compound binding, heterocyclic compound binding, nucleic acid binding, ECM-receptor interaction, focal adhesion, and PI3K-Akt signaling pathway occurring during skin rejuvenation. Four peptides are selected to test their effects on skin fibroblasts function. These peptides revealed distinct roles in skin fibroblasts proliferation, migration and apoptosis. Furthermore, preliminary data of quantitative real time PCR and western blot demonstrate that these peptides could promote collagen expression in skin fibroblasts. Overall, our study proves that adipose-derived stem cells secreted peptide affects skin fibroblasts function *in vitro.* Further mechanism analysis and *in vivo* study are still needed.

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DAHP synthase deficiency of gut microbiota promotes host longevity

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Abstract

Treating aging is the key to antagonize numerous associated chronic diseases. By employing a highly efficient model system, *Caenorhabditis elegans* and its sole microbiota *Escherichia coli*, we have discovered that deletion of the bacterial *aroG* gene, encoding 3-deoxy-D-arabino-heptulosonate 7-phosphate (DAHP) synthase, results in dramatically prolonged reproductive period and lifespan(Han, Sivaramakrishnan et al. 2017). We propose to identify cellular and molecular mechanisms for this cross-kingdom regulation, shedding lights on the seminal idea of manipulating gut microbiota for health and longevity promotion. We performed a transcriptome analysis for the *C. elegans* colonized by the *ΔaroG* mutation to reveal that expression of a huge cluster of genes affecting sensory cilium development is differentially regulated, highlighting a novel concept that the neuronal activities directly modulate aging. These causal relationships were confirmed by RNAi inacitivation of these down-regulated genes. Meanwhile, we demonstrated that the *hsp-6* gene is upregulated by *ΔaroG*, indicating that the bacterial mutation functions via stimulating mitochondrial unfold protein response. Therefore, we sketch the regulating network for the DAHP synthase deficiency to exert anti-aging effects. We characterize the mechanisms underlying longevity effect of a specific microbial factor for the first time. The rationale behind our work will provide insights for modifying gut microbiota in order to shape health of the host, a perspective hardly explored and highly promising in curing many severe diseases.

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Analysis of SUL1 mediated replicative lifespan regulation in the yeast *Saccharomyces cerevisiae*

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Sulfate uptake is critical for cellular metabolism and proliferation. Accumulating evidence suggests that SUL1 serve as the plasma membrane transporters governing extracellular sulfate entrance into budding yeast. Using a system biology methodology, we identified SUL1 may be a core gene orchestrating genetic regulatory network for modulation yeast replicative lifespan (RLS). Furthermore, we confirmed that RLS was significantly prolonged by 26.71% in SUL1 knockout strains. In addition, we analyzed the mRNA expression profiles of yeast deletion collections (~ 1484 genes, GSE42528) and found that SUL1 is highly related to genes participating in the sulfate assimilation pathway (SAP), which incorporate sulfate into sulfate intermediates, such as cysteine, methionine and S-adenosylmethionine. To dissect the SUL1 centered core genetic regulatory network underlying longevity, we compared the transcriptome of SUL1 deletion strain with wild-type strain. Our data showed that the majority of methylation related genes responsible for RNA and histone methylation are down-regulated in SUL1 knockout strain, indicating that SUL1 might contribute to yeast replicative aging through methylation mediated gene expression. Collectively, our pilot study suggests that SUL1 may be an important regulator of sulfate anabolic metabolism, methylation and longevity.

Key words

SUL1, sulfate assimilation pathway, methylation, replicative lifespan, yeast

This work was supported by grant from the National Science Foundation of China NSFC81673338.

The involvement of TYS1 in replicative lifespan regulation of Saccharomyces cerevisiae

