Granulocyte-colony stimulating factor and umbilical cord blood cell transplantation: Synergistic therapies for the treatment of traumatic brain injury

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Abstract:

Traumatic brain injury (TBI) is now characterized as a progressive, degenerative disease and continues to stand as a prevalent cause of death and disability. The pathophysiology of TBI is complex, with a variety of secondary cell death pathways occurring which may persist chronically following the initial cerebral insult. Current therapeutic options for TBI are minimal, with surgical intervention or rehabilitation therapy existing as the only viable treatments. Considering the success of stem-cell therapies in various other neurological diseases, their use has been proposed as a potential potent therapy for patients suffering TBI. Moreover, stem cells are highly amenable to adjunctive use with other therapies, providing an opportunity to overcome the inherent limitations of using a single therapeutic agent. Our research has verified this additive potential by demonstrating the efficacy of co-delivering human umbilical cord blood (hUCB) cells with granulocyte-colony stimulating factor (G-CSF) in a murine model of TBI, providing encouraging results which support the potential of this approach to treat patients suffering from TBI. These findings justify ongoing research toward uncovering the mechanisms which underlie the functional improvements exhibited by hUCB + G-CSF combination therapy, thereby facilitating its safe and effect transition into the clinic. This paper is a review article. Referred literature in this paper has been listed in the reference section. The datasets supporting the conclusions of this article are available online by searching various databases, including PubMed. Some original points in this article come from the laboratory practice in our research center and the authors' experiences.

Keywords:

Central nervous system disorders, granulocyte-colony stimulating factor, human umbilical cord blood, regenerative medicine, stem-cell therapy, traumatic brain injury

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Introduction

Traumatic brain injury (TBI) – defined as a physical insult which damages brain tissue by exceeding the protective capacity of the cranium – has continued to persist as a public health concern.[1] Approximately 3.5 million TBIs were reported in 2009 alone, with 2.1 million resulting in emergency room visits and 53,000 in death.[2] Moreover, a dramatic increase in blast injuries has paralleled the rise of improvised explosive devices in current armed conflicts, causing TBI to become the "signature wound" for American troops. The severity of TBI can vary, ranging from a mild change in mental status to coma and induction of amnesia after the injury. (National Institute of Neurological Disorders and Stroke, National Institutes of Health). Mortality following TBI spans from 1% in mild TBI

cases to upward of 30%–50% following severe brain injuries;[3] mild TBI, however, constitutes the majority of TBI cases at 70%–80%.[4]

Following the primary cerebral insult, complex pathological sequelae propagate neural death which may persist days, months, or even years.[5,6] The initial cause of TBI can be focal, such as from a penetrating head wound, or diffuse, such as from a blast-induced insult.[7] The secondary injuries stem from this primary trauma and result in multiple pathological cascades including excitotoxicity, hypoxia/ischemia, mitochondrial dysfunction, neuroinflammation, oxidative stress, and cerebral edema, which all contribute to the persistence of neurodegeneration and chronic functional deficits.[5,8-13] These secondary effects are often the most devastating and influential component of TBI progression, responsible for the delayed mortality and symptom development seen both in patients and animal models of TBI.[5,14-16] In search of novel therapeutics, halting the progression of these secondary pathologies presents an appealing target.

Beyond the physiopathology of the primary and secondary brain injury, TBI in humans is often associated with broader complications such as hydrocephalus, posttraumatic ventricular enlargement, seizures, nerve and vascular injuries, and polytrauma (National Institute of Neurological Disorders and Stroke, National Institutes of Health). Moreover, high-functioning impairments in cognition, communication, sensory–motor integration, and mental status (i.e., anxiety, aggression, and depression) may accompany chronic human TBI.[17-20] TBI survivors have also been observed to present with symptoms which mimic neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD), dementia pugilistica, and posttraumatic dementia.[18,19,21-23]

A general lack of awareness as to the prevalence of mild TBI has exacerbated this public health concern, with patients often forgoing treatment until symptoms begin worsening.[4] Even when seeking treatment, TBI patients' therapeutic opportunities are extremely limited.[24] In severe cases, surgical intervention may be beneficial in the repair or excision of damaged vasculature or tissue, while the various other symptoms – such as seizures, headaches, chronic pain, behavioral abnormalities, and depression – are relegated to management through prescription drugs and rehabilitation therapy.[24-30] Unfortunately, these treatment plans fail to prevent or reverse the underlying pathology. Thus, a substantial medical gap exists in the availability of TBI therapies which effectively treat the progressing secondary injury mechanisms and facilitate lasting functional recovery.

