INCT de Processos Redox em Biomedicina

Redoxoma

http://www2.iq.usp.br/redoxoma/

Process: 573530/2008-4

ANNUAL ACTIVITY REPORT

24/4/2009 a 24/4/2010

INCT OF REDOX PROCESSES IN BIOMEDICINE
REDOXOMA

Mission- To enable a concerted effort to attack key questions bridging meaningful gaps in the field of redox processes in biomedicine. Our efforts will foster integration of multiple disciplines and Institutions in Brazil and result in advances with educational, scientific, environmental and socioeconomic impact.

Implications- The study of redox processes has high potential to elucidate integrative biological mechanisms, due to the ubiquity and strength of their effects. Many studies involve the role of redox mechanisms in diseases. However, the complexity of this field has increased concerning structures, structure-function relationships, methods, molecular and sub-cellular pathology of redox-regulated proteins, genomics, proteomics and metabolomics of oxidative stress. Thus, a multidisciplinary approach has become essential for meaningful advances in the field. Also, emerging groups have difficulty to address relevant points and sharpen educational skills. The main purpose of our Redoxome Network is to foster integrative collaborations, promote sustained development and assist emerging groups.

Goals- Our goal is to perform studies that allow the design and assessment of novel antioxidant strategies with clinical applicability. We will address issues relevant toward overcoming limitations in knowledge of redox processes, as follows: 1) ROS generation and control in biological systems; 2) Chemical reactivity of reactive oxygen species (ROS) in biological environments and consequent changes in structure and function of biomolecules; 3) Mechanisms and networks involved in redox signaling processes relevant to human diseases. 4) Diagnostic and therapeutic applications of redox processes.

Network

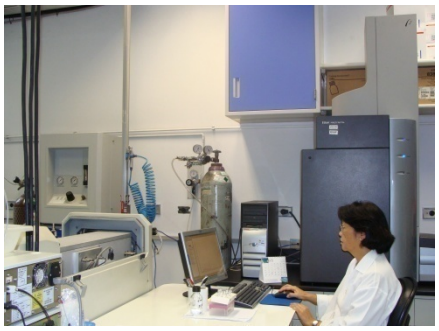
Headquarters- Instituto de Química, Universidade de São Paulo, São Paulo, SP

- Faculdade de Ciências da Saúde — Universidade Federal do Amazonas
- Centro de Biociências — Universidade Federal do Rio Grande do Norte
- Centro de Ciências Biológicas e da Saúde — Universidade Federal de Sergipe
- Instituto de Ciências Biológicas — Universidade de Brasília
- Instituto de Ciências Biológicas — Universidade Federal de Minas Gerais
- Universidade Federal de Alfenas — Departamento de Ciências Exatas
- Faculdade de Farmácia — Universidade Federal Fluminense
- Instituto de Química — Universidade Federal Fluminense
- Faculdade Medicina — Universidade de São Paulo
- Instituto Butantan
- Instituto de Biociências — Universidade de São Paulo
- Instituto de Química — Universidade de São Paulo
- Instituto do Coração — Universidade de São Paulo
- Universidade Federal de São Paulo — Campus de Diadema
- Centro Politécnico — Universidade Federal do Paraná
- Instituto de Biotecnologia — Universidade de Caxias do Sul, Centro de Ciências

Instrumentation and facilities available in the headquarters

Mass spectrometry

The INCT of Redox Processes in Biomedicine is equipped with four mass spectrometers (Ettan MALDI-TOF Pro mass spectrometer (Amersham Biosciences); Quattro II mass spectrometer (Micromass); API-4000 QTRAP mass spectrometer (Applied Biosystems); and GC-MS QP2010 plus (Shimadzu)). We will soon receive a long waited instrument, the Mass Spectrometer for Ultra High Resolution, type Quatrupolo - Time of Flight and Electrospray Ionization). The availability of these instruments allows both quantitative and structural determinations to be performed in the INCT-Redoxoma projects as well as offer support to other investigators.



Ettan MALDI-TOF Pro mass spectrometer (Amersham Biosciences

Access to additional mass spectrometry instrumentation is available through the “Analytical Facility of the Chemistry Institute-USP. The Facility is equipped with Bruker Daltonics Esquire 3000 Plus Ion trap LC-MS/MS, LC-MSMS 3200 Q-trap (Applied Biosystems), GC-MS QP2010 plus (Shimadzu), Brucker Daltonics LC-MS-microTOF.

EPR (electron paramagnetic resonance)

The INCT of Redox Processes in Biomedicine is equipped with two EPR spectrometers (Bruker EMX). EPR detects species with unpaired electrons been useful to study free radicals in test tubes, cells and biological fluids.

EPR Bruker EMX

HPLC- electrochemical detection

Analysis of oxidative DNA damage and reduced glutathione/oxidized glutathione ratio are performed by HPLC with electrochemical detection

2D-Gel electrophoresis

The techniques for protein profiling include the use of 2-dimensional electrophoresis with subsequent identification via mass spectrometry. 2D-Gel electrophoresis is performed using an Ettan 2-D Electrophoresis and an Ettan IPGphor 3 IEF System (GE Healthcare).

Comet assay

Single cell gel electrophoresis (SCGE), is a sensitive and rapid technique for quantifying and analyzing DNA damage in individual cells. Individual cells are embedded in a thin agarose gel on a microscope slide, the DNA undergoes electrophoresis, allowing the broken DNA fragments or damaged DNA to migrate away from the nucleus. The resulting image that is obtained resembles a "comet" with a distinct head and tail.

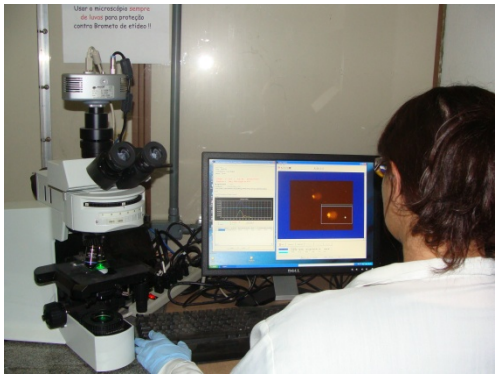


Image analysis is performed by fluorescence microscopy Olympus BX51. Comets on each slide are visually analyzed using a Komet 6.0 software.

Oxygen consumption

Just received via INCT the oxygraph from Oroboros is changing the sensitivity standards for monitoring oxygen consumption by cells and organelles.

Oroboros Instrument model 2K

Other instrumentation

The Instituto de Química Universidade de São Paulo also maintains mass spectrometry, confocal microscopy, flow cytometry, NMR and animal facilities. All of them provide basic services but require improvements to attain international standards. In particular, the animal facility is far from satisfactory despite many efforts to improve it.

2009 Seminars

12:00 h Instituto de Química Building 6- Seminars are followed by Lunch Discussion

Date	Speaker	Title
16/02	*Sayuri Myamoto*	Does peroxynitrite generate singlet oxygen
30/03	*Leda Vieira*	Free radicals and resistance to intracellular parasites
27/04	*Diogo Silva*	Analysis of protein modification by LC-MS/MS
25/05	Nadja C de Souza Pinto	Molecular mechanisms of repair of DNA oxidative lesions
29/06	*Roger Chammas*	Adaptation to oxidative stress in melanoma progression
27/07	*Marilene Demasi*	Glutathiolation to modulate protein function
1/08	*A confirmar*	
21/09	Anibal Vercesi	Nitric oxide and permeabilty transition
26/10	*Humberto Reis Matos*	Evaluation of the antioxidant activity from leaves of Cissuas sicyoides in oxidative stress induced alloxan-diabetes rats
30/11	*Wilson da Costa Santos*	Eugenia punicifolia as a possible source of antioxidants

2010 Real time seminars

12:00 h Instituto de Química Building 6- Seminars are followed by Lunch Discussion except for the first seminar of 2010 that inaugurated the Redoxoma real time seminars.