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Abstract

TYS1 functions as tyrosyl-tRNA synthetase catalyzing tRNATyr tyrosylation which is essential for protein translation and cell viability. We previously applied system biology methodology to predict lifespan and found that TYS1 might be a crucial core gene orchestrating genetic regulatory network for replicative aging in yeast. Here, we confirmed that partial reduction of TYS1 extended yeast replication lifespan by 23.22%. To dissect the genetic regulatory network of TYS1 in replicative aging, we compared the whole mRNA expression profiling of TYS1 knockdown strain with the wild-type strain. Our data showed that differential expressed genes (DEGs) are classified into two major biological process terms. One term is linked to the RNA polymerase III promoter which is responsible for small RNA, such as tRNA and rRNA, transcription. Interestingly, almost all DEGs in this term are down-regulated in TYS1 knockdown strain. We inferred that the loss of TYS1 probable cause defects in the export of tRNA and rRNA into the cytosol, reduce the cellular protein anabolism, thus contribute to lifespan extension. Another term is associated with the genes required for ergosterol biosynthesis. Ergosterol is a sterol that resides on the cell membranes of fungi and acts to maintain cell membrane integrity. The synthesis of ergosterol is achieved by multi-enzyme catalyzing complex biosynthetic pathways. We found that in the TYS1 mutant strain, the abundance of most ergosterol synthetic genes is increased, indicating that ergosterol might contribute to the replicative aging of yeast. Our pilot study provides novel insights on TYS1 for lifespan regulation, but the detailed mechanism remains to be further examined.

Key words

TYS1, RNA polymerase III, Ergosterol, Lifespan, Yeast

This work was supported by grant from the National Science Foundation of China NSFC81673338.

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Involvement of complement protein C4b in mouse brain aging

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Abstract

The complement system plays a critical role in synaptic pruning during normal brain development, whereas aberrant activation of the classical complement cascade contributes to the pathogenesis of some neurological disorders, such as schizophrenia. Our previous bulk transcriptomic data showed that C4b mRNA expression was increased in the cerebral cortex, hippocampus and kidney in an age-dependent manner. Here we interrogated the possible contribution of complement proteins, especially C4b, in brain senescence. GSEA analysis revealed that the genes being responsible for the complement pathway were broadly activated in the aforementioned tissues during aging. Furthermore, both RNA sequencing and qPCR analysis demonstrated the expression of C4b, as well as C1q and C3, two core genes acting upstream or downstream of C4b during complement activation, was simultaneously upregulated with age. To further evaluate the effects of C4b engaged in neural tissue aging, we utilized the CRISPR-CasRx system to knockdown C4b expression in neurons. In vitro experiments showed that the deficit of C4b in hippocampal neurons facilitates neuronal dendrite growth. Intriguingly, we found that the aged mice depleted C4b by CRISPR-CasRx in hippocampal dentate gyrus significantly alleviate age-dependent impairment of learning and memory compared with their counterparts. Our findings suggested that C4b may be associated with cognitive memory decline in the aging brain, thus may represent a potential therapeutic target of brain aging.

Key words

Complement pathway, C4b, aging, nervous tissue, hippocampus, CRISPR-CasRx

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Hsp90 improved sleep behaviour of *Drosophila melanogaster* during aging process

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Abstract

Hsp90 (Heat shock protein 90) is a crucial molecular chaperone inside the cell. Studies have shown that Hsp90 can affect aging process of organisms by regulating protein homeostasis, but the specific regulation manner remains to be explored. In previous research, we found that systemic overexpression of Hsp90 significantly prolonged the life span of Drosophila and improved its sleep behaviour as well. Thus, in this study we explored the relationship between Hsp90, sleep behaviour and aging process of Drosophila. Transgenic fly strains had been constructed to overexpress Hsp90 through whole body or specifically in central nervous system respectively. Longevity statistics and sleep analysis showed that compered to wild type flies, systemic or central nervous systemic overexpression of Hsp90 both prolong the life span and improved the tolerance to environmental pressure as well as sleep behaviour during aging process. Moreover, we found that overexpressed Hsp90 in central nervous system specifically improved the abnormal rhythmic behaviours caused by systemic overexpression of Hsp90, such as the prolonged free-running period, etc. These results indicated that Hsp90 might improve the sleep behaviour during aging process by regulating the homeostasis and thus delay aging, and more precise neuron could be found for Hsp90.

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Three-dimensional Facial Aging Clock Reveals Ethnic Variations Between Asia and Africa Cohorts

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Abstract

As the significant variations among ethnic groups, we collect 1,200 Africa samples 3D facial images with baseline information in Ghana to study African aging mechanisms. Firstly, we construct the first three-dimensional facial aging clock with highly accuracy to predict Asian biological age by ensemble 3 CNNs. Mean Absolute Deviation (MAD) is 4.92 years that is comparable with classical methylation clocks but less accurate than our Asia models (Xia et al., 2020). Secondly our Ghana model shows potential strong generalization ability of cross-ethnic prediction. Furthermore. we systematically compare the aging patterns between Asia and Africa cohorts, and aim to reveal SNPs of facial structure (Claes et al., 2018) playing different roles in 2 ethnic groups.

