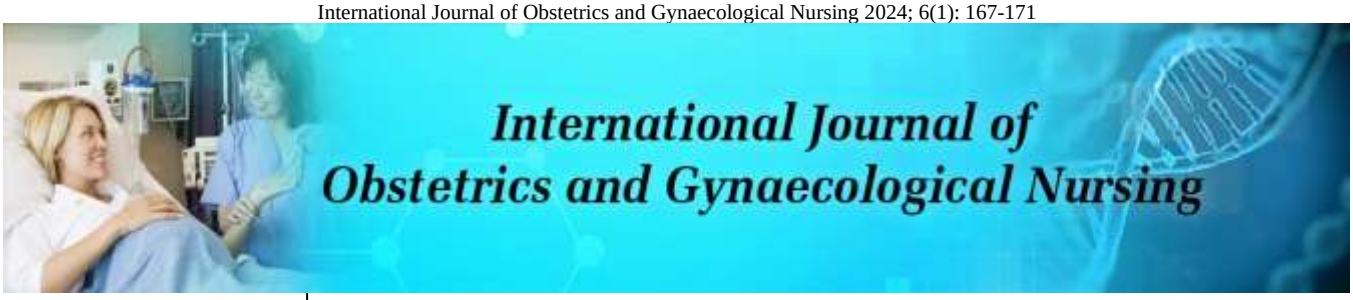

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Stem cells in the umbilical cord

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Abstract
The future of medicine lies in stem cells. It is believed that stem cells hold enormous medicinal and biotechnological promise. In addition to replacing damaged or malfunctioning cells, this will also allow the cells to be salvaged and/or deliver therapeutic proteins after they have been modified to do so. Both embryonic and foetal stem cells are currently surrounded by ethical and scientific questions that prevent their widespread use. On the other hand, postnatally recovered stem cells from the umbilical cord, such as umbilical cord blood cells, amnion/placenta, umbilical cord vein, or umbilical cord matrix cells, are an easily accessible and reasonably priced source of cells that are "multipotent," meaning they can form a wide variety of cell types. This review will compare adult stem cells with those produced from the umbilical cord.

Keywords: Stem cells, umbilical cord, biotechnological promise

Introduction

Stem Cells Defined

Cells that satisfy three fundamental requirements are referred to as stem cells. In order to sustain the stem cell population, stem cells first replenish themselves throughout life by dividing to create identical daughter cells. The second feature of stem cells is their ability to differentiate into specialized progeny cells. During the process of differentiating, stem cells have the ability to divide asymmetrically, producing a daughter cell that has the morphology, phenotype, and physiological characteristics of a differentiated cell type, thereby classifying it as a tissue-specific cell. “Pluripotent" stem cells can differentiate into ectoderm, endoderm, and mesoderm—tissues originating from all three germ layers. Originating from the inner cell mass of early embryos, embryonic stem cells (ESCs) are the greatest example of pluripotent stem cells. The majority of well-characterized stem cells, in contrast to ESCs, are multipotent, meaning they can develop into derivatives of two of the three germ layers. One of stem cells' three characteristics is their ability to regenerate the tissues they inhabit. According to the definition of "stem cells," cells found in all tissue compartments. contribute to the production of replacement cells at different rates depending on the area of the body. For example, proper health requires regular replacement of stem cells that produce the skin, the intestinal epithelium, and the blood. As opposed to this, the neural system's neural replacement cells, or stem cells, are largely dormant, incapable of promoting tissue growth or replacing damaged or diseased neurons. Stem cells reside in certain "niches" within the body, which are made up of extracellular matrix and stem cell support cells. The niche microenvironment controls stem cell proliferation and differentiation. It is useful to comprehend the function of the different "support" cells and the niche environment while manipulating and maintaining stem cell populations in vitro. For instance, stem cells find it more favourable to thrive under "hypoxic" circumstances (2-3% oxygen) than in regular atmospheric concentrations of 21%. The extracellular matrix, growth, and angiogenic factors, among other niche constituents, are involved in the control of stem cells. Although it is outside the purview of this article, understanding the stem cell microenvironment is an essential topic that is fast emerging.

