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Molecular biology of stress responses

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INTRODUCTION

Stress molecular biology is one of the burning subjects in the modern biological sciences. An urgent need to enhance the knowledge of and to promote research on the responses mounted by all living organisms to environmental, physiological, and pathological stresses is being felt by researchers worldwide, but few meetings have been held outside of North America and Europe. To fill this gap, an international workshop on molecular biology of stress responses was organized by S.C. Lakhotia (lakhotia@bhu.ac.in), Wolfgang Schumann (wolfgang.schumann@uni-bayreuth.de), and Anil K. Tripathi (Banaras Hindu University, Varanasi, India) in 1997 (Csermely and Lakhotia 1998). Building on the success of this meeting, biologists have made this workshop a regular event. The Cell Stress Society International has given strong support to this venture. The second workshop in this series was organized by Tangchun Wu (wut@tjmu.edu.cn) and colleagues in 1999 at Wuhan, China.

The Third International Workshop on the Molecular Biology of Stress Responses was organized by Daniel Ciocca (dciocca@lab.cricyt.edu.ar) and colleagues at Mendoza, Argentina (10–13 October 2001). Mendoza is world-famous for its wines and for its natural landscapes provided by the magnificent Andes mountains, of which nearby Aconcagua is the highest peak in the Americas. All the participants enjoyed the excellent local hospitality extended by the organizers by way of special cultural programs and dinners. This meeting was attended by about 100 researchers from a large number of countries, such as USA, Venezuela, France, Canada, Germany, Brazil, Japan, Hungary, China, Denmark, Spain, Argentina, Uruguay, Austria, Italy, and India. In all, 8 platform sessions were organized in this workshop. Also, there were 2 poster sessions with about 25 posters. The overall quality of these posters, mostly presented by students from Argentina and other neighboring countries (Uruguay, Chile, and Brazil), was excellent. The presenters of the posters were called for brief platform summaries as well, a novel aspect of this workshop.

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STRESS BIOLOGY—BASIC TENETS

The cellular stress response is evolutionarily conserved in all living organisms, and a major role is attributed to the induced heat shock proteins (Hsps) and other molecules that confer stress protection. The molecular responses elicited by the cells dictate whether the organism adapts, survives, or, if injured beyond repair, undergoes death. Most of the time these responses are beneficial to the organisms, but sometimes cells like cancer cells mount defensive mechanisms that interfere with therapies. Our detailed understanding of stress responses has paved the way for the development of stress-tolerant crops in several instances (Grover et al 1999). Considering all these, studies on stress responses turned out to have broad biological applications in microorganisms, plants, animals, and humans in health and in disease.

HEAT SHOCK PROTEINS

F. Ritossa discovered the heat shock response (Hsr) in Drosophila salivary glands in 1962. In 1974–1975 H. Mitchell and A. Tissières demonstrated that heat shock induced the expression of a set of new proteins under these conditions that were called the Hsps, and the induction of this response was subsequently found to be universal. For plants, early work on heat shock–induced alterations in protein profiles appeared independently from the groups of J.P. Mascarenhas and Joe L. Key.

Although the meeting formally started on 10 October 2001, a special introductory course was organized on 9 October to give a general overview in Spanish and English on molecular biology of stress responses, mainly for the local students from Latin America. This special course emphasized the following themes:

1. As several agents other than heat can also induce Hsr,

the Hsps are also called stress proteins. In general, there are several classes of Hsps categorized according to their apparent subunit molecular weights, including a small Hsp family with molecular masses ranging from 14 kDa to 29 kDa, Hsp40 family, Hsp60 family, Hsp70 family, Hsp90 family, and Hsp110 family. Hsps are now recognized as important to a range of physiological and cellular functions under both normal growth conditions and in response to stresses other than heat shock. Characterization of the individual Hsp has also led to the realization that most cells contain constitutively expressed homologs of the inducible Hsp that are essential to specific Hsp functions.

2. Starting in the mid-1980s, the concept of molecular chaperones evolved from the work of biochemists and cell biologists, and several Hsps were soon recognized as having such chaperoning functions.

HSP EXPRESSION AND CANCER BIOLOGY

On 10 October, the workshop was opened formally by Drs Larry Hightower (Editor, *Cell Stress and Chaperones*, lawrence.hightower@uconn.edu), Robert Tanguay (President-elect, CSSI, robert.tanguay@rsvs.ulaval.ca), and Daniel Ciocca (Chairman, Organizing Committee, dciocca@lab.cricyt.edu.ar).

