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Review

Recent advancements in stem cell and gene therapies for neurological disorders and intractable epilepsy

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ABSTRACT

The potential applications of stem cell therapies for treating neurological disorders are enormous. Many laboratories are focusing on stem cell treatments for CNS diseases, including spinal cord injury, Amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, multiple sclerosis, stroke, traumatic brain injury, and epilepsy. Among the many stem cell types under testing for neurological treatments, the most common are fetal and adult brain stem cells, embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells. An expanding toolbox of molecular probes is now available to allow analyses of neural stem cell fates prior to and after transplantation. Concomitantly, protocols are being developed to direct the fates of stem cell-derived neural progenitors, and also to screen stem cells for tumorigenicity and aneuploidy. The rapid progress in the field suggests that novel stem cell and gene therapies for neurological disorders are in the pipeline.

1. Introduction

Neural stem cell-based therapies are now being developed to treat a spectrum of neurological conditions once thought to be incurable. Because of their unique potential to repair neural circuits, stem cell and gene therapies are attractive forms of intervention (Kim and de Vellis, 2009). This review discusses some of the well-studied neural stem cell types and treatments for neuronal injury and neurological disorders, with an emphasis on stem cell-based treatments for intractable epilepsy.

Several sources of neural stem cells and neural precursors have been explored for treating neurological disorders including ischemic stroke, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), spinal cord injury, and epilepsy (Aubry et al., 2008; Bacigaluppi et al., 2008; Bjorklund and Lindvall, 2000; Carpentino et al., 2008; Hattiangady et al., 2008; Lindvall, 1994; Maisano et al., 2009; Raedt et al., 2007; Rao et al., 2007; Ruschenschmidt et al., 2005; Turner and Shetty, 2003; Zaman and Shetty, 2001). The first clinical trial of an embryonic stem cell-based therapy was authorized in 2009. Based partly on landmark studies showing functional recovery in rats after spinal cord grafts of oligodendrocyte precursors derived from human embryonic stem cells (hESCs) (Keirstead et al., 2005), the U.S. Food and Drug Administration gave approval to Geron Corporation to begin the first clinical trial of hESC therapy aimed at regenerating myelin in patients with spinal cord lesions (Alper, 2009; Barde, 2009). Subsequently, NeuralStem was approved to test a stem cell therapy in patients with amyotrophic lateral sclerosis. Additional stem cell therapies are focusing on resident adult neural stem cells in the brain, mesenchymal stem cells, and induced pluripotent stem cells.

Efforts to generate specific types of neural precursors benefit from studies of the sequential stages of neural differentiation in the embryonic brain (Scheffler et al., 2006). Researchers have also mapped the stages of differentiation of adult-born neurons that will help to evaluate neural repair therapies based on stem cell-derived neural precursor grafts (Alvarez-Buylla et al., 2002; Doetsch, 2003). Understanding how strokes, spinal cord injuries, and epilepsy create an inhospitable environment for grafts of neural precursors is another enormous challenge. Moreover, cell-based therapies for these disorders must replace multiple types of neurons that degenerate (Buhnemann et al., 2006).

Advances in the stem cell field are rapidly leading to the production of genetic modifications to human stem cell lines that

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allow the transplanted cells to be tracked within the CNS. Routinely, assessment of graft incorporation includes quantitative estimates of graft size and dispersion, *in situ* hybridization, immunohistochemistry, and electron microscopy to evaluate neurotransmitter expression, patch-clamp electrophysiological recordings in brain slices to characterize their functional properties, and intracellular staining to visualize dendritic and axonal morphologies. Experimental models of epilepsy now rely on electroencephalography as the standard method for evaluating whether grafts ameliorate seizures. Together with behavioral analyses, it is now possible to determine whether transplanted neural stem cells successfully survive, integrate, and provide functional recovery in different models of neurological disease. However, therapeutic applications require surmounting a number of additional technical hurdles and safety issues associated with tumor formation and graft rejection (Gruen and Grabel, 2006).

2. Definitions of stem cells and endogenous populations of neural progenitors

Neural stem cells are defined by their potential to self-renew and generate both neurons and glia by asymmetric divisions. When grown individually in adherent cultures, neural stem cells are able to form colonies that contain neurons and glia, or when grown in three-dimensional cell cultures, they form structures called neurospheres. Within the developing brain, neural stem cells are found in the germinal zones, called the ventricular zone. Multipotent stem cells are found within specialized stem cell niches in the adult brain, including the subependymal zones, while other proliferative cells located within the subgranular zone of the dentate gyrus are defined as progenitors, because separate populations give rise to neurons or glial cells and they show only limited self-renewal. Classification systems to further distinguish these brain-specific populations operationally are still evolving (Seaberg and van der Kooy, 2003). Adult stem cells are difficult to find in other tissues of the adult body, but they do exist.

Fetal neural precursor cells (NPCs), adult neural stem cells, and embryonic stem (ES) cells have each been tested in experimental models of neurodegenerative diseases and neurological disorders. Fetal precursors harvested from different regions of the embryonic brain can produce adrenergic, cholinergic, dopaminergic, and GABAergic neurons. Alternatively, a mixture of different cell types can be obtained from the fetal or neonatal hippocampus, striatum or spinal cord for transplantation. A high percentage of fetal NPCs adopt appropriate neurotransmitter phenotypes and become electrophysiologically active after they are transplanted and lead to recovery of function (Bjorklund and Lindvall, 2000). For example, studies in the adult hippocampus after forebrain lesions showed extensive axonal outgrowth, restoration of rhythmic brain activity and improved spatial navigation after transplantation of different types of fetal NPCs (Buzsaki et al., 1987, 1988; Dunnett et al., 1982, 1986; Kimble et al., 1986; Kromer et al., 1983; Low et al., 1982).