When are Stem Cells Found?

Almost every stage of life has produced isolated stem cells. That is, both the inner cell mass of 5-day-old embryos and the olfactory epithelium of elderly people have been used to

harvest stem cells. Human embryo-derived stem cells and stem cells obtained from human foetal tissues have brought up moral and ethical questions that our society has not yet sufficiently addressed. Through federally mandated support constraints, investigations by blue ribbon panels, ethical discussions, legal actions, and political posturing, these society-level concerns have a direct impact on the research endeavour. All things considered, the states' disparities in law and support for embryonic stem cell research are a reflection of the United States' lack of cohesive leadership and clear, consistent research goals. These are big problems that need to be taken seriously. They are not covered in this review. Significantly, for the purposes of biomedical research, ESCs are the de facto pluripotent cells. Cell-based therapies and biopharmaceutical testing and manufacturing, according to proponents, will be made possible by ESCs. On the other hand, scientific studies employing stem cells and tissues taken from foetuses have produced more therapeutic applications and raised less controversy thus far. This is most likely due to the discovery, approximately 40 years ago, that patients with bone marrow deficits could be saved by using bone marrow and blood stem cells. This effort led to the establishment of the national bone marrow registry in the United States in 1986. The application of adult bone marrow-derived stem cells highlighted the presumed limitations of these cell types. Scientific orthodoxy specifically claims that the ability of adult-type stem cells to proliferate in vitro is limited. According to preliminary research, bone marrow-derived mesenchymal stem cells (bmMSCs) undergo senescence, or stop proliferating in vitro, at passages 6-10. Furthermore, because the red marrow area turns into a yellow marrow (packed with fat) as we age, it is said to be harder to remove bone marrow-derived stem cells from the marrow cavity during normal aging. The best bone marrow aspirates contain stem cells from young donors (e.g., 18-19 years old; 9a). It would seem that fat-derived MSCs would be a good substitute for marrow-derived MSCs in autologous grafting of elderly patients. Whether this will be the case is unknown. It is well established that bmMSCs are more common than fat-derived MSCs. Thus, before being used therapeutically, extraction and expansion might be necessary. The prevailing consensus is that stem cells from "younger" tissues—that is, from the early embryo or foetus—would have longer telomeres and be able to proliferate longer in culture before being senescent. This claim is supported by certain data.

Sources of Stem Cells for Therapeutic Use Over the past ten years, research has demonstrated the therapeutic value of umbilical cord blood in the recovery of patients with inborn metabolic errors and deficiencies connected to the bone marrow. Because umbilical cord blood has a lower incidence of graft versus host illness, can be utilized allogenically, and does not require complete human leukocyte antigen (HLA) tissue matching, it has advantages over bone marrow. Additionally, cord blood is "off-the-shelf" and can be used by banking it. A federally funded initiative was launched last year with the goal of expanding the nationwide umbilical cord blood banks to accommodate a diverse range of HLA types. More than 6000 cord blood stem cell units were stored as of 2004. It is believed that there were roughly 300,000 units in public and commercial banks in the US as of January 2006. Marrow-derived MSCs, or marrow stromal cells, are the most extensively researched stem cells in bone marrow, second only to hematopoietic stem cells. The adult marrow cavity contains the highest quantity of MSCs. MSCs are present in peripheral, adipose, and other tissues, but at lower densities in blood.

It is possible to separate MSC-like cells from amniotic fluid, placenta, umbilical cord blood, and Wharton's jelly, the tissue that surrounds the umbilical cord vessels. It is simpler and less expensive to obtain MSC-like cells from tissues that are discarded at birth than it is to extract MSCs from a bone marrow aspirate. There is no harm to the mother's or the baby's health throughout the tissue collecting process. Theoretically, decades after being cryogenically stored, these cells may be frozen and thawed to produce stem cells for medicinal purpose.