Umbilical Cord Blood Cells and a Viable Donor Source for Transplantation in Traumatic Brain Injury

By attenuating the toxic cell damage and detrimental edema which accompany TBI, neuroprotective pharmaceuticals and nontraditional agents aim to inhibit the development of secondary brain injuries.[24] Completed clinical trials investigating the safety and efficacy of select neuroprotective agents which exhibited preclinical success including glutamate inhibitors, nimodipine, magnesium sulfate, scavenging agents, and competitive N-methyl-D-aspartate receptor antagonists have failed to exhibit efficacy in TBI patients.[11,28,31-33] Testifying to the complexity of human TBI pathophysiology, these failed therapies indicate the need for new and improved treatment modalities.

In light of the extended therapeutic time window associated with chronic TBI, treatment strategies have been tailored to pursue chronic phase neuroregenerative efforts as opposed to targeting the narrow neuroprotective window of acute TBI.[34,35] the forefront of regenerative medicine has been stem cell-based therapies, having displayed promising applications in many neurological disorders such as TBI and having reached limited clinical trials.[34,36-41] A rigorous analysis of the safety, efficacy, and mechanisms of action has been critical to translating the use of stem cells for the treatment of neurological ailments. This has included extensive research into a multitude of transplantable cell types including fetal stem cells, cancer-derived neuron-like cells, embryonic stem cells, induced pluripotent stem cells, and adult stem cells, such as umbilical cord blood, bone marrow (BM) stromal cells, and amnion cells, among others.[39-47] Of particular interest has been adult stem cell donor sources as they evade the ethical, logistical, and oncogenic concerns which plague transplantation of embryonal or fetal-derived stem cells.[48]

Many laboratories, including our own, have gauged the clinical value of human umbilical cord blood (hUCB)-derived cells for the treatment of neurological disorders such as cerebral palsy, stroke, PD, and Huntington's disease.[49,50] These investigations have resulted in limited clinical trials of hUCB cells in cerebral palsy, stroke, and metabolic disorders.[50-53] The advantages of hUCB cell transplantation are a low immunogenicity, an ability to retain effectiveness after years of cryopreservation, ease of harvesting, ease of in vitro expansion, stemness potency, and successful history within the clinic for hematopoietic disorders.[54] Experimental models of TBI have responded favorably to hUCB treatment; transplantation of the mononuclear fraction of hUCB resulted in neuroprotective effects through reduced inflammation, heightened neurogenesis,

and a rescue of functional outcomes.[55-57] Moreover, mesenchymal stem cells (MSCs) derived from hUCB conferred neuroprotective and neuroregenerative benefits through improved angiogenesis and vasculogenesis.[49,58,59] The transition of hUCB cell transplantations for the treatment of TBI in the clinic will demand extensive basic science and translational research initiatives to uncover the intricate mechanisms of action, as well as the ideal timing, dosage, and route of administration. Furthermore, establishing the most appropriate and reproducible source of these cells will be essential for quality assurance, quality control, and reproducibility of experimental outcome measures.[36]

Despite inflammation and the harsh postinjury microenvironment being unconducive to long-term graft survival,[60,61] a robust functional recovery is still attainable in animal models through bystander effects; achieving significant recovery in the clinic, however, will likely necessitate dampening the harsh microenvironment and making it more receptive to stem cell transplant survival. Indeed, rendering the harsh postinjury microenvironment more amenable to stem cells through adjunctive agents may enhance their effectiveness and facilitate their advancement into the clinic for the treatment of TBI.

