What Do We Know About the Detailed Mechanism on How Stem Cells Generate Their Mode of Action

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1. Introduction

Transplantation of stem cells may provide cures for the damaged Central nervous system (CNS). They hold an enormous potential in cell replacement therapy following traumatic brain injury (TBI) and received a great scientific and public interest in recent years. TBI remains the leading cause of long-term neurological disabilities, including cognitive, sensory, motor and emotional impairments among children and young adults. It has been suggested that stem cells hold great potential for the repair of the damaged nervous system. The therapeutic potential of stem cells has been examined in experimental brain injury using a variety of approaches. Although these results emphasized their potential therapeutic role in traumatic brain injury, crucial mechanism on how stem cells take effect, e.g. timing of stem cell implanation, stem cell survival and integration, effect of brain microenvironment and local trophic support, will be explained in this Overview of Different In-vivo/In-vitro Experimental Settings.

TBI is the leading cause of death and disability worldwide (Bruns 2003). Thus, TBI is a highly relevant medical and socio-economic problem of modern society. During the last two decades, improvements in acute pre- and inhospital care, time management, diagnostic procedures, and rehabilitation strategies have substantially improved the level of care and outcome following TBI (Maegele 2007). But still, to date, no therapeutic approach has been proven effective in reversing the pathologic cellular sequelae underlying the progression of cell loss and in improving neurobehavioral outcome. As the brain has limited capacity for self-repair, restorative approaches with focus on replacement and repair of dysfunctional and dead cells by transplantation of cells (eg stem cells) into the traumatically injured brain have been studied. In the last 15 years various types of cells have been tested for their potential to restore the function in animal models after TBI. These cells include fetal cells, adult stem cells isolated from bone marrow as well as pluripotent stem cells (see review Schouten 2004).

In the traumatically injured brain, several experimental studies have been performed using engrafted hNT cells. These are post-mitotic human neurons (NT2N cells, commercially known as hNT cells, or LBS-neurons; Layton Bioscience Inc., Palo Alto, CA), derived from a human embryonal teratocarcinoma line (NT2 cell line) and differentiated into an exclusively neuronal phenotype by retinoic acid treatment *in vitro* (Trojanowski 1993). These cells appear to possess many of the key features of normal developing and mature human neurons, and survive up to 1 year in the brain after transplantation in immunodeficient neonatal or adult mice (Trojanowski et al., 1997). Muir (1999) first transplanted hNT cells into the injured cortex at 24 h after lateral Fluid Percussion (FP) brain injury in adult rats. The hNT transplant remained viable for up to 2 weeks, although no significant effect on acute posttraumatic neurologic motor function was observed. A follow-up study reported long-term (4-week) survival of hNT cells transplanted into the injured cortex 24 h following lateral FP brain injury in non-immunosuppressed adult rats. Integration of the graft in the peri-injured cortex was noted, again without significant improvement in motor or cognitive function (Philips 1999). More recently, hNT cells genetically engineered *ex vivo* to express NGF, transplanted into the medial septum at 24 h following Controlled Cortical Impact (CCI) brain injury in mice, attenuated cognitive dysfunction for up to 4 weeks post-transplant (Watson 2003; Longhi 2005).

Bone marrow stromal cells (BMSCs) have been evaluated in the CCI model of TBI in adult rats, administered by intra-arterial or intravenous injection at 24 h post-injury were subsequently found in multiple organs, including the brain. In these studies, improvement of neurological outcome and cellular expression of both the neuronal marker NeuN and the astrocytic marker GFAP in the engrafted cells were observed at 1 and 2 weeks post-administration (Lu 2001; Mahmood 2001). Intraparenchymal transplantation of whole bone marrow into the pericontusional tissue at 24 h after CCI brain injury in rats also resulted in improved functional outcome and differentiation of transplanted cells into populations of cells expressing neuronal and glial markers up to 4 weeks post-transplantation (Mahmood 2001).The mechanism by which BMSCs limit damage or promote repair has been suggested to be either via cell replacement by proliferation and differentiation of transplanted BMSCs into the phenotype of the damaged and/or lost cells, via trophic support, or via manipulation of the environment to stimulate endogenous regeneration (Hofstetter 2002). However, Breitbach showed, that the developmental fate of BM-derived cells is not restricted by the surrounding tissue and that the MSC fraction may underlie extended bone formation. These findings seriously question the biologic basis and clinical safety of using BM and in particular MSCs to treat nonhematopoietic disorders (Breitbach 2007).

