

**5th International Symposium : Nutrition, Oxygen Biology And Medicine
Development And Aging**

Nutrition, Epigenetics and Lifestyle and the Healthspan

5 - 7 June, 2013, Campus des Cordeliers, Paris, France

Joint Meeting of

The Societe Française de Recherches sur les Radicaux Libres

(Correspondent of the SFRR-Europe) and

Oxygen Club of California

<http://www.oxyclubcalifornia.org/Paris2013/index.php>

Contact: lab-biocel-vegetale@univ-rennes1.fr

Unofficial Meeting Notes by **John D. Furber**

**Contents: ** Introduction ** Disclaimer ** Highlights of the Meeting **
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Introduction: This meeting was organized by Professeur Josiane Cillard, César G. Fraga, and Bertrand Friguet. Professeur Cillard is President of the French Society for Free Radical Research and Professor in the Faculté de Pharmacie, Université de Rennes 1, Rennes, France.

<http://oxyclubcalifornia.org/Paris2013/index.php>

Disclaimer: These are my informal notes from the meeting. They are definitely incomplete, and probably contain some errors.

Permission is granted to the meeting organizers, the Societe Française de Recherches sur les Radicaux Libres, and the Oxygen Club of California to use or adapt these notes for their newsletters and web sites. I welcome comments and feedback, especially if you find errors.

La **Societe Française de Recherches sur les Radicaux Libres** was founded in 1993 by Dr Ingrid Emerit. Since 2005, it has been organizing joint meetings with the OCC every two years in Paris.

The **OCC** was founded in 1994. It has been meeting in alternate years in Santa Barbara and at the **Linus Pauling Institute** at Oregon State University, Corvallis Oregon.

INTERNATIONAL ADVISORY COMMITTEE: Regina Brigélius-Flohé (Nuthetal), Enrique Cadenas (Los Angeles), Pierre Cillard (Rennes), Kelvin J.A. Davies (Los Angeles), Arlette Delamarche (Rennes), Patricia I. Oteiza (Davis), Nesrin Kartal-Ozer (Istanbul), Lester Packer (Los Angeles), Helmut Sies (Düsseldorf), Maret Traber (Corvallis), Giuseppe Valacchi (Ferrara), Steven Zeisel (Kannapolis)

<http://www.oxyclubcalifornia.org>

Abstracts of all talks and posters were in the conference booklet. The complete program, abstracts, and many photographs from the meeting are available for viewing and download on the OCC website. http://www.oxyclubcalifornia.org/Paris2013/congress_material.php

Video of the meeting presentations was recorded by Jean-Philippe Cillard. It can be seen on the web at http://www.youtube.com/user/TheNOBM5/videos?sort=dd&view=0&flow=list&live_view=500 More information on the work of any presenter can be found by searching PubMed or Google Scholar or Scirus, and reading their papers. Consequently, my notes here are not a comprehensive chronicle, but rather a sketchy introduction to people and ideas that you

might wish to investigate further.

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Thank you for your encouragement and support.

- **Society for Free Radical Research - Europe 2013** will meet in September 23-25, 2013, Athens. "*The new era of -omics in Free Radicals in Biology and Medicine*". Organized by Efsthios Gonos. <http://www.sfrr-europe2013.gr/>
- **Society for Free Radical Biology and Medicine, South American Group** will meet in October 14-17, 2013, Buenos Aires, Argentina. Organized by Cesar G. Fraga and Alberto Boveris. http://www.oxyclubcalifornia.org/SFRBM_SA/index.php
- The next meeting of **The Oxygen Club of California World Congress** will be held on May 7-10, 2014, at the University of California Davis Convention Center. "*Nutrition and Redox Biology in Development and Health*" will be organized by Maret Traber, Patricia Otezia, and Helmut Sies
- During 4-7 September 2014, the **Society for Free Radical Research - Europe** meeting will be held in Paris. Organized by Bertrand Friguet, Josiane Cillard, Anne-Laure Bulteau, Isabelle Petropoulos. "*Free Radicals: insights in signaling and adaptative homeostasis.*" <http://www.sfrr-europe.org/>

Highlights of the Meeting

(More details on these excerpts are found further down in the extended notes of each talk.)

Valérie Schini-Kerth: Chronic intake of Red wine polyphenols (RWPs) by young rats prevents ageing induced endothelial dysfunction. Young rats run more than old rats. Giving old rats RWPs partially restores their young running behavior. It is important to start the polyphenols in young life for benefits later in life.

César G. Fraga: Cocoa or tea consumption lowers human blood pressure. (-)-Epicatechin could prevent inflammation.

Gerald Rimbach: Candidates for CR mimetic drugs: Metformin, Rapamycin, 2-DeoxGlucose. All have side effects. However, the MediterrAsian diet mimics beneficial aspects of CR.

Balz Frei: Long term black tea consumption improves flow-mediated dilation (FMD) of arteries.

Manfred Eggersdorfer: Vitamin D has a major impact on reducing risk of diabetes.

Emily Ho: We all need zinc (Zn). See (Rando TA, and Chang HY. *Cell*, 2012 Jan 20;148(1-2):46-57

Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock.) Zn is an essential micronutrient. There is not much storage of Zn in the human body, so it must be replenished frequently. Zinc requirement is 11 mg/day in males; 8 mg/day in females. Food sources of Zn are proteins, including seafood, especially oysters, meat, nuts, legumes, and whole grains. Oysters are one of the number-one zinc-containing foods.

Zolt Radak: Age-associated declines in mitochondrial biogenesis and protein quality control factors are minimized by exercise training

Li Li Ji: Exercise is very important. Skeletal muscle mass changes with altered use. It loses mass and function within a rather short time of disuse. Exercise can be a healthy, hormetic pro-oxidant.

Pauline Larroque-Cardoso: EGF receptor activation by 4-hydroxynonenal alters TGF- β -induced elastogenesis in fibroblasts. TGF- β 1 is a strong stimulator of elastin expression and elastin mRNA stabilizer. Aldehydes interfere in receptor signaling. 4-HNE is impairing TGF- β 1 signaling. HNE induces EGF receptor activity. There is loss of elastin with aging. With age, HNE levels rise.

Bharat B. Aggarwal: Curcumin comes from Turmeric. Curcumin modulates the expression of dozens of genes. Curcumin physically binds to and inhibits activity of many proteins. Curcumin downregulates expression of cell proliferation, antiapoptotic, and metastatic genes. White vs yellow curcumin: Yellow curcumin binds to HAT. White curcumin (tetrahydro) has no effect at all on HAT. Curcumin is as effective as metformin in activating AMPK, but requires only 1/400th the dose for the same effectiveness. Curcumin is effective as a treatment for multiple sclerosis. Cooking turmeric with olive oil and black pepper is a fine way to get the curcumin. Curcumin is about 2-5% of turmeric. Curcumin and turmeric are lipophilic, so they are more bioavailable with oil or fat. Another traditional way of getting bioavailable curcumin is to mix turmeric with whole milk or yogurt. It forms an emulsion with the dairy fat. A good dose would be 150 mg curcumin, twice per day. Mice are a bad model for studying human cancer development because they live only a couple of years, which is much less than the time for human cancer development. With many cancers late in life, lifestyle and nutrition in the preceding early life and young adulthood are important. Eskimos never get cancer.

