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Stem Cell Therapies for the Resolution of Radiation Injury to the Brain

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Abstract

Purpose of review—To encapsulate past and current research efforts focused on stem cell transplantation strategies to resolve radiation-induced cognitive dysfunction.

Recent Findings—Transplantation of human stem cells in the irradiated brain was first shown to resolve radiation-induced cognitive dysfunction in a landmark paper by Acharya *et al.*, appearing in PNAS in 2009. Since that time, work from the same laboratory as well as other groups have reported on the beneficial (as well as detrimental) effects of stem cell grafting after cranial radiation exposure. Improved learning and memory found many months after engraftment has since been associated with a preservation of host neuronal morphology, a suppression of neuroinflammation, improved myelination and increased cerebral blood flow. Interestingly, many (if not all) of these beneficial effects can be demonstrated by substituting stem cells with microvesicles derived from human stem cells during transplantation, thereby eliminating many of the more long-standing concerns related to immunorejection and teratoma formation.

Summary—Stem cell and microvesicle transplantation into the irradiated brain of rodents has uncovered some unexpected benefits that hold promise for ameliorating many of adverse neurocognitive complications associated with major cancer treatments. Properly developed, such approaches may provide much needed clinical recourse to millions of cancer survivors suffering from the unintended side effects of their cancer therapies.

Keywords

Ionizing radiation; Cranial Irradiation; Stem cells; Transplantation; Cognitive dysfunction

Introduction

Radiotherapy comprises one of the principle therapies for primary and metastatic brain tumors in addition to chemotherapy and surgery, with approximately 200,000 patients receiving brain radiation treatment each year in the United States [1]. These treatments have

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Compliance with Ethical Standards

Conflict of Interest

Sarah M. Smith and Charles L. Limoli declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

become increasingly effective in improving the prognosis for patients afflicted with central nervous system (CNS) cancers. As progress has been made in the early detection and treatment of cancer, survival rates have increased [2], adding to the importance of preserving the quality of life for cancer survivors. One of the most common and most damaging iatrogenic effects of cancer treatment is cognitive dysfunction, including impairments in working memory, learning ability, executive function, and attention, with the neurocognitive sequelae typically manifesting many months to years following the cessation of treatment [3–7]. Each year, roughly 100,000 patients with brain tumors survive for at least six months, which is sufficient time for the development of radiation-induced cognitive decrements, which afflict between 50% and 90% of adults who survive at least that long with some degree of impairment [8, 9].

The deleterious effects of cranial ionizing radiation exposure are progressive, particularly in pediatric populations, and are exacerbated with increasing dose, volume of irradiated brain, and by concomitant use of chemotherapeutic agents that elevate neurotoxicity. While the precise mechanisms underlying radiation-induced cognitive dysfunction remain to be elucidated, much of the underlying pathology believed to be contributory if not causal is related to decreased hippocampal neurogenesis, increased neuroinflammation (activated microglia and pro-inflammatory cytokines), microvascular injury, and alterations in neuronal structure that disrupts dendritic morphology, spine density and synaptic proteins [1, 8–11]. Increased oxidative stress likely plays a critical role, by perpetuating cycles of inflammation and damage that prolong the signature of radiation injury in the brain [12–14]. Pharmacologic therapies currently under investigation to either prevent or restore neurocognitive functionality after radiation treatment are limited, and include anti-inflammatory agents such as peroxisomal proliferator-activated receptor agonists, renin-angiotensin system blockers such as angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers, and inhibitors of adenosine kinase [8, 15]. Stem cell-based transplantation strategies have also shown considerable promise in ameliorating the negative effects of cranial irradiation. Given the prominent role that cognitive health plays in the quality of life for survivors of brain tumors [16], continued exploration and refinement of stem cell therapies to treat radiation-induced cognitive decrements could have a profound effect on the lives of thousands of cancer patients, particularly those surviving childhood malignancies.

