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The promises of neurodegenerative disease modeling

Les promesses de la modélisation des maladies neurodégénératives

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ABSTRACT

The rise in the prevalence of neurodegenerative diseases parallels the rapid increase in human lifespan. Despite intensive research, the molecular and cellular mechanisms underlying the onset and progression of these devastating diseases with age are still poorly understood. Many aspects of these diseases have been modelled successfully in experimental animals such as the mouse, the zebrafish *Brachydanio rero*, the nematode worm *Caenorhaditis elegans* and the fruit fly *Drosophila melanogaster*. This review will focus on the advantages offered by the genetic tools available in *Drosophila* for combining powerful strategies in order to tackle the causative factors of these complex pathologies and help to elaborate efficient drugs to treat them.

RÉSUMÉ

La prévalence des maladies neurodégénératives augmente avec l'accroissement rapide de la longévité humaine. En dépit d'efforts de recherche intensifs, les mécanismes moléculaires et cellulaires sous-jacents à l'apparition et à la progression avec l'âge de ces maladies dévastatrices demeurent mal compris. De nombreux aspects de ces maladies ont été reproduits avec succès chez des organismes modèles comme la souris, le poisson zèbre *Brachydanio rero*, le ver nematode *Caenorhaditis elegans* et la mouche *Drosophila melanogaster*. Cette revue est centrée sur les avantages offerts par les outils génétiques disponibles chez la drosophile pour appliquer une combinaison de stratégies puissantes à l'étude de facteurs responsables de ces maladies complexes et contribuer à l'élaboration de médicaments efficaces pour les soigner.

1. Introduction

The worldwide and continuous extension of human lifespan has met with a concomitant increase in the incidences of age-related diseases such as Alzheimer's disease (AD) or Parkinson's disease (PD). This rise in neurodegenerative diseases makes modern societies face a huge challenge in terms of social and medical management of this situation. Although early diagnostic of these diseases has greatly improved in recent years with advances in medical imaging [1] and the availability of biomarkers [2], our ability to prevent, treat or simply slowdown the degenerative processes remains an elusive goal. Intensive research is currently devoted to the deciphering of the cellular and molecular mechanisms

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underlying neurodegeneration. A more integrated picture has emerged with the recognition of similar and common features between the different neurodegenerative diseases such as the prevalence of protein misfolding and aggregates formation or neuronal death for example. But further advances are crucially needed for a true understanding of the causative factors and the development of efficient treatments.

As an important part of this research, remarkable advances in molecular genetics over the last three decades have allowed many aspects of these diseases to be modelled in animals in order to carry out investigations, which cannot be performed on human beings. A variety of these animal models have been devised with the prominent use of transgenic mice [3], but their repertoire has been largely extended recently to simpler organisms such as the zebrafish *Brachydanio rero*, the nematode worm *Caenorhaditis elegans* and the fruit fly *Drosophila melanogaster*.

This short review, which is not intended to be comprehensive, will be focused on two aspects of this extension. Firstly, I will discuss briefly the key steps in the development of molecular genetics approaches that allowed these new animal models to be devised and studied. I will then examine what has been achieved in this context using *D. melanogaster* as a model system and the further contributions of this particular organism to the study of human degenerative diseases with the development of new strategies and drugs to tackle these complex pathologies.

A brief overview only of the major results obtained in recent years with these models will be given here and the reader is referred to excellent recent reviews for more detailed accounts on the progress made in modelling specific diseases [4–18].

2. Molecular genetics and the diversification of animal model organisms

The rapid development of molecular biology from the early 1960s led to the emergence of molecular genetics as a new discipline based on a wide range of genetic and molecular tools, which deeply transformed the methodological approaches used in all fields of biological research. In this context, three major technological breakthroughs were instrumental for a great diversification of experimental model organisms.

The first has been the advent of recombinant DNA cloning which made possible to splice DNA fragments of any origin together with a plasmid or viral vector suitable for introduction and amplification in a recipient bacterial host. This gave for the first time an access to the biochemical isolation of genes, their in vitro manipulation or modification and eventually the determination of their complete nucleotide sequence using the DNA sequencing methods, which became soon available. One direct consequence has been a rapid increase in the knowledge of the organization of the genes and the deciphering of the general regulatory mechanisms of their expression with the identification of promoters and tissue-specific enhancer elements. This opened the possibility to devise modular constructs for controlling the expression of cloned genes to be reintroduced in eukaryotic cells.

DNA cloning and engineering technologies paved the way to the development of genetic transformation or transgenesis for the permanent integration of exogenous genetic material into the genome of the germ line of a recipient host and the transmission to its offspring [10,19]. It became thus possible to transfer into the genome of a model organism one of its cloned and engineered genes or a cloned gene from a different organism. This additive transgenic approach was first applied to the mouse in the early 1980s and shortly after to *Drosophila* [19]. It has remained however limited until recently to a few number of model organisms where its efficiency was high enough for making it practical for the introduction of recombinant constructs with stable germ line transmission.

The development of a site-directed gene editing by homologous recombination in mouse embryonic stem cells gave a very strong impetus to the development of a novel transgenesis approach in the mouse model as it opened the possibility to either inactivate or "knock out" a target gene of interest or replace its coding sequence by "knocking in" a modified copy or the coding sequence of an unrelated gene [20]. This knock out knock in technology, together with additive transgenesis, was used extensively to generate numerous mouse models and a few rat models of Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis and Huntington's disease which have already provided major insights into the cellular and molecular basis of the degeneration processes (for extensive reviews, see references [3] and [10]).

A third major advance has resulted from the very fast progress in DNA sequencing technologies and bioinformatics which led to the development of the new field of genomics and has given access without any limitation to whole genome sequences of all living organisms. This has been of a great importance regarding animal modelling of human diseases. First, the determination of the sequence of the human genome has allowed the development of genome-wide association studies (GWAS) for uncovering in human populations genetic variations associated with complex diseases thus leading to the identification of novel candidate genes to be examined for their role in the onset and progression of a particular condition [21]. Whole genome sequencing has also revealed the profound degree of evolutionary conservation of the genes throughout all extant organisms of the three domains of the living world, Bacteria, Archea and Eucarya, linked by descent from a common ancestor. Importantly, not only the structure of the encoded proteins is conserved but also in many cases their biochemical function and their interaction with other proteins in molecular complexes or functional pathways recruited in diverse settings during development and differentiation. The most striking example of this evolutionary conservation is that of the Hox genes which play a crucial role in the laying down of the body plan of animal organisms and were first characterized in *Drosophila* through the identification of the Homeobox, a highly conserved amino acid sequence motif shared by this class of genes [22]. Finally, an important outcome of whole genome sequencing has been to open the possibility to devise short DNA probes to measure accurately and simultaneously the level of expression of all the genes of