Madrid 7 — 9 May 2018

cnio stop cancer

Molecular, Cellular and Organismal Hallmarks of Aging

Organisers

Maria A. Blasco
Spanish National Cancer Research Centre (CNIO), Madrid, Spain

Alejo Efeyan
Spanish National Cancer Research Centre (CNIO), Madrid, Spain

Kathleen Collins
University of California at Berkeley, US

Thomas Rando
Stanford University, US

Speakers

Johan Auwerx
Federal Polytechnic School of Lausanne (EPFL), Switzerland

Salvador Aznar Benitah
Institute for Research in Biomedicine, Bacelona, Spain

Shelley Berger
Perelman School of Medicine, Philadelphia, US

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Jan Hoeijmakers
Erasmus MC Rotterdam, Netherlands

Steve Horvath
UCLA, David Geffen School of Medicine, Los Angeles, US

Juan Carlos Izpisua Belmonte
Salk Institute for Biomedical Studies, La Jolla, US

Matt Kaeberlein
University of Washington, US

Cynthia Kenyon
University of California at San Francisco; Calico Laboratories, US

Thomas Rando,
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Manuel Serrano
Institute for Research in Biomedicine (IRB), Barcelona, Spain

David Sinclair
Harvard Medical School, Boston, US

Jan van Deursen
Mayo Clinic, Rochester, US

EXCELENCIA SEVERO OCHOA 2012 - 2019

GOBIERNO DE ESPAÑA · MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD · ISC Instituto de Salud Carlos III

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"la Caixa" Banking Foundation

Madrid 7 — 9 May 2018

cnio "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2018

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Molecular, Cellular and Organismal Hallmarks of Aging

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

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CENTRE

Madrid 7 — 9 May 2018

cnio "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2018

Molecular, Cellular and Organismal Hallmarks of Aging

Summary

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

Madrid 7 — 9 May 2018

cnio "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2018

Molecular, Cellular and Organismal Hallmarks of Aging

Programme

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

Madrid 7 - 9 May 2018

Molecular, Cellular and Organismal Hallmarks of Aging

Venue:
Spanish National Cancer Research Centre – CNIO Auditorium
Madrid, Spain

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David Sinclair
Harvard Medical School, Boston, US

Jan van Deursen
Mayo Clinic, Rochester, US

6th May 2018 - Sunday

20:00 - 21:30 *Welcome Cocktail for all participants*
Venue: Don Pio Hotel (Av. de Pío XII, 25, 28016 Madrid)

7th May 2018 - Monday

09:45 - 10:00 Opening Remarks

10:00 - 13:45 **Session#1 STEM CELLS AND REGENERATION**
Chairperson: Cynthia Kenyon

Keynote Lecture
10:00 - 11:00 **Juan Carlos Izpisua Belmonte**
Salk Institute for Biomedical Studies, La Jolla, US
"Genetic and Epigenetic Approaches to Organ Regeneration and Aging"

11:00 - 11:30 **Thomas Rando**
Stanford University, US
"Stem cell aging: functional consequences and rejuvenation strategies"

11:30 - 12:00 Coffee break (social room)

12:00 - 12:30 **Salvador Aznar Benitah**
Institute for Research in Biomedicine, Barcelona, Spain
"Stem cell rhythms in homeostasis and aging: why what we eat matters"

12:30 - 12:45 SHORT TALK **Pura Muñoz**
CNIC, Madrid, Spain
"Understanding muscle stem cell regenerative decline with aging"

12:45 - 13:00 SHORT TALK **Pekka Katajisto**
University of Helsinki, Finland
"Metabolic determination of cell fate through selective inheritance of mitochondria"

13:00 - 14:30 Lunch break (cafeteria)

7th May 2018 - Monday

14:30 - 17:15 **Session#2 GENOME INSTABILITY**
Chairperson: David Sinclair

14:30 - 15:00 **Maria A. Blasco**
Spanish National Cancer Research Centre, Madrid, Spain
"Targetting telomeres in aging & age-related pathologies"

15:00 - 15:15 SHORT TALK **Elsa Logarinho**
Instituto de Biologia Molecular e Celular-IBMC, i3S, Porto University, Portugal "
"Molecular basis of mitotic decline and aneuploidy-driven senescence during human aging"

15:15 - 15:45 **Jan Hoeijmakers**
Erasmus MC, Rotterdam, Netherlands
"From DNA damage to aging, neurodegeneration and proteinopaties and the effect of nutritional interventions"

15:45 - 16:15 Coffee break (social room)

16:15 - 16:45 **Kathleen Collins**
University of California at Berkeley, US
"Pathways for human telomerase assembly and activity at telomeres, and their compromise in human disease"

16:45 - 17:15 **Oskar Fernández Capetillo**
Spanish National Cancer Research Centre, Madrid, Spain
"Exploring the role of replicative stress in ageing"

17:15 - 18:30 Poster Session & Wine and cheese (social room)

8th May 2018 - Tuesday

09:30 - 14:15 **Session#3 NUTRIENTS**
Chairperson: Manuel Serrano

09:30 - 10:00 **Matt Kaeberlein**
University of Washington, Seattle, US
"Translational geroscience:
Targeting mTOR to promote healthy longevity"

10:00 - 10:30 **Alejo Efeyan**
Spanish National Cancer Research Centre, Madrid, Spain
"Nutrient Signalling in Physiology and Desease"

10:30 - 10:45 SHORT TALK **Paula Martínez**
CNIO, Madrid, Spain
"Rapamycin-induced lifespan extension requires telomerase"

10:45 - 11:00 SHORT TALK **Juan Poyatos**
CNB, Madrid, Spain
"Tolerance to NAD redox imbalance explains chronological lifespan in Saccharomyces cerevisiae"

11:00 - 11:45 Group Picture & coffee break (CNIO main door & social room)

11:45 - 12:15 **Cynthia Kenyon**
University of California San Francisco, US
"Aging (or not) in *C. elegans*"

12:15 - 12:45 **David Sinclair**
Harvard Medical School, Boston, US
"Genes and small molecules to slow the pace of aging"

12:45 - 14:15 Lunch break (cafeteria)

8th May 2018 - Tuesday

14:15 - 16:30 **Session#4 SENESCENCE**
Chairperson: Salvador Aznar-Benitah

14:15 - 14:45 **Jan van Deursen**
Mayo Clinic, Rochester, US
"Senescent cells: an emerging target for diseases of aging"

14:45 - 15:15 **Judith Campisi**
Buck Institute for Research on Aging, Novato, US
"The double edged sword of cellular senescence"

15:15 - 15:45 **Manuel Serrano**
Institute for Research in Biomedicine, Barcelona, Spain
"An integrated view of senescence, plasticity and reprogramming"

15:45 - 16:15 **Shelley Berger**
The Perelman School of Medicine at the University of Pennsylvania, US
"Profound nuclear and chromatin alterations in senescence and aging"

16:15 - 16:30 **Andrew Koff**
SHORT TALK
Memorial Sloan Kettering Cancer Center, NY, US
"Uncovering regulators of irreversible growth arrest during therapy induced senescence"

8th May 2018 - Tuesday

16:30 - 18:15 **Session#5 ENERGY AND MITOCHONDRIA**
Chairperson: Thomas Rando

16:30 - 17:00 **José Antonio Enríquez**
Spanish National Center
for Cardiovascular Research, Madrid, Spain
"Mitochondrial genetics,
metabolism and ageing"

17:00 - 17:30 **Johan Auwerx**
Ecole Polytechnique Fédérale de Lausanne,
Switzerland
"Systems genetics approaches
to explore mitochondria and aging"

17:30 - 17:45 **Maria Mittelbrunn**
SHORT TALK
12 de Octubre Hospital, CBMSO,
Madrid, Spain
"Mitochondrial failure in cells of the
immune system regulates aging
and age-associated diseases"

17:45 - 18:15 **Marcia Haigis**
Harvard Medical School, Boston, US
"Aging and Mitochondria"

18:15 - 19:00 Poster Session & Wine and cheese (social room)

9th May 2018 Wednesday

09:30 - 12:00 **Session#6 EPIGENETICS**
Chairperson: Kathleen Collins

09:30 -10:00 **Manel Esteller**
The Bellvitge Biomedical Research Institute, Barcelona, Spain
"Epigenetics, Aging and Cancer: A Complex and Twisted Relationship"

10:00 - 10:15 **Juan José Montero**
CNIO, Madrid, Spain
"TERRA-dependent recruitment of polycomb to telomeres is essential for the assembly of histone trymethylation marks at telomeric heterochromatin"

10:15 - 10:45 Coffee break (social room)
Certificate of attendance and invoice will be available at the reception desk

10:45 - 11:45 **Steve Horvath**
UCLA David Geffen School of Medicine, Los Angeles, US
"Epigenetic clock and telomere maintenance"

11:15 - 11:30 SHORT TALK **Maria Carmo-Fonseca**
Institute of Molecular Medicine, Lisbon, Portugal
"Targeting the antisense RNA Zeb2-NAT facilitates reprogramming of aged fibroblasts"

11:30 - 12:00 **Anne Brunet**
Stanford University, US
"The plasticity of aging"

12:00 Closing remarks, Poster Price

Molecular, Cellular and Organismal Hallmarks of Aging

Session#1

STEM CELLS AND REGENERATION

Chairperson: ***Cynthia Kenyon***

Genetic and Epigenetic Approaches to Organ Regeneration and Aging

Juan Carlos Izpisua Belmonte
Professor. Gene Expression Laboratories
Salk Institute for Biological Studies
La Jolla, California. USA.

Aging can be defined as the progressive decline in the ability of a cell or organism to resist stress and disease. Recent advances in cellular reprog- ramming and gene editing technologies have enabled analyses of the aging process. I will discuss how cellular reprogramming allows for a further understanding of the role that epigenetics plays in organ regeneration and aging and how new gene-editing approaches may help to increase our understanding, and perhaps treatment, of aging-associated diseases.

Stem Cell Aging: Functional Consequences and Rejuvenation Strategies

Thomas A. Rando
Stanford University, Stanford, California, USA

There is an age-dependent decline in stem cell functionality in many tissues. Many molecular, biochemical, and functional features of aged stem cells have been characterized. Supported by data from studies of heterochronic parabiotic pairings of mice, it is clear that the aged phenotype can be modified when old stem cells are exposed to a youthful systemic milieu. Our studies of muscle stem cells (MuSCs) have revealed that extrinsic influences can modify quiescent stem cells, in some cases in a lasting manner, during aging and in response to interventions that target the underlying processes of cellular aging. Therefore, we have sought to understand better the regulation of stem cell quiescence and how those regulatory processes change during aging and in response to local and systemic signals. We have found that there are clear transcriptional and epigenetic alterations associated with MuSC aging and that subsets of these changes can be restored to youthful states by aging-targeted interventions. In parallel, we have found that systemic factors associated with injury and exercise can modify quiescent MuSCs in ways that alter their functionality, in each case mediated by components of known longevity pathways. More recently, we have explored in greater detail the transcriptional and translational profiles of quiescent MuSCs in vivo, as opposed to profiles from FACS-isolated MuSCs. These data have revealed important features of both steady-state levels and dynamics of transcriptional and translational control of the quiescent stem cell compartment and how they change substantially during the very early stages of stem cell activation and isolation. These studies are likely to provide more refined analyses of how stem cell homeostasis is maintained across the lifespan, how stem cell functionality is altered during aging, and how stem cells may be rejuvenated by interventions that reprogram the quiescent epigenome.

Aging of adult stem cells and their niches

Salvador Aznar Benitah
ICREA Research Professor
Foundation Botin Researcher
Stem Cells and Cancer Lab, Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain

We interested in studying how adult stem cells maintain tissue homeostasis, and why and how their striking regenerative capacity is altered during aging. We have previously shown that the activity of adult stem cells is under robust circadian control. This allows stem cells to temporally segregate functions that would cause harm if coincident. Importantly, we and others have shown that stem cell circadian arrhythmia leads to a premature ageing phenotype and shortened lifespan. Moreover, our recent results show that the oscillating transcriptome is extensively reprogrammed in physiologically aged stem cells, switching from genes involved in homeostasis to those involved in tissue-specific stresses. I will discuss the functional consequence of circadian rewiring in several tissues, how it is influenced by dietary interventions, and present new data using a novel mouse model of reverse circadian arrhythmia to define its consequences on tissue and organismal ageing. I will also discuss new results on how the epidermal stem cell niche ages.

SHORT TALK

Understanding muscle stem cell regenerative decline with aging

Laura García-Prat[1,2], Antonio L. Serrano[1], Mireia Vaca[1,2], Sonia Alonso-Martín[1], Marta Flández[1], Victoria Moiseeva[2], Joan Isern[2], Jessica Segalés[1,2], Xiaotong Hong[1], Guiomar Solanas[3], Salvador Aznar-Benitah[3,4], Eusebio Perdiguero[1], **Pura Muñoz-Cánoves[1,2,4]**

[1]Centro Nacional de Investigaciones Cardiovasculares, CNIC, Madrid, Spain
[2]Pompeu Fabra University (UPF)/CIBERNED, Barcelona, Spain
[3]Institute for Research in Biomedicine (IRB), Barcelona, Spain
[4]ICREA, Barcelona, Spain

Skeletal muscle has a remarkable capacity to regenerate by virtue of its resident Pax7-expressing stem cells (satellite cells), which are normally quiescent in the adult. Upon injury, quiescent satellite cells activate and proliferate, to subsequently differentiate and form new myofibers or self-renew to restore the quiescent satellite cell pool. Through a combination of global gene expression/bioinformatics and molecular/cellular assays, we found that resting satellite cells have basal autophagy activity, which is required to maintain the quiescent state. Impaired autophagy in old satellite cells or Atg7 deletion in young cells provoked loss of proteostasis and oxidative stress. This proteotoxicity led to loss of quiescence, with subsequent entrance into full senescence in aged and Atg7-deficient satellite cells in response to muscle damage, causing regenerative failure. Pharmacological and genetic reactivation of autophagy could restore regenerative functions in aged satellite cells. Finally, we will show recent findings demonstrating that adult muscle stem cells, despite being in a quiescent state, are subjected circadian control, and that they undergo circadian reprogramming with aging. Interestingly, autophagy was identified as one of the intracellular processes that are oscillatory in adult, but not aged, muscle stem cells. Thus, we propose that, through controlling distinct activities, proteostasis maintains muscle stem cell homeostasis, while its decay is causally implicated in stem cell aging, a process that can be targeted for rejuvenation.

