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MEETING REVIEW

When the Cell Stress Society International became South American: meeting report of the IX International Workshop on the Molecular Biology of Stress Responses

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Abstract The International Workshop on the Molecular Biology of the Stress Response organized by the Cell Stress Society International was held in Porto Alegre, Brazil, on May 27–30, 2012, as part of the development of the Latin American Chapter of the Society, a superb initiative headed by Drs. Antonio De Maio and Larry Hightower. The meeting took place in the wonderful facilities of the *Pontifícia Universidade do Rio Grande do Sul* (PUCRS) and was warmly chaired by Professor Cristina Bonorino. Thirty-four invited speakers presented their work to more than 200 scientists and, even more importantly, to 150 registered students, who were the main beneficiaries of the meeting. The first day of the workshop was dedicated to an educational program for students, young investigators, and participants who were unfamiliar with the field of molecular chaperones and the stress response. Speakers in this pre-workshop were Dr. Harm Kampinga, Dr. Lea Sistonen, Dr. Larry Hightower, Dr. Ivor Benjamin, Dr. Daniel Ciocca, and Dr. Linda Hendershot. Then, the scientific sessions discussed below followed.

Introduction

The most common types of stress are physical (temperature, exhausting activities, loud noise, radiation, etc.) or chemical (oxidative or reductive environments, poisons, toxins, etc.), but they can also be psychological stemming, for example, from feelings of anxiety, remorse or sadness. Everyone copes with stress in different ways, but it is an unavoidable fact of everyday life for us all. The meeting, however, was an exception to this rule. It gave us the opportunity to discuss new developments in a relaxed and friendly atmosphere where stress only occurred in the titles of the talks. The heat shock proteins (HSPs) of every participant were expressed only at a very basal level. We were indebted to the local organizers for such a pleasant and friendly environment.

Speakers described the latest work in the chaperone field and the regulation of the stress response (see the meeting blog site at http://workshopcellstress2012.blogspot.com/), and the topics of each session were primarily selected according to their relevance to cellular stress response research by South American groups.

Stress responses in the nervous system

Vilma Martins (*Hospital AC Camargo*, *São Paulo*, *Brazil*) opened this session with a report on how astrocytes secrete a population of microvesicles of different size and morphology that not only contain classical exosomal markers but also stress-inducible protein 1, a co-chaperone that lacks peptide signals to be secreted and leads to neurotrophic and neuroprotective actions upon binding to the prion protein PrP^C at the neuronal surface.

María Soledad Matus (*Universidad de Chile*, *Santiago*, *Chile*) discussed the complex network of protein misfolding stresses generated in the most common neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and Huntington's disease and

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how cells activate the unfolded protein response, assessing the role of endoplasmic reticulum stress in these disorders. The roles of some factors such as SOD1, BP1, and ATF4 were discussed as possible targets of therapeutic strategies.

Ian R. Brown (*University of Toronto*, *Canada*) examined the role of Hsp70B (HSPA6) in differentiated human neuronal cells. Following heat shock, this stress-inducible chaperone was detected concentrated at centrosomes and then at foci in the nucleus that are associated with active transcription sites and RNA splicing, perhaps as a protective mechanism. Celastrol, a traditional compound used in traditional Chinese medicine, induces the expression of Hsp70B, suggesting that this triterpene could be useful as a neuroprotective drug.

María Estela Andrés (*Pontificia Universidad Católica de Chile*, *Santiago*, *Chile*) showed that particular epigenetic mechanisms could regulate Hsp70 expression in rat cortical neurons and PC12 cell models. While HSF1 is induced and translocated to the nucleus during the onset of heat shock, it does not bind to DNA. The chromatin environment on the Hsp70 gene promoter does not show features of heterochromatin, and a significant increase of H3 acetylation is not enough to induce Hsp70 expression. Also, the repressed state of Hsp70 expression in neurons is not related to the LSD1-CoREST repressor complex regulation. Therefore, it was suggested that another fine-tuned dialog between histone postranslation modifications and chromatin architecture could be responsible for triggering Hsp70 gene transcription in neurons.