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Human Oral Microbiome and Blood Metabolome Reveal Heterogeneity of Aging Rate and Impact of Lifestyle

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Abstract
Using metagenomics and metabolomics approach, we derived tongue-coating microbiota and blood metabolome from a northern Chinese Han population-based cohort where clinical metadata and aspects of their lifestyles were also recorded to explore the associations of tongue-coating microbiota and facial aging rate difference, blood metabolome and clinical measurements, and the impacts of lifestyles. Finally, we identified 2 main co-occurrence groups of microbes, one is centered with a good bacterium, Neisseria flavescens, which is negatively-correlated with blood triglycerides, the other is featured with enrichment of periodontitis-related pathogens which can accelerate facial aging rate. The two main groups stand out in associations of tongue-coating microbiota with clinical measurements. And we generated a tripartite network of lifestyle–species–health parameters using a causal-inference framework and found out many key species as potential mediators, among which N. flavescens is a promising anti-aging microbe, with a specific pathway, ubiquinol-8 biosynthesis pathway beneficial to optimizing blood lipid metabolism.

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The regulation of telomerase gene and human longevity

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Abstract

hTERT (human telomerase reverse transcriptase) is the catalytic component of human telomerase complex. It adds telomeric DNA to chromosomal ends that prevents telomere shortening and cellular senescence. The expression of hTERT is highly regulated and likely relevant to human aging. Multiple independent sequence variants of the hTERT locus have been associated with telomere length and cancer risks in genome-wide association studies. Here, we identified an intronic variable number tandem repeat, VNTR2-1, as an enhancer-like element, which activated hTERT transcription in a cell in a chromatin-dependent manner. VNTR2-1, consisting of 42-bp repeats with an array of enhancer boxes, cooperated with the proximal promoter in the regulation of hTERT transcription by basic helix–loop–helix transcription factors and maintained hTERT expression during embryonic stem-cell differentiation. Genomic deletion of VNTR2-1 in MelJuSo melanoma cells markedly reduced hTERT transcription, leading to telomere shortening, cellular senescence, and impairment of xenograft tumor growth. Interestingly, VNTR2-1 lengths varied widely in human populations; hTERT alleles with shorter VNTR2-1 were underrepresented in African American centenarians, indicating its role in human aging. Therefore, this polymorphic element is likely a missing link in the telomerase regulatory network and a molecular basis for genetic diversities of telomere homeostasis and age-related disease susceptibilities.

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Facial Thermal Imaging Technology in the Prediction of Aging and Disease

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Abstract

Aging is a problem that bothered us for thousands of years. Aging Markers measure aging[1-2]. 3D images of human faces have been verified as a feasibility aging marker[3].

Recently, surface temperature of the human body has been widely used in the prediction of psychological diseases[4]. The spontaneous radiation of the human body is more stable and more robust than radiation from external (e.g. sun light) and it has advantage in reflecting the body's functional state. DNN has been widely used in various researches and due to its ability to process image tasks, it is becoming one of the most popular algorithms, we choose to use ResNet-34 to build thermal aging clock.

Firstly, it is verified that there are differences in facial thermal imaging, and then we constructed a DNN model based on facial thermal imaging to predict age and aging. After visualizing the difference information of the activation map, it is found that the faces of the elderly have more specific aging activation areas.

Using DNN and thermal imaging, this study analyzes the feasibility of using thermal imaging as a marker of aging.

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Landscape of aging-dependent transposable elements

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Abstract

Aging is a biological process associated with many complex human diseases[1]. And previous studies have demonstrated that tansponsable elements(TEs) can promote aberrant transcription, alternative splicing, insertional mutagenesis, DNA damage and genome instability[2] during many biological process. Here, we profiled the transcriptomes of peripheral blood mononuclear cells (PBMCs) using ribo-minus RNA-seq of 280 individuals from the same cohort, and aims to explore the roles of TEs during aging. Basing on the dataset, we identified a set of aging- dependent TEs (mainly simple-repeats). And these TEs are enriched of binding motif of IRF TF families. Besides, aging-dependent TEs prefer to have overlaps with histone marker signals, such as H3K4me3, H3K27ac.