The limited supply of human fetal tissue and ethical concerns about deriving neural progenitors from aborted fetuses, have limited the use of fetal neurons in clinical applications. However encouraging results have been obtained with fetal transplants in rodent models of Parkinson's disease, epilepsy, spinal cord injury and ALS. For example, prior studies demonstrated that human neural progenitors from fetal spinal cord form functional connections when transplanted into injured adult rodent spinal cord and improve motor performance (Koliatsos et al., 2008; Xu et al., 2006, 2009).

Mouse or human neural progenitor cells (mNPCs and hNPCs) derived from the fetal brain can be propagated as neurospheres to increase yields of neural precursors. While studies indicate that grafts of NPCs are rarely tumorigenic, a recent study found that *in vitro* propagation of hNPCs may select for cells that show chromosome 7 and 19 aneuploidy (Sareen et al., 2009). Trisomy of these chromosomes enhances the expression of telomerase, and increases proliferation, survival, and neuronal markers, but also leads to premature senescence after 50–60 divisions. These observations underscore the need for cytogenetic screening of hNPCs prior to their use in clinical applications.

3. Other sources of stem cells – embryonic stem cells, induced pluripotent stem cells and bone marrow stromal cells

Embryonic stem cells (ESCs) or induced pluripotent stem cells (IPSCs) are attractive alternatives to fetal hNPCs. ESCs derived from the inner cell mass of the blastocyst can generate all tissue types that comprise the body. Under special *in vitro* conditions, it is possible to direct their differentiation into neuronal and glial progenitors (Maisano et al., 2009). Because they have the potential to divide indefinitely in culture, producing large quantities for research or therapy is considered a major advantage. However, adaptive chromosomal changes occur that give some cells a growth advantage; trisomy of chromosomes 12 and 17 is the most frequent defect in hESCs and routine cytogenetic tests for aneuploidy are recommended (Meisner and Johnson, 2008). In contrast to mouse ESCs (mESCs), hESCs require more specialized cell culture protocols. For clinical applications, hESCs must be grown in animal cell-free and serum-free conditions and derivation of the first hESC line with these properties was a major advance for clinical applications of stem cell therapy (Klimanskaya et al., 2005).

Recently scientists discovered how to generate fibroblast-derived induced pluripotent stem (IPS) cells by expressing four genes in the cells (Takahashi et al., 2007a,b). This discovery is fueling speculation that stem cell therapies of the future may use the patient's own skin to generate neural stem cells for autologous cell therapy. In an IPS cell-based therapy, there is little need for immunosuppression, because IPS cells are obtained from a patient's own skin or other tissues. Also, the need to destroy fertilized eggs to obtain the stem cells is obviated. The IPS cells can be subjected to genetic modifications to correct for genetic mutations, allow fluorescence-activated cell sorting, and track the cells after transplantation. Work on IPS cells is relatively new and fewer studies have examined the ability of IPS cells to generate specific neuronal types for treating neurodegenerative conditions.

4. Identifying regulatory mechanisms for neural stem cell integration into damaged circuits

Some important insights into the critical variables for successful transplants have emerged, such as: methods for preparing the cells prior to transplanting them; the graft location in the host brain; the age and type of donor cells and the host; the type of brain injury; and the interval between acute injury and transplantation. Fetal neural stem cell integration and dispersion is superior when they are dissociated prior to transplantation, rather than maintained as solid tissue grafts. The reasons are not entirely clear, but the enhanced survival of dissociated cell grafts may be due to the smaller diameter needles or pipettes that can be used to deliver the cells, reducing mechanical damage as the cells are stereotaxically injected into the brain. Additionally, dissociation may increase the interface between the host brain and the graft.

The region of the host brain receiving the transplant and the age of the host are also important considerations. For example, fetal neural precursors show enhanced survival in the white matter and the lateral ventricles compared to the hippocampus (Shetty and Turner, 1996). The local neighborhood of the graft also influences

the types of cells that are generated by neural progenitors or embryonic stem cell-derived progenitors. Acute injury transiently stimulates the release of trophic factors and chemokines that may promote survival, migration, and integration of transplanted fetal neurons. Therefore, the most favorable therapeutic window for transplantation may occur days or weeks after lesions (Shetty and Turner, 1996). Younger animals typically show greater migration and dispersion of transplanted fetal neural precursors, compared with older animals, possibly due to migratory cues that are present in the developing, but not adult brain. Definition of the molecular signals regulating NPC survival and differentiation is just beginning. NPC differentiation into GABAergic interneurons and integration into the mouse cerebral cortex are strongly influenced by the neuronal lineage-specific protein BM88/Cend1. This protein links exit from the cell cycle to programs for neural differentiation (Makri et al., 2009). Additionally NPC integration into injured regions of the adult brain is enhanced by multiple factors, including polysialylated neural cell adhesion molecule (NCAM) (Glaser et al., 2007), the adhesion molecule L1 (Bernreuther et al., 2006), nerve growth factor (NGF) (Sinson et al., 1996), glial derived neurotrophic factor (GDNF) (Bakshi et al., 2006), tenascin-R (Hargus et al., 2008) and cytokines such as stromal cell-derived factor 1 alpha (SDF-1α) (Shyu et al., 2008).