Hugo Peluffo (*Instituto Pasteur de Montevideo*, *Montivedeo*, *Uruguay*) presented studies on the regulation of neuronal survival by the CD300f immunoreceptor in the normal and injured brain. This receptor (normally expressed in monocytes and neutrophiles) has recently been described in neurons and is up-regulated after brain injury, particularly in the white matter. The ligand appears to be produced by glial cells, and its nature is still poorly understood. In view of these novel findings, it is postulated that the overexpression of CD300f may represent a feasible gene therapy strategy.

Transcription factors in heat shock responses

Maria Gabriella Santoro (*Università di Roma Tor Vergata*, *Rome*, *Italy*) gave a full overview of the complex functional interplay between HSF1 activation and inflammatory signaling factors, important components of the tumor microenvironment. HSF1 was recently hypothesized to regulate the expression of non-HSP genes in a non-canonical and poorly understood manner. The talk integrated the pathways of some of these players, which seem to be connected to HSF1 function. NFkB is inhibited by HSF1 upon the onset of heat shock increasing apoptosis of B cell malignancies and myelomas, where NFkB appears to be constitutively active. Also discussed was arsenite-inducible RNA-associated protein, the heat shock gene whose expression is temperature-dependent and strictly controlled by HSF1. Moreover, it was shown that heat stress promotes the expression of cyclooxygenase-2, a key regulator of inflammation controlling prostanoids and thromboxane synthesis.

Lea Sistonen (*Åbo Akademi University*, *Turku*, *Finland*) focused her talk on the interplay between HSF1 and HSF2 in both cell stress and developmental processes. In view of the newly expanded repertoire of HSF targets well beyond chaperone-encoding genes, a genome-wide mapping of the target sites of HSF1 and HSF2 was performed in human K562 erythroleukemia cells that are either freely cycling or arrested in mitosis. A comparison of the target loci occupied by either HSF1 or HSF2 reveals a clearly distinct set of targets in cells under normal growth conditions. Upon exposure to heat stress, the number of targets increases remarkably, and HSF1 and HSF2 share a majority of their targets and recognize identical *cis*-acting DNA sequences. Therefore, a number of post-translational modifications of HSF1 were analyzed. Phosphorylation and sumoylation of HSF1 occur rapidly on heat shock, whereas the kinetics of acetylation (where deacetylase SIRT1 plays a pivotal role) are delayed and coincide with the attenuation phase of the HSF1 activation cycle.

Ayesha Murshid (*Harvard Medical School*, *Boston*, *USA*) reported on the mechanisms of HSF1 regulation that may become compromised with age and found that HSF1 binds to the catalytic domain of protein kinase A (PKAcα) and becomes phosphorylated. It was shown that PKA triggers a cascade involving HSF1 binding to p300 and p-TEFb and phosphorylation of the C-terminal domain of RNA polymerase II. It was suggested that this cascade appears to play a key role in protein quality control in neuronal cells expressing aggregation-prone proteins with long polyglutamine (poly-Q) tracts since they form inclusion bodies that could be resolved by HSF1 activation during heat shock.

Stress proteins and microbiology

Steve Witkin (*Weill Cornell Medical College*, *NY*, *USA*) underlined the role for HSPs in various aspects of women's health, in particular as biomarkers for the development of recurrent vulvo-vaginal infections, recurrent miscarriages, and genital malignancies. Dr. Witkin showed the importance of early detection of IgM antibodies against Hsp70 as a potential marker for CMV infections.

Lara Linhares (*Universidade de São Paulo*, *São Paulo*, *Brazil*) discussed the relevance of screening tests for the

detection of *Chlamydia trachomatis* infections. Chronic exposure to chlamydial Hsp60 can lead to induction of an immune response against conserved epitopes that are also present in human Hsp60. Since Hsp60 is one of the first proteins expressed by the human embryo, these antibodies and activated T lymphocytes that recognize the human Hsp60 increase the likelihood of inflammation-related pregnancy failure.