Date	Speaker	Title
07/04	*Rafael Radi* Universidad de La Republica	Cytochrome c tyrosine nitration: a "trigger" for an alternative conformation and function
26/04	Wilson Jacob Faculdade de Medicina, USP	Aging: challenges and oportunities
31/05	Lucymara Agnez Lima Universidade Federal do Rio Grande do Norte	
28/06	Vitor Ferreira Universidade Federal Fluminense	
26/07	Maisa Brigagão Universidade Federal de Alfenas	
30/08	Lia Nakao Universidade Federal do Parana	
27/09	Falvia Meotti Universidade Federal de Santa Catarina	Oxidation of uric acid by myeloperoxidase and its physiological relevance in inflammatory processes
25/10	Emerson Silva Lima Universidade Federal do Amazonas	
29/11	Glaucia Regina Martinez Universidade Federal do Parana	The role of melanin in cellular oxidative damage triggered by singlet oxygen

News during April 2009-April 2010

March 16, 2009

Article by researcher of the INCT of Redox Processes in Biomedicine-Redoxoma is cover of Chemical Research in Toxicology (CRT)

The use of exocyclic DNA adducts as biomarkers of lipid oxidation and indicators of disease development, a review by Marisa HG Medeiros, of the INCT of Redox Processes in Biomedicine, is the cover story in the March issue of Chemical Research in Toxicology (CRT), the journal of the American Chemical Society. (http://pubs.acs.org/journal/crtoec)

In the article, the researcher analyzes the potential use of these adducts as new tools for studying diseases related to oxidative stress and for determining the risks and etiology of various cancers, and highlights the challenges to develop specific methods for clinical studies.

Exocyclic adducts produced from DNA attack by aldehydes generated during lipid peroxidation have been the research focus of Marisa Medeiros and her group at the Chemistry Institute, Universidade de São Paulo, for many years. Recently, the group characterized the adducts resulting from reaction between DNA and acetaldehyde. This aldehyde is a product of incomplete combustion and metabolism of alcohol. The adduct characterized may prove to be interesting as a biomarker of diseases related to alcoholism and, in Brazil, air pollution, due to the increasing number of alcohol-fueled cars in our cities.

The review of worldwide research on exocyclic DNA adducts, published by Marisa in CRT, indicates that they are involved in many pathological conditions including inflammation, chronic infection and cancer. However, the extremely low levels of these adducts in tissues and biological fluids such as urine and blood, require ultrasensitive technologies based on mass spectrometry for its quantification and subsequent application in clinical analysis. The author concludes that, despite considerable progress in elucidating the mechanisms and roles of these adducts, their use as biomarkers has yet to be clearly demonstrated and is therefore a challenge for the coming years. This is one of the tasks the INCT of Redox Processes in Biomedicine wants to accomplish.

May 7, 2009

Researcher of INCT Redoxoma wins Women Scientist Award 2009

The researcher Lucymara Fassarella Agnez Lima, INCT of Redox Processes in Biomedicine, won the Women Scientist Award 2009 in category Senior Researcher, awarded by the Foundation for Research Support of Rio Grande do Norte (FAPERN).

Lucymara is associate professor at the Federal University of Rio Grande do Norte, permanent advisor in graduate courses in Biochemistry (UFRN) and Renorbio (Multinstitucional) and collaborative courses in Biological Sciences (UFRN), Health Sciences (UFRN) and Biotechnology (USP). Since 2000, Lucymara and her group participate in the project genome of sugar cane, supported by FAPESP. In the same year, the group ran for open bidding by MCT / CNPq for the formation of the National Network of sequence, obtaining approval as part of the 25 laboratories genome sequence of Chromobacterium violaceum. In 2008, research on oxidative stress carried by Lucymara started to be supported also by CNPq / FAPERN through the Support Program for Centers of Excellence (PRONEX). The group currently coordinates the Network metagenomic NE, supported by the edict RENORBIO / CNPq. The network is composed of students and researchers from around the Northeast and has as objective the identification and investigation of genes with potential for biotechnological applications in several areas.

October 6, 2009

Coordinator of the INCT of Redox Processes in Biomedicine wins Brazil Scopus Awards 2009

Profs Hernan Chaimovich, Ohara Augusto, Shirley Schreier e Walter Colli, from Departmento de Bioquímica, Instituto de Química, Universidade de São Paulo

Professor Ohara Augusto, Coordinator of the INCT of Redox Processes in Biomedicine, was one of the winners of the fourth edition of the Award Scopus Brazil, offered by Elsevier, with support from the Coordination of Improvement of Higher Education Personnel, Ministry of Education (CAPES / MEC). The prize includes researchers with significant scientific production and was delivered on September 28, at the Copacabana Palace in Rio de Janeiro.

The criteria for choosing the Scopus Award winners are based on evaluation of scientific literature, as reflected by the number of articles published and indexed in the database Scopus, the number of citations by other researchers, the H index and the number of masters and doctoral graduates according to the Curriculum Lattes. Sixteen Brazilian researchers were awarded in this issue, four at the Departmento de Bioquímica, Instituto de Química, Universidade de São Paulo. Besides Augusto, were awarded Hernan Chaimovich, Shirley Schreier and Walter Colli.

Scopus is an international database that contains abstracts and references from over 18 thousand scientific, technical and medical papers of five thousand publishers. Elsevier is one of the oldest publishers in the world and is headquartered in Amsterdam, Holland. It publishes over 2,000 journals and 1,900 new books per year.

Developing research on free radicals and oxidants, and with over 110 articles published in refereed journals, Professor Augusto is a recognized leader in chemistry and biochemistry of free radicals. In recent years her research helped to put in the scenario of Biology oxidants hitherto little considered, such as peroxynitrite ($ONOO^-$/ONOOH), carbonate radical ($CO_3^{\bullet -}$) and nitrogen dioxide ($NO_2^{\bullet}$). Currently, Augusto and her group investigate the participation of these species in inflammatory and neurodegenerative disorders. In parallel, they evaluate the effects of non classic antioxidants in controlling these processes.

Ohara Augusto is Full Professor at the Departmento de Bioquímica, Instituto de Química, Universidade de São Paulo, a member of the Brazilian Academy of Sciences and Commander of the Order of Scientific Merit. In 2002 she received the Medal for Biology and Medicine of the International EPR Society. In 2008, her career was highlighted in the magazine of the American Society for Biochemistry and Molecular Biology (ASBMB). She is the author of the book Free Radicals: Good, Bad and Natural, published in 2006. Her research is focused on the biochemistry of free radicals and oxidants and application of electron paramagnetic resonance (EPR) in biomedicine.

October 13, 2009

Young researchers of the INCT of Redox Processes in Biomedicine receive award from SFRBM

Researchers of Redoxoma Fernanda Cerqueira and Danilo Medinas were awarded the SFRBM Travel Awards (Society for Free Radical Biology and Medicine) to attend its 16th Annual Congress. Each year, SFRBM awards young doctoral researchers and post-doctors, based on assessing the quality of submissions of which they are first authors.