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Global and gene-specific translational regulation in *E. coli* across different conditions

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Abstract

How well transcript level represents protein abundance remains a controversial issue. Especially, the correlations between mRNA and protein abundance for a single gene across conditions exhibit remarkable variability. Translational regulation is one of the key factors contributing to this mismatch. To verify whether gene-specific translational regulation is a universal rule in response to environmental changes and what the possible mechanism might be, we quantified genome-wide transcriptome and translation efficiency under 12 conditions by combination of ribosome profiling and RNA-seq. We observed a diverse range of gene-specific translational regulations in response to nutrient limitations of carbon (C), nitrogen (N), and phosphate (P). Intriguingly, we found that many genes regulating translation are themselves subject to translational regulation, suggesting possible direct feedbacks. Furthermore, using a random forest model, we confirmed that codon usage contributes to part of the translation efficiency variability across conditions. These findings broaden the understanding of translational regulation under environmental changes, and provide novel strategies for synthetic biology.

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The causality among lipid metabolites and bone mineral density

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Abstract
Accumulative evidence indicated that there was a potential association between lipid metabolism and osteoporosis, but epidemiologic studies did not reach consistency.
Objective: To explore the causal relationships among lipid metabolites and bone mineral density (BMD).
Methods: A two sample Mendelian randomisation (MR) study was conducted based on the European population. Data of lipid metabolites was from a GWAS research of Kettunen et.al, summarizing the single nucleotide polymorphisms (SNPs) associations with levels of 123 circulating lipid metabolites. The GWAS summary statistics of BMD was extracted from the Genetic Factors for Osteoporosis Consortium (GEFOS). The SNPs associated with lipid metabolites independently (r^2<0.0001) and reaching the GWAS significance (P<5×10^{-8}) were selected as instrumental variables (IVs). Inverse variance weighted (IVW) random effect model was mainly used for data analysis. MR-Egger regression model was adopted to evaluate the pleiotropy of the IVs. Considering random errors in the process of selecting and incorporating IVs, the leave-one-out sensitivity analysis was used to ascertain whether the association was disproportionately influcend by a single IV.
Results: Two lipid metabolites—omega-3 fatty acids instrumented by 4 independent SNPs, and VLDL.P (concentration of chylomicrons and extremely large very low-density lipoprotein (VLDL) particles) instrumented by 7 independent SNPs—were associated with BMD significantly. The IVW random effect model observed an average of 0.097 (95%CI: 0.001, 0.193) g/cm^2 and 0.080 (95%CI: 0.011, 0.148) g/cm^2 decrement in BMD at lumbar spine and femur neck, respectively, in response to per unit increment in omega-3 fatty acids and VLDL.P. No significant pleiotropy was found for the instrumenting IVs. And no single IV had significant impact on the whole association estimates.
Conclusion: Genetically predicted increasing levels of lipid metabolites as omega-3 fatty acids and VLDL.P contributed to reduced lumbar spine and femur neck BMD. Future studies are still needed to elucidate the underlying mechanism for their associations.

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Allosteric type and pathways are governed by the forces of protein-ligand binding

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I. Introduction

Allostery is central to many cellular processes, by up- or down-regulating target function. However, what determines the allosteric type remains elusive and currently it is impossible to predict whether the allosteric compounds would activate or inhibit target function before experimental studies.

II. Materials and methods

We demonstrated that the allosteric type and allosteric pathways are governed by the forces imposed by ligand binding to target protein using the anisotropic network model and developed an allosteric type prediction method (AlloType).

