Biomere

COMMUNITY BLOG

NHP MODELS FOR NEURODEGENERATIVE DISEASES

Neurodegenerative diseases encompass several disorders that are typically associated with the death of specific neuron types resulting in loss of motor, cognitive and other abilities, and most of these diseases are ultimately fatal. It is estimated that there are more than 600 neurodegenerative disorders that impact 50 million Americans each year[1]. Despite the growing unmet clinical needs, there has been limited progress in developing new therapies for neurodegenerative diseases. Drug discovery and development rely heavily on preclinical *in vitro* and *in vivo* models to study disease biology, identify new drug targets and test therapies. While different models have distinct advantages and drawbacks, the selection of a given model should be carefully done to answer specific biological questions. For example, cell-based models derived from primary disease state neurons or induced pluripotent stem cells (iPSC) lines are widely used to study disease pathology and identify mechanism of action for new drug targets[2]. Additionally, cell-based models are well suited to screen small molecules or biomolecules to identify candidate therapies to test in animal models. Traditionally, cell-based models consisted of simple 2D cell cultures but increasingly there is a shift towards using more complex 3D cell models that are cultured on a scaffold to mimic the tissue environment[2]. While the *in vitro* models are useful in the early stages of drug discovery, the gold standard to evaluate therapeutic efficacy and safety are animal models.

Several rodent models of neurodegenerative disease are used in preclinical discovery programs for new therapies. These models include transgenic models where specific disease-causing mutations are introduced or chemically induced models to induce neurological damage[3]. Despite the large number of publications and funding, mouse models of neurodegenerative disease have been shown to have limited translation to human patients as therapies that were shown to be efficacious in mouse models had very limited effect in humans[3]. One of the key reasons for this is that the rodent CNS is very different from the human CNS in terms of anatomy, physiology and neuronal complexity[3]. Additionally, rodents have a short lifespan so it is difficult to model age-related neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. Nonhuman primates (NHPs) are better suited to model neurodegenerative diseases as the NHP CNS is well suited to evaluate changes in cognition, brain function and motor skills that are hallmarks of neurodegenerative diseases. Aged NHPs have been reported to develop age-related issues such as neuron loss, plaque formation and cognitive deficits similar to humans[4]. However, it is expensive and complicated to maintain an NHP colony for long time periods to study the natural development of neurodegenerative diseases. Therefore, the development of induced disease models is of interest. For example, the injection of beta-amyloid containing brain tissues into NHP brains were shown to induce plaque formation, neuroinflammation and other neuronal issues[4] associated with Alzheimer's disease. However, NHP models of Alzheimer's disease have not been widely adopted likely due to ethical and cost issues. Animal models of Parkinson's disease can be induced by the injection of specific chemicals such as MPTP or 6-hydroxydopamine. These compounds can be injected directly into the brain or systemically into the vasculature, skin or muscle. NHP models injected with MPTP recapitulated the motor skill deficits associated with Parkinson's disease[4]. More recently, intracerebral injections of gene therapy vectors encoding mutant alpha-synuclein or Lewy body extracts in rhesus macaques and cynomolgus NHPs induced neuronal cell loss and increased expression of alpha-synuclein but these physiologic changes did not translate to motor skill changes[4].

While Alzheimer's disease and Parkinson's disease are challenging to model since the exact genetic drivers of disease development are not fully known. In contrast, the disease driver for Huntington's disease has been identified as an expansion in the number of CAG repeats in the *huntingtin* gene. Researchers have introduced the mutant huntingtin gene using lentiviral vectors into specific brain regions of cynomolgus macaques and demonstrated the development of Huntington's disease symptoms[4]. An attempt to develop a transgenic NHP model was reported but the animals with the mutant *huntingtin* gene had very short lifespans[4]. To overcome this disease-related challenge, researchers have developed iPS cell lines from transgenic NHP models of Huntington's disease to study disease biology and reported the development of an NHP iPSC-derived astrocyte model for Huntington's disease[5].

In summary, while NHP models are highly translational and recapitulate several hallmarks of neurodegenerative diseases, the complexity of developing and maintaining these models pose significant challenge

References:

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