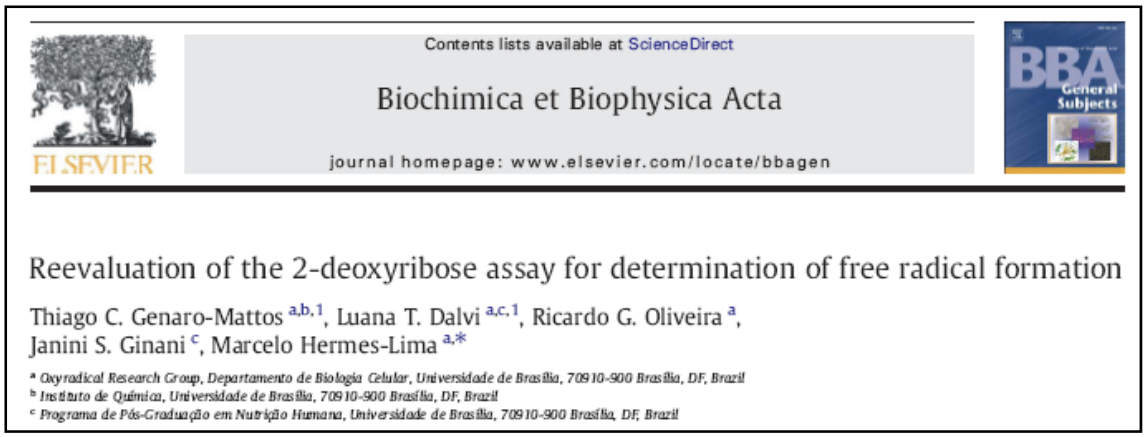
Fernanda Cerqueira presents the work: The Effects of Caloric Restriction and Mild Mitochondrial uncoupling on Mitochondrial Plasticity, eNOS Activity and Antioxidant Defenses.

Danilo Medinas presents the work: MS Characterization of the Human SOD1 Dimmer Covalent Enzyme Produced from the Peroxidase Activity. Implications to ALS.

The 16th Congress of SFRBM will be held from 18 to 22 November in San Francisco, California, United States.

October 13, 2009

Brasilia's group perfects method to detect the hydroxyl radical



Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Reevaluation of the 2-deoxyribose assay for determination of free radical formation

Thiago C. Genaro-Mattos [a,b,1], Luana T. Dalvi [a,c,1], Ricardo G. Oliveira [a], Janini S. Ginani [c], Marcelo Hermes-Lima [a,*]

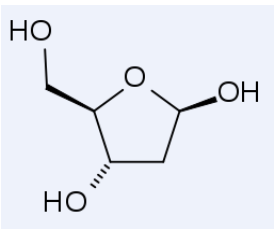
[a] Oxyradical Research Group, Departamento de Biologia Celular, Universidade de Brasília, 70910-900 Brasília, DF, Brazil
[b] Instituto de Química, Universidade de Brasília, 70910-900 Brasília, DF, Brazil
[c] Programa de Pós-Graduação em Nutrição Humana, Universidade de Brasília, 70910-900 Brasília, DF, Brazil

Method of "super white" for the detection of HO• radical

Marcelo Hermes-Lima

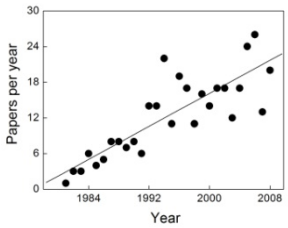
The more reactive free radical that exists in the solar system (including living beings) is the hydroxyl radical ($HO^{\bullet}$). It is formed, for example, by breaking the water molecule into $H^{\bullet}$ and $HO^{\bullet}$, or the hydrogen peroxide (H_2O_2 - widely known by fake blondes), $HO^{\bullet}$ and hydroxide anion (OH^-, which is almost the same as water).

There are many ways to detect the radical $HO^{\bullet}$. Some are expensive and popular (yes, science has these things) and others are cheap and popular. The expensive way involves detection of a stable free radical formed by reaction of certain groups of organic molecules with the radical $HO^{\bullet}$. This stable radical is detected by a magnetic resonance machine (or EPR), after placing a solution containing stable free radicals under the action of a powerful magnet (which generates a magnetic field). The signal that can be verified is a sort of fingerprint of the radical. Great, but to do these experiments you need to have access to EPR equipment.



Among the cheap, simple and popular methods, the most widely used is the 2-deoxyribose (or 2-DR). This method was created in the 80's and consists in detecting oxidation products of 2-DR with radical $HO^{\bullet}$. One product is an aldehyde (malondialdehyde) that can be quantified (i) after reacting with thiobarbituric acid (TBA - a reagent known since the 40s), forming a pink product, or (ii) by HPLC (see in Wikipedia what is HPLC), which may or may not use TBA.

The method of 2-DR is very popular among researchers studying antioxidant (or pro-oxidant) properties of single compounds or plant extracts. Since the mid-80s, more than 350 papers have used this methodology (including the one which used the colorimetric TBA test or HLPC) to measure radical $HO^{\bullet}$ (see picture beside). My research group at UNB has been a "customer" of this method since the 90s. Until 2006 everything seemed fine with this method.



But before you begin to criticize the method, let us know the most popular way of producing $HO^{\bullet}$. It is through the Fenton reaction, ie, $H_2O_2 + Fe^{2+}$. This reaction produces radical $HO^{\bullet}$ + hydroxide anion (OH^-) + Fe^{3+}. In mid-2006 found that Fe^{3+} reacted with 2-DR producing malondialdehyde. So what does that mean? That the reaction product of the Fenton reaction was reacting with the $HO^{\bullet}$.detector. The expected was that only $HO^{\bullet}$. would react with 2-DR. Now this was causing what we scientists call "background noise" or "artifact." See the reaction below:

$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + HO^- + HO^{\bullet}$ (Fenton reaction)

Expected reaction:

$HO^{\bullet}$ + 2-DR → malondialdehyde

Reaction "anomalous":

Fe^{3+} + 2-DR → malondialdehyde

We decided then to investigate if this "noise, anomalous" reaction of Fe^{3+} with a 2-DR, could cause problems with the method of 2-DR in studying the Fenton reaction. We spent the years 2007 and 2008 investigating many ways to produce HO• (and detect it through the test of 2-DR) and studying the influence of the anomalous reaction. We changed the type of buffer in between, we varied the concentrations of H_2O_2, Fe^{2+} and 2-DR in the reaction medium, add antioxidants and even fruit extracts. What we found was that in certain situations, something between 20 to 80% of the oxidative damage observed in 2-DR was caused by Fe^{3+} (Fenton reaction product) and not by $HO^{\bullet}$. What problem!

For the method of 2-DR to be used appropriately, we proposed a parallel control called "super white", to make adjustments in the data - a posteriori. In this reaction, a quantity of Fe^{3+} is added, which has to be the same as the concentration of Fe^{2+} in the reaction used "for real". Hence you do the subtraction:

reaction "for real" - super white = corrected result

We found that worked for all situations tested. What a relief! Well, we are now studying the mechanism of the reaction of Fe^{3+} with a 2-DR. This part is still in progress. We have obtained preliminary results of kinetics and thermodynamics of the reaction - but this discussion is for another day. For those interested in our study, it is available on the journal website BBA General Subjects. We are confident that in the coming years, many researchers (in several areas such as biology, nutrition, toxicology and agronomy) will benefit from this method of correction of 2-DR. This can give in a good number of citations.

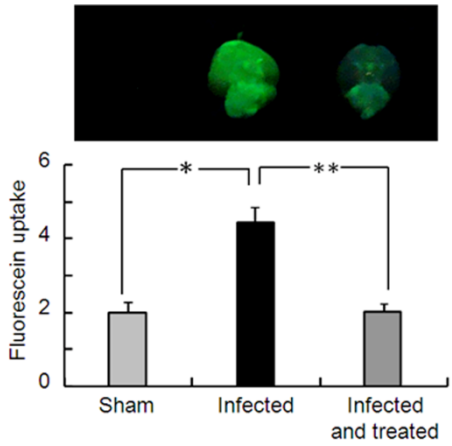
January 26, 2010

.**Study shows effectiveness of tempol in the treatment of multiple sclerosis in mice**

Researchers of INCT of Redox Processes in Biomedicine, Instituto Butantan and the Centre for Neurodegeneration of the Faculty of Medicine, Universidade de São Paulo, obtained good results when using the antioxidant tempol in the treatment of mice with encephalomyelitis. Neurological symptoms were markedly attenuated and survival of the animals was 70% higher in relation to those that were not treated. The work was published in the journal Free Radical Biology & Medicine (doi: 10.1016/j.freeradbiomed.2009.12.013). The results pave the way for the development of therapeutic strategies based on nitroxides for the treatment of neuroinflammatory diseases like multiple sclerosis, which is the most prominent neurological disorder among young adults in areas of moderate climate. Multiple sclerosis is an inflammatory disease and / or demyelinating disease of the central nervous system (CNS). The destruction of myelin affects neurotransmission and produces the various symptoms of the disease, that is degenerative and disabling. Although its causes are not yet fully known, it is believed that MS is an autoimmune disease.

