*Press release*

# The 19th *Colloque Médecine et Recherche* of the *Fondation Ipsen* in the Neuroscience series: "Epigenetics, Brain and Behavior"

## After having evidenced the crucial role of genes in the nervous system function, and in its related diseases, neurobiology explores mechanisms that control gene expression.

**Paris (France), April 19, 2011** – The "one gene – one protein" dogma has been very successful in identifying the mutant genes and dysfunctional proteins associated with a range of inherited conditions, from muscular dystrophy to Alzheimer's disease. The approach has been less useful with many diseases affecting the nervous system and behavior. Over the past few years it has become increasingly apparent that gene transcription and translation into proteins is only a small part of a complex story. Rather like the queen bee in a beehive, each gene is embedded in a network of molecules, now known as the epigenome, that links the environment to the mechanisms regulating gene expression. At the 19th Colloque *Médecine et Recherche* of the *Fondation Ipsen* in the Neuroscience series, held in Paris on 18 April 2011, researchers from leading laboratories have explored how knowledge of epigenetic regulation is contributing to understanding the links between nervous system function and behavior in health and disease. The meeting has been organised by Paolo Sassone-Corsi (University of California at Irvine, Irvine, USA) and Yves Christen (Fondation IPSEN, Paris, France).

The contributions to this meeting provide a sample of the huge palette of knowledge of epigenetic effects. The potential for the development of diagnostic and therapeutic tools is huge but the complexity of the epigenome and the important consequences of even small changes should be a warning that pitfalls may lie ahead on the road to the clinic, as with any cellular regulatory mechanism.

The standard picture of the naked DNA helix is misleading: in cells, the DNA strand is wound round small spherical proteins termed histones to form the complex known as chromatin. The relationship between DNA and histones is one part of epigenetic regulation, that organises the transcription of genes: of the roughly 20,000 genes in every adult human cell only a small percentage are transcribed and the functions of each differentiated cell are determined by which set of genes this is. Although the mechanisms of epigenetic regulation are still being unravelled, it is already clear that they enable very subtle changes in gene transcription that fine tune the cell to current needs and that they often coordinate several or many genes involved in a particular function, such as metabolism and synaptic transmission (Sassone-Corsi; Abel). Long-term alterations in epigenetic regulation may even be inherited without any changes to the DNA (Isabelle Mansuy, *University of Zurich, Zurich, Switzerland*; Michael Meaney, *McGill University, Montréal, Canada*).

One important mechanism of epigenetic regulation is chromatin remodelling through acetylation and methylation of histones: enzymes alter the shape and function of particular histones and their relationship to the surrounding DNA by attaching or removing one or more

acetyl or methyl groups on specific amino acids. Much of the subtlety and diversity of epigenetic regulation derives from the position and number of these attached groups. Methyl groups also attach to DNA itself and lower the probability of a gene being transcribed.

The transcription of many genes is stimulated by transcription factors, molecules produced in the cytoplasm in response to external or internal signals that link changes in the environment or in demand to the production of new proteins. These factors trigger transcription by binding to a special region of the gene, the promoter, an interaction that requires various helper molecules. One class of helper, involved in most transcription processes, is the nucleosome remodelling factors, which are enzymes that give flexibility to the chromatin. According to their precise structure, nucleosome remodelling factors can target specific genes and either activate or repress them (Peter Becker, *Ludwig-Maximilians-Universität München, Munich, Germany*). In yeast cells, nucleosome remodelling factors are one of several epigenetic pathways regulating the aging of cells (Shelley Berger, *University of Pennsylvania School of Medicine, Philadelphia, USA*). Another pathway uses Sirtuins, a type of histone deacetylase that removes acetyl groups from histones in the end region of the chromosome, the telomere, long known to have a role in aging. These multiple controls are typical of the complexity of epigenetic regulation. In neurons, a specific histone methyl transferase has been identified that has a key role in regulating the expression of genes that code for neuron-specific proteins in adult brain; this enzyme seems to participate in at least two neuron-specific pathways (Anne Schaefer, *The Rockefeller University, New York, USA*).

