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2.1 Introduction

Stroke was not originally thought to be a good target for development of a neural transplantation therapy. Unlike Parkinson's disease in which a specific cell population is lost and therefore could conceivably be replaced, cell loss post stroke is not limited to a specific neuronal cell type or even neurons, making it more complicated to rebuild the neural circuitry. Even so, the first studies that used cell therapy for the treatment of stroke were performed over 20 years ago and published in 1988. In one study, fetal cortical neurons were transplanted directly into the cortex of adult rats that had undergone temporary middle cerebral artery occlusion (MCAO) (Mampalam et al. 1988). These grafts survived, developed appropriate neurotransmitter phenotype as demonstrated with nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) and acetylcholinesterase (AChE) expression, and had neurites that left the transplant and integrated into the host brain. The other study focused on a labeling strategy to identify the transplanted fetal neurons in the host after ischemia induced by 4-vessel occlusion (4VO) (Farber et al. 1988). Shortly, thereafter, another research group demonstrated that grafted fetal hippocampal neurons integrated into hippocampal CA1, receiving fiber ingrowth from septum that made synaptic contacts with the grafted neurons and projecting to posterior levels of host CA1 (Tonder et al. 1989). These early studies demonstrated proof of principle that fetal neurons could survive and engraft in infarcted brain. Subsequent studies examined the ability to rebuild neural circuits and reduce functional deficits.

In these earlier days of cell therapy, it was inconceivable that cells could be transplanted outside the central nervous system (CNS) and have a therapeutic effect. Therefore, all the early studies employed either direct implantation into the injured

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brain (parenchymal) or into the nearby ventricular system (intracerebroventricular or i.c.v.). In more recent years, observations that bone marrow-derived cells could enter the brain and express microglial or astrocytic antigens after intravenous (i.v.) administration (Eglitis and Mezey 1997) led researchers to ask if other routes of cell delivery could be efficacious. The first report of i.v. delivery examined cell efficacy in a rodent model of traumatic brain injury (Lu et al. 2001), followed shortly thereafter by a publication from the same research group demonstrating that intra-arterial (i.a.) administration of bone marrow stromal cells was effective at inducing functional recovery in a MCAO model of stroke (Li et al. 2001a). Since that time, the literature on cell therapies using these nontraditional routes of delivery has greatly expanded. In fact, when the route of administration is compared over time, there is a shift in the route of administration that is predominantly used, based on the cell types that are studied (Table 2.1). In this chapter, we will not provide an exhaustive review of the field, but we will provide a short overview of the cell therapy literature focusing on the benefits and risks of these different routes of administration, discussing intraparenchymal, vascular, and ventricular routes of administration.

2.2 The Intraparenchymal Route of Cell Delivery

All the early neural transplantation studies for stroke used either the intraparenchymal or intraventricular route of delivery of fetal neurons. The goal of these studies was predominantly to determine the feasibility of replacing lost neurons and rebuilding neural circuits. The site of transplantation depended on the stroke model employed. For example, in the four-vessel occlusion model, neurons are lost in CA1. Transplants of fetal hippocampal neurons from embryonic day 17–19 (E17–E19) rats survived well for extended periods of time (>100 days post transplant) and expressed appropriate region-specific receptors (Aoki et al. 1993). Further, the cells significantly improved performance on a spatial memory task (Netto et al. 1993). Transplantation of neural stem cells (NSCs) in this region also produces recovery if sufficient cells survive and express neuronal proteins (Toda et al. 2001). Using the similar bilateral occlusion model, investigators have transplanted NSCs into cortex, hippocampus, or striatum, depending on the experimental question to be addressed (Shichinohe et al. 2010; Ohtaki et al. 2008; Nodari et al. 2010).

