

IC-ISS (DAMSA-MBM) Workshop

Report of Contributions

Contribution ID: 1

Type: **not specified**

Introduzione e presentazione degli istituti

Wednesday, 26 January 2022 09:00 (20 minutes)

Presenters: Dr GIANNINI, Cinzia (CNR - Istituto di Cristallografia); Dr TESTAI, Emanuela (ISS - Dip. DAMSA - Rep. MBM)

Session Classification: Sessione

Contribution ID: 2

Type: **not specified**

Mitochondrial dysfunction in Cockayne syndrome: the role of DRP1 protein

Wednesday, 26 January 2022 09:20 (30 minutes)

Cockayne syndrome (CS) is a rare genetic progeroid disorder characterized by growth and development defects, severe cutaneous photosensitivity, cachectic dwarfism, progressive neurological dysfunction, and precocious aging.

The molecular basis of these clinical traits are still unknown. Cells derived from CS patients present as pathological hallmarks excessive oxidative stress, intense glycolytic metabolism, mitochondrial fragmentation and apoptosis associated with hyperactivation of the mitochondrial fission Dynamin related protein 1 (DRP1). By using human cell models, we investigated the interplay between DRP1 and CSA and we determined whether pharmacological or genetic inhibition of DRP1 could ameliorate the molecular traits of CS patients and thus the disease progression. Both reactive oxygen and nitrogen species are in excess in CS-A cells and when the mitochondrial translocation of DRP1 is inhibited a reduction of these species is observed together with a recovery of mitochondrial integrity. Moreover, a significant decrease of apoptosis was also observed. A causal link between modulation of DRP1 activation by CSA and regulation of metabolism, mitochondrial health and apoptosis is suggested, indicating DRP1 as a potential therapeutic target in the treatment of CS patient.

Finally, we propose that the dual role of CS proteins in both repair of oxidatively-induced DNA lesions and modulation of metabolic pathways activated by chronic oxidative stress/energy failure converge into mitochondrial dysfunction that is a prominent feature of neurodegeneration onset and progression.

Presenter: Dr PASCUCCI, Barbara (CNR - Istituto di Cristallografia)

Session Classification: Sessione

Contribution ID: 3

Type: **not specified**

Obesity and post-bariatric surgery: in a search for predictive biomarkers

Wednesday, 26 January 2022 09:50 (30 minutes)

The higher cancer susceptibility of severe obese people and the relationship among diet, obesity and gut microbiota are well established. However, the molecular mechanisms that underlie this crosstalk are still under investigation. A chronic low-grade inflammation, oxidative stress and circulating microbial metabolites are common features in obese people. In order to find predictive biomarkers, we carried out a longitudinal study on 36 severe obese patients who had to undergo bariatric surgery (BS, sleeve gastrectomy). The 16S rRNA metagenomics sequencing in stool and saliva sample was performed, before and after intervention. Analyses of i) clinical/anthropometric parameters; ii) circulating inflammatory/oxidative markers; iii) NMR serum metabolic profiles and iv) reverse phase protein array of specific DNA damage response players were also carried out. After BS, a significant increase of alpha and beta diversity and specific changes of microbial composition strongly suggest the restoration of eubiosis. A pro-health profile is also supported by clinical/anthropometric parameters, by the reduction of circulating inflammatory and oxidative markers as well as by the metabolic profiles' changes.

Furthermore, significant variations have been also observed in saliva microbiota. To gain insight into the molecular mechanisms that underlie the obesity-related comorbidities remission, a correlation network will be discussed.

