Cellular repair of CNS disorders: an immunological perspective

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Cellular repair is a promising strategy for treating central nervous system (CNS) disorders. Several strategies have been contemplated including replacement of neurons or glia that have been lost due to injury or disease, use of cellular grafts to modify or augment the functions of remaining neurons and/or use of cellular grafts to protect neural tissue by local delivery of growth or trophic factors. Depending on the specific disease target, there may be one or many cell types that could be considered for therapy. In each case, an additional variable must be considered—the role of the immune system in both the injury process itself and in the response to incoming cells. Cellular transplants can be roughly categorized into autografts, allografts and xenografts. Despite the immunological privilege of the CNS, allografts and xenografts can elicit activation of the innate and adaptive immune system. In this article, we evaluate the various effects that immune cells and signals may have on the survival, proliferation, differentiation and migration/integration of transplanted cells in therapeutic approaches to CNS injury and disease.

INTRODUCTION

Cellular transplantation has been considered for therapy for more than 100 years. One of the first tissue grafting experiments reported in the scientific literature was performed by W.G. Thompson in the late nineteenth century. Dr. Thompson transplanted pieces of neocortex from one dog to another dog—with outcome described as ‘that the brain tissue has sufficient vitality to survive for seven weeks the operation of transplantation without wholly losing its identity as brain substance’ (1). In the intervening years, a myriad of transplantation strategies have been tried in both animals and humans.

One of the most well-explored human models involves tissue or cell transplantation for the treatment of Parkinson’s disease (PD). The goal has been to restore the abundance of dopamine—a chemical neural transmitter produced by the cells that die in PD. Levo-DOPA, the precursor to dopamine, can be taken orally and is the standard of care but the dosage must be increased as the disease progresses and the side effects of systemic delivery eventually outweigh the benefit. Transplantation of dopamine producing cells has been pursued as a way to produce dopamine only where needed. Various tissue sources rich in dopamine have been used including adrenal medulla, carotid body and embryonic ventral mesencephalic tissue (the ventral mesencephalon is the brain region where the dopaminergic neurons affected in PD normally reside). Each tissue type has shown promise in animals and has ultimately been tested in clinical trials. Adrenal medulla and carotid body transplantation gave only modest and transient improvement though this has not continued in widespread use (2,3). In contrast, over 300 patients have been transplanted worldwide with human fetal ventral mesencephalic tissues. It has been shown that the transplanted dopaminergic neurons can survive and re-innervate part of the host striatum. Dramatic effects have been observed in some individuals (4). As might be imagined, human fetal tissue is not in abundant supply and it has been very difficult to standardize transplantations, and variability and potential negative side effects have plagued this strategy [reviewed by (5)]. In a double-blind clinical study, more than 50% of patients receiving bilateral fetal nigral transplantation developed “off”-medication dyskinesia [e.g. uncontrolled movement (6)]. The authors speculate that dopamine asymmetries across grafted striatum, altered synapse formation and partial immune rejection, may have caused this effect.

Alternative tissue sources are being considered for central nervous system (CNS) transplantation. A common goal is to gain control of the specific attributes of the transplanted

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cells and improve efficacy. Cellular grafts, such as those generated from embryonic stem cells (ESCs), fetal tissue-derived neural stem cells, adult neural stem cells, stem cells transdifferentiated from other types of adult tissues and xenogeneic tissue/cell grafts may provide the consistency and reproducibility needed for bringing transplantation therapy into mainstream clinical use [reviewed by (7)].

**THERAPEUTIC STRATEGIES**

**Cell grafts to modify a disease or injury process**

One of the most promising applications of cellular grafts in the CNS is to use the graft to modify the disease or injury process and thus protect from further decline of function. This can be potentially accomplished using grafts that locally produce growth factors or immune modifying signals. For example, glial cell-derived neurotrophic factor (GDNF) is a potent neuroprotective agent for dopaminergic neurons, and GDNF infusion into PD patient brains has shown early clinical efficacy (8). As an alternative to continuous mechanical delivery, cells have been considered as vehicles for the stable and long-term delivery of GDNF at a transplant site. Work by Svendsen et al. provides a good key example of this strategy using human fetal brain tissue-derived neural stem cell cultures. In this model, transplant of human neural progenitor cells (hNPCs) that have been genetically engineered to produce high levels of GDNF were introduced into the rodent and non-human primate striatum in models of dopamine cell death related to PD. The cells survived at least 3 months and enhanced host dopamine cells survival and fiber outgrowth (9).

