



Cord blood for brain injury

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Abstract

Recovery from neurological injuries is typically incomplete and often results in significant and permanent disabilities. Currently, most available therapies are limited to supportive or palliative measures, aimed at managing the symptoms of the condition. Because restorative therapies targeting the underlying cause of most neurological diseases do not exist, cell therapies targeting anti-inflammatory, neuroprotective and regenerative potential hold great promise. Cord blood (CB) cells can induce repair through mechanisms that involve trophic or cell-based paracrine effects or cellular integration and differentiation. Both may be operative in emerging CB therapies for neurologic conditions, and there are numerous potential applications of CB-based regenerative therapies in neurological diseases, including genetic diseases of childhood, ischemic events such as stroke and neurodegenerative diseases of adulthood. CB appears to hold promise as an effective therapy for patients with brain injuries. In this Review, we describe the state of science and clinical applications of CB therapy for brain injury.

Key Words: *brain injury, cell therapy, regenerative medicine, umbilical cord blood*

Introduction

Neurological injuries can result from any number of insults to the brain, including traumatic, vascular, infectious, genetic and environmental etiologies. Although the cause and mechanism of damage may vary, brain injuries share certain unifying features: as a group they are common, affecting people of all ages and races; they are costly, often causing chronic disabilities that carry significant medical and societal costs; and their current treatment options are extremely limited. Although recovery from a brain injury is typically incomplete, the brain's capacity for self-renewal—albeit limited—has recently been recognized. Concurrently, substantial advancements have been made in the field of stem cell biology. For these reasons, great interest has been generated in developing stem cell therapies as potential treatments to repair damage, regain function and improve quality of life in patients with neurological disorders. In this article, we will review the potential applications of umbilical cord blood (CB) as a source of stem cells for such therapies and some of the brain injuries in which they may be effective.

Umbilical CB as a source of stem cells for neurological applications

Several properties unique to CB make it an attractive source of stem cells for regenerative and restorative purposes. (i) Stem cell characteristics: CB is rich in highly proliferative stem and progenitor cells of the hematopoietic and other lineages mobilized by placental signals promoting homing to developing organs [1,2]. Compared with stem cells obtained from adult bone marrow (BM), CB stem cells are less mature and therefore have longer telomeres and greater proliferating potential [3]. CB-derived cells have been differentiated into numerous cell types throughout the body, including neural cells. Recently, induced pluripotent stem cells (iPS) have also been isolated from CB with simpler methods and greater efficiency as compared with adult cell sources [4–6]. There is also mounting preclinical evidence that cellular therapies act through paracrine and trophic mechanisms of cell signaling to enhance neuroprotection and restoration [7]. (ii) Availability: There are more than 130 million births per year worldwide, so there is ample opportunity to collect CB units for regenerative purposes. Processes are well established

for the collection, testing, characterization and storage of CB units, which can be cryopreserved for decades for future use. Over the past 20 years, approximately 700,000 unrelated donor CB units have been collected, characterized and banked for public use, and an additional 2 to 3 million CB units have been stored privately for family use. (iii) Safety profile: CB can be collected non-invasively without risk to the mother or infant donor. Compared with adult BM stem cells, CB cells are less immunogenic and less likely to transmit infections through latent viruses. In more than 25 years of use in allogeneic, unrelated hematopoietic stem cell transplantation, CB has not been shown to cause teratomas or solid tumors. (iv) Noncontroversial: Given that cord blood was historically discarded as medical waste with the placenta after birth, it remains a noncontroversial source of stem and progenitor cells. All of these features make CB an attractive source of cells for cellular therapies and regenerative medicine. Of note, umbilical cord tissue is also readily available for harvest at the time of delivery. Mesenchymal stromal cells (MSCs) have been directly isolated or expanded from cord tissue and studied in animal models. These tissues are currently under study in early-phase clinical trials for arthritis, spinal cord injury, Alzheimer's disease and autism. However, the safety and efficacy of these cells is not currently established, and the optimal methods of processing, storing and manufacturing cell products from cord tissue are still the subject of investigation.

Since the first unrelated donor CB transplant in 1988, more than 30,000 CB transplants have been performed, and CB has become a proven source of stem cells for hematopoietic reconstitution for myelo-ablative stem cell transplantation. Additionally, CB also contains non-hematopoietic stem cell populations that are capable of differentiating into numerous cell types throughout the body. In particular, the CB-derived unrestricted somatic stem cell first described by Koehler is a non-hematopoietic multipotent cell with the ability to differentiate into several lineages *in vitro* and *in vivo*, including osteoclasts, hepatocytes and neurons, among others [8–10]. CB-derived cells can also differentiate into MSCs, chondrocytes, osteocytes, adipocytes, cardiac and skeletal muscle myocytes, hepatocytes, pancreatic cells, skin cells, endothelial colony-forming cells and neural cells [11–22]. Though the specific cell of origin that gives rise to neural cells has not yet been identified, neurons, astrocytes, oligodendrocytes and microglia have all repeatedly been derived *in vitro* from CB progenitor cells by means of gene transfection, *ex vivo* culture with and growth factor supplementation, through generation of iPS and/or the use of chemical agents [10,22–30].

Evidence of neural differentiation has also been detected *in vivo*. Donor CB-derived tissue-specific cells have been identified in multiple organs in both animals and humans after HSCT, including the liver, lung, pancreas, skeletal muscle and brain [19,31,32], indicating that CB cells are capable of repopulating more than just the hematopoietic system. This may be due to the presence of a true embryonic-like stem cell in CB and/or small numbers of committed, tissue-specific, non-hematopoietic progenitors. It is important to note that observations of *in vivo* engraftment and differentiation have occurred in immunocompetent, xenogenic animal models, but in humans only after receiving myelo-ablative and immuno-ablative preparative therapies. It is not clear if infusions of CB into an immunocompetent person will produce similar results.

Potential mechanisms of CB-derived therapies in brain injuries

Although CB cells have the ability to differentiate into tissue-specific cells and integrate into host organs, there is growing evidence that their therapeutic effects probably are mediated by an ability to influence tissue damage and repair by signaling and activation of host cells through trophic and/or paracrine effects. Although the exact mechanisms of neural sparing and/or recovery remain the subject of preclinical investigations, several mechanisms have been hypothesized [33]. The survival potential of host neural cells may be enhanced by the delivery of trophic factors from infused and/or transplanted CB cells that provide anti-inflammatory and neuro-protective effects [34–37]. Brain plasticity may be increased by enhancing synaptogenesis, instigating endogenous repair mechanisms, stimulating angiogenesis resulting in neovascularization and inducing migration and proliferation of endogenous neural stem cells [38–40]. To a lesser degree, CB stem cells may also migrate, integrate, proliferate and differentiate into “replacement” neuronal and glial cells and play a role in re-myelination [41]. Additionally, many neurologic diseases involve activation of pro-apoptotic signal transduction, which could be harnessed to attract cells to brain lesions in those diseases. Thus, CB-derived cells could also potentially act as a vehicle to deliver neuroprotective and restorative factors or signal endogenous cells to act in a targeted way toward damaged brain tissue. Given their numerous potential mechanisms of action, CB-derived therapies may be applicable to a wide range of neurological injuries including, but not limited to, genetic diseases of childhood, ischemic damage (acute and/or chronic) and neurodegenerative diseases of adulthood. The remainder of this

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