Cord Blood

Establishing a National Hematopoietic Stem Cell Bank Program

Committee on Establishing a National
Cord Blood Stem Cell Bank Program

Board on Health Sciences Policy

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Contents

UMBILICAL CORD BLOOD IN REGENERATIVE MEDICINE

Although the primary use of cord blood has been to restore hematopoietic function, a number of other potential applications are possible, but these require further research. While there have been limited successes in controlled laboratory settings, it is unlikely that any of these studies will translate into clinical applications in the near future. Rather, they should be considered a guide for future studies using carefully thought-out animal models. Table 3-2 summarizes the present areas of nonclinical research underway with cord blood.

One of the earliest reports that HPC might be capable of generating other tissues was in 1998 (Goodell, 2004). In that study, researchers lethally irradiated rats and damaged their skeletal muscles. After the rats received a bone marrow transplant, donor nuclei were found in the skeletal muscles at very low frequencies. Similar studies found that donor-derived cells could also be found in heart, liver, gastrointestinal, and neural tissues. The prevalence of these transdifferentiation events has varied widely, and some researchers feel the event is actually cell fusion rather than transdifferentiation. However, research has continued.

TABLE 3-2 Summary of Current Research

Type of Research	Reference	Status
Cardiac repair	Perry and Roth (2003)	Capillary-like tubes are grown in culture
	Vanelli et al. (2004)	Transplants in animals have led to improved cardiac function
Central nervous system disease	Newman et al. (2004)	Mice with amytropic lateral sclerosis improved after transplantation
Spinal cord injury	Saporta et al. (2003)	HPCs engrafted in the area of injury in rats
Stroke	Taguchi et al. (2004)	Vascular activity in damaged area in mice increased post-transplantation
	Willing et al. (2003)	Motor improvement was noted in mice post-transplantation
Brain damage	Jensen et al. (2003)	Hypoxic mice showed improvement posttransplantation
Liver injury	Di Campli et al. (2004)	Potential for transdifferentiation was first noted in humans posttransplantation
Gastrointestinal	Ishikawa et al. (2004)	Minimal transdifferentiation for intestinal tissue was noted

Because early research focused on whole bone marrow, the next step was to refine the marrow to ensure that it was the HPCs and not other cells in the bone marrow that served as the source of the observed donor cells. This has been achieved in several cases and the donor cells have been observed at very low frequencies.

Researchers have observed donor cells in nonhematopoietic tissue among humans who have received sex-mismatched transplants. Most scientists believe, however, that this does not demonstrate transdifferentiation so much as it demonstrates the ability of the donor cells to circulate (Goodell, 2004).

A final open question with regard to cord blood in nonhematopoietic applications is the presence or absence of the more plastic MSCs. MSCs are a rare form of multipotent progenitor cells capable of supporting hematopoiesis and of differentiating into osteogenic, adipogenic, myoblastic, and chondrogenic cell lines. Several investigators (Wexler et al., 2003; Gang et al., 2004; Bieback et al., 2004) have been able to culture MSCs from human bone marrow, but they have been unable to do so with umbilical cord blood. For this reason, these researchers have concluded that given the current level of knowledge, cord blood is unsuitable for cell therapy applications. Similarly, research by Yu et al. (2004) demonstrated the ability to isolate MSCs from cord blood collected after preterm deliveries, but not from blood extracted after full-term pregnancies.

Bieback et al. (2004) have, however, been able to isolate MSC-*like* cells from cord blood. Their success, however, is relatively isolated (63 percent of 59 units), and they were successful only under optimized isolation and culture conditions. It is also worth noting that they were able to generate only osteogenic and chondrogenic progenitor cell lines but were not able to develop adipogenic-like cells. Gang et al. (2004) were able to grow myogenic precursor cells; however, their ability to do so was limited and growth seemed to peak at day 3 after the initiation of culture, indicating the need for further research.

Some of the more specific research being conducted is summarized in the following sections.

Cardiac Repair

Perry and Roth (2003) have described the present potential for reconstructing human cardiac cells from bone marrow, peripheral blood, and cord blood. They described a study in which cord blood stem cells were treated with vascular endothelial growth factor and basic fibroblast growth factor and noted the formation of capillary-like tubes. Other research discussed by Perry and Roth isolated HPCs from cord blood, cultured them in a pulse duplicator bioreactor on a conduit artery scaffold, and found that

the constructs were very similar to those of native tissues (Perry and Roth, 2003).

Vanelli et al. (2004) indicated that the study of cardiac stem cell precursors in human cord blood and bone marrow will lead to a better understanding of the biology of human cardiac cell differentiation, in addition to providing practical applications. They write that studies with animal models have shown that transplantation has led to improved cardiac function. They further note, however, that when transplanting large populations of unsorted marrow or unmanipulated cord blood, researchers should take into account the fact that only a small fraction of such cells will reach the desired organ.

Central Nervous System Disease

Newman et al. (2004) have described some of the current research being conducted using HPCs from cord blood to treat diseases of the central nervous system. A study involving the transplantation of HPCs into mice with amyotropic lateral sclerosis found that the mice showed improvements in motor function, lost weight, and lived longer than the mice that did not receive the HPCs. The mice in that study received the transplant before the onset of significant motor deficits. They were then analyzed for evidence of donor cells. Some of the donor cells located in the central nervous system were found to express neural cell phenotypes. These are the first data to suggest that donor HPCs are capable of both in vivo differentiation and migration to the brain and spinal cord in the absence of injury.

Again, however, much more research is needed before these successes can be considered indicative of what might happen in humans.

Spinal Cord Injury

Saporta et al. (2003) noted the ability of cord blood cells to target and migrate to areas of damage and engraft therein after intravenous infusion. Building on this knowledge, they examined the ability of cord to target a zone of compression injury in the spinal cord of adult male Sprague-Dawley[2] rats.