5. Anti-inflammatory effects and neuroprotection mediated by neural stem cells

In addition to replacing cells that have undergone neurodegeneration, transplants of fetal NPCs, human ESC-derived neural progenitors, or mesenchymal stem cells may result in behavioral recovery through direct anti-inflammatory and immunosuppressive effects. For example, neural precursor grafts in the spinal cord led to behavioral recovery of motor function in experimental autoimmune encephalomyelitis, a rodent model of multiple sclerosis, although very few of the grafted precursors differentiated into myelin-forming oligodendrocytes (Einstein et al., 2007). In another example transplants of human mesenchymal stem cells enhanced motor neuron survival, improved motor performance, and reduced microglial activation in an experimental model of ALS in mice (Vercelli et al., 2008). These studies suggest that neural stem cell therapy may be beneficial in some situations because of neuroprotection rather than neuronal replacement. Additional positive effects may be due to the ability of stem cell grafts to suppress inflammation or elicit trophic factor-mediated responses in the host brain, or both.

6. Advances toward successful cell-based therapies to treat epilepsy

Fetal NSC and ESC-derived neural progenitors have been tested for their ability to integrate and restore function in rodent models of epilepsy. A therapeutic goal in epilepsy is to restore the normal balance between excitation and inhibition. Work on fetal neural precursor grafts has shown that they can enhance neuronal inhibition or cause hyperexcitability, depending upon the type of tissue that is used for transplantation and the location of the grafted cells. The two broad categories of epilepsy syndromes are generalized and partial epilepsy. In generalized epilepsy, seizures are initiated simultaneously in both hemispheres, whereas in partial epilepsies the seizures arise from one or more localized foci, but may spread throughout the brain. Many generalized epilepsies have a genetic basis, involving mutations in ion channels or are caused by neuronal migration disorders. These forms of epilepsy need treatments that target large regions of the nervous system. Partial epilepsies are often acquired following injury to a focal region of the brain (Chang and Lowenstein, 2003) but are also prevalent among patients suffering from strokes or Alzheimer's disease. The most common form of partial epilepsy involves the temporal lobes and the hippocampus.

Patients with temporal lobe epilepsy (TLE) resulting from an acute brain injury frequently require high doses of anti-epileptic drugs (AEDs) associated with cognitive impairments, depression or dementia. Anti-convulsant medications fail to control the seizures in many of these patients and only a minority of the patients with epilepsy are candidates for surgical resection of the seizure focus. With bilateral foci in the hippocampus, surgery is not feasible, because removing both hippocampi destroys the ability to form new declarative memories. TLE in young children is also associated with cognitive impairments (Bjornaes et al., 2001) and it is common for these patients to develop drug resistance. While the majority of TLE patients are successfully treated with drugs that decrease neuronal excitation or increase inhibition, one-third do not experience seizure control with any available medication. Both clinical and experimental animal data suggest that intense limbic seizures can directly cause brain damage, although this is still under debate. For those patients who fail to respond to these more established procedures for seizure control, TLE can be life-threatening and debilitating.

Head trauma or other traumatic brain injuries such as infection, stroke, or prolonged status epilepticus (SE), often lead to TLE after a latent period. This interval, consisting of a few weeks or as long as several years, is when maladaptive plasticity begins, promoting hyperexcitability and the emergence of spontaneous recurrent seizures. Neuroplastic changes include atrophy of hilar neurons, the birth of new ectopic granule neurons, and mossy fiber sprouting (Mathern et al., 1995). The remarkable diversity of cellular and molecular changes in the limbic system after seizures underscores the special challenge of treating acquired chronic epilepsy and suggests that multiple approaches will be necessary to reverse hyperexcitability in this region of the brain.

Many of the pharmacological treatments for TLE enhance inhibitory neural transmission. When cells genetically modified to secrete GABA were transplanted into rodent models of epilepsy, they were shown to reduce seizure severity, suggesting that cell-based therapies that enhance inhibitory neural transmission could be therapeutic in patients with TLE. Transplantation of fetal neurons into the cerebral hemispheres of normal mice has been shown to alter levels of excitation in cortical and hippocampal neural circuits. For example, cortical neuron excitability was decreased by grafts of neural progenitors from the ganglionic eminence (GE), a source of forebrain GABAergic interneurons (Alvarez-Dolado et al., 2006), whereas hippocampal seizure activity was increased by grafts into the hippocampus of excitatory fetal neurons (Buzsaki et al., 1991). The mechanism for these changes in levels of neuronal excitation was synaptically mediated; when transplanted into normal mouse cortex, GE-derived precursors increased postsynaptic inhibitory currents in cortical pyramidal neurons by approximately 25%. Moreover, when GE transplants were made into the cerebral cortex of mice with spontaneous seizures caused by a loss-of-function mutation of a Shaker-like potassium channel (*Kv1.1/Kcna1*), the GE-derived cell grafts markedly reduced the number of electrographic seizures (Baraban et al., 2009).