The focus of the studies using this route of delivery depends on the cells being studied. In those studies that have transplanted primary fetal neurons, the experimental questions concerned whether the grafts survived, for how long, and if survival could be modified (Koshinaga et al. 1995). They also asked whether the fetal neurons could mature into an adult phenotype that was appropriate for the region they were transplanted into (Mampalam et al. 1988; Nishino et al. 1993a). Did these cells express neurotransmitters and have neuritic processes from graft and host developing synaptic contacts (Mampalam et al. 1988; Grabowski et al. 1992a, b; Onizuka et al. 1996; Aihara et al. 1994; Belichenko et al. 2001)? Most importantly, questions of the ability of the cells to decrease infarct volume (Johnston et al. 2001) and improve motor, cognitive, or somatosensory function were also

Table 2.1 Routes of cell administration for treatment of experimental stroke: analysis over time^a

Year	Cell type	# of studies	Route				Primary outcomes ^b
			Parenchymal	Vascular	Ventricular	Other	
1991 ^c	Fetal neurons	3	3				2, 3, 5, 7, 12
	NSCs						
	Bone marrow						
	Umbilical cord						
	Other	1	1				2, 6, 12
2001	Fetal neurons	2	2				1, 3, 5, 12
	NSCs	2	2				1, 2, 14, 15
	Bone marrow	5	2	3			2, 3, 4, 5, 6, 8, 9, 10
	Umbilical cord	1		1			2, 3, 5, 6, 9
	Other	4	4				1, 2, 3, 7, 12
2011	Fetal neurons	1	1				3, 5, 12
	NSCs	13	7	3	2	1	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12
	Bone marrow	23	5	18			1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16
	Umbilical cord	5	1	3		1	1, 2, 3, 7, 9, 10, 11, 12, 13, 16
	Other	2	1	1			1, 2, 3, 5, 6, 7

^aThe analysis was performed using the OVID and PUBMED literature database programs. The search strategy was as follows: (cerebral ischemia or cerebral hemorrhage or cerebrovascular accident or stroke) AND (cell therapy or cell transplantation or fetal tissue transplantation or fetal neurons or bone marrow or umbilical cord or mesenchymal stem cells, stem cells, endothelial progenitor cells)

^bPrimary outcome variables:

(1) infarct size, (2) functional outcome, (3) cell survival, (4) proliferation, (5) differentiation, (6) migration, (7) trophic support, (8) anti-inflammatory, (9) cell dose, (10) induction of neurogenesis, (11) induction of angiogenesis, (12) dendritic/synaptic plasticity, (13) cortical reorganization, (14) safety, (15) feasibility, (16) timing

^cIncludes years 1988–1991

addressed (Zeng et al. 1999; Nishino and Borlongan 2000; Nishino et al. 1993b; Borlongan et al. 1998a, b). Later studies that tested NSCs as a treatment for stroke not only examined these same issues but were also concerned with the ability of the stem cells to proliferate (Darsalia et al. 2007), differentiate into appropriate neuronal types (Darsalia et al. 2007), and migrate to the site of injury (Darsalia et al. 2007; Hoehn et al. 2002; Lee et al. 2010a). The studies that have used non-neural cells as potential treatments have addressed issues of the ability of the cells to transdifferentiate, becoming neurons, astrocytes, or oligodendrocytes (Chen et al. 2001a, b). Alternative mechanisms of recovery such as trophic support

(Chang et al. 2002; Ferrer et al. 2001; Lin et al. 2011), anti-inflammation (Shen et al. 2010), and induced neurogenesis (Li et al. 2001b) or angiogenesis (Lee et al. 2010a) were also explored.

2.2.1 Intraparenchymal Routes of Delivery in Clinical Studies

The first cell therapy study for stroke patients was conducted in the late 1990s and the first paper published in 2000. The cells chosen were the LBS neurons, derived from a human teratocarcinoma, that had been shown in earlier studies to differentiate into neuron-like cells (Andrews 1984; Lee and Andrews 1986; Pleasure et al. 1992; Thompson et al. 1984; Trojanowski et al. 1993). In animal studies, these cells improved outcome after direct transplantation into the striatum of rats subjected to MCAO (Borlongan et al. 1998a, b). In this study, LBS neurons were injected into 12 patients with fixed deficits after lacunar stroke. European Stroke Scale score improved and PET scans performed 6 months post transplant showed increased metabolic activity at the implant site. Upon post-mortem examination from the first deceased patient, the cells did survive and express neuronal antigens; no tumor growth was detected (Nelson et al. 2002). The second phase II study was published in 2005 (Kondziolka et al. 2005). In this study, 5 or 10 million LBS neurons derived were transplanted into 25 sites in the brains of nine patients with fixed motor deficits after subcortical ischemic stroke and 9 patients with fixed motor deficits after hemorrhagic stroke. There were some improvements in motor function observed, but the primary endpoint did not change. Later analysis of cognitive function showed that some of the patients had marked improvement (Stillely et al. 2004). There were no adverse effects observed (Kondziolka et al. 2004). The study demonstrated safety and feasibility, but not efficacy.