Presenter: Dr FORTINI, Paola (ISS - Dipartimento Ambiente e Salute)

Session Classification: Sessione

Contribution ID: 4

Type: **not specified**

Mitochondria in life and diseases

Wednesday, 26 January 2022 10:20 (30 minutes)

Life is the interplay between structure and energy, and Mitochondria, recognized as the cell's powerhouse, have been probably essential for the evolution of multicellular organisms. Mitochondria are best known as those organelles where the energy required for life is produced in the form of ATP molecules with the highest effectiveness, by the process called oxidative phosphorylation (OXPHOS). According to the endosymbiont theory, it all started around two billion years ago when an anaerobic precursor of the eukaryotic cell engulfed an α -proteobacterium, capable of producing energy via the more effective oxidative phosphorylation. This initiated a mutually fruitful collaboration, where the host cell could benefit from a more efficient ATP production while constantly providing its guest with protection, food, and oxygen. However beside being more effective, the use of OXPHOS to convert dietary calories into usable energy, also generates reactive oxygen species (ROS) as a toxic by-product. Thus, it is not surprising that the mitochondrial function is involved in a wide range of age-related disorders and in various forms of cancer.

The last decade has witnessed enormous progress and conceptual advances made in the field of mitochondrial biology. Nowadays Mitochondria are viewed as multi-functional organelles, regulating a plethora of cellular functions, spanning from physiological metabolism to stress responses and death. Mitochondria interact and communicate with other organelles, modulating complex metabolic networks involved in cell survival, apoptosis, redox control, calcium homeostasis and many metabolic and biosynthetic pathways.

Finally, but not less important, mitochondria hold their own DNA (mtDNA), present in thousands of copies per cell, encoding essential genes for energy production. Thus, the delayed-onset and progressive course of the age-related diseases might result from the accumulation of somatic mutations in the mtDNAs of post-mitotic tissues. The variation in the individual and regional predisposition to degenerative diseases and cancer may result from the interaction of modern dietary caloric intake and ancient mitochondrial genetic polymorphisms. Therefore, the mitochondria might provide a direct link between our environment and our genes and the mtDNA variants that permitted our forebears to energetically adapt to their ancestral homes are influencing our health today.

This webinar aims at providing an overview of the molecular mechanisms that enable mitochondria to sustain cell survival, coordinate stress responses, and mediate cell death.

Presenter: Dr TOMASELLO, Marianna Flora (CNR - Istituto di Cristallografia)

Session Classification: Sessione

Contribution ID: 5

Type: **not specified**

High-fat diet, oxidative damage and susceptibility to obesity: a study in transgenic mice

Wednesday, 26 January 2022 11:00 (30 minutes)

Several lines of evidence show that an increase in body fat mass is linked to oxidative stress and that the accumulation of radical oxygen species (ROS) contributes to develop the metabolic syndrome.

ROS induce DNA damage with a consequent activation of DNA damage response, an orchestrated set of proteins which trigger a systemic inflammatory response.

Mice defective in DNA damage processing genes are highly susceptible to obesity if exposed to high-fat diet (HFD), suggesting a link between genomic instability and metabolic dysfunction.

In our laboratory we obtained a transgenic mouse which expresses high levels of the human MutT homologue (hMTH1). MTH1 is a hydrolase which protects cells by oxidative damage by removing oxidized precursors from pool of nucleotides, thus avoiding their incorporation in DNA. Interestingly, when compared with wild-type counterpart, our transgenic mouse (hMTH1-Tg) shows: a) protection against neurodegeneration induced by treatment with 3-nitropropionic acid, which causes symptoms that resemble those of Huntington's disease; b) a decrease in oxidative damage, both in nuclear and in mitochondrial DNA; c) an increased longevity; d) a delay in the ageing process; e) a reduced anxiety and an enhanced investigation of environmental and social cues; f) a best mitochondrial functionality.

Our preliminary data suggest that MTH1 plays a pivotal role in modulating oxidative DNA damage in response to HFD. Moreover, we obtained data by magnetic resonance spectroscopy (MRS) that show a higher interscapular brown adipose tissue in hMTH1-Tg mouse compared to wild type, which is correlated to a low cardiovascular disease risk.