An Introduction to Granulocyte-colony Stimulating Factor

First discovered in the mid-1960s, granulocyte-colony stimulating factor (G-CSF) is a hematopoietic glycoprotein growth factor released from various cell types including endothelial cells, activated macrophages, and fibroblasts.[62,63] Initially, G-CSF was characterized to have roles in regulating differentiation, proliferation, survival, and function of neutrophil granulocyte progenitor cells and mature neutrophils.[62,63] G-CSF is now known to have a more broad set of functions; these are inducing growth of primarily neutrophilic granulocyte colonies in a colony-forming units-granulocyte macrophage assay, enhancing production of the chemotactic peptide N-formylmethionyl-leucyl-phenylalanine binding to mature neutrophils, and well-characterized regulation of the proliferation and differentiation of granulocyte precursor cells.[63-65] In addition, experiments utilizing G-CSF knockout mice revealed the role which this growth factor has in maintaining appropriate levels of circulating neutrophils in baseline myelopoiesis.[63,64]

Specific cellular queues trigger the production and release of G-CSF in the BM, whereby it can proceed to bind specialized receptors such as the canonical G-CSF receptor in a variety of cell types including hematopoietic progenitor cells, monocytes, platelets, neurons, endothelial cells, and small-cell lung cancer cells.[66-70] Upon activation of these receptors, signaling cascades are initiated which have been implicated in cell proliferation, anti-inflammatory processes, and anti-apoptotic pathways as well as stem cell mobilization toward sites of injury.[44,67,70-77] Furthermore, G-CSF has been implicated in brain function and recovery due to its ability to bypass the blood–brain barrier (BBB) and promote neural recovery,[78-80] indicating its candidacy as a possible treatment for neurodegenerative diseases.[81]

Monotherapeutic applications of granulocyte-colony stimulating factor

With neutropenia or febrile neutropenia potentially resulting from myelosuppressive or myeloablative chemotherapies, G-CSF has been approved by the Food and Drug Administration (FDA) for the treatment of appropriate cancer patients.[82] Clinic trials of G-CSF for small-cell lung cancer patients showed that treatment reduced the occurrence of infection, need for antibiotics, and decreased hospitalization rates for patients.[83,84] Other randomized, controlled clinical trials have shown a reduced duration of neutropenia, decreased hospitalization, and reduced antibiotic treatment in lymphoma patients subjected to myeloablative chemotherapy and autologous BM transplantation.[85] Interestingly, stem cell transplantation can generate prolonged neutropenia.[86] In patients with lymphoma, injection of G-CSF 24 h after autologous marrow transplantation resulted in quicker recovery of granulocyte count.[87] Accelerated recovery of neutrophil levels has also been reported in other studies of G-CSF-treated patients ailed with lymphoma, leukemia, and germ cell tumors.[88,89] Finally, G-CSF has been demonstrated as valuable for patients undergoing consolidation therapy as well as other idiopathic, congenital, or cyclic neutropenic conditions.[90-92]

Early clinical trials in cancer patients receiving G-CSF revealed that a 100-fold increase in circulating colony-forming progenitor cells accompanied treatment.[93] These findings initiated a quest to determine if peripheral blood progenitor cells (PBPC) mobilized by G-CSF could rehabilitate hematopoiesis[94] or if G-CSF could mobilize granulocytes in healthy donors. Indeed, in poor-prognosis nonmyeloid malignancy patients, it was observed that G-CSF-mobilized PBPC treatment stimulated platelet recovery.[95] It has also been shown that G-CSF-mobilized PBPCs can be safely and effectively harvested from donors.[96] Studies utilizing G-CSF-mobilized PBPCs (as opposed to BM stem cells) in allogeneic transplantation have prompted the clinical use of G-CSF for mobilization and collection of PBPC for disease treatment. The long history of safe and effective G-CSF use in the clinic makes it an appealing option from a therapy-development standpoint as entry of repurposed drugs into the clinic is typically expedited.

Further indications for the use of granulocyte-colony stimulating factor

The ability of G-CSF to mobilize BM stem cells into circulation has been the basis for a number of investigation into this recombinant protein's potential regenerative benefits in myocardial infarction.[97] A number of clinical trials of G-CSF for cardiac repair which have inconclusive with their reports of efficacy are included in these investigations.[97] Still, valuable knowledge was attained from these studies regarding the therapeutic mechanisms of G-CSF and relevant signaling pathways which modulate homing and prompt engraftment.[97]