In this study, researchers infected mice with hepatitis virus neurotropic (MHV-59A), which caused them to develop an encephalomyelitis that holds several similarities with human disease and is therefore considered an animal model of multiple sclerosis. In animals that were not treated, neurological symptoms appear quickly and 90% of them died ten days after inoculation of the virus. The few survivors had neurological deficits. Treatment with tempol attenuated the neurological symptoms such as lethargy and weakness or paralysis of the legs, and increased animal survival by 70%, with half of the survivors

continuing to behave like normal mice. The integrity of the central nervous system was maintained, including the blood brain barrier (see figure). Furthermore, the treatment reduced the viral concentration in the CNS, infiltration of macrophages and T lymphocytes and the levels of inflammatory markers.



To Ohara Augusto, coordinator of the INCT of Redox Processes in Biomedicine-Redoxoma and coauthor of the article, the results indicate that tempol altered the redox state of the infectious environment, contributing to a reduction of inflammatory response of the CNS. Although it is a defensive response, the inflammatory response, when exacerbated, leads to damage of nervous tissues. Apart from multiple sclerosis, neurodegenerative diseases like Alzheimer, Parkinson and ALS have inflammatory components and might be alleviated with the use of tempol. Likewise, the tempol could mitigate the consequences of brain injury, which also involves inflammatory processes. "We hold today that the antiinflammatory and antioxidant activities of tempol are interrelated, but we need to better understand these relationships at the molecular level for eventual use in humans," says the researcher.

Although tempol is a free radical of the class of nitroxide, it is quite stable in solution and acts on an almost catalytic form in biological fluids. Also several studies in animals show that it has low toxicity to mammals. Thus, the development of therapeutic strategies based on nitroxides might be interesting for the treatment of certain human diseases. The use in humans, however, still depends on greater understanding of its means of action in vivo.

January 28, 2010

Papers by investigators of the INCT of Redox Processes in Biomedicine are highlighted on the Web

Works of nvestigators of the INCT of Redox Processes in Biomedicine - Redoxoma appear on Top Ten lists - the ten most downloaded articles - of the online versions of journals in which they were published.

In December 2009, the review Sensitized formation of oxidatively generated damage to cellular DNA by UVA radiation, by Paolo Di Mascio with collaborators in France (Cadet J, Doukas T, Ravanat JL), was among the ten most downloaded from the Photochemical & Photobiological Sciences .

In the period from July to September 2009, the review Mitochondria and reactive oxygen species, by Alicia Kowaltowski and Nadja C. de Souza Pinto and colleagues at UNICAMP (Castilho RF, Vercesi AE), was number one in downloads from Free Radical Biology & Medicine.

In the period from March to June 2009, the article Aging defined by the chronologic-replicative protein network in Saccharomyces cerevisiae: an interactome analysis, by Fernanda Barea and Diego Bonatto, was among the ten most downloaded from journal Mechanisms of Ageing and Development

February 4, 2010

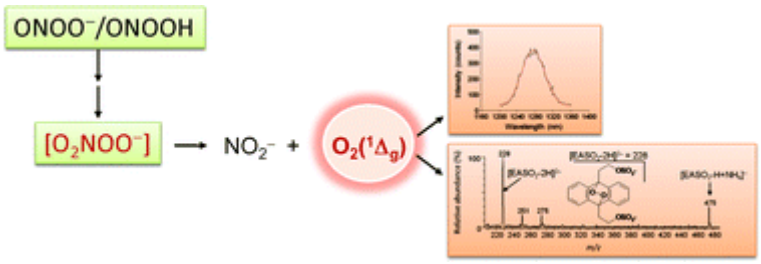
Highlighted Papers

Again, articles of researchers of INCT of Redox Processes in Biomedicine were highlighted in the magazines they were published.

The journal Dalton Transactions considered as "Hot Article" article Direct Evidence of singlet molecular oxygen generation from peroxynitrate, the decomposition product of peroxynitrite, by Paolo Di Mascio and colleagues (Sayuri Miyamoto, Graziella E. Ronsein, Thais C. Correa, Glaucia R. Martinez, Marisa HG Medeiros). (Dalton Trans., 2009, 5720-5729, DOI: 10.1039/b905560f).

Direct evidence of singlet molecular oxygen generation from peroxynitrate, a decomposition product of peroxynitrite
Sayuri Miyamoto, Graziella E. Ronsein, Thaís C. Corrêa, Glaucia R. Martinez, Marisa H. G. Medeiros and Paolo Di Mascio

The decomposition of peroxynitrite to nitrite and dioxygen at neutral pH follows complex kinetics, compared to its isomerization to nitrate at low pH. Decomposition may involve radicals or proceed by way of the classical peracid decomposition mechanism. Peroxynitrite ($ONOOH/ONOO^-$) decomposition has been proposed to involve formation of peroxynitrate (O_2NOOH/O_2NOO^-) at neutral pH (D. Gupta, B. Harish, R. Kissner and W. H. Koppenol, *Dalton Trans.*, 2009, DOI: 10.1039/b905535e, see accompanying paper in this issue). Peroxynitrate is unstable and decomposes to nitrite and dioxygen. This study aimed to investigate whether O_2NOO^- formed upon $ONOOH/ONOO^-$ decomposition generates singlet molecular oxygen [O_2 ($^1\Delta_g$)]. As unequivocally revealed by the measurement of monomol light emission in the near infrared region at 1270 nm and by chemical trapping experiments, the decomposition of $ONOO^-$ or O_2NOOH at neutral to alkaline pH generates O_2 ($^1\Delta_g$) at a yield of *ca.* 1% and 2-10%, respectively. Characteristic light emission, corresponding to O_2 ($^1\Delta_g$) monomolecular decay was observed for $ONOO^-$ and for O_2NOOH prepared by reaction of H_2O_2 with NO_2BF_4 and of H_2O_2 with NO_2^- in $HClO_4$. The generation of O_2 ($^1\Delta_g$) from $ONOO^-$ increased in a concentration-dependent manner in the range of 0.1-2.5 mM and was dependent on pH, giving a sigmoid profile with an apparent pKa around pD 8.1 (pH 7.7). Taken together, our results clearly identify the generation of O_2 ($^1\Delta_g$) from peroxynitrate [$O_2NOO^- \rightarrow NO_2^- + O_2$ ($^1\Delta_g$)] generated from peroxynitrite and also from the reactions of H_2O_2 with either NO_2BF_4 or NO_2^- in acidic media.



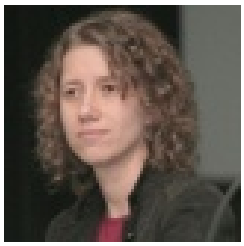
The review Exocyclic DNA adducts: Challenges in Developing methods for clinical studies, by Marisa Medeiros, not only was the cover of Chemical Research in Toxicology (CRT), the journal of the American Chemical Society, as also was highlighted and recommended by the publisher of the magazine (Chem . Res Toxicol., 2009, 22 (3), pp 419-425 DOI: 10.1021/tx800367d).