SHORT TALK

Metabolic determination of cell fate through selective inheritance of mitochondria

JJulia Döhla[1,2], Johanna I Englund[1], Ana Amaral[2], Nadja Gebert[3], Ella S Salminen[1], Swetha Gopalakrishnan[1], Reijo Käkelä[4], Alessandro Ori[3], **Pekka Katajisto[1,2,4]**

[1]Institute of Biotechnology, HiLIFE, University of Helsinki, Finland
[2]Department of Biosciences and Nutrition, Karolinska Institutet, Sweden
[3]Leibniz Institute on Aging - Fritz Lipmann Institute (FLI), Jena, Germany
[4]Faculty of Biological and Environmental Sciences, University of Helsinki, Finland

Tissue renewing adult stem cells are controlled by multiple mechanisms to maintain homeostasis. When this control fails, imbalanced self-renewal and differentiation can either increase risk of cancer, or result in loss of tissue function due to stem cell exhaustion – one of the hallmarks of aging. Interestingly, fate changes in stem cells are paralleled by profound metabolic rewiring, making cellular metabolism one possible level for controlling their activity. We have studied the role of cellular metabolism in the context of asymmetric cell divisions to address how metabolism is determined immediately after cell division, and whether asymmetric fate determination is controlled by metabolism. We have discovered that the chronological age of mitochondria inherited from the mother cell, determines daughter cell metabolism and fate upon asymmetric division in stem-like human mammary epithelial cells (HMECs). Old mitochondria are apportioned selectively to the differentiating daughter cell, while progeny omitting old mitochondria retains stem-like properties. Age-specific isolation and profiling of mitochondria revealed that proteomic and lipidomic composition, as well as organelle function changes as mitochondria mature, and results in more active oxidative metabolism in old mitochondria. Upon asymmetric segregation, inherited mitochondrial metabolism prompts metabolic bias in daughter cells, and has the capacity to preserve stem-like properties or induce differentiation. Our results demonstrate that cell fate programs are susceptible to modulation by metabolism immediately after division of stem-like cells, and that the asymmetric apportioning of old mitochondria may be one of the first fate determinants in adult stem cell divisions. We are currently studying whether age-induced alterations can drive stem cell exhaustion via cellular metabolism, and the role of age-selective segregation of mitochondria during aging.

cnio "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2018

Molecular, Cellular and Organismal Hallmarks of Aging

Session#2

GENOME INSTABILITY

Chairperson: ***David Sinclair***

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

Targetting telomeres in aging & age-related pathologies

Maria A. Blasco
Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

Over the past years our laboratory has contributed to dissect the role of telomerase and telomere length as key molecular pathways underlying cancer and aging, as well as has addressed the potential use of telomerase activation as a therapeutic strategy for telomere syndromes and age-related diseases (Blasco et al., *Cell*, 1997; Tomás-Loba, *Cell*, 2008). More recently, we have developed a telomerase-based gene therapy strategy that allows telomerase activation in adult organism (Bernardes de Jesus et al., *EMBO Molecular Medicine*, 2012) and that has shown therapeutic effects in age-related pathologies in mice, such as myocardial infact (Bär et al., *Nature Communications*, 2014) as well as in mouse models for the telomere syndromes aplastic anemia (Bär et al., *Blood*, 2016) and pulmonary fibrosis (Povedano et al., *Cell Reports*, 2015; Povedano et al., eLife, 2018).

SHORT TALK

Molecular basis of mitotic decline and aneuploidy-driven senescence during human aging

Joana Catarina Macedo[1], Sara Vaz[1], Bjorn Bakker[2], Rui Ribeiro[1], Petra Bakker[2], Jose Miguel Escandell[3], Miguel Godinho Ferreira[3], René Medema[4], Floris Foijer[2] and **Elsa Logarinho[1*]**

[1]Aging and Aneuploidy Laboratory, IBMC, Instituto de Biologia Molecular e Celular, i3S, Universidade do Porto, Porto, Portugal
[2]European Research Institute for the Biology of Aging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[3]Instituto Gulbenkian de Ciência, Oeiras, Portugal
[4]Division of Cell Biology I, The Netherlands Cancer Institute, The Netherlands
[*]Corresponding author/lead contact: email: elsa.logarinho@ibmc.up.pt

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

From DNA damage to aging, neurodegeneration and proteinopaties and the effect of nutritional interventions

Jan H. J. Hoeijmakers
Dept. of Molecular Genetics, Erasmus Medical Center,
Rotterdam and Princess Máxima Center for Pediatric Oncology, Utrecht,
The Netherlands and CECAD, Cologne, Germany

Ageing in various organisms appears remarkably plastic: e.g. suppressing insulin signaling extends lifespan. However, virtually all premature aging syndromes in man link with genome instability. We have generated mouse models which strikingly mimic human DNA repair deficiency syndromes and display wide-spread accelerated aging. E.g. *Ercc1*$^{\Delta/-}$ mice defective in four repair pathways show numerous accelerated aging features limiting lifespan to 4-6 month. Simultaneously, they exhibit an anti-aging `survival response', which suppresses growth and enhances maintenance, resembling the longevity response induced by dietary restriction (DR). Interestingly, subjecting these progeroid mutants to 30% DR tripled median and maximal lifespan, and drastically retarded accelerated aging, e.g. DR animals retained 50% more neurons and maintained full motoric function. The same findings were made in repair-deficient *Xpg*$^{-/-}$ mice, extending this observation beyond *Ercc1*$^{\Delta/-}$. The DR response in *Ercc1*$^{\Delta/-}$ mice resembled DR in wild type animals including reduced insulin signaling. Interestingly, ad libitum *Ercc1*$^{\Delta/-}$ liver expression profiles showed gradual preferential extinction of expression of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions, which affect long genes more than short ones. DR largely prevented this decline of transcriptional output, indicating that DR prolongs genome function. We present phenotypes of conditional DNA repair models targeting aging to selected organs, and striking parallels with Alzheimer's disease. Our findings strengthen the link between DNA damage and aging, establish *Ercc1*$^{\Delta/-}$ mice as powerful model for identifying interventions to promote healthy aging, reveal untapped potential for reducing endogenous damage and hence also cancer, provide new venues for understanding the molecular mechanism of DR, identify transcriptional stress as aging mechanism in post-mitotic tissues, explain the aging component and protein aggregates in all proteinopathies in dementia and suggest a counterintuitive DR-like therapy for human progeroid genome instability syndromes and DR-like interventions for preventing neurodegenerative diseases.

Pathways for human telomerase assembly and activity at telomeres, and their compromise in human disease

Kathleen Collins
Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, US

Telomere re-setting by active telomerase in the human embryo establishes a reservoir of telomeric repeats to be counted down with each telomerase-negative somatic cell division. Mutations in telomerase subunit genes lead to premature exhaustion of somatic proliferative capacity, manifest in a broad range of onset ages and tissue pathologies. Severe forms of disease are caused by mutations in subunits that telomerase shares with a large family of H/ACA small nucleolar and small Cajal body RNAs, which distinct from telomerase, function to guide site-specific modification of non-coding RNAs. In order to understand the role of H/ACA RNP assembly in human telomerase biogenesis and action at telomeres, as well as the putatively telomerase-specific impact of mutations in shared RNP subunits that underlie human disease, we have used structural, biochemical, gene editing, and imaging approaches. We find that the vertebrate-specific telomerase RNA adoption of an H/ACA RNA biogenesis pathway allows human telomerase RNA (hTR) and telomerase reverse transcriptase (TERT) to co-assemble as active enzyme at their low, endogenous cellular expression levels; however, the hTR H/ACA RNP biogenesis pathway becomes inessential for association to TERT if TERT expression level is increased. Furthermore, in contrast to popular models, the Cajal body localization of telomerase, and Cajal bodies per se, are not critical for telomere elongation; however, their roles become clear under particular conditions of telomere length or rate of elongation. To understand how disease-causing H/ACA-subunit mutations impose telomerase-specific defects, we solved the structure of human telomerase holoenzyme using cryoEM at a resolution of ~8 Å. This combined with previous biochemical studies reveals how the mutations impact interactions that compromise telomerase versus other H/ACA RNPs.

A role of the SMC5/6 complex in suppressing ageing and kidney disease

Oskar Fernández-Capetillo
Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

Structural Maintenance of Chromosome (SMC) complexes are well known as regulators of chromosome architecture. Besides the well-known roles of SMC1/3 in cohesion and SMC2/4 in condensation, a third SM5/6 complex plays an essential role in genome maintenance, although how it exerts this function remains rudimentarily understood. Using mouse models of NSMCE2, a SUMO ligase that is part of the SMC5/6 complex, we previously showed that the genome maintenance activity provided by this pathway suppresses ageing in mammals. We have now characterized the ageing phenotypes in detail and discovered a distinct phenotype in the kidneys of NSMCE2-deficient mice. NSMCE2 deficiency leads to Karyomegalic interstitial nephritis (KIN), which is a rare hereditary disease in which the kidneys accumulate giant nuclei and ultimately fail due to fibrosis. Of note, Chronic Kidney Disease (CKD) is a common age-associated disorder which represents a major health burden, and KIN is one of the few genetic conditions associated to CKD. The only gene previously linked to KIN was the endonuclease FAN1, mainly known for its role in interstrand cross-link (ICL) repair, and which has suggested that the exposure to ICLs might play a role in age-related kidney dysfunction. However, KIN is not present in other ICL-repair mutants and the role of *FAN1* in KIN seems to be independent to its role in ICL. Moreover, our work indicates that the link between KIN and NSMCE2 is related to its function in suppressing polyploidy upon topological stress. In summary, our data reveal the second genetic condition that can lead to KIN in mammals, and suggests a role for topological stress in the ontogeny of this disease.

Federica Schiavoni[1], Rouse J[2] and Oscar **Fernandez-Capetillo**[1,3]

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Molecular, Cellular and Organismal Hallmarks of Aging

Session#3
NUTRIENTS

Chairperson: ***Manuel Serrano***

Translational geroscience: Targeting mTOR to promote healthy longevity

Matt Kaeberlein
Department of Pathology, University of Washington,
Seattle, US

A primary goal of geroscience is to improve health, longevity, and quality of life for people through basic and translational research into the biology of aging. The FDA approved drug rapamycin is currently the most effective pharmacological intervention to increase lifespan and improve measures of healthspan in mice. Nevertheless, important questions exist regarding the translational potential of rapamycin and other mTOR inhibitors for human aging, and the optimal dose, duration, and mechanisms of action remain to be determined. Here I will report on our studies examining the effects of transient with rapamycin in middle-aged mice and companion dogs. Prior work by other groups have shown that short-term treatment with rapamycin is sufficient to rejuvenate age-related declines in cardiac and immune function in mice. We have found that similar rapamycin treatment regimens are sufficient to increase life expectancy by more than 50%, attenuate age-related periodontal disease, and prevent diet induced obesity in laboratory mice. In companion dogs, we have defined a dose of rapamycin that is well tolerated, and initial results are consistent with improvements in age-associated cardiac function similar to those observed in rapamycin-treated mice. These data suggest that rapamycin may be suitable for translational applications in both veterinary and human medicine to improve healthy longevity during normative aging.

Nutrient Signaling in Physiology and Disease

Alejo Efeyan
Metabolism and Cell Signaling Lab,
Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

Fluctuations in energy and nutrient levels trigger evolutionary-conserved cellular responses that control anabolism and catabolism accordingly. Chronic nutrient excess contributes to aging, while nutrient limitation can delay aging. Among the cellular cascades that impact on aging is the mechanistic target of rapamycin (mTOR) signaling pathway, which integrates cues from cellular nutrient levels and systemic hormones, such as insulin, to control cellular metabolism. Over-activation of the mTOR pathway drives the development of aging-related pathologies, and conversely, pharmacological inhibition of mTOR delays aging in yeast, flies, worms and mammals. While our knowledge of the molecular architecture of the cellular nutrient signaling cascade leading to mTOR activation has substantially increased over the last years, we still lack fundamental information on its impact on mammalian physiology. Hence, we have engineered a number of mouse strains with gain- and loss-of-function alleles encoding the Rag GTPases (a family integrated by RagA, B, C, and D), which link cellular nutrient sufficiency with mTOR activation. RagA resulted essential for development and for sustaining rapid proliferation of the intestinal epithelium of adult mice. Hepatocyte-specific deletion of RagA caused a profound inhibition of mTORC1, and improved glucose homeostasis. Mice expressing a constitutively-active RagA variant locked in GTP-bound state died shortly after birth with a profound metabolic crisis. When expressed in adult mice, the constitutively-active form of RagA drove several metabolic perturbations consistent with an insulin resistant state. We also engineered activating mutations in the RagC locus identified in human B cell lymphomas. These variants, when endogenously expressed in mice, outcompeted wt cells during B cell development, exacerbated B cell responses in a cell-autonomous manner, and drove autoimmunity and lymphomagenesis. In addition, we observed spontaneous development of cardiac insufficiency. In summary, physiological perturbations of the nutrient signaling cascade of mTORC1 uncovered aging-related pathologies connected to its aberrant activation.

SHORT TALK

Rapamycin-induced lifespan extension requires telomerase

Iole Ferrara-Romeo, **Paula Martínez**, Maria A. Blasco

Spanish National Cancer Research Centre (CNIO)

The mTOR pathway is known to modulate aging since inhibition of this pathway with rapamycin is known to increase lifespan in mice (Harrison et al., 2009). On the other hand, we have proposed telomere shortening as one of the primary hallmarks of aging (Lopez-Otin et al., 2013). Indeed, mice deficient for telomerase show a progressive shortening of telomeres and decreased median and maximum lifespan with increasing mouse generations (Blasco et al., 1997; Lee et al., 1998). Up to date, however, a connection between telomere biology and the mTOR pathway has not been found. To address this, we subjected both wild-type and second generation (G2) telomerase knockout mice (Terc-/-) to chronic rapamycin treatment from 3 months of age onwards. We found that rapamycin extended the median survival of wild-type mice by 23% and 43% in females and males, respectively. Strikingly, rapamycin did not increase the lifespan in telomerase deficient mice. In particular, while no differences in survival are observed between the rapamycin-treated and the control females, rapamycin-fed males show a decrease of 19% in median lifespan compared to Terc-/- G2 controls. These findings indicate that the effects of rapamycin in mTOR pathway inhibition are telomerasedependent, revealing an unprecedented connection between telomere biology and metabolism. We will describe the metabolic and telomere length homeostasis effects of TOR signalling inhibition in telomerase deficient mice.

