Press release

The 26th *Colloque Médecine et Recherche* of the *Fondation Ipsen* in the series Alzheimer Disease :

"Protein Quality Control in Neurodegenerative Diseases"

The consensus confirms the hypothesis that damaged proteins'expression initiate a cascade of molecular pathways leading to the development of neurodegenerative diseases. Controlling the quality of these proteins in the proteome (all proteins expressed within a cell) is therefore crucial as the cell is permanently exposed to environmental and physiological stress, to aging and to the chronic expression of proteins associated with a disease.

Paris (France), May 10, 2011 – The 26th *Colloque Médecine et Recherche* in the Alzheimer's disease series, hosted by the Fondation Ipsen, has brought together leading cell and molecular biologists to examine the ways in which cells process rogue proteins. This knowledge is helping in understanding the causes of neurodegeneration and is providing new leads to prevention and treatment of these devastating conditions. The meeting, which took place in Paris on May 9, 2011, has been organized by Richard Morimoto (*Northwestern University, Evanston, USA*) and Yves Christen (*Fondation Ipsen, Paris, France*).

Cells are highly ordered complexes of protein molecules, each of which has an intricate three-dimensional structure that is essential for the protein to function properly. Inevitably, as a result of accident, mutation, stress, infection, inflammation or aging, some proteins do not fold correctly when they are generated, while others later become damaged and misshapen. If these aberrant molecules remain in the cell, they inevitably upset the finely tuned balance required for the cell to function smoothly. A range of mechanisms, known collectively as protein homeostasis or proteostasis, has evolved to identify, isolate and destroy such deleterious molecules. These include the unfolded protein response, which regulates the folding of newly formed protein chains, and various ways of labeling and destroying damaged molecules, all of which have to work in concert to maintain the health of the cell.

Certain proteins pose a particular challenge because they can exist in either a globular, soluble state or as pleated sheets that form insoluble aggregates in cells. A typical example is the amyloid-beta protein that accumulates in neurons in Alzheimer Disease. This protein is involved in many degenerative diseases, especially those of the nervous system. Such proteins are large molecules with certain structural characteristics. As they tend to participate in several key functions in the cell, the formation of aggregates increases the cell's stress responses (Ulrich Hartl, *Max-Planck-Institut für Biochemie, Martinsried, Germany*). One of these is the production of so-called heat-shock proteins (Jeffery W. Kelly, *Scripps Research Institute, La Jolla, USA*; Hartl). Named after experiments in the fruit fly that led to their discovery, heat-shock proteins are a type of molecule termed chaperones, which assist in, monitor and maintain the folding of protein chains. By associating with proteins in the sheet form, their availability for their normal functions is reduced (Hartl). These include determining how a damaged protein should be dealt with: refolded, broken down or enclosed in a membrane-bound body to remove it from causing harm (Judith Frydman, *Stanford University, Palo Alto, USA*). Learning about the spatial and temporal organisation of these processes will help with understanding why protein aggregates cause degeneration.

The role of chaperones is best characterized in the initial folding of newly synthesized proteins, which takes place in the endoplasmic reticulum, a system of tubules within the cytoplasm that is dedicated to protein synthesis and folding. The unfolded protein response maintains a balance between unfolded proteins and chaperones by regulating the rate of transcription and translation of chaperone proteins (David Ron, *University of Cambridge, Cambridge, UK*). The unfolded protein response also has to be in equilibrium with other proteostasis pathways in the cytosol. Mutations or external stresses that upset other parts of the proteostasis response, such as aggregates of insoluble proteins like amyloid-beta in the cytosol, can in turn stress the unfolded protein response.

Both the unfolded protein response and heat-shock type chaperones are reduced in cells that contain wrongly folded and dysfunctional molecules but activation of certain other proteins can reverse this trend, indicating that the decline in function associated with age is not inevitable. The nematode worm, *Caenorhabditis elegans*, is providing a useful model for analyzing proteostasis (Richard Morimoto, *Northwestern University, Evanston, USA*). An evolutionnary-conserved transcription factor, FOXO, that both protects against aging and integrates signaling pathways involved in differentiation, cell survival and proteostasis is being examined using the nematode as a model for Huntington's disease (Christian Neri, *Inserm U894 and Université Paris Descartes, Paris, France*). In these modified worms, signaling molecules well-known for their neurodevelopmental role, compromise the activity of FOXO, suggesting that dysfunctional neurons in Huntington's disease may well be unable to develop an efficient pro-survival response through the inappropriate use of developmental mechanisms.