MSC-like cells have been isolated from tissues of the umbilical cord in five separate labs. There have been some documented variation ns in the ease of isolating MSC-like cells from different organs. Crucially, the techniques for separating MSC-like cells are reliable; that is, MSC-like cells can be independently isolated from these tissues in laboratories all over the world. This makes room for large-team approaches, scalable production, and independent verification. On the other hand, while there are multiple accounts of adult pluripotent cell isolation, independent validation of this research is necessary. Ensuring the authenticity of pluripotent cells is crucial because adult-derived pluripotent cells provide the best of both worlds: therapeutic pluripotent cells and adult-consented (no debate there) cell collection. We'll talk about two of these cell kinds in brief later. The multipotent adult progenitor cell (MAPC) research conducted by Dr. Verfaillie's lab has drawn a lot of interest. Based on prolonged passage in cell culture, their results suggest that the MAPC is pluripotent and somewhat mysterious. According to Kogler *et al*, a cell known as the universal somatic stem cell (USSC) was discovered in umbilical cord blood. Another uncommon cell is the USSC (average of 16 cells in initial isolate; isolated in 50% of attempted cords). As an embryo-safe pluripotent cell, the USSC, like the MAPC, holds great potential. When the techniques for isolating these two cells become reliable enough that any laboratory can do so and yet make a contribution to the field, then adoption of these two cells will be widespread.

Characterization of Umbilical Cord-Derived MSCs

A blue-ribbon team of scientists has discussed the minimum defining criteria of MSCs. Three traits were identified by this panel as defining MSCs. Initially, MSCs that are kept in regular culture conditions attach to plastic. Second, MSCs do not express HLA-DR, CD45, CD34, CD14 or CD11b, CD79 or CD19, or CD105, CD73, or CD90. Instead, they exhibit these cell surface markers. Third, in vitro, MSCs differentiate into adipocytes, chondroblasts, and osteoblasts. A comparatively consistent set of surface markers is shared by mesenchymal-like cells extracted from the placenta, umbilical cord, perivascular space, and placenta blood. This finding appears to support the theory that these cells are MSC-like.

Our work has focused on human umbilical cord matrix (UCM) cells. There are cells isolated in large numbers from the Wharton’s jelly of human cords. Two other research labs have published on the isolation and characterization of cells from the Wharton’s jelly: Dr. Davies’ lab at the University of Toronto and Dr. Y. S. Fu at the National Yang-Ming University, Taipei. All three groups reported that UCM cells

are MSC-like cells and are robust. These cells can be isolated easily, frozen/thawed, clonally expanded, engineered to express exogenous proteins, and extensively expanded in culture. Human UCM cells express a marker of neural precursors, nestin, without exposure to differentiation signals. In response to differentiation signals, human UCM cells can differentiate to catecholaminergic neurons, expressing tyrosine hydroxylase TH. Human UCM cells meet the basic criteria established for MSCs described previously. Similarly, MSC-like cells are derived from other umbilical cord tissues, e.g., umbilical vein sub-endothelium, umbilical cord blood, amnion, placenta, and amniotic fluid.

Whether UCM cells are MSC-like or fit into a unique niche is currently not clear. For example, when the vital stain Hoechst 33342 was used in the dye exclusion test, about 20% of UCM cells were found to exclude dye. About 85% of the UCM cells expressed CD 44, the hyaluronate receptor marker found on several stem cell populations, and about 85% of the cells expressed ABCG2, the receptor thought to mediate dye exclusion. Attempts to enrich the Hoechst-dim cells were partially successful, with maximal enrichment at about 32%. It is assumed that culture conditions are the limiting factor for further enrichment of what is assumed to be the most primitive populations.

A literature review revealed a question about the stability of umbilical cord cells in culture. Two groups found that the cell surface marker expression shifted over passage. Sarugaser' work indicated that HLA-1 was lost as a result of cryopreservation. Whereas, umbilical cord perivascular cells lost cell surface staining for HLA-1 with freeze-thaw, HLA-1 surface staining was consistent out to passage 5 for cells maintained in culture. In contrast, reported a decrease in the percentage of cells expressing CD49e and CD105 when human UCM cells were maintained in culture for passage 4-8 and no significant changes in HLA-1 expression. This question about the stability of surface marker expression may indicate that epigenetic phenomena associated with cell culture are influencing the cord MSC-like cells. Further characterization of the cord MSC-like cells is needed to understand the mechanisms of these changes.