Manuel A. Barbieri (*Florida International University*, *Miami*, *USA*) presented data showing how exotoxin-S from *Pseudomonas aeruginosa* directly affects the activation of one or more Rab5-specific guanine nucleotide exchange factors in macrophages by down-regulation during bacteria invasion and how Rin-1 reverses such inactivation of Rab5.

Wolfgang Schumann (*University of Bayreuth*, *Bayreuth*, *Germany*) talked about the role of the *Bacillus subtilis* FtsH metalloprotease during initiation of sporulation. This ATP- and Zn^{2+}-dependent protease is required for the initiation of sporulation, which results in the production of phosphorylated Spo0A, a master regulator to allow cells to enter the second phase. FtsH controls the amount of negative regulators of active Spo0A, the phosphatase Spo0E able to specifically dephosphorylate phospho-Spo0A being identified as one of these regulators.

Oxidative and nitrosative stress

Ivor Benjamin (*University of Utah*, *Salt Lake City*, *USA*) provided a comprehensive overview of the importance of a balanced redox state in the response pathways, particularly in cardiomyocytes where differences among their organelles are more notorious than in other cell types due to the highly oxidative metabolism of their mitochondria. He showed how CryAB (HSPB5) mutants recapitulate human cardiopathies by generating redox imbalance and protein misfolding and aggregation. Since only half of these specialized cells are replaced during the human life span, strategies for maintenance of these cells relies on uninterrupted renewal of their components, among them, key transient interactions of cardiac proteins with molecular chaperones.

Claudina Rodrigues-Pousada (*Instituto de Tecnologia Química e Biológica*, *Universidade Nova de Lisboa*, *Portugal*) presented studies on the genome-wide response of *Saccharomyces cerevisiae* exposed to arsenic. Her data showed that the transcription factor Yap1 (Yeast AP-1 like) is responsible for maintaining cellular redox homeostasis and regulates the expression of genes involved in the Fe-S protein biosynthesis. Among them, Fet3, a ferroxidase required for high-affinity iron uptake, is drastically decreased, whereas *fet3* mutants show arsenate resistance, suggesting that Fet3 plays a role in arsenic toxicity. Unexpectedly, arsenic treatment activates non-reductive iron uptake systems. It was shown that this arsenic disruption of iron homeostasis also occurs in mammalian cells, which could be relevant to clinical applications.

Magnus Ake Gidlund (*Faculdade de Medicina*, *Pontifícia Universidade Católica*, *Porto Alegre*, *Brazil*) discussed the oxidative stress response and atherosclerosis generation relationship, and the different ways of evaluating the damage that leads to increased oxidized lipoproteins. Since antibodies against oxidized lipoproteins are produced, it was proposed that in adults without atherosclerotic disease, the metabolic regulation and carotid atherosclerosis of oxidized LDL antibodies and oxidized LDL groups characterize a dual attribute in the former as a contributor to carotid atherosclerosis (less than oxidized LDL), and with a modest atheroprotective role.

Norma Possa Marroni (*Universidade Federal do Rio Grande do Sul-HCPA*, *Porto Alegre*, *Brazil*), analyzed the effects of glutamine treatment on oxidative/nitrosative stress and VEGF-Akt-eNOS signaling pathway in a portal hypertension model. It was shown that glutamine can be useful in reducing oxidative/nitrosative damage. While the treatment could have a beneficial role, it does not reduce angiogenesis by stimulating the overproduction of VEGF.

Chaperones

Harm Kampinga (*Department of Cell Biology*, *SSCB*, *Groningen*, *The Netherlands*) showed data on the role of molecular chaperones as possible therapeutic targets in the routing of misfolded and aggregated proteins in neurodegenerative diseases. DNAJB6 and DNAJB8 form large oligomeric complexes able to prevent aggregation in a manner that depends on regulation by HDAC4. Unlike canonical DNAJ proteins such as DNAJB1, those DNAJ proteins do not assist HSP70 but bind small peptides and can prevent "aggregate seeding" of thermally denatured proteins. Transgenic mice with brain-specific overexpression of the human DNAJB6 were tested for their susceptibility to poly-Q mediated neurodegeneration, and data suggest that this DNAJ protein prevents poly-Q aggregation, toxicity, and, potentially, neurodegeneration.