Stem cells and regenerative medicine

Stem cell-based interventions have been investigated to repair and regenerate radiation-associated injuries outside of the brain as well (for review see [17]). Radiation-induced lung injury, such as pneumonitis and fibrosis, is a critical complication of radiotherapy for thoracic cancers [18, 19]; caudal vein injections of mesenchymal stem cells abated early lung damage, oxidative stress, and radiation-associated increases in proinflammatory and profibrotic cytokine plasma concentrations in mice that underwent thoracic irradiation, increasing survival while attenuating lung fibrosis [20, 21]. Salivary gland damage as a result of irradiation to treat head and neck cancer can result in chronic xerostomia [22]. Cells isolated from murine submandibular glands and cultured into salispheres have yielded cells expressing stem cell markers such as c-Kit [23]. Transplantation of these stem cell

preparations into irradiated salivary glands of mice has been shown to recapitulate the morphology of unirradiated glands and dramatically increase saliva production [24, 22, 25, 23]. External radiotherapy frequently results in cutaneous radiation reactions (with up to 95% of those treated with irradiation showing some adverse effect) [26]. Human mesenchymal stem cell (MSC) transplantation has been shown to moderate the severity of radiation dermatitis and hasten the healing process in an immunodeficient NOD/SCID mouse model [27], and injection of adipose tissue-derived stromal cells facilitated wound healing, re-epithelization, and angiogenesis in murine models following irradiation [28, 29]. Injections of CD34+ hematopoietic stem cells (HSC) decreased liver degeneration and necrosis and improved liver function following abdominal irradiation in immunodeficient mice, with the transplanted stem cells migrating to the liver and differentiating into hepatocytes [30]. Finally, bone marrow-derived stromal and MSC transplantations have demonstrated beneficial effects in alleviating the negative response of gastrointestinal tissue to irradiation, promoting structural recovery, decreasing radiation-induced apoptosis, and increasing survival in murine models [31–36]. Further, cognitive dysfunction associated with other cancer therapies, such as chemotherapy, is ameliorated with stem cell transplantation, as shown in studies of cyclophosphamide- and adriamycin-induced chemobrain [37, 38]. Encouraging results in the utilization of stem cell-based therapies to address radiation injury in other organ systems and the application of stem cells to restore cognition after treatment with chemotherapeutic agents portends the therapeutic potential of stem cells for mitigating radiation-induced cognitive dysfunction.

Stem cells in the irradiated CNS

Acharya *et al*. were the first to demonstrate the potential therapeutic value of transplanting stem cells into the irradiated brain in 2009 [39]. Intrahippocampal transplantation of human embryonic stem cells (hESCs) into cranially irradiated athymic nude rats improved cognitive function on a hippocampal-dependent task. In that work, transplanted cells were found to migrate throughout the hippocampus, differentiating into neurons (concentrated in the dentate subgranular zone) and astrocytes [39]. A later study by the same group showed that human neural stem cell (hNSC) grafting into the hippocampus also ameliorated radiation-induced cognitive dysfunction as evidenced by performance on the same task at both one month and four months post-surgery [40]. These cells were also shown to migrate throughout the hippocampus, with 23% and 12% of the transplanted cells surviving one and four months after grafting, respectively, while differentiating into neuronal (chiefly in the dentate subgranular zone and CA1) and astroglial lineages (most evident in the corpus callosum) lineages. Intriguingly, upon exploration of novelty, a fraction (11%) of the transplanted cells were also found to co-express the mature neuronal marker NeuN and the activity-regulated cytoskeleton-associated protein (Arc), a behaviorally-induced immediate early gene, one month following irradiation [40]. Since expression of *Arc* has been used to map the activity of neuronal circuits [41, 42], these data suggested that transplanted cells were functionally integrated into host hippocampal circuitry [40]. Follow-up studies comparing the outcomes of transplanted hESCs to hNSCs in cranially irradiated animals confirmed that engrafting of both cells types rescued cognitive function at one month and four months post-surgery [43]. While survival of the hESCs was higher (35% at one month