Cell transplant for disease or injury modification is also considered in spinal cord injury (SCI). Bone marrow cells are known to modulate the microenvironment of the spinal lesion by protecting against excitotoxicity (10), secreting support proteins, such as brain natriuretic peptide, brain-derived neurotrophic factor (BDNF) and GDNF (11–13). This combination of natural modifying effects appears to provide a permissive growth substrate for limited native regeneration and also suppresses the destructive inflammatory processes that lead to sub-acute tissue loss, and animals show reduced cavity formation and lesion volume (14). Bone marrow cells can also be easily isolated from a patient’s own marrow, thus avoiding any concern over tissue matching and graft rejection.

Similar strategies are contemplated for treatment of multiple sclerosis (MS). Experimental autoimmune encephalitis (EAE), a rodent model for MS, is often used to study the immune brain interaction that underlies the MS disease process. Transplantations of appropriately primed immune cells that modify the ongoing destructive inflammatory process have shown efficacy in animal models (15). Unexpectedly, even NPCs themselves appear to have immunomodulatory effects that can be beneficial. Pluchino et al. (16) have injected adult NPCs directly into the brain or, curiously, even through intravenous routes, and found that the cells home to areas of MS lesions. At these sites, they note reductions in immune cell content and improvements in remyelination, mediated both by the infused NPCs and also by enhanced activity of endogenous oligodendroglia.

**Cell grafts to replace neurons or glia**

Throughout the history of cellular therapy in animals and humans, the ultimate goal has been to replace damaged neural circuitry. This would require replacement of neurons that were lost due to the injury or disease as well as supporting cells such as glial and vascular cells. Such extensive remodeling, however, has been very hard to achieve. In PD rodent models, fetal tissue grafts placed into the substantia nigra—the normal location for neurons lost in PD—failed to extend axons to the normal target areas in the striatum and no functional benefit was achieved (17). Transplantation of dopaminergic cells directly into the striatum does allow the cells to integrate and provide local dopamnergic inputs, and this has led to success in animals and variable but promising outcome in humans. Human embryonic stem cells now provide one of the only known alternatives for producing human midbrain dopaminergic neurons in large numbers without resorting to human fetal brain tissues. Relatively standardized protocols have been established to differentiate ES cells into midbrain dopamine neural precursors and transplants of those ES-derived cells into rodent parkinsonian models have shown survival of tyrosine hydroxylase (TH) positive cells and significant improvement of motor tests (18,19). Multiple groups are progressing towards clinical trials but much work remains to adequately control the risks that may be associated with the use of these cultured cells—the most important being the risk of tumor formation if the graft contains undifferentiated hESC (20).

Many other CNS injuries or diseases accompany PD as early targets in cellular therapy. As in PD, the goal often focuses on replacing or augmenting neural circuit function by adding neurons. However, other cell types in the brain are equally important therapeutic candidates. In spinal injury and MS, a loss of myelinating oligodendrocytes in the white matter is one of the key features of the injury or disease process. Transplantations of oligodendrocyte progenitor cells have been shown effective in animal models (21,22). Until recently, sources of renewable human oligodendrocyte progenitor cells have not been readily available but Keirstead et al. (23) have recently shown that hESC can be used to derive human oligodendrocyte progenitor cells and that transplantation of these cells into adult rat spinal cord injuries enhances remyelination and promotes improvement of motor function. Although still early in preclinical validation and safety testing, Keirsted and his corporate partner Geron are moving quickly toward clinical trials in spinal injury with this approach [reviewed by (24)].