The circadian clock, the internal mechanism that couples physiological processes to the 24-hour cycle of day and night, is a good example of epigenetic coordination: the many genes that control metabolism are coherently regulated by the influence of clock proteins through histone acetylation and methylation (Sassone-Corsi). A homologue of the yeast Sirtuins provides such a link and a specific methyl transferase that is rhythmically recruited to the promoters of clock genes has been found.

Synaptic transmission and plasticity are also functions requiring the coordination of many intracellular processes and so it is not surprising that epigenetic mechanisms play a large part in their regulation (Jean-Pierre Changeux; *Institut Pasteur, Paris, France*; Ted Abel, *University of Pennsylvania, Philadelphia, USA*; David Sweatt, *University of Alabama at Birmingham, Birmingham, USA*; Li-Huei Tsai, *Massachusetts Institute of Technology, Boston, USA*; Eric Nestler, *Mount Sinai School of Medicine, New York, USA*). Chromatin remodelling through histone acetylation and methylation is crucial for various types of memory formation and storage in animal models (Abel; Sweatt; Tsai) and in the modified neuronal plasticity that leads to abnormal behavior in drug addiction (Nestler). Identifying sites where chromatin remodelling has occurred as a result of exposure to drugs is aiding in the identification of affected genes. Addictive drugs may also have a direct effect on chromatin remodelling enzymes.

Similarities between the mechanisms being discovered in the regulation of synaptic plasticity and memory and those found in embryonic development and cell differentiation indicate that these processes have a common origin (Sweatt). On a more theoretical level, the interaction between environment and the state of the synaptic network that leads, through epigenetic regulation, to the stability of synapses may have contributed significantly to the increase in the complexity of connections in the brain in primate evolution, while in humans the long post-natal period allows for social and cultural inputs to brain development (Changeux).

Mutations affecting the functioning of proteins that participate in epigenetic regulation may of course result in incorrect or absent activation of genes essential for normal neuronal function and mental health (Schaefer; Tsai; Thomas Bourgeron, *Institut Pasteur, Paris, France*; Adrian Bird, *University of Edinburgh, Edinburgh, UK*; Lisa Monteggia, *University of Texas Southwestern Medical Center at Dallas, Dallas, USA*). Defects in synaptic transmission are being identified in some forms of autistic spectrum disorder, which may in some cases be associated with abnormal sleep homeostasis and changes in the melatonin/serotonin pathway that is integral to sleep regulation (Bourgeron). Rett syndrome, a profound autistic condition, is characterised by reductions in neuron size, the complexity of connections, neurotransmission and synaptic plasticity (Bird; Monteggia). Central to the condition is the loss of a protein known as methyl CpG binding protein 2 (MeCP2), which is very abundant in normal neurons. MeCP2 binds to particular methylated sites in the promoters of many genes, alters chromatin structure and is involved in histone acetylation; its loss affects the transcription of various genes required for synaptic plasticity and learning (Monteggia; Sweatt). In a mouse model, Rett-like symptoms have been reversed by activating a silent Mecp2 gene (Bird).

A challenging aspect of epigenetic regulation is that changes in the epigenome may be transmitted to future generations if they are present in the germ cells. Stress in early life is known to be a risk factor for later psychiatric illness, which in some families seems to heritable (Mansuy). In mice, chronic and unpredictable maternal separation results in depressive and impulsive behavior that has been transmitted to offspring. The early trauma is associated with persistent changes in DNA methylation in several promoters in germ cells and in the brains of the offspring, with altered gene expression in the brain when these mice become adult. The quality of maternal care also affects the transcription of genes implicated in the stress response, particularly in the hypothalamus-pituitary-adrenal axis (Meaney). In rats, changes in DNA methylation have been found across the genome in response to variations in maternal care, including in genes that regulate neural development.

***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 211 issues of a widely distributed bimonthly newsletter *Alzheimer Actualités*. It has also awarded more than 100 prizes and grants.

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