Stress down south: meeting report of the fifth International Workshop on the Molecular Biology of Stress Responses

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INTRODUCTION

Since their initial discovery in the early 1960s, heat shock proteins (Hsps) have been implicated in the response to a variety of stressors and pathological conditions. In addition, they have been found to play a major role in several cellular processes during normal conditions. Particular interest has been directed at the role of Hsps in protein folding. Recently, Hsps have also been found to interact with lipids modulating vesicle trafficking. Similarly, research on Hsps has been centered on their capacity to protect cells and confer tolerance to subsequent insults. Moreover, Hsps have been found to regulate the immune response when these proteins leave their natural intracellular environment and appear in circulation. The role of Hsps in many diseases is “in crecento.” Thus, they are an important factor involved in Alzheimer, Huntington, and Parkinson diseases; cancer; autoimmunity; and many other conditions (De Maio 1999; Multhoff 2002). The attention on Hsps has been shared both by countries that use a good portion of their gross national product to finance research and by less-developed nations with fewer scientific resources. Even with this global interest, the participation at international meetings tends to lean heavily toward individuals from developed countries rather than nations in development. In an effort to reduce this imbalance, Professors S.C. Lakhota (Varanasi, India) and W. Schumann (Bayreuth, Germany) organized the first workshop on the Molecular Biology of Stress Re-

sponses at Banaras University in Varanasi, India, in 1997 (Csermely and Lakhota 1998). The idea behind this initial workshop was to bring state-of-the-art research to those investigators that would normally miss out on participating in international meetings because of a lack of resources. The workshop was a success and was soon followed by sibling events in Wuhan, China, in 1999, organized by Tangchun Wu; Mendoza, Argentina, in 2001, organized by Daniel Ciocca (Grover 2002); and Wuhan/Yichang, China, in 2004, again organized by Tangchun Wu (Currie et al 2004).

The fifth International Workshop on the Molecular Biology of Stress Responses was held in Concepcion, Chile, 21–25 March 2006. Sponsored by The Cell Stress Society International, the workshop was organized by Antonio De Maio (University of California, San Diego, USA), Sandra Nicovani (Universidad Santo Tomas, Chile), Virginia Vega (University of California, San Diego, USA), and Robert Tanguay (Université Laval, Canada) under the auspices of the University of Concepción, with particular support from the vice-chancellor's office (Vice-rector Administrativo). Located in the southern part of the country, Concepción is the second largest city in Chile and was the perfect setting for a heated workshop. With temperatures up to 30°C (86°F), the weather was fantastic for what was Chile's early autumn. The Chilean people were friendly and gracious and the Chilean food was delicious. Perhaps inspired by the sunny weather, warm hospitality, and great eating, participants and speakers kept things heated inside the workshop with a series of hot discussions. The aim of the workshop was to discuss progress on basic research and medical applications of the stress response, and it examined the biological roles and functions of nearly all Hsps. With over 100 registered partic-

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Fig 1. The University of Concepción in Chile provided a beautiful backdrop for the 5th International Workshop on the Molecular Biology of Stress Responses. Students and seasoned investigators alike enjoyed the busy schedule of events that included professional presentations, lively discussions and a nice mix of Chilean music, dancing and fun.

ipants from 17 countries—half of whom were from Latin America—and heavy participation of students, the workshop was a diverse forum for discussion. To increase the interaction between students and invited speakers, a lunch was organized as a casual way for the students and speakers to mingle and chat. In addition, many participants flew into Chile's capital city, Santiago, and enjoyed an organized bus tour to Concepción that included a lunch stop at the prestigious Chilean winery, Miguel Torres. The formal workshop was preceded by a tutorial (preworkshop) to introduce the basic concepts of heat shock protein biology to newcomers to the field. Speakers in this preworkshop were Antonio De Maio, Linda Hendershot, Ivor Benjamin, David Smith, Jacques Landry, and Andrei Laszlo. The workshop was initiated Tuesday night by words from the University Vice Chancellor, Ernesto Figueroa; Larry Hightower, founding president of the society and editor-in-chief of the journal *Cell Stress and Chaperone*; and Antonio De Maio, representing the organizing committee. The opening ceremony concluded with a reception and a splendid display of typical Chilean folk dances performed by the group *Huenuican* (a word from the mapuche language meaning "to be friends with"), which was composed of students from the University of Concepción.

