

some cases, this affects alternative splicing of the CPEB regulated transcripts. This is a new function for CPEB, where hundreds of mRNAs are regulated by alternative processing in the nucleus in a coordinated manner and associated with cell cycle and tumor development. A global model for the regulation of gene expression by the CPEB family of proteins in cell cycle and cell differentiation will be presented.

## S02.4 Autophagy and Protein Homeostasis

### S02.4-1

#### Protein folding stress in neurodegenerative disease: an interplay between ER stress and autophagy

C. Hetz

*Biomedical Neuroscience Institute (BNI), Faculty of Medicine, University of Chile, and Center for Molecular Studies of the Cell, ICBM, University of Chile, Santiago, Chile*

The most common neurodegenerative diseases, such as Alzheimer's Disease, Parkinson's Disease, Amyotrophic lateral sclerosis, and Huntington's disease, affect millions of people worldwide, but there is neither preventive nor curative therapy for them. These diseases share a common neuropathology, primarily featuring the presence of abnormal protein inclusions containing specific misfolded proteins. Recent evidence indicates that alteration in organelle function is a common pathological feature of protein misfolding disorders. The endoplasmic reticulum (ER) is an essential compartment for protein folding, maturation, and secretion. Signs of ER stress have been extensively described in most experimental models of neurological disorders. ER stress is caused by functional disturbances, which result in the accumulation of unfolded/misfolded proteins at the ER lumen. To cope with ER stress, cells activate an integrated signaling response termed the Unfolded Protein Response (UPR), which aims to reestablish homeostasis through transcriptional upregulation of genes involved in protein folding, quality control and degradation pathways. In this talk we overview our efforts to assess the role of ER stress in protein misfolding disorders, and discuss possible strategies to target the UPR with therapeutic benefits.

Support from FONDECYT no. 1100176, FONDAP grant no. 15010006, Millennium Institute No. P09-015-F, Muscular Dystrophy Association, Alzheimer Association, and the Michael J. Fox Foundation for Parkinson research (to CH).

### S02.4-2

#### Functional characterization of Atg8-interacting proteins in selective autophagy

T. M. Roberts<sup>1</sup>, M. Klijanska<sup>1</sup>, E. Siergiejuk<sup>1</sup>, C. Wilson-Zbinden<sup>1</sup>, K. Hofmann<sup>2</sup>, C. Kraft<sup>1,\*</sup> and M. Peter<sup>1</sup>

<sup>1</sup>*Institute of Biochemistry, ETH-Hönggerberg, Zürich, Switzerland,* <sup>2</sup>*Institute for Genetics, University of Cologne, Cologne, Germany.* \*Present address: Max F. Perutz Laboratories, University of Vienna, Vienna, Austria.

Several lines of evidence suggest the existence of different types of selective autophagic degradation pathways, which target single proteins and various cellular structures such as protein aggregates, peroxisomes, ribosomes and mitochondria for degradation in lysosomes/vacuoles. However, the mechanism of cargo recognition is not well understood. Structural studies have uncovered a critical role of the ubiquitin-like protein Atg8/LC-3, which specifically interacts with specific autophagic receptors through conserved WXXL-like sequences, called the LC3 interacting region

(LIR) (Noda et al., 2007). LIRs function in various autophagic receptors such as Atg19 in the cytoplasm-to-vacuole targeting (Cvt) pathway, p62 and neighbour of BRCA1 gene 1 (NBR1) in autophagic degradation of protein aggregates, and Atg32 and Nix in mitophagy, and may link the target-receptor complex to the autophagic machinery.

Here we report on a careful bioinformatic analysis to search the yeast proteome for potential LIR motif containing proteins. Promising candidates were then tested biochemically and functionally for their involvement to regulate autophagy or to target specific cargo for destruction. Interestingly, this approach identified possible receptors that may specifically be required to target misassembled pre-60S ribosomes to the vacuole for degradation. Moreover, we found that yeast Atg1 interacts with Atg8, as has been found for the mammalian Atg1-homologue Ulk1 (Behrends et al., 2010). This interaction is abolished by mutations in the LIR and results in a partial loss of Cvt and autophagy activity. Interestingly, available experiments suggest that Atg8-removes Atg1 from the phagophore assembly sites (PAS), and promotes its association with autophagosomal membranes. Taken together, these results imply that Atg8 may fulfil multiple roles in autophagy, including Atg1 regulation and recognition of specific cargo.

### S02.4-3

#### Cyclic GMP, colon cell cytotaxis and autophagy

S. Visweswariah

*Indian Institute of Science, Bangalore, India*

The intestine is the largest organ in the body, and along with the microbiome, has a profound influence on the health and well being of an individual. Cyclic nucleotide signalling mechanisms are important in regulating fluid and ion secretion in the intestine, but recently, cGMP has emerged as a regulator of cell cycle progression in intestinal epithelial cells, thereby influencing the progression of colon cancer. Receptor guanylyl cyclase C (GC-C) is the target for the gastrointestinal hormones guanylin, uroguanylin and the bacterial heat stable enterotoxins (ST) that cause watery diarrhoea. We now show that activation of this receptor results in p53-independent regulation of p21, leading to cell cycle arrest and senescence. GC-C knock-out mice are more susceptible to carcinogen-induced tumour formation, and the number of pre-cancerous lesions was not reduced on administration of ST peptide to these mice, in contrast to that seen in wild type mice. These results therefore provide a new role for GC-C in maintaining homeostasis in the intestine. Recently, we have characterized a novel hyperactivating mutation in GC-C that is found in patients with symptoms of recurrent and frequent diarrhea. Many patients report bowel obstruction and ileal inflammation, and some were diagnosed with Crohn's disease. Given the recent link between autophagy and Crohn's disease, we will also present our recent findings on the regulation of autophagy in intestinal cells by cGMP, and consequently, GC-C.

### S02.4-4

#### Molecular bases for population variation: from SNP to SAP

J. Wu

*Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Shanghai, China*

Single-nucleotide polymorphisms (SNPs) are recognized as one kind of major genetic variants in population scale. However, polymorphisms at the proteome level in population scale remain elusive. Recently, we have analyzed amino acid variances derived from SNPs within coding regions, which is named as single