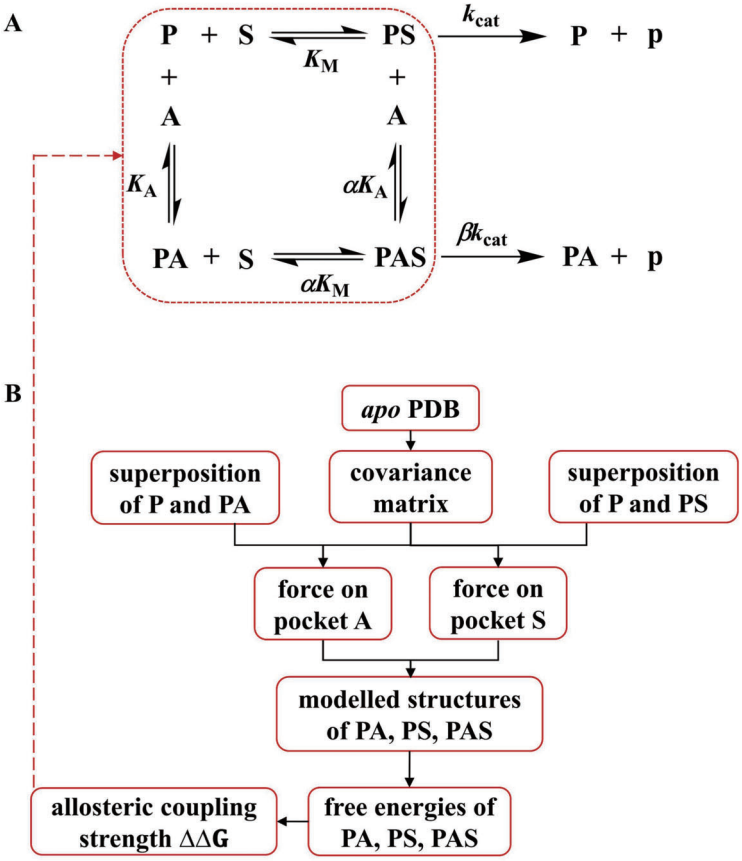

Figure 1. (A) Typical thermodynamic cycle for a protein (P) that binds a substrate (S) and an allosteric effector (A) to form PS, PA, PAS complex, and finally converts to a product (p). K_M and K_A refer to the dissociation constant of substrate and allosteric effector, respectively. The k_{cat} refers to the catalysis constant. α and β indicate the allosteric coupling strength. (B) Workflow of calculating allosteric coupling strength.

III. Results

AlloType correctly predicted 13 of the 16 allosteric systems in the data set with experimentally determined protein and complex structures as well as verified allosteric types, which was also used to identify allosteric pathways.

When applied to glutathione peroxidase 4, a protein with no complex structure information, AlloType could still be able to predict the allosteric type of the recently reported allosteric activators, demonstrating its potential application in designing specific allosteric drugs and uncovering allosteric mechanisms.

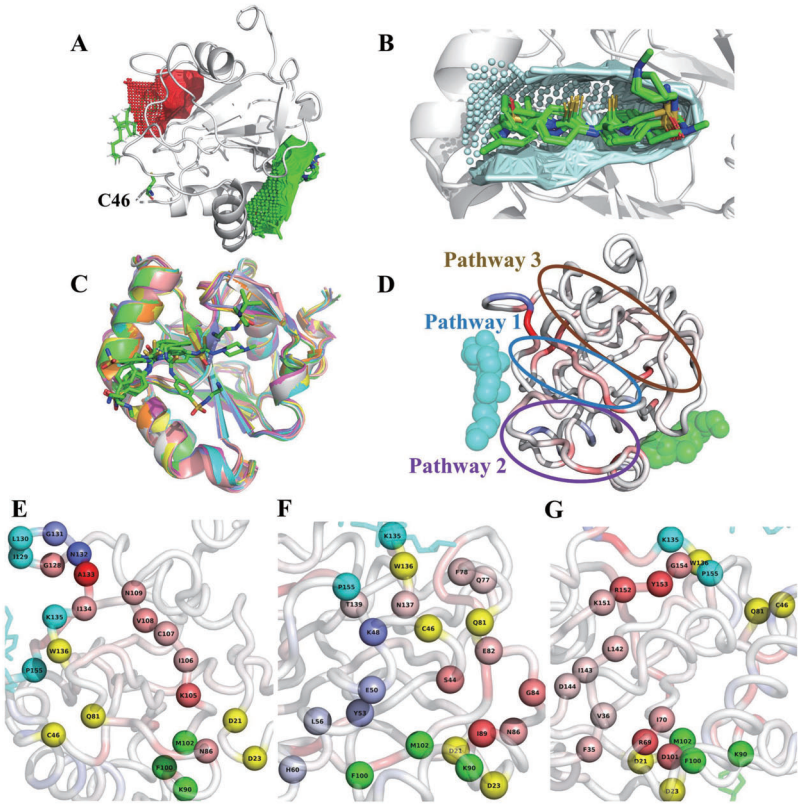

Figure 2. (A) Predicted orthosteric pocket (red) and allosteric pocket (green) of GPX4. (B) Docking of eight allosteric modulators into the allosteric pocket. (C) Eight representative conformations of eight PA states of GPX4 by clustering snapshots from each MD trajectory. (D) Predicted three allosteric pathways in GPX4. (E–G) Detailed information on allosteric pathways 1, 2, 3.