To further test whether cell transplantation might be an effective approach for controlling seizures and cognitive deficits associated with epilepsy, more studies are needed in additional animal models that have been developed to study inherited forms of human epilepsy (Noebels, 2001; Sarkisian, 2001). Ideally, the model system and the assessment should closely mimic the conditions used for particular types of human epilepsy patients. Seizure-

induced effects on the brain are also age-dependent and several excellent pediatric epilepsy models have been developed (Price et al., 2009; Scantlebury et al., 2007).

In addition to heritable forms of epilepsy, stem cell treatments are beginning to be studied for acquired forms of epilepsy. The spontaneous recurrent seizures induced in mice and rats by systemic injections of pilocarpine, a strong M1 muscarinic agonist, closely resemble severe human TLE resulting from traumatic brain injury or prolonged febrile seizures (Curia et al., 2008; Sarkisian, 2001; Scorza et al., 2009; Shibley and Smith, 2002; Turski et al., 1984). These features include: 1) an initial precipitating event such as SE; 2) a latent period; 3) a chronic seizure phase with recurrent spontaneous seizures; 4) hippocampal sclerosis and reorganization of connections.

In acquired epilepsy induced by focal or systemic injections of kainate or pilocarpine, SE results in neuronal circuit reorganization and inflammation that leads to the development of spontaneous recurrent seizures. The latent period between the initial SE and the appearance of spontaneous recurrent seizures is highly variable and less distinct in mice than in humans. One important methodological issue for studies testing cell therapies in rodent models of acquired epilepsy is that there may be high variability in the length of the latent period between animals. A recent analysis of the latent period in the systemic kainic acid model of TLE in rats has shown that the development of spontaneous recurrent seizures is not a step function of time, but rather the seizures occur in clusters with variable inter-seizure intervals (Williams et al., 2009). While the inter-seizure intervals are longer initially, the intervals between seizures shorten over time as seizures increase in frequency, and these progressive changes can continue over the first 3 months. Because of the variability between animals, the progressive nature of the seizures, and their tendency to occur in clusters, it is important to use long-term continuous electrographic monitoring to assess treatments.

Histological studies in rodents show that irreversible degeneration of GABAergic interneurons occurs within days after prolonged SE induced by systemic injections of pilocarpine (Curia et al., 2008). Bilateral hippocampal degeneration is also observed after focal injections of kainic acid (Magloczky and Freund, 1993, 1995; Represa et al., 1995). Seizures are often associated with alterations in adult granule cell neurogenesis, granule neuron migration, gliosis (Hattiangady and Shetty, 2009; Parent, 2007), synaptic plasticity (Morimoto et al., 2004), and neuroinflammation (Shapiro et al., 2008). Atrophy and death of GABAergic interneurons in the hilus and CA1 regions also follows status epilepticus in several rodent chemoconvulsant models (Obenaus et al., 1993). Alterations in the functional properties of surviving interneurons may be another form of neuroplastic changes caused by severe seizures. For example, the somatostatin-positive interneurons in the hilus of the dentate gyrus that survive SE hypertrophy and form more extensive axonal arbors with granule cell dendrites in the molecular layer (Zhang et al., 2009).

Changes in gene and protein expression include noteworthy neuroplastic changes such as altered expression of nerve growth factor and brain-derived neurotrophic factor mRNAs (Hunsberger et al., 2005; Madsen et al., 2003; Newton et al., 2003), and epigenetic changes in promoter regions of growth factor genes (Ma et al., 2009). Whether GABA ergic stem cell transplants could suppress these hypertrophic changes is an important issue for further research.

Many TLE models have tested whether bilateral grafts of GABA-releasing cells or matrices suppress seizures or prevent focal seizures from generalizing. Kokaia et al. (1994) implanted GABA-releasing polymers into kindled rats to show that it limited the spread of focal limbic seizures (Kokaia et al., 1994). However, the effects were short-lived, presumably due to depletion of the GABA from the implants. In other studies, cell lines engineered to release GABA were transplanted into the piriform cortex and shown to reduce thresholds for kindling seizures (Gernert et al., 2002). GABA-releasing neurons transplanted into the substantia nigra transiently reduced spontaneous seizures in rats that were already kindled (Nolte et al., 2008). Moreover, spontaneous recurrent seizures were reduced when fetal striatal precursors are transplanted into the hippocampus in the rat kindling or the kainic acid models (Hattiangady et al., 2008; Loscher et al., 1998). Several studies have also shown the utility of fetal hippocampal cell grafts, or transplants of cells engineered to release GABA in rodents that had developed recurrent spontaneous seizures (Nolte et al., 2008; Thompson, 2005; Thompson and Suchomelova, 2004). Taken together, prior work suggests that augmenting GABAergic transmission in several different experimental models of TLE suppresses both the development of seizures and recurrent spontaneous seizures.

Because TLE is often associated with memory impairments and other cognitive deficits, it is interesting to note that grafts of fetal neurons into the adult hippocampus improve cognitive deficits in a spatial maze (Kimble et al., 1986; Low et al., 1982; Mickley et al., 1990).

