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COMMENTARY

BERASHIS CELLS IN HUMAN UMBILICAL CORD BLOOD VS. EMBRYONIC STEM CELLS

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Over the past 3 years there have been numerous articles in medical journals, biological journals and the lay press concerning the great potential of embryonic stem cells (Weissman, 2002). This has provoked extensive controversies, ethical, political, patient rights, attracting numerous television and press reports. Throughout these articles, the potential for some of the cells found in cord blood collected from normal infants has been essentially ignored. Even though these human cells have been demonstrated to be therapeutically effective both in non transgenic animal models and in transgenic models, including such diverse diseases as a mouse model for human lupus erythematosus to transgenic mice for Huntington disease, little attention has been paid to this subject.

As far back as 1990 we were aware that human umbilical cord blood had unique cells that were able to produce a temporary xenograft in mice that would allow the animal to survive lethal levels of irradiation. (Ende, Ponzio *et al.*, 1992) Later we were able to demonstrate that human cord blood cells would increase the rate of recovery of the animal's own hematopoietic system (Czarneski, Lin *et al.*, 1999; Rameshwar, Smith *et al.*, 1999) and delay the onset of an autoimmune disease in mice similar to human lupus erythematosus (Ende, Czarneski *et al.*, 1995). These findings were all suggestive that there were cells in human cord blood, in addition to variously designated or partially designated stem cells, that had reparative ability for various organs and probably had a similar functional potential to those that have been predicted for embryonic stem cell. We speculated that these transplanted human cells either by direct or indirect activity provided cells or caused the mouse to produce cells required to repopulate various organ systems. We first described these cells in 1995, and to distinguish them from embryonic stem cells, fetal stem cells, adult stem cells, designated stem cells or organ specific stem cells, we used the term beginning cells (i.e., *Berashis* meaning *"In the beginning"*) (Ende, 1995). They are probably closely related to fetal stem cells that are obtained from aborted fetuses.

Throughout our studies on human cord blood, several characteristics appear to be constant: (a) There are very few of these cells in cord blood in comparison to the total number of nucleated cells. Based on replatable blast cell colonies we estimate they vary from 0-18 per ml. of cord blood. (b) Their clinical effect on mice appears to be directly proportional to the dose of total nucleated cells given to the animals (c) These human cells are difficult to locate when given intravenously to the animals (d) The cells appear to withstand storage for seven to fourteen days at 4°C (Ende, 1995; Ende, 2000; Chen and Ende, 2000; Ende, Lu. *et al.*, 1999).

These early findings led to our hypothesis that a large dose of human umbilical cord blood mononuclear cells could provide an adequate number of these critical Berashis cells to produce a significant clinical effect in mice with human transgenes that are related to manifestations of specific diseases. Extending this concept, we administered large doses of mononuclear cells obtained from cord blood to the following transgenic strains of mice to evaluate its effect on

prolongation of life and delay in onset of symptoms: Amyotrophic Lateral Sclerosis [B6SJL-TgN(SOD1-G95A)1GUR]; Alzheimer's Disease [Tg(HuAPP695. SWE)2576]; Huntington's Disease [B6CBA-tgN(Hdexon1)62Gpb]; Parkinson's Disease B6 CBACa-AW-J/A-Kcnj6<wv> and type I Diabetes (NOD/LtJ) (Ende, 2000; Chen and Ende, 2000; Ende and Chen, 2002; Ende, Chen *et al.* in press). In all instances, mice injected with human cord blood mononuclear cells (70 - 130 x 10^6) exhibited survival patterns that were significantly better statistically than untreated controls.

Prior to the studies on transgenic mice, we had been able to delay the onset of vasculitis and double the life span of MRL Lpr/Lpr mice with the injection of human umbilical cord blood mononuclear cells. These mice develop an autoimmune disease that is similar to human lupus erythematosus (Ende, Czarneski *et al.*, 1995). In addition, human cord blood mononuclear cells given in conjunction with irradiation therapy, considerably increased the life span of MMTVneu mice (Jackson Lab) with breast tumors and delayed or prevented primary B cell lymphoma development in SJL/J mice (Ende, 2000). Furthermore, the use of human cord blood cells significantly increased the life span of C57BL/6J mice used in ageing studies (Ende, 2000).

It should be noted that these results closely parallel the clinical results predicted for embryonic stem cells. In contrast, however, in the mice that were the recipients of these cells with or without immunosuppression, there was no evidence to indicate that cord blood cells produced neoplasms nor was any evidence of graft vs. host disease demonstrated.

Throughout the development of the fetus there is extensive remodeling and growth. Although proliferation and growth dominates the development of the fetus, there is significant cell death throughout the process, particularly related to the remodeling which occurs extensively in the developing mammal. If the dying cells act as an attraction for growth or repair of the fetal organs, a similar type of tropism could account for these immature undesignated stem cells being attracted to the dead cells. This could cause the release of cytokines or adhesion molecules to create or stimulate the designated stem cells in the affected area. The recent description of human umbilical cord blood

being able to produce significant repair of neurological defects in rats following occlusion of the middle cerebral artery would be supportive of this concept (Chen, Sanberg *et al.*, 2001). In addition, the same group of researchers have demonstrated that human cord blood cells can be converted to neurogenic cells (Sanchez-Ramos, Song *et al.*, 2001). It is of interest that only a small quantity of donor cells were identified by the research group in the infarcted region and, according to the authors, were insufficient to produce the improvement noted in the animals. The authors speculated that the observed repair of neurological defects could be primarily due to the host animal's response to the human umbilical cord blood cells, i.e., "that these cells act as sources of tropic factor production" (Chen, Sanberg *et al.*, 2001). In the chronic neurological diseases in mice in which we have seen significant clinical responses following injection of cord blood mononuclear cells, a similar mechanism may occur. The dying cells or apoptotic cells produces a trophism, attracting essential components that the umbilical cord donor cells (Berashis cells) are able to supply.

These various findings suggest that there are a small number of undesignated stem cells that are probably totipotential in umbilical cord blood. Although they may not be immortal, they probably have considerable proliferate ability and, or, can produce proliferation of the host's cells. They do not demonstrate any potential for malignancy. They are plentiful, as there are 3 million live births each year in this country and most of the cord blood is discarded. Shouldn't these naturally occurring cells, which have all the potential of embryonic stem cells, but without their negative attributes, be seriously considered for clinical use by the medical community?

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