With G-CSF able to penetrate the BBB and bind to neural receptors, its potential in the treatment of central nervous system disorders is significant. G-CSF has been demonstrated to incite a number of neuroprotective pathways which indicate its relevance in treating neurodegenerative diseases; among these, effects are mobilizing peripheral stem cells, stimulating neuronal lineage differentiation of endogenous stem cells, promoting angiogenesis, and dampening inflammation, all acting in concert to reduce apoptosis.[98-101] Stroke, in particular, has been revealed as highly amenable to G-CSF therapy, with properly dosed treatments resulting in increased CD34+ cells,[102] reduced glutamate excitotoxicity,[103] altered apoptotic pathways,[99,100] reduced edema and interleukin-1 expression,[104] and decreased infarct size.[105] This promising preclinical evidence has precipitated clinical studies into the safety and efficacy of G-CSF treatment in ischemic stroke patients.[106-108] Positive indications have also been derived from clinical trials of G-CSF in AD, with appropriate dosages being well-tolerated and improving performance in hippocampal-dependent cognitive tests.[42] The potential of G-CSF to induce neuroregeneration – within the central nervous and peripheral nervous system – has been proposed. Indeed, studies have shown G-CSF to promote function recovery from spinal cord injury (SCI) by increasing neuron survival and oligodendrocyte protection.[109,110] The safety and feasibility of G-CSF treatment for SCI was demonstrated in phase I/IIa clinical trials, signifying the promise of G-CSF to confer functional benefits in acute SCI patients.[111]

With discrepant results being produced in studies of G-CSF for the treatment of experimental TBI – some reporting improved histological markers and behavioral performance, others finding minimal effect on neurological outcomes – the merit of this protein as a stand-alone therapy for TBI is inconclusive.[44,112,113] Despite the inconsistent efficacy results, a clinical trial has been initiated for G-CSF in TBI patients on the basis of its solid safety profile and positive indications in both ischemic stroke and AD.[42,104,108,114,115] The multitude of positive findings for the use of G-CSF in various neurological conditions warrants ongoing investigation into the potential applications of G-CSF in TBI treatment.

Granulocyte-colony Stimulating Factor as an Adjunctive Option

Different mobilizing agents may promote the dissemination of BM stem cells with different phenotypic profiles and biological characteristics; thus, G-CSF has been used adjunctively with other mobilization compounds agents, such as stem cell factor (SCF), to enhance and optimize the mobilization of stem cells.[116,117] Working synergistically, co-administration of G-CSF and SCF resulted in a 250-fold increase in circulating pluripotent hematopoietic stem cells.[118] Consistent with these findings, myocardial infarct studies have reported that such combination therapy resulted in improved left ventricular function, reduced mortality and infarct size, and improved homing of BM stem cells to the affected myocardium, resulting in the formation of new cardiomyocytes.[116] Chronic stroke studies revealed the adjunctive therapy of G-CSF and SCF augment functional recovery better than either treatment alone, citing increased neurogenesis, angiogenesis, and indirect neural network promotion as the mechanisms underlying the improvements.[116]

Similarly, co-administration of G-CSF and cytokine fms-like tyrosine kinase 3 (Flt3), demonstrated therapeutic effects in models of SCI and acute myocardial infarction which were more effective than either single-agent treatment.[92,115,119] An extended period of mobilized BM cells was associated with the improvements in tissue regeneration, morphological, and behavioral measurements observed following the adjunctive treatment.[119,120] Further, when combined with transplantation of the mononuclear fraction of BM cells, G-CSF treatment produced combinatorial effects in a mouse model of ischemic stroke, potentially through enhanced proliferation and differentiation of BM stem cells which, in turn, promoted regeneration.[121]

The efficacy of G-CSF alone or in combination with BM-MSC was investigated after experimental stroke in aged rats.[98] Despite significant upregulation of angiogenesis in the infarct core and penumbral region, the neuroprotective effects of the combination therapy were less pronounced than those afforded by G-CSF alone.[98] These findings, however, are in agreeance with previous studies which described the pro-survival properties of G-CSF in aged rats.[122] Thus, additional studies into the interactions between G-CSF and stem cells are warranted to better understand the lack of synergism reported in this study.[98]

In a model of spinal cord transection, BM-MSC transplantation with G-CSF did displayed synergistic effects on recovery, attributed largely to increased proliferation and differentiation of BM stem cells, and subsequent neural regeneration.[123] The additive effects may have also been due to increased neurogenesis of both the endogenous neurons and neural lineage-committed transplant cells in the transverse SCI.[121] Using G-CSF adjunctively with other therapeutic agents has been employed with pharmacotherapies,[124] erythropoietin,[125] amniotic membrane wrappings,[126] and other tools in experimental neurological disease models. When compared to single-agent interventions, the majority of these investigations report synergism through combination therapies, supporting the concept of heightened therapeutic potency with G-CSF as an adjunctive therapy.