The gene expression analysis and reverse-transcription polymerase chain reaction (RT-PCR) of MSCs from the umbilical cord was reported by one lab using the National Institutes on Aging (NIA) human 15k gene array. That work indicated that human UCM cells express genes found in cells derived from all three germ layers to some extent. At least one report indicates that UCM cells express the pluripotency gene markers *Oct-4, nanog*, and *Sox-2* at low levels relative to ESCs. One interpretation of these findings is that cord matrix stem cells are pleiotropic and express a relatively large number of genes in relatively low abundance. On the other hand, it may serve as evidence that the cord matrix cell population has a subset of primitive stem cells. Because gene array is not a sensitive method by which to examine low copy number message, we suggest that massively parallel signature sequencing (MPSS) is a more appropriate method of assessing matrix cell gene expression. RT-PCR alone is not useful for characterizing cord matrix stem cells: quantitative RT-PCR is needed to make meaningful statements about gene expression and to compare gene expression between experimental conditions.

Properties of Umbilical Cord Matrix Stem Cells

Several groups have isolated MSC-like cells from the umbilical cord tissues or blood and have reported that those cells may express neural markers when differentiated, and differentiate into neural cells upon transplantation into rat brain. This is not too surprising, because adult bone marrow-derived MSCs injected into fetal rat brain engrafted, differentiated along neural-like lineages, and survived into the postnatal period. Similarly, demonstrated convincingly that bone marrow-derived MAPCs could be differentiated in vitro to become cells with electrophysiological properties of neurons. Increasingly, reports are indicating that bone marrow-derived cells may differentiate, first to neurospheres and then to neurons with proper neuronal electrophysiological characteristics.

In 2003, we reported that UCM cells can be induced in vitro to become cells with morphological and biochemical characteristics of neurons. These findings have been extended by others, for example, neurons, cardiac muscle, bone, and. Using two in vitro differentiation methods, found that umbilical cord matrix stem (UCMS) cells could be induced to exhibit cardiomyocyte morphology and synthesize cardiac muscle proteins such as *N*-cadherin and cardiac troponin I. The cells responded to five azacytidine or culture in cardiomyocyte-conditioned media. Fu *et al*. used media conditioned by primary rat brain neurons to induce human UCMS cells to synthesize NeuN neurofilament. Furthermore, they could invoke an inward current in UCM cells with glutamate. In that report, exposure to neural-conditioned media also increased the proportion of cells synthesizing the astroglial protein glial fibrillary acidic protein (GFAP) from 94% initially to 5% after 9 d, although the percentage had declined to about 2% by day 12. The multilineage potential of UCMS cells was also verified by Wang and colleagues, who showed that they could be induced in vitro into chondrogenic, osteogenic, and adipogenic lineages.

MSC-like cells derived from Wharton's jelly adjacent to umbilical vessels (termed human umbilical cord perivascular cells) cultured in nonosteogenic media nevertheless contained a subpopulation that demonstrated a functional osteogenic phenotype with the elaboration of bone nodules; addition of osteogenic supplements further enhanced this population. These findings suggest that cord matrix stem cells, like bmMSCs, are multipotent: capable of making ectoderm- and mesoderm-derived cells.

We have shown that porcine UCM stem cells can be xeno-transplanted into nonimmune-suppressed rats, where they engrafted, proliferated in a controlled fashion, and exhibited TH expression in some cells. Most recently, our lab, and others have reported that UCM cells ameliorate behavioral deficits in the hemi-parkinsonian rat, and UCM cell transplantation resulted in significantly more dopaminergic neurons in the substantia nigra compared with lesioned, non transplanted rats that responded to the transplant. In contrast with our work, in which UCM cells were transplanted without prior differentiation, subjected UCM cells to an in vitro induction protocol utilizing neuron conditioned media, sonic hedgehog, and fibroblast growth factor (FGF)-8 to increase the number of tyrosine hydroxylase positive cells. After transplantation of these predifferentiated human UCMS cells into hemi-parkinsonian rats, Dr. Fu's lab reported that they prevented the progressive degeneration/ deterioration in their Parkinson's disease model.