Carlos Ramos (*Instituto de Química*, *UNICAMP*, *Campinas*, *Brazil*) presented studies on the structure–function relationship of molecular chaperones by using biophysical tools. In spite of the fact that the function of a protein is directly dependent on its three-dimensional structure, high-resolution information is not always available and is difficult to obtain for proteins with high molecular mass or high oligomerization state, as is the case with chaperones. Studies on the quaternary structure of several chaperones were discussed, highlighting those on the orientation of the J-domain in Hsp40s, the relationship between oligomerization and

function in small Hsps and on the characterization of Hsp90 and Hsp100 in plants.

Linda Hendershot (*St. Jude Children's Research Hospital*, *Memphis*, *USA*) discussed her work on chaperones of the endoplasmic reticulum. It is not known how the ER can distinguish between proteins that have not yet folded and those that cannot fold. Recent data suggest that molecular chaperones might be able to participate in both protein folding and degradation through the association of distinct subsets of co-chaperones. In addition, the finding that folding and degradation might be spatially separated in the ER provides a possible mechanism for establishing different environments to allow these opposing functions to exist within a single organelle.

Mariana Borsa (*Centro de Ciências Biológicas*, *Universidade Federal de Santa Catarina*, *Florianópolis*, *Brazil*) summarized studies on ATF6, one of the three sensors of ER for stress (along with PERK and IRE1) in HIV-infected patients. That protein leaves the endoplasmic reticulum when it is activated and transits to the Golgi complex where it suffers proteolytic cleavage. Its 50-kDa domain acts as transcription factor when it is free in the cytoplasm and induces the expression of chaperones. The study showed how the HIV promotes UPR activation through the ATF6 pathway in cells from HIV-positive patients undergoing different antiretroviral therapies.

Vince Guerreiro (*University of Arizona*, *Tucson*, *USA*) provided evidence that HspBP1, an Hsp70 co-chaperone identified by this laboratory, has activity both inside and outside the cell. HspBP1 binds to the ATPase domain of Hsp70, which results in the removal of bound nucleotides and prevents the protein refolding activity of Hsp70. The N-terminal region of 39–44 amino acids is not present in other vertebrates and is the region required for inhibition of refolding activity. Overexpression of HspBP1 inhibits tumor growth and is also detected in serum. Interestingly, tumor growth was inhibited following i.v. injection of HspBP1.

Mario Galigniana (*Universidad de Buenos Aires-Instituto de Biología y Medicina Experimental*, *Buenos Aires*, *Argentina*) presented a novel model where the expression balance of FKBP51 and FKBP52, two Hsp90-binding immunophilins, regulate several basic process of the cell. While FKBP51 is associated with unliganded steroid receptor-Hsp90 complexes and released upon binding of the hormone, FKBP52 occupies the same binding site on Hsp90 and interacts with the dynein motor protein, which favors the transport of the receptor to the nucleus. FKBP52 (but not FKBP51) interacts with structures of the nuclear pore facilitating nuclear translocation of the cargo. Contrary to previous conclusions, data showed that receptor transformation (i.e., Hsp90 dissociation) is not cytoplasmic but is a nuclear event. At the transcriptional level, while FKBP51 is a negative regulator, FKBP52 shows as a positive factor. Similar observations were performed for NFkB in cells stimulated with phorbol esters, although the effects of the immunophilins are Hsp90-independent. FKBP52 is also a protein related to neurodifferentiation, a property counteracted by FKBP51. Currently, drugs are being developed and tested to regulate selectively the biological action of factors associated with these two immunophilins.

Maristela Camargo (*Universidade de São Paulo*, *São Paulo*, *Brazil*) presented work on the dysfunctional unfolded protein response as a cause of hypogammaglobulinemia. B cells from a patient suffering common variable immunodeficiency (CVI) do not have typical membrane-bound IgM. Unfolded IgM chains co-localized with chaperone BiP inside the ER, and treatment of these cells in vitro with chemical chaperones restored folding/secretion of IgM. Some of these patients had a decreased number of mature B cells and an increased number of immature B cells that in earlier stages were normally restricted to lymphoid tissues. One of these patients presented chronic ER stress, suggesting an inability to deal with physiological demands for protein folding.