**IMMUNOLOGICAL CONSIDERATIONS**

Human embryonic stem cells are thought to be one of the most promising new technologies available for CNS therapies, but the hESC lines derived from blastocysts will never provide an exact tissue match. One issue that has remained a concern with transplants of allogeneic tissue to the brain is the role of immune recognition in transplant outcome and efficacy. Immune processes are specialized within the brain and differ considerably from immunological processes in the periphery. Grafts of poorly matched tissue can be well tolerated.
However, the immune system effects—either elicited by the injury/disease or in response to the transplant—may still strongly influence the efficacy of a given approach. The involvement of immune cells in human transplant paradigms is well illustrated in post-mortem evaluation of fetal tissue grafts introduced into the brains of PD patients. Two cases have been evaluated involving dissociated fetal nigral tissue implants with immunosuppressant treatment of cyclosporine for 6 months. In both instances, the patients died of unrelated causes at roughly 18 months after transplantation. Numerous immune cells including macrophages, CD4-positive or CD8-positive T cells and B cells were present at the graft site. Immune cells were absent from adjacent areas of the brain suggesting that the unmatched grafts were recognized, even though robust dopamine neuron survival was observed even after cessation of cyclosporine (25). Whether the sum total of immune cell influence plays a net protective or detrimental role remains undetermined.

The innate immune response in the brain

The innate immune response serves as the first line defense against bacterial and viral pathogens and also is evoked in the acute stages of tissue injury. In the periphery, this response is triggered by neutrophils, natural killer cells, dendritic cells and macrophages. In the CNS, microglia and astrocytes have similar roles in mounting an innate immune response.

Microglia. Microglia sense changes in the local milieu through ‘pattern recognition’ receptors, which are receptors that recognize stereotypical proteins or antigens produced by pathogens or released from tissues following injury or severe stress. These receptors recruit adaptor proteins within responding immune surveillance cells and subsequent activation of the NF-κB pathway leads to the production of proinflammatory cytokines and other ligands that mediate the initial immune activation response. These classically include tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, prostaglandin E2 (PGE2), adenosine triphosphate, nitric oxide (NO), BDNF etc. (26–29).

Astrocytes. Although the CNS strongly relies on microglia for innate protection, increasing evidence demonstrates that astrocytes also participate in the innate immune response. Astrocytes express Toll-like receptors, mannose receptor and complement receptors, each of which upon activation, can stimulate production of soluble immune mediators, including proinflammatory cytokines, chemokines and neurotrophic factors [reviewed by (30)].

Adaptive immune response in the brain

The brain was once regarded as an immune privileged organ, incapable of mounting a tissue rejection response. However, it is now known that this privilege is not absolute. Decades of research have shown that xenografts are rejected in <30 days in immune competent hosts. The process is indeed slower than for tissues placed peripherally, yet rejection ultimately proceeds to complete clearance of the grafted tissues (31) and the aggressiveness of the response appears to be related to the donor–host phylogenetic distance (i.e. extent of evolutionary separation) (32).

In the periphery, the adaptive response is initially triggered by the release of innate proinflammatory cytokines. These activate local vasculature as well as circulating lymphocytes. The activated lymphocytes must then enter the CNS where they encounter foreign antigens and are further activated and amplified to carry out cytolytic elimination of the foreign tissue. It appears that activated CD4 T cells are capable of crossing blood brain barrier (BBB) regardless of the antigen specificity, perhaps even in the absence of an inflammatory focus (33). Activated CD8 T cells enter brain through an antigen-specific pathway (34). The necessary disruption of BBB during the surgery required for cellular or tissue transplant also assists the recruitment of peripheral components of the immune system.

There is considerable interplay between central and peripheral immune processes. For example, stimulation of a peripheral graft rejection response can precipitate the rejection of a previously introduced CNS graft. Dissociated embryonic ventral mesencephalic tissue from Lewis rats was injected into the striatum of allogeneic Sprague-Dawley rats following lesion of the endogenous dopamine system to mimic PD. The recipient rats were challenged with Lewis rat skin graft either simultaneously with the CNS graft or after 2 or 6 weeks. All the neural allografts introduced with a simultaneous peripheral graft were completely rejected. A delayed peripheral challenge had reduced effects but in each case the number of surviving dopamine neurons from the transplant was significantly reduced, demonstrating that adaptive immune responses can influence allograft survival and function at anytime following transplantation if the peripheral immune system is adequately activated (35).