A significant proportion of damaged proteins are degraded after they have been sequestered in vesicles that subsequently fuse with digestive bodies known as lysosomes. This process of macroautophagy, common to all cells, has been characterized in yeast, where over 30 genes are involved and parts of the process are now understood (Daniel J. Klionsky, *University of Michigan, Ann Arbor, USA*). Many of these genes have counterparts in mammals. Macroautophagy has been found to participate in processes ranging from embryonic development and cell differentiation to tumor suppression and the removal of microbes (Noboru Mizushima, *Tokyo Medical and Dental University, Tokyo, Japan*). Different mechanisms for forming and locating the autophagic bodies seem to be used for different proteins. The details of the signaling steps in two of these pathways are being elucidated (Mizushima; Christian Behl, *Universität Mainz, Mainz, Germany*). Macroautophagy is only one of three types of autophagy that have been identified: the others are microautophagy and chaperone-assisted autophagy (Ana Maria Cuervo, *Albert Einstein College of Medicine, Bronx, USA*). Malfunctions in these mechanisms contribute to a range of diseases, including cancer and neurodegenerative conditions. How the different pathways participate in removing pathogenic proteins and conversely how the damaged molecules impact on the functioning of the different forms of autophagy will be discussed.

Proteostasis is not only an intracellular process: evidence is gathering for systemic signals that coordinate the responses of individual cells. In the nematode worm, stress signals detected by sensory neurons participate in the heat-shock response and over-excitation of this pathway can lead to misfolded protein in muscles (Morimoto). Stress signals also seem to be transmitted within the mammalian central nervous system by signaling molecules dubbed 'stress-kines' (Andy Dillin, *The Salk Institute for Biological Studies, La Jolla, USA*). A further complexity is the growing realization that some classes of neuron are more vulnerable than others (Dillin; Steve Finkbeiner, *University of California, San Francisco, USA*). Specially developed techniques are showing that neurons in the striatum, which die in Huntington's disease, are damaged by the aberrant protein huntin, whereas cortical neurons are not. The inclusion bodies in striatal neurons that characterize the disease rather than being part of the degenerative process, protect the neurons by sequestering the damaging protein (Finkbeiner).

Points are being identified thanks to new approaches in all of these mechanisms where therapeutic interventions may be possible, although extreme care will be needed when intervening with such intricately balanced networks that are central to cell health. With macroautophagy, for example, too little can cause degeneration while too much can result in cell death (Klionsky). Another instance is the unfolded protein response. The complex feedback loops in which it is embedded means that

consequences of manipulation are hard to predict, as already found in a mouse model of amyotrophic lateral sclerosis, which produced results opposite to those expected (Ron). Controlling the quality of proteins is therefore crucial for the development of new therapeutic opportunities for certain neurodegenerative diseases.

La Fondation Ipsen

Established in 1983 under the aegis of the *Fondation de France*, the mission of the *Fondation Ipsen* is to contribute to the development and dissemination of scientific knowledge. The long-standing action of the *Fondation Ipsen* aims at fostering the interaction between researchers and clinical practitioners, which is indispensable due to the extreme specialisation of these professions. The ambition of the *Fondation Ipsen* is to initiate a reflection about the major scientific issues of the forthcoming years. It has developed an important international network of scientific experts who meet regularly at meetings known as *Colloques Médecine et Recherche*, dedicated to six main themes: Alzheimer's disease, neurosciences, longevity, endocrinology, the vascular system and cancer science. Moreover, in 2007, the *Fondation Ipsen* started three new series of meetings. The first series is an annual meeting organized in partnership with the Salk Institute and *Nature* and focuses on Biological Complexity; the second series is the “Emergence and Convergence” series with *Nature*, and the third with *Cell* and the Massachusetts General Hospital entitled “Exciting Biologies”. Since its beginning, the *Fondation Ipsen* as organised more than 100 international conferences, published 70 volumes with renowned publishers and 215 issues of a widely distributed bimonthly newsletter *Alzheimer Actualités*. It has also awarded more than 100 prizes and grants.

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