The theme of apoptosis or programmed cell death was given a great deal of emphasis in this workshop (Leist and Jäättelä 2001). This sophisticated system of genetically regulated cellular suicide is involved in many biological processes, such as embryonic morphogenesis, metamorphosis, development and selective removal of damaged, infected, and superfluous cells. Altered programmed cell death has been associated with pathological processes, such as cancer, infectious and chronic inflammation. A balance between proapoptotic and antiapoptotic molecules, which mediate or suppress the process of cell death, respectively, determines the susceptibility of mammalian cells to apoptosis. Among the best-studied mediators in this regard are the members of the Bcl-2 gene family. This family regulates the release of cytochrome *c* from the mitochondria to the cytosol to form a complex called the apoptosome that includes cytochrome *c*, an apoptosis-inducing factor (Apaf-1), and an initiator caspase. Apoptosis is mediated by extrinsic (receptor-mediated) and intrinsic (mitochondria-mediated) signaling pathways that converge in the activation of caspases. Cysteine protease activation is an early hallmark of apoptosis. The activation of the inactive pro-caspases occurs in a hierarchic cascade in which the apoptotic signal activates an initiator caspase, which in turn activates the effector caspases. These proteases initiate the degradation phase of programmed cell death, giving rise to the morphological features of apoptosis (cytoplasmic and nuclear condensation, cytoplasmic shrinkage, cell membrane blebbing, chromatin clumping at the periphery of the nucleus, endonuclease-mediated deoxyribonucleic acid [DNA] cleavage, and formation of apoptotic bodies). Recent evidence suggests that Hsps may block the cell death pathways at different levels. Because cellular homeostasis is a balance between survival and death, Hsps and other chaperones play a pivotal role to support this sensitive balance. With respect to cancer treatment, chemotherapy is one of the most common therapies. Unfortunately, antineoplastic drug resistance, attributable in part to blocked apoptosis, is an important cause of failure in cancer treatment.

Dr Stuart K. Calderwood (Boston, USA, stuart_calderwood@dfci.harvard.edu) explained that under highly concentrated conditions, proteins are at risk of aggregation, which is a cellular catastrophe. Such effects, however, rapidly trigger the activation of the heat shock transcription factor (Hsf) and the expression of Hsp molecular chaperones. This group studied the regulation of Hsf1, Hsf2, and Hsf4 in normal cells and in prostate carcinoma during malignant transformation and under conditions of exposure to cancer therapy. Expression-profiling studies indicated that each of the factors is expressed at equivalent levels during malignant progression, in line with the high degree of conservation of the response. However, Hsf1 activity and Hsp expression played significant roles in the generation of the malignant phenotype and in the resistance to clinical cancer treatment. Michel Morange (Paris, France, morange@wotan.ens.fr) observed that Hsf2-deficient mice are viable. However, they suffered from brain abnormalities characterized by the enlargement of the lateral and third ventricles. Hsf2 knockout mice were also affected in spermatogenesis. Hsf2-deficient females were subfertile and exhibited multiple reproduction problems (Manuel et al 1999). R.W. Currie (Nova Scotia, Canada, wcurrie@is.dal.ca) observed that Hsps are synthesized in abundance in the heart and the brain after mild injury, such as heat shock or brief ischemia. In brain ischemic injury, epileptic seizure activity caused increased expression of Hsp70 in neurons and Hsp27 in glial cells. In the heart, Hsp27 is localized normally in cardiomyocytes. Heat shock also induced a cell-type–specific expression of Hsp70 in blood vessels (Krueger-Naug et al 2000; Leger et al 2000).

According to Jacques Landry (Quebec, Canada, jacques.landry@med.ulaval.ca), heat shock activates within minutes several signaling pathways that are likely to be involved in generating immediate homeostatic responses. These include early heat shock signal transduction through the p38 MAP kinase pathway (Charette et al 2000, 2001). Peter Csermely (Budapest, Hungary, peter_csermely@rex.biorex.hu) observed that chaperones probably associate with numerous mutant proteins, keep-

ing the resulting phenotype hidden until exposed by a stressful event. Because chaperone action becomes compromised during the aging process together with an increase in damaged proteins, silent mutations may be exposed in aged subjects. This phenomenon may contribute to the appearance of the so-called diseases of civilization, such as diabetes and atherosclerosis. He further discussed the pleiotropic cytoprotective effects of Biorex drug candidates (Hsp induction, membrane protection, etc) toward preventing cellular damage, as well as their diverse pharmacological actions (Csermely 2001a, 2001b).