Blasco MA et al., *Cell* 91, 25 (1997)
Harrison DE et al., *Nature* 460, 392 (2009)
Lee HW et al., *Nature* 392, 569 (1998)
López-Otín C et al., *Cell* 153, 1194 (2013)

SHORT TALK

Tolerance to NAD redox imbalance explains chronological lifespan in Saccharomyces cerevisiae

Alvar Alonso, Djordje Bajic and **Juan F Poyatos**

Logic of Genomic Systems Laboratory, CNB-CSIC, Madrid, Spain
Department of Ecology & Evolutionary Biology, Yale University, USA

Maintenance of energetic equilibrium appears fundamental to prevent the deleterious consequences of cellular aging. The basic molecular agents in which this equilibrium rests are redox coenzymes, this including NADH. Among its many roles, NADH acts as a global signal capable to alter metabolic and regulatory pathways, what associates changes in redox balance (NADH/NAD equilibrium) to significant readjustments of cell physiology. To what extent does the tolerance to NADH/NAD disequilibrium anticipate the aging phenotype?

In this talk, I will address this issue by combining genome-scale metabolic models and experimental measurements of chronological life span in Saccharomyces cerevisiae (1). With the use of the metabolic model, I will introduce a "tolerance profile" that quantifies how much variations of NADH/NAD equilibrium impact on cellular fitness (i.e., growth rate). Notably, examining the metabolic signatures underlying this profile links redox imbalances to the occurrence of seemingly inefficient metabolisms, as seen in the Warburg effect, overflow metabolism or the Crabtree effect. I will then discuss how the tolerance to disequilibrium changes as a function of particular genetic mutations, and how "mutant profiles" correlate with measurements of chronological lifespan (number of days that a cell survives after the end of its replicative life), one of the basic measures to study aging in yeasts and a model for the aging of post-mitotic tissues in mammals.

This talk is complemented with a poster presented by one my students (Alvar Alonso).

Aging (or not) in *C. elegans*

Cynthia Kenyon
Vice President, Aging Research
Calico Life Sciences LLC | South San Francisco,
University of California San Francisco,
San Francisco, US

This talk will discuss the regulation of cellular quality control and aging in C. elegans focusing on natural mechanisms that can reverse signs of aging in both the germ lineage and the soma.

Reversal of aging by small molecules that raise NAD

David Sinclair
Harvard Medical School, Boston, US

Abhirup Das[1], Michael Bonkowski[1], Alban Longchamp[2], George Huang[1,3], Jay Mitchell[2], Zolt Arani[3], Lenny Guarente[4], Lindsay Wu[1], and **David A. Sinclair[1]**

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[2]School of Public Health, Harvard Medical School, Boston, US
[3]U. Penn, Perelman School of Medicine, Philadelphia, US
[4]Biology, MIT, Cambridge, Massachusetts, US

Endothelial dysfunction and a progressive loss of capillary density are significant causes of mortality, contributing to cardiovascular diseases, Alzheimer's disease, osteoporosis, liver failure, sarcopenia, and frailty. Understanding why the body's vasculature ages and how to reverse it are therefore key to future gains in human health and lifespan. Precursors of NAD+ have attracted attention for their ability to boost mitochondrial function and reverse aspects of aging by activating the sirtuins (SIRT1-7), a family of NAD+-dependent protein deacylases that mimic the beneficial effects of dietary restriction (DR) and exercise. Similarly, hydrogen sulfide (H_2S) has recently been shown to extend the lifespan of lower organisms, also by mimicking the effects of DR. Here we show that deletion of the SIRT1 gene specifically in endothelial cells (EC) of mice mimics the loss of capillary density in muscle and exercise capacity that accompanies aging, while overexpression of SIRT1 has the opposite effect, maintaining endurance levels with progressing age. Treatment of elderly mice with the NAD+ precursor nicotinamide mononucleotide (NMN) with a dose that does not increase mitochondrial activity increases endurance by promoting a SIRT1-dependent increase in capillary density. During nutrient deprivation is mediated by the production of H_2S. Co-treatment of elderly mice with NMN and the H_2S donor sodium hydrosulfide (NaHS), dramatically improves muscle capillary density and exercise capacity of aged mice via endothelial SIRT1. Thus, the ability of SIRT1 to increase endurance may be largely due to an endothelial-specific role in H_2S-mediated angiogenesis rather than increasing mitochondrial function, a finding that has major implications for treating the multitude of age-related diseases that result from the age-dependent decline in vascular density.

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Molecular, Cellular and Organismal Hallmarks of Aging

Session#4
SENESCENCE

Chairperson: ***Salvador Aznar-Benitah***

Senescent cells: An emerging target for diseases of aging

Jan van Deursen
Mayo Clinic,
Rochester, US

Cellular senescence has emerged as a potentially important contributor to aging and age-related disease and as an attractive target for therapeutic exploitation. Direct evidence for the deleterious effects of senescence in aging originates from BubR1-progeroid mice in which inactivation of the *p16*^{Ink4a} senescence pathway or the elimination of *p16*^{Ink4a}-positive senescent cells dramatically attenuates aging. Using transgenic mouse models that selectively kill *p16*^{Ink4a} positive cells, we have investigated the role of senescence in health and life span of normal mice, as well as its role in common age-related diseases. The implications of these studies for the design and effectiveness of senotherapies to extend healthy lifespan will be discussed.

The double-edged sword of cellular senescence

Judith Campisi
Buck Institute for Research on Aging and Lawrence Berkeley National Laboratory, Novato, US

Cellular senescence limits the proliferation (growth) of stressed or damaged vertebrate cells, while engaging a multi-faceted senescence-associated secretory phenotype (SASP). The growth arrest is a potent and well-established tumor suppressive mechanism, whereas the SASP is more complex: it can have beneficial and deleterious consequences, depending on the biological context. Despite their essentially irreversible inability to divide, senescent cells remain metabolically active and can cause significant changes to tissue microenvironments, largely through the SASP. Additionally, senescent cells increase with age in most, if not all, tissues. The SASP is a highly plastic phenotype that differs in composition depending on the cell type, senescence inducer and time. Its highly variable composition includes many biologically active proteins, lipids, small metabolites and nucleic acids. Thus, senescent cells can have local and systemic effects that depend strongly on which cells, which stressors and at which times after senescence induction the tissue experiences their presence. Recent evidence from new transgenic mouse models in which it is possible to inducibly eliminate senescent cells has now established that senescent cells, again largely through the SASP, are a prime cause or major contributor to many of the prominent phenotypes and pathologies that are associated with aging. These phenotypes and diseases range from neurodegeneration to, ironically, late life cancer. This new evidence has also spawned the successful search for pharmacological agents, termed senolytic agents or senolytics, that can mimic the activity of the mouse transgenes. These agents will likely target specific classes of senescent cells, making it imperative that we more completely understand how senescent cells arise, especially in humans, and how their phenotypes differ and vary.

An integrated view of senescence and reprogramming

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

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

Profound nuclear and chromatin alterations in senescence and aging

Shelley L. Berger
Epigenetics Institute
Departments of Cell and Developmental Biology, Genetics, Biology
University of Pennsylvania
Philadelphia, US

We are investigating chromatin alterations during senescence and aging, to identify potential points of intervention to prevent negative consequences, such as loss of regenerative capacity and tissue damage. In previous surprising findings, we discovered that autophagy, a well-known cytoplasmic process, initiates in the nucleus and degrades portions of the nuclear lamina and associated chromatin (Ivanov et al., 2013, *JCB*; Dou et al., 2015, *Nature*). Here we show that the resulting cytoplasmic chromatin fragments (CCF) activate the innate cellular immunity cytosolic DNA sensing cGAS-STING pathway, triggering short-term beneficial inflammation to suppress activated oncogenes, but long-term tissue destructive inflammation (Dou et al., 2017, *Nature*). Further changes are gain of new enhancers and gain of new gene-internal transcriptional initiation sites, mediated by chromatin mechanisms, which together drive senescence and aging in mouse models.

SHORT TALK

Uncovering regulators of irreversible growth arrest during therapy induced senescence

Mary E. Klein[1], Caroline Gleason[1], Marta Kovatcheva[1,3], and **Andrew Koff[1,2]**

[1]The Louis V. Gerstner Graduate School of Biomedical Sciences, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY, US
[2]Program in Molecular Biology, Memorial Sloan Kettering Cancer Center, New York, NY, US
[3]Institute for Research in Biomedicine, Parc Cientific de Barcelona, Barcelona Spain

Senescence is the culmination of a process in which a number of phenotypes are acquired over time. The strictest definition of cellular senescence encompasses irreversible cell cycle arrest, elaboration of a growth factor and cytokine secretion program known as the SASP, and resistance to apoptosis. Although the community is teasing apart the regulation of the SASP and has begun to leverage knowledge about apoptotic resistance to therapeutic removal of senescent cells, insight into how cells become irreversibly arrested and how this is integrated with the other phenotypes is limited.

CDK4/6 inhibitor (CDK4i) therapy-induced senescence (TIS) provides a unique opportunity to gain insight into the relationship among different senescent phenotypes. CDK4 inhibition induces cancer cells to exit the cell cycle into quiescence, and once arrested, some cell lines will progress further into senescence. MDM2 degradation is one of the earliest molecular events we have identified during this transition, and stabilizing MDM2 can prevent treated cells from progressing into senescence. Thus, to acquire insight into how reversibly quiescent cells progress into senescence we generated cells in which we could enforce the expression of MDM2 under the control of a tetracycline-inducible promoter. Treatment with doxycycline and CDK4i induces cell cycle exit, but prevents progression into senescence. After removing doxycycline, the cells progress synchronously into senescence, acquiring different phenotypes over time. By enriching synchronized populations transitioning into senescence, we have been able to gain insights into how cells move from a reversible cell cycle exit into one hat is irreversible, and have begun to understand with unprecedented resolution how senescence programs are integrated.

In this meeting we will present this system and discuss how RNA-seq and GSEA revealed that a subset of the SASP is transcribed coincident with irreversible growth arrest and participate.

Molecular, Cellular and Organismal Hallmarks of Aging

Session#5

ENERGY AND MITOCHONDRIA

Chairperson: ***Thomas Rando***

Mitochondrial genetics, metabolism and ageing

José Antonio Enríquez
Spanish National Center for Cardiovascular Research,
Madrid, Spain

Cells and animals harbouring identical nuclear genomes but with different mtDNA haplotypes generate functionally different OXPHOS systems that shape their metabolism, fuel utilization and, in animals, determine heathy ageing[1,2]. We will discuss the molecular basis of this influence and at what extension is the interaction mtDNA/nDNA or just the mtDNA variant what matters. Mitochondrial DNA (mtDNA) is present in multiple copies in each nucleated cell of the body, all derived from the clonal expansions of those in the oocyte. Therefore, all mtDNAs of a given cell are essentially identical, a situation named homoplasmy. Heteroplasmy refers to the presence of more than one variant of mtDNA co-existing in the same cytoplasm. Heteroplasmy is actively combated in nature by several mechanisms, including degradation of the paternal mtDNA upon fertilization, and the existence of a genetic mtDNA bottleneck in oocyte development, but the evaluative pressure driving the rejection of heteroplasmy remain unknown. Heteroplasmy, however may be naturally generated by mutagenesis during mtDNA replication, but also can be caused by novel medical technologies. In the latest case the natural barriers preventing the confrontation of mtDNAs with significant differences in their natural history are broken. We will discuss the impact of heteroplasmy in OXPHOS performance and organismal metabolism and ageing.

[1]Centro Nacional de Investigaciones Cardiovasculares Carlos III; Madrid (SPAIN)
[2]CIBERFES C/ Melchor Fernández-Almagro 3, 28029 Madrid, (SPAIN)

[1]Latorre-Pellicer et al. Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. *Nature* **535**, 561–565 (2016).
[2]Moreno-Loshuertos et al. Differences in reactive oxygen species production explain the phenotypes associated with common mouse mitochondrial DNA variants. *Nat Genet*. **38**:1261-8. (2006).

Systems genetics approaches to explore mitochondria and aging

Johan Auwerx
Ecole Polytechnique Fédérale de Lausanne,
Swiss Federal Institute of Technology in Lausanne,
Lausanne, Switzerland

Our understanding of genetic mechanisms that define complex traits has been hindered by the difficulty of obtaining comprehensive omics datasets across a broad range of biological "layers". Complete data on the genome of individuals can be readily obtained, but the full complexity of the transcriptome, proteome, metabolome, and phenome have remained largely out of reach. This is, however, beginning to change, with the development of robust multi-layered omics strategies that are pioneered in model organisms. We here profiled the healthspan and lifespan in >80 cohorts of the BXD mouse genetic reference population. Large variability was observed across all omics layers; to understand how these differences stem from genetic variance, we exploited a multilayered set of molecular phenotypes—genomics, transcriptomics, proteomics, and metabolomics. With this multi-omics strategy, large networks of proteins could be analyzed and causal variants identified in proteins involved in determination of lifespan (e.g. *Mrps5, Jmjd3*), glucose homeostasis (e.g. *Dhtkd1*), hypertension (*Ubp1*) and mitochondrial supercomplex formation (*Cox7a2l*). These new candidates were then validated using cross-species genetic strategies in C.elegans, mouse, and human. Our large-scope multi-omics measurements in mouse populations combined with cross-species validation hence provided us with robust conserved and mechanistically defined pathways that underpin complex traits involved in metabolism and aging.