Immortalized cells, eg HiB5 cells, derived from the embryonic rat hippocampus and conditionally immortalized, were first transplanted into the neonatal brain, where they acquired neuronal and glial morphologies appropriate to the site of transplantation. Stable transduction of HiB5 cells to secrete (Nerve Growth Factor) NGF in vivo have been observed up to 9 months following transplantation into the medial septum, resulting in a prevention or reversal of cholinergic neuronal atrophy and related behavioral impairments normally occurring with age (Martinez-Serrano 1996, 1998). In non-immunosuppressed rats subjected to lateral FP brain injury, HiB5-NGF cells were transplanted in the injured cortex, 24 h after injury (Philips 2001). Thereby brain-injured animals receiving either the HiB5-

NGF cells or untransduced HiB5 cells showed significant improvements in neuromotor function and spatial learning, but hippocampal cell death was significantly reduced only in the HiB5-NGF cell transplant group, indicating that the transplantation of HiB5 cells genetically engineered to secrete trophic factors may have behavioral and neuroprotective effects after brain injury (Philips 2001).

The C17.2 cell is a clonal multipotent progenitor cell derived from the external germinal layer of the neonatal murine cerebellum, immortalized by retroviral transduction of the avian gene myc (Ryder 1990). The cells were also marked with a second retrovirus for expression of bacterial X-galactosidase. A recent study form our working group has evaluated the behavioral effects of engrafted C17.2 cells following experimental TBI. In adult mice subjected to CCI brain injury, transplantation of C17.2 cells into the cortex (either ipsilateral or contralateral to the injury) at 3 days after injury significantly improved motor function but not cognitive function over a 12-week post-transplantation period (Riess 2002). Following engraftment, the C17.2 cells expressed either neuronal or astrocytic markers when transplanted ipsilateral to the lesion, while after contralateral transplantation only neuronal differentiation was observed.

Pluripotent murine embryonic stem cells (ESC) have been shown to survive in the implanted healthy and hypoxic injured brain. Furthermore they differentiate into neural cell types following transplantation into rat brains in an experimental stroke model. Additionally it was shown, that they migrate along the corpus callosum to the ventricular walls and they populate the border zone of the damaged brain tissue on the hemisphere opposite to the implantation site, indicating that ES cells have high migrational dynamics (Hoehn 2002, Erdoe 2003). Based on these results, our working group has implanted these undifferentiated, eGFP-expressing ES-D3 cells into the ipsi- or contra-lateral cortex of rat brains following the induction of a moderate lateral fluid-percussion (FP) brain injury (Riess 2007, Molcanyi 2007).

As one result we were able to show, that the differentiation and integration of transplanted ES-D3 cells was barely observed at any time point. But sporadic tumor formation was observed. However, ES-D3 cell grafted animals demonstrated a significant improvement in functional outcome on a range of behavioral tasks. Motor function improvements were observed as early as one week following implantation. Other observers are reporting that transplantation of pre-differentiated ES cells improved behavioural outcome on sensorimotor and locomotor tests but failed to improve cognitive function during memory tasks assessed by Morris water maze (Hoane 2004). An improvement of motor function was also demonstrated when motoneuron enriched neural cells derived from mouse embryonic stem cells were transplanted after cryogenic brain injury (Chiba 2003).

