Neurochemistry International 106 (2017) 114–121

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Is there a place for human fetal-derived stem cells for cell replacement therapy in Huntington's disease?

Sophie V. Precious [a, 1], Rike Zietlow [a, 1], Stephen B. Dunnett [a, b], Claire M. Kelly [a, c, 2], Anne E. Rosser [a, b, d, *, 2]

[a] Brain Repair Group, Sir Martin Evans Building, School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF10 3AX, UK
[b] Wales Brain Repair and Intracranial Neurotherapeutics Unit (B.R.A.I.N), School of Medicine, Cardiff University, Cardiff CF14 4XN, UK
[c] School of Health Sciences, Cardiff Metropolitan University, Western Avenue, Cardiff, CF5 2YB, UK
[d] MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Cardiff CF14 4XN, UK

ARTICLE INFO

Article history:
Received 10 January 2017
Accepted 24 January 2017
Available online 27 January 2017

Keywords:
Huntington's disease
Stem cell
Neural transplantation
Cell therapy
Human embryonic germ cells
Fetal-derived neural precursors

ABSTRACT

Huntington's disease (HD) is a neurodegenerative disease that offers an excellent paradigm for cell replacement therapy because of the associated relatively focal cell loss in the striatum. The predominant cells lost in this condition are striatal medium spiny neurons (MSNs). Transplantation of developing MSNs taken from the fetal brain has provided proof of concept that donor MSNs can survive, integrate and bring about a degree of functional recovery in both pre-clinical studies and in a limited number of clinical trials. The scarcity of human fetal tissue, and the logistics of coordinating collection and dissection of tissue with neurosurgical procedures makes the use of fetal tissue for this purpose both complex and limiting. Alternative donor cell sources which are expandable in culture prior to transplantation are currently being sought. Two potential donor cell sources which have received most attention recently are embryonic stem (ES) cells and adult induced pluripotent stem (iPS) cells, both of which can be directed to MSN-like fates, although achieving a genuine MSN fate has proven to be difficult. All potential donor sources have challenges in terms of their clinical application for regenerative medicine, and thus it is important to continue exploring a wide variety of expandable cells. In this review we discuss two less well-reported potential donor cell sources; embryonic germ (EG) cells and fetal neural precursors (FNPs), both are which are fetal-derived and have some properties that could make them useful for regenerative medicine applications.

Contents

Abbreviations: HD, Huntington's disease; hEG, human embryonic germ cells; PGCs, primordial germ cells; FNPs, fetal-derived neural precursors; MSN, medium spiny striatal neurons; WGE, whole ganglionic eminence; ES, embryonic stem cells; iPS, induced pluripotent stem cells.

* Corresponding author. Brain Repair Group, Sir Martin Evans Building, School of Biosciences, Cardiff University, Museum Avenue, Cardiff CF10 3AX, UK.
E-mail address: rosserae@cf.ac.uk (A.E. Rosser).

[1] Joint first authors.
[2] Joint senior authors.

http://dx.doi.org/10.1016/j.neuint.2017.01.016

1. Introduction

Most neurodegenerative conditions are currently untreatable and, for the majority, treatments able to positively influence the underlying pathogenesis are likely to be a long way off (Bartus and Johnson, 2016; Gribkoff and Kaczmarek, 2016; Wild and Tabrizi, 2014). This makes strategies such as cell replacement therapy attractive, because a condition may be a target for cell replacement as long as there is relatively focal (at least in the early stages) loss of defined groups of neurons. There has been interest over the last couple of decades in treating Huntington's disease (HD) with cell replacement therapy. HD is a slowly progressive condition in which there is relentless deterioration of cognitive, motor and psychiatric faculties over a 20–30year period. Currently there is no available disease-modifying treatment, but it represents a good target for cell replacement therapy as it is a well characterised monogenetic condition in which there is relatively focal loss of medium spiny striatal neurons (MSN) (Rosser and Bachoud-Lévi, 2012). Furthermore, it is anticipated that progress made towards achieving functionally effective grafts in HD will be applicable to other neurodegenerative conditions (Dunnett and Rosser, 2014).

One of the key requirements for cell replacement therapy to be functionally effective is that the donor cells have the capacity to be precisely differentiated into the target cell type, i.e., MSNs for HD (Precious and Rosser, 2012). The most convincing evidence so far that cell replacement can be effective in HD comes from both animal and human studies using donor cells derived from the *whole ganglionic eminence* (WGE) in the fetal brain (Pauly et al., 2012; Mazzocchi-Jones et al., 2009; Döbrössy and Dunnett, 2003). The WGE is the area that will eventually become the adult striatum and is where MSNs are born and develop (Deacon et al., 1994; Olsson et al., 1995, 1998; Marin et al., 2000; Evans et al., 2012; Straccia et al., 2016). Thus, MSNs differentiating from WGE have been committed to an MSN lineage during the process of normal development. Such cells are currently regarded as the “gold standard” for cell replacement in HD.