SHORT TALK

Mitochondrial failure in cells of the immune system regulates aging and age-associated diseases

Gabriela Desdin-Mico[1,2], Elisa Carrasco[2], Juan Francisco Aranda[2], Jorge Oller[2], Gonzalo Soto-Heredero[2], Eva Maria Blanco[1,2], Francesc Baixauli[3] and **María Mittelbrunn[1,2]**

[1]Instituto de Investigación del Hospital 12 de Octubre, Madrid, Spain
[2]Centro de Biología Molecular Severo Ochoa, CSIC-UAM, Madrid, Spain
[3]Max Planck Institute of immunobiology and epigenetics, Freiburg, Germany

Mitochondrial dysfunction is a hallmark of aging. Our main goal is to characterize how perturbations of mitochondrial function, specifically in cells of the immune system, affect organism homeostasis and lifespan. To this aim, we generated a mouse model whose mitochondrial function is compromised by genetic ablation of the mitochondrial transcription factor A (Tfam), specifically in CD4 immune cells (CD4Tfam-/-). A lack of Tfam induces a severe decrease in mtDNA content, and a failure to express the key components of the electron transport chain resulting in severe mitochondrial dysfunction and impaired oxidative phosphorylation, thus forcing a metabolic switch towards glycolysis. Glycolytic immune cells acquire proinflammatory features characterized by an increased secretion of IL6, TNF-α, and IFN-γ cytokines. CD4Tfam-/- mice display reduced body weight, kyphosis, altered glucose homeostasis, induction of lipolysis, sarcopenia, and cardiovascular alterations. On the whole, CD4Tfam-/- mice serve as an innovative genetic model for frailty and premature aging, and reflect the importance of tight immunometabolic control in preventing sterile inflammation and delaying aging and the onset of age-associated diseases.

This work is supported by the research grant CP 14/00219 from Fondo de Investigación Sanitaria del Instituto de Salud Carlos III, Fondo Europeo de Desarrollo Regional (FEDER), the European Research Council (ERC-2016-StG 715322-EndoMitTalk) and the Instituto de Salud Carlos III (FIS16/188).

Mitochondria and Aging

Marcia Haigis
Harvard Medical School,
Boston, US

Mitochondria are dynamic organelles that provide cells with energy and metabolites needed for survival and growth even during dramatic changes in diet, stress and development. The dysregulation of mitochondria is associated with aging and in numerous diseases, such as cancer, diabetes, and mitochondrial syndromes. Today I will discuss our lab's focus on identifying novel molecular mechanisms within mitochondria that allow cells to adapt to external stresses and changes in nutrient availability. Ultimately, we are interested in uncovering the physiological relevance for dysregulation of these pathways in the context of human diseases and aging.

Molecular, Cellular and Organismal Hallmarks of Aging

Session#6
EPIGENETICS

Chairperson: ***Kathleen Collins***

Epigenetics, aging and cancer: A complex and twisted relationship

Manel Esteller
The Bellvitge Biomedical Research Institute,
Barcelona, Spain

Aging is a complex process that results in compromised biological functions of the organism and increased susceptibility to disease, such as cancer, and death. Although the molecular basis of aging is currently being investigated in many experimental contexts, there is no consensus theory to fully explain the aging process. Epigenetic factors, including DNA methylation, histone modifications, and microRNA expression, may play central roles in controlling changes in gene expression and genomic instability during aging. The field of aging epigenetics is ripe with potential, but is still in its infancy, as new layers of complexity are emerging in the epigenetic network. As an example, we are only beginning to understand the relevance of non-coding genome to organism aging or the existence of an epigenetic memory with transgenerational inheritance. Addressing these topics will be fundamental for exploiting epigenetics phenomena as markers of aging-related diseases or as therapeutic targets.

SHORT TALK

TERRA-dependent recruitment of polycomb to telomeres is essential for the assembly of histone trymethylation marks at telomeric heterochromatin

Juan Jose Montero1, Isabel López-Silanes[1], Diego Megías[2], Mario F. Fraga[3], Maria A. Blasco[1]

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Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Spain

Telomeric RNAs or TERRAs are long non-coding, nuclear RNAs generated from the telomeres, which have been attributed to a plethora of telomeric functions, as well as extra-telomeric functions. Lack of TERRA knock-out models, however, has hampered understanding of a direct role of TERRAs in those functions, as well as on their role in vivo. We recently identified chromosome 20q as one of the main origins of human TERRAs, allowing us to generate the first 20q-TERRA knock-out models and to demonstrate that TERRAs are essential for telomere protection and telomere length maintenance. TERRAs can also bind in cis and trans to chromosome ends and are thought to contribute to the establishment of telomeric chromatin. Here, we used human ALT cells knock-out for 20q-TERRA to address a direct role of TERRAs in telomeric heterochromatin formation. We found that 20q-TERRAs are essential for the establishment of histone H3K9me3 and H4K20me3 tri-methylation heterochromatin marks at telomeres but dispensable for subtelomeric DNA hypermethylation. We also found the facultative heterochromatin mark H3K27me3 at telomeres, and show that TERRAs are essential for its establishment at telomeric chromatin. At the mechanistic level, we find that TERRAs bind to Polycomb Repressive Complex 2 (PRC2) components Ezh2 and Suz12, responsible for catalysing H3K27 tri-methylation, and that localization of these components to telomeres, is TERRA dependent. We further demonstrate that PRC2-dependent H3K27me3 at telomeres is required for the establishment of H3K9me3, H4K20me3 and HP1 binding at telomeres. Together, these findings demonstrate an important role for TERRAs in telomeric heterochromatin assembly.

Epigenetic clock and telomere maintenance

Steve Horvath
Prof. Human Genetics and Biostatistics,
University of California,
Los Angeles, US

DNA methylation age is an accurate biomarker of chronological age and predicts lifespan. Human cohort studies have shown that epigenetic age acceleration has at best a very weak correlation with leukocyte telomere length (LTL). After adjusting for age and cell type composition, LTL does not appear to be correlated with DNAm age. However, genome-wide association studies of intrinsic epigenetic aging rates in blood demonstrate that variants associated with longer LTL in the telomerase reverse transcriptase gene (*TERT*) paradoxically confer higher intrinsic epigenetic age acceleration. hTERT immortalized human cells continue to age according to the epigenetic clock and experimental hTERT-expression in primary human fibroblasts engenders a linear increase in DNA methylation age with cell population doubling number. Together, these findings indicate a critical role for hTERT in regulating the epigenetic clock, in addition to its established role of compensating for cell replication-dependent telomere shortening.

Targeting the antisense RNA Zeb2-NAT facilitates reprogramming of aged fibroblasts

SHORT TALK

Bruno Bernardes de Jesus and **Maria Carmo-Fonseca**

Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal

Ageing imposes a barrier to somatic cell reprogramming through poorly understood mechanisms. We studied the age-associated decline in reprogramming efficiency of fibroblasts derived from transgenic mice carrying doxycycline-inducible Oct4, Sox2, Klf4, and c-Myc. We found that fibroblasts from old mice express higher levels of Zeb2, a transcription factor that activates epithelial-tomesenchymal transition. Synthesis of Zeb2 protein is controlled by a natural antisense transcript named Zeb2-NAT. Transfection of adult fibroblasts with specific LNA Gapmers induced a robust downregulation of Zeb2-NAT transcripts and Zeb2 protein, enhancing the reprogramming of old fibroblasts into pluripotent cells. We further observed that Zeb2-NAT expression is precociously activated by differentiation stimuli in embryonic stem (ES) cells. Knocking-down Zeb2-NAT maintained ES cells challenged with commitment signals in the ground state of pluripotency. Thus, we have identified a novel RNA target for rejuvenation strategies.

Understanding and modeling aging

Anne Brunet
Stanford University,
US

Age is the greatest risk factor for most diseases, including neurodegenerative diseases, cardiovascular diseases, cancer, metabolic disorders, diabetes, and autoimmune diseases. However, our understanding of aging is still rudimentary because aging is an extraordinarily complex process that defies many conventional rules in biology. My lab aims to discover new, fundamental principles of aging regulation that can ultimately be translated to humans. We have broken new ground by pioneering the naturally short-lived African killifish as a new model to study aging and diseases in the context of aging in vertebrates. This new model has allowed us to generate a high throughput platform to not only model diseases by also screen for the impact of genetic pathways and chemical compounds on disease. In addition to developing this fish, my lab is also using *C. elegans* and mice, as well as cells from mice and humans, to identify genetic and epigenetic mechanisms involved in the regulation of lifespan and understand their mode of action. This approach has already generated new insights on the epigenetic regulation of aging. Our work has the promise to transform our understanding of why aging is at the heart of so many human diseases.

NOTES

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SPEAKERS' BIOGRAPHIES

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Johan Auwerx

Ecole Polytechnique Fédérale de Lausanne - Swiss Federal Institute of Technology in Lausanne, Switzerland

Johan Auwerx is Professor at the École Polytechnique Fédérale in Lausanne, Switzerland. He is using systems physiology and genetics to understand the link between transcription, mitochondria, metabolism, and aging, and his research has spurred the development of new drugs, such as resveratrol, nicotinamide riboside and PARP inhibitors, for the treatment of metabolic diseases. Johan Auwerx was elected as a member of EMBO in 2003 and has received many international scientific prizes.

Salvador Aznar Benitah

ICREA Research Professor
Foundation Botin Researcher
Stem Cells and Cancer Lab, Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain

Dr. Salvador Aznar Benitah obtained his Honours BSc in Biochemistry and Molecular Biology at *McGill University* in 1998. In 2007, after a postdoctoral work at the London Research Institute (Cancer Research UK), he established is lab at the *Center for Genomic Regulation as a Junior ICREA researcher*. In 2014 Salvador was promoted to *ICREA Research Professor*, and moved to the Institute for Biomedical Research in Barcelona as a senior researcher. His lab aims at understanding the mechanisms underlying adult stem cell function during homeostasis, ageing and cancer, with special interests in epigenetics, spatiotemporal regulation, and diet.

Shelley Berger

The Perelman School of Medicine at the University of Pennsylvania, US

Shelley Berger, Ph.D., is the Daniel S. Och University Professor at University of Pennsylvania, and joined the Penn faculty in 2009. She is a member of the Departments of Cell & Developmental Biology, Genetics, and Biology. She serves as founding and current director of the Epigenetics Institute in Penn Perelman School of Medicine. Dr. Berger earned her PhD from University of Michigan and was a post-doctoral fellow at Massachusetts Institute of Technology. She previously held the Hilary Koprowski Professorship at the Wistar Institute in Philadelphia. Dr. Berger's research focuses on the role of histone and factor post-translations modifications in chromatin regulation and of the tumor suppressor p53; her lab investigates the role of histone modifications in cellular aging and senescence, in cancer, in learning and memory, and underlying organismal level behavior. Dr. Berger received the Ellison Foundation Senior Scholar Award in Aging and an HHMI Collaborative Research Award. She is a fellow of the American Association for Advancement of Science, a member of the American Academy of Arts and Sciences, and a member of the National Academy of Medicine.

Maria A. Blasco
Director of the Centro Nacional de Investigaciones Oncológicas
Head of the Telomeres and Telomerase Group - CNIO
Madrid, Spain

Maria A. Blasco obtained her PhD in 1993 at the *Centro de Biología Molecular "Severo Ochoa"* under the supervision of M. Salas. That same year, Blasco joined the Cold Spring Harbor Laboratory in New York (USA) as a Postdoctoral Fellow under the leadership of C. W. Greider. As a postdoc she isolated one of the telomerase essential genes and generated the first telomerase deficient mouse model, which served to demonstrate the importance of telomerase in telomere maintenance, chromosomal instability and disease. In 1997, she returned to Spain to start her own research Group at the *Centro Nacional de Biotecnología* in Madrid. She joined the *Spanish National Cancer Research Center* (CNIO) in 2003 as Director of the Molecular Oncology Programme and Leader of the Telomeres and Telomerase Group. In 2005, she was also appointed Vice-Director of Basic Research at CNIO. Since June 2011, she is the CNIO Director.

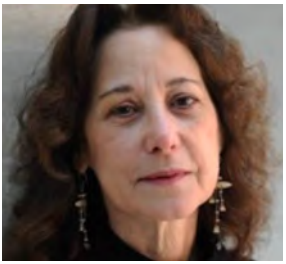
For more than 20 years, Blasco´s work has focused in demonstrating the importance of telomeres and telomerase in cancer, as well as in age-related diseases. Blasco has published more than 250 papers in international journals and has an h-index of 81. Her achievements have been recognized by the following international and national awards: Josef Steiner Cancer Research Award, Swiss Bridge Award for Research in Cancer, Körber European Science Award, the EMBO Gold Medal, the "Rey Jaime I" Award in Basic Research, the Fundación Lilly Preclinical Research Award, and the "Santiago Ramón y Cajal" National Award in Biology. Blasco holds two Doctorate Honoris Causa from the *Universidad Carlos III* of Madrid and from *Universidad de Alicante*.

Anne Brunet

Michele and Timothy Barakett Professor of Genetics, Stanford University School of Medicine
Co-director of the Paul F. Glenn Laboratories for the Biology of Aging at Stanford University
Stanford University, US

Dr. Brunet obtained her B.Sc. from the Ecole Normale Supérieure in Paris, France and her Ph.D. from the University of Nice, France. She did her postdoctoral research training in Dr. Michael Greenberg's lab at Harvard Medical School. Dr. Brunet is interested in the molecular mechanisms of aging and longevity, with a particular emphasis on the nervous system. Her lab studies the molecular mechanism of action of known longevity genes. She is particularly interested in the role of longevity genes in neural stem cells during aging. Another goal of the Brunet lab is to discover novel genes and processes regulating longevity using two model systems, the invertebrate C. elegans and an extremely short-lived vertebrate, the African killifish *N. furzeri*. Dr. Brunet has received several grants from the National Institute on Aging. She has published over 80 peer-reviewed papers, reviews, and book chapters. She has received a number of awards, including the Pfizer/AFAR Innovation in Aging Research Award, a Junior Investigator Award from the California Institute for Regenerative Medicine, a Glenn Foundation for Medical Research Award, an Ellison Medical Foundation Senior Scholar Award, and the Vincent Cristofalo "Rising Star" Award in Aging Research. She was awarded a Pioneer Award from the NIH Director's fund, an award that supports scientists of exceptional creativity, who propose pioneering and transforming approaches to major challenges in biomedical research.

Website: https://med.stanford.edu/profiles/anne-brunet



Judith Campisi

Buck Institute for Research on Aging,
Novato, US

Judith Campisi trained at the State University of New York and Harvard Medical School. She joined the Boston University Medical School faculty before moving to the Lawrence Berkeley National Laboratory and the Buck Institute for Research on Aging. At both institutions, she established a broad program to understand the relationship between aging and disease, with an emphasis on cancer. Her laboratory made several pioneering discoveries in these areas, and her research continues to challenge and alter existing paradigms. Campisi received several awards for her research, and serves on numerous editorial and scientific advisory boards.