The comment about the review was as follows:

Special Features
A quick look at this month's In This Issue reveals a prevalence of articles on DNA damage and DNA damaging agents. This was a purely chance occurrence, resulting from the recommendations of reviewers and editors, but it illustrates the relevance that the topic of DNA damage continues to have for mechanistic toxicology. Thus, the review by Marisa Medeiros (p 419) on exocyclic DNA adducts as biomarkers of lipid oxidation is particularly timely. Be sure to take advantage of this opportunity to learn more about this important topic.

Febraury 19, 2010

INTERVIEW: Alicia Kowaltowski, Professor of Biochemistry of the Department of Chemistry Institute at USP and member of the National Institute of Science and Technology of Redox Processes in Biomedicine.



Indicated as coordinator of the Gordon Research Conference on Oxygen Radicals of 2014, Professor Alicia Kowaltowski highlights the opportunity to increase the international recognition of Brazilian and Latin American science.

How would you evaluate Gordon in relation to other meetings, as, for example, the meeting of SFRBM?

Gordon meetings involve a limited number of researchers (150-200), occur in an isolated location and include lodging and all meals and social activities, encouraging interaction among the attendants. Also, they attempt to discuss highly innovative data, not yet published.To enable this discussion without researchers feelling uneasy of exposing data to competitors, Congress does not publish summaries, does not allow photography or recording and reported data are considered confidential. As a result, very innovative scientific discussions occur. Thus, Gordon Conferences made a lot of prestige over the years and is frequented by top researchers.

What is the importance for Latin American and Brazilian research to be appointed as coordinator of Gordon?

Coordinating the conference, I will have a decisive role in preparing the scientific program, which establishes the researchers in the field that will be invited to present their data. It will be an excellent opportunity to invite Latin American researchers of excellence, increasing its international visibility. Our region produces high-quality science, but we are geographically isolated, resulting in a lower recognition of our work. Events like this are an important way to obtain international recognition.

What about your research and your career?

The coordinators of the Gordon Conferences are chosen during the Congress, by direct election by the participants. The fact of having been elected means that I am a researcher acknowledged by my peers, not only for my scientific work, but also by the ability to manage. For me it's a validation that our work really got international recognition, and an encouragement to continue. I attribute much of this recognition to my work with the SFRBM, driven by the group Redoxoma [INCT of Redox Process in Biomedicine]. The Redoxoma is formed by a group of researchers with high international visibility, working together to promote higher quality and visibility of our science. Achievements like that prove that this kind of initiative works.

March 1st, 2010

Redoxoma evaluates goals

The second meeting of INCT of Redox Processes in Biomedicine - Redoxoma was held on February, at the Instituto de Química, Universidade de São Paulo, with the purpose of evaluating the development of goals, correcting directions and planning the future

During the two-days meeting, the researchers had the opportunity to explain the development of the goals they had set at the first meeting of the group and mention their most interesting results. They also discussed the upcoming events organized by Redoxoma, such as the course "Oxygen and Redox Processes" during the Annual Meeting of the XXXIX SBBq (18-21 May 2010 in Foz do Iguacu) and the biannual Congress of the group "South American Free Radical " to be held in 2011.

According to Professor Ohara Augusto, coordinator of Redoxoma, the discussions were extremely productive. It was evident that the interactions between laboratories have been strengthened and this should be augmented with the real-time seminars that are expected to begin this semester. Everyone recognized the importance of the Network for the evolution of their work and reaffirmed the commitment to develop the research goals, human resource training, scientific dissemination and transfer of technology of Redoxoma.

March 13, 2010

Research of the INCT of Redox Processes in Biomedicine - Redoxoma is awarded with the Order of Scientific Merit

Professor Vitor Francisco Ferreira, of the Institute of Chemistry at Universidade Federal Fluminense and INCT of Redox Processes in Biomedicine, was awarded the National Order of Scientific Merit, which recognizes national and foreign personalities who have distinguished themselves by outstanding contributions to science and technology.

For the researcher, "to be awarded a prize of this magnitude is a recognition that our work has impact on the national scene and that was recognized by people in the area. Surely you start to have more prominence and it stimulates you to work harder and get better results. However, I must emphasize that I believe I would not have received such recognition if not for the students' work and collaborations like these that I have made in Redoxoma. Working with people from different area is very gratifying. "

Professor at Universidade Federal Fluminense, a researcher 1B from CNPq, Scientist of our State (since the first edition) and member of the Brazilian Academy of Sciences, his professional experience includes the areas of organic chemistry, with emphasis on organic synthesis-oriented methodologies asymmetric and bioactive molecules, acting on the following topics: carbohydrates (monosaccharides), nucleosides, diazocompostos heterocycles and naphthoquinones.

April 15, 2010

Real time seminar

Researchers and students of the INCT of Redox Processes in Biomedicine - Redoxoma of Belo Horizonte, Curitiba and Aracaju watched in real time the seminar of Professor Rafael Radi, from the Facultad de Medicina, Universidad de la Republica, Uruguay, held in the Instituto de Química da Universidade de São Paulo, at December 7. The theme of the lecture was Cytochrome c tyrosine nitration: a trigger for an alternative conformation and function.

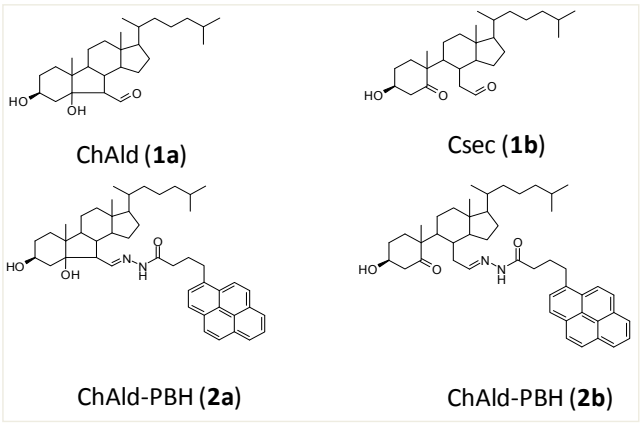
This was the first experience of the group with the videoconferencing system, recently bought and installed by Redoxoma under the responsibility of Cristhina Nadja de Souza-Pinto (Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo). For Ohara Augusto, coordinator of the INCT -

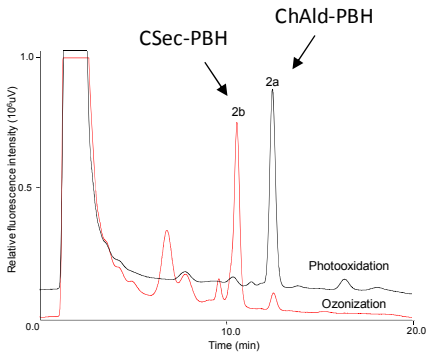
Redoxoma, the experience was very exciting and promising, although technical adjustments are still necessary to improve the transmission and allow the connection of all the associated laboratories.

Selected examples of recent publications openning new perspectives

1. Highly sensitive fluorescent method for the detection of cholesterol aldehydes formed by ozone and singlet molecular oxygen. Mansano FV, Ronsein GE, Prado FM, Uemi M, Di Mascio P, Miyamoto S. *Analytical Chemistry*. Submitted (March 2010).

Cholesterol oxidation gives rises to a mixture of oxidized products. Different types of products are generated according to the reactive species being involved. Recently, attention has been focused on two cholesterol aldehydes, 3β-hydroxy-5β-hydroxy-B-norcholestane-6β-carboxyaldehyde (ChAld, 1a) and 3β-hydroxy-5-oxo-5,6-secocholestan-6-al (ChSec, 1b). These aldehydes can be generated during ozone-, as well as by, singlet molecular oxygen-mediated cholesterol oxidation. It has been suggested that ChSec is preferentially formed by ozone and ChAld by singlet molecular oxygen. In this study we describe the use of 1-pyrenebutyric hydrazine (PBH) as a fluorescent probe for the detection of cholesterol aldehydes. The formation of the fluorescent adduct between ChAld with PBH was confirmed by HPLC-MS/MS. The fluorescence spectra of PBH did not change upon binding to the aldehyde. Moreover, the derivatization was also effective in the absence of an acidified medium. This is critical to avoid the formation of cholesterol aldehydes through Hock cleavage of 5α-hydroperoxycholesterol. In conclusion, PBH can be used as an efficient fluorescent probe for the detection/quantification of cholesterol aldehydes in biological samples. Its analysis by HPLC coupled to a fluorescent detector provides a sensitive and specific way to quantify cholesterol aldehydes in the low fentomol range.