THE CHAPERONE MACHINE

Costa Georgopoulos (Geneva, Switzerland) led off the workshop with an excellent overview on the functional synergistic interplay among the various chaperone machines, including DnaK/DnaJ/GrpE and Trigger Factor and the antagonist effect between the SecB and Trigger Factor in *Escherichia coli* at physiological and lower temperatures (Genevaux et al 2004; Ullers et al 2004).

Harm Kampinga (Groningen, The Netherlands) outlined the actions of the 11 members of the mammalian Hsp70 family in concert with their cofactors. Using a folding of heat-denatured proteins in an *in vivo* assay, he showed that Hsp70s prevent protein aggregation without directing the subsequent fate of the bound substrate toward refolding, degradation, or storage in the aggregates. However, the presence of the cofactors Hsp40 and Hip directed the process toward protein refolding, whereas the presence of Bag-1 and CHIP favored protein degradation. He also demonstrated that the phosphorylation state of Hsp27 was crucial for its role as a chaperone. Finally, he demonstrated that aggregates were asymmetrically segregated among daughter cells during division (Kampinga 2006).

Peter Csermely (Budapest, Hungary) talked about the networking of ecosystems and Hsps. These mathematically based networks might be helpful in the design of

new multitarget drugs and their interactions with the respective substrates. Cellular networks also provide an important tool for understanding the role of various proteins in the collective, emergent properties of the cell, such as signaling, apoptosis, differentiation, and proliferation responses. Chaperones seem to occupy key, weakly linked, intermodular positions in protein-protein networks, which might contribute to their buffering effects in the evolvability of organisms (Csermely et al 2005; Pal et al 2006).

Martin Feder (Chicago, IL, USA) presented a summary on the evolution of *hsp* genes and the relevance of transposons. By screening the promoters of *hsp* genes in natural *Drosophila* populations, he showed that certain regions are distinctively susceptible targets for natural transposon insertion, which varies in allelic frequency depending on geographic and environmental gradients (Brown and Feder 2005; Shilova et al 2006).

Lawrence Hightower (Storrs, USA) talked about *Hsp70B*, which is a member of the Hsp70 family. This gene is expressed in response to stress, but it is down-regulated very rapidly compared with *Hsp70A* (*Hsp72*). The expression of these 2 genes is cell density-dependent.

Klaus-Dieter Scharf (Frankfurt, Germany) discussed the complex network of heat shock transcription factors (Hsfs) in plants and their dependency on adaptation to environmental stress. Functional analyses demonstrate that these various Hsfs are involved in distinguishable roles in tomato plants. Among >20 Hsfs in plants, only Hsf-1 could be identified as a master regulator of the heat stress response, which resulted in the development of thermotolerance. In contrast, HsfA-2 and HsfB-1, which were both found to be heat dependent, were not necessary for the induction of thermotolerance. Transgenic plants with a modified HsfB-1 expression level showed differences in growth and development that might be associated with differences in their chaperone levels. These plants resemble natural mutants that are induced by epigenetic variations. Potential molecular mechanisms were discussed that showed a connection between the specialized function of HsfB1 as a general transcription coactivator and an increased sensitivity of the developmental program of plants (Bharti et al 2004).

HEAT SHOCK PROTEINS, REPRODUCTION, STRESS, EXERCISE, AND AGING

David Smith (Scottsdale, USA) presented studies demonstrating that Hsp90 cochaperones not only influence Hsp90 activity but also are critical for the physiological activity of specific Hsp90 client proteins, such as steroid hormone receptors. Using knockout mice, he demonstrat-

ed the critical role that FKBP52, an Hsp90-binding co-chaperone found in androgen and progesterone receptor complexes, plays in both male and female reproductive processes.