Kathleen Collins

Professor, Molecular and Cell Biology,
University of California at Berkeley, US

Professor Collins received her PhD from Massachusetts Institute of Technology, US. After postdoctoral studies with Dr. Carol Greider, then at Cold Spring Harbor Laboratory, she began her faculty position at the University of California, Berkeley in 1995. Her laboratory studies non-coding RNAs and their RNPs, from RNA processing and RNP biogenesis to shuttling between nuclear compartments, with the goal of understand cellular specificities at a biochemical level. Her lab has made pioneering discoveries in the telomerase field and others including endogenous RNA silencing, tRNA cleavage and fragment function, and RNA sequencing.

Alejo Efeyan
Group Leader, Metabolism and Cell Signaling Lab,
Spanish National Cancer Research Centre, CNIO,
Madrid, Spain

After obtaining his BSc degree in Buenos Aires, Alejo Efeyan received his PhD from the Autonomous University of Madrid, for his studies on the tumor suppressive functions of p53, directed by Manuel Serrano. He then moved to the Whitehead Institute at MIT for postdoctoral training in the David M Sabatini Lab, studying the biology of mTOR and nutrient signaling. Alejo Efeyan settled his laboratory at the CNIO in 2016, where his team studies the links between nutrient signaling, physiology and disease by combining mouse genetics and biochemistry.

Jose Antonio Enriquez
Spanish National Cancer Research Centre, CNIO,
Madrid, Spain

José Antonio Enríquez graduated in Biochemistry and Molecular Biology at the *Universidad Autónoma de Madrid* and obtained his PhD from the *Universidad de Zaragoza* in 1992.

From 1993 to 1997 he worked with Giuseppe Attardi at the California Institute of Technology, where he studied the pathogenic action of mutant mitochondrial tRNAs. His work in this period contributed to define the molecular mechanism underlying this phenomenon, and helped to establish the general methodologies for studying mitochondrial tRNAs. José Antonio established his own laboratory on his return to the *Universidad de Zaragoza*, where he became a Full Professor in 2007. His group has made important contributions to the understanding of mitochondrial biogenesis and bioenergetics, the role of mitochondria in apoptosis, the structure, formation and regulation of the respiratory chain, and the pathological consequences of altered mitochondrial function in human disease. He recently established a possible explanation for the phenotypes associated with common mouse mtDNA variants affecting ROS production. He joined the CNIC in 2009, where his work focuses on the molecular processes underlying the involvement of mitochondrial dysfunction in cardiovascular disease and ischemic processes.

Dr. Enríquez career related to mitochondrial physiopathology has developed the publication of a total of 121 publications. He has organized the conference EUROMIT VIII (Zaragoza 2011). He is part of the editorial board of the Frontiers in Physlology and Redox Biology journals.

Manel Esteller

The Bellvitge Biomedical Research Institute,
Barcelona, Spain

Manel Esteller graduated in Medicine from the Universitat de Barcelona, where he obtained his Ph.D. in human molecular genetics. Dr. Esteller continued his research at the Johns Hopkins University where he studied DNA methylation and cancer. His work was decisive in identifying promoter hypermethylation of tumour suppressor genes. From 2001 to 2008 he directed the CNIO Cancer Epigenetics Laboratory. Dr Esteller is the Director of the Cancer Epigenetics and Biology Program (PEBC) in Barcelona. His research elucidates the epigenome maps of normal and transformed cells. Author of more than 485 original peer-reviewed manuscripts, he is the recipient of prestigious awards.

Oskar Fernández Capetillo
ViceDirector
Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

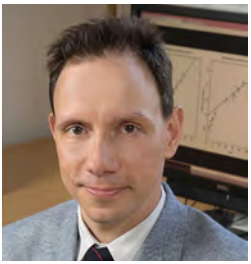
Oscar Fernandez-Capetillo did his PhD in the University of The Basque Country working with mouse models of autoimmunity with Dr. Ana Zubiaga. For his postdoctoral stay he joined the group of André Nussenzweig, where he started to work on DNA repair and the role of histone H2AX. In 2005, he joined CNIO to lead the Genomic Instability Group where he has been ever since. His main focus has been on exploring the role of replicative stress in cancer and ageing, for which the group has combined cell biology, mouse models and drug development projects. Since 2015 Oscar is also the Vicedirector of CNIO, and professor at the Karolinska Institute in Sweden.

Marcia C. Haigis
Harvard Medical School,
Boston, US

Marcia C. Haigis, Ph.D. obtained her Ph.D. in Biochemistry from the University of Wisconsin performed postdoctoral studies at MIT studying mitochondrial sirtuins. In 2006, Dr. Haigis joined the faculty of Harvard Medical School, where she is currently an Associate Professor in the Department of Cell Biology. The Haigis lab focuses on: 1) identifying novel molecular mechanisms that regulate mitochondria in response to stress, and 2) understanding how these mechanisms contribute to aging and age-related diseases.

Jan Hoeijmakers
Erasmus MC Rotterdam,
Rotterdam, The Netherlands

Jan Hoeijmakers (Erasmus University Rotterdam) cloned the first human DNA repair gene, *ERCC1*, followed by many more allowing elucidation of the mechanism of nucleotide excision repair. He co-discoved a surprising link with transcription, clarified the basis of human repair disorders Cockayne syndrome and trichothiodystrophy, and identified a new class of `basal transcription disorders'. His team generated numerous mouse repair mutants, disclosed an initially highly controversial connection between DNA damage and (accelerated) aging and a cancer-aging trade-off. He identified DNA damage-driven transcriptional stress as major cause of aging explaining the basis of proteinopathies and discovered a surprising effect of nutrition, with implications for repair syndromes, dementia's, chemotherapy and surgical ischemia reperfusion injury.



Steve Horvath
Professor, Human Genetics, Biostatistics
Department of Human Genetics
Gonda Research Center
David Geffen School of Medicine,
Los Angeles, US

Professor, Human Genetics and Biostatistics David Geffen School of Medicine, University of California, Los Angeles Dr Horvath's research lies at the intersection of aging research, epidemiology, chronic diseases, epigenetics, genetics, and systems biology. He works on all aspects of biomarker development with a particular focus on genomic biomarkers of aging. He developed a highly accurate multi-tissue biomarker of aging known as the epigenetic clock. Salient features of the epigenetic clock include its high accuracy and its applicability to a broad spectrum of tissues and cell types.

Dr Horvath developed systems biologic approaches such as weighted gene co-expression network analysis which lend themselves for integrating gene expression-, DNA methylation-, microRNA, genetic marker-, and complex phenotype data. These methods have been used for a broad spectrum of age related diseases including neurodegenerative diseases, cancer, cardiovascular disease.

Dr. Horvath received a Vordiplom in Mathematics and Physics (1989) from the Technical University of Berlin, a Ph.D. in Mathematics from the University of North Carolina, Chapel Hill in 1995 and a Doctorate of Science in Biostatistics from the Harvard School of Public Health in 2000.

Juan Carlos Izpisua Belmonte

Professor. Gene Expression Laboratories
Salk Institute for Biological Studies
La Jolla, California, US

M.Sc., University of Valencia, Spain 1985. Ph.D. University of Bologna, Italy and University of Valencia, Spain 1987. Bewteen 1987-1993 conducted postdoctoral studies at the EMBL, Heidelberg, and University of California Los Angeles. He is a professor at the Salk Institute for Biological Studies in La Jolla, California, since 1993. His scientific interests include developmental biology, organ regeneration and aging. His work is helping to discover new molecules and specific gene/cell treatments to prevent and cure diseases affecting mankind both in the adult and embryonic stages.

Matt Kaeberlein
Department of Pathology
University of Washington,
Washington, US

Matt Kaeberlein is a Professor of Pathology, Adjunct Professor of Genome Sciences, and Adjunct Professor of Oral Health Sciences at the University of Washington. He has published 170+ scientific papers and is a Fellow of the American Aging Association, the Gerontological Society of America, and the American Association for the Advancement of Science. He serves on the Board of Directors for both FASEB and the American Aging Association. He is the co-Director of the University of Washington Nathan Shock Center of Excellence in the Basic Biology of Aging, founding Director of the Healthy Aging and Longevity Research Institute at the University of Washington, and co-Director of the Dog Aging Project.

Cynthia Kenyon
University of California at San Francisco / Calico Laboratories,
San Francisco, US

Cynthia Kenyon's discovery in 1993 that a single-gene mutation could double the lifespan of healthy, fertile *C. elegans* roundworms sparked an intensive study of the molecular biology of aging. Her discoveries led to the realization that a universal endocrine network influences the rate of aging in many organisms, likely including humans, and that the same genes that affect basic aging also affect age-related disease.

Dr. Kenyon graduated valedictorian in chemistry from the University of Georgia in 1976. She received her PhD from MIT in 1981 and was a postdoctoral fellow with Nobel Laureate Sydney Brenner in Cambridge, England. In 1986, she joined University of California, San Francisco, where she was the Herbert Boyer Distinguished Professor and an American Cancer Society Professor. Dr. Kenyon is a member of the US National Academy of Sciences, the American Academy of Arts and Sciences and the National Academy of Medicine. She is a past president of the Genetics Society of America, and she has received many scientific awards. In 2014 Dr. Kenyon became a UCSF Emeritus Professor, and Vice President of Aging Research at Calico Life Sciences, a new basic- and applied-sciences company initiated by Google that aims to understand the biology and regulation of aging with the goal of maintaining healthy youthfulness and increasing the quality of life as we age.

Thomas A. Rando
Stanford University,
Stanford, California, US

Thomas A. Rando, MD, PhD is Professor of Neurology and Neurological Sciences and Director of the Glenn Center for the Biology of Aging at Stanford University. Research in the Rando laboratory concerns the basic biology of stem cells how their function is altered in degenerative diseases and during aging. Groundbreaking work from his laboratory using heterochronic parabiosis showed that the age-related changes in stem cell function can be reversed by a youthful environmental. Dr. Rando has received many awards including an NIH Director's Pioneer Award, and he is an elected member of the National Academy of Medicine.

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

Manuel Serrano obtained his PhD in 1991, from the Universidad Autónoma de Madrid. From 1991 to 1996, Serrano worked in the team of David Beach in Cold Spring Harbor Laboratory, NY. During this period, Serrano made his most important discovery with the identification and characterization of the gene p16, one of the most important genes for anti-cancer protection. Serrano returned to Spain in 1997 to lead a research group, first at the National Center of Biotechnology (CNB), and then, from 2003 to 2017, at the Spanish National Cancer Research Center (CNIO), both in Madrid. In 2017, Serrano moved to the Institute for Research in Biomedicine (IRB), in Barcelona.

Manuel Serrano is internationally recognized in the field of tumor suppression. In addition to the discovery of p16, one of his main discoveries has been the identification of cellular senescence as a main anti-oncogenic response. Recently, his laboratory has also shown that cellular senescence participates in several tissue remodeling processes during embryo development. The Serrano team was pioneer in the generation of genetically-modifed mice resistant to cancer and found a link between tumor suppressor genes and aging.

In recent years, the research interests of Manuel Serrano have extended to metabolism and cellular reprogramming in relation to aging. The Serrano laboratory was first in demonstrating that cellular reprogramming into pluripotency is possible within an organism, and this discover was considered Advance of the Year 2013 by *Nature Medicine*. More recently, Serrano has reported in *Science* that *in vivo* reprogramming is enhanced by the coexistence of tissue injury thanks to the production of the interleukin IL-6.

The focus of his laboratory is now to apply their knowledge on senescence and reprogramming to degenerative diseases such as lung, kidney and heart fibrosis.

David A. Sinclair
Harvard Medical School,
Boston, Massachusetts, US

David A. Sinclair, Ph.D. is a tenured Professor of Genetics at Harvard Medical School, co-Director of the Paul F. Glenn Center for the Biology of Aging at Harvard Medical School, a Professor at University of New South Wales, Sydney, and Honorary Professor at the University of Sydney. He received his Ph.D. from the University of New South Wales (1995), did his postdoctoral work at M.I.T. in Boston (1995-1999) with Lenny Guarente. He has published 150 papers, is a co-inventor on 40 patents, co-founded ten biotechnology companies in the areas of aging, vaccines, diabetes/cancer, biodefense, forensics and bioinformatics.

Jan M. van Deursen

Professor of Biochemistry, Molecular Biology and Pediatrics, Mayo Clinic, Rochester, US

Jan van Deursen, received his Ph.D. degree in Cell Biology at the University of Nijmegen, Netherlands in 1993. He joined the staff of Mayo Clinic in 1999, where he directs a curiosity-driven research program focused on the basic biology of cancer and aging. He also directs of the transgenic and gene knockout core facility, the senescence program of the Robert and Arlene Kogod Center on Aging, the cell biology program of the comprehensive cancer center, the cancer and cell aging platform of the center for biomedical discovery, and the Paul Glenn laboratories of senescence. He is also chair of the Department of Biochemistry and Molecular Biology. Dr. van Deursen employs integrated genetic, genomic, cell biological and biochemical approaches to address fundamental questions regarding the biology of cancer and aging. The lab's primary focus is on long-standing gaps in basic knowledge that have the potential to yield unexpected findings of high impact.

NOTES

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

Madrid 7 — 9 May 2018

cnio "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2018

Molecular, Cellular and Organismal Hallmarks of Aging

POSTER SESSION

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

1

Genome-scale metabolic models reveal unconventional lifespan extending capabilities of conventional nutrients

Alvar Alonso, Djordje Bajic and Juan F Poyatos

Logic of Genomic Systems Lab (CNB-CSIC), Madrid, Spain.
Department of Ecology & Evolutionary Biology, Yale University, US

As an addition to our work on the tolerance of yeast mutants to NAD/NADH imbalances and its relationship to chronological lifespan, we present a protocol that help recognize how specific nutrient conditions (cofactors, vitamins, small carbon sources and other metabolites) can increase the cell's lifespan by promoting its tolerance to pathological redox imbalances of the NAD/NADH pair.

We measured the nutrient effect on tolerance to NAD/NADH deviations by using the same scores that yielded the highest correlations between genetic mutations and chronological lifespan discussed in the main talk[1].