Selected examples of recent publications openning new perspectives

2. Insights into the specificity of thioredoxin reductase-thioredoxin interactions. A structural and functional investigation of the yeast thioredoxin system. Oliveira MA, Discola KF, Alves SV, Medrano FJ, Guimarães BG, Netto LE*. Biochemistry March 2010, on line*

The enzymatic activity of thioredoxin reductase enzymes is endowed by at least two redox centers: a flavin and a dithiol/disulfide CXXC motif. The interaction between thioredoxin reductase and thioredoxin is generally species-specific, but the molecular aspects related to this phenomenon remain elusive. Here, we investigated the yeast cytosolic thioredoxin system, which is composed of NADPH, thioredoxin reductase (ScTrxR1), and thioredoxin 1 (ScTrx1) or thioredoxin 2 (ScTrx2). We showed that ScTrxR1 was able to efficiently reduce yeast thioredoxins (mitochondrial and cytosolic) but failed to reduce the human and Escherichia coli thioredoxin counterparts. To gain insights into this specificity, the crystallographic structure of oxidized ScTrxR1 was solved at 2.4 Å resolution. The protein topology of the redox centers indicated the necessity of a large structural rearrangement for FAD and thioredoxin reduction using NADPH. Therefore, we modeled a large structural rotation between the two ScTrxR1 domains (based on the previously described crystal structure, PDB code 1F6M), which allowed us to make structural considerations on the ScTrxR1-ScTrx2 complex (figure 1). Employing diverse approaches including enzymatic assays, site-directed mutagenesis, amino acid sequence alignment, and structure comparisons, insights were obtained about the features involved in the species-specificity phenomenon, such as complementary electronic parameters between the surfaces of ScTrxR1 and yeast thioredoxin enzymes and loops and residues (such as Ser(72) in ScTrx2). Finally, structural comparisons and amino acid alignments led us to propose a new classification that includes a larger number of enzymes with thioredoxin reductase activity, neglected in the low/high molecular weight classification.

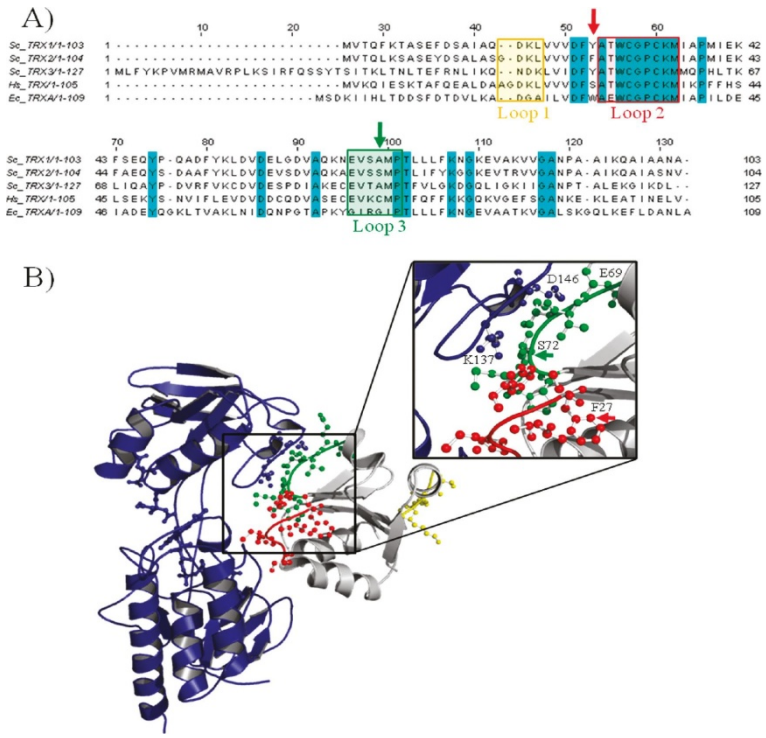
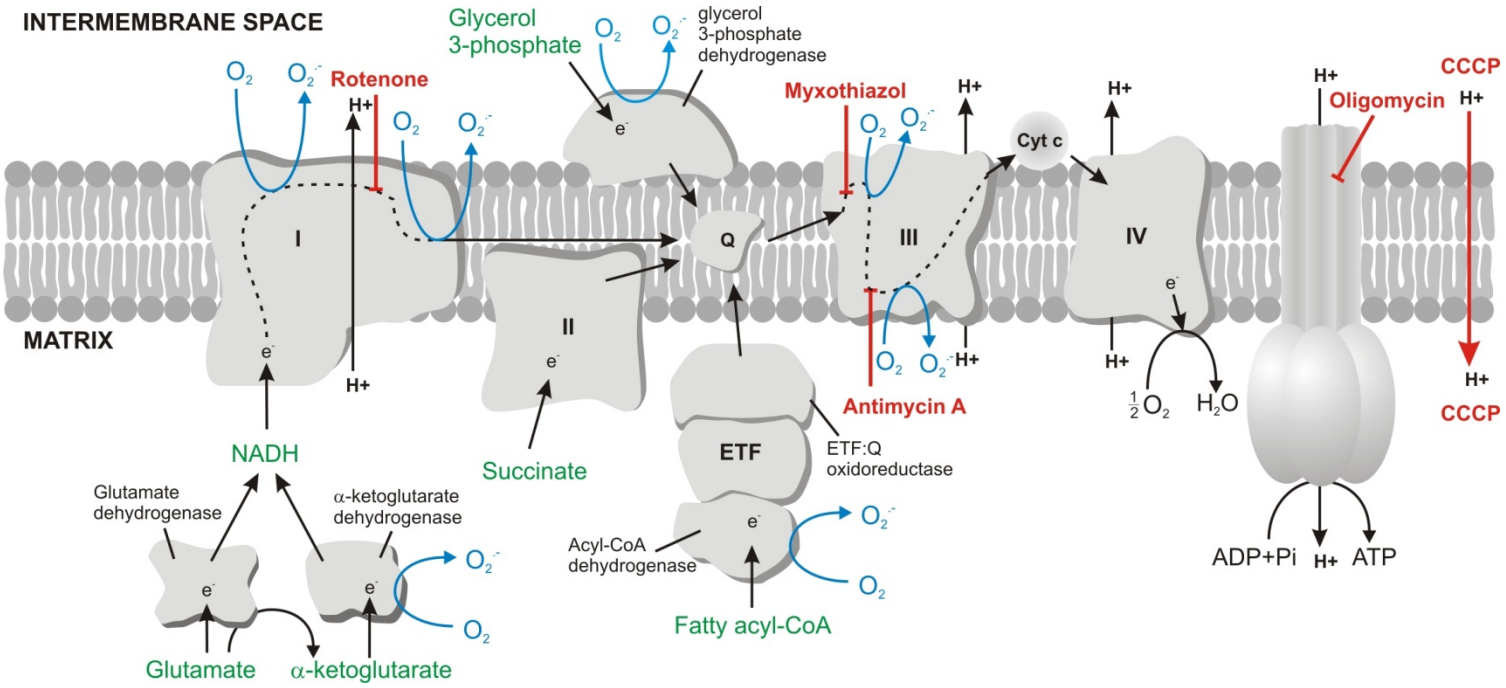


FIGURE 1: Thioredoxin loops involved in TrxR interaction. (A) Alignment of the amino acid sequences of ScTrx1, ScTrx2, ScTrx3, HsTrx, and EcTrx. Identical residues are highlighted in cyan, and the colored boxes denote the three flexible interacting loops (yellow, loop 1; red, loop 2; green, loop 3).Alignments were performed using ClustalX software (39). (B) The ScTrxR1 FRmodel (blue) and the crystal structure of ScTrx2 (gray) were individually superposed over the corresponding E. coli complex (PDB code 1F6M). ScTrx2Glu69 and Ser72 from loop 3 can form polar interactions with Lys137 and Asp146 from ScTrxR1. The Trx loop residues are represented as balls and sticks in yellow (loop 1), red (loop 2), and green (loop 3). The green and red arrows show the position of ScTrx2F27 and ScTrx2S72 (A and B), and residues are represented as balls and sticks (B).