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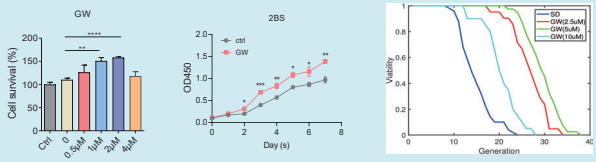
A compound extends lifespan of mice significantly through action upon PAKs

Yongpan An, Jie Zhu, Yao Dang , Tianyu Zhang, Baoxue Yang, Zhengwei Xie

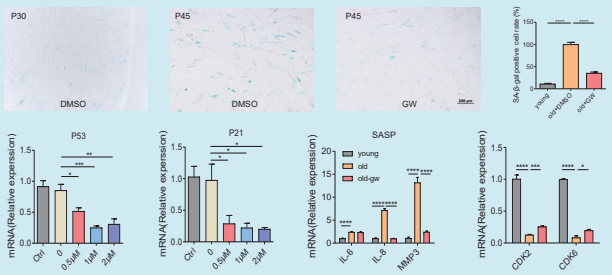
Abstract

Aging is a risk factor for many diseases, and aging-related diseases have become an important cause of human death. Cell senescence and decreased mitochondrial function have become important causes of aging. It is of great significance to develop new broad-spectrum safe drugs for the treatment of aging syndrome. Herein, we first predicted the anti-aging effect using aged gene signatures as input in the connectivity map (CMAP) pipeline. We found GW, a compound of kinase, was able to extend the lifespan of yeast, C57BL / 6J mice, ICR mice by 92.18%, 31.9% and 142.9%, respectively. Mechanistically, GW can ameliorate cellular senescence by elevating mitochondrial function, restoring SA-β-gal staining, p21, SASP markers, rescued the histomorphological changes in hippocampus, heart, kidney and liver. As for mode of action (MOA), we found that GW's anti-aging effects depend on STE20 (PAK1's homolog), and it binds to PAK1 with KD equals to 0.82 μM. The 2.6Å resolution structure of PAK1 in complex with GW we obtained in this study reveals a characteristic protein kinase fold containing smaller N-terminal and larger C-terminal lobes connected by a hinge region, with the inhibitor GW occupying the ATP binding site. Further, inhibition of PAKs is beneficial to delaying aging. We show that GW has good clinical prospects and provides new tools for study of anti-aging mechanisms.

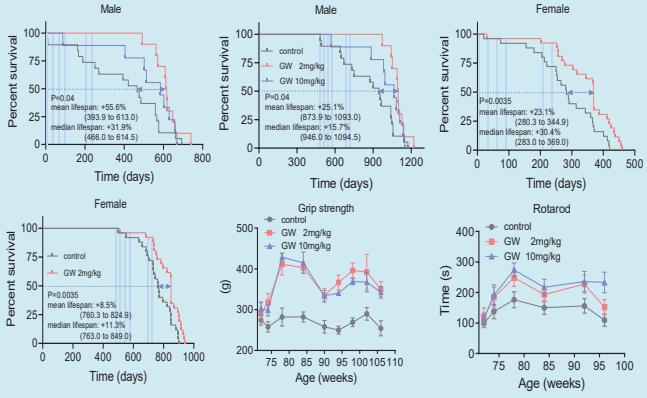
GW screened by CMAP promotes the proliferation of senescent cells and extends the lifespan of yeast