George Parks: Fitness level is very important. Nutrition advice must be in the context of how much exercise is being done.

Pamela Starke-Reed: I sit on a US government steering committee for setting dietary guidelines. The guidelines are for healthy people, not for treating diseases. More than diet, the whole lifestyle is important, including exercise, and stress levels. Folic acid supplementation in grains has been helpful for some to prevent neural tube defects, as well as some older people. But on the other hand, it has increased cancer rates in some over-responders.

Kelvin Davies: Some diseases are not the result of our diets. Now more people are living long enough to develop Alzheimer's.

Conversations, Comments, & Discussion

Regina Brigelius-Flohé: If you are healthy and have a balanced diet, then you don't need supplements. But if you are sick or don't have adequate diet, then you need supplements.

Bharat B. Aggarwal: With many cancers late in life, lifestyle and nutrition in the preceding early life and young adulthood are important. Eskimos never get cancer.

Li Li Ji: Exercise is very important. It can be a healthy, hormetic pro-oxidant.

Christiaan Leeuwenburgh: Most dose/response nutrition studies are done on young people. We need more funding to study different population groups.

Steven H. Zeisel: In many cases, you can have more effect by intervening early in life.

George Parks: Fitness level is very important. Nutrition advice must be in the context of how much exercise is being done.

Pamela Starke-Reed: I sit on a US government steering committee for setting dietary guidelines. The guidelines are for healthy people, not for treating diseases. More than diet, the whole lifestyle is important, including exercise, and stress levels. Folic acid supplementation in grains has been helpful for some to prevent neural tube defects, as well as some older people. But on the other hand, it has increased cancer rates in some over-responders.

Kelvin Davies: Some diseases are not the result of our diets. Now more people are living long enough to develop Alzheimer's.

John Maguire: The purpose of the OCC is to encourage excellent meetings with excellent scientists.

George Wondrak: UVA ruins lysosomes in skin cells. You can see lipofuscin in fibroblasts.

Extended Notes of the Talks

WEDNESDAY, JUNE 5

14:45 – 15:00 WELCOME

Josiane Cillard – *President of the Société Française de Recherche sur les Radicaux libres*, FACULTY OF PHARMACY, UNIVERSITY OF RENNES 1, RENNES, FRANCE

Lester Packer – *Founder and Honorary President of the Oxygen Club of California*
UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, USA

The OCC has been holding joint meetings with the *Société Française de Recherche sur les Radicaux libres* for several years. This year, the focus is on *Epigenetics*. In the early 1800's, a theory of evolution on inheritance of acquired traits was advanced by French Scientist Jean-Baptiste Lamarck. His theory foreshadowed current understandings in epigenetics.

Bertrand Friguet, UNIVERSITY PIERRE ET MARIE CURIE - PARIS 6, PARIS, FRANCE

During 4-7 September 2014, the **SFRR Europe** meeting will be held in Paris. Organized by Bertrand Friguet, Josiane Cillard, Anne-Laure Bulteau, Isabelle Petropoulos. "Free Radicals: insights in signaling and adaptative homeostasis.

César Fraga

PHYSICAL CHEMISTRY, SCHOOL OF PHARMACY AND BIOCHEMISTRY, UNIVERSITY OF BUENOS AIRES, BUENOS AIRES, ARGENTINA

The SFRBM will be meeting in Buenos Aires, Argentina, 14-17 Oct 2013.

Nesrin Kartal-Özer - *President of SFRR-Europe*

DEPARTMENT OF BIOCHEMISTRY, FACULTY OF MEDICINE, MARMARA UNIVERSITY, ISTANBUL, TURKEY

In September 2013, the SFRR Europe meeting will be held in Athens.

SESSION I PLANT NUTRIENTS AND HEALTHY AGING

CHAIRPERSONS: *Fabio Virgili*, NATIONAL RESEARCH INSTITUTE FOR FOOD AND NUTRITION, ROME, ITALY

Giuseppe Valacchi, DEPARTMENT OF LIFE SCIENCE AND BIOTECHNOLOGIES, UNIVERSITY OF FERRARA, FERRARA, ITALY

OP1 Federico Leighton Memorial Lecture - Introduced by *César G. Fraga*

Novel antioxidant reactions of cinnamates in wine

Andrew Waterhouse, DEPARTMENT OF VITICULTURE AND ENOLOGY, UNIVERSITY OF CALIFORNIA, DAVIS, CA, USA

Federico enjoyed wine and dancing. I think he would have enjoyed this presentation on wine. Waterhouse is collaborating with Skibsted Team of the University of Copenhagen, Ryan Elias, Nomascorc, and American Vineyard Foundation.

In the distant past, old wine would get oxidized within a year and would become vinegar. Today winemakers have a choice of how much O₂ they expose their wine to.

O₂ ==> HOO* (hydroperoxyl radical) + HO* (hydroxyl radical)

Wine Quinones can react in various reactions.

Sulfur dioxide can prevent wine oxidation by removing quinone.

Catechin + 3- mercaptohexanol.

Fenton reaction by Iron-II (Fe²⁺) creates the extremely reactive hydroxyl radical, HO*.

Ethanol in wine is at a concentration 2 molar (2M).

Some oxidation is required for proper aging and coloring of wine. Sherry is extensively oxidized.

Fenton reaction can convert H₂O₂ to acetaldehyde. This reaction is inhibited by (Hydro)Cinnamic Acid and (Hydro)Caffeic Acid. Cinnamates reduce acetaldehyde production by 50%.

OP2 From free radical scavengers to nucleophilic tone: A paradigm shift in nutraceutical antioxidants: from free radical scavenging to para-hormesis

Fulvio Ursini, DEPARTMENT OF BIOLOGICAL CHEMISTRY, UNIVERSITY OF PADOVA, PADOVA, ITALY

In the past, thinking has been that free radical scavengers in plant polyphenols prevent oxidative damage. But actually, the chemistry of scavenging does not happen. Other than superoxide dismutation, there are no free radical scavenging reactions inside of cells. Instead there is Nrf2 activation and nucleophilic displacement. Rosemary, Olive leaf, and cruciferous vegetables have small molecule activators of Keap1/Nrf2. Also, the "healthy CLA" found in dairy products is an activator of Keap1/Nrf2.

The targets of electrophiles are redox-labile cysteine (Cys) residues in proteins.

Signaling is activated by oxidative redox switches. For example: Embryogenesis, wound healing, cancer growth.

HIF1, PI3K, ERK NFκB, cSRC.

He calls this "Para-hormesis" because the signaling molecule is not toxic.

We believe that the term "polyphenols" will replace the term "antioxidants" for describing the beneficial activities of plant components to human health.

OP3 Potential of polyphenol-rich products to improve ageing-related impairment of the vascular function

Valérie Schini-Kerth

LABORATOIRE DE BIOPHOTONIQUE ET PHARMACOLOGIE, FACULTY OF PHARMACY, UNIVERSITY OF STRASBOURG, FRANCE

Endothelium is important in vascular homeostasis.

Nitric Oxide (NO) is a signaling molecule that triggers vascular relaxation. Endothelial cells form NO in response to various protective activators. Chronic intake of Red wine polyphenols (RWPs) by young rats prevents ageing induced endothelial dysfunction.