Selected examples of recent publications openning new perspectives

3. Tissue-, Substrate- and Site-Specific Characteristics of Mitochondrial Reactive Oxygen Species Generation. Erich B. Tahara, Felipe D. T. Navarete and Alicia J. Kowaltowski (2009) *Free Radic Biol. Med. 46, 1283-1297.*

Reactive oxygen species are a byproduct of mitochondrial oxidative phosphorylation, derived from a small quantity of superoxide radicals generated during electron transport. We conducted a comprehensive and quantitative study of oxygen consumption, inner membrane potentials and H_2O_2 release in mitochondria isolated from rat brain, heart, kidney, liver and skeletal muscle, using different respiratory substrates (α-ketoglutarate, glutamate, succinate, glycerol phosphate and palmitoyl-carnitine). The location and properties of reactive oxygen species formation were determined using oxidative phosphorylation and respiratory chain modulators oligomycin, rotenone, myxothiazol, antimycin A and the uncoupler CCCP. We find that in mitochondria isolated from most tissues incubated under physiologically relevant conditions, reactive oxygen release accounts for 0.1 - 0.2% of O_2 consumed. Our findings support an important participation of flavoenzymes and complex III and substantial role of reverse electron transport to complex I as reactive oxygen species sources. Our results also indicate that succinate is an important substrate for isolated mitochondrial reactive oxygen production in brain, heart, kidney and skeletal muscle, while fatty acids generate significant quantities of oxidants in kidney and liver. Finally, we find that increasing respiratory rates is an effective manner to prevent mitochondrial oxidant release under many, but not all, conditions. Altogether, our data uncover and quantify many tissue-, substrate- and site-specific characteristics of mitochondrial ROS release.



Mitochondrial substrate metabolism, respiratory chain organization, electron leakage sites and effects of respiratory modulators.

Selected examples of recent publications openning new perspectives

4. The recombination protein RAD52 cooperates with the excision repair protein OGG1 for the repair of oxidative lesions in mammalian cells. Souza-Pinto NC, Maynard S, Hashiguchi K, Hu J, Muftuoglu M, Bohr VA (2009). *Mol. Cell. Biol.*, 29 (16):4441-54.

Oxidized bases are common types of DNA modifications. Their accumulation in the genome is linked to aging and degenerative diseases. These modifications are commonly repaired by the base excision repair (BER) pathway. Oxoguanine DNA glycosylase (OGG1) initiates BER of oxidized purine bases. A small number of protein interactions have been identified for OGG1, while very few appear to have functional consequences. We report here that OGG1 interacts with the recombination protein RAD52 in vitro and in vivo. This interaction has reciprocal functional consequences as OGG1 inhibits RAD52 catalytic activities and RAD52 stimulates OGG1 incision activity, likely increasing its turnover rate. RAD52 colocalizes with OGG1 after oxidative stress to cultured cells, but not after the direct induction of double-strand breaks by ionizing radiation. Human cells depleted of RAD52 via small interfering RNA knockdown, and mouse cells lacking the protein via gene knockout showed increased sensitivity to oxidative stress. Moreover, cells depleted of RAD52 show higher accumulation of oxidized bases in their genome than cells with normal levels of RAD52. Our results indicate that RAD52 cooperates with OGG1 to repair oxidative DNA damage and enhances the cellular resistance to oxidative stress. Our observations suggest a coordinated action between these proteins that may be relevant when oxidative lesions positioned close to strand breaks impose a hindrance to RAD52 catalytic activities.

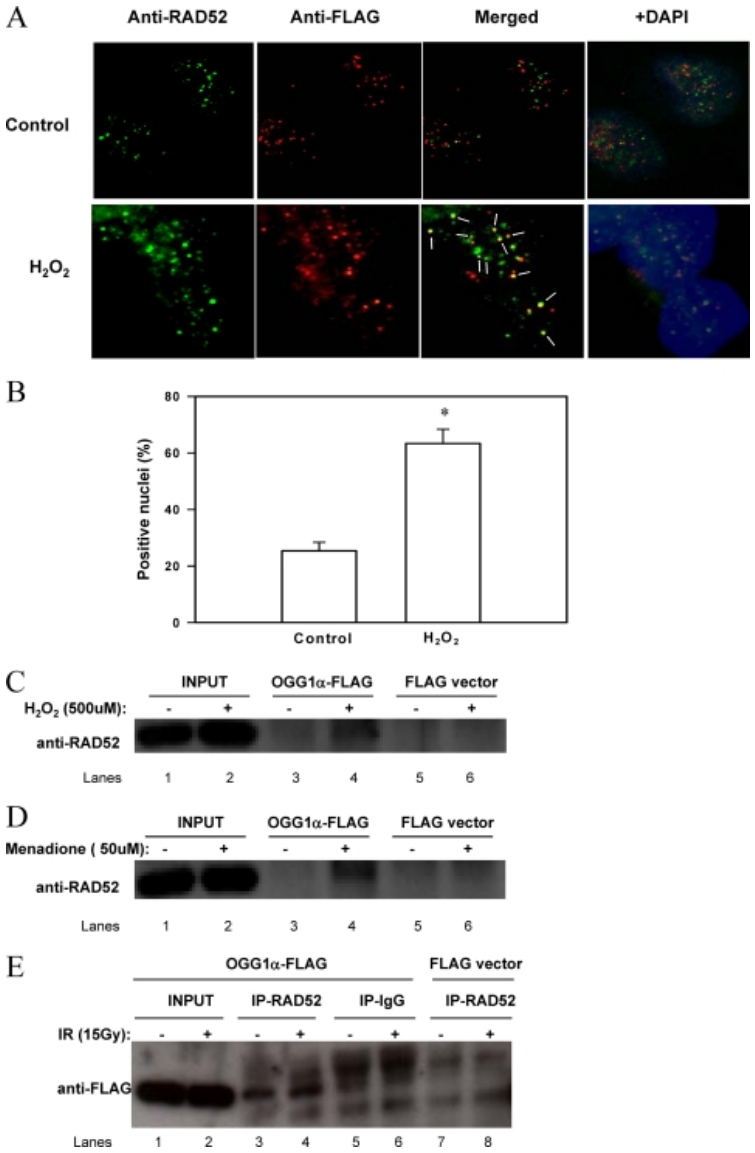


FIG. 6. OGG1 and RAD52 colocalize *in vivo* after DNA damage. (A) HEK293 cells expressing FLAG-OGG1-α were exposed to either buffer alone (Control) or 500 μM H2O2 in medium for 0.5 h and fixed as described. Primary antibodies used were anti-RAD52 (Genetex) at 3.5 μg/ml and anti-FLAG (Sigma) at 2 μg/ml; the secondary antibodies were Alexa Fluor 488-conjugated anti-mouse IgG (green) and Alexa Fluor 568-conjugated anti-rabbit IgG (red) at 1:1,000 dilutions. Nuclei were stained with DAPI. Images were acquired by using a Zeiss fluorescence inverted microscope with a ×40 objective magnification for all images. (B) A total of 50 nuclei per experiment were scored for colocalization of RAD52 and FLAG-OGG1-α. Nuclei were counted as positive if 50% of OGG1-α foci colocalized with RAD52 foci. The data points show the averages ± the standard deviations of three independent experiments. The asterisk denotes significantly higher colocalization at $P < 0.01$. (C, D, and E) RAD52/OGG1-α complexes were immunoprecipitated from HEK293 cells expressing FLAG-OGG1-α, treated or not with 500 μM hydrogen peroxide for 0.5 h (C) or 50 μM menadione for 1 h (D). From cells irradiated (IR) with 15 Gy (E), protein complexes were precipitated using mouse anti-RAD52 antibodies (or normal IgG, as the negative control). Extracts from HEK293 transfected with empty vector were used as a negative control in all experiments.