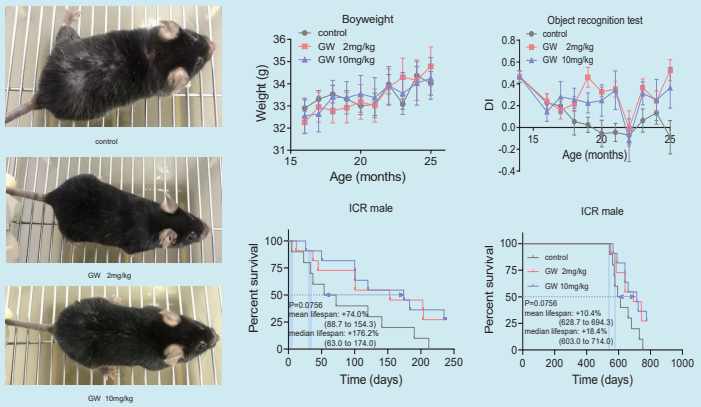


GW ameliorates SA-β-gal, p21 and other aging markers

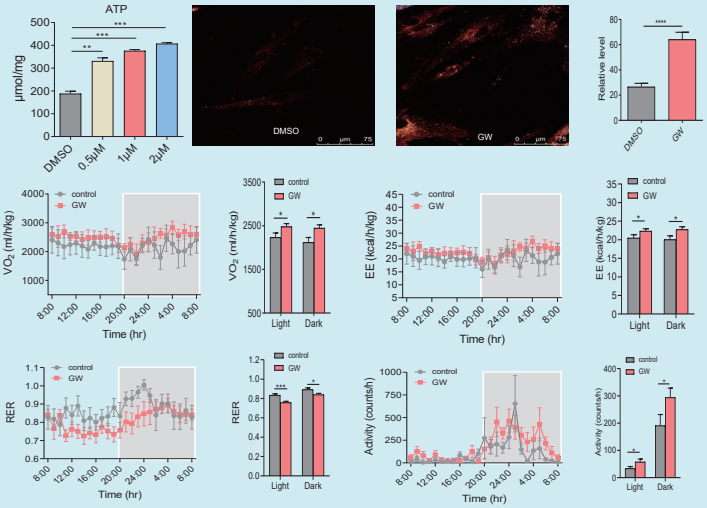


GW extends the lifespan and healthy lifespan of mice

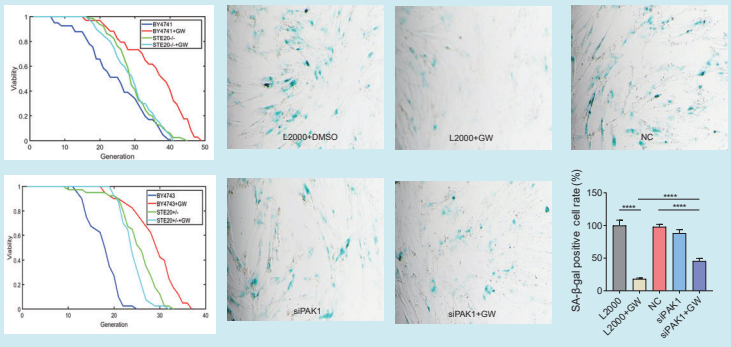


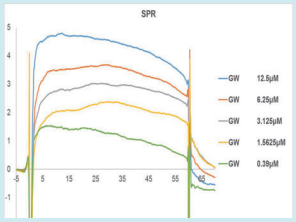


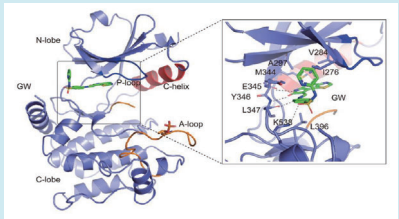
GW may delay aging by improving mitochondrial function



GW exerts partial anti-aging effects through PAK1







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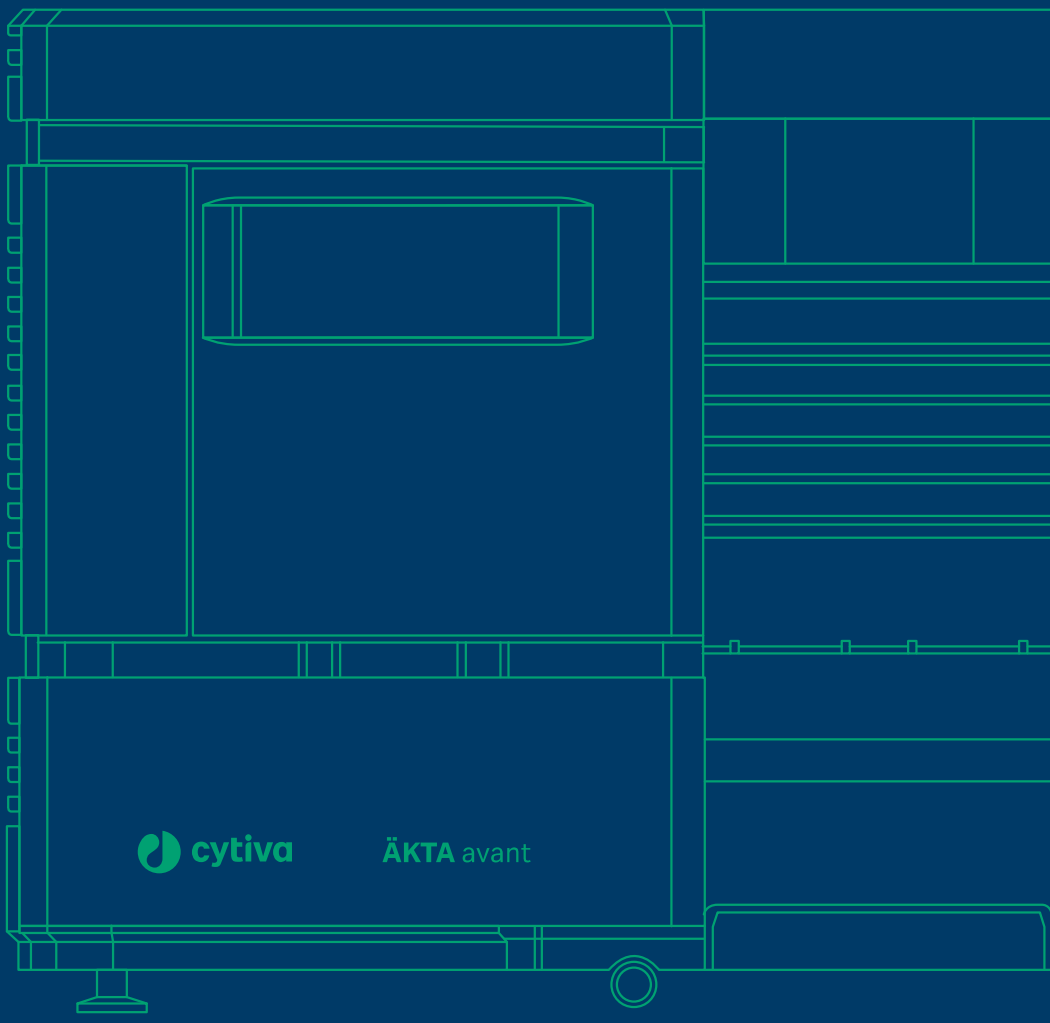

