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Ageing and Neurodegenerative Diseases

Editorial

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Animal models for research on neurodegenerative diseases

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Animal models play a crucial role in investigating neurodegenerative diseases and developing effective treatments. Genetically modified rodents have been extensively utilized to model neurodegenerative diseases, providing valuable insights into disease pathogenesis. More recently, the advent of the gene-editing tool CRISPR-Cas9 has enabled the creation of large animal models (such as rabbits, pigs, and monkeys) that can replicate important pathological features observed in human brains. This Special Issue aims to explore the strengths and limitations of animal models from various species and provide an overview of their utility in advancing our understanding of neurodegenerative disease pathogenesis and the development of effective therapies.

In a Special Issue on the topic of "Animal Models of Different Species for Investigating Neurodegenerative Diseases", four articles were included that described animal models, different from the commonly used mouse models, for studying neurodegenerative diseases (NDs). These articles focused on genetically modified large animals and emphasized their value in modeling NDs.

Novati *et al.* discussed the use of rat models in investigating Alzheimer's, Parkinson's, and Huntington's diseases[1]. Genetically modified rat models have been employed for studying human diseases over the past 20 years and have proven to be valuable tools for investigating NDs. Rats offer several advantages over mice, such as genetic similarities to humans and larger body size, which allow for a more precise evaluation of therapeutic effects. Numerous behavioral tests and electrophysiological assays have been developed for rats, enabling a more robust assessment of behavioral and cellular phenotypes in these models. Additionally, rats exhibit a more complex behavioral repertoire than mice, allowing for a more sophisticated extrapolation to the human condition. While rats are less commonly used in biomedical studies compared to mice, they fill a gap when genetic mouse models fail to replicate certain aspects of diseases and can provide additional insights into disease mechanisms. However, similar to mouse models, rats also face challenges in recapitulating the overt and selective neurodegeneration observed in patient brains with NDs.

Zhang *et al.* introduced rabbit models, with a focus on genetically modified rabbits, for investigating human diseases[2]. Rabbits are docile and easy to handle, and their short reproductive cycle and high reproductive performance ensure a sufficient sample size for experiments. Additionally, the efficiency of model production and the low demand for rearing and surgical operation equipment make rabbits easy to maintain and handle. Moreover, rabbits have an intermediate lifespan, longer than rodents but shorter than large animals such as non-human primates. Compared with rodents, rabbits are phylogenetically closer to humans and exhibit greater similarity in brain development, suggesting that they may provide better precision in disease modeling. With the development of targeted genome editing tools, it has become feasible to produce targeted genome-edited rabbit models for human neuronal disorders. To date, more than 50 genome-edited rabbits have been constructed. However, there are very few rabbit models established for modeling NDs, and the evaluation criteria for rabbit neurodegenerative disease models are not well established. Despite these limitations, rabbits could serve as an alternative animal model to investigate whether they can accurately replicate important neurodegenerative features.

Li *et al.* described the use of pig models for investigating neurodegenerative diseases[3]. Pigs possess a brain structure and function that is very similar to humans, making them an excellent choice for studying important brain diseases. Unlike small animals, pigs have sulci and gyri, and their brain volume is comparable to that of humans. These characteristics offer distinct advantages in studying NDs. Additionally, pigs have a short reproductive cycle (5 months-6 months of sexual maturity) and can produce multiple litters (an average of 7 piglets-8 piglets), making them more advantageous than non-human primates. Moreover, pigs can be ethically used for translational research.

The relatively fast breeding and reproduction of pigs allow for a sufficient number of animals to evaluate the therapeutic effects of drugs and other interventions. Another advantage of using pigs is the availability of somatic nuclear transfer technology, which enables genetic modification of endogenous pig genes to create knock-in or knock-out pig models. An excellent example is the establishment of a Huntington disease (HD) knock-in pig model using a combination of CRISPR/Cas9 and somatic nuclear transfer. This pig model exhibits behavioral phenotypes and selective neurodegeneration similar to HD patients, providing the first evidence that disease genes expressed at the endogenous level can lead to neurodegeneration in large animals (Yan *et al.*, 2018)[4]. Therefore, genetically modified pig models will play an increasingly important role in the study of age-dependent neurological diseases in the future.

Non-human primates are closer to humans in terms of genomic regulation, aging process, metabolism, and physiology than other species. Monkeys provide a more accurate genomic context for investigating molecular pathogenesis. For instance, genome-wide association studies have identified the APOE ε4 allele as

the first genetic risk factor for Alzheimer's disease (AD), which is present in primates but absent in rodents. Non-human primate models are particularly valuable for studying behavioral abnormalities that are also observed in NDs. Li *et al.* provided an overview of several non-human primate models used in ND research[5]. Among the recently established models, the monkey model with mutations in the *PINK1* gene, which cause early-onset Parkinson's disease (PD), offers unique insights into disease pathogenesis. Knocking out the PINK1 gene in rodents and pigs failed to reproduce the severe phenotypes and neurodegeneration observed in patients with PINK1 mutations. However, CRISPR-mediated PINK1 gene mutations in monkeys result in severe neurodegeneration (Yang *et al.*, 2019)[6]. Further investigations of the PINK1 mutant monkey model suggest that the loss of PINK1 causes neurodegeneration through a mitochondria-independent mechanism (Yang *et al.*, 2022)[7]. Therefore, non-human primate models can reveal important pathogenetic mechanisms that may not occur in small animals but are unique to primate brains.

Although large animals possess many advantages for investigating NDs, there are challenges in widely utilizing them in research. Scaling up studies on large animals is difficult due to the high cost of maintaining them and the long reproduction and breeding periods. Despite recent advances in genetic editing tools, establishing knock-in monkey models remains challenging. Additionally, behavioral and functional assessments for large animal models are not as well-established as those for rodents. In the future, mouse models will continue to be valuable and widely used in biomedical research. However, it is important to consider large animal models as important alternatives to bridge the gap between small animals and humans. They can help discover pathogenic events and mechanisms that may be specific to primates, and more importantly, validate crucial therapeutic targets and effects.

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