From these findings, it is suggested that UCM cells offer advantages over stem cells as a source of therapeutic cells.

First, UCM cells are derived from a noncontroversial, inexhaustible source, and can be harvested noninvasively at low cost. Second, unlike human ESCs, UCM cells did not induce teratomas or death after 1×10^6 to 6×10^6 human UCM cells were transplanted either intravenously or subcutaneously into severe combined immunodeficient beige mice (Rachakatla, Medicetty, Burton, Troyer, and Weiss, unpublished observations). Third, UCM cells are easy to start and do not require feeder layers or medium containing high serum concentrations to be maintained. Fourth, they are not acutely rejected when transplanted as xenografts in nonimmune-suppressed rats. For example, we demonstrated that pig UCM cells undergo a moderated expansion following transplantation into rat brain without obvious untoward behavioral effects or host immune response.

Immune Suppression

MSCs are reported to have immune-suppressive effects. To comment human fetal and adult MSCs are not inherently immunostimulatory in vitro and fail to induce proliferation of allogeneic lymphocytes. In one human case, fully mismatched allogeneic fetal liver-derived MSCs were transplanted into an immunocompetent fetus with osteogenesis imperfecta in the third trimester of gestation. No immunoreactivity was observed when patient lymphocytes were re-exposed to the graft in vitro, indicating that MSCs can be tolerated when transplanted across MHC barriers in humans. Similarly, after intrauterine transplantation of human MSCs into sheep, the cells persisted long-term and differentiated along multiple mesenchymal lineages. Instead, the cells are immunosuppressive and reduce lymphocyte proliferation and the formation of cytotoxic T-cells and natural killer cells when present in mixed lymphocyte cultures. The mechanism whereby MSCs suppress lymphocyte proliferation is still largely unknown but appears to, at least in part, be mediated by a soluble factor. Several factors, including MSC-produced prostaglandin E2, indoleamine 2,3-dioxygenase-mediated tryptophan depletion, transforming growth factor-β1, and hepatocyte growth factor have been proposed to mediate the suppression, but the data remain controversial.

There is indirect support for an immune-suppressive effect of the MSC-like cells derived from umbilical cord: two labs have transplanted UCM cells xenogenically in nonimmune-suppressed hosts without observation of frank immune rejection. In preliminary work, we have found that human UCM cells suppress the proliferation of rat splenocytes exposed to the mitogen ConA, and that a diffusible factor is likely involved (Anderson, Medicetty, and Weiss, unpublished observations). These data would support the hypothesis that UCM cells, like MSCs, may have immunosuppressive effects. We speculate that these effects may facilitate the engraftment of other therapeutic cells, that has been reported recently for co-grafts of MSC with hematopoietic cells.

Homing

In addition to their immune-suppressive properties, MSCs appear to exhibit a tropism for damaged or rapidly growing tissues. For example, following injection into the brain, MSCs migrate along known pathways when injected into the corpus striatum. MSCs migrated throughout forebrain and cerebellum, integrated into central nervous system cytoarchitecture, and expressed markers typical of mature astrocytes and neurons after injection into the lateral ventricle of neonatal mice. MSCs injected into injured spinal cord were found to form guiding "cord," ushering in regenerating fibers. MSCs may assist with regeneration in stroke or myocardial ischemia by release of trophic factors such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, or angiogenic factors.

The tissue infiltration response of MSCs is seen in experimental stroke and myocardial ischemia, in addition to the infiltration in injured nervous system tissue listed previously.