Luciana Gallo (Buenos Aires, Argentina), from Mario Galigniana's group, discussed the role of Hsp90-binding immunophilins, FKBP52 and FKBP51, on localization and function of the glucocorticoid receptor (GR). She showed that FKBP52 replaces FKBP51 in the cytoplasmic GR-Hsp90-p23 complex hormone binding. This new complex is maintained on nuclear localization, in particular on nuclear speckles.

Gabriela Chiosis (New York, USA) reported on synthetic Hsp90 inhibitors designed on the specific fold adopted by ATP on binding to Hsp90. These compounds, particularly a new set of water soluble derivatives, displayed anti-tumor activities in both in vitro and in vivo cancer models. They appeared to accumulate in tumors while being rapidly cleared from normal tissue (Chiosis et al 2006).

Kathy Gabrielson (Baltimore, USA) presented research that showed an increase in the receptor tyrosine kinase, ErbB2, in the left ventricle of a rat doxorubicin-induced cardiomyopathy model while showing a decrease in Hsp90 levels.

George Lindsey (Rondebosch, South Africa) described the membranous localization of Hsp12 in the cell wall of *Saccharomyces cerevisiae*, which resulted in an increase in the flexibility of this region.

Earl Noble (London, Canada) presented studies indicating that Hsp70 accumulates after physical exercise, particularly in contracting skeletal and cardiac muscles where it can exert a cardioprotective effect. He also showed that the heat shock response exhibits sexual dimorphism. Moreover, the estrus cycle affects the heat shock response after exercise.

Geneviève Morrow and Robert Tanguay (Québec, Canada) discussed the role of small Hsp during aging, particularly their ability to protect against oxidative stress damage. They showed that different small Hsps increased lifespan through different mechanisms. They showed that overexpression of Hsp22 and Hsp23 in *Drosophila* affected the insulin/IGF signaling pathway, which is a key regulator of lifespan (Morrow et al 2006).

Andrei Laszlo (St. Louis, USA) showed that exposure to heat stress results in the appearance of foci containing the phosphorylated form of histone H2AX, γ -H2AX, a process that has been associated with an early response to DNA double strand breaks and replication stress induced by various genotoxic agents. Therefore, heat radiosensitization might involve heat-induced perturbations in the ionizing radiation-initiated signaling pathways (Kam-ping and Laszlo 2005).

HEAT SHOCK PROTEINS AND MEMBRANE BIOLOGY

Alejandro Barbieri (Miami, USA) showed that insulin receptor-mediated endocytosis was enhanced in cells expressing Rin1, a multifunctional protein containing several domains, including a Ras binding site and a Rab5 GEF domain.

Antonio De Maio (San Diego, USA) in collaboration with Nelson Arispe (Bethesda, USA) presented data demonstrating the interaction of Hsp70 with lipid membranes. The possible role of Hsps as enhancers of endocytosis was speculated to be part of the cellular response to stress to modulate the cell surface. In addition, the interaction of Hsp70 with lipids was further demonstrated by their intrinsic capacity to open ion conductance pathways or by aggregating liposomes. The interaction of Hsp70s with lipids was highly dependent on the presence of phosphatidylserine (PS) on the vesicle. Moreover, Hsp70 showed toxicity toward cells presenting PS on their surfaces (Arispe et al 2004).

Virginia Vega (San Diego, USA) showed an increase in phagocytosis by macrophages after induction of the stress response either by heat shock or after treatment with geldanamycin (Vega and De Maio 2005).

Gabriele Multhoff (Regensburg, Germany) speculated about a potential role for tumor-derived lipid vesicles that were identified as exosomes (Gastpar et al 2005). Functionally, these Hsp70-carrying exosomes were able to stimulate the cytolytic and migratory capacity of resting natural killer (NK) cells. In tumor murine models and in a phase I clinical trial, the biological activity of Hsp70 peptide-activated NK cells has been demonstrated (Krause et al 2004; Stangl et al 2006).

Linda Hendershot (Memphis, USA) reported on the up-regulation of the unfolded protein response (UPR) in poorly vascularized solid tumors. The increase in the UPR renders cells resistant to topoisomerase II poisons (Gray et al 2005).