- Established findings. Nutrients that are known to increase lifespan, nutrients that one would expect to help reduce NAD/NADH deviations, and nutrients that share those two properties. These can be considered to support the reliability of our protocol.
- New discoveries. Nutrients which lifespan/extending capabilities haven't been researched, and nutrients that cannot be assigned redox-balance-protecting properties intuitively. These are a genuine product of our protocol, in that it predicts them to be therapeutic elements as powerful as those discussed in the established findings, but they are yet unknown to have such properties. Other elements of interest to be included: comments on genes, enzymes and carriers.

We will discuss two main results types of results:

[1]This poster is complemented with a talk by Juan F Poyatos.

Characterization of the role of Spry genes in cellular senescence

Carlos Anerillas Aljama, Marta Vaquero, Sara Cuesta-Sancho, Joan Ribera, Joaquim Egea and Mario Encinas

Universitat de Lleida/ IRB Lleida,
Lleida, Spain

Classically, members of Sprouty family of genes (Spry1-4) have been assumed to be inhibitors of signaling initiated by receptor tyrosine kinases. Previous data from our group demonstrate that Spry1 promotes cellular senescence in the thyroid gland, in an ERK-independent manner. To better understand the mechanisms elicited by Spry in senescence, we decided to trigger this cellular response with several known inductors in IMR90 cells. We found that Spry1 and Spry2 are upregulated in cells facing different stressors, such as DNA damage, oxidative stress or aberrant Ras activation. Conversely, ectopic expression of different Spry members implements cellular senescence in IMR90 cells while the removal of some relevant residues from Spry1 prevents its ability to induce this response. Surprisingly, senescent program executed by Spry in IMR90 cells lacks the production of inflammatory SASP. From all of the point mutants explored, we decided to gain insight into the role of Y53A in senescence as it has been described as a dominant negative mutation in Spry1. Interestingly, by interfering Spry function expressing a Y53A allele, some of the cellular senescence markers, including inflammatory SASP elements, are downregulated after induction of senescence with etoposide. To further describe the role of this mutation, we took advantage of knockin mice bearing Spry1 Y53A mutation generated in our group. When placed in a 3T3 scheme, skin fibroblasts from knockin mice, but not from Spry1 knockout or wild type littermates, escape cellular senescence. Consistent with the importance of Spry genes for senescent response in skin cells, the rate of cutaneous wound closure is robustly delayed in Spry1 Y53A mutant mice when compared to wild type littermates. Thus, these results point to a role of Spry genes as broad mediators of senescence and unveil them as novel players of this cellular process.

3

New therapies against metabolic syndrome: searching for natural PI3K inhibitors

Marta I. Barradas Solas, Luís Filipe Costa Machado, Pablo J. Fernández-Marcos

IMDEA Food,
Madrid, Spain

Metabolic syndrome (MS) is a group of pathologies caused by a prolonged imbalance between energy intake and expenditure, and it is strongly related to the degenerative process of aging. The main MS-associated pathologies are obesity, diabetes, cardiovascular diseases and cancer, which makes MS one of the main health challenges of developed countries.

It has been shown that moderate inhibition of PI3K signaling reverses some of the negative conditions associated with MS in mice and monkeys. This makes of PI3K inhibitors good candidates as therapeutic agents against MS in humans.

Our goal is to find new natural PI3K inhibitors, ideally food-derived, and develop them with the final aim of performing nutritional trials against MS in humans. To do that we tested more than 1,000 pure compounds and extracts obtained from natural sources. We checked their ability to inhibit PI3K signaling making use of the cell line U2OS-EGFP-FOXO3, a system that has been proved as a powerful tool to isolate inhibitors of proteins upstream of FOXO, such as PI3K. Phosphorylation of FOXO3 proteins by AKT results in the nuclear exclusion of FOXO3, while PI3K inhibition induces FOXO3 dephosphorylation and its nuclear accumulation. Based on this regulatory mechanism of FOXO proteins we have developped an imagebased high-throughput screening platform to identify compounds that regulate FOXO3 subcellular localization, among which many will be PI3K inhibitors (PI3Ki). We have validated a first set of hits, and selected the bona fide PI3Ki. We are currently characterizing the mode of action of the most promising products using cells in culture, and their safety and efficacy in the treatment of MS using mouse models. As a proof of principle, we show the data we are obtaining with a potent PI3Ki already in use for an unrelated pathology in humans, the IMDEA PI3Ki, with strong and safe effects against MS in mouse models.

Centenarian descendants display specific, centenarian-type, microRNA expression profile

Consuelo Borras[1], Marta Ingles[2], Eva Serna[1], Jose Vina[1]

[1]Department of Physiology, Faculty of Medicine, University of Valencia. CIBERFES, Valencia, Spain
[2]Department of Physiotherapy, Faculty of Medicine, University of Valencia. CIBERFES, Valencia, Spain

Centenarians exhibit extreme longevity showing a compression of morbidity. We showed previously that microRNA expression profiles and plasma protein carbonylation in centenarians and young people are similar, whereas they are very different from that found in old individuals. This suggests that centenarians have a better control of homeostasis and are protected against oxidative damage. In this study, we aimed to determine if such characteristic microRNA expression profile and lower protein oxidation status in centenarians may be inherited by their offspring. For this purpose, we collected plasma and peripheral blood mononuclear cells from 90 septuagenarians, 68 centenarians and 46 centenarian offspring. MicroRNA expression profile was performed using the Genechip miRNA 2.0 Array and protein carbonylation by "OxyBlot TM Protein Oxidation Detection kit". Our results showed that microRNA expression pattern in centenarians is similar to centenarian offspring and different to septuagenarians. We observed a significant decrease in plasma protein carbonylation levels in centenarians and centenarian offspring when compared to septuagenarians. In conclusion, centenarian offspring resemble centenarian characteristics, and could be a model of healthy aging in humans.

5

Sirt1 protects from KRas-driven lung carcinogenesis

Luis Filipe Costa-Machado[3,*], Daniel Herranz[1,2,*], Roberto Martín-Hernández[4], Miguel Ángel Sanchez[5], Katharina Hess[1], Marta Barradas[3], Cian Lynch[1], Daniel de la Nava[3], Lola Martinez[5], Marta Sanchez-Carbayo[6], Manuel Serrano[1,*], Pablo J. Fernandez-Marcos[1,3,*]

[1]Tumor Suppression Group (CNIO), Madrid, Spain
[2]Institute for Cancer Genetics, Columbia University, New York, US
[3]Bioactive Products and Metabolic Syndrome group - BIOPROMET, Madrid Institute for Advanced Studies, IMDEA in Food, CEI UAM+CSIC, Madrid, Spain
[4]GENYAL Nutrigenomic Platform Madrid Institute for Advanced Studies - IMDEA in Food, CEI UAM+CSIC, Madrid, Spain
[5]Flow Cytometry Unit (CNIO), Madrid, Spain
[6]Translational Oncology Lab, Lucio Lascaray Research Center, University of the Basque Country, Vitoria-Gasteiz, Spain

The NAD+-dependent protein deacetylase SIRT1 can be oncogenic or tumor suppressive depending on the tissue. Little is known about the role of SIRT1 in nonsmall cell lung carcinoma (NSCLC), one of the deadliest cancers in humans, frequently associated to mutations in KRAS. We investigated the effect of SIRT1 on KRAS-driven lung carcinogenesis. We observed that SIRT1 protein levels are negatively regulated by oncogenic KRAS in a MEK and PI3K-dependent manner in mouse embryo fibroblasts (MEFs) and in several human lung cancer cell lines. We then observed that Sirt1 transgenic (Sirt1-Tg) expression in mice delays the appearance of oncogenic KRas-driven lung adenocarcinomas, reducing the number and size of carcinomas and lengthening survival. We extended these findings to human NSCLCs, where low levels of SIRT1 were associated to worse prognostic. To understand the mechanism of this protection, we isolated mouse Sirt1-Tg pneumocytes shortly after oncogenic KRas activation, and identified several main pro-tumorogenic pathways downregulated by SIRT1. Our work proves a tumor suppressive role of SIRT1 in the development of KRas-driven lung adenocarcinomas in mice and humans.

Mitochondrial and protease dysfunction in progeroid Cockayne syndrome cells and during age-associated processes

Clément Crochemore, Laurent Chatre, and Miria Ricchetti

Stem Cells & Development, CNRS UMR3738 Team Stability of Nuclear & Mitochondrial DNA, Institut Pasteur, Paris, France

Ageing is dramatically accelerated in some rare genetic disorders like the Cockayne syndrome. Dissecting the molecular defect(s) in these diseases is critical to develop treatments, and elucidate dysfunctions that may lead to normal ageing.

Cockayne syndrome (CS) is characterized by dramatically precocious ageing, neurodegeneration, and hypersensitivity to sunlight (UV). We discovered that this disorder, normally considered due to DNA repair impairment, has rather characteristics of a mitochondrial disease. Indeed, in cells from CS patients mitochondrial ATP production is reduced due to depletion of the mitochondrial DNA polymerase (POLγ), resulting from accumulation of the serine protease HTRA3 (Chatre et al, 2015, PNAS 112: E2910-9). HTRA3 overexpression in CS cell in turn depends on nitrosative and oxidative stress, but the underlying mechanism is still unknown. These defects seem independent from the UV sensitivity defect. Importantly, we rescued alterations in CS patient cells by scavenging reactive oxygen and nitrogen species, and opened possibilities for treatments, which are presently lacking for CS patients.

We wondered whether alterations specific to CS cells were also present during processes linked to normal ageing. We discovered that HTRA3 is overexpressed in senescent cells and events leading to its expression precede established senescence markers. Thus HTRA3 overexpression appears linked to early cell senescence determinants. Our data also show that factors able to rescue alterations in CS cells delay senescence in normal cells. Thus, our data suggest that factors specifically implicated in progeroid cellular defects are recapitulated in cellular senescence, a process linked to ageing.

7

Molecular defects in progeroid Cockayne syndrome cells and in ageing cell models

Cristina Fernández Molina, Clément Crochemore and Miria Ricchetti

Stem Cells & Development, CNRS UMR3738 Team Stability of Nuclear & Mitochondrial DNA, Institut Pasteur, Paris, France

Understanding the cause of the progeroid defect(s) in syndromes where ageing is greatly accelerated may reveal clues also on the process of regular ageing, in addition to provide insight for therapeutically challenge the disease. Cockayne syndrome (CS) is a human disorder characterized by photosensitivity, severe neurological and developmental defects, oxidative stress sensitivity, and dramatically precocious ageing. The lab has recently identified a novel pathway that is altered in cells derived from CS patients, and that is possibly determinant to the progeroid phenotype (Chatre et al, 2015 PNAS). They discovered that oxidative and nitrosative stress promote overexpression of the HTRA3 protease, which leads to degradation of the mitochondrial DNA polymerase POLG1 responsible for replication of the organelle genome, thereby affecting mitochondrial respiration and leading to mitochondrial dysfunction.

Our current research aims to evaluate the effect of the impaired replication machinery on mitochondrial DNA (mtDNA), including the assessment of respiratory complexes content, which are partially encoded by mtDNA, and their activity. To overcome the difficulty of assessing molecular alterations in cells with different genetic backgrounds, we are currently generating an isogenic CS model, using CRISPR/Cas9 technology to correct the CSB mutation in CS cells and introduce this mutation in normal cells. We are also studying the effects of nutrient restriction (NR), one of the most robust interventions that increases the lifespan in progeroid model organisms, in CS cells. CS-specific defects will be also evaluated in the context of ageing cell models.

Identification of ICAM-1 as the FTH1 receptor for inflammasome-induced IL-1β secretion in hepatic stellate cells

Manuel A. Fernandez-Rojo[1,2,7], Anita G. Burgess[1], Maria P. Ikonomopoulou[1,2,7], Diem Hoang-Le[1,2], Michael A. Pearen[1], Sujeevi Nawaratna[1], Maura Poli[4], Geoffrey N. Gobert[1,3], Andrew J. Brooks[6], Alun Jones[5], Paolo Arosio[4] and Grant A. Ramm[1,2]

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[2]School of Medicine, The University of Queensland, Brisbane, Herston, Australia.
[3]School of Biological Sciences, Queen's University Belfast, UK
[4]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy
[5]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia
[6]The University of Queensland Diamantina Institute, The University of Queensland, Translational Research Institute, Brisbane, Australia
[7]Madrid Institute for Advanced Studies | IMDEA · IMDEA-Food, Madrid, Spain

Background and Aims. Cellular damage and aging-induced stress causes tissuespecific NF-κB activation and inflammation, hallmarks during the progression of aging-related diseases including cancer and cardiovascular disorders. Conversely, immunotherapy has emerged as a promising strategy against cancer. Hence, targeting inflammation has become an attractive approach to delay aging and agingassociated diseases. Elevated serum ferritin levels are a marker of hepatic inflammation and severity in chronic liver disease, Type-2 diabetes and aging. Previously, we have described that H-Ferritin (FTH1) stimulates IL-1β expression in hepatic stellate cells (HSCs) in an iron-independent, PKCζ/NFκB-dependent manner. Now, we identify the FTH1-signaling receptor in HSC and its impact on inflammasome activation.

Methods. We used one-year old ex-breeder rats (~forty-year-old humans). FTH1-receptor candidates were identified in primary rat HSCs using ligand-receptor glycocapture and mass spectrometry. Candidates were validated in gain- and lossof-function studies following disruption of plasma membrane-endocytic trafficking pathways. The FTH1-induced inflammasome activation was assessed via western blot, qRT-PCR and ELISA.

Results. This study identifies ICAM-1 as the HSC-specific FTH1-receptor mediating IL-1β secretion. Accordingly, ICAM-1 depletion prevented FTH1-induced IL-1β secretion, while ICAM-1-GFP overexpression enhanced IL-1β transcript levels. In an ICAM-1 and clathrin-coated pit endocytosis-dependent-manner and using early endosomes as the physical signalling platform, FTH1 stimulated inflammasome-NLRP3, but not NLRP1, protein levels in HSCs. Finally, we show that FTH1 stimulate IL-1β mRNA expression in mouse liver tissue *ex-vivo*.

Conclusion. This study identifies ICAM1 as the FTH1 receptor and its implication in the activation of NLRP3-inflammasome in HSCs as a novel mechanism that might contribute to chronic liver disease and aging-associated hepatic inflammation.

