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Mini Review

Human umbilical cord-derived stem cells

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ABSTRACT

This review focuses on the umbilical cord (UC) and cord blood (CB) stem cells harvested from the Wharton's Jelly (WJ), vessels walls and blood. UC and CB are accepted as promising sources of stem cells for research and clinical applications. Stem cells obtained from UC and CB have gained much attention over the last years since they can be easily isolated, without any ethical concerns, from a tissue, which is discarded after birth. It is ethically reliable, its ample supply, immunological immaturity and high plasticity make UC and CB as desired sources of stem cells when compared with other tissues including bone marrow. In this review, the authors firstly define the major component filling the inner part of UC; WJ where the mesenchymal stem cells reside in, secondly describe the characteristics and functions of UC vessel pericytes, and finally discuss the advantages and limitations of CB hematopoietic stem cells.

Keywords: Hematopoietic stem cells, mesenchymal stem cells, stem cells, umbilical cord, vessels, Wharton Jelly's

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INTRODUCTION

Human Umbilical Cord (UC)

During pregnancy the UC connects the fetus to the placenta and supplies oxygen and nutrients to the baby through cord blood (CB). At the end of pregnancy, the UC of 50-70 cm length and 1-1.5 cm thicknesses is discarded as medical waste. Today, this perinatal tissue is considered as a valuable source of stem cells [1]. Perinatal stem cells represent a bridge between embryonic and adult stem cells [2]. They are characterized by their pluripotency capacity but they do not form tumors when transplanted. The surface of the UC is comprised of the cuboidal amniotic epithelium contiguous with the placenta and fetus. Amniotic epithelium is the outer envelope of the tissue, and it represents the only epithelium in the tissue. This layer is not a source of mesenchymal stem cells (MSCs) [3]. The inner part of the cord made up of gelatinous connective tissue known as Wharton's Jelly (WJ) and vessels; two arteries and a single vein [4].

WJ and MSCs

WJ is composed of cells (MSCs, 5%) and mostly extracellular matrix proteins (collagen IV, proteoglycans and hyaluronic acid, 95%) [5]. This jelly has physical properties much like a polyurethane pillow. The crucial role of the WJ is to prevent the mechanical force such as compression, torsion, and bending of the umbilical vessels which provide the flow of the gas (oxygen) and nutrients (glucose and amino acids) to the fetus, while also depleting the fetus and placenta of carbon dioxide and other waste products [6]. WJ cells lock into the WJ early in embryogenesis during their migration from the aortic-gonadotropinmesonephric region to the fetal liver through the UC [7]. These cells are referred as WJ-MSCs and have the ability to differentiate osteogenic, adipogenic and chondrogenic lineages and possess expression of cell surface markers such as CD105, CD73 and CD90. They also express embryonic stem cell markers Tra-1-60, Tra-1-81, SSEA-1 and 4, alkaline phosphatise, Oct-4, Nanog and Sox-2 [6]. These cells have an increased proliferative capacity, a higher frequency of colony forming unit fibroblast and a shorter population doubling time. Explants culture and enzymatic digestion are two basic methods to isolate MSCs from the human UC [8]. Culture condition such as oxygen (normoxic condition), glucose intake, growth factors (basic fibroblast growth factor, epidermal growth factor, platelet derived growth factor) affect cell expansion and differentiation [9]. WJ-MSCs have been reported to be immune privileged. MSCs invoke only minimal immune reactivity due to the lake of expression of MHC Class II antigens and may possess anti-inflammatory and immuno-modulatory effects due to their cytokine, chemokine and growth factor expression profiles [10]. WJ-MSCs do not require tissue matching, thus, allowing for an allogeneic cell therapy source [11]. Tamura *et al*. have demonstrated that these cells produce several

secretory proteins that in turn promote the cell death of cancer cells and stop the cell cycle [12]. Transplantation of WJ-MSCs has also been tested in liver fibrosis. There was a remarkable decrease in the liver fibrosis in the rats treated with WJ-MSCs compared with the rats that were not treated with the WJ-MSCs [12].

