How to create animal models using genetic knowledge?

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Animal models have been used to address a wide variety of scientific fields, from basic research to drug development and evaluation. The use of animals relies not only on the many biological similarities observed in most mammals, but also on the fact that human diseases often affect other animal species. This is particularly the case for most infectious diseases but also for very common diseases such as type I diabetes (1), hypertension, allergies, cancer, epilepsy, myopathies (2) and many others. Not only are these diseases shared, but the mechanisms are also so close that 90% of the veterinary drugs used to treat animals are identical or very similar to those used to treat humans. Many major advances in basic or medical research have been possible thanks to observations and tests on animals. In all cases, the animal model is essential to understand certain elements of a disease, to test innovative therapies, or even to reinvest traditional treatments to know the new possibilities and limits. Far from being the Alpha and Omega of biological research, the animal is nevertheless a central link, essential in the medical procedure which consists, for any new treatment, to evaluate the benefit/risk ratio for the patient.

NATURAL MODELS

It has long been believed that there are natural patterns of human neurodegenerative diseases. Numerous neurological phenotypes, such as those observed in the mouse lines Reeler, Weaver and Staggerer, presenting disorders of balance and gait, have indeed been identified and then selected in farm animals. The lesions, related to a loss of function of the mutated protein, mainly concern the development of the cerebellum. Contrary to what one might have thought, these three lineages are not models of human ataxia. The mutation of the Reln gene (3) causes an abnormality of neuronal migration responsible for cerebellar lesions in the Reeler mice but, in humans, lissencephaly (4). Reelin - the product of the Reln gene - has also been implicated in cases of schizophrenia (5). In the Weaver mouse, cerebellar grain cells and dopaminergic neurons of substantia nigra are selectively affected (6,7). The nonsense mutation concerns the gene Girk2, but the search for a mutation in the homologous human gene has hitherto proved to be negative. In Staggerer mice, atrophy of the cerebellum is due to loss of Purkinje cells and cells of the seed layer. The staggerer gene encodes the transcription factor RORα, a nuclear receptor (8) whose mutation has never been identified in humans. In conclusion, the phenotypes of the natural models evoked those of the human affections, and this similarity suggested that the selected lines could be useful for the research of physiopathological mechanisms (9). These were mostly false leads, and most predictions proved to be erroneous, demonstrating, once again, that phenotypic analogy does not mean mechanistic kinship.

STRATEGIES FOR DEVELOPING ANIMAL MODELS

The introduction of a mutated human gene or its inactivation in a laboratory animal is a more direct approach than the identification of natural phenotypes. The mouse is the animal of choice. It is easier to handle and maintain than the rat, let alone the primate, and the murine and human genomes are relatively close in structure. Additional transgenesis, the first method developed, is rarely ideal: blind insertion of multiple copies of the gene; sometimes massive overexpression of the protein that it codes; possible and unforeseen modification of embryonic development; sometimes abnormal expression topography, conditioned by the promoter associated with the transgene or by a natural promoter depending on the insertion site; variable effects according to the genetic background; persistence of wild gene expression. The alterations observed in the transgenic animal therefore often lead to choosing between two alternative interpretations: a real pathophysiological mechanism or translation of an artificial pathway of degradation in relation to an overproduction or an ectopic production of the protein in question? Homologous recombination (knock-in, KI), which invalidates the wild-type gene and places the transgene under the control of the natural promoter, or conditional expression to control the timing of transgene expression, alleviates some of the disadvantages mentioned above. Transgenic models, even evolved, do not reproduce all aspects of the human disease that usually involves a network of proteins interacting partners: the probability that all the protein partners of a species (the mouse) have the same reciprocal affinities that human molecules is indeed very weak. The chance to mimic an effect diminishes with the number of interactions that separates it from the mutated protein. Finally, the expression topography of the protein is often different in animals and humans, and depends on the promoter of the transgene.

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