Granulocyte-colony stimulating factor and human umbilical cord blood cell transplantation – evidence toward clinical translation

Based on the previous successes of G-CSF as both an adjunctive and stand-alone therapy for neurological disorders – and in light of the discordant findings with G-CSF in TBI models – we investigated the merit of a combinatorial approach in treating the controlled cortical impact model of TBI with transplantation of hUCB and co-administration of G-CSF.[127] Our study demonstrated greater therapeutic benefits offered through combination therapy of hUCB and G-CSF than either agent alone.[127] Moreover, these functional improvements prevailed for a longer period than in the monotherapy groups.[127] These results attest to the ability of complementary brain repair processes not only to afford functional recovery but also to potentially sustain these benefits. Secretions of hUCB grafts, G-CSF-mobilized endogenous stem cells, and possible graft-host interactions[128] may have exerted cooperative regenerative mechanisms which resulted in neurological recovery surpassing that afforded by G-CSF or hUCB treatments alone.[112,127]

Considering our group's long-standing interest in the inflammatory basis of neurodegeneration, we utilized MHC-II staining of activated microglia to determine the effects which G-CSF + hUCB combination therapy exerted on TBI-induced neuroinflammation.[127] In line with the functional improvements we noted, the combination therapy group displayed a reduction in the TBI-induced upregulation of MHC-II microglia in the cortex, striatum, subventricular zone (SVZ), dentate gyrus (DG) of the hippocampus, corpus callosum, fornix, thalamus, and cerebral peduncle compared to either stand-alone treatment.[127] Preclinical evidence has demonstrated the ability of hUCB transplantation to induce neurogenesis, angiogenesis, and attenuate neuroinflammation in models of TBI as well as stroke

and aging.[129-131] G-CSF treatment has similarly been noted to promote neurogenesis in TBI models.[115] Our results support the notion that these two treatment modalities can combine synergistically, encouraging neurogenesis in the DG and SVZ, dampening neuroinflammation, and preserving hippocampal cells to confer functional benefits which surpass that of either monotherapy.[112,127]

Complementary interactions between hUCB and G-CSF likely facilitated the aforementioned widespread effects seen in the TBI brain. G-CSF has been shown to mobilize stem cells which can infiltrate damaged brain tissue and promote repair,[104,114] while also crossing the BBB itself where it can interact with neurons and glial cells to downregulate pro-inflammatory mediators and increase neurogenesis.[72,131,132] Furthermore, G-CSF may encourage the hUCB cells to maintain stemness and even promote neural lineage commitment.[71,133] Combination treatment of G-CSF and SCF was shown to promote senescence and neural lineage commitment of hematopoietic stem cells, possibly through neurogenin-1 activation.[134] Simultaneously, the mobilized BM stem cells can exert bystander effects by the way of paracrine signaling/immunomodulation through cytokines, chemokines, and trophic factors.[38,56,113,135] These diverse and cooperative mechanisms likely underlie the anti-inflammatory, neurogenic, and pro-survival effects seen in cases treated with G-CSF and hUCB.

Conclusion

Shifting the paradigm of TBI from an acute event to a progressive, neurodegenerative disease has paved the way for novel therapeutic opportunities which target this extended pathological window. These opportunities are welcomed as treatment options for TBI are practically nonexistent, with patient treatment relegated to symptom management and rehabilitation therapy. Stem cells have been proposed as a biological agent which may effectively target the progressive degeneration of chronic TBI, largely due to promising preclinical data in experimental models of TBI and various neurological disorders. Importantly, it is becoming increasingly evident that optimizing stem-cell therapy may require adjunctive therapies which work synergistically with the stem cells to promote significant and sustained functional recovery. We have provided experimental evidence that one such adjunctive option – G-CSF co-administered with hUCB cells – is a viable and effective modality and may present a means of overcoming the innate limitations that exist in monotherapy with either therapeutic. This evidence warrants further investigation into G-CSF + hUCB combination therapy, as well as other promising combinations, in an attempt to demonstrate their safety and efficacy, eventually propelling these

regenerative therapeutic approaches into the clinic for the treatment of TBI.

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Conflicts of interest
There are no conflicts of interest.

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