2.3 The Vascular Delivery Route

The vascular delivery route became more common with the demonstration that bone marrow stromal cells could induce functional recovery even when they were delivered i.v. (Lu et al. 2001). As demonstrated in Table 2.1, there are now an abundance of studies that show that both i.v. and i.a. delivery are efficacious in animal models of stroke.

2.3.1 Intravenous

There have been a number of animal studies that have examined the ability of cells (bone marrow cells, umbilical cord cells, neural stem cells, etc.) delivered i.v. to reduce infarct size or, more importantly, to induce functional (motor and/or cognitive) recovery. The specific vein that the cells are injected into may vary, but the most common are the tail vein and jugular vein, although femoral and penile are

also common. In 2001, the first i.v. bone marrow stromal cell transplants (Chen et al. 2001c) and human umbilical cord blood cells (Chen et al. 2001b) for stroke studies were published. The goal of both studies was to demonstrate that the cells could improve motor and cognitive function after stroke and set the basic parameters for the timing of transplantation. In both studies, the cells produced the greatest recovery when administered at 24 h post stroke. When comparing across studies, the cord blood seemed to be marginally better at inducing recovery on the Rotarod test (~85 % compared to 75 % of baseline). There was no effect of cell delivery on infarct size and only about 10 % of the transplanted cells were present in the infarcted hemisphere in either study. In later studies that looked at the biodistribution of those cells, when MSCs, NSCs, multipotent adult progenitor cells (MAPCs), or bone marrow mononuclear cells were injected i.v. in a normal rat, less than 1 % of the MSCs, NSCs, or MAPCs were observed in arterial circulation, with most of these cells being found in lung, kidney, spleen, and liver (Fischer et al. 2009). The exception was the bone marrow mononuclear cells which are smaller than the other cells. Fully 5 % of these cells reached arterial circulation, although the majority of the cells were found in the kidney, spleen, and liver.

Even while survival of human umbilical cord blood cells in the brain was minimal, these cells consistently improved outcome after MCAO. In our subsequent studies, we determined that i.v. delivery was better than intraparenchymal delivery in the injured striatum (Willing et al. 2003), we optimized the number of cells necessary to maximize behavioral recovery and minimize infarct size (Vendrame et al. 2004) and delineated the ideal timing of cell delivery (Newcomb et al. 2006). While we and others showed that the cells could directly interact with all neural cells (Dasari et al. 2008; Hall et al. 2009a; Jiang et al. 2010, 2011) and they could migrate toward extracts of infarcted brain (Chen et al. 2001b; Jiang et al. 2008; Newman et al. 2005), the cells did not have to enter the brain to induce recovery (Borlongan et al. 2004; Nystedt et al. 2006; Makinen et al. 2006). The beneficial effects of i.v. HUCB delivery included local (Vendrame et al. 2005; Leonardo et al. 2010) and systemic (Vendrame et al. 2006; Hall et al. 2009b) anti-inflammatory properties as well as induction of neurogenesis and angiogenesis (Taguchi et al. 2004). In the bone marrow literature, similar findings were observed (Li et al. 2001b; Barbosa de Fonseca et al. 2010; Chen et al. 2002, 2003; Le et al. 2010; Shen et al. 2006).