HEAT SHOCK PROTEINS, IMMUNOLOGY, AND CANCER

Stuart Calderwood (Boston, USA) showed evidence indicating that Hsp70 is released from prostate carcinoma cells through an active secretory mechanism that involves the endolysosomal compartments. The extracellular Hsp70 is then taken up by other cells through interaction with members of the scavenger receptor family, Lox-1, SREC-1, and FEEL1 (Calderwood et al 2006).

Daniel Ciocca (Mendoza, Argentina) reported on the contrasting effects of intracellular and extracellular localized Hsps. Regarding the chemotherapeutic drug doxorubicin, Hsp27 and Hsp70 mediate protection against ap-

optosis, which is not related to the multidrug resistance gene and, perhaps, is due to an increase in DNA repair. On the other hand, several Hsps have the capacity to generate a tumor-specific CD8 T-cell immune response against cancer. Autologous gp96-based tumor vaccines have been tested in clinical trials. In a novel approach, the purification of gp96-peptide complexes was performed on hydroxyapatite columns, in collaboration with Patrick Frayssinet (St. Lys, France), who described the methodology. In this technique, gp96 is absorbed into hydroxyapatite ceramic powder at neutral pH and low ionic strength, which is an uptake via phago- or endocytosis.

Cristina Bonorino (Porto Alegre, Brazil) showed an important role of inducible Hsp70 in tumor metastases of breast cancers. Breast cancer patients with high Hsp70 expression showed a better prognosis compared with those with low Hsp70 production. Relapsed patients that died within 3 years had low Hsp70 expression levels. These data could be confirmed in a tumor mouse model (Torronteguy et al 2006).

Evgeny Nudler (New York, USA) presented elegant studies indicating that the activation of Hsf-1 by heat shock is mediated by a ribonucleoprotein complex containing the translation elongation factor eEF1A and a novel noncoding RNA. This noncoding RNA was termed heat shock RNA-1 (HSR-1). HSR-1 serves as a cellular thermosensor, whereas eEF1A links Hsp expression to translational shutdown and the collapse of the cytoskeleton (Shamovsky et al 2006).

Andrea Gómez (Santiago, Chile) identified a new regulatory molecule, CoRest, which was found to interact with Hsp70, repressing the activation of the human Hsp70 promoter.

John Williams and Claire Hunter-Lavin (Chester, UK) identified Hsp70 and Hsp60 as serum-derived danger signals. Danger signal means a response to a threatening event, including infections or other environmental stressors. A potential source for extracellular Hsp70 was peripheral blood mononuclear cells. The release of Hsp70 could be increased by factors such as exposure to bacterial antigens (Child et al 2006).

Alexzander Asea (Tempe, USA) talked about the role of circulating Hsp70 in the host defense system. He described 2 current mechanisms of intracellular Hsp70 release: passive, from necrotic cell death, and active, via exosomes (Bausero et al 2005).

Steve Witkin (New York, USA) showed a provocative correlation between the presence of *Mycoplasma hominis* and the presence of Hsp70 in amniotic fluid. In addition, the addition of exogenous Hsp70 to amniotic fluid epithelial cells stimulated tumor necrosis factor (TNF) production. Release of Hsp70 into the amniotic fluid might provide a rapid mechanism for the fetus to regulate proinflammatory immunity (Jean-Pierre et al 2006).

Patrick Arrigo (Lyon, France) presented a correlation between long-lasting heat shock stimulation of a TNF-related apoptosis-inducing ligand (TRAIL) in transformed T lymphocytes and enhanced DR5 and DR4 cell surface receptor expression. He described studies in which a mild heat shock at 42°C stimulates TRAIL-mediated apoptosis of leukemic T lymphocytes and promyelocytic cells, but not normal T lymphocytes. The death rate was maximal when the heat treatment was performed at the beginning of the incubation with TRAIL. However, enhanced apoptosis was still observed when TRAIL was added 1 day after heat shock. The phenomenon was transcription and translation independent, suggesting that newly made heat shock proteins were not involved. A long lasting increased ability of TRAIL to recognize and bind DR4 and DR5 appears to be a key event induced by hyperthermia that enhances the apoptogenic efficiency of TRAIL. T lymphocytes from chronic lymphocytic leukemia patients were tested and showed a good response to TRAIL plus heat shock in 25% of the subjects.

