Mice may be the key to a cure for Huntington's disease

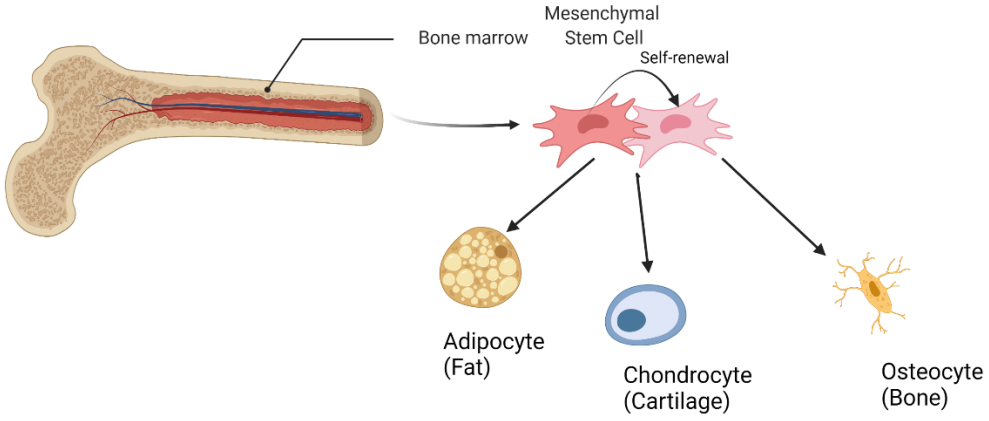
By Tracy Onate

Huntington's disease (HD) is a brain disorder that afflicts approximately 1 in 10,000 individuals in the United States. HD is an autosomal dominant disorder, meaning that it has a fifty percent chance of being passed from parent to child. HD is caused by a defective gene known as the huntingtin gene. This mutated gene produces a version of the huntingin protein that is much larger and stickier than the normal protein, which causes it to build up in the brain cells of people who have HD. As the protein accumulates, the brain atrophies, and the health of the person with HD declines. Symptoms usually appear after the age of thirty and include cognitive decline; psychiatric disorders, such as anxiety and depression; and chorea, a movement disorder characterized by rapid, uncontrollable movements. Unfortunately, there is no cure, and the disease is fatal approximately 10 to 15 years after the onset of symptoms. The current treatments available are palliative and only treat the chorea and psychiatric symptoms. But there is nothing available to slow down or stop the atrophy in the brain [1].

With new developments and discoveries in the making, there may be a cure for HD in the not-so-distant future. A recent breakthrough has involved mesenchymal stem cells (MSCs), which can help repair the brain tissue damaged by HD. MSCs are a cell type

that can be isolated from many sources, such as the umbilical cord, molar tissue, amniotic fluid, fat, skin, and in the case of this study, bone marrow (Figure 1). MSCs have many attractive characteristics, such as the ability to develop into multiple cell types, ease inflammation, and assist in the healing of damaged tissue. MSCs can even be modified to act as delivery vehicles to secrete other beneficial therapeutics. The Institute of Regenerative Cures at the University of Davis created MSCs that were specifically modified to secrete brain-derived neurotrophic factor (BDNF) [2].

Figure 1. MSCs can be derived from bone marrow and differentiated into different cell types Created with BioRender.com



Previous studies showed that loss of BDNF plays a role in HD. BDNF promotes the survival of neurons (nerve cells) by assisting in the growth, maturation, and maintenance of the cells. Research has found that artificially lowering BDNF levels in mice yields similar brain structures as individuals with HD. In addition, postmortem

examinations of human HD brains showed a decrease in BDNF protein levels. These studies beg the question—will increasing the amount of BDNF improve symptoms in those with HD?

This is the question that the Nolta lab at UC Davis tried to answer in 2015. In this study, they used mouse models of HD, including YAC128 mice which have the same mutated gene as human HD patients. They treated these mice with MSCs in conjunction with BDNF to determine if there would be an improvement in disease symptoms. The researchers injected the YAC128 mice with MSCs containing a viral vector that helped facilitate BDNF secretion (Figure 2). A viral vector is a virus lacking infectious properties is engineered to carry different genetic information; in this situation, it the genetic information was BDNF. This is possible because viruses can incorporate outside genetic information within their genomes. The results of this study were impressive; not only did the mice that received the BDNF-secreting MSCs show cognitive improvement, but there was also an overall improvement of the brain structure [3].

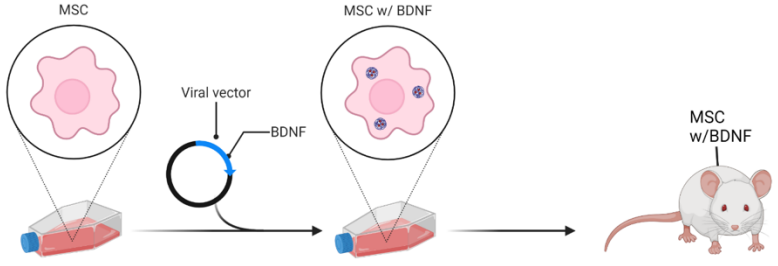


Figure 2. MSCs can be manipulated genetically then reintroduced to an organism

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Despite the exciting results, there were some limitations and challenges with the experiment. The MSCs injected into the mice were derived from humans, meaning the mice's immune systems initiated immune responses to these cells. Thus, the MSCs in the mice only survived for seven days. To extend the MSC retention, immunosuppression drugs were administered, which extended the lifespan of the MSCs to 28 days. However, there are limitations to these drugs—in particular, the drugs cannot render the mice fully immunodeficient, meaning the mice will still deplete the MSCs to some extent. In addition, the immunosuppressants eventually become toxic to the mice.

This year, scientists at the University of Davis addressed the immunosuppression problem by developing the YACNSG mouse line. This mouse line is immunodeficient and also contains the full-length mutated huntingtin gene. The mouse was created by the crossing YAC128 mouse line with a well-known immunodeficient mouse, the NSG line. Preliminary results show that this new mouse line can retain the MSCs for the same amount of time as the YAC128 line + immunosuppressant drugs. These mice also have the same HD-related behavioral characteristic as the YAC128 mouse line. This is exciting because now research can be done without the effects of toxic immunosuppression medications [4], which ultimately means we can continue moving closer to a novel cell-based therapeutic for the treatment of HD.

References

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