Fernanda Sodré (*Universidade de São Paulo*, *São Paulo*, *Brazil*), a student from Dr. Camargo's group, presented a complementary study attempting to identify gene mutations that could explain the defective activation found in CVI patients and how these mutations impair the ability to fold and secrete immunoglobulins. About 90 non-conservative substitutions of amino acids or gaps on the BiP sequence of these patients were found. All of them were able to disrupt BiP chaperone folding activity, which may explain the accumulation of immunoglobulins in the ER, and ultimately, the hypogammaglobulinemia exhibited by these patients.

HSP and cancer

Daniel Ciocca (*Instituto de Medicina y Biología Experimental de Cuyo*, *Mendoza*, *Argentina*) discussed the interrelation between caveolin-1 and heat shock proteins in cancer. Tissue sections of stromal and tumor epithelial cells were analyzed from two cohorts of breast cancer patients. It was found that the expression of caveolin-1 in the tumor microenvironment rather than in the tumor epithelial compartment correlates with the clinical outcome. This observation was also supported by studies of Her2/Neu-driven tumor development in caveolin-1 null mice, where tumor onset is accelerated in the absence of stromal caveolin. On the other hand, it was analyzed how caveolin-1 interacts with β-catenin, HSPB1 (Hsp27/Hsp25), and HSPA/Hsp70, and the regulation of caveolae endocytosis by the actin cytoskeleton, and how HSPB1 regulates actin polymerization. It was finally suggested that stromal caveolin-1 could be a new prognostic

marker for breast cancer progression and that the disruption of its gene may cause alterations of specific Hsps favoring tumor development.

Daiana Alvarez-Olmedo (*Instituto de Medicina y Biología Experimental de Cuyo*, *Mendoza*, *Argentina*), a student from Dr. Ciocca's group, completed the previous picture by evaluating the effects of a class 1 carcinogen such as cadmium on the expression and localization of β-catenin, Hsp27, and caveolin-1 in ERα-positive and -negative cancer cells lines. In MCF-7 cells, β-catenin localization was modified from membrane to the perinuclear region. Caveolin-1 changed from a cytoplasmic distribution to a paranuclear location, and Hsp27 was observed in the cytoplasm with noticeable dots in the nuclei.

Gisela Castro (*Instituto de Medicina y Biología Experimental de Cuyo*, *Mendoza*, *Argentina*), another student from Daniel Ciocca's group, studied the differential expression of HSPs in different subtypes of gliomas and their histopathologic features, and correlated this with the molecular marker LOH. It was demonstrated that in oligodendroglial tumors, Hsp27 could be used as a surrogate marker of the conventional prognosis marker LOH.

Pramod Srivastava (*University of Connecticut Health Center*, *Farmington*, *USA*) reported that dendritic cells sequester antigenic epitopes in an immunologically active form for weeks after the initial encounter with the antigen and long after the intact antigen is degraded beyond detection. This was demonstrated in vitro and in vivo and appears to be mediated through the interaction of the antigen with Hsp90 during the initial uptake of antigen. It was proposed that the ability of dendritic cells to store antigenic epitopes as a part of a stress-inducible system may be advantageous for immune responses to viruses and cancers.

María Bausero (*Instituto de Investigaciones Biológicas Clemente Estable*, *Montevideo*, *Uruguay*) proposed the usage of nanotechnology approaches for silencing HSPs related to tumor development. Hsp25/Hsp27 silencing by siRNA or lentivirus-iRNA technology abrogated the metastatic potential and induced the regression of established breast tumors. On the other hand, silencing of the Hsp27 gene led to induction of caspase-3/7-dependent apoptosis and inhibition of cell growth in vitro. Since delivery of siRNAs is difficult to achieve; it was proposed to use nano-polymers of polyamidoamine (PAMAM) for the treatment of solid tumors in a murine breast cancer model. Since PAMAM dendrimers are good carriers of hydrophobic drugs, they will be able to enhance their solubility and consequently, their bioavailability.