Graham Pockley (Sheffield, UK) showed that the administration of the stress protein gp96 could significantly delay the rejection of rat cardiac transplants. He reported that gp96 has no apparent effect on the phenotype and function of antigen-presenting dendritic cells but that it does bind to and induce the secretion of anti-inflammatory cytokines from T cells in vitro. The administration of gp96 in vivo induced a state of peripheral T cell hyporesponsiveness. He proposed that these anti-inflammatory properties of gp96 might influence the qualitative nature of immune responses to a range of co-encountered antigenic challenges and inflammatory events.

Mladen Korbely (Vancouver, Canada) talked about photodynamic therapy (PDT), which is clinically applied for the eradication of tumors and lesions and induces oxidative stress, thus initiating Hsp70 synthesis, protein expression, and release. PDT resulted in the expression of Hsp70 on the surface of tumor cells. Moreover, Hsp70 expression was up-regulated in the liver and spleen tissues of mice bearing PDT-treated tumors (Korbely et al 2005).

HEAT SHOCK PROTEINS AND NEURODEGENERATIVE AND CARDIOVASCULAR DISEASES

Ian Brown (Toronto, Canada) mentioned that neurodegenerative diseases such as Alzheimer, Parkinson, and amyotrophic lateral sclerosis (ALS) exhibit common molecular mechanisms associated with protein misfolding and aggregation in differentiated neurons in the human brain. Hsps have been implicated in many aspects of protein homeostasis, including the prevention and disruption of protein aggregation; hence, the search is on to identify

compounds that are potential therapeutic candidates for inducing Hsps in differentiated neuronal cells in the human brain. A drug screen study has indicated that celastrol promotes the reduction of protein aggregation in tissue culture assays. Therefore, a cerebral up-regulation of Hsps, which have the capacity to solve protein aggregates, might be useful in the treatment of these diseases. Celastrol has been identified as an inducer of Hsps in both undifferentiated and differentiated neuronal cells.

Jacques Landry (Québec, Canada) spoke about complexes comprising the chaperones Hsp70, Hsp90, or both that can recognize misfolded proteins and, in concert with a number of cochaperones including Bag-1 and Bag-2, sort them for either refolding or ubiquitin-dependent proteasomal degradation. A new chaperone complex composed of the small Hsp protein HspB8 and Bag-3 was described. The Bag-3/HspB8 complex prevents the accumulation of aggregated polyglutamine by stimulating the degradation of misfolded polyglutamine through macroautophagy (Chavez Zobel et al 2005).

William Currie (Halifax, Canada) showed that heat shock with an elevated expression of Hsps in the heart suppresses angiotensin II, induces inflammation, and suppresses activation of NF-kappa B. Inhibition of the heat shock response with the use of small interfering RNA against Hsf-1 depleted Hsp27 and exacerbated inflammation.

Ruben Mestril (Maywood, USA) presented data indicating that transgenic mice overexpressing Hsp70 exhibited resistance to several pathophysiologic conditions, such as cardiac ischemia-reperfusion injury, cerebral ischemia, endotoxemia, neurodegenerative disorders, skeletal muscle injury, and diabetes. These studies confirmed the cytoprotective nature of Hsp70 and its potential therapeutic use.

Andrew Miller (London, UK) addressed the question of how diadenosine polyphosphates (Ap_nAs) interact with GroEL and GroES, assisting protein folding/refolding in *E. coli*. It has been shown that diadenosine tetraphosphate (Ap_4A) produced by many prokaryotic and eukaryotic cells under stress binds to GroEL in a site allosteric with respect to the well-known ADP/ATP binding site. Biophysical investigations suggested that Ap_4A acts as a repressor to encourage GroEL to remain in an active chaperoning state rather than enter a protein storage state. Therefore, Ap_4A allows *E. coli* to maintain a skeleton physiology and metabolism under stress conditions and then assists in the restoration of normal cell function once stress conditions subside (Jones et al 2006).