However, the success of TX depends not only on cell type and their differentiation state, but also on several other important parameters, such as inflammatory response after injury, microenvironment of the host tissue, time window for TX, immune response to cell TX, immunosuppression, site of TX.

2. Location for TX

Miyazono (Miyazono 1995) demonstrated that the proliferation, differentiation and survival of implanted cells were modulated by the anatomical target site into which the

grafts were placed. The implantation of undifferentiated Ntera-derived cells into rat cortex resulted into formation of lethal tumors within 70 days posttransplantation. In contrast, the same cells implanted into caudoputamen ceased to proliferate and progressively differentiated into postmitotic neuron-like cells. Following transplantation of C17.2 NSCs following CCI brain injury, our working group was able to show, that cell differentiation depends on the location of the implantation site. Thirteen weeks after the transplantation under the contusion cavity, NSCs were found in the ipsilateral hippocampus and in the cortical parenchyma adjacent to the injury cavity. NSCs transplanted into the contralateral hemisphere were also detected in the contralateral hippocampus and the contralateral cortex. The NSCs in the injured cortex were found to express neuronal and astrocytic markers, implicating differentiation into neurons and glia, whereas the NSCs transplanted into the uninjured contralateral cortex showed an almost exclusively neuronal phenotype. The reasons underlying these apparent variations in differentiation remain unclear, although the demand for both neurons and glial cell replacement may be far greater in the areas of the injured hemisphere that have sustained significant tissue loss.

3. Timepoint for TX

Beyond cell specific effects on functional improvement following TX Soares and coworkers suggested that an optimal time window for TX may exist (Soares 1991). However, studies evaluating optimal time for transplantation in models of experimental TBI are still pending. In most studies cells were implanted between 24 and 72 hours following TBI. However this relatively early time point for transplantation may be appropriate for avoiding the peak of any inflammatory reaction and may allow the integration, migration and differentiation of cells prior to formation of the astroglial scar that may counteract these processes. Glial scar formed by CNS injury is considerd as the main inhibitory barrier of nerve regeneration. Many efforts have been made to prevent scarring and to pomote axonal regeneration after injury (see review: Sofroniew 2010). In their experiment, Soares and coworkers demonstrated that there is a temporal window in which fetal cortical transplants can attenuate glial scarring as well as be successfully incorporated into host brains following FP injury. They showed that cells transplanted two days, one week and two weeks after injury survived and were incorporated into the host tissue whereby the cells transplanted at later time points (4 weeks) failed to incorporate. This phenomenon was explained by the fact that there was a little evidence of a glial scar formation at day two and one week time points, whereas the scarring raised significantly thereafter (Soares 1991). More evidence for a optimal time window for TX is shown by comparing the following experiments in experimental Spinal Cord Injury. Han (Han 2002) reported that immediately TX of neuronal restricted progenitors (NRPs) after injury gives rise to neurons and survived for at least one month. However, after transplantation 10 days after spinal cord injury, NRPs did not give rise to neurons, suggesting that the environment of the injured spinal cord influences the implanted cells (Cao 2002). The influence of ES cells due to host environment was also proven in the following in vitro experiment. Hereby, we have shown that the extract derived from rat brains in the acute phase following TBI impairs survival of undifferentiated murine ES

cells and induces rapid differentiation of surviving cells. This observation suggests that during the early acute phase of traumatic injury the cerebral environment contains detrimental as well as protective signals that may induce neurogenic processes following ES cell transplantation (Bentz 2010). However, it is also likely that different cell types will have different transplantation time points for optimal survival, migration, and proliferation. For example, bone marrow-derived stem cells (BMSCs) have been suggested to engraft better as damage progresses in injured tissue (Prockop 2002).