The researchers compressed the spinal cords of these rats and infused cord blood at either 1 or 5 days post injury. By prelabeling the cells, the researchers were able to demonstrate that the cord blood engrafted in the areas of the spinal cord injury. They postulate that the cord blood entered the areas of damage through damaged blood vessels at the site of the injury

[2]A widely accepted, dependable, and general-purpose strain of rat used as a research model.

or through a compromised blood-brain barrier at sites of secondary damage. The harvested cells did not, however, show evidence of differentiation.

In addition to the evidence of engraftment, the rats also showed significant behavioral improvement compared with the behaviors of the rats that had not received the cord blood. The number of cells transplanted, however, was not enough to restore significant motor function.

Recent reports (AFP, 2004) from Korea, however, indicate that cord blood transplantation may have promising applications in humans with spinal cord injury. A 37-year-old woman who had been paralyzed for almost 20 years reportedly regained the ability to walk after she received a cord blood injection directly in the damaged part of the spinal cord. Other researchers (Willenbring et al., 2004) caution against drawing conclusions from this isolated incident and believe that this research needs to be reliably replicated before it can be regarded as a potential therapy.

Brain Injury

Stroke

In individuals with stroke, blockage of the blood vessels leading to certain areas of the brain causes focal ischemia and subsequent degeneration of the tissue (Peterson, 2004). The severity of degeneration depends on the location and the extent of the injury. In most cases, however, recovery from stroke is not a result of the recovery of the tissue but, rather, is a result of the development of new neural pathways in undamaged regions.

Taguchi et al. (2004) modeled stroke in genetically modified SCID mice. Human $CD34^+$ cells from cord blood were administered to the mice via the tail vein within 48 hours after an induced stroke. Mice that received the cells displayed new vascular activity within 24 hours of the transplant and had significantly enhanced cerebral blood flow (Taguchi et al., 2004). These mice also displayed significant improvement on behavioral tests compared with behaviors of control mice and mice that received $CD34^-$ cells (Taguchi et al., 2004).

Willing et al. (2003) have found that mononuclear cells in cord blood function similarly to MSCs in bone marrow. These investigators also transplanted cord blood into rats with stroke, and although the number of rats was small, they also noted significant improvements in motor skills and behavior compared with those of the rats that did not receive cord blood.

Non-Stroke-Related Brain Damage

Jensen et al. (2003) researched the potential of cord blood transplantation as a treatment for children who were brain damaged because of hy-

poxic incidents during birth. They note that the central nervous system, unlike other tissues, has a limited regenerative potential. The transplantation of cord blood, they argue, could be a new therapy.

They reproduced the hypoxic injuries in rats and after transplantation noted markedly improved behavior in the rats that received cord blood transplants compared with the behavior of untreated control rats.

Toxic Liver Injury

Di Campli et al. (2004) compared several studies using both animal models and humans and have highlighted the potential of HPCs to transdifferentiate into nonhematopoietic cells. Marrow-derived hepatocytes were first noted in a rat model that showed male cells in female recipients. Those cells not only had the physical characteristics of liver cells, but also demonstrated the appropriate synthetic and metabolic functions.

Di Campli et al. (2004) noted, however, that the time course of the transdifferentiation process has never been fully explored. They also noted that the number of cells present is well below the therapeutic level needed for the effective treatment of some disorders.

Gastrointestinal Disorders

Inflammatory bowel disorders, such as Crohn's disease and ulcerative colitis, often require novel treatments. Ishikawa et al. (2004) analyzed the capacity of human bone marrow- and cord blood-derived progenitor cells to generate gastrointestinal epithelial cells. To do this, they analyzed gastrointestinal specimens from pediatric and juvenile recipients of allogeneic sex-mismatched progenitor cell transplants and looked for evidence of donor-derived cells (Ishikawa et al., 2004). None of the human patients exhibited any chimerism. However, upon closer inspection under an electron microscope, donor-derived cells could be found at frequencies between 0.4 and 1.9 percent.

The researchers then performed similar experiments with mice and T-cell-depleted human bone marrow and cord blood mononuclear cells. They injected these cells into newborn mice after the mice were subjected to total body irradiation. After determining that the mice exhibited hematological chimerism, the researchers harvested gastrointestinal tissues from the mice. The results of this experiment indicated that xenogenic transplantation can regenerate epithelial cells in intestinal tissue as well as reconstitute lymphocytes.

Gene Therapy

Newman et al. (2004) postulated that HPCs are promising targets for gene therapy. In theory, the progenitor cells within the mononuclear cell population of cord blood can be used as cell-based gene therapy.

DEVELOPING RESEARCH PRIORITIES

The general consensus is that HPCs can be incorporated into nonhematopoietic tissue, but with very low efficiency. Whether cord blood will be the optimal source for the regeneration of nonhematopoietic tissues is unknown (Goodell, 2004). However, strategies are being developed to improve the efficiency of transdifferentiation with the long-term aim of using HPCs in therapies for nonhematopoietic diseases. Further research, including adequate animal studies, is clearly needed to better understand the nonhematopoietic potential of cord blood. Furthermore, given the limited availability of cord blood for research purposes it is important that nonclinical units not be discarded or destroyed.

Recommendation 3.1: Federally funded umbilical cord blood banks should have a mechanism by which they can make available for research use units not appropriate for clinical use according to the priority standards developed by the National Cord Blood Policy Board proposed by the committee (see Chapter 7).

The committee suggests that the proposed National Cord Blood Policy Board consider that the following types of research be given priority for nonclinical use of cord blood:

- research funded by the National Institutes of Health,
- peer-reviewed research receiving other government funding,
- other peer-reviewed research, and
- other unfunded but innovative research proposals.

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