Mathias Gehrmann (*Technische Universitaet Muenchen, Muenchen*, *Germany*) discussed the lipid association of membrane-bound Hsp70 and its implications on tumor therapy. Hsp70 expression has been shown induced in many tumor cells and primary tumors, such that Hsp70 could be a good diagnostic and prognostic marker for tumors. In this study, an association of membrane-expressed Hsp70 with the tumor-specific lipid raft component globotriaosylceramide, as well as with phosphatidylserine, which is found on the outer membrane leaflet following stress was reported.

José Alexandre Barbuto (*Instituto de Ciências Biomédicas-Universidade de São Paulo*, *Brazil*) addressed the interrelation of HSPs and dendritic cell maturation in cancer patients. Although responses to stress are orchestrated in a highly sensitive manner by dendritic cells (DCs), tumors are not detected as a potential danger and the immune response is not triggered. Monocytes from cancer patients were studied and showed a distinct pattern of activation, including a different pattern of suppressors of cytokine signaling, before any differentiation signal is delivered to them. Upon differentiation, the ensuing DCs show increased levels of Hsp27 mRNA, but not intracellular Hsp27 protein, indicating that cell stress upon monocytes and DCs has a complex response pattern that needs to be better characterized in cancer patients.

HSPs and immune tolerance

Willem van Eden (*Utrecht University*, *Utrecht*, *The Netherlands*) reported that T cell epitopes of Hsp70 can be targets for epitope-specific immunotherapy in inflammatory diseases via the activation of antigen-specific regulatory T cells. Nasal application of a cross-reactive T cell epitope (B29) of *Mycobacterium tuberculosis* Hsp70 in mice suppressed proteoglycan-induced arthritis. Treatment with the peptide, both nasally and parenterally activated a potent $CD4^{+}CD25^{+}$ regulatory T cell population that reduced arthritis, showing that antigen-specific Treg function in vivo can be enhanced after immunization with antigens associated with inflammation. It was proposed that these peptides could be used to amplify the naturally existing Hsp-specific regulatory T cell response in patients with chronic inflammatory diseases.

Verónica Coelho (*Faculdade de Medicina da Universidade de São Paulo*, *São Paulo*, *Brazil*) described strategies to identify immunoregulatory Hsp60 peptides. Hsp60 is a homeostatic molecule involved in the fine-tuning of inflammation. It also shows a potential risk of triggering pathological autoimmunity. Therefore, it is necessary to develop strategies to select Hsp60 peptides bearing predominantly regulatory or inflammatory properties. To facilitate the selection of the most promising combination of peptides, the proposed strategies involve the analysis of the functional immunologic profile of peptides by studying their interactions with a panel of different cell types, the evaluation of electrostatic properties of peptides, the study of interactions with receptors, and the creation of a platform able to integrate structural and functional data from the literature.

Kamal Moudgil (*University of Maryland School of Medicine*, *Baltimore*, *USA*) presented work on the modulation of

autoimmunity by cytokine responses and immune tolerance against Hsp65. Using an experimental model of rheumatoid arthritis, the qualitative and quantitative aspects of the immune response to Hsp60 was studied in rats that possess the same MHC haplotype but display differential susceptibility to adjuvant arthritis. The temporal kinetics of cytokine secretion and the resulting balance contribute significantly to disease susceptibility. IL-27 and interferon-γ regulate the arthritic disease process by inhibition of the IL-17 response. It was shown that a variety of compounds induce protection via down-modulation of the IL-17 response to HSP60.

In the spirit of the workshop where students played a major role, the last two talks were given by PhD students. Like the others previously summarized here, the subjects were selected from the submitted abstracts.