Perhaps a more surprising application of the i.v. route of delivery has been for delivery of NSCs. One of the advantages of NSC treatments was assumed to be their ability to differentiate into neurons, astrocytes, and oligodendrocytes in order to rebuild the local neural structure. But in recent years, it has become clear that the environment in the injured adult brain is not optimal for this and recovery after NSC treatment is actually occurring through growth factor-mediated or anti-inflammatory processes similar to those observed with bone marrow or HUCB cells (Sun et al. 2010; Lee et al. 2008). For example, in the collagenase model of intracerebral hemorrhage, i.v. administration of human NSC decreased both brain and spleen cytokine expression and splenectomy reversed this effect (Lee et al. 2008). NSCs respond to many of the same chemotactic cues as marrow- or cord blood-derived cells, so it

was not too far-fetched to believe that they could also migrate to the site of injury when administered by a vascular route. Minnerup and associates recently reported that neural progenitor cells administered i.v. improved performance on the adhesive removal test of rats that had previously undergone photothrombotic stroke (Minnerup et al. 2011). While few of the LacZ-labeled cells were identified in the injured cortex, those that were expressed doublecortin suggesting they were going to become neurons. Even more interesting, these cells did not induce endogenous neurogenesis, but they did enhance dendritic outgrowth leading the authors to postulate that this was the mechanism underlying behavioral recovery. When embryonic stem cells were injected i.v. and migration examined with SPECT imaging, they also did not migrate to brain (Lappalainen et al. 2008).

2.3.2 Intra-arterial

It has been suggested that the i.a. route of delivery is superior to the i.v. route because the cells would be directly delivered to the brain where they could act to decrease infarct size and increase functional recovery. The first report of i.a. cell administration involved the injection of BrdU-labeled BMSCs through the internal carotid artery 24 h after transient MCAO (Li et al. 2001a). Compared to vehicle-treated controls, cell-injected animals scored significantly better on the neurological severity score and the adhesive removal test, but there were no significant differences in infarct size between groups. Approximately 21 % of the delivered cells were observed in the infarcted hemisphere, but no data were reported on distribution of the rest of the transplanted cells. Later studies using noninvasive imaging techniques found that by 24 h post injection, 95 % of the injected cells were found in the spleen (Keimpema et al. 2009). In follow-up studies, i.a. transplantation increased angiogenesis and proliferation of NG2-positive oligodendrocyte progenitors (Shen et al. 2006).

As with the i.v. route of delivery, NSCs or neural progenitor cells have also been delivered by the i.a. route. There are a number of studies that have reported injecting neural stem or progenitor cells via this route. The first study was a side-by-side comparison of intraparenchymal, i.v., and i.a. transplantation of human ES-derived neural cells and rat hippocampal cells. After i.v. delivery, the cells were found mainly in the liver but also in the spleen and kidney using SPECT imaging; no cells were found in the brain (Lappalainen et al. 2008). With i.a. delivery of the human ES-derived cells, the cells were also found in the brain, but not to the same extent as was found with direct implantation of rat hippocampal neurons. In another study, red fluorescent protein-labeled cells were tracked using bioluminescence imaging (Pendharkar et al. 2010). After i.a. delivery, the fluorescent signal was observed in the head region; this signal was still visible 7 days later. With the i.v. route, the fluorescent signal was only visible in the torso and was not evident 7 days post injection. These results were verified with SPIO labeling of neural stem cells and histology. Immediately after i.a. injection, the cells were present in the vasculature, but by 2 weeks post injection they were observed in the parenchyma. In the third study, the i.a., i.v., and intracisternal routes were compared (Li et al. 2010). Within 4 h, magnetic-labeled NPCs were observed in the infarcted hemisphere. With intracisternal

and i.v. delivery, the cells only appeared in the infarcted hemisphere 2–3 days later and there were significantly fewer of these cells. These results are generally consistent with the observations of the previous study. What is more interesting is that mortality in the three groups was significantly different. Forty-one percent of animals in the i.a. group died compared to 8 % in the i.v. group, which was similar to MCAO only (10 %). So while these studies both suggest that i.a. is the preferred route of delivery when it is necessary to get cells into the brain, the high mortality would suggest that caution should be used in employing this route.