Selected examples of recent publications openning new perspectives

5. Aging defined by a chronologic-replicative protein network in *Saccharomyces cerevisiae:* an interactome analysis F. Barea, D. Bonatto (2009) *Mechanisms of Ageing and Development*, 130: 444-460

Aging is a multifactorial condition that results in the loss of an organism's fitness over time. Different theories have been formulated to explain the mechanisms of aging, but a synthesis of these theories has not been possible until now. In addition, the increase in molecular data gathered by proteomics projects utilizing different organisms has permitted a better picture of proteins that function in aging. In this sense, the yeast Saccharomyces cerevisiae is a biological model for aging, and it shows two distinct aging states: a replicative state termed the replicative lifespan (RLS) and a quiescent state known as the chronological lifespan (CLS). Interestingly, both RLS and CLS appear to share common groups of proteins, but a combined model of both aging mechanisms has not been defined. Thus, by applying systems biology tools that allow mining of the yeast proteins associated with aging, it was possible to obtain an interactome network in which both RLS and CLS are represented. In addition, four subgraphs comprising ubiquitin-dependent proteasome/regulation of cell growth, nucleic acid metabolism, carbohydrate metabolism/RNA metabolism, and carbohydrate-organic acid-amino acid/DNA metabolism were found within the interactome, defining a new model of aging for yeast termed the chronologic-replicative protein network (CRPN).

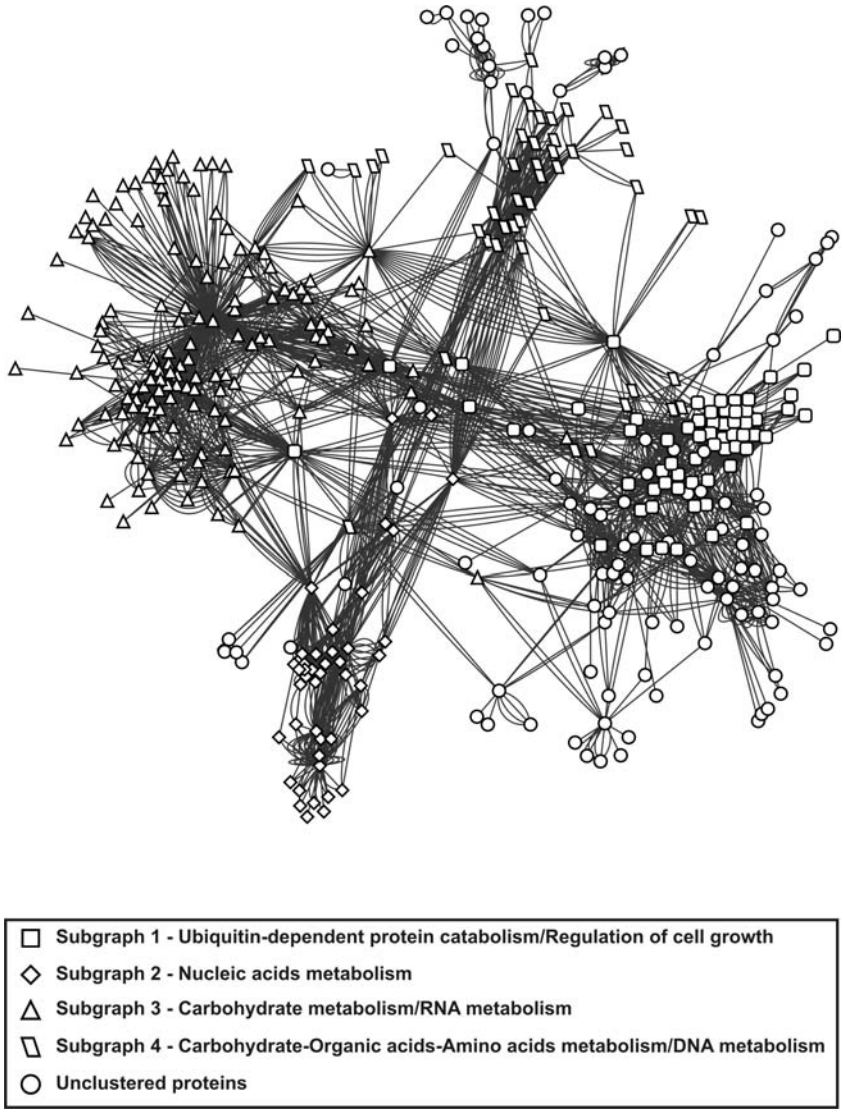


Figure 1. An interactome network (physical protein–protein network) of major proteins that act in replicative lifespan (RLS) and in chronological lifespan (CLS). Both clustered proteins (composing different subgraphs) and unclustered proteins are represented by nodes of different shapes, as indicated in the inset. The number of edges linking the nodes indicates the strength of the interaction among proteins.

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up to April 4, 2010

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Ferreira CL, Marques FL, Okamoto MR, Otake AH, Sugai Y, Mikata Y, Storr T, Bowen M, Yano S, Adam MJ, Chammas R, Orvig C.
Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada.

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Barbosa LF, Cerqueira FM, Macedo AF, Garcia CC, Angeli JP, Schumacher RI, Sogayar MC, Augusto O, Carrì MT, Di Mascio P, Medeiros MH.
Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, São Paulo, Brazil.

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Poletto NP, Henriques JA, Bonatto D.
Instituto de Biotecnologia, Centro de Ciências Biológicas e da Saúde, Universidade de Caxias do Sul, Rio Grande do Sul, Brazil.

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Insights into the Specificity of Thioredoxin Reductase-Thioredoxin Interactions. A Structural and Functional Investigation of the Yeast Thioredoxin System.

Oliveira MA, Discola KF, Alves SV, Medrano FJ, Guimarães BG, Netto LE.
Departamento de Biologia, Universidade Estadual Paulista, Sao Vicente, Brazil.

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Instituto de Química, Universidade Federal do Rio de Janeiro, LABRMN, Ilha do Fundão, 21949-900 Rio de Janeiro, Brazil.

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Tsuhako MH, Augusto O, Linares E, Chadi G, Giorgio S, Pereira CA.
Laboratório de Imunologia Viral, Instituto Butantan, 05503-900 São Paulo, Brazil.

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Maynard S, de Souza-Pinto NC, Scheibye-Knudsen M, Bohr VA.
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Laboratory of Molecular Gerontology, National Institute on Aging-Intramural Research Program, National Institutes of Health, Baltimore, Maryland, USA; andDanish Center for Molecular Gerontology and Danish Aging Research Center, Department of Molecular Biology, Aarhus University, Aarhus, Denmark.

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da Silva EN Jr, de Deus CF, Cavalcanti BC, Pessoa C, Costa-Lotufo LV, Montenegro RC, de Moraes MO, Pinto Mdo C, de Simone CA, Ferreira VF, Goulart MO, Andrade CK, Pinto AV.
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Oxyradical Research Group, Departamento de Biologia Celular, Universidade de Brasília, 70910-900 Brasília, DF, Brazil; Instituto de Química, Universidade de Brasília, 70910-900 Brasília, DF, Brazil.

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