Conflicts of interest: The authors have no competing financial interests or personal conflicts to declare. MAF-R and GAR are the authors of a provisional patent No. 2017901713.

9

Fasting and fasting mimetics as nutritional strategies against metabolic syndrome and cancer

Luis Filipe Costa Machado[1], Marta Barradas[1], Daniel Herranz[2], **Pablo J. Fernandez-Marcos[1]**

[1]Madrid Institute of Advanced Studies - IMDEA Food, Madrid, Spain
[2]The Cancer Institute of New Jersey, US

Nutritional interventions are powerful approaches to the prevention of human pathologies, since they rely on the precise modulation of common nutritional patterns without the safety concerns of pharmacological interventions. During the last few years, several reports have shown the beneficial effects of short-term fasting on different health aspects, such as metabolic syndrome, cancer or aging.

Here, we describe three lines of research focused on fasting:
(1) High-throughput screenings of pure natural compounds and plant extracts searching for bioactive products with the ability to inhibit the insulin-PI3K pathway or reversibly depolarize the mitochondrial potential, two stimuli associated with reduced body weight and improved metabolic performance. We have tested our hits on mouse models of obesity and diabetes, aiming at their development as human nutritional supplements against metabolic syndrome.
(2) Study the molecular mechanisms mediating the ability of fasting to enhance chemotherapy in two ways: reducing chemotherapy toxicity; and inhibiting tumorinfiltrating regulatory T-cells after chemotherapy, thus increasing the number of cytotoxic, tumor-attacking lymphocytes. In our laboratory, we have shown that fasting can induce the expression of the cell cycle regulator p21. We hypothesize that the increased expression of p21 promotes cell cycle arrest in highly proliferating, non-tumoral cells, protecting them against chemotherapy toxicity; and that p21 can also be involved in the enhanced immune response against chemotherapy-treated tumors after fasting.
(3) Study the roles of Sirt1 and Sirt3 in lung and liver cancer development, respectively. We have found that oncogenic KRas reduces Sirt1 protein stability, and Sirt1 overexpression delays the appearance of KRas-mediated lung adenocarcinomas in mice. We also have found that specific ablation of Sirt3 in hepatocytes disrupts the protection against hepatocarcinoma development observed in female mice.

Understanding muscle stem cell regenerative decline with aging

Laura García-Prat[1,2], Antonio L. Serrano[1], Mireia Vaca[1,2], Sonia Alonso-Martín[1], **Marta Flández[1],** Victoria Moiseeva[2], Joan Isern[2], Jessica Segalés[1,2], Xiaotong Hong[1], Guiomar Solanas[3], Salvador Aznar-Benitah[3,4], Eusebio Perdiguero[1], Pura Muñoz-Cánoves[1,2,4]

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[4]ICREA, Barcelona, Spain

Skeletal muscle has a remarkable capacity to regenerate by virtue of its resident Pax7-expressing stem cells (satellite cells), which are normally quiescent in the adult. Upon injury, quiescent satellite cells activate and proliferate, to subsequently differentiate and form new myofibers or self-renew to restore the quiescent satellite cell pool. Through a combination of global gene expression/bioinformatics and molecular/cellular assays, we found that resting satellite cells have basal autophagy activity, which is required to maintain the quiescent state. Impaired autophagy in old satellite cells or Atg7 deletion in young cells provoked loss of proteostasis and oxidative stress. This proteotoxicity led to loss of quiescence, with subsequent entrance into full senescence in aged and Atg7-deficient satellite cells in response to muscle damage, causing regenerative failure. Pharmacological and genetic reactivation of autophagy could restore regenerative functions in aged satellite cells. Finally, we will show recent findings demonstrating that adult muscle stem cells, despite being in a quiescent state, are subjected circadian control, and that they undergo circadian reprogramming with aging. Interestingly, autophagy was identified as one of the intracellular processes that are oscillatory in adult, but not aged, muscle stem cells. Thus, we propose that, through controlling distinct activities, proteostasis maintains muscle stem cell homeostasis, while its decay is causally implicated in stem cell aging, a process that can be targeted for rejuvenation.

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Telomere control of age-dependent heart regeneration

Esther Aix, Dorota Bednarek, Alex Gallinat, Carlos Garrido, Manuel José Gómez, **Ignacio Flores**

Centro Nacional de Investigaciones Cardiovasculares – CNIC
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With age, mammalian organs lose their capacity to regenerate. This age dependence applies to most organs, including the heart, generally considered a non-regenerative organ. Human and mouse hearts can recover from myocardial injury during the first day after birth, but this capacity is lost shortly after. It remains unclear what cellular and molecular mechanisms determine this postnatal drop in the regenerative response. Our recent results show that the loss of regenerative ability in the mouse heart is associated with rapid telomere shortening and DNA damage triggered by postnatal telomerase inactivation in cardiomyocytes. In this meeting, I will present new data implicating increased telomere dysfunction and cardiomyocyte ploidy in the age-dependent inhibition of the cardiac regenerative response. The rapid postnatal telomere shortening in the heart makes this organ a valuable model for studying the consequences of more gradual telomere attrition in other organs.

The senolytic properties of venom-derived compounds

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In the Translational Venomics Project, We study the therapeutic potentials of animal venoms in human diseases and conditions. Consistent with their diverse pharmacology, peptides derived from venomous animals have been developed as drugs to treat disorders as diverse as hypertension, diabetes and chronic pain. Cellular senescence has been found to be involved in many disorders including aging and thus, there is a great therapeutic interest in finding mechanisms for eliminating senescent cells. Currently there have been identified only few compounds with senolytic activity. This project aims to identify, characterize and produce venom derived peptides with senolytic properties. To achieve this goal, we have screened a large and unique venom library composed of various animals such as spiders, centipedes, scorpions, snakes and jellyfish to identify new venom-derived peptides that specifically target senescent cells. We have already identified two venoms exhibiting senolytic properties. The next step is to reveal the compounds responsible for the senolytic activities of these venoms. These compounds will then be chemically synthesized, validated and molecularly characterized *in vitro* and *in vivo*. Furthermore, using medicinal chemistry, nuclear magnetic resonance spectroscopy and structure-activity relationship we will design analogues with optimized, enhanced and specific senolytic activity. Thus, we will reveal the amino acid domains and the structural conformations responsible for the senolytic activity of our compounds, essential for deciphering their mode of action. Most importantly, we will investigate their effects on reducing the impact of accumulated senescent cells in aging, aging-associated diseases mouse models and with the perspective of evaluating the potential therapeutic applications of senolytic compounds to delay aging and eradicate aging-related diseases.

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Lysosomal trapping of palbociclib and its functional implications

Susana Llanos[1,*], Diego Megias[1,&], Carmen Blanco-Aparicio[1,&], Helena Hernández-Encinas[1] and Manuel Serrano[1,2]

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Palbociclib is a selective inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) approved for the treatment of some cancers whose main effect on responsive cells is to induce cell cycle arrest and senescence. Here, we report that palbociclib is reversibly sequestered into intracellular acidic vesicles both in palbociclib-responsive and palbociclib-resistant cells. This process is known as lysosomal trapping and explains properties of palbociclib previously unreported. In particular, a single short-term treatment of responsive cells with palbociclib is sufficient to produce a durable cell-cycle arrest that eventually leads to senescence. Moreover, palbociclib-treated cells, even if they are resistant to palbociclib, release palbociclib to the extracellular milieu and, in this manner, are able to induce cell-cycle arrest and senescence on bystander susceptible cells. Finally, other lysosomotropic drugs, such as chloroquine, potentiate the efficacy of palbociclib by promoting its traslocation from the lysosome to the cytosol. We conclude that lysosomal trapping is an important feature of palbociclib with pharmacological implications.

SOX2 regulates stem cell ageing, cognitive function and healthspan

Ander Matheu[1], Leire Moreno-Cugnon[1], Miren Revuelta[1], Manolo Moreno[1]

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Ageing is a multifactorial degenerative process that affects all organs and tissues. The main feature of this process is the decline of the functional capability of the tissues to maintain the homeostasis as well as their ability to respond to the physiologic necessities under stress conditions. Stem cell exhaustion is a critical process involved in the decline of the regenerative potential capacity linked to ageassociated damage accumulation and consequently has been postulated as one of the hallmarks of aging. SOX2 is one of the factors responsible for iPS reprogramming and marks and maintains the activity of stem and progenitor cell populations in multiple adult tissues. Our aim is to study the impact of SOX2 in aged-associated stem cell exhaustion longevity, and ageing with particular attention in the central nervous system.

To study SOX2 function in stem cell ageing, we first characterized its expression in the subventricular zone (SVZ) and dentate gyrus (DG) neurogenic niches in young vs aged C57Bl/6 mice. We detected lower expression of SOX2 in 2-years compared to 2-months old mice *in vivo* and also in neurosphere assays *in vitro*. SOX2 reactivation in neurospheres from 2-years mice rejuvenated NSCs activation. Taking advantage of haploinsufficient Sox2EGFP mouse model, in which one copy of Sox2 has been substituted for GFP, we found that type A and B stem cells together with neuroblasts were decreased in Sox2EGFP mice in vivo in young and old mice. Furthermore, we observed diminished number of neurospheres in Sox2EGFP mice. Of note, buried food test showed a decline in the olfactory capacity of the aged Sox2EGFP mice. These aged mice also exhibited impaired cognitive function measured in open field, hole board and T-maze behavioural tests. Altogether, our results demonstrate that SOX2 mediates NSC ageing, neurogenesis and cognitive activity.

Moreover, aged Sox2EGFP mice present impaired health span and signs of premature ageing measured as (i) reduced size, (ii) decreased neuromuscular coordination, (iii) impaired muscle activity and function measured in tightrope, grip strength and treadmill tests. At cellular level, they present increased accumulation of oxidative stress and DNA damage, as well as decreased telomere length. These results correlate with a significant reduction in the median lifespan of Sox2EGFP mice compared to wt littermates. Altogether, our results confirm that SOX2 plays a major role in longevity and ageing.

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Modulation of telomere protection by the PI3K/AKT pathway

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- (*co-first)

Telomeres and the insulin/PI3K pathway are considered hallmarks of aging and cancer. Here, we describe a role for PI3K/AKT in the regulation of TRF1, an essential component of the shelterin complex. PI3K and AKT chemical inhibitors reduce TRF1 telomeric foci and lead to increased telomeric DNA damage and fragility. We identify the PI3Kα isoform as responsible for this TRF1 inhibition. TRF1 is phosphorylated at different residues by AKT and these modifications regulate TRF1 protein stability and TRF1 binding to telomeric DNA *in vitro* and are important for *in vivo* TRF1 telomere location and cell viability. Patient-derived breast cancer PDX mouse models that effectively respond to a PI3Kα specific inhibitor, BYL719, show decreased TRF1 levels and increased DNA damage. These findings functionally connect two of the major pathways for cancer and aging, telomeres and the PI3K pathway, and pinpoint PI3K and AKT as novel targets for chemical modulation of telomere protection.

Understanding senescence in aging muscle stem cells

Victoria Moiseeva[1], Pedro Sousa-Victor[1], Eusebio Perdiguero[1] and Pura Muñoz-Cánoves[1,2]

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[2]Spanish National Cardiovascular research Centre, Madrid, Spain

Regeneration of skeletal muscle depends on a population of adult stem cells (satellite cells) that remain quiescent throughout life. Satellite cell regenerative functions decline with aging. We have found that geriatric satellite cells are incapable of maintaining their normal quiescent state in muscle homeostatic conditions, and this irreversibly affects their intrinsic regenerative and self-renewal capacities. In geriatric mice, resting satellite cells lose reversible quiescence by switching to an irreversible pre-senescence state, caused by derepression of p16INK4a. Upon injury, these cells fail to activate and expand, undergoing accelerated entry into a full senescence state. Our preliminary results suggest that, in addition to satellite cells, other muscle resident cells undergo senescence with aging. At present, we are trying to understand the kinetics and nature of these senescent cells and their function during tissue regeneration.

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p38MAPkinase activity promotes age-related neural stem cell decline and cognitive impairment

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Aging is defined as a functional decline that occurs in all organisms, during this process there is a decrease in the efficiency of cellular reparation and maintenance. This could be due to the decline in the number and function of stem/progenitor cells in several tissues, including the CNS. The molecular pathways that cause the diminishment of the number of neural stem cell during ageing and cognitive dysfunction remain largely unknown. P38MAPK activity has been associated with adult stem/progenitor cell homeostasis in various tissues. In this work, we show that the decline in stem/progenitor proliferation in the subventricular zone and hippocampus with age correlates with increased expression and activity of p38MAPK. Moreover, pharmacological inhibition of p-P38 in aged neural stem/progenitor pool improves their activity in vitro. Genetic deletion of P38α (p38αΔ) in neurons significantly delays the exhaustion of neural stem cells *in vitro* and *in vivo* and improves cognitive activity. Together, these data show a relevant role of p-P38 in neural stem/progenitor cell ageing in the CNS and provides a new pharmacological target for neural stem cell therapy and cognitive impairment.

Cellular senescence and Stem cells in human lung tissue homeostasis

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Cellular senescence and stem cell exhaustion are two critical processes on tissue dysfunction and aging. How cells and tissues age and/or, whether they become more susceptible to development of pathologies depends on the equilibrium of these two mechanisms. Senescent cells undergo cell cycle arrest and promote a secretory phenotype with secretion of several cytokines, most of them with a proinflamatory function. In the other hand, senescence displays deleterious effects in different situations and pathologies during the process of aging, where the accumulation of senescent cells has been consistently described.Therefore, the tight and efficient regulation of these process leads to optimal tissue homeostasis; by contrast, its dysregulation is associated with tissue deterioration and higher risk of pathologies formation. The majority of these conclusions have been observed in mouse models. In this work we present the expression of cellular senescence marker (p16 ink4a), stem cells and progenitors precursors markers (Sox-2, p63, CK5/6, CK14), transcription factor evolved in differentiation process (TTF-1) and marker of cell proliferation index (Ki-67) in human lung tissue derived from autopsy of patients of different ages (embryo young, adult and elderly). Among the elderly, we present data of two different groups, one without pulmonary pathology, and the other with lung pathology (non-cancer) and fibrosis.