2.3.3 Vascular Routes of Delivery in Clinical Studies

Both i.a. and i.v. routes have been used in clinical trial of bone marrow-derived cells. In the first study, just as reported in the animal studies, most of the cells were found in liver, lung, spleen, kidney, and bladder after i.a. delivery (Battistella et al. 2011). Only in two patients were the cells observed in the brain, but even at 6-month follow-up there were no adverse events. Another study that examined i.v. administration of bone marrow mononuclear cells also found no adverse effects that were attributable to the cell infusion (Savitz et al. 2011). Patients exhibited functional improvements on multiple neurologic scales out to 6 months. Intravenous administration of MSCs has also been performed (Bang et al. 2005). In this study, five patients with severe neurologic deficits after a stroke in the MCA territory received a total of 10^8 autologous MSCs over two injections. Imaging was performed to determine infarct volume and National Institutes of Health Stroke Scale (NIHSS), Barthel Index, and modified Rankin Scale for functional recovery. There were no significant differences at study enrolment between these patients and the control group of untransplanted patients ($n=25$). Lesion volume did not change over the ensuing year, although ventricular dilation was significantly more prominent in the control patients. There were significantly improved scores on the Barthel Index and a tendency toward improvement on the modified Rankin Scale. This research group expanded the initial study to examine survival and long-term outcomes of stroke patients with ($n=16$) or without ($n=36$) MSC transplantation after 5-year follow-up (Lee et al. 2010b). Mortality of the transplanted patients was 25 % compared to 58.3 % of the control group. There were significant improvements in the modified Rankin Scale scores of the treated group, and no difference between groups in comorbidities (such as seizures) and no side effects observed. Taken together, these data suggest that i.v. administration of MSC is safe and efficacious.

2.4 Administration into the Ventricular System

There are a few studies that have examined the ability of cell transplants in the ventricular system (i.c.v., intracisternal, or intrathecal) to migrate to the infarcted hemisphere, integrate into the local brain circuitry, and induce anatomical and functional repair in a stroke model. One of the issues, especially when there are early progenitors or stem cells within the cell preparation, is the overgrowth of the ventricles.

Folkerth and Durso (1996) published a case report in which a Parkinson's patient that had received i.c.v. transplants from a fetus 5–6 weeks of age died suddenly 23 months after transplantation. Upon autopsy, the grafts which filled the left lateral ventricle and the fourth ventricle were composed of mesenchymal and ectodermal cells, but not neurons.

2.4.1 Intracerebroventricular Route

In 1999, Kopen and associates demonstrated that bone marrow stromal cells became integrated into forebrain and cerebellum by 12 days after they were injected into the lateral ventricles of neonatal rats (Kopen et al. 1999), demonstrating that the cells were capable of migrating into the brain. While this study provided evidence that cells administered by the i.c.v. route could enter the brain, there have been few studies that have followed suit. One exception was a study that used transplantation of microglia 1 h after MCAO induction to examine the role of microglia in neuroprotective repair after injury (Kitamura et al. 2004). Those animals that were injected with microglia had significantly more neurons surviving in lesioned cortex than did vehicle-treated controls.

2.4.2 Intracisternal

When NSCs derived from subventricular zone were injected, MRI was used to track ferromagnetic-labeled NSCs from young adult rat when they were injected into the cisterna magna 48 h after MCAO (Zhang et al. 2003). Fully 85 % of the MRI signal was observed in the ischemic striatum; almost 6,000 labeled cells of the 100,000 transplanted were present by 35 days post transplant. Functional recovery on the foot fault and adhesive removal tests was observed in transplanted animals. The 6 % survival rate of the transplanted tissue is similar to that observed in other studies of neuronal transplantation.

2.4.3 Intrathecal

There have been few studies that have examined the efficacy of administering cells intrathecally. In a recent article, Seyed Jafari and colleagues (2011) examined whether adult PKH-26-labeled neural stem cells (NSCs) administered by lumbar puncture could migrate to the infarcted brain and develop into neurons and astrocytes. They found labeled cells expressing S100 and β -tubulin floating in the ventricles and attached to the ventricular wall 1 month after transplantation. Cells were not observed around the infarct, and while performance improved significantly on the Rotarod test of motor coordination, performance was still considerably impaired. Further, these authors provided no indication of how many cells were found in the brain ventricles or where else they were found. This will be critical to determine based on a recent report of an ataxia-telangiectasia patient that received NSC transplants both intracerebellar and intrathecally (Amariglio et al. 2009). Within 6 months

of treatment, the patient had developed both a brainstem tumor and a tumor at level L3–4 of the spinal cord attached to the cauda equina nerve roots; there were satellite tumors around both of the larger masses. Molecular analysis of the cauda equina tumor suggested it was derived from the NSC donor.