7. Interneuron diversity and vulnerability in epilepsy

Recent work demonstrates that GABAergic inhibitory interneurons can be efficiently derived from mouse or human ES cells and fetal cortical neural progenitors by different approaches (Aubry et al., 2008; Bosch et al., 2004; Chatzi et al., 2009; Erceg et al., 2008; Kallur et al., 2008; Kitazawa and Shimizu, 2007; Laeng et al., 2004; Sarichelou et al., 2008; Spiliotopoulos et al., 2009). These promising findings suggest that GABA cell therapy may be possible in patients with neurodegenerative disorders or epilepsy; however, successful cell replacement therapy for these patients may require replacing specific types of GABAergic neurons. These cells are extremely diverse anatomically, neurochemically, physiologically, and in terms of their specific patterns of innervations (Gupta et al., 2000). A better understanding is needed of how they develop. These neurons express mRNAs for two isoforms of the GABA synthetic enzymes glutamate decarboxylase (GAD65 and GAD67) and may be either local circuit-forming neurons or projection neurons. Their axonal terminals form distinctive stratifications within particular regions of pyramidal neuron or granule neuron dendritic arbors (Freund and Buzsaki, 1996; Houser, 2007). Because of their tremendous diversity, multiple criteria are used to identify subtypes, including morphology, neurochemical phenotype, and electrophysiological properties.

The somatostatin and parvalbumin subclasses of GABAergic interneurons in the hilus of the dentate gyrus in the hippocampus serve critical roles in controlling granule cells excitability and have been well-studied by immunohistochemistry as well as intracellular recording and biocytin staining. A subset of somatostatin-expressing interneurons in the hilar region of the dentate gyrus terminate on the distal granule cell dendrites in the outer molecular layer, where excitatory inputs comprising the perforant pathway arrive from the entorhinal cortex (Freund and Buzsaki, 1996). Sometimes described as “gatekeepers” for the dentate gyrus, these neurons exert feed-forward inhibition in the hippocampus. Subsets of these interneurons express neuropeptide Y (NPY), which serves an important anti-epileptic role in dentate gyrus neural circuits (Baraban et al., 1997). In both humans and rodents, these neurons are highly vulnerable to head injury or prolonged status epilepticus, whereas the parvalbumin-expressing interneurons in this region are relatively resistant to cell death

(Binaschi et al., 2003; Buckmaster and Dudek, 1997; Buckmaster and Jongen-Relo, 1999; de Lanerolle et al., 1989; Kobayashi and Buckmaster, 2003; Swartz et al., 2006). It is estimated that 16 percent of the GABAergic cells in the dentate gyrus express somatostatin and they account for the majority of interneurons that degenerate after SE (Freund and Buzsaki, 1996).

Basket cells are another type of interneuron in the dentate gyrus, most of which are positive for the calcium binding protein parvalbumin (Freund and Buzsaki, 1996). This GABAergic subtype innervates the soma and proximal dendrites of excitatory cells, enabling them to greatly influence the activity of their targets. Basket cells in the dentate gyrus are located near the granule cell layer and the hilus, and make connections with granule cells. However, other parvalbumin interneurons make vast connections to pyramidal neurons in the CA1 region of the hippocampus (Klausberger, 2009). These interneurons are also critical modulators of cortical gamma rhythms onto theta rhythms of the hippocampus (Wulff et al., 2009). Although parvalbumin immunoreactivity is dramatically reduced in temporal lobe epilepsy, these neurons are relatively resistant to seizure-induced excitotoxic cell death compared to the more vulnerable hilar mossy cells and somatostatin-positive interneurons in the dentate gyrus (Sloviter et al., 2003).

Prior studies have applied three major strategies to generate GABAergic progenitors from ES cells (Table 1). These include: the conditioned medium (CM) approach, forcing gene expression using viral vectors, or growing ES cells in chemically defined media (Maisano et al., 2009; Naegele and Maisano, 2010). To determine whether CM obtained from embryonic progenitors dissected from specific regions in brain induces GABAergic cell fates in neural stem cells, Trinh and colleagues (Trinh et al., 2006) exposed cerebrocortical neural progenitors to media that had been conditioned with a region of the embryonic ventricular zone called the medial ganglionic eminence, the region of the forebrain where GABAergic interneurons are specified (Anderson et al., 2002; Butt et al., 2007; Wonders et al., 2008). In one study chick dorsal root ganglion (DRG)-CM was found to promote differentiation of mouse ES cells into neurons; approximately one-quarter became motor neurons, whereas the GABAergic lineage only comprised 8.7 percent of the total cells (Kitazawa and Shimizu, 2007). These results illustrate several possible differences in the composition of CM from different brain regions and the utility of using CM to direct neural stem cell fates, but the molecular basis for these results remains unclear.

An alternative method is to induce expression of transcription factor codes in stem cells to produce particular neuronal lineages (Marquardt and Pfaff, 2001). This could be an effective strategy to obtain homogenous neuronal populations from ESCs because much information is available about neuronal specification. For example, expression of neurogenin 2 (Ngn 2) specifies dorsal forebrain (pallium) neurons whereas the expression of Dlx1/2 and Mash1 transcription factors are required for specifying subpallial-derived populations (Cobos et al., 2007, 2005; Long et al., 2009). In addition, Nkx2.1 serves a primary role in directing cortical interneuron fate in medial ganglionic eminence (MGE) by activating the LIM-homeodomain proteins Lhx6 and by suppressing more dorsally expressed Pax6 (Butt et al., 2008). In cultures of NSCs from human fetal striatum, Pax6 overexpression increases the percentage of GABA-positive neurons to 50% of the total cells, suggesting an important role for Pax6 in striatal interneuron specification (Kallur et al., 2008).