NADPH oxidase is an enzyme in the cell membrane. Young rats run more than old rats. Giving old rats RWPs partially restores their young running behavior. It is important to start the polyphenols in young life for benefits later in life. Polyphenols inhibit Angiotensin II vasoconstriction and promote vasodilation.

Lester Packer: Have these kind of experiments been done with humans?

Helmut Sies: Dusseldorf has done study of flow-mediated dilation comparing young and old people.

OP4 Flavanols improving health: evidence and potential mechanisms

César G. Fraga PHYSICAL CHEMISTRY, SCHOOL OF PHARMACY AND BIOCHEMISTRY, UNIVERSITY OF BUENOS AIRES, ARGENTINA

In the past, nutrients were mostly identified by the association of their deficiencies with disease or unhealthy conditions. We believe consumption of fruits and vegetables is good for your health. But how do we identify which F&V are the healthiest? Can we identify and quantify the phytonutrients responsible for the health effects? Which mechanisms are responsible for the health effects.

Flavanols are polyphenols. Flavanols and flavonoids and plant polyphenols have multiple reaction centers, so they can exert multiple molecular actions.

Cocoa or tea consumption lowers human blood pressure.

Epicatechin procyanidins interact with lipid rafts in intestinal cells.

(-)-Epicatechin could prevent inflammation.

The SFRBM-South America will meet in Buenos Aires, 14-17 Oct 2013.

Enrique Cadenas: Very important point. Hexamers.

OP5 Nutrition and healthy aging-calorie restriction or "MediterrAsian" diet?

Gerald Rimbach, INSTITUTE OF HUMAN NUTRITION AND FOOD SCIENCE, CHRISTIAN-ALBRECHTS-UNIVERSITY KIEL, KIEL, GERMANY

Dietary plant bioactives studies in cell culture, rodents, and human volunteers.

Asian diet: Soy, green tea, oily fish, vegetables, turmeric, EGCG, Genistein, Curcumin

Mediterranean diet: Red wine, olive oil, oily fish, vegetables

CR has improved health and increased lifespan in some model organisms.

Many humans go on "Yo-yo diet" of restriction and relapse. In mice, benefits of CR on gene expression persist after they return to ad lib feeding. They tried 6 months of CR followed by 6 months of ad lib. Compared that with 12 months of ad lib. Look at gene expression and protein levels. CR improved stress resistance, lower body wt, but... Body weight is fully regained within 2 weeks after returning to an ad lib diet. Body fat, blood lipids, triglycerides is regained within 6 months. Many gene expression levels are regulated by CR, but they return to ad lib levels shortly after CR ends.

CR results in decrease of major urinary proteins > postpone reproduction > increase lifespan.

How does 6 months CR compare with 3 week CR? Short term CR slightly reduces body wt and body fat but does not improve stress response in mice (eg autophagy).

Conclusion: CR must be maintained throughout life to keep its beneficial effects. It seems worthwhile to evaluate possible CR mimetics or food intake patterns that are able to reproduce metabolic and protective benefits of CR.

Candidates for CR mimetic drugs have been proposed: Metformin, Rapamycin, 2-DeoxyGlucose. But they all have side effects.

Can dietary plant bioactives mimic effects of CR? Genistein, Quercetin, Phloridzin (apples).

Compare hepatic differential gene expression from GEO database of mouse gene expression. The MedAsian diet partly mimics the hepatic differential gene expression of CR.

OP6 Flavonoids: phytochemicals, phytonutrients, or dietary antioxidants?

Balz Frei, PhD, LINUS PAULING INSTITUTE, OREGON STATE UNIVERSITY, CORVALLIS, OREGON, USA

A nutrient is considered *essential* if it must be obtained from an external source (ie. it is not made in our cells. eg. vitamins).

A phytochemical is a plant chemical. eg. potassium, quercetin, Vitamin C, epicatechin, fructose.

Quercetin is a flavonol.

Antioxidant capacity is the number of available electrons/hydrogen atoms per antioxidant molecule. It is measured by various lab tests, such as ORAC, TEAC, FRAP, etc.

In vitro addition of black tea polyphenols dose dependently inhibits lipid peroxidation in human plasma. But drinking black tea does not inhibit lipid peroxidation in human plasma ex vivo.

Compare this with vitamin C, which gives dose-dependent inhibitory effect.

F2-isoprostanes levels in humans are not decreased by consumption of plant polyphenols.

Flavonoids may increase NO bioavailability. Oral flavin-3-ol

Acute and chronic black tea consumption improves flow-mediated dilation (FMD) of arteries.

OP7 Micronutrient intake in the Western world – status and implications on public health

Manfred Eggersdorfer, Sr. VP Nutrition Science, DSM NUTRITIONAL PRODUCTS, BASEL, SWITZERLAND

Adequate nutrition is an important challenge for this century, with increasing population and aging population. About 50 nutrients are important for human health. More than 2 billion people suffer from inadequate micro-nutrient intake (hidden hunger.)

Vitamin D has a major impact on reducing risk of diabetes.

Q: We should not over-calculate the number of people who are undernourished. That is because the government agencies take the expected required amount of each nutrient and double it for their recommendations. That is to catch outliers and provide a margin of safety.

A: Correct. Nonetheless, we got our figures from UN WHO.

Cocktail Reception and Poster Viewing

THURSDAY, JUNE 6

SESSION II REDOX BIOLOGY OF MITOCHONDRIA

CHAIRPERSONS: *Jean Cadet*

LABORATOIRE "LÉSIONS DES ACIDES NUCLÉIQUES", INSTITUT NANOSCIENCES ET CRYOGÉNIE, CEA/GRENOBLE, GRENOBLE, FRANCE

Helmut Sies, INSTITUTE OF BIOCHEMISTRY AND MOLECULAR BIOLOGY I, FACULTY OF MEDICINE, HEINRICH-HEINE-UNIVERSITY, DUSSELDORF, GERMANY

OP8 Mitochondrial redox metabolism in cell fate signaling

Shazib Pervaiz, DEPARTMENT OF PHYSIOLOGY, YONG LOO LIN SCHOOL OF MEDICINE, NATIONAL UNIVERSITY OF SINGAPORE

The intracellular ratio of two main ROS, superoxide to H₂O₂ determines cancer cell response to death signals: superoxide promotes survival; H₂O₂ promotes cell death (Clement. Cell Death Diff 10(11):1273-75, 2003).

Bcl-2 promotes mitochondrial import of COX Va (Subunit Va of mitochondrial complex IV).

Q: Do you have a determination of the SOD activity?

A: We have done SOD1 gene silencing. We see more superoxide when SOD1 is knocked out.

OP9 Targeted bioactive and probe molecules to understand mitochondrial redox metabolism

Michael Murphy, MEDICAL RESEARCH COUNCIL MITOCHONDRIAL BIOLOGY UNIT, WELLCOME TRUST, CAMBRIDGE, UK

During and after a heart attack, most of the damage occurs during reperfusion, when oxygenated blood returns, and a burst of ROS occurs. To minimize the damage, they are working with mitochondria-targeted antioxidants and MitoQ: Covalently link the antioxidant to a lipophilic cation. Due to the negative voltage gradient across the mitochondrial inner membrane (the MMP or mitochondrial membrane potential), these targeted antioxidants accumulate several hundred-fold within the mitochondria.

