Stem cells as a novel therapy for amyotrophic lateral sclerosis

P. J. A. MOORE

School of Medicine, Dentistry and Biomedical Sciences, Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast, Northern Ireland, UK

Amyotrophic lateral sclerosis (ALS) is a devastating, progressive neurodegenerative disease that affects 5000 people in the UK.[1] Motor neurons in the cortex, brainstem and spinal cord are affected, leading to paralysis, dysphagia and eventually death due to respiratory failure within five years of diagnosis.[2] Loss of controlled motor function has obvious effects on the patient's quality of life, and independence decreases until death. To date, the drug riluzole is the only licensed therapy used to treat ALS, which extends patient survival time by two to three months.[2] Promising preclinical research has suggested that stem cells could be used in treating ALS.

A stem cell is a cell that can both reproduce itself and generate offspring of different functional cell types.[3] Since mechanisms for obtaining them in the late 20th century were developed,[4] there has been much excitement over the idea that 'new' cells can be grown to repair diseased and damaged tissue (Fig. 1).[5] Human embryonic stem cells (hESCs) are the most versatile type of stem cell, as they are pluripotent (i.e., can transform into any cell type within the human body, as well as having the ability to replicate, producing more stem cells). Unused *in vitro* fertilisation (IVF) embryos (within 15 days of fertilisation) are used as an initial source of these cells, before tissue culture is employed under special conditions to allow the cells to proliferate while remaining undifferentiated.[4] Differentiation into the desired cell type can then be achieved by changing the chemical composition of the culture, altering the culture dish surface or inserting specific genes into the cell (e.g., via a virus).[4] Although this can be achieved with relative ease, there are many ethical considerations that make use of hESCs extremely limited within Western Europe and North America.[3]

Correspondence to: Peter Moore
Email: pmoore33@qub.ac.uk

A much less controversial approach is to use adult stem cells, or somatic stem cells, obtained from consenting donors. Some somatic cells can be engineered to behave like an embryonic stem cell; these are called induced pluripotent stem cells (iPSCs). Although iPSCs and ESCs can both be rapidly cultured and remain pluripotent, they are prone to result in teratomas,[6] causing harm to the patient. A safer alternative would be to use tissue-specific stem cells. An example of this would be the transdifferentiation of fibroblasts to motor neurons. This can be done by directly culturing them and introducing a specific set of seven transcription factors via a non-pathogenic virus.[7] These induced motor neurons have not yet shown to have the ability to form connections with skeletal muscle and, while this may seem to be a potential therapy, it has been documented that the surrounding glial cells have an important role in the progression of ALS.[8]

Glial cells can be generated from mesenchymal stem cells (MSCs), which are isolated from connective tissue, bone marrow and adipose tissue. A small-scale study involving nine patients saw the MSCs suspended in autologous cerebrospinal fluid (CSF) before being transplanted onto the surgically exposed spinal cord at multiple thoracic levels. The delivery was made intraspinally as the MSCs are unable to pass the blood-brain barrier to reach the motor neurons. Follow-up four years after the treatment has shown that four of the patients have experienced a transient slowing down in decline of the forced vital capacity,[9] which is a marker showing progression of neurodegenerative illnesses. Although the findings of this study may seem modest, it is important to note that the MSCs used were unmodified and autologous. This means that the procedure is much safer than when using modified stem cells, and eliminates the need for immunosuppression. This phase I study supports the opinion that the use of unmodified MSCs is relatively safe in humans.[10]

Mesenchymal stem cells can also be differentiated into cells that have the ability to produce neurotrophic factors (MSC-NTFs); however, data from the ongoing clinical trials have not yet been published.[2]

Neural stem cell (NSC) therapies have also been investigated in treating ALS. They can be harvested from post-mortem fetal samples before undergoing tissue culture to increase their number.[11] Neural stem cells have the capability of developing into the main cell types of the CNS,