A third method for enriching specific populations of neural stem cells from ES cells is to propagate the neural stem cells in media containing defined growth factors and signaling molecules. Some important candidates for this approach include members of the wingless (Wnt) family of signaling molecules, sonic hedgehog (SHH), fibroblast growth factor (FGF), and brain-derived neurotrophic factor (BDNF). Wnt signaling has been implicated in maintaining the self-renewal and pluripotent capacity of ES cells (Ille and Sommer, 2005) and down-regulating Wnt signaling induces neural differentiation. As shown in Table 1, several studies report protocols for successfully generating GABAergic neurons by adding SHH, FGF-2, BDNF, and/or RA to the culture medium for varying lengths of time. BDNF promotes cell survival and neurite outgrowth (Bernd, 2008) and is commonly added to the embryonic stem cell-derived neural precursor (ESNP) cultures during neural differentiation. Additionally small signaling molecules, such as retinoic acid (RA), have been used to promote neural differentiation (Chatzi et al., 2009). The Wnt inhibitor dickkopf-1 and SHH have been used to obtain higher percentages of GABAergic neural progenitors from hESCs (Aubry et al., 2008). Because of the ease of this approach, it could be one of the more reliable strategies from a pharmaceutical standpoint, but studies have not yet defined the medium and the sequence of exposing the cells to signaling molecules to provide a means for routinely generating functionally distinct classes of mature GABAergic neurons.

8. Fetal neural precursors for GABAergic neurons originate in the basal forebrain

One strategy discussed above for generating neural precursors is to force the expression of transcription factors that will direct ESCs them into specific progenitor cell types. This concept is still untested, but recent work suggest that unique transcription factor codes specify the functionally distinct cell types in the spinal cord (Marquardt and Pfaff, 2001). All hippocampal and cerebral cortical GABAergic interneurons are specified by combinatorial codes of transcription factors expressed in a transient embryonic structure called the ganglionic eminence (GE) (Wonders et al., 2008). The GE can be subdivided into lateral (LGE), medial (MGE), and caudal (CGE) regions, each of which expresses a unique transcriptional code within progenitor populations that specifies functional

Table 1
Protocols for producing GABAergic precursors from human and mouse Embryonic Stem cells, neural stem cells, and cerebrocortical neural precursors.

Cell Type	Treatment	Duration of Treatment	Enrichment (%)	Citation
Human ES cells	BDNF, SHH, DKK-1	23–36 DIV	8%	(Aubry et al., 2008)
Human ES cells	RA, FGF-2	42 DIV	81% (of Tuj1-expressing neurons)	(Erceg et al., 2008)
Human NS cells	Pax6 overexpression	28 DIV	50%	(Kallur et al., 2008)
ESC-derived mouse NSCs	FGF-2, BDNF	21 DIV	85%	(Spiliotopoulos et al., 2009)
Mouse ESCs	DRG-CM	10 DIV	8.7%	(Kitazawa and Shimizu, 2007)
Mouse ES cells-derived EB	RA, FGF-2, EGF	14 DIV	96%	(Chatzi et al., 2009)
Rat NS cells	RA, KCl	15 DIV	74%	(Bosch et al., 2004)
Rat NS cells	FGF-2, VA	8 DIV	26%	(Laeng et al., 2004)
Mouse NPCs	GE	5 DIV	8%	(Trinh et al., 2006)

Abbreviations: BDNF, brain-derived neurotrophic factor; CM, conditioned medium; DIV, days *in vitro*; DKK-1, dickkopf-1; DRG, dorsal root ganglion; EB, embryonic body; EGF, epidermal growth factor; ESC, embryonic stem cell; FGF-2, fibroblast growth factor 2; GABA, γ-aminobutyric acid; GE, ganglionic eminence; NSC, neural stem cell; NPC, neural precursor cells; RA, retinoic acid; SHH, sonic hedgehog; VA, valproic acid.

subclasses of GABAergic interneurons. The transcriptional codes within the MGE have been deduced through knockout experiments. This work suggests that the transcription factor Nkx2.1 is required for specifying MGE-derived GABAergic interneurons (Sussel et al., 1999).

GABAergic interneuron subclasses expressing parvalbumin or somatostatin are generated within the MGE, and account for 60 percent of all hippocampal and neocortical GABAergic interneurons (Wonders et al., 2008; Xu et al., 2004). In contrast, the progenitor cells in the LGE are Nkx2.1-negative and give rise to striatal GABAergic neurons (Wichterle et al., 2001). The CGE is partially Nkx2.1-positive and has been implicated in the generation of calretinin-expressing interneurons (Nery et al., 2002). CGE and the MGE have been shown to be Dlx1/2 positive (Xu et al., 2004). Fetal neurons derived from the LGE and MGE can be readily harvested from mouse or rat embryos on gestational days 11–13 and are highly migratory. Moreover, they survive transplantation into embryonic postnatal or adult rodent brains and differentiate into a variety of cell types including interneurons, oligodendrocytes, and astrocytes (Alvarez-Dolado et al., 2006; Eriksson et al., 2003; Nery et al., 2002; Olsson et al., 1998; Valcanis and Tan, 2003; Yozu et al., 2005).