Protein S-nitrosation: protein-SH group + NO ==> protein-SNO. This is reversed by glutathione (GSH). They developed a mitochondrial NO donor, MitoSNO, which is protective against cardiac ischemia-reperfusion injury. It S-nitrosates a thiol group on mitochondrial complex I, which slows its activity, so that it does not produce ROS during reperfusion.

Q: Have you looked at brain mitochondria? Brain cells do even worse than cardiomyocytes.

A: Yes, we are looking at the brain during a stroke model. It would be good to also look at the brain during a cardiac event.

OP10 Importance of the mitochondrial Lon protease in stress-adaptation and aging

Kelvin Davies SCHOOL OF GERONTOLOGY, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, CALIFORNIA, USA

Adaptive stress-response model, which some people call "hormesis". Pre-treatment with low dose H₂O₂ allows the cells to later survive better in the presence of high dose H₂O₂. 50-60 genes are upregulated during pretreatment, and 50-60 genes are downregulated. *lon* is a stress-responsive gene. LON protease, as well as proteasomes are upregulated, including 26S, 20S, and immuno-proteasomes. LON protease is a stress-responsive protein, which is induced by multiple stressors, including heat shock, serum starvation, and oxidative stress. LON induction, by pre-treatment with low-level stress, protects against oxidative protein damage, diminished mitochondrial function, and loss of cell proliferation, induced by toxic levels of H₂O₂. In older cells, however, LON activity declines, and adaptational responses become sluggish or even ineffectual. Declining Lon activity and declining responsiveness to stress may contribute to aging and age-related diseases.

Immediately during stress, the 19S units come off the 26S proteasome. Then 11S subunits attach to the 20S proteasome, making them more sensitive to digesting oxidized proteins. The LON protease is like one of the 4 rings of the proteasome. The LON protease ring dilates upon exposure to ATP, and is ready to degrade proteins. LON is NOT ONLY a straightforward protease. During periods of non-stress, LON is bound to the mitochondrial genome, and is required for mitochondrial biogenesis.

Senescent WI-38 fibroblasts have lower LON levels than younger cells.

The *Free Radical Theory of Aging Revisited* includes diminished repair capacity contributing to the

increase in accumulation of oxidized proteins, lipids, and nucleic acids.

OP11 Oxidative and glycoxidative mitochondrial proteome alterations during aging and cellular senescence

Bertrand Friguet LABORATOIRE DE BIOLOGIE CELLULAIRE DU VIEILLISSEMENT, UNIVERSITÉ PIERRE ET MARIE CURIE, PARIS, FRANCE
(Levine RL, Stadtman ER. Oxidative modification of proteins during aging. *Exp Gerontol.* 2001 Sep;36(9):1495-502. Review. PubMed PMID: 11525872.)

Across species, they looked at the accumulation of oxidized carbonylated proteins as fraction of lifespan. It is level at first, then rises. This is partly due to increase in ROS with age, and partly due to failure of protein maintenance with age. They have set up a database of proteins modified by carbonylation, glycation, and lipid peroxidation products during aging and age-related diseases in various organ systems (Baraibar 2012, *Oxid Med Cell Longev*, 2012:919832). Several proteins become increasingly modified by HNE in WI-38 fibroblasts. Some proteins become increasingly carbonylated. Some become modified by AGE formation. These proteins are involved in energy metabolism, protein maintenance, and cytoskeleton. More than half the modified proteins are in the mitochondria. Glutamate dehydrogenase and catalase are among those modified increasingly with age. When fibroblasts are subjected to oxidative stress, they lose their proliferative capacity. Oxidation also inhibits proteasome activity. Modified proteins impair metabolic energy production, TCA, oxidative phosphorylation. These studies underscore the importance of performing proteomic analyses addressing different aspects, such as expression levels and modifications by carbonylation or glycoxidation, to have a broader view of the age-related changes affecting the cellular proteome.

Kelvin Davies: Have you tried to do a carbonylation curve to look for a threshold where carbonylation reaches a level to inhibit protein repair and then carbonylation increases greatly?

Helmut Sies: What is the consequence of glycation of catalase enzyme?

OP12 The lysosomal-mitochondrial theory of aging revisited

Tilman Grune DEPARTMENT OF NUTRITIONAL TOXICOLOGY, INSTITUTE OF NUTRITION, FRIEDRICH-SCHILLER UNIVERSITY JENA, GERMANY
The end product of heavily oxidized and cross-linked proteins is lipofuscin.

Lysosomal cathepsins are able to digest many kinds of proteins. Normally, the proteasome only digests oxidized, unfolded proteins, but not aggregates. (Brunk and Terman. *Eur J Biochem* 2002) Early work suggested that lipofuscin is only formed in lysosomes. Lipofuscin is contributing to an increased level of radical formation in senescent fibroblasts. Lipofuscin is able to catalyze its own formation. In contrast to the currently accepted view, their experimental results suggest that lipofuscin can form in the cytosol, without needing to form inside of lysosomes or autophagosomes. They conclude this because lipofuscin accumulates within the cytosol if autophagy or lysosomal activity is inhibited. Therefore they conclude that lipofuscin can form in the cytosol and then be imported into the lysosome by autophagosomes. If import of lipofuscin into the lysosomes is decreased, as occurs during aging, the toxicity of the cytosolic lipofuscin increases. Furthermore, the cytosolic lipofuscin inhibits the activity of the proteasomal system. Ubiquitinated proteins accumulate. Tilman is an editor of *Redox Biology*.

Kelvin Davies: Ubiquitinated proteins accumulate. This shows that they were not degraded by the proteasome.

Lester Packer: Is there any lipofuscin in the nucleus?

A: I wish I could answer. We could not detect any protein aggregates in the nucleus. Aggregated histones have been found outside the nucleus. Proteolysis is different in the nucleus than in the rest of the cell.

Nesrin Kartal-Özer: Can this degradation be modulated by micronutrients?

A: Yes. We can activate the proteasome by secondary plant metabolites. They might activate the proteasome by the activity of Nrf2. The proteasome enzyme is methylated, so it can be modified by micronutrient compounds.

SESSION III MITOCHONDRIA, ENERGY, AND METABOLIC DISEASES

CHAIRPERSONS: *Enrique Cadenas*,

PHARMACOLOGY & PHARMACEUTICAL SCIENCES, SCHOOL OF PHARMACY, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, USA

Alberto Boveris PHYSICAL CHEMISTRY, SCHOOL OF PHARMACY AND BIOCHEMISTRY, UNIVERSITY OF BUENOS AIRES, ARGENTINA

OP13 New insights into metabolic regulation by protein-tyrosine phosphatase 1B

Fawaz Haj, DEPARTMENT OF NUTRITION, UNIVERSITY OF CALIFORNIA, DAVIS, CALIFORNIA, USA

Tyrosine phosphorylation is reversible. It is important in regulation of cellular homeostasis.

PTP1B (Protein-Tyrosine Phosphatase 1B) is a physiological regulator of glucose homeostasis and adiposity.

