



Tuesday, December 8, 2015

10:00am to 5:00pm

Académie des sciences – Grande salle des séances
23 quai de Conti, 75006 Paris

CAN EPIGENETICS EXPLAIN TRANSGENERATIONAL TRANSMISSION OF ACQUIRED TRAITS?

Coordinators: **Geneviève ALMOUZNI, Jean-François BACH,
François CUZIN, Edith HEARD**

10h00 Opening remarks

Bernard MEUNIER, *Président, Académie des sciences*

10h05 Introduction

Jean-François BACH, *Secrétaire perpétuel, Académie des sciences*

10h10 Who acquires what? Reflections on a Lamarckian stereotype

Pietro CORSI, *Modern History Department, University of Oxford*

10h30 Discussion

10h35 Epigenetics from yesterday to nowadays, introductory elements

Geneviève ALMOUZNI, *Institut Curie Research Center, Académie des sciences*

10h55 Discussion

11h00 Demystifying transgenerational epigenetics

Vincent COLOT, *Institut de Biologie, École Normale Supérieure (IBENS)*

11h20 Discussion

11h25 Mechanisms and biology of transgenerational transmission in *C. elegans*

Eric MISKA, *Gurdon Institute, University of Cambridge*

11h45 Discussion

11h50 Polycomb Protein and Epigenetic Inheritance of Chromatin States

Giacomo CAVALLI, *Institute of Human Genetics – CNRS*

12h10 Discussion

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14h30 Maternal nutrition and the transgenerational cycle of obesity

Karen LILLYCROP, *University of Southampton*

14h50 Discussion

15h00 Mouse models of RNA-mediated non Mendelian inheritance

François CUZIN, *Université de Nice, Académie des sciences*

15h20 Discussion

**15h30 Non-genetic transgenerational inheritance of the effects of trauma :
Potential mechanisms in germ cells**

Isabelle MANSUY, *Laboratory of Neuroepigenetics, University and ETH Zürich*

15h50 Discussion

**16h00 The role of epigenetic mechanisms in the transgenerational transmission of
acquired traits**

Eva JABLONKA, *Evolutionary Biology, Genetics, Developmental Biology, Tel Aviv University*

16h20 Closing remarks

Jean-François BACH, *Secrétaire perpétuel, Académie des sciences*

16h30 General debate and conclusion

Edith HEARD, *Institut Curie Research Center*, **François CUZIN**, *Université de Nice*.

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Who acquires what ? Reflections on a Lamarckian stereotype

Pietro CORSI

More quoted than read, more misrepresented than understood, Jean-Baptiste Lamarck remains a fascinating, controversial figure in the history of evolutionary biology. For some the true founder of evolution, for others a mind prone to unrestrained flights of imagination, views and doctrines have been attributed to Lamarck that bear no resemblance to his actual writings. Lamarck is still seen as the man talking of giraffes stretching their necks, in spite of the fact that the example occurs only four times in his corpus (<http://www.lamarck.cnrs.fr>). He is supposed to have argued for an inner drive pushing life to gain higher levels of organisation, from monad to man, as Charles Lyell put it, and for having asserted that it is the organism's "will" that causes change and new forms of adaptation. Darwin insisted on Lamarck's foolishness in calling upon "will" to explain adaptation, in spite of Lamarck saying exactly the same. The French naturalist is also credited for the ill-famed theory of the inheritance of acquired characteristics. A view, it will be argued, that Darwin endorsed with greater determination than Lamarck. True, Darwin's acquired characters had to be submitted to the complex process he and we call "natural selection". Yet, the principle of acquired characteristics was elaborated by Darwin in much finer detail than in Lamarck: indeed, the latter held a very restrictive view of its action. Moreover, it was never a "character" that was transmitted to the progeny, but a slight modification of organic fluid dynamics that in the course of very long periods of time contributed to alter the organic structure as a whole. The question is not to vindicate Lamarck against Darwin: for the historian, the real issue is to understand the past for what it was, not according to our scientific, ideological or political prejudices.

