Primate Model to Study Disease Mechanism and Cell-gene Therapy

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Primate animal is an ideal model for human disease mechanism study because of their genetic background and physical characteristics that are very similar to humans, and also is one of the most appropriate animals for safety evaluation and efficacy of cell and gene therapy.

Parkinson's disease (PD) is one of complex disease and no effective treatments yet. We generate genetically engineered mesenchymal stem cells encoding three critical genes for dopamine synthesis (DOPA- MSCs). DOPA-MSCs retain their MSC identity and stable ability to secrete dopamine during passaging. Following transplantation, DOPA-MSCs reinstate striatal dopamine levels and correct motor function in PD rats and monkeys. Importantly, after grafting into the caudate and putamen, DOPA-MSCs provide homotopic reconstruction of midbrain dopamine pathways by restoring striatal dopamine levels, and safely and long-term (up to 51 months) correct motor disorders and nonmotor deficits in acute and chronic PD rhesus monkey models of PD even with advanced PD symptoms. The results support the idea that the development of dopamine-synthesized engineered cell transplantation is an important strategy for treating PD.

Duhenne muscular dystrophy (DMD) is an X-linked lethal muscle-wasting disease caused by mutations in the DMD gene, resulting in abnormal function of dystrophy protein. Currently, there is no effective treatment available. The lack of ideal animal models and a thorough understanding of the molecular and cellular mechanisms during disease progression have hindered drug development. We generate rhesus monkey model of DMD using CRISPR/cas9. The monkey model reveals that in the early stages of DMD, muscle degeneration primarily manifests in changes within the microenvironment and cellular composition of muscle tissues, particularly involving mononuclear cells within muscle, such as immune cells, fibro-/adipogenic progenitors, and muscle stem cells. The dynamic changes in these cell fates and their functional abnormalities significantly impact early disease progression. This study

provides a crucial insight into the molecular and cellular mechanisms underlying early DMD pathogenesis and offers an important foundation for developing new therapeutic strategies.

RTT syndrome is a neurodegenerative disorder caused by MECP2 gene mutation. Our previous work demonstrated that MECP2 mutations cause damage to multiple brain regions in the monkeys. However, the earliest occurrence of this damage is hard to notice in time and location due to technical limitations. Using our recent established ex utero monkey embryo culture system, we found that MECP2 mutations caused epiblast development abnormality in gastrulation, which triggered a series of embryo and brain pathosis changes. These unpublished data suggest that the ex utero culture system could help to understand the mechanisms of complex diseases in early stage.