Michael Sherman (Boston, USA, sherman@bbri.org) elaborated that Hsp70, when expressed in cells at high levels, suppresses activation of protein kinases JNK and p38 by various stressful treatments, including heat shock, UV-irradiation, oxidative stress, cytokines, and others. This observation has implications for many aspects of cell physiology that are controlled by JNK and p38. Matthias Gaestel (Hannover, Germany, gaestel.matthias@mh-hannover.de) explained that MAPKAP kinase 2 (MK2) and MK5 are 2 of the several kinases that are regulated via direct phosphorylation through p38 MAP kinase, the central component of a stress-activated kinase cascade. Both kinases are mainly localized in the nuclei of nonstressed cells and, as a consequence of a conformational change, are rapidly exported to the cytoplasm as a result of activation in response to stress (Kotlyarov et al 1999; Neininger et al 2001). Larry Hightower (Connecticut, USA) presented an evaluation of stannous chloride, a potentially useful inducer of the cellular stress response and cytoprotectant in intact rats and cultured human HT-29 cells (House et al 2001). Masataka Mori (Kumamoto, Japan, masa@gpo.kumamoto-u.ac.jp) observed that excess nitric oxide (NO) induces apoptosis in certain cell types, including macrophages and pancreatic β-cells. This group concluded that the endoplasmic reticulum stress response pathway is involved in early steps of NO-mediated apoptosis in pancreatic β-cells (Gotoh et al 2001; Oyadomari et al 2001).

Ian R. Brown (Toronto, Canada, ibrown@utsc.utoronto.ca) observed that fever-like increases in body temperature triggered apoptosis in dividing cell populations of the testis and the thymus but not in mature, postmitotic cells of the adult cerebellum. He also examined death in regions of the embryonic brain and early postnatal mammalian cells. These proliferative neural regions were found to be highly susceptible to hyperthermia-induced apoptosis, suggesting that actively dividing neural cell populations are more prone than postmitotic neural cells to cell death (Bechtold et al 2000; Khan and Brown 2001). Marja Jäättelä (Copenhagen, Denmark, mhj@biobase.dk) described the control of tumor cell apoptosis by Hsp70. According to this group, Hsp may confer a survival advantage to tumor cells because of its ability to protect cells from a wide range of apoptotic and necrotic stimuli (Nylandsted et al 2000; Leist and Jäättelä 2001). Speaking on the quality control of glycoprotein folding in endoplasmic reticulum, Armando J. Parodi (Buenos Aires, Argentina, aparodi@inti.gov.ar) elaborated on the emerging principles by which *N*-glycan processing participates in quality control (Parodi 2000).

On the association of inducible Hsp71 and its antibodies with environmental stresses and diseases, Tangchun Wu (Wuhan, China, wut@mails.tjmu.edu.cn) observed that Hsp and autoantibodies against Hsp may play a role in the pathogenesis or prognosis (or both) of some diseases. Their findings have also suggested that harsh workplace conditions can increase the production of antibodies against Hsp71 and that the presence of antibodies to this stress protein may be associated with hypertension (Wu et al 1999, 2001a, 2001b). Elaborating on the effect of heat shock on the inflammatory response, Antonio De Maio (Baltimore, USA, ademaio@mail.jhmi.edu) stated that sepsis is a major health problem with over 500 000 cases reported every year in the USA with a mortality rate of 40–60%. The effect of heat shock on cells involved in the inflammatory response is complex, and it is likely that several mechanisms are responsible for the protection from toxicity observed in heat-shocked rodents because of lipopolysaccharide (a component of the outer membrane of gram-negative bacteria that is shed from the pathogen during infection) (De Maio 1999). Daniel R. Ciocca (Mendoza, Argentina) observed that several members of the Hsp family are involved in key processes in cancer cells and tissues, such as cell proliferation, cell differentiation, apoptosis, tumor cell invasion, disease prognosis, response to endocrine therapy, and immune response (Vargas Roig et al 1997; Ciocca et al 1998). Laura Vargas-Roig (Mendoza, Argentina, vargasl@lab.cricyt.edu.ar) talked about her findings on Hsp27 and Hsp70 in serial biopsies from breast cancer patients treated with doxorubicin (Vargas-Roig et al 1998). Increased nuclear accumulation of Hsp27 and Hsp70 was a relatively late event in invasive tumors, and some tumor cells showed membrane localization of these proteins. Following chemotherapy, increased expression of these 2 Hsps was observed in certain stromal fibroblasts. For Hsps in thyroid and cutaneous tumors, Juan J. Cabrera-Galvan (Canary Island, Spain, jcabrera@cicei.ulpgc.es) showed a significant increment of Hsp27 in papillary carcinomas in comparison with follicular carcinomas, with papillary carcinomas showing a better prognosis. Kerstin Bellmann (Quebec, Canada, kerstin.bellmann@crhdg.ulaval.ca) described the sensitization of cells by c-myc to undergo apoptosis via the activation of stress-activated kinases. Kindås-Mügge (Vienna, Austria, ingela-margaret.kindas-muegge@univ.ac.at) showed that Hsp27 overexpression may influence the invasive and metastatic potential of a human melanoma cell line in vitro. Hsp27-overexpressing cells showed decreased invasiveness relative