T cells play an important role in xenograft survival. Xenograft rejection is typically much more aggressive than seen for more closely matched allografts, yet graft survival can be dramatically prolonged with CD4+ T lymphocyte depletion. Administration of two successive high doses of anti-CD4 monoclonal antibody treatments results in indefinite concordant (between closely related species) neural xenograft survival; anti-CD4 monoclonal antibody treatment enhances discordant (between distantly related species) neural xenograft survival but not indefinitely. The study indicates important roles of CD4 T cells in concordant xenograft rejection and also implies the involvement of immune components other than CD4 T cells in discordant xenograft rejection (36).

B Cells and immunoglobulin are also important in graft survival and function. The importance of immunoglobulin is addressed by comparison of discordant xenograft (suspension of embryonic porcine ventral mesencephalon) survival between immunoglobulin deficient and normal mice. The majority of immunoglobulin knockout mice had surviving grafts for up to 4 weeks, whereas survival was minimal in control mice beyond 4 days. The data suggest that immunoglobulins play an initiating role in the rejection of discordant neural xenografts. After a prolonged graft survival of ~4 weeks, a cellular response with a large proportion CD8-positive cells leads to rejection in immunoglobulin knockout mice (37).
ADDITIONAL CONCEPTS IN IMMUNE SIGNALING EMERGING FROM THE STUDY OF NEURAL STEM/PROGENITOR CELLS

Graft rejection is not the only outcome measure that is important in transplantation therapy. In parallel with the translational and clinical studies discussed above, literature is also accumulating that describes effects of immune signaling on cell survival, proliferation, differentiation, migration and functional integration—each of these are critical processes that control overall outcome. Although these processes would affect any graft-based strategy, the effects have become particularly evident in studies that use neural stem and progenitor cells (Fig. 1).

Cell survival

Oxidative stress. Reactive microglia, macrophages and proinflammatory T cells are the primary source of free radicals in brain. Free radicals can be sub-categorized into reactive oxygen species (ROS) and reactive nitrogen species (RNS), both of which can modify proteins, lipids and nucleic acids. NO expression is upregulated in inflammatory contexts by many types of cells in brain. Microglia-derived ROS cannot traverse cellular membranes efficiently and thus is not of much harm to transplanted grafts. However, once ROS react with NO in the extracellular space, the resulting peroxytnitrite can readily cross cell membranes and damage intracellular components [reviewed by (38)].

T cell–NPC interaction. CD80 and CD86 are well-studied co-stimulatory molecules that modulate T cell activation and cytolytic response in the peripheral system and are normally produced on the membrane of antigen presenting cells. Interestingly, endogenous NPCs at the subventricular zone also express CD80 and CD86. Expression of CD80 in NPCs is upregulated by proinflammatory cytokines TNF-α and interferon-γ (IFN-γ), and cross-linking of the NPC’s surface CD80 with ligands present on T cells induces apoptosis of NPCs (39).

Microglia–neuron direct interaction. Neurons produced by stem cells would also be affected by immune status in the transplant site. Using an oxygen–glucose deprivation (OGD)-induced injury model, Neumann et al. (40) found that microglia engage in close physical cell–cell contact with neurons in tissue culture and can protect against ischemic neuronal damage when added to the neuron culture 24 h before and up until 4 h after OGD, but not at 6 h after OGD. The protective effect is not seen from lipopolysaccharide-pretreated microglia that are placed into a strong proinflammatory state showing that the effects of resident immune cells are dependent on the specific inflammatory status of cells that may interact with the incoming graft. The authors claim that there may be a short ‘protective time window’ for microglia in acute injury such as trauma or stroke. However, chronic activation microglia may alter immune cell status and generate detrimental effects in the sub-acute or chronic stage of the injury response.