PKM2 is implicated in cancer metabolism and tumor growth. PKM2 KD results in reduced ability to form tumors. PKM2 is a substrate of PTP1B.

OP14 Age-associated declines in mitochondrial biogenesis and protein quality control factors are minimized by exercise training via sirtuin activation

Zolt Radak, SEMMELWEIS UNIVERSITY, RESEARCH INSTITUTE OF SPORT SCIENCE, BUDAPEST, HUNGARY

Exercise training prevents the age-associated declines in SIRT1 activity, AMPK, pAMPK, PGC-1 α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha), UCP3, and LON protease.

Exercise training also prevents the age-related detrimental increases in NRF1, TFAM, Fis1, Mfn1, and PNPase (polynucleotide phosphorylase) levels. Exercise increases SIRT1 and SIRT3 content/activity. SIRT1 suppress the activity of OGG1. It appears that exercise training can help minimize detrimental skeletal muscle aging deficits by improving mitochondrial protein quality control and biogenesis.

Q: What is the mechanism of SIRT1 regulation? Which comes first?

A: We have a paper coming out.

George Brooks: During exercise, how do we change the levels of cellular NAD?

A: During exercise, the level goes down.

Q: Did you test different types of exercise?

A: We tested only aerobic exercise.

12:30 Group Photo, Lunch, Poster viewing

OP15 Autophagy induction with life-long and late-onset interventions: caloric restriction combined with resveratrol

Christiaan Leeuwenburgh, DEPARTMENTS OF AGING AND GERIATRIC RESEARCH, UNIVERSITY OF FLORIDA, GAINESVILLE

Many processes are involved in health maintenance during aging: inflammation, protein synthesis and quality control, autophagy, etc.

Protein quality control includes: The ubiquitin-proteasome system. The autophagy-lysosome system.

They studied autophagy inducers, including Rapamycin and Resveratrol. They studied mouse atrial HL-1 cardiomyocytes and AC16 Human ventricular cardiomyocytes.

Fluorescent imaging of GFP-LC3 shows autophagosomes.

They used Antimycin A (AMA) as a stress inducer, which increased mitochondrial superoxide generation, decreased mitochondrial membrane potential (MMP), enhanced cell death, increased DNA and RNA oxidative damage, and decreased mitochondrial respiration. Rapamycin rescued the cells. They also tested resveratrol and various other compounds from food, such as caffeine, for their ability to upregulate autophagy.

Doxorubicin is a chemotherapeutic agent used against cancer. But it damages the heart by inducing oxidative stress.

Next, they looked at muscle biopsies in a small sample of older overweight women. Then put them on a regimen of moderate exercise and modest diet. They found upregulation of some of the autophagy proteins. Also they saw upregulated proteins involved in ubiquitylation and turnover of damaged proteins.

Does aging decrease PGF1 gene expression and mitochondrial biogenesis? The role of exercise.

Training reverses the aging effect and upregulates PGC1 expression.

OP16 **PGC-1 α overexpression attenuates mitochondrial disorder and inflammatory responses in muscle disuse atrophy**

Li Li Ji, LABORATORY OF PHYSIOLOGICAL HYGIENE AND EXERCISE SCIENCE, UNIVERSITY OF MINNESOTA, MINNEAPOLIS, USA

Skeletal muscle mass changes with altered use. It loses mass and function within a rather short time of disuse. Two pathways regulate muscle protein degradation: autophagy (FoxO) and inflammation (NF κ B). Ubiquitin E3 ligases target components of contractile proteins.

PGC-1 α reverses the immobilization effect. PGC-1 α increases mitochondrial biogenesis and reduces inflammation.

Kelvin Davies: You said that some of the damage looks like ischemia reperfusion. Could it be muscle blood-flow? Could the the immobilization bandaging be causing ischemia-reperfusion when the bandage is removed?

A: We did not bandage very tightly, but perhaps there was some ischemia-reperfusion when the immobilization is released. The ankle was turned down, so the stretched muscle might have had an effect.

A: For astronauts, it is the reloading of the muscles upon return to Earth that causes massive oxidative stress damage. Being in space is not the major cause of damage.

OP17 **Modern concepts in mitochondrial biogenesis and dynamics**

George A. Brooks, PhD,

EXERCISE PHYSIOLOGY LABORATORY, DEPARTMENT OF INTEGRATIVE BIOLOGY, UNIVERSITY OF CALIFORNIA, BERKELEY,

Mitochondria exist in cells as components of a 3-dimensional mitochondrial network, or reticulum, not as separated mitochondrial capsules. The reticulum extends from the cell surface to deep within the cell. Why is mitochondrial morphology important? The mitochondrial reticulum powers us. (Packer and Skulachev, et. al 1977)

In fact, if you isolate a mitochondrion, you have damaged the mitochondrial network.

The reticulum helps to transport O₂ and create the chemi-osmotic gradient.

Mitochondrial CO_x and LDH. Pyruvate enters the TCA cycle.

Mitochondrial Dynamics: Elements of the mitochondrial reticulum continuously fuse and fission.

Four GTPases are involved: 3 fusion proteins: Mitofusin-1 (Mfn1), Mfn2, Opa1.

2 fission proteins: Drp1, Fis1

(Ogata and Yamasaki 1997) drawings show reticula in white and red human muscle fibers.

Lactate is the biggest redox signal. The heart burns lactate. The brain burns lactate. The muscles make and export lactate. Anything red takes up lactate. Mitochondria actually respire lactate much more than pyruvate.

Q: You said that when mitochondria are isolated that they are damaged. Are the centrifugation methods being updated to get better measurements of respiration?

Enrique Cadenas: You showed the mitochondrial network in muscle. Does it look the same in brain?

A: There are micrographs that show a network in neurons.

Q: What is respired in mitochondria? pyruvate or lactate?

A: Both are respired.

Q: How does the network fit with the endosymbiotic theory of mitochondrial origins?

http://en.wikipedia.org/wiki/Endosymbiotic_theory

A: I don't believe the endosymbiotic theory.

CHAIRPERSONS: *Juan Sastre*, DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF VALENCIA, VALENCIA, SPAIN

Bertrand Friguet, LABORATOIRE DE BIOLOGIE CELLULAIRE DU VIEILLISSEMENT, UNIVERSITÉ PIERRE ET MARIE CURIE, PARIS, FRANCE

OP18 **Communication between endoplasmic reticulum and mitochondria by thioredoxin**

Junji Yodoi DEPARTMENT OF BIOLOGICAL RESPONSES, INSTITUTE FOR VIRUS RESEARCH, KYOTO UNIVERSITY, KYOTO, JAPAN AND

DEPARTMENT OF BIOINSPIRED SCIENCE, EWhA WOMANS UNIVERSITY, SEOUL, KOREA

Thioredoxin (TRX) suppresses croton oil induced dermatitis.

Natural TRX product from Japanese sake extract.

TBP2= TRX Binding Protein 2.

Redox regulation by a TRX-TBP2 system.

The Redoxosome concept: Redox-sensitive signalosome/ inflammasome: TRX-TBP2 regulating signal complex.

TRX Barrier to protect against inhaled disease transmission.

TRX skincare is now on sale.

GHSI: A virtual R&D consortium.