Several studies have demonstrated the efficacy of fetal GABAergic progenitor grafts for controlling seizures. In a recent study by Baraban et al. (2009), MGE-derived neural precursors transplanted into the postnatal neocortex of mice with generalized epilepsy reduced the frequency of spontaneous seizures by 86 percent, compared to sham controls, as assessed by EEG recordings (Baraban et al., 2009).

9. Growth factors, neurotrophic factors and anti-apoptotic agents significantly enhance the survival of fetal neurons after transplantation

A consistent observation from transplantation studies in the adult brain is that fetal neurons have poor survival after transplantation into the adult brain. To address this problem, cells are pretreated with neurotrophic factors such as BDNF, fibroblast growth factor 2 (FGF2) and caspase inhibitor (Rao et al., 2007). Fibroblast growth factor (FGF) pretreatment increases the expression of neurogenin, a transcription factor required for neural differentiation (Vergano-Vera et al., 2009) and enhances the survival of GABAergic interneurons after they are transplanted (Rao et al., 2007). In addition to pre-incubating cells prior to transplantation, graft survival and integration is promoted by intraventricular injections of erythropoietin at the time of transplantation (Jing et al., 2009).

10. Host brain influences on the migration and integration and transplanted cells

As discussed above, the extensive reorganization of temporal lobe circuits after seizures suggests that understanding the permissiveness of the host brain environment is an important variable for successful stem cell therapies. Inflammation and recruitment of microglia may make the brain less hospitable for young neurons, although evidence from other models of injury suggests that lesions provide signals that stimulate brain repair. For example, lesions stimulate neurogenesis from endogenous neural stem cell populations in the adult brain and spinal cord (Chen et al., 2004; Magavi et al., 2000). In addition, some work suggests that lesions caused by ischemic insults provide a chemotactic signal for human and mouse embryonic stem cell-derived neural precursors (Chu et al., 2004; Hoehn et al., 2002). Our understanding of migratory signals for directing transplanted cells to sites of damage is still developing, indicating an important area for future research that is likely to have a large impact on the success of stem cell therapies for neurodegenerative disorders, including epilepsy.

11. Immunosuppression and cell transplantation into the brain

The possibility of graft rejection remains a major roadblock for clinical applications of stem cell therapies. The CNS has been regarded as an immune privileged site that is more hospitable for tissue grafts due to the blood brain barrier (BBB) (Barker and Billingham, 1977; Medawar, 1948). A tight seal of endothelial cells lines the blood vessels and forms the BBB, hindering entry of immune cells into the brain (Knopf et al., 1998; Risau and Wolburg, 1990). However, the concept of immunologic privilege in the brain has come into question because of evidence for brain-specific phagocytes called microglia that trigger inflammation, apoptosis, and phagocytosis of dying cells in response to neuronal injury (Galea et al., 2007). But persistent microglia activation and reactive gliosis after seizures and other injuries suggests that these cells may also reduce graft survival. Due to differences in host *vs.* graft expression of cell surface major histocompatibility complex (MHC), microglia and other immune cells may recognize transplanted cells as "non-self" and release cytokines, including interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α). This can lead to an inflammatory cascade and apoptosis. To avert graft rejection, immunosuppression is required for patients receiving autologous cell grafts and immunodeficient rodents are often used in research involving neural stem cell grafts. Because the nonsteroidal drug cyclosporine A (CsA) inhibits lymphokine production, interleukin release without myelotoxicity, it is the preferred agent to induce immunosuppression for transplantation studies. This drug is also neuroprotective and has been shown to prevent mitochondrial permeability transition, cytochrome c release, and caspase 3-dependent apoptosis (Gieseler et al., 2009). However, CsA has some adverse side effects including inducing high blood pressure and toxicity to kidney and liver. Proper monitoring and dose adjustment are used to reduce toxicity associated with immunosuppression strategies.

12. Diagnosing seizures in epilepsy models and evaluating transplant efficacy with behavioral methods and electroencephalography

Electroencephalography (EEG) is a key diagnostic tool for evaluating epilepsy patients and may also be used to monitor treatment efficacy. Video-EEG monitoring may also be used to quantify changes in seizure frequency, duration and intensity in experimental epilepsy models. The spontaneous seizures in the chemoconvulsant-induced seizure models in rodents often occur in clusters, so that continuous and long-term video-EEG monitoring is optimal for evaluating treatment-induced improvements in seizure frequency, duration and intensity (Bertram et al., 1997). The kainate model does not produce spontaneous seizures in most strains of inbred mice, but it reliably produces them in rats, and the seizures are clustered with variable intervals with increasing severity over time (Williams et al., 2009).