There is now compelling evidence that MSCs, guided by chemokines and other cues emanating from areas of pathology such as tumors, will "home" specifically to those areas. The supporting connective tissue stroma of a tumor is formed in a manner similar to wound healing and scar formation, and tumours generate signals to recruit stromal cells from contiguous regions as well as from bone marrow to sustain themselves. Because UCM stem cells are very closely related to MSCs, it would not be surprising to find that they also will home to tumors, and in fact such a phenomenon has been observed in preliminary experiments in our laboratory (unpublished observations). The exact signals that recruit transplanted or endogenous cells to regions of inflammation or neoplasia remain obscure. However, stromal cell-derived factor-1α plays a crucial role in recruitment of bone marrow-derived cells to the heart after myocardial infarction. Matrigel invasion assays have implicated such molecules as platelet-derived growth factor-BB, epidermal growth factor, and stromal cell-derived factor-1α as chemokines for MSCs; however, neither basic FGF (bFGF) nor vascular endothelial growth factor (VEGF) had an effect. In any event, the directed trafficking of umbilical and other mesenchymal stem cells to tumors opens the enticing prospect that they may be a platform for targeted delivery of high local levels of protein. Often, such proteins have a short half-life and/or cause major side effects when given systematically.

MSCs Support Expansion of Other Stem Cells

Mesenchymal cells have been reported to act as supporting cells that promote the expansion of other stem cell types. For example, MSCs and MSC-like cells support ex vivo expansion of hematopoietic stem cells. When co-grafted, MSCs and MSC-like cells support in vivo engraftment of hematopoietic stem cells, too. This work suggests that MSCs from a variety of sources, including umbilical cord, may facilitate engraftment of hematopoietic stem cells. This addresses two significant problems found in umbilical cord blood transplantation: (1) getting enough cells to engraft an adult and (2) increasing the speed of engraftment. Theoretically, cografting or ex vivo expansion may enable transplantation of cord blood units into larger patients and speed the engraftment in other patients. In addition to hematopoietic cells, Mesenchymal cells derived from Wharton's jelly are useful as feeder layers for the propagation of other stem cell types. For example, equine embryonic stem cell-like cells derived from the inner cell mass were propagated successfully for more than 350 divisions on a feeder layer derived from stem cells isolated from Wharton's jelly of equine umbilical cords. The equine ES-like cells could be maintained without leukaemia inhibitory factor (LIF) as long as they were on the cord matrix cells.

UCM Cells for Tissue Engineering

A major potential application of stem cells in medicine is for "tissue engineering," in which the ultimate goal is to provide off-the-shelf tissues and organs. UCM cells demonstrate excellent cell growth properties on bioabsorbable polymer constructs. UCM cells were used to seed blood vessel conduits fashioned from rapidly bioabsorbable polymers and grown in vitro in a pulse duplicator bioreactor. Recently, living patches engineered from UCMS cells and cord-derived endothelial precursor cells have been described for potential use in human paediatric cardiovascular tissue engineering.

Summary

MSCs and MSC-like cells are useful multipotent stem cells that are found in many tissues. While MSCs can be isolated from adults via peripheral blood, adipose tissue, or bone marrow apiration, MSCs derived from the discarded umbilical cord offer a low-cost, pain-free collection method of MSCs that may be cryogenically stored (banked) along with the umbilical cord blood sample. From the umbilical cord, isolation of cells from the Wharton's jelly has the greatest potential for banking, presently, because the most cells can be isolated consistently. The challenge for the future is to define industrial-grade procedures for isolation and cryopreservation of umbilical cord-derived MSCs and to generate Food and Drug Administration (FDA)-approved standard operating procedures (SOPs) to enable translation of laboratory protocols into clinical trials. This represents a paradigm shift from what has been done with umbilical cord blood banking because the cord blood cells do not require much in the way of processing for cryopreservation or for transplantation (relatively). For such a challenge to be met, researchers in the field of umbilical cord-derived MSC need to organize and reach consensus on the characterization, freezing/thawing, and expansion of clinical-grade cells for therapies and tissue engineering. Thus, more and more umbilical cord stem cells can be diverted from the biohazardous waste bag and into the clinic, where their lifesaving potential can be realized.

Conflict of Interest

Not available

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Not available

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