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Demystifying Trans-Generational Epigenetics

Vincent COLOT

Until recently, a key assumption in biology has been that DNA mutations are the only source of heritable phenotypic diversification and therefore that adaptation is impossible in the absence of DNA sequence variants. However, this view is being increasingly challenged by the observation that changes in chromatin states, which are pivotal for the control of genome activity in eukaryotes, can sometimes become locked in and inherited across multiple sexual generations, independently of any change in the genome sequence. This system of inheritance, called epigenetic, is best documented in plants and often involves differential DNA methylation of repeat sequences, notably transposable elements. However, there is still a lack of systematic studies on the stability of epigenetic variants and their phenotypic consequences. Thus, the ecological or evolutionary impact of this type of variation, which could be different from that of DNA sequence variants by potentially providing a more rapid and reversible route to adaptation, remains unclear. I will present our efforts at addressing some of these issues experimentally using a population of near-isogenic, epigenetic Recombinant Inbred Lines (epiRILs) in Arabidopsis.

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Mechanisms and biology of transgenerational transmission in *C. elegans*

Eric MISKA

Since August Weismann (1834-1914) formulated the distinction between innate and acquired characteristics at the end of the 19th century, the debate relating to the inheritance of acquired traits has raised many controversies in the scientific community. Following convincing arguments against (e.g. William Bateson), this debate was then set aside by the majority of the scientific community. However, a number of epigenetic phenomena involving RNA, histone modification or DNA methylation, in many organisms, have renewed interest in this area. Transgenerational effects likely have wide-ranging implications for human health, biological adaptation and evolution, however their mechanism and biology remain poorly understood. We recently demonstrated that a germline nuclear small RNA/chromatin pathway can maintain epi-allelic inheritance for many generations in *C. elegans*. This is a first in animals. We named this phenomenon RNA-induced epigenetic silencing (RNAe). We are currently further characterizing the mechanism of RNAe. In addition, we are testing the hypothesis that RNAe provides a transgenerational memory of the environment (“Lamarckism”). We are currently exploring related phenomena in mice. We are also working towards establishing iPS cells differentiating into germ cells as a model to study the mechanism of transgenerational epigenetic inheritance.

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Polycomb-Mediated Repression in Transgenerational Epigenetic Inheritance

Giacomo CAVALLI

Transgenerational epigenetic inheritance is a hotly debated phenomenon whereby a non-genetically determined phenotype can be transmitted to the next generation. So far, this mode of inheritance has been described in few cases and it was suggested that chromatin components might be involved, including Polycomb group proteins, which act as repressors of key developmental genes and coordinate cell differentiation and proliferation. The molecular mechanisms linking Polycomb-mediated silencing to transgenerational epigenetic inheritance are far from being understood. Therefore, we developed an experimental system in *Drosophila melanogaster* to induce stable transgenerational epigenetic inheritance, in which alternative gene expression states can be inherited in the presence of the same genetic sequence. Starting from these highly stable epialleles, we could dissect the genetic properties of the induced epialleles, such as their quantitative inheritance and their ability to trans-communicate. Moreover, the epialleles displayed synergy in their expression and transmission. The molecular signature of the epialleles is the differential presence of the Polycomb repressive complexes and their related epigenetic marks. This diverse distribution is independent of the transcriptional activity of the downstream genes, at least in an early developmental stage, and could influence the three-dimensional organization of the locus involved. Our results make a case for strong, stable and fully reversible transgenerational epigenetic inheritance in metazoan and provide a model that is amenable for the molecular dissection of this phenomenon.

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Maternal nutrition and the transgenerational cycle of obesity

Karen LILLYCROP

There is now substantial evidence from both human epidemiological studies and animal models that an adverse intrauterine environment induced by a variety of environmental and maternal factors such as diet, body composition or endocrine factors can induce a phenotype in the offspring that is characterized by an increased risk of developing chronic non-communicable diseases in later life. The mechanism by which cues about nutrient availability in the prénatal environment are transmitted to the fetus and the process by which different, stable phenotypes are induced, are beginning to be understood and involve the epigenetic regulation of specific genes. Epigenetic processes induce heritable change in gene expression without altering gene sequence. The major epigenetic mechanisms include DNA methylation, histone modification and non coding RNAs. The epigenetic changes induced in response to nutritional cues from the mother may allow the fetus to adjust its developmental programme in order to be better adapted to the future environment, while inappropriate adaptations may predispose an individual to increased risk of a range of non-communicable diseases. Some studies have also suggested that environmental challenges in early life can induce an altered phenotype which can be transmitted between generations.