Not all pilocarpine-injected rodents develop SE, but in those that do, the resulting behavior is marked by repetitive and debilitating seizure events (Scorza et al., 2009). SE is frequently terminated by injections of diazepam after 60–120 min. SE lasting less than 30 min does not produce reliable hippocampal damage sufficient enough to mimic human TLE and elicit spontaneous recurrent seizures (SRS) (Curia et al., 2008). Based on the Racine scale, Shibley and Smith (Shibley and Smith, 2002) developed

a rating system to quantify seizure behavior either previously recorded on video or by direct observation (Curia et al., 2008; Shibley and Smith, 2002). While behavioral assessment is useful for analyzing generalized seizures, partial seizures cannot always be detected by observing the animal's behavior (Curia et al., 2008). Therefore, behavioral assessment should be combined with EEG recordings. Following the initial episode of SE, the latent period may vary from several days to weeks, before SRS manifest. One study in mice showed that the mean latent period is two weeks on average, ranging from 4 day to 42 days after SE (Cavalheiro et al., 1996). In another study in rats, video-EEG recordings showed average latencies of approximately 7 days (ranging from 5.2 to 17.2 days) (Goffin et al., 2007). These discrepant findings may be due to disparate methods for monitoring seizures as well as strain-specific differences. During the chronic phase, seizure frequencies of 2–3 per day (Scorza et al., 2009) or less have been reported (Curia et al., 2008), with inter-seizure intervals of 7–10 days, and a mean seizure duration of 40 s can be expected in mice (Goffin et al., 2007). Because of the variable length of the seizure clusters, it may be necessary to carry out extended EEG monitoring over a period of 3–6 weeks to fully compare differences in experimental and sham operates.

13. Gene therapy for temporal lobe epilepsy

In contrast to stem cell-based therapies for neurological disorders and epilepsy, relatively few studies have examined gene therapies (Boison, 2006; Loscher et al., 2008; Nolte et al., 2008). For successful application of gene therapy in epilepsy, several hurdles need to be overcome, including toxicity and selective tropism. While progress has been made toward producing viral vectors such as adeno-associated virus (AAV) with low toxicity, the nonselective nature of these vectors poses a hurdle, because successful therapies would ideally direct the transgene to particular cell types (Haberman et al., 2002). The most well-studied gene therapies for treating epilepsy target adenosine kinase (Li et al., 2007; Ren et al., 2007), galanin (Haberman et al., 2003; Lin et al., 2003) and neuropeptide Y (NPY) (Noe et al., 2007, 2008; Richichi et al., 2004).

13.1. Adenosine kinase

One theory of epileptogenesis is that astrogliosis rapidly occurs after brain injury, increasing glial expression of an adenosine metabolizing enzyme called adenosine kinase (ADK). ADK decreases adenosine, an endogenous anti-convulsant, and this deficiency promotes seizures (Boison, 2008). Gene therapy targeting the adenosine system, either alone or in combination with cell therapy, appears to have gained experimental support as a rationale approach for seizure remediation. There is strong experimental support for the adenosine kinase hypothesis of epilepsy (Boison, 2008). Transplants of ES cells genetically engineered to lack ADK into the rat hippocampus increase adenosine secretion, delay the rate of kindling, and reduce after-discharges (Li et al., 2007). Moreover, grafts of human mesenchymal stem cells releasing adenosine reduce the duration of excitotoxic seizures by 35% (Li et al., 2009). The effect is specific to adenosine release because transplants of cell lines with ADK fail to disrupt seizures and overexpression of ADK in CA3 can trigger seizures (Li et al., 2008). Lentiviral RNA interference to reduce ADK has also been tested and shown to prevent CA3 cell loss after KA-induced seizures by more than 60% (Ren et al., 2007).

13.2. Galanin

This short neuropeptide has diverse functions including modulating seizure sensitivity. When adeno-associated viral vectors carrying the galanin gene as a secreted form are infused unilaterally into the hilus region after focal injections of kainic acid (KA), hilar cell death is reduced on the side of the AAV injection and seizures are also attenuated (Haberman et al., 2003). Similarly, when the vector is infused into the piriform cortex it greatly attenuated, or eliminated, behavioral seizures induced by KA (McCown, 2006). The threshold for electrical kindling of seizures in the same brain region is elevated in rodents receiving AAV-delivery of galanin, demonstrating that gene therapy facilitating the expression and secretion of galanin is applicable for controlling seizures. Gene delivery of inhibitory factors in a secreted form bypasses the problem of possibly targeting the wrong cell population.

13.3. Neuropeptide Y

Neuropeptide Y (NPY) might serve an important anti-convulsant role by inhibiting synchronized glutamate release from active synapses during seizures (Sorensen et al., 2008). NPY is expressed in subsets of interneurons in the hilus and CA regions in physiological conditions and in TLE models it increases and spreads to the outer molecular layer of the dentate gyrus, marking the mossy fiber sprouting (Nadler et al., 2007). NPY has multiple functions in the normal brain, but AAV-mediated overexpression of NPY reduces sensitivity to both electrical kindling induced seizures (Sorensen et al., 2009) and kainic acid-induced seizures (Richichi et al., 2004). Conversely, NPY-deficient mice have more kainate-induced seizures and higher mortality (Baraban et al., 1997).

14. Summary and conclusions

Although efficient protocols for generating most of the neuronal lineages in the nervous system are not yet developed, some types of neuronal and glial precursors can now be routinely derived *in vitro* from human and mouse ESC-derived neural progenitors. Testing the efficacy of these neural precursors, as well as novel gene therapies, is underway in a broad range of experimental animal models for neurological disorders and epilepsy. Work in this area of investigation may potentially lead to stem cell-based therapies that facilitate regeneration of damaged neural circuits (Emsley et al., 2004). Before these exciting clinical prospects can be realized, the risks associated with stem cell and gene therapies will need to be decreased. Challenges for future work are to determine how to promote long-term survival and integration of neural precursor transplants in the adult brain and to optimize modulation of neural activity to reverse behavioral and cognitive deficits in neurodegenerative disorders and epilepsy.

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