Optimal grafts result when transplants are derived from fetal WGE collected during the peak period of MSN neurogenesis (i.e., approximately embryonic day 14 in rat and 8–10 weeks gestation in human) (Dunnett and Rosser, 2011). Transplantation of developing MSNs into the degenerating striatum has been shown to ameliorate motor and cognitive deficits in animal studies, primarily in rats and primates (Schackel et al., 2013; McLeod et al., 2013; Paganini et al., 2014; Yhnell et al., 2016). Such studies have allowed the mechanisms underlying the functional improvement to be explored, and have shown that implanted cells can integrate into the circuitry and make functional synaptic connections, providing that they are of the appropriate phenotype (i.e., destined to become MSNs) and were procured within the appropriate developmental window (Dunnett and Rosser, 2014). Preliminary evidence of functional efficacy in human transplants comes from a seminal French study that reported human fetal-derived graft survival and significant improvements in both motor and cognitive function in three patients over an approximately six-year period (Bachoud Lévi et al., 2000; 2006). Enhanced FDG-positron emission tomography signal in the frontal cortex of these individuals suggested that the implanted cells had integrated into the striatal neural circuitry and made functional connections with relevant cortical regions (Gallina et al., 2014). The proof-of-concept provided by this study is encouraging and demonstrates that transplantation of “native” developing MSNs into the damaged striatum can produce functional improvements in at least some patients with HD. Nevertheless, there is still a pressing need to undertake further studies of fetal WGE transplantation both to confirm the ability of transplanted WGE cells to improve function and to identify the parameters necessary to increase the reliability of the process and understand which patients are most likely to benefit.

For the longer term, however, it will be necessary to identify expandable sources of donor cells for clinical application, as primary fetal cells present several challenges: they are scarce (an issue compounded by the fact that bilateral transplants in HD require cells from approximately four fetuses, i.e., eight WGEs); they cannot be stored long-term (thus causing logistical problems for coordinating cell collection, surgery and pathological screening of cells); and they are difficult to standardise. Thus, in addition to continuing primary fetal transplants for the reasons outlined above, it is also important to identify cells that can be expanded in number *in vitro* and stored to facilitate GMP (Good Manufacturing Practice) production, whilst maintaining the capability to generate striatal MSNs.

Expandable sources of cells, including human embryonic stem (ES) and human adult-derived induced pluripotent stem (iPS) cells, which can be directed down neural lineages and specified to the required cell type are reviewed extensively elsewhere (Bachoud-Lévi and Perrier, 2014; Choi et al., 2014; Ross and Akimov, 2014; Chen et al., 2014). Here we discuss the potential of two types of expandable cells derived from human fetal tissue; embryonic germ (EG) cells and fetal neural precursor (FNP) cells, as potential donor cells for cell replacement therapy in HD. The reasons for being interested in these cell sources are first, that human fetal tissue will need to be collected for some time to come in order to supply cells for proof-of-concept and optimisation studies as outlined above, and secondly that both cell types have theoretical advantages over hES and hiPS cells for regenerative medicine applications, as discussed further below.

2. Human embryonic germ (hEG) cells

EG cells are derived from primordial germ cells (PGCs) that reside in the gonadal ridge of first trimester embryos. PGCs are induced from pluripotent epiblast cells very early in embryonic development (Ohinata et al., 2005), and continue to express markers of pluripotency such as Oct4, Nanog and SSEA-1 (Pashai et al., 2012). *In vivo*, PGCs are unipotent and destined to give rise exclusively to gametes, however, *in vitro* exposure of mouse PGCs to exogenous fibroblast growth factor (FGF) 2, leukaemia inhibitory factor (LIF) and stem cell factor (SCF) can cause conversion to EG cells, which proliferate rapidly and form colonies similar to those observed when culturing ES cells (Durcova-Hills et al., 2008). EG cells show all the hallmarks of pluripotency, including differentiation into cell types from all three germ layers, as well as formation of teratomas and chimeras (Labosky et al., 1994; Stewart et al., 1994). So far, only a small number of laboratories have reported successful conversion of human PGCs to human EG (hEG) cells using FGF2, LIF and membrane-bound SCF provided through feeder cells (Pan et al., 2005; Turnpenny et al., 2003; Shamblott et al., 1998; Liu et al., 2004). However, most groups report that, unlike their mouse counterparts, hEG cells do not form teratomas and cannot be maintained in culture long-term, due to their high tendency to differentiate rather than preserving pluripotent traits (Turnpenny et al., 2006). Although resistance to pluripotency and indefinite culture presents some challenges, it also presents a theoretical advantage in that neuronal precursors derived from such sources may be less likely to overgrow or form tumours post-transplantation; something that is currently a problem for many hES cell derived donor cells (Master et al., 2007).

To explore the possibility that hEG cells could be used for cell replacement applications, we attempted to generate our own hEG cell cultures. Human fetal tissue was collected through the *South Wales Initiative for Transplantation* (SWIFT) program in accordance