Thiago Borges (*Pontificia Universidade Católica do Rio Grande do Sul*, *Porto Alegre*, *Brazil*), from Dr. Cristina Bonorino's group, analyzed mechanisms of inhibition of acute rejection induced by mycobacterial Hsp70 (TBHsp70). He investigated the role of TLR2 and downstream signaling pathways involved in the effect of IL-10 production by bone marrow dendritic cells stimulated with TBHsp70. TLR2 expression remained critical in the allograft, but not in the recipient, for the inhibition of acute graft rejection induced by TBHsp70. This process was dependent on MyD88 and IL-10 expression in the allograft. The results presented here also led to the conclusion that a maximal IL-10 production by the cells stimulated with TBHsp70 is dependent on TLR2 and ERK and independent of p38.

Ana Cristina Gomes-Santos (*Universidade Federal de Minas Gerais*, *Belo Horizonte*, *Brazil*), from Ana M. Faria's group, investigated the effects of Hsp65-secreting *Lactococcus lactis* in intestinal inflammatory disease models and characterized the immunological mechanisms involved in such intervention. It was shown that Hsp65 delivered by *Lactococcus lactis* prevented intestinal inflammation via IL-10 and TLR2 pathways. It was proposed that this type of approach may lead to long-term management of inflammatory bowel disease in genetically susceptible hosts.

Poster sessions

The well-attended poster sessions took place in the main hall of the PUCRS facility. A total of 83 posters were discussed dealing with the different aspects of the workshop.

Concluding remarks

This *9th International Workshop on the Molecular Biology of Stress Responses* provided an overview of the latest work in the molecular biology of chaperones covering many aspects of the field. We particularly hope that it also opened new opportunities for young new researchers entering this exciting field.

Today, we still recall the original discovery by Prof. Ferrucio Ritossa, thanks to the combined effects of good fortune, a great sense of inquisitiveness, and above all, knowledge and vision to understand a phenomenon that many people would let inadvertently pass. It is 50 years since the publication of his pioneer observation that cells exposed to high temperature can mount high transcriptional activity for specific proteins, when the term heat shock response was coined. We recall too that Prof. Ritossa experienced many setbacks before publishing his amazing discovery because, according to the editor of a major journal who first rejected his manuscript, "the studies lacked biological importance." Fifty years later, the incredible overview of the field given during this meeting demonstrated who was right and who was not.

Nonetheless, while significant progress has been made in unraveling the molecular mechanisms governing the activity of major chaperones in protein folding, a number of important questions still remain to be answered. Among many others are questions about the still unknown natural substrates for many chaperones and about how different types of heat shock proteins cooperate in a given biological system. For those of us who are working in the field, this is a challenge to be solved; it also makes more likely that we will keep our jobs for a long time (fortunately).

The first CSSI workshop was organized in 1997 by Professors S.C. Lakhotia (Varanasi, India) and W. Schumann (Bayreuth, Germany) at The Banaras University, Varanasi, India. The idea behind that initial workshop was to bring state-of-the-art research to investigators who would normally miss out on participating in international meetings because of a lack of resources. In this regard, the following paragraph is reproduced from the meeting report written by Dr. Peter Csermely and Dr. Subhash Lakhotia (*Cell Stress Chaperones* (1998) 3:1–5): "Our proposal suggests the sponsorship of stress-related conferences not in Europe or in USA/Canada as a vehicle to propagate the newest results of stress research to the interested scientific community of the developing countries." In view of the advances achieved since then and the current proposal to develop a Latin American Chapter of the Society, it can be said that the original goals have been successfully achieved mainly because of the high participation of investigators from developing countries at all nine workshops. Secondly, a high number of collaborations have come about as a result of these workshops, and third, an important decision for the future of the cellular stress response field in South America was taken during a luncheon meeting chaired by Professor Antonio De Maio. Attendees from various South American countries voted for the creation of the South American Chapter of the CSSI.

Its organizing committee will consist of one member from each of the participating countries, and Dr. María Bausero from Uruguay was elected as first chairperson. Accordingly, it was unanimously agreed that the next South American Chapter Meeting will be held in Montevideo, Uruguay, in 2014. Given the tremendous speed of research in the chaperone field, it is expected that many of the still unanswered questions described above will be solved by that time. We all wish the best to María and will support her in this new and challenging endeavor.

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