2.5 Other Routes of Delivery: Intraperitoneal

This route of delivery has only been applied in the stroke field in rat models of neonatal hypoxia-ischemia. The first study describing this approach injected MSC i.p. 2 h after birth and then determined location and phenotype of the cells 14 days postnatally. More cells were found in the ischemic hemisphere than on the contralateral side and few expressed neural proteins (Guan et al. 2004). No behavioral measures were employed.

More recently, two studies have expanded on this early work. In the first study, the Rice-Vannucci model of neonatal hypoxia-ischemia was used to determine the ability of human cord blood-derived mononuclear cells to repair the damaged neonatal brain (Pimentel-Coelho et al. 2010). The cells were injected 3 h after neonatal hypoxia-ischemia and a neurologic testing regimen including the cliff aversion reflex, the negative geotaxis reflex, and gait, was examined. Cord blood cells improved reflex behavior, but not gait and decreased cell death.

In the second study, Geißler et al. (2011) showed that HUCB cells were able to migrate into the brain after hypoxia-ischemia at 7 days as determined with immunohistochemistry for HLA-DR. Again no indication of how many cells survived in the brain or distribution to other tissues was given. The cells were able to induce more long-term recovery on the forelimb asymmetry test that appeared to be the result of a reorganization of cortical maps controlling sensorimotor function as determined electrophysiologically.

The choice of an i.p. delivery route is based more on ease of delivery in the neonate than any other consideration. It is not clear that this route would be efficacious in an adult. Barrier function in the neonate may not be as immutable yet as in the adult. Growth and trophic factor expression in the neonate may be more amenable to long-range migration and integration of the transplanted cells into the injured brain. These are cells that are usually found in blood, bone marrow, or lymphoid organs. They are usually extravasated into tissue from blood in response to injury or disease. They do not usually get taken up into the blood stream directly by “intravasation.” The more likely route of uptake is through lymphatic drainage of the peritoneal cavity. Further, neither research group offers an explanation of how the cells may affect functional recovery with this delivery route. These questions remain to be answered.

2.6 What Is the Best Route for Cell Delivery?

Very few studies have directly compared routes of administration. In the earliest such study, we directly compared intraparenchymal into striatum and i.v. delivery of human cord blood-derived mononuclear cells after permanent MCAO (Willing

et al. 2003). Long-term functional recovery was better with i.v. delivery; at one month post MCAO, both groups demonstrated good recovery on a battery of behavioral tests, but at two months that recovery was only maintained by the group that received i.v. cells. In fact, performance of the group receiving cells into the striatum was even worse than the MCAO-only group, demonstrating that testing at longer post-stroke survival times is essential. As discussed earlier in this chapter, comparisons among the vascular routes have also been performed, demonstrating that cells do appear in the brain after i.a. delivery, but not after i.v. or intracisternal delivery (Li et al. 2010). There are no consistent studies that look at functional recovery and infarct size across all routes of delivery. When choosing the delivery method for a study, the best approach is to first ask what the underlying mechanism of repair is. For example, if we believe that human umbilical cord blood cells reduce infarct size and improve functional outcomes by altering the systemic inflammatory milieu, then it does not make sense to implant them directly into the brain. If, on the other hand, we believe that the major benefit of a NSC therapy is through the cells ability to differentiate into neurons, astrocytes, and oligodendrocytes, then it is more appropriate to deliver them directly into the brain or i.a. than to inject them i.v. Other benefits often attributed to the i.v. route, such as lower cost, relative safety, and ease of delivery, are of minor consideration next to this. Safety risks such as demonstrated increased risk of mortality with the i.a. route or tumorigenesis must also be considered.

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