post-transplantation, 17% at four months) relative to the hNSCs, hNSCs showed preferential neuronal differentiation compared to the hESCs [43]. Moreover, at eight months post-transplantation, hNSCs conferred improvement in cognition while hESCs failed to do so [44]. At eight months following the transplantation of hNSCs, only 4.5% of the engrafted cells survived, but the number of activated microglia were reduced significantly in the transplanted animals relative to animals that had been irradiated and received sham surgery [45]. Interestingly, and again following the recent exploration of novelty, behaviorally-induced *Arc* expression was rescued in host neurons located in the CA1 and dentate gyrus of the hippocampus [45]. As opposed to the earlier expression of *Arc* in transplanted cells, these latter findings pointed to a trophic support mechanism whereby engrafted cells enhanced the functional plasticity of host neuronal circuits [45]. Furthermore, intrahippocampal transplantation of FDA-approved human fetal-derived neural stem cells into irradiated rats also improved behavioral performance on hippocampal-dependent tasks of spatial memory and contextual fear conditioning, with migration of grafted cells throughout the CA1 and CA3 subfields and preferential differentiation to neuronal fates [46].

In addition, the Limoli laboratory has examined the optimal window for stem cell transplantation into the hippocampus following irradiation [47]. As opposed to prior work targeting a 2-day post-irradiation transplantation time, this study found that stem cell grafting four weeks after irradiation yielded more improvement in cognitive function than earlier transplantation times [47]. Protracting the transplantation time also revealed that stem cells were distributed along the septotemporal axis of the hippocampus, with favored differentiation into neuronal fates, and significantly decreased microglial activation throughout all hippocampal subfields, indicating that radiation-induced neuroinflammation was reduced [47]. The clinical utility of stem cell transplantation strategies to offset normal tissue damage caused by irradiation may be limited by the downstream potential for teratoma formation and immune rejection. To circumvent such caveats, work by Baulch *et al*. demonstrated the promise of using transplanted human neural stem cell-derived microvesicles, in place of stem cells [48]. Intrahippocampal grafting of microvesicles ameliorated the cognitive decrements associated with cranial radiation exposure, decreased neuroinflammation, and preserved dendritic morphology in rats. The transplanted microvesicles were found to migrate throughout the hippocampus and fuse with host brain cells, as determined by tracking a fluorescent marker protein expressed on the surface of the grafted microvesicles [48]. The foregoing data provided some provocative insight into the mechanisms of cognitive improvement following irradiation, and suggested that the bioactive cargo within microvesicles conferred neurotrophic support to the host brain.

Past and present studies have built upon the seminal approach pioneered by the Limoli laboratory [39] that implemented stem cell transplantation for the amelioration of radiation-induced cognitive dysfunction. Early studies showed that oligodendrocyte progenitor CD4+ cells transplanted into the spinal cord by laminectomy following irradiation migrated throughout the spinal cord without differentiating, contributing to the remyelination of demyelinated areas [49, 50]. Irradiation was found to enhance the subsequent survival of transplanted oligodendrocyte progenitor cells, likely due to radiation-induced depletion of the endogenous oligodendrocyte progenitor population, providing the transplanted cells the

opportunity to enter a previously-occupied “niche” [49, 50]. In fact, survival of transplanted CD4 cells was limited in the non-irradiated spinal cord. Evidence for the enhanced survival of stem cells transplanted into the CNS following radiation was bolstered by studies from Niranjan *et al.* [51] and Marshall *et al.* [52], which noted the increased survived of neural stem cells transplanted into the brain and multipotent astrocytic stem cells transplanted into the lateral ventricle, respectively. Intramedullary transplantation of neural stem cells three months after local irradiation of the spinal cord were found to significantly ameliorate indications of myelopathy in a rat model [53]. However, it was thought that transplantation of oligodendrocyte progenitor cells had limited clinical utility because the radiation dose needed to deplete endogenous oligodendrocyte progenitor cells to the requisite level to allow for significant survival of the transplanted cells was high enough to approach the ED50 (~20 Gy) for radiation necrosis [54].