to controls. Local or regional application of specific agents or delivery of genes for induction of Hsp27 may provide a concept for the development of new strategies for treatment of solid malignancies (Jantschitsch et al 1998; Kindås-Mügge et al 1998).

E. Noessner (Munich, Germany, noessner@gsf.de) dealt with the cross-presentation of human shared tumor antigens by dendritic cells. The results of this group show for the first time that HSP70-peptide complexes mediated the cross-presentation of nonmutated, naturally expressed human tumor antigen by human dendritic cells (Kuppner et al 2001). Alexander Asea (Boston, USA, alexzander_asea@dfci.harvard.edu) spoke on the role of toll-like receptors in Hsp70-induced signaling. They have recently shown that Hsp70 family members can bind to the surface of human monocytes with high affinity, elicit a rapid intracellular calcium flux, activate nuclear NF-κB and upregulate the expression of proinflammatory cytokines tumor necrosis factor-α, interleukin 1β, and interleukin 6 (Asea et al 2000a, 2000b). Gabriele Multhoff (Munich, Germany, gabriele.multhoff@klinik.uni-regensburg.de) discussed how the Hsp60, Hsp70, and Hsp90 families play key roles in cancer immunity by acting as carrier molecules for tumor-derived peptides and through functions as chaperokines (Hantschell et al 2000; Multhoff et al 2001).

HSP EXPRESSION IN PROKARYOTES AND INSECTS

Wolfgang Schumann (Bayreuth, Germany) elaborated on the efforts of his group in understanding the regulation of the expression of heat shock genes in *Bacillus subtilis*. His work over the last 10 years has revealed about 200 heat shock genes that can be grouped into 6 different classes, where members of each class are regulated by a different mechanism (Schumann et al 2001). The search for thermosensors and the topic of heat shock regulation in *E. coli* and the plant pathogen *Agrobacterium tumefaciens* (an important vector system in plant biology) were discussed by Takashi Yura (Kyoto, Japan, tayura@ip.media.kyoto-u.ac.jp). The induction of Hsp occurs primarily as the result of the increased level or activity (or both) of sigma32 in most gram-negative bacteria studied so far. *E. coli* GroEL functions as a chaperone essentially by modulation of its affinity for folding intermediates through binding and hydrolysis of adenosine triphosphate (ATP). According to Chih-Chen Wang (Beijing, China, chihwang@sun5.ibp.ac.cn), the cooperative effects of the coenzyme reduced nicotinamide adenine dinucleotide and GroEL mediate GroEL-assisted dehydrogenase folding in an ATP-independent way (Zhang and Wang 1999). Robert Tanguay (Quebec, Canada) observed that Hsp22, Hsp23, Hsp26, and Hsp27 of *Drosophila* perform distinct function(s) in vivo by acting as chaperones of specific molecules in distinct intracellular compartments or in distinct cell types (or both) during differentiation (Michaud et al 1997; Morrow et al 2000).

STRESS PROTEINS IN PLANT AND PLANT-RELATED SYSTEMS

In recent years, the genome projects have yielded valuable information on stress responses. R. Costa de Oliveira (Sao Paulo, Brazil, reginaco@umc.br) presented her findings on identification and functional analysis of oxidative stress response genes in *Xylella fastidiosa*, a phytopathogenic bacterium. A. Grover (New Delhi, India, grover_anil@hotmail.com) dealt with the structural and functional characterization of rice Hsp100 protein (Agarwal et al 2001). Rice is the most important food crop in the world. This group has noticed that transformation of Δhsp100 yeast cells with rice hsp100 complementary DNA (cDNA) enabled partial recovery of the thermotolerance effects in yeast cells. Subsequently, they have developed transgenic rice overexpressing hsp100 cDNA that shows enhanced thermotolerance (Grover et al 2001).

CONCLUDING REMARKS

The next workshop in this unique series of small, highly interactive international meetings hosted by developing countries will probably be held in 2004, in a location to be decided. CSSI President-elect Robert Tanguay announced that the inaugural Cell Stress Society International Congress is being planned for Quebec City in the fall of 2003.

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