Presenter: Dr SIMONELLI, Valeria (ISS - Dipartimento Ambiente e Salute)

Session Classification: Sessione

Contribution ID: 6

Type: **not specified**

Shwachman Diamond Syndrome (SDS) a rare disease but common problems - study of the proteins involved in its molecular mechanism.

Wednesday, 26 January 2022 11:30 (30 minutes)

Shwachman-Diamond Syndrome (SDS) is a ribosomopathy with a wide spectrum of clinical presentations [1] associated with the loss of function of Shwachman-Bodian-Diamond Syndrome (SBDS) protein [2] and as we described for the first time [3], the Elongation Factor-Like 1 (EFL1). Together, these proteins remove the anti-associationfactor eIF6 from the surface of the pre-60S ribosomal subunit to promote the formation of mature ribosomes. Due to the lack of knowledge of the molecular mechanisms responsible for SDS pathogenesis, current therapy is nonspecific and focuses only at alleviating the symptoms. For that reason, we studied [4] the interaction mechanism of the proteins in solution and demonstrated that binding SBDS*EFL1 consists of two independent and cooperative events, with domains 2–3 of SBDS directing the initial interaction with EFL1, followed by docking of domain 1. In solution, both proteins exhibited large flexibility and consisted of an ensemble of conformations, as demonstrated by Small Angle X-ray Scattering (SAXS) experiments [4, 5]. SAXS is a powerful technique for structural investigation of macromolecules in solution as for nanoparticles in solution or in solid state. Building on the recent observation that EFL1 single-point mutations clinically manifest as SDS-like phenotype, we carried out comparative Molecular Dynamics (MD) simulations on three mutants, T127A, M882K and R1095Q and wild type EFL1 [6] combining with SAXS experiments. This study supports the notion that EFL1 function is governed by an allosteric mechanism involving the concerted action of GTPase domains and can help point towards new approaches to SDS treatment.

Presenter: Dr SILIQI, Dritan (CNR - Istituto di Cristallografia)

Session Classification: Sessione

Contribution ID: 7

Type: **not specified**

An in vitro approach for genotoxic evaluation of nanomaterials

Wednesday, 26 January 2022 12:00 (30 minutes)

Manufactured nanomaterials (MNMs) are extensively produced worldwide and used in many different consumer products due to their unique physico-chemical properties. It is obvious that, as the properties change, unwanted properties (i.e. toxicity) are to be expected as well. While the production of MNMs is growing exponentially, research into the toxicological impact and possible hazard of nanoparticles to human health and the environment is still lagging and the strategy for a thoroughly evaluation of their possible adverse effects is under study. With this aim, in vitro tests are especially relevant in hazard assessment for screening purposes and for identification of potential toxicity endpoints (OECD, ECHA, EFSA). In vitro approaches applied for testing traditional chemicals are suitable also for testing MNMs with some adaptations to take into account their specificities.

As first step, towards definition of reliable strategy for MNMs evaluation, developing preparation and characterization procedures based on standardized protocols are mandatory. Furthermore, in the last years scientific community is dealing with the identification of limits of available in vitro tests and setting new methods to overcome such limits.

Screening of genotoxic properties is part of risk assessment evaluation of MNMs. However, among the genotoxicity assays not all tests can be applied to MNMs (for instance the Ames test) or, alternatively, need some modifications due to the possible interference of NMs with assay procedures (for instance Comet or Micronucleus assays).

Based on the experience in national and international projects (e.g. NANoREG, NanoReg2), specific procedures for MNMs batch dispersion preparation and characterization as well as for the evaluation of their genotoxic potential will be discussed.

Presenter: Dr ANDREOLI, Cristina (ISS - Dipartimento Ambiente e Salute)

Session Classification: Sessione

Contribution ID: 8

Type: **not specified**

Discussioni e Conclusioni

Wednesday, 26 January 2022 12:30 (30 minutes)

Speakers: Dr.ssa Cinzia Giannini (CNR - Istituto di Cristallografia) e Dr.ssa Emanuela Testai (ISS -Dipartimento Ambiente e Salute)