More recently, Piao *et al.* demonstrated that the transplantation of human embryonic stem cell-derived oligodendrocyte progenitors into the corpus callosum of irradiated animals improved performance on behavior tasks that interrogated learning and memory capabilities [55]. The transplanted animals exhibited restoration of the glial cell population and remyelination of axons [55]. Likewise, transplantation of oligodendrocyte progenitors into the cerebellum improved motor balance and coordination, and induced remyelination within the cerebellum [55]. Work by Joo *et al.* showed that mouse fetal neural stem cells administered through the caudal vein in an irradiated mouse model migrated to the brain, exhibited multipotent differentiation, and improved short-term spatial memory as measured by the Morris water maze [56]. The stem cell injections also protected structural aspects of the brain from radiation damage, maintaining the depth of the granular layer of the dendate gyrus of the hippocampus and the cerebral cortex [56]. This study also found that nerve growth factor was elevated in the brains of mice receiving stem cell injections, indicating a protective neurotrophic effect, while the fate of other transplanted cells were found to trans-differentiate into endothelial cells, exhibiting a reparative effect on cerebral blood flow [56]. In work by Belkind-Gerson *et al.*, enteric neuronal stem and progenitor cells administered systemically through the caudal vein were also shown to home to the irradiated brain and differentiate into neurons, particularly in germinal zones such as the subependymal layer of the ventricular zone and the dentate gyrus, and in white matter tracts [57]. However, Osman *et al.*, indicated that intrahippocampal transplantation of autologous enteric neural stem/progenitor cells in young irradiated mice actually had a deleterious effect on learning [58]. Grafted mice exhibited increased neuroinflammation and deterioration of the granular cell layer of the dentate gyrus, while grafted cells showed limited survival and differentiation [58]. Similarly, neural stem and progenitor cells derived from mouse brains and grafted into the hippocampus of irradiated mice also caused deterioration of the granular cell layer and astrogliosis [59], revealing further potential limitations of the utility of stem cell-based therapy for resolving the adverse effects of radiation on the brain.

Conclusions

The promise of regenerative medicine continues to move forward, bolstered by a wealth of data pointing to the capability of such interventional strategies to hasten the recovery of injured tissues throughout the body [17]. For survivors of cancer, radio- and chemotherapy

treatments have long been associated with adverse neurocognitive complications, unwanted side effects that diminish quality of life with relatively little clinical recourse. Cranial and/or systemic transplantation of neural and related stem and progenitor cells has now been shown to provide a host of neurological benefits that include improved learning and memory and motor control, reduced inflammation, preservation of host neuronal morphometry, increased myelination, protection of the microvascular bed, and increased cerebral blood flow. At early times post-transplantation (≤3–4 months) many of the beneficial effects may be due in part to functional integration of grafted cells into host neuronal circuitry. At latter times (>4 months) the majority of these benefits are most certainly derived from a variety of trophic support mechanisms that act to protect and restore CNS functionality. Despite these exciting developments, stem cell therapies will not be suitable for everyone afflicted with a declining cognitive reserve. Patients will need to be stratified and assessed on an individual basis for various risk factors that will depend greatly on disease status and prognosis, and other social and career variables that inform proper medical decision-making. Immunorejection and teratoma formation remain genuine risks to most transplantation procedures, and while technology has minimized many (but not all) of these potential problems, graft survival seldomly approaches the projected life span of many cancer survivors. Nonetheless, for those suffering from debilitating cognitive impairment, unable to maintain routine duties or unable to conduct prior job duties to acceptable levels, stem cell therapy may one day provide much sought-after relief. For the here and now however, stem cell research must continue to elucidate further the mechanism of action, the duration of action, and the optimal routes of administration and cellular dosing to provide bona-fide therapeutic efficacy and to deliver useful targeted approaches to personalized medicine.

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