4. Inflammatory response

Inflammatory leukocytic recruitment and diffuse neuronal degeneration are pathological processes resulting from TBI. While the normal brain is generally considered to be a relatively immunologically privileged organ, the injured brain is certainly not. The presence of an inflammatory response in the injured parenchyma may increase damage of the host brain in the early post-traumatic phase, while becoming more beneficial in the chronic phase (Allan 2001, Lenzlinger 2001). The effects of this inflammatory reaction on the graft survival following TX are still poorly understood. Our working group examined the time dependent fate of ES cells following ipsi- and contralateral implantation into rat brains injured via FP injury. Double-staining for GFP and macrophage antigens revealed stem cells phagocytosed by infiltrated and activated macrophages, indicating the loss of implanted stem cells was due to an early posttraumatic inflammatory response. Macrophage infiltration was shown to be less pronounced when stem cells were implanted into completely intact healthy brains. We therefore suggested that the massive macrophage infiltration at graft sites might be ascribed to the combined stimulus exhibited by the FP brain injury and the cell implantation (Molcanyi 2009).

5. Tumor formation

It has to be taken into consideration that the highly proliferative characteristics (selfrenewal potential) of ES cells combined with the ability to differentiate into all embryonic germinal layers (pluripotency) present a potential threat of tumor development (teratoma, teratocarcinoma) when they are transplanted into the adult CNS. However, tumorigenesis has been observed after implantation of undifferentiated human ESCs into healthy rat brains, giving rise to teratomas and malignant teratocarcinomas (Thomson 1998). Accordingly, Erdö compared the tumorigenic outcome after implantation of D3, clone BAC-7 ESCs in a homologous (mouse to mouse) vs. xenogeneic (mouse to rat) stroke model. In injured and healthy mouse brains, both transplanted undifferentiated and pre-differentiated murine ESCs produced highly malignant teratomas, while mouse ESCs xenotransplanted into injured rat brain migrated towards the lesion and differentiated into neurons at the border zone of the ischemic infarct, suggesting that tumorigenesis may be related to the host animal rather than to the differentiation status of the implanted cells (Erdo 2003)
Our scientific group has repeated an analogous experiment in the model of traumatic brain injury vs. healthy rat brain. After TBI we observed a scarce tumor formation, but in healthy rat brains the above mentioned cell line lead to formation of malignant teratocarcinomas in the majority of engrafted animals. The absence of tumor formation in animals suffering from

traumatic brain injury was linked to the already described inflammatory response. As we believe, the tumorigenic fraction of implanted graft may have been scavenged by activaed macrophages, alongside with concomitant survival of stem cells turning into healthy neural phenotypes. Great caution is needed when stem cells are implanted in experimental settings of diseases associated with inflammatory response (such as stroke or traumatic brain injury) as the tumorigenic threat may stay unveiled (in case tumorigenic fraction is being removed by activated immune cells) (Molcanyi 2009).

6. Functional outcome

Neurobehavioral assessment of outcome has always played an integral part in traumatic brain injury (TBI) research (Hamm 2001).

After transplantation of the C17.2 Neural Stem Cells intracerebrally in the acute period after TBI we were able to show, that these cells survive, differentiate, and attenuate posttraumatic neurological deficits in the chronic postinjury period. Brain-injured mice that received NSC transplants showed significantly improved performance in the rotating pole test during the 8-week observation period. In addition, brain-injured animals that received NSCs in the ipsilateral hemisphere exhibited improved performance in the rotarod test during the 12-week observation period. Similar effects were achieved by, transplantation of undifferentiated ES cells following experimental traumatic brain injury. Hereby the TX significantly attenuates the impairment of motor function. Performance on the rotarod test and sensorimotor scores improved significantly when brain injured animals received ES cells. This is in accordance with previous brain injury studies that also reported recovery of function following cell transplantation. Improved behavioural outcome on sensorimotor and locomotor tests in brain injured animals was also demonstrated following transplantation of pre-differentiated ES cells, or minced fetal cortical grafts (E16), respectively (Hoane 2004).