Tumor necrosis factor-α. Tumor necrosis factor-α, FAS ligand and TRAIL all belong to the TNF superfamily and are mediators of apoptotic signaling. Up to date, evidence is lacking that TNF-α, FAS ligand or TRAIL pathways have direct effects on the apoptosis of NPCs (41,42) but the oligodendrocytes and neurons derived from NPCs (that ultimately provide therapeutic benefit) are sensitive to immunologically induced TNF-α cell death mechanisms. Some reports indicate that TRAIL is involved in cellular death in MS. Both microglia and T lymphocytes express TRAIL following immune activation (43,44) whereas oligodendrocytes and mature neurons produce TRAIL receptors. Ligation of TRAIL receptors induces death of oligodendrocytes in an in vitro system (45). Blockade of TRAIL after induction of EAE substantially reduces clinical severity whereas intracerebral delivery of TRAIL to animals with EAE substantially increased clinical deficits (46). Cellular therapies that target such environments will need to address the ongoing inflammatory processes in order to maximize the potential efficacy.

Proliferation

Cell proliferation following grafting can influence the overall abundance of cells that survive transplant. Some cytokines can directly influence the proliferation of NPCs. TNF-α is upregulated in many CNS disorders and acts through TNFR1 and TNFR2. The proliferation of endogenous NPCs at the dentate gyrus is increased in the TNFR1 −/− but not the TNFR2 −/− mice in both the intact and injured status epilepticus brain, indicating that TNFR1 is a negative regulator of neural progenitor proliferation (47). Another cytokine produced in response to inflammatory signaling is transforming growth factor-β1 (TGF-β1). It arrests NPCs in the G0/G1 phase of the cell cycle but does not affect the self-renewal capacity or the differentiation fate of these cells (48,49).

Differentiation

Interleukin-6. Neural progenitor cell differentiation is regulated at many levels and one of the best characterized signaling pathways involves the action of notch and notch ligands, delta and jagged. Notch signaling inhibits neural stem cells from adopting neuronal fate by stimulation the transcriptional activation of notch receptor and its signaling partner gp130. The IL-6 receptor also uses a gp130-mediated signaling pathway and recent work shows that IL-6 promotes astrocyte differentiation via the activation of the JAK/STAT and MAPK pathways (50). Overexpression of IL-6 in animals inhibits natural neurogenesis (51) and blockade of IL-6 present in conditioned medium from activated microglia has been shown to prevent the suppression of neuronal differentiation when NPCs are exposed to microglial signaling molecules in vitro (52).

Transforming growth factor-β. Transforming growth factor-β is also implicated in altering NPC differentiation, particularly at the level of neuronal subtype specification. There are three isoforms of TGF-β, TGF-β1, TGF-β2 and TGF-β3. In brain, TGF-β2, TGF-β3 and TGF-β receptors are widely distributed, whereas TGF-β1 is expressed mostly in response to injury.
and/or aging. TGF-β2 and TGF-β3 are essential signals for differentiation of midbrain progenitors toward neuronal fate and dopaminergic phenotype. Treatment of dissociated neurospheres isolated from ventral midbrain with TGF-β increases the number of TH-immunoreactive cells.

In vivo, TGF-β2/TGF-β3 double-knockout mouse embryos revealed significantly reduced numbers of TH-labeled cells in ventral mesencephalon. In addition, TGF-β may ectopically induce TH-immunopositive cells in dorsal mesencephalon in vitro, in a sonic hedgehog (Shh)- and fibroblast growth factor (FGF8)-independent manner (53).

TGF-β2 signaling is known to be affected by inflammation in the CNS. In the chronic relapsing EAE model of MS, TGF-β2 expression is downregulated, in contrast to the upregulation of TGF-β1. IFN-γ, TNF-α and other factors from activated microglia suppress astrocyte-mediated TGF-β2 secretion (the major intracerebral producers of TGF-β2), whereas activated microglia induce TGF-β1 expression through soluble factors. Reciprocally, TGF-β2 can influence the functions of microglia by downregulating major histocompatibility complex class II expression and costimulatory/adhesion molecules—and thus alter the mechanisms by which microglia modulate T cells and cytolytic responses in the CNS (54).