OP19 Nanoparticles and mitochondrial activity

Prof. Bertrand Rihn, EA CITHEFOR, FACULTÉ DE PHARMACIE, UNIVERSITÉ DE LORRAINE, NANCY, FRANCE

We are exploring use of nanoparticles (NP) to deliver drugs. Are those NP immunotoxic? Do they interact with macrophages? They used polymeric Eudragit=Poly(meth)acrylates: RS (6%) or RL (12% NH₄ groups).

Polymeric Eudragit NP (PENP-RS) are prepared by nanoprecipitation. They used NR8383 Rat alveolar macrophages, Human CD14+ cells, THP-1 human monocytes, Human mammary epithelial cells (HMEC). For all cells, incubate 24 hrs.

NR8383 PENP-RS uptake occurs by a clathrin-dependent mechanism. It increases metabolic activity, but PENP-RL do not.

Some cell types increase their metabolic activity in response to PENP-RL.

Other cell types decrease their metabolic activity in response to PENP-RL.

Some cell types increase their metabolic activity in response to PENP-RS.

Other cell types decrease their metabolic activity in response to PENP-RS.

They conclude that NP can be a specific means of drug delivery.

Q: What is your opinion? Should they be used as drug carriers? Are they toxic?

A: This is very complicated issue because of different interactions specific to various cell types. We should check every kind of cell and carefully do the *in vivo* studies. We should design biodegradable NPs. These PENPs are not biodegradable.

OP20 Hormesis: scientific foundations, mechanisms and biomedical applications

Eduardo J. Calabrese, DEPARTMENT OF PUBLIC HEALTH, UNIVERSITY OF MASSACHUSETTS, AMHERST.

Hormesis is a shape of a dose-response curve, in which low dose can be beneficial while high dose can be harmful.

He believes that Hormesis is showing a Capacity for biological plasticity. Beneficial or harmful should not be part of the definition of "Hormesis". eg. An antitumor drug that kills tumors in high doses, but low doses stimulates growth of tumor cells.

e.g. Some memory drugs enhance memory at low doses, but decrease memory at higher doses.

Each hormetic mechanism is unique to the model, tissue, endpoint, and agent. He gives many examples. Studying hormetic mechanisms by receptor agonists or signaling pathway inhibitors.

Ethanol has a hormetic effect on social activity of adolescent rats. At low doses, they are more social; at high doses, they are less social.

Low dose morphine inhibits seizures, while high dose morphine facilitates seizures.

Low dose DDT inhibits rat liver tumor formation, but high dose DDT causes more rat liver tumors.

SESSION IV ORAL PRESENTATIONS BY YOUNG INVESTIGATORS

CHAIRPERSONS:

Nesrin Kartal-Özer, DEPARTMENT OF BIOCHEMISTRY, FACULTY OF MEDICINE, MARMARA UNIVERSITY, ISTANBUL, TURKEY

João Laranjinha, CENTER FOR NEUROSCIENCES AND CELL BIOLOGY, UNIVERSITY OF COIMBRA, COIMBRA, PORTUGAL

OP21 EGF receptor activation by 4-hydroxynonenal alters TGF- β -induced elastogenesis in fibroblasts

Pauline Larroque-Cardoso, INSERM UMR 1048, TOULOUSE, FRANCE

TGF- β 1 is a strong stimulator of elastin expression and elastin mRNA stabilizer. Aldehydes interfere in receptor signaling. Is 4-HNE impairing TGF- β 1 signaling? Yes. HNE induces EGF receptor activity.

There is loss of elastin with aging. With age, HNE levels rise.

John Maguire: The half life of elastin in humans is 70 years. How long is it in mice?

A: I suppose it is faster because mice have a 2 year lifespan.

John Maguire: Why is it different?

A: I don't know.

OP22 Selenoprotein N as a new player in mitochondrial homeostasis in skeletal muscle cells

Sandrine Arbogast, UMR787 - INSERM - UNIVERSITÉ PIERRE ET MARIE CURIE, PARIS, FRANCE

Selenoprotein N (SelN) plays a role in cell protection against oxidative stress. Absence of SelN leads to oxidative stress and more protein carbonylation. The dietary supplement NAC (N-acetyl cysteine) is an effective treatment for SelN deficiency. SelN is coded by the SEPNI gene. Knockdown of the SEPNI gene results in lower ATP production and increased production of superoxide by mitochondria.

OP23 Autophagy as quality control mechanism: Impact on aging of *Podospora anserina*

Andrea Hamann, J. W. GOETHE-UNIVERSITY, INSTITUTE FOR MOLECULAR BIOSCIENCES & CLUSTER OF EXCELLENCE, FRANKFURT, GERMANY

Autophagosome number increases with aging.

Conclude that autophagy is a pro-survival mechanism in *P.anserina*.

Gala Dinner in the Palais du Luxembourg

FRIDAY, JUNE 7

SESSION V EPIGENETICS AND NUTRIGENOMICS: DEVELOPMENT AND AGING

CHAIRPERSONS: *Steven H. Zeisel*, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, KANNAPOLIS, NORTH CAROLINA, USA

Patricia Oteiza, DEPARTMENT OF NUTRITION, UNIVERSITY OF CALIFORNIA, DAVIS, CALIFORNIA, USA

OP25 You are what your mother ate: nutrition and epigenetics influence development

Steven H. Zeisel, UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, KANNAPOLIS, NORTH CAROLINA, USA

Choline is essential. 550 mg/day is recommended for men; 450 is recommended for women who are smaller. It can act as a methyl donor, which could be important for methylation of DNA and histones. That can affect gene expression and associated changes in stem cell proliferation and differentiation. Only young women are able to make it *de novo*. If there is deficiency of choline in diet, the body makes it in liver from methionine (Met) and SAM and AdMet, which become depleted. Endogenous choline synthesis via PEMT is turned on by estrogen. 44% of women have SNPs that prevent them from being able to synthesize choline in response to estrogen. During pregnancy, placenta can take large amount of choline to the fetus. Breast milk can deliver large amount of choline to nursing infant. Choline during critical periods of brain development improves memory. In rodents, it is important for neurogenesis and development of the hippocampus, septum, and retina. Common prenatal vitamin supplements do not contain adequate choline.

Q: Do low choline mice have a fertility problem?

A: No.

Q: What about TMAO?

A: Ingested choline can be converted by gut bacteria to TMAO. TMAO is cleared by the kidney, unless there is kidney problem. With kidney problems, TMAO can contribute to atherosclerosis.

OP26 Redox signaling and histone acetylation in acute inflammation. Relevance of protein phosphatase PP2A

Juan Sastre, DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF VALENCIA, VALENCIA, SPAIN

Acute pancreatitis starts with abdominal pain. It requires hospitalization. Inflamed pancreas secretes inflammatory cytokines into blood, which can result in death by acute multiple organ failure. They created lab models of pancreatitis to study the disease.

There is crosstalk between oxidative stress and pro-inflammatory cytokines through serine/threonine protein phosphatases, Tyr protein phosphatases, and MAPK (mitogen-activated protein kinase) that amplifies an inflammatory cascade and tissue injury.