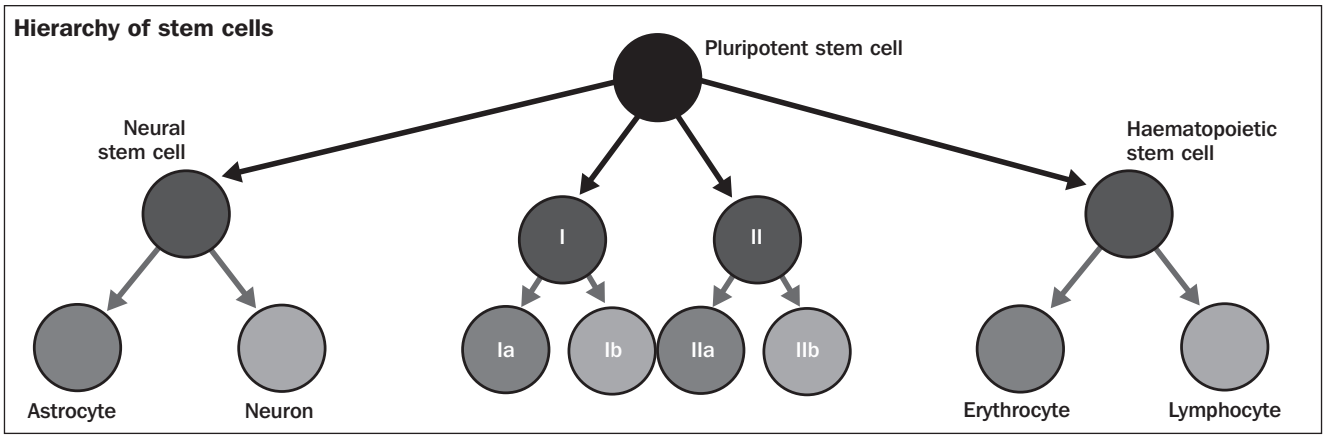

Fig. 1. Diagram showing how tissue-specific stem cells are derived from pluripotent stem cells. I: Skin stem cell; Ia: Hair follicle; Ib: Sweat gland; II: Gut stem cell; IIa: Goblet cell; IIb: Enterendocrine cell (Adapted from BioVision Inc, 2014).

both neurons and glial cells (e.g., oligodendrocytes and astrocytes). One particular cell line, known as NSI-566RSC, has been cultured for use with ALS treatment.[12] These cells have been transplanted into the lumbar spinal cord of ALS-affected mice; encouragingly, this resulted in motor function being retained for longer, and lifespan was extended by up to 12 days, compared to control mice.[13] If NSI-556RSC cells are transplanted into the cervical spinal cord as well as lumbar spine, lifespan is increased to 17 days.[14] It is thought that the reason for this improvement is the increase in neurotrophic factors that occurs post-transplantation.[13] A phase I US Food and Drug Administration (FDA)-approved trial is currently ongoing (ClinicalTrials.gov identifier: NCT01348451) transplanting the NSU-556RSC cell line (sourced from human spinal cord) into the spinal cord of ALS patients; final results are expected in December 2015. Initial findings show that this procedure can be well tolerated and there is even evidence to suggest the progression of ALS is slowing.[15]

In conclusion, stem cells show potential to be used in the treatment of ALS, as shown by the animal and human studies outlined above. Ethical and legislative barriers are arguably more difficult to overcome than the scientific techniques underpinning these therapies; however, this is not unusual in the field of stem cell research. Unfortunately, the data that have been published to date cannot be used to show conclusive evidence that stem cell therapy produces a significant effect in slowing or reversing the effects of ALS. It would now be useful for a large-scale trial to be carried out as current sample sizes are very small. The introduction of blinding the study and using a placebo has been suggested; however, this could result in control patients having high-risk surgical procedures (e.g., the surgical exposure of the spinal cord). Owing to the debilitating nature of ALS, even minor improvements to an individual's situation are desirable and can result in a much improved perceived quality of life. Stem cell therapies may be the best potential method of achieving such a result.

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Investigation into the misidentification of Hazard Group 3 gastrointestinal pathogens and associated health and safety risks

S. CONNELL, M. CHATTAWAY, D. POWELL, C. JENKINS, K. GRANT, E. DE PINNA and G. GODBOLE

Gastrointestinal Bacteria Reference Unit, Public Health England, Colindale, London

The Gastrointestinal Bacteria Reference Unit (GBRU) at Colindale, London, receives isolates from a network of frontline local hospital and Public Health England (PHE) laboratories in England and Wales for confirmation of identification and typing, for purposes of surveillance and outbreak investigation. Many gastrointestinal (GI) pathogens are zoonotic and/or foodborne and investigations at GBRU enable PHE to monitor the safety of food and the environment.[1,2] Certain GI pathogens, notably *Salmonella enterica* subspecies *enterica* serovar Typhi (*S.* Typhi), *Salmonella enterica* subspecies *enterica* serovar Paratyphi (*S.* Paratyphi) and verocytotoxin-producing *Escherichia coli* (VTEC) cause severe disease that can be fatal.[3,4]

In England, the frontline microbiology laboratories isolate GI pathogens from faecal specimens from symptomatic cases using selective media and identify the species by performing biochemical tests and serology.[5] In recent years, automated identification platforms, such as Phoenix, VITEK and matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) have emerged as rapid, cost-effective methods of identifying pathogens in diagnostic microbiology laboratories.[6] Although these platforms reduce the turnaround times for identification of bacterial species, they lack discrimination in some areas.

Correspondence to: Steve Connell

Email: steve.connell@phe.gov.uk