Cord Vessels and Pericytes

The walls of arteries and veins are composed of endothelial cells, smooth muscle cells, fibroblast and extracellular matrix. These are arranged into three layers: Intima, media and adventitia [13]. The UC vessels are well known as a source of endothelial cells; human umbilical vein endothelial cells [14]. It has been shown that these cells support hematopoiesis through synthesis of cytokines and adhesion molecules then induce maintenance and proliferation of UC blood hematopoietic stem cells (HSCs) [15]. The wall of blood vessels is surrounded by perivascular cells [4,13]. These cells are awarded the name of pericytes and are accepted as MSC ancestors that line the abluminal side of endothelial cells in the perivascular space [16]. They can be identified by a combination of perivascular and MSCs markers such as 3G5, CD146, NG2, platelet-derived growth factor receptor-beta (PDGFRβ), α-smooth muscle actin, CD29, CD44, CD73, CD90, CD105 and alkaline phosphatase, lack of hemato-endothelial cell markers; CD31, CD34, CD45, CD144, von Willebrand factor expression [17]. Their first isolation from various tissues using CD146 marker was published by Crisan *et al*. [18]. They are fibroblast-like in appearance with a prominent nucleus and little cytoplasm [19]. Pericytes have been shown to differentiate into mesodermal lineages including bone, cartilage, fat and muscle. Endothelial cells and pericytes regulate vessel formation, maturation, and specification [20]. They communicate with each other by direct cell contact and by paracrine signaling pathways including platelet-derived growth factor B/PDGFR-β, angiopoietin-Tie2, S1P/Edg Signaling and Notch Signaling [20,21]. Pericytes play a crucial role in angiogenesis and vascular maintenance, they induce maturation and regulation of the vessel integrity, structure and function due to high level of α-smooth muscle action and myosin presence [20]. Unlike the endothelial cells, they show the contraction that protects the vessel from stretching during inflammation [22]. They play a role in the inflammatory process controlling the rate at which inflammatory cells leave the blood stream and migrate to the wound site. They also play a role in the matrix formation process of wound healing [21]. The migratory potential of human perivascular cells is an important parameter in seeking to ensure homing to injured tissues [23].

CORD BLOOD HSCS

At the end of pregnancy 50-150 mL of umbilical cord blood (UCB) is also discarded as medical waste. However, it is well known that UCB is a rich source of HSCs that differentiate to form hematopoietic lineages for use in transplantation. Stem cell transplants are used to restore the hematopoietic system when the bone marrow of the patients has been destroyed by disease, chemotherapy or radiation [24-26]. UCB is naturally enriched in hematopoietic stem and progenitor cells, but the absolute numbers are small since only 50-150 mL of UCB is typically obtained. CD34+ cells contain both primitive HSC with long term regenerative ability and more mature progenitors which mediate short term hematopoiesis [27]. The minimum accepted UCB cell dose to achieve engraftment is reported to be 2 and 3 × 10^7 mononuclear cells/kilogram per recipient while the content per UCB unit ranges between 0.4 and 1.0 × 10^9 total mononuclear cells, which is the major reason for the limitation of this stem cell source in adult patients [28]. Besides the limited number of stem cells available in a typical UCB unit, delayed engraftment [29] (neutrophils [22-30 days] and platelets [56-100 days] [30-33] [depends on related/non-related donors or disease]) and aberrant immune reconstitution, all leading to a higher mortality are the main problems after infusion of an UCB unit. It has been reported that there is a correlation between the dose of nucleated cells infused and the recovery of neutrophils and platelets after transplantation [34,35]. The earliest consideration that was investigated to accelerate engraftment and improve immune reconstitution was to expand the primitive UCB progenitors *ex vivo* and transplant with or without the unmanipulated portion of UCB [36]. Co-transplantation of two or more partially unrelated UCB units is one approach that is being explored to overcome the limitation of low cell dose in single unit UCB transplantation [37,38].

Efforts to expand UCB hematopoietic cells in liquid cultures by the use of proper combinations of cytokines result in an increase in the number of progenitors, but expansion of cells with repopulating potential remains limited at this time [39]. It is clear that additional studies focusing on the composition and quality of HSCs in UCB are required [40].

In vitro systems are limited because they generally support the development of only one or a few hematopoietic lineages. Because mammalian cells can adapt to tissue culture condition, long term culture initiation may not be a reliable indicator of HSC function. Protocols for obtaining extremely pure preparations of progenitor cells have been developed in many laboratories [41-43]. The initial selection of primitive hematopoietic progenitor cells (CD34+) will be necessary for the expansion of hematopoietic progenitors *in vitro* prior to transplant [35,44]. Cultivation of isolated stem and progenitor cells has some distinct advantages such as simplicity, clinical applicability and the possibility to use standard cell culture techniques [45]. Over the past decade, technologies have

developed rapidly with advances in our understanding of hematopoiesis which enables us to begin mimicking hematopoiesis *ex vivo* [46,47]. Novel technologies, such as tissue engineering, co-culture systems, three-dimensional bioreactors, microfluidic systems and gene therapy must be explored to improve the expansion of HSCs [48].

CONCLUSION

UC and CB can be accepted as promising sources of stem cells for research and clinical applications. It is ethically reliable, its ample supply, immunological immaturity and high plasticity makes UC and CB as desired sources of stem cells than bone marrow or others. However, a number of questions remain to be further investigated.

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