There is an increase in the number of p16Ink4a in biopsies from elderly compared to young and adult individuals whereas the expression of stem cell/progenitor markers and Ki67 decreases. We also observed that pathological lung tissues from aged-healthy lungs compared to pathology ones has more fibrosis, higher p16Ink4a positive cells as well as reparative cellular marker CK14. We also found a higher decrease in stem cell numbers in lung tissues from aged-healthy lungs compared to pathology ones, with increased proliferative index and higher expression of TTF-1.

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Role of p38 MAPK in muscle stem cell senescence

Pedro Maseres[1], Monica Zamora[1], Jessica Segalés[1,3], Antonio L. Serrano[1], Victoria Moiseeva[1], Pura Muñoz-Cánoves[1,2,3], **Eusebio Perdiguero[1]**

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In skeletal muscle tissue, aging is associated with a reduction in muscle mass and fitness named sarcopenia, which occurs in conjunction with a progressive drop in muscle stem cell (satellite cell) number and function resulting in faulty tissue regeneration. Several extrinsic factors have been shown to influence satellite cell function during aging, being increased in their niche (in old muscle fibers or the interstitial cells milieu) and/or systemically in the circulation. Impairment of satellite cell function during aging also involves cell-intrinsic or cell-autonomous mechanisms, including telomere attrition, increased DNA damage, global epigenetic alterations, elevated level of the cell cycle inhibitor p16INK4a and loss of proteostasis resulting in accumulation of damaged proteins, mitochondrial dysfunction and increased oxidative stress. Overall, this cell-intrinsic decline leads to a pre-senescent state which turns into full cellular senescence upon proliferative signals (geroconversion). Through bioinformatic analysis of previous data from our lab, we investigated the signal transduction pathways that may contribute to agerelated deficits in satellite cells, and uncovered p38 MAPK signal transduction pathway as the more overrepresented module. Using p38α-deficient mice, we show our recent findings supporting the notion that the lack of p38α in aged satellite cells makes them resistant to geroconversion by preventing epigenetic derepression of the INK4a locus.

Role of p38 MAPK in muscle stem cell senescence

Pedro Maseres[1], Monica Zamora[1], **Jessica Segalés[1,3],** Antonio L. Serrano[1], Victoria Moiseeva[1], Pura Muñoz-Cánoves[1,2,3], Eusebio Perdiguero[1]

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Mechanisms of circadian clock rewiring during ageing

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The circadian clock regulates the physiology of tissues and tissue-specific stem cells by controlling their daily oscillations. These oscillations are crucial for the stem cells to carry out their functions properly, which include providing a homeostatic environment. It was widely believed that the circadian clock was dampened during ageing, losing amplitude and synchronization as the organisms aged. This dogma was recently refuted when it was shown that the circadian clock machinery retains a core circadian machinery during aging, adapting to specific functions required by each tissue with age. However, the mechanisms and by which adult stem cells reprogram their circadian transcriptome during aging still remains unknown. We are aiming to unravel this by analyzing the general state of the chromatin and RNA expression at different times of the day in young and aged mice. Using ATACsequencing and Nascent RNA sequencing, as well as comparing between different timepoints in both young and aged mice, will allow us to determine the regions of the chromatin open at each specific condition, and the specific RNA being transcribed at the specific time.

In addition, it is also crucial to determine who the main players of the circadian reprogramming are. This is why we are studying if Bmal1 is responsible of the reprogramming by ChIP-sequencing in young and aged mice, analyzing if the genes regulated by Bmal1 are the ones seen to be activated during ageing. Then, we will also use Mass spectrometry analysis to study if the co-factors associated to Bmal1 are also altered during the reprogramming. This will all lead to further understanding how the circadian clock is wired, as well as defining how this whole machinery changes during ageing.

Aged stem cells reprogram their daily rhythmic functions to adapt to stress

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Tissue-resident stem cells ensure homeostasis by providing a constant input of healthy cells in response to the loss of non-functional or damaged cells. The function of stem cells is therefore instrumental for maintenance of the tissue in the long-term, posing as a key element in progressive tissue deterioration upon ageing. Normal homeostatic functions of adult stem cells have daily oscillations that ensure their proper timing to coordinate them and therefore render them more efficient. The circadian clock of tissue-resident stem cells acts as an integrator of environmental cues, translating these signals into the rhythmic transcription of the genes needed to comply with the new requirements. We analyzed the effects of aging on the functional rhythms of stem cells in two tissues with very different cellular turnover rates: the epidermis and the skeletal muscle. We have discovered that aged epidermal and muscle stem cells retain a robustly rhythmic core circadian machinery, breaking a long-held dogma in the field that maintained that the core clock oscillations lost amplitude with age. However, the oscillating transcriptome is extensively reprogrammed in aged stem cells, switching from genes involved in homeostasis to those involved in tissue-specific stresses. Epidermal stem cells, with a very high turnover rate, have to face DNA damage accumulation. Conversely, due to their low rate of proliferation, skeletal muscle stem cells require autophagy to recycle damaged cellular components. We have observed that the rhythmicity of autophagy of muscle stem cells is lost during ageing. While age-associated rewiring of the oscillatory diurnal transcriptome is not recapitulated by a high-fat diet in young adult mice, it is significantly prevented by long-term caloric restriction in aged mice. Thus, stem cells rewire their diurnal timed functions to adapt to tissuespecific age-related traits.

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Knockdown of APE1 causes the upregulation of E-Cadherin and has no effect on N-Cadherin Levels

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Apurinic/Apyrimidinic endonuclease 1 (APE1) is a multifunctional protein that is involved in multiple important cellular pathways such as DNA repair, coactivation of transcription factors and cleavage of RNAs. APE1 has been shown to be implicated in cancer but its role in epithelialmesenchymal transition (EMT) remains unclear.

Here we report that the downregulation of APE1 expression by transfecting cells with siRNA against APE1 in a liver cancer cell line (HepG2) caused an elevation of E-Cadherin levels in HepG2 cells. However, N-Cadherin levels did not show a clear pattern of change when APE1 was downregulated. Previous studies have shown that loss of E-Cadherin is associated with epithelial– mesenchymal transition which is involved in cancer metastasis and invasiveness. Therefore, normal expression of E-cadherin functions as a tumor suppressor. However, the implications of E-cadherin overexpression in HepG2 cells have not been well characterised yet.

Whether the interaction between APE1 and E-cadherin is a direct or an indirect action through other intermediate factors is currently unknown and needs further investigation. Also, the role of E-Cadherin overexpression in HepG2 cell will also also be investigated by performing phenotype and invasiveness assays before and after E-cadherin levels are manipulated.

Belal Tafech has completed his Biology bachelors degree (Cells, Molecules and Physiology stream) at Simon Fraser Universtiy in Burnaby, BC, Canada. He is currently completing a Biochemistry Masters degree in cancer research at the University of Northern British Columbia, Prince George, BC, Canada.

Understanding senescence in aging muscle stem cells

Victoria Moiseeva[1], **Mireia Vaca[2],** Pedro Sousa-Victor[1], Eusebio Perdiguero[1] and Pura Muñoz-Cánoves[1,2]

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Regeneration of skeletal muscle depends on a population of adult stem cells (satellite cells) that remain quiescent throughout life. Satellite cell regenerative functions decline with aging. We have found that geriatric satellite cells are incapable of maintaining their normal quiescent state in muscle homeostatic conditions, and this irreversibly affects their intrinsic regenerative and self-renewal capacities. In geriatric mice, resting satellite cells lose reversible quiescence by switching to an irreversible pre-senescence state, caused by derepression of p16INK4a. Upon injury, these cells fail to activate and expand, undergoing accelerated entry into a full senescence state. Our preliminary results suggest that, in addition to satellite cells, other muscle resident cells undergo senescence with aging. At present, we are trying to understand the kinetics and nature of these senescent cells and their function during tissue regeneration.

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Mitochondrial DNA damage and mutations are induced by reactive oxygen species

William Valente and Jason Bielas

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- Translational Research Program, Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, US

Aberrations in the mitochondrial genome are associated with neurodegenerative diseases, metabolic syndromes, cancer, and pathologies of aging; although establishing direct links between cause and consequence of mtDNA mutagenesis has remained elusive. The mitochondrial theory of aging posits mtDNA mutations arise from genomic damage by reactive oxygen species (ROS). However, recent publications raise doubt that ROS play a prominent role in mtDNA mutagenesis, and instead implicate stochastic polymerase errors in the accumulation of mtDNA mutations seen in aging, largely based on the interpretation of mutation spectra. However, the mutation signatures of polymerase misincorporation and oxidative damage overlap, which obfuscates interpretation of spectra. Thus, we sought to directly test the hypothesis that ROS induce mtDNA mutations. To accomplish this, we produced transgenic cell lines which express either of two mitochondrialtargeted ROS generators, SuperNova or D-amino acid oxidase (DAAO). The modified fluorescent protein, SuperNova, emits superoxide upon excitation, whereas the peroxisomal enzyme DAAO reduces non-standard D-amino acids into achiral imino acids, and in the process generates hydrogen peroxide. Mitochondrialtargeted versions of SuperNova (mSN) and DAAO (mDAAO) demonstrated localized ROS production, which subsequently yielded polymerase-blocking lesions in mtDNA. Using the recently developed Droplet Digital Random Mutation Capture (dRMC) assay, we quantified point mutations in mtDNA after subchronic exposures to activated mSN or mDAAO. Both exposure regimens exhibited significant, dose-dependent increases in mtDNA point mutations. The induction of mutation by ROS seen in this study affirms a tenet of the mitochondrial theory of aging and may serve to refocus mtDNA mutagenesis in the lens of oxidative metabolism. These findings have significant implications for the mechanistic interpretation of ROS and mitochondria in models of aging.

Centenarians overexpress pluripotency-related genes

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INTRODUCTION: Adult human dermal fibroblasts can be reprogrammed to become pluripotent by the addition of four transcription factors (known as the Yamanaka factors), OCT3/4, SOX2, c-MYC, KLF4. One of the most widely studied hallmarks of ageing is senescence, which is linked to a lower expression of these pluripotency genes. Since we have recently reported that centenarians overexpress BCL-xL, which has been shown to improve pluripotency, we aimed to determine whether centenarians overexpress pluripotency-related genes.

METHODS: To test this hypothesis, we recruited 22 young, 32 octogenarians and 42 centenarians belonging to two different centenarian cohorts: Alzira (Valencia) and Sassari (Sardinia). We determined the mRNA expression of the four Yamanaka factors (OCT3/4, SOX2, KLF4 and c-MYC) and other pluripotency-related genes (VIMENTIN, BMP4, NCAM, BMPR2) in peripheral blood mononuclear cells (PBMCs) by reverse transcription polymerase chain reaction (RT-PCR).

RESULTS: We found that centenarians overexpress OCT3/4, SOX2, c-MYC, VIMENTIN, BMP4, NCAM and BMPR2 gene expression, when compared to octogenarians ($p<0.05$). No differences were found in KLF4 gene expression among groups.

CONCLUSIONS: We conclude that centenarians overexpress Yamanaka Factors and other pluripotency-related genes, which may contribute to their remarkable maintenance of homeostasis and successful aging.

NOTES

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Madrid 7 — 9 May 2018

cnio "LA CAIXA" FOUNDATION FRONTIERS MEETINGS 2018

Molecular, Cellular and Organismal Hallmarks of Aging

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2017

MOLECULAR CHAPERONES IN CANCER

02/05/2017 – 04/05/2017

Organisers: Nabil Djouder, Wilhelm Krek, Paul Workman, Xiaohong Helena Yang

PRIMARY AND SECONDARY BRAIN TUMORS

19/02/2017 – 22/02/2017

Organisers: Massimo Squatrito, Manuel Valiente, Richard Gilbertson, Michael Weller

2016

CANCEROMATICS III – TUMOR HETEROGENEITY

13/11/2016 – 16/11/2016

Organisers: Fátima Al-Shahrour, Núria Malats, Alfonso Valencia, Chris Sander

2015

METASTASIS INITIATION: MECHANISTIC INSIGHTS AND THERAPEUTIC OPPORTUNITIES

28/09/2015 - 30/09/2015

Organisers: David Lyden, Yibin Kang, Gemma Alderton, Victoria Aranda, Li-kuo Su, Héctor Peinado

NEW TRENDS IN ANTICANCER DRUG DEVELOPMENT

22/03/2015 - 25/03/2015

Organisers: Manuel Hidalgo, Alberto Bardelli, Lillian Siu, Josep Tabernero

2013

CHROMOSOME INSTABILITY AND ANEUPLOIDY IN CANCER

27/05/2013 - 29/05/2013

Organisers: Robert Benezra, Ana Losada, Marcos Malumbres, René Medema

2012

ALLOSTERIC REGULATION OF CELL SIGNALLING

17/09/2012 - 19/09/2012

Organisers: Francesco Gervasio, Ermanno Gherardi, Daniel Lietha, Giulio Superti-Furga

2011

RECAPTURING PLURIPOTENCY: LINKS BETWEEN CELLULAR REPROGRAMMING AND CANCER

07/11/2011 - 09/11/2011

Organisers: Maria A. Blasco, Konrad Hochedlinger, Manuel Serrano, Inder Verma

CANCEROMATICS II : MULTILEVEL INTERPRETATION OF CANCER GENOME

28/03/2011 - 30/03/2011

Organisers: Søren Brunak, Stephen Chanock, Núria Malats, Chris Sander, Alfonso Valencia

BREAST CANCER

07/02/2011 - 09/02/2011

Organisers: Joaquín Arribas, José Baselga, Miguel Ángel Piris, Lajos Pusztai and Jorge Reis-Filho

2010

CANCER PHARMACOGENETICS: PERSONALIZING MEDICINE

22/11/2010 - 24/11/2010

Organisers: Javier Benítez, William E. Evans, Miguel Martín and Magnus Ingelman-Sundberg

MOLECULAR CANCER THERAPEUTICS

08/03/2010 - 10/03/2010

Organisers: Gail Eckhardt, Roy S. Herbst and Manuel Hidalgo

2009

THE ENERGY OF CANCER

02/11/2009 - 04/11/2009

Organisers: Toren Finkel, David M. Sabatini, Manuel Serrano and David A. Sinclair

CANCER-OM-ATICS : MULTILEVEL INTERPRETATION OF CANCER GENOME DATA

06/07/2009 - 08/07/2009

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