But, the effects on neurobehavior outcome can be influenced by the medication the animals receive. Cyclosporin A (CsA) is widely used in clinical situations to attenuate graft rejection following organ and central nervous system transplantation. Therefore, we evaluated the influence of post-injury CsA administration on behavioral recovery after TBI. Hereby we found that, injured animals treated with CsA showed a significant improvement in motor function and in sensorimotor function, when compared to vehicle treated, injured animals. In conclusion, the treatment with CsA improves certain aspects of motor and sensorimotor function following experimental TBI. Therefore in animal studies analyzing functional outcome, these effects have to be controlled for (Riess 2001).

However, all the mechanisms of how stem cells attenuate a neurologic impairment are not completely clarified, yet. In the light of the recent data, the true cell replacement of lost/injured tissue seems to be highly unlikely. Humoral/trophic mechanisms accompanied by cell-cell interactions have been proposed to play a central role of stem cell grafting effect. Our scientific group has investigated the behaviour of stem cells in-vitro after conditioning with the cerebral extract derived from healthy and injured rat brain. Stimulated cells have produced statistically significant amounts of various neurotrophic factors, proving this phenomena to be possibly one of the regenarative mechanisms following stem cell transplantation (Bentz 2007).

7. Conclusion and further prospectives

In the present review we have summarized our experience with in-vivo and in-vitro set-ups of cell therapy in TBI. Our results demonstrate the influence of brain microenvironment on alterations on stem cell fate, the significance of appropriate timepoint for TX and the effect of the time dependent inflammatory response following TBI. However, despite the promising results concerning functional improvement following ES cell TX following TBI the clinical use of ES cells is complicated due to ethical and immunological concerns (Molcanyi 2007, Riess 2007, Erdö 2003). These concerns might be overcome by using autologous pluripotent stem cells derived from a patient's own somatic cells by ectopic expression of pluripotency factors (Hochedlinger 2006). These, induced pluripotent stem (iPS) cells are widely recognised as a powerful alternative to ES cells as potential therapeutic agents, with unique advantages. Like ES cells, they are pluripotent and can be used to obtain tissue-specific cells or progenitors of therapeutic interest (such as neurons and their progenitors). But on the other side, iPS cells are likely to carry a higher risk of tumorigenicity than ES cells, due to the inappropriate reprogramming of these somatic cells, the activation of exogenous transcription factors, or other reasons (Tsuji 2010). In a most recent study it has been shown that the transplantation of iPS-derived neurospheres into the spinal cord directly after contusive injury in mice resulted in cell differentiation into all three neural lineages without forming teratomas or other tumors. These cells also participated in remyelination and induced the axonal regrowth of host 5HT-positive serotonergic fibers, promoting locomotor function recovery. These findings suggest that iPS cell-derived neurospheres may be a promising cell source for therapy of spinal cord injury (Tsuji 2010). It is required, that the therapeutic potency of these cell-source will also be evaluated in models of TBI to prove their effectiveness and safety as a clinical therapy for human after TBI.
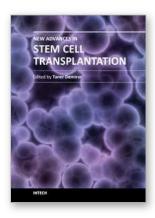
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New Advances in Stem Cell Transplantation

Edited by Prof. Taner Demirer

This book documents the increased number of stem cell-related research, clinical applications, and views for the future. The book covers a wide range of issues in cell-based therapy and regenerative medicine, and includes clinical and preclinical chapters from the respected authors involved with stem cell studies and research from around the world. It complements and extends the basics of stem cell physiology, hematopoietic stem cells, issues related to clinical problems, tissue typing, cryopreservation, dendritic cells, mesenchymal cells, neuroscience, endovascular cells and other tissues. In addition, tissue engineering that employs novel methods with stem cells is explored. Clearly, the continued use of biomedical engineering will depend heavily on stem cells, and this book is well positioned to provide comprehensive coverage of these developments.

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