Robert Tanguay, standing in for Tangchun Wu (Wuhan, China), presented studies correlating the presence of Hsps in Chinese workers with several environmental stresses.

Carmen Garrido (Dijon, France) showed that Hsp70 is

a major regulator of erythropoiesis by preventing caspase-3-mediated cleavage of GATA-1. Therefore, she proposed that Hsp70 exerts a new major antiapoptotic role during erythropoiesis (Didelot et al 2006).

HEAT SHOCK PROTEINS, MICROORGANISMS, AND OXIDATIVE STRESS

Ivor Benjamin (Salt Lake City, USA) stated that the redox machinery is essential for cardiomyopathy and heart failure. Reactive oxygen species might have an important effect on intracellular reducing equivalents like reduced glutathione (GSH) or the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH). Mice with a genetically induced imbalance in their redox system show several symptoms, including protein aggregation, cytotoxicity, and organ failure (Kim et al 2005).

Rosa Maita (Caracas, Venezuela) showed data indicating the expression of Hsp70 in cardiac wall and posterior skeletal muscles in rats treated with adriamycin.

Juan Saèz (Santiago, Chile) provided evidence for the presence of gap junction hemichannel activity on cells that are under metabolic inhibition. He showed that the activity of these channels is regulated by reactive oxygen species concomitant with dephosphorylation, nitrosylation, and glutathiolation of the protein subunit that forms the pore connexion 43 (Retamal et al 2006).

Luis Sobrevia (Santiago, Chile) talked about studies of the alteration of L-arginine transport and nitric oxide (NO) synthesis during gestational diabetes or intrauterine growth restriction.

Liliana Lamperti (Concepción, Chile) spoke about the antioxidant activity of the plant extract *Ugni molinae* Turcs in the oxidative modification of low-density lipoprotein and its protective role in the endothelial dysfunction associated with the L-arginine/NO pathway.

Claudina Rodrigues-Pousada (Oeiras, Portugal) discussed the family of b-ZIP Yap proteins in *Saccharomyces cerevisiae*, which are implicated in a variety of stress responses. YAP1 is the major regulator of oxidative stress, whereas YAP4 expression is highly induced under conditions of high external osmolarity. Microarray analysis showed a broad influence of YAP4 over a large set of genes activated in response to osmolarity changes.

Wellington de Araujo (Sao Paulo, Brazil) talked about the interaction between endophytic bacteria and a plant host and the ability of these bacteria to induce plant resistance against pathogens.

Wolfgang Schumann (Bayreuth, Germany) showed that the expression of about 60 alkali-inducible *Bacillus subtilis* genes was controlled by the alternative sigma factor W, which is sequestered by an anti-sigma factor. Release of sigma-W after an alkali shock requires the consecutive

action of 3 different proteases, leading to the interaction of the anti-sigma factor (Schöbel et al 2004).

POSTERS

In spite of an unexpected rain, the poster section of the workshop was well attended and displayed an array of topics, including oxidative stress, hypoxia, hypothermia, acetaminophen toxicity, parasites, diabetes, oncology, metastasis, and the influence of circulating Hsps on the immune system. Participants at the poster section were entertained by a performance of authentic Chilean music by the group Suyay (meaning hope), formed by students from the University of Concepción, some of whom were workshop participants.

CONCLUDING REMARKS

The importance of Hsps is now well established, and the research has been expanded to several fields of modern biology. This workshop was a great example of the diversity of the heat shock response. In addition, the heavy participation of students, both graduate and undergraduate, gave a fresh air to the discussion. The workshop came to a closure with a very entertaining farewell party that included plenty of excellent Chilean wine, dancing, and music and brought together international and local participants. The true success of this workshop can only be measured by the future accomplishments of the many participating students who interacted for 4 days with established investigators. We hope that we were able to contribute to the opening of new opportunities and the broadening of horizons of these young individuals. We wish the best of luck to Professor Schumann, who is organizing the next workshop in Bangkok, Thailand, in 2008.

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