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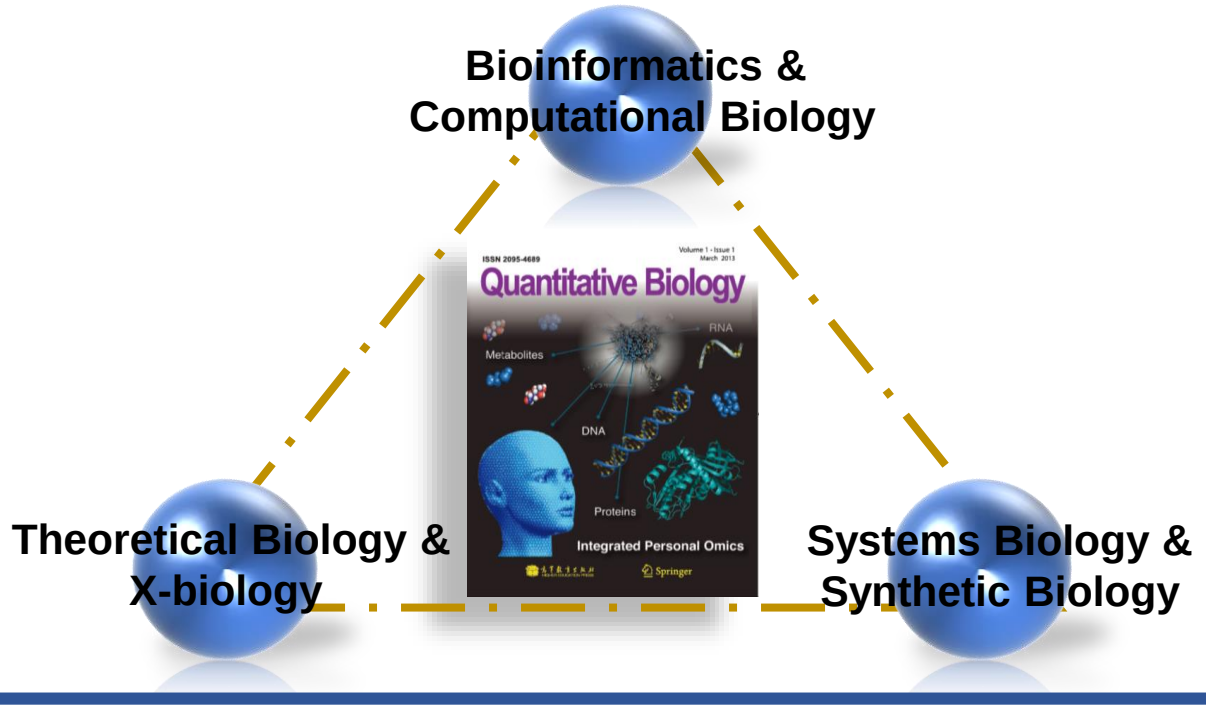

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