Researchers develop new muscular dystrophy treatment approach using human stem cells

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Researchers from the University of Minnesota's Lillehei Heart Institute have effectively treated muscular dystrophy in mice using human stem cells derived from a new process that – for the first time – makes the production of human muscle cells from stem cells efficient and effective.

The research, published today in *Cell Stem Cell*, outlines the strategy for the development of a rapidly dividing population of skeletal myogenic progenitor cells (muscle-forming cells) derived from induced pluripotent (iPS) cells. iPS cells have all of the potential of embryonic stem (ES) cells, but are derived by reprogramming skin cells. They can be patient-specific, which renders them unlikely to be rejected, and do not involve the destruction of embryos.

This is the first time that human stem cells have been shown to be effective in the treatment of muscular dystrophy.

According to U of M researchers – who were also the first to use ES cells from mice to treat muscular dystrophy – there has been a significant lag in translating studies using mouse stem cells into therapeutically relevant studies involving human stem cells. This lag has dramatically limited the development of cell therapies or clinical trials for human patients.

The latest research from the U of M provides the proof-of-principle for treating muscular dystrophy with human iPS cells, setting the stage for

future human clinical trials.

"One of the biggest barriers to the development of cell-based therapies for neuromuscular disorders like muscular dystrophy has been obtaining sufficient muscle progenitor cells to produce a therapeutically effective response," said principal investigator Rita Perlingeiro, Ph.D., associate professor of medicine in the Medical School's Division of Cardiology. "Up until now, deriving engraftable skeletal muscle stem cells from human pluripotent stem cells hasn't been possible. Our results demonstrate that it is indeed possible and sets the stage for the development of a clinically meaningful treatment approach."

Upon transplantation into mice suffering from muscular dystrophy, human skeletal myogenic progenitor cells provided both extensive and long-term muscle regeneration which resulted in improved muscle function.

To achieve their results, U of M researchers genetically modified two well-characterized human iPS cell lines and an existing human ES cell line with the PAX7 gene. This allowed them to regulate levels of the Pax7 protein, which is essential for the regeneration of skeletal muscle tissue after damage. The researchers found this regulation could prompt naïve ES and iPS cells to differentiate into muscle-forming cells.

Up until this point, researchers had struggled to make muscle efficiently from ES and iPS cells. PAX7 – induced at exactly the right time – helped determine the fate of human ES and iPS cells, pushing them into becoming human muscle progenitor cells.

Once Dr. Perlingeiro's team was able to pinpoint the optimal timing of differentiation, the cells were well suited to the regrowth needed to treat conditions such as muscular dystrophy. In fact, Pax7-induced muscle progenitors were far more effective than human myoblasts at improving

muscle function. Myoblasts, which are cell cultures derived from adult muscle biopsies, had previously been tested in clinical trials for muscular dystrophy, however the myoblasts did not persist after transplantation.

"Seeing long-term maintenance of these cells without major adverse side effects is exciting," said Perlingeiro. "Our research proves that these differentiated stem cells have real staying power in the fight against muscular dystrophy."

According to John Wagner, M.D., scientific director of clinical research at the University's Stem Cell Institute and renowned blood and marrow transplant expert, "This research is a phenomenal breakthrough. Dr. Perlingeiro and her collaborators have overcome one of the most significant obstacles to moving stem cell therapies into the treatment of children with devastating and life threatening muscular dystrophies."

The U of M researchers say alternative methods of Pax7 induction will need to be investigated before this study can be turned into a human clinical trial. Their method of delivering the Pax7 protein involved genetic modification of cells with viruses and because viruses sometimes cause mutations, they add risk to a clinical trial. But the U of M researchers are committed to developing a safe and effective clinical protocol, and are actively testing alternate methods of delivering Pax7.

Provided by University of Minnesota