Inflammation modulates effect of neuronal activity on NPCs?. Neuronal activity has been shown to be one of the determinants involved in the differentiation of neural stem cells into neurons. NPCs can sense local neuronal activity through NMDA receptors and L-type calcium channels. Excitation of NPCs through this pathway acts to inhibit expression of the glial fate genes Hes1 and Id2 and increase expression of NeuroD, a positive regulator of neuronal differentiation (55). TGF-β2/3 is also known to be upregulated by neuronal activity in an in vitro culture system, thus further promoting neuronal differentiation (56). Neuronal activity is also
necessary for the integration of newborn NPCs within the adult dentate gyrus. Ambient γ-aminobutyric acid (GABA) released within the hippocampus accompanied with neuronal activity initially exerts an excitatory action on newborn neurons owing to their high cytoplasmic chloride ion content. GABA-induced depolarization is necessary for the subsequent neuronal integration since conversion of GABA-induced depolarization (excitation) into hyperpolarization (inhibition) in newborn neurons leads to marked defects in their synapse formation and dendritic development (57). Whether and how inflammatory signaling may affect the activity-induced neurogenesis is almost entirely unknown yet remains a very interesting question.

Migration and integration

Regeneration is inhibited in an injury context. After spinal injury, resident microglia become activated, and macrophages, neutrophils and T cells migrate in from the periphery. The inflammatory environment can ablate the neural differentiation of endogenous NPCs as well as inhibit the axonal growth of transplanted NPCs into injured spinal cord. Cytokines produced during SPI, such as IL-1 and IFN-γ, assist in the initiation and propagation of astrogial scar formation, which forms a physical barrier as well as produces molecules that inhibit axonal growth (58,59). Chondroitin sulfate proteoglycans (CSPGs) generated by astrogial scar tissue and Nogo on oligodendrocytes have been shown to be important in suppressing axonal regeneration (60).

Glial activation and subsequent scar formation are uniformly associated with the inhibition of endogenous regeneration. Transplanted cells can be equally affected and it is known that allograft or xenograft response can further stimulate immune signaling and contribute to poor axonal growth of endogenous and transplanted neural progenitors. Researchers have speculated that regenerative capacity may be greatly enhanced in the absence of the injury process. This concept is supported by data from the Macklis lab showing that the endogenous adult NPCs in the cortex of the brain can differentiate into highly complex long-projection motor neurons and send new projections to distant targets if the local tissues are not disrupted by aggressive injury or degenerative processes. They achieved this by loading a photo-activatable dye into neurons and then selectively ablating these neurons with laser light. This led to discrete apoptosis of specific neurons in the absence of gross tissue disruption. Endogenous neural progenitors produced new neurons that reconnected to distant spinal cord targets (61), reconstructed interhemispheric connections (62) and corticothalamic connections (63). They also identified that insulin-like growth factor-1 (IGF-1) is one of the key factors that enhances axonal growth while BDNF promotes arborization and branching (64).

**DURAL ROLE OF INFLAMMATION**

Of course, the effect of immune system in the CNS is complex. There is also evidence that immune components play supportive roles in cellular repair. The immune cells can produce BDNF, nerve growth factor (NGF), neurotrophin-3 (NT-3), NT-4/5, GDNF and leukemia inhibitory factor (LIF) etc (65). The trophic effects of immune cells can become more pronounced in specific experiment settings. It seems that the net effect in any particular pathological situation is determined by the balance of pro-inflammatory versus immunomodulatory signaling. It may be possible to manipulate the activity of immune cells to bias them towards a more supportive direction.

