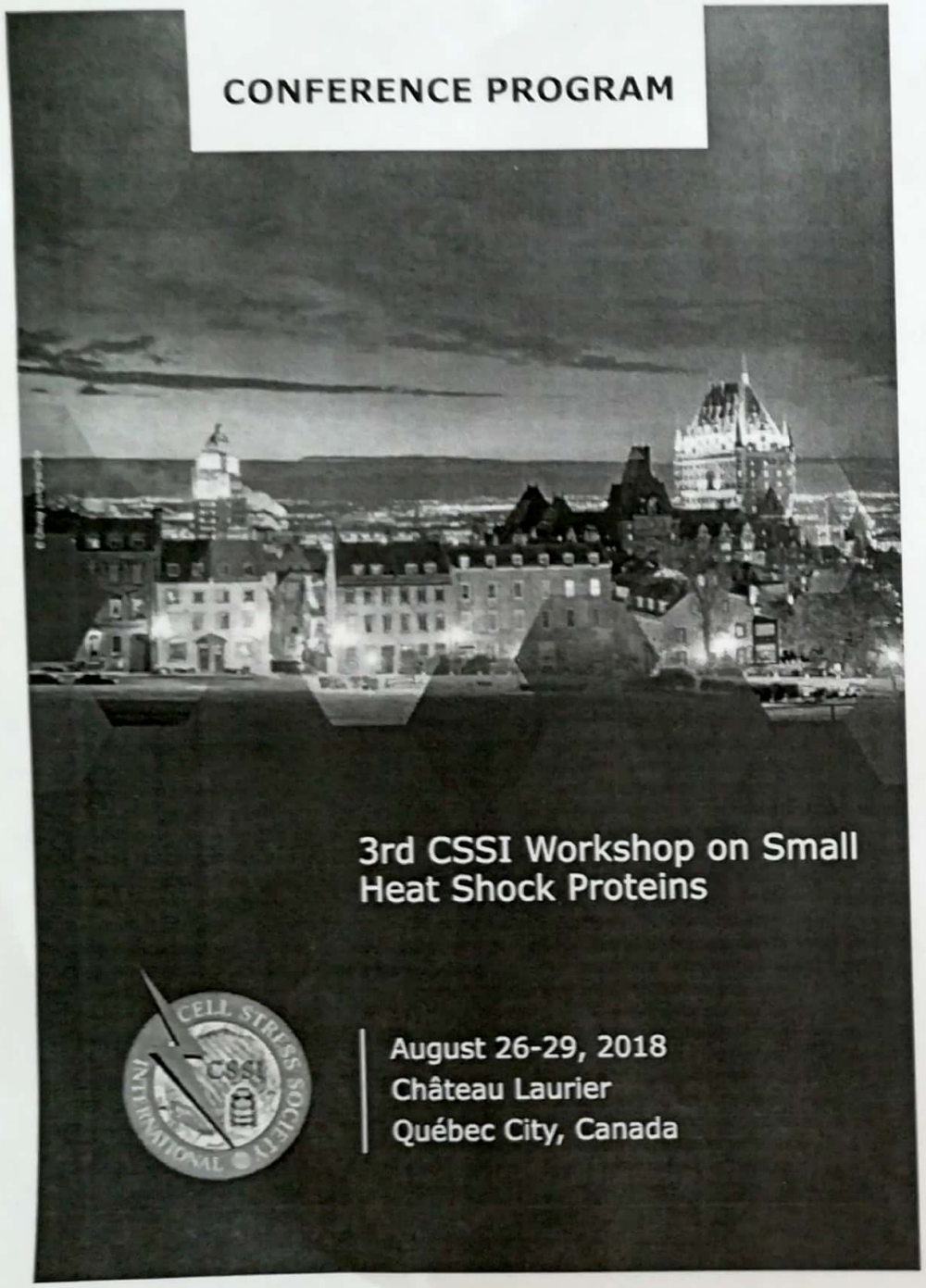

THE SMALL HEATH SHOCK PROTEIN B8 AT THE INTERPLAY BETWEEN THE INTRACELLULAR DEGRADATIVE PATHWAYS IN MOTONEURON DISEASES

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Motor neuron diseases (MNDs) are a large class of neurodegenerative diseases in which upper cortical and lower spinal cord motorneuron are affected. Several MNDs, like spinal and bulbar muscular atrophy (SBMA) or amyotrophic lateral sclerosis (ALS) have been linked to specific gene mutation which results in the production of aberrant proteins prone to misfold and to aggregate. To counteract he accumulation of these misfolded proteins cells, including neurons have developed a finely tuned protein quality control (PQC) system. The degradative systems are major components of the PQC system and comprise the ubiquitin–proteasome pathway and the autophagic pathways. specifically involved in the maintenance of a normal cell proteostasis. By working in association to selected molecular chaperones, the degradative systems are essential components of the intracellular protein quality control (PQC) system. Misfolded proteins are neurotoxic and are recognized by chaperones and delivered to the degradative systems for their clearance. A tightly molecularly regulated equilibrium oversees the final fate of aberrant proteins. This equilibrium is crucial to maintain proteostasis in neurons and may chance under various stimuli, and its alteration give rise to a vicious cycle of protein accumulation and PQC system damage that might lead to cell death. Among chaperones, the small heat shock protein (HSP) B8, is able to facilitate autophagy and assists the removal of misfolded proteins prone to aggregate in MNDs. HSPB8 associates to BAG3 HSP70 and CHIP (an ubiquitinating enzyme) to deliver misfolded protein to autophagosome and this form of autophagy is called Chaperone-assisted selective autophagy (CASA) and this complex based on HSPB8/BAG3 is named CASA complex. HSPB8 is induced in response to several neuronal stresses such has proteotoxic and oxidative stresses. We found that HSPB8 is highly induced in the two main targets of misfolded protein toxicity in tg mice models of SBMA and ALS, the motorneurons and the muscle. The pharmacological or genetic induction of HSPB8 expression is protective in MNDs, while its silencing has opposite effects. We also showed that HSPB8 protects from a misfolded protein induced aberrant phenotype in fly models of ALS. By increasing the HSPB8-mediated selective targeting of misfolded proteins to autophagy neurons and muscle reduce their proteasome-mediated clearance limiting its possible overwhelming. Therefore, pharmacological approached which potentiate the HSPB8-BAG3 autophagic pathway could contribute to maintain a correct proteostasis in motorneuron and muscle cells and might have therapeutic implication in MNDs.

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