Can a Cell Transplant Treat Duchenne's Muscular Dystrophy?

By Heather Farjado

What if I told you that a cell transplant could treat a genetic disorder? That's what's on the docket for a common genetic condition that causes muscle degeneration. That's right, I'm talking about a potential breakthrough treatment for Duchenne's muscular dystrophy (DMD)! DMD is characterized by progressive muscle loss caused by a mutated muscle protein called dystrophin. Normally, dystrophin helps protect the muscle cell during contraction. When dystrophin is mutated in a way that prevents it from functioning, muscles are more prone to damage, and eventually get replaced by tough, fibrous tissue or fat.

DMD is a hereditary disorder that causes muscle weakness and degeneration, leading to wheelchair-dependence by age 15 and an average life expectancy of 26. The disease is "sex-linked," so it is only present when all X-chromosomes in the patient carry the DMD mutation – since females have two X-chromosomes and males have one, it's much more likely for males to be affected by DMD. In fact, this severe disease is more common than you think; it affects 1 in 3,500 males[1]. Currently, there's no cure for DMD, so it's important to find effective treatments.

A hallmark of DMD is the loss of muscle over time. To treat DMD, scientists would ideally like to make new muscle to replace the muscle that is lost. But how do we make muscles, anyway? Normally, during embryonic development, muscles are made in a process called "myogenesis" ("myo" is Greek for "muscle"). During myogenesis muscle stem cells make intermediates called muscle progenitor cells, which eventually produce mature muscle cells. But this process doesn't just happen when we are in utero. As adults, we also have muscle stem cells, called satellite cells, that help us maintain our muscle. We make new muscles all the time when we damage our muscle fibers through exercise. For DMD patients, muscle cells are damaged more easily, which puts their satellite cells in overdrive to keep up with the rapid loss of muscle cells. Eventually, the population of satellite cells and muscle progenitor cells is diminished, so the body can no longer make new muscle.

So, what about that cell transplant? Scientists are trying to find a way to give DMD patients new muscle progenitor cells that can make functional muscle cells capable of producing the dystrophin protein. This could lead to long-term treatment options, since any damaged muscle that occurs as a result of everyday life could be replaced by the muscle progenitor cells. The cool thing about this type of cell transplant is that we can take our own cells, fix the mutation, and re-implant those cells to treat our own medical conditions. We don't need to take new medications – our own cells are the medicine!

Cell transplants begin with our own cells, which can be taken into a lab and "re-programmed" to become stem cells. This unlocks all kinds of potential because these cells, called induced pluripotent stem cells (iPSCs), can become any kind of cell in our body! By using DMD patients' cells, scientists can create iPSCs that are autologous, or belong to the patient for whom they will

be used. The problem is that DMD patients have a mutation in their DNA that causes their disease. How can we fix it?

CRISPR is a gene editing system that can remove and modify genes, and it's commonly used in stem cell research. If scientists harness the editing power of CRISPR in autologous iPSCs, they can repair the mutation that causes DMD. Repairing the mutation involves both removal of the mutated dystrophin DNA and insertion of new dystrophin DNA in the iPSCs. CRISPR is a powerful tool, and when it is combined with homology-directed repair (HDR), a DNA repair mechanism that enables the highly specific insertion of the new, un-mutated DNA, you get an accurate and efficient gene edit. Through the stepwise removal of the mutation via CRISPR and addition of the gene repair via HDR, CRISPR and HDR are a match made in gene therapy heaven.

In order for a cell transplant to work, the iPSCs with the repaired mutation must be differentiated , or transformed, into muscle progenitor cells. These will serve as a source of new muscle cells in DMD patients. Scientists induce differentiation by causing the iPSCs to over-express certain muscle-specific genes, leading to the iPSCs taking on characteristics of muscle progenitor cells. This is significant because the muscle progenitors without the DMD mutation can produce new, mature muscle cells that can make dystrophin! As a therapy, this cell transplant strategy could allow DMD patients to synthesize new muscle cells that are fully functional, thus treating their disease (Figure 1).

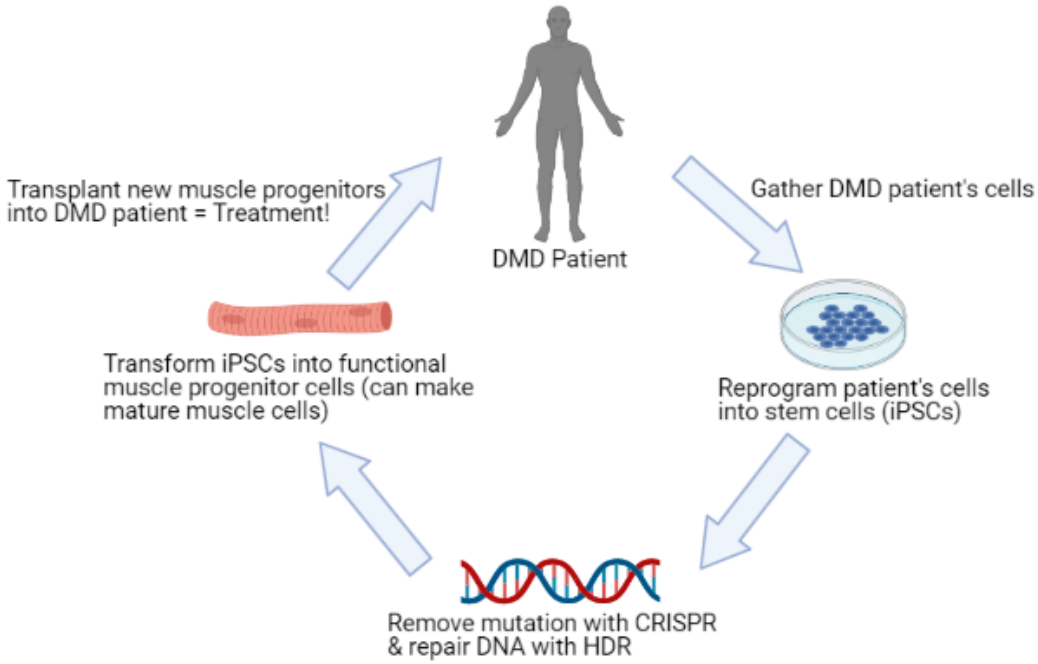

Figure 1. Schematic for DMD cell transplant therapy

As of 2020, scientists have successfully administered this therapy in mice. They made iPSCs from DMD mouse cells, edited and repaired the mutation with CRISPR and HDR, differentiated the iPSCs into muscle progenitors, and transplanted those cells into a DMD mouse muscle, which produced mature muscle cells that expressed dystrophin[2]. This exciting new cell transplant therapy is still a long way from clinical trials, but it shows promise that effective and long-term treatment for DMD lies on the horizon.

References

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2. Jin, Y., Shen, Y., Su, X., Weintraub, N. L., & Tang, Y. (2020). Effective restoration of dystrophin expression in iPSC Mdx-derived muscle progenitor cells using the CRISPR/Cas9 system and homology-directed repair technology. Computational and structural biotechnology journal, 18, 765-773.