Work from Schwartz et al. (66) clearly demonstrates that microglia can exist in either beneficial or detrimental signaling states depending on how they were stimulated. For example, it is known that treatment of microglia with lipopolysaccharide stimulates a pro-inflammatory state that strongly inhibits neurogenesis from NPCs but microglia treated with the immunomodulatory cytokine IL-4 results in immune signaling that is strongly supportive of NPC-mediated neuron production and retention (67). As above, they found that this is mediated, in part, by the strong upregulation of IGF-1. Overall, there is clear motivation to better understand how immune signaling status influences regenerative mechanisms and the efficacy of cellular therapies.

**NEW STRATEGIES AND INTERVENTIONS**

There are many transplantation-based strategies considered for therapy in the CNS, and the choice of cell type transplanted can vary from neural stem/progenitor cells to partially differentiated neurons, astrocytes or oligodendrocytes. The specific makeup of the graft will be strongly influenced by the condition being treated. For example, intervention early in a degenerative disease process may focus on neuroprotection by transplant of cells that produce a protective effect, either by growth factors that promote the health of the affected brain region or by modifying the injury or degeneration-induced immune response. Replacement of cells is also contemplated and the introduction of oligodendrocyte progenitors is progressing rapidly toward clinical applications. Restoration of neuronal circuitry is more complicated and additional work is needed to identify ways to improve differentiation and axonal connections that restore or augment function. Regardless of the specific goals, it is becoming increasingly obvious that outcome will be strongly influenced by the immune signaling in the damaged CNS.

Immune signaling can influence the outcome of cellular therapy at several levels (Fig. 2). Inflammation from a prior injury or continuing disease can impair cell survival, differentiation and connectivity. Immune recognition of the incoming cells can also have similar effects as well as risk of outright graft rejection. Immune response to the incoming cells has typically been addressed with immunosuppressive drugs such as cyclosporine which blocks T-cell cytolytic responses. Chronic use of immunosuppressive drugs places the patient at risk and most clinical studies have discontinued the use after a period of time—the impact of which is not well understood.

In recent months, several advances have now made it possible to contemplate stem cells that are generated from an individual’s own somatic cells. One method involves the introduction of a somatic cell nucleus into an oocyte to effectively reprogram the genome. Nuclear reprogramming through
somatic cell nuclear transfer (SCNT) was recently accomplished in old world primates, suggesting that human SCNT will follow with minimal delay (68). A somatic cell nucleus can also be reprogrammed by genetic modification and such strategies have come to fruition with human cells, though some work remains to determine whether this reprogramming can be accomplished without permanently altering the genome by inserting foreign genes (69, 70). Both strategies—SCNT and genetically-induced pluripotent stem cells—are capable of generating embryonic stem cells that are identical to the donor.

The use of autologous stem cells would be a major step forward in avoiding immune complications but neither autografts nor the use of traditional immunosuppressive drugs would entirely prevent the activation of the innate response. Cellular transplantation will always be subject to immunological signaling, either as a result of the injury or disease or simply as a result of the minor injury caused by injecting cells. Here, methods to modify the innate response are needed, and a recent work shows that the use of non-steroidal anti-inflammatory drugs (NSAIDs) to modulate the innate response shows significant promise. In two separate injury models affecting the hippocampal formation, broad spectrum NSAIDs were shown to partially restore the natural regenerative process of neurogenesis observed in adult animals (66, 71). Other strategies might include the introduction of cells that specifically modify the inflammatory state, such as pre-treated microglia (67) or bone marrow-derived immunomodulatory cells (72, 73). Even the use of specific agonists or antagonists of immune signaling molecules may improve outcome and it is likely that the future will bring about highly specialized interventions that target the specific signaling and cellular requirements relevant to a given disease and brain region. The future of CNS therapies may indeed become highly personalized with the tailored application of cells, drugs and other interventions that specifically address the needs of a specific individual.

CONCLUDING REMARKS

Immunological signaling can affect the outcome of cellular repair at many different levels and through multiple cellular or molecular mediators. The complexity of CNS disorders and the pleiotropic effects of immunological components warrant careful consideration of each application and a careful search for the best cellular source for individual CNS disease and combinational therapeutic intervention to achieve optimum clinical effects.

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