This talk will describe how transient and sustained nutritional challenges can induce progressive transgenerational changes in the epigenome and phenotype following nutritional transition. Further understanding of how the environment shapes the epigenome over generations will provide valuable insights into the mechanism of adaptation and the ability of mammals to deal with changes environmental conditions.

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Diet-induced metabolic syndrome, heredity of telomere length : mouse models of RNA-mediated paternal heredity

François CUZIN

We reported over the recent years several instances of non-Mendelian heredity in the mouse (paramutations). Transcriptional upregulation of major control loci resulted either in fur color variation (Kit gene), heart hypertrophy (Cdk9 gene), or in increased body size and cognitive ability (Sox9). Experiments involving microinjection of purified RNAs in fertilized eggs had led us to the conclusion that sperm RNA was the transgenerational vector of these epigenetic states. We further observed a requirement for cytosine methylation by the Dnmt2 methyltransferase at defined sites in the inducer and target RNAs [1-4]. Further examples of sperm RNA-mediated inheritance were recently reported by others, namely a distinct instance of the Kit paramutation [5] and heritable neuropathological conditions [6, 7, Isabelle Mansuy, this Colloquium].

Transgenerational determination by sperm RNA provides theoretical grounds for several unexplained but well documented instances of non Mendelian paternal heredity and suggests experimental approaches. We will report mouse models of paternal RNA-mediated determination pertinent to two pathologies, hereditary transmission of the diet-induced metabolic syndrome (obesity, type 2 diabetes) [8, K. Lillycrop, this Colloquium] and the paternal control of the length of telomeres and of the telomere diseases [9].

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Non-genetic inheritance of the impact of traumatic stress across generations in mice

Isabelle MANSUY

Behavior in mammals is strongly influenced by environmental factors, particularly when experienced during early postnatal life. While positive factors can favor proper behavioral responses, negative factors such as traumatic events can alter behavior and induce diseases like borderline personality disorder, bipolar depression and antisocial behaviors. Such disorders are usually marked in the individuals directly exposed but can affect their offspring sometimes across several generations. The biological mechanisms responsible for the transmission of trauma-induced symptoms from parent to offspring are thought to involve non-genetic mechanisms. This talk will present an experimental model of early traumatic stress in mice and show evidence for the implication of non-genetic mechanisms in the expression and inheritance of the impact of such trauma. This mouse model exhibits altered social behaviors, depressive-like symptoms, cognitive deficits, and impaired glucose regulation in adulthood. The symptoms are pronounced and persist throughout life, but are also transmitted to the following offspring across several generations, through both females and males. They are associated with epigenetic alterations involving persistent changes in DNA methylation at the promoter-associated CpG island of several genes, in the brain of the offspring and the germline of their father. Further to DNA methylation, other non-genetic mechanisms involving regulation by non-coding RNAs and histone posttranslational modifications are also involved. These findings suggest that non-genetic processes largely contribute to the impact of negative environmental factors in early life on adult behavior, and its inheritance.

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The role of epigenetic mechanisms in the transgenerational transmission of acquired traits

Eva JABLONKA

Just like the notion of “innate traits”, the notion of “acquired traits” is full of conceptual ambiguities. Moreover, there is no consensus about what epigenetics means, so it is not surprising that role of epigenetic inheritance in the transgenerational transmission of acquired traits is the subject of endless debates. I first discuss the term “acquired trait” and show in what sense it is used in modern research today, typically with relation to phenotypic plasticity. I then discuss the notion of epigenetics, with a focus on epigenetic mechanisms, drawing on recent studies of transgenerational inheritance. I argue that when “acquired trait” and “epigenetics” are clearly defined, epigenetic mechanisms can be said to underlie most cases of the transgenerational inheritance of acquired traits, albeit in different ways and through different routes. Finally, I suggest that the conceptual clarifications of these loosely used terms can contribute to the articulation of research questions in epigenetics.

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