In contrast, histone deacetylases (HDACs) and protein phosphatases are mainly involved in the

attenuation of inflammation. Protein phosphatases are a major target of ROS and redox signaling in the inflammatory cascade. In acute pancreatitis, PP2A activity is silenced by formation of intramolecular disulfide bonds. This leads to ERK phosphorylation and upregulation of interleukin 6, TNF α , and chemokine CXCL1.

Q: Where is PPT2 located?

A: In the cytosol and the nucleus. Probably not in the ER.

OP 27 Getting to know curcumin –the golden spice– through epigenetic changes

Bharat B. Aggarwal, CYTOKINE RESEARCH LABORATORY, DEPARTMENT OF EXPERIMENTAL THERAPEUTICS, MD ANDERSON CANCER CENTER. THE UNIVERSITY OF TEXAS, HOUSTON, TEXAS, USA

He was formerly in Lester Packer's lab.

Chronic inflammation plays a very important role in chronic diseases, including cancer, diabetes. When under control, small amounts of inflammation and pro-oxidants are healthy. It is uncontrolled inflammation and pro-oxidants that can cause diseases.

Inflammation can come from many environmental and lifestyle factors, including UV, fried foods, radiation, environmental pollutants, red meat, smoking, high-caloric diet, etc. Transcription factors NF κ B and STAT3 are activated by lifestyle risk factors.

NF κ B is at the center of an inflammation network, which can cause cancer. Inflammation is regulated by epigenetic changes, which are indicated by histone modifications by histone deacetylases and histone acetyltransferases. Also by DNA methylation induced by DNA methyltransferase. Also by alteration of gene expression induced by miRNA. The whole process can take **30 years**. [JDF: Does it take this long in mice, or are mice not a good model for this?]

How can we control NF κ B? Anti-inflammatory foods, spices, ayurvedic medicine, and traditional Chinese medicine all have things that help.

Curcumin comes from the plant *curcuma longa* or Turmeric. curcumin = Diferuloylmethane. It is 2-5% of turmeric. Curcumin modulates the expression of dozens of genes. Curcumin physically binds to and inhibits activity of many proteins. Curcumin downregulates expression of cell proliferation, antiapoptotic, and metastatic genes.

But today, will talk about epigenetic regulation induced by curcumin and other natural products. TNF activates HAT, which nutraceuticals can inhibit.

Evodiamine blocks p65 acetylation.

Indole 3 carbinol blocks NF κ B and p65 acetylation.

Anacardic acid also blocks p65 acetylation.

Also TCM God of Thunder Vine (Triptolite) blocks p65 acetylation.

White vs yellow curcumin: Yellow curcumin binds to HAT. White curcumin (tetrahydro) has no effect at all on HAT.

Valerian is the best known inhibitor of HDAC.

Curcumin is as effective as metformin in activating AMPK, but requires only 1/400th the dose for the same effectiveness. Curcumin is effective as a treatment for multiple sclerosis.

DimethylFormamide was recently FDA approved in 2013 as a treatment for MS.

JDF: I cook with turmeric in olive oil. Am I getting adequate curcumin that way, or is there an advantage to taking the extract?

A: We are still developing biomarkers to determine how much is enough. But the method of cooking turmeric with olive oil and black pepper is a fine way to get the curcumin. Curcumin is about 2-5% of turmeric. Curcumin and turmeric are lipophilic, so they are more bioavailable with oil or fat. Another traditional way of getting bioavailable curcumin is to mix turmeric with whole milk or yogurt. It forms an emulsion with the dairy fat. A good dose would be 150 mg curcumin, twice per day.

JDF: You said that NF κ B is at the center of an inflammatory network, which can take 30 years to develop into cancer. Does this happen much faster in mice, or are mice a bad model for studying human cancer development.

A: Mice are not a good model for studying human cancer development.

CHAIRPERSONS: *Kelvin Davies*, SCHOOL OF GERONTOLOGY, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, CALIFORNIA, USA

Arlette Delamarche, LABORATORY « MOVMENT, SPORT & HEALTH », UNIVERSITY OF RENNES 2, ENS CACHAN, UFR-APS, RENNES, FRANCE

OP28 **Impact of gestational and early-life postnatal factors in the development of obesity and fatty liver in Hispanic children**

Michael I. Goran, PREVENTIVE MEDICINE AND CHILDHOOD OBESITY RESEARCH CENTER, KECK SCHOOL OF MEDICINE, UNIVERSITY OF SOUTHERN CALIFORNIA, LOS ANGELES, CALIFORNIA, USA

Hispanic people are particularly susceptible to accumulation of liver fat, which can increase the risk of liver disease. Restriction of dietary sugar is effective. Consumption of sugary beverages is especially harmful. Consumption of non-starchy vegetables is protective. The polyphenols, especially catechins, in the vegetables inhibit the digestion and absorption of dietary sugars. Exposure to fructose during pregnancy and early development can predispose the child to later fatty liver disease.

So, sugary beverages, especially those sweetened with fructose or high fructose corn syrup are harmful. So are filtered fruit juices, such as apple juice. **However, whole fruits are beneficial**, despite containing some fructose, because:

- The whole fruit contains less fructose than juices or artificially sweetened beverages.
- Fiber in the fruit slows absorption of the natural sugars.
- The cell wall slows absorption of the natural sugars.
- The fruits contain other beneficial polyphenols.

Billy Fraga: What exactly do you mean by "Hispanic"? Many of the people you study came from Mexico. Many of them are descended from Asians, rather than Europeans.

A: I agree. Most of our study population are Mexican or Central American.

OP29 **Recent understanding of hypoxia-induced endothelial dysfunction in development of metabolic syndromes**

Tzu-Ching Meng, INSTITUTE OF BIOLOGICAL CHEMISTRY, ACADEMIA SINICA, NANKANG, TAIPEI, TAIWAN

NO is produced by the endothelium. It can diffuse to smooth muscle around arteries and signal to them. Decrease in NO is a key step toward atherogenesis development. NO can target guanylyl cyclase. Cys163 of Caspase-3 can get nitrosylated by NO. In ancient China, nitrate was used to treat people after heart attack.

We need vegetables because they provide us bioactive nitrate and nitrite.

Q: How much nitrosamines would be formed in the gut from the nitrates and nitrites in vegetables?

A: The levels of nitrate in the bloodstream from eating vegetables would be 1-10 mM. These levels are considered to be beneficial, and unlikely to be problematical.

OP30 **Inflammatory response in mice is associated with age-related zinc deficiency and epigenetic dysregulation of zinc transporters**

Emily Ho, PhD, LINUS PAULING INSTITUTE, OREGON STATE UNIVERSITY, CORVALLIS, OREGON, USA

We all need zinc (Zn). It is involved in many diverse processes. There are over 300 metalloenzymes, and over 1000 zinc dependent transcription factors contain Zn. Zn is an essential micronutrient. Zn deficiency during pregnancy can cause birth defects. There is not much storage of Zn in the human body, so it must be replenished frequently.

EAR = estimated average requirement. RDA = Recommended Dietary Amount.

Zinc requirement is 11 mg/day in males; 8 mg/day in females. Food sources of Zn are proteins, including seafood, especially oysters, meat, nuts, legumes, and whole grains. Oysters are one of the number-one zinc-containing foods.

A reliable sensitive biomarker for Zn deficiency has not been found. They studied human volunteers and put them on a zinc-depletion diet. The plasma Zn concentration did not change. Aging is associated with a progressive dysregulation of immune functions. Aging is associated with chronic inflammation.

Effects of Zn deficiency is similar to effects of aging on immune functions:

- increases in inflammatory cytokines.
- reduced thymic output.

- depressed adaptive immunity,
- impaired host defense,
- increased risk to opportunistic infections.

Aged mice have reduced intracellular Zn in immune cells, even though they are eating enough Zn which would be adequate for young mice.

(Rando TA, and Chang HY. *Cell*. 2012 Jan 20;148(1-2):46-57 Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock.)

Zn requirements might change with age; age-specific requirements for Zn may be warranted. Zn levels are often depressed in aged people, even when they are consuming a diet which would provide adequate Zn to young people.

Robert: What form is best?

A: Protein bound Zn is more bioavailable, but even ZnSO₄ will give you enough.

Jarrow Rogovin: Zn-L-Met has been approved by FDA for animal feeds as a source of dietary Zn.

A: Nobody has studied them in humans.

12:30 – 13:30 *Lunch and Poster Viewing*

Centenarians up regulate the expression of microRNAs

José Viña DEPARTMENT OF PHYSIOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF VALENCIA, VALENCIA, SPAIN

For many centenarians, their healthspan approaches their lifespan. Centenarians upregulate their expression of miRNAs. They are studying which mRNAs are regulated by which miRNAs. They used Ariadne software to analyze the subnetworks, 102 mRNAs are upregulated in centenarians, compared with octagenarians, while only one is downregulated.

7 miRNAs are upregulated in Centenarians and in young people, although in most octagenarians, they are downregulated.

(<http://www.nature.com/srep/2012/121211/srep00961/full/srep00961.html>)

OP 32 Epigenetics and aging: the role of the environment

Mario Fraga

CANCER EPIGENETICS LABORATORY, INSTITUTO UNIVERSITARIO DE ONCOLOGÍA DEL PRINCIPADO DE ASTURIAS, UNIVERSITY OF OVIEDO, SPAIN

DNA methylation is necessary for normal development in higher organisms. DNA methylation signatures of aging are found in blood.

Q: Statistical power. How do you get valid answer asking 50,000 questions?

AWARDS

YOUNG INVESTIGATOR AWARDS

(See abstracts on OCC website for poster titles and abstracts.)

- **OXYGEN CLUB OF CALIFORNIA AWARD : EMILIA GOSPODARSKA - POSTER N° 52**
- **LINUS PAULING INSTITUTE AWARD : SHERZAD RASHID - POSTER N° 28**
- **SOCIÉTÉ FRANÇAISE DE RECHERCHE SUR LES RADICAUX LIBRES AWARD:
SANDRINE ARBOGAST - POSTER N° 50**
- **EXON AWARD (ASSOCIATION OF CELL AND MOLECULAR BIOLOGY TEACHER-RESEARCHERS OF THE
FACULTIES OF PHARMACY) : AUDREY DESVERGNE - POSTER N° 68**
- **SOCIETY FOR FREE RADICAL RESEARCH – EUROPE AWARD: ANDREA HAMANN - POSTER N° 70**
- **THE OXIDATIVE STRESS COLLEGE AWARD: ELEONORA CREMONINI - POSTER N° 35**
- **FACULTY OF PHARMACY OF RENNES AWARD: PAULINE LARROQUE- CARDOSO - POSTER N° 78**
- **FACULTY OF SPORT SCIENCE OF RENNES AWARD : THOMAS BRIOCHE - POSTER N° 84**
- **ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS (ELSEVIER) AWARD (1): HOI SHAN WONG
POSTER N° 42**
- **ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS (ELSEVIER) AWARD(2): CASSILDA PEREIRA
POSTER N° 31**
- **FOOD AND FUNCTION - RSC PUBLISHING AWARD : ABDENOUR BELKACEMI - POSTER N°46**

Jury, Awards Committee :

John Maguire (Président, Oakland), Jean Cadet (Grenoble), Pierre Cillard (Rennes), Nesrin Kartal-Ozer (Istanbul), Emily Ho (Corvallis), Joao Lanranjinha (Coimbra), Joël Pincemail (Liège), Amélie Rébillard (Rennes), Françoise Rannou-Bekeno (Rennes)

PROGRESS IN HEALTHSPAN RESEARCH AWARD

- **JOSE VINA - ORAL PRESENTATION OP 31**

Jury, Award Committee :

Angela Mastaloudis (Salt Lake City), Jarrow Rogovin (Los Angeles), Helmut Sies (Düsseldorf).

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SPECIAL THANKS TO SENATEUR EDMOND HERVE

Abbreviations:

aa = amino acids; ab = antibodies.
AD = Alzheimer's Disease; Alz = Alzheimer's.
Abeta = A β = amyloid beta.
apop = apoptosis.
Apgy = autophagy
BBB = blood-brain barrier
bp = base-pairs of DNA
C.e. = C.elegans = nematode = worm.
CR = calorie restriction = DR = dietary restriction
cv = cardiovascular; cvd = cardiovascular disease
dsDNA=double-stranded DNA; ssDNA = single-stranded DNA; nDNA=nuclear DNA;
mtDNA=mitochondrial DNA
Dros = Drosophila melanogaster = fly.
EtBr = Ethidium Bromide
ESC = embryonic stem cell
exp = gene expression.
fn = function
GSH = Glutathione (reduced); GSSG = Glutathione (oxidized)
GPCR = G-protein coupled receptor
GWAS = Genome-wide association study
Hb = hemoglobin, the oxygen-carrying protein in RBCs.
HBO = Hyperbaric oxygen (greater than atmospheric pressure)
HSC = hematopoietic (blood-forming) stem cell
IGF = insulin-like growth factor
IP = intellectual property
iPSC = iPS cells = iPC = induced pluripotent stem cells
KD = gene knock down; KO = gene knockout.
life ext= lifespan extension.
LF = lipofuscin, a heterogeneous polymer that accumulates in aging lysosomes.
miR = miRNA = microRNA
mito = mitochondrion; mt = mitochondrial; mtDNA = mitochondrial DNA.
MSC = mesenchymal stem cells
mTOR = mammalian Target Of Rapamycin
NAC = N-acetyl-L-cysteine
NIA = National Institute on Aging of the U.S. National Institutes of Health
phosylate = phosphorylate = covalently bind a phosphate group to a molecule
RBC = red blood cell = erythrocyte
NAC = N-acetyl-cysteine
ROS = reactive oxygen species or free radicals
SASP = senescence associated secretory phenotype
Tase = telomerase; Tmere = telomere
TLN = translation of RNA to protein; TXN= transcription of DNA to RNA.
vs = versus, compared with
w = with ; wo = without.
wt = wild-type gene. +/- = homozygous normal gene. KO = gene knockout.
KD = gene knock down; -/- = homozygous KO; +/- = heterozygous gene.
8-oxo-dG = 8OHdG = marker of oxidized DNA.
In biochemical or genetic pathways:
blockage or inhibition -| Activation or causation =>
Q: or Name: question or comment from the audience.
A: answer from the speaker
[JF: Editorial comments by John Furber.]