REVIEW ARTICLE

Novel Sources of Fetal Stem Cells for Future Regenerative Medicine

Yani Lina[1,2]* and Andi Wijaya[1,3]

[1]Post Graduate Program in Clinical Biochemistry, Hasanuddin University, Jl. Perintis Kemerdekaan Km.10. Makassar, Indonesia
[2]Prodia Stemcell Indonesia, Jl. Kramat VII No.7, Jakarta, Indonesia
[3]Prodia Clinical Laboratory, Jl. Cisangkuy No.2, Bandung, Indonesia
*Correspondence: yani_lina1979@yahoo.com

Abstract

Mesenchymal stromal cells are multipotent cells considered to be of great promise for use in regenerative medicine. However, the cell dose may be a critical factor in many clinical conditions and the yield resulting from the *ex vivo* expansion of mesenchymal stromal cells derived from bone marrow may be insufficient. Thus, alternative sources of mesenchymal stromal cells need to be explored.

There are multiple extra-embryonic tissues emerging during gestation including umbilical cord blood (UCB), amniotic fluid (AF), Wharton's jelly, the amniotic membrane and the placenta, which are all discarded following birth. Fetal stem cells from these sources actually represent a new class of stem cells developmentally and operationally located between the state of embryonic stem cells and adult stem cells, sharing and exhibiting features of pluripotency and multipotency, without necessarily implying that they can generate every type of tissue.

Fetal stem cells have been recently isolated from several tissues (amniotic fluid, umbilical cord, Wharton's jelly, amnion and placenta). They are derived either from the fetus proper or from the supportive extra-embryonic structures. They represent ideal sources for regenerative medicine since they are easily accessible, exhibit high proliferation rates, do not form teratomas and present no ethical reservations like embryonic stem cells (ESC). Their functional features indicate that they actually represent intermediates between ESC and adult stem cells.

KEYWORDS: Mesenchymal stem cells, fetal stem cells, amniotic fluid, umbilical cord, placenta, Wharton's jelly

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Introduction

Mesenchymal stem cells (MSC) are a prototypical adult stem cell with capacity for self-renewal and differentiation with a broad tissue distribution (1). In 1970, Friedenstein and colleagues demonstrated that bone marrow (BM) contained a population of hematopoietic stem cells (HSC) and a rare population of plastic-adherent stromal cells. These plastic adherent cells, initially referred to as stromal cells, is now commonly called MSC (2). Friedenstein was the first investigator to demonstrate the ability of MSC to differentiate into mesoderm-derived tissue and to identify their importance in controlling the hematopoietic niche (3). In 1980, MSC were shown to differentiate into osteoblasts, chrondrocytes, and adipocytes (4-5). Caplan demonstrated that bone and cartilage turnover was mediated by MSC, and the surrounding conditions were critical to inducing MSC differentiation (6). In late 1990, Kopen *et al.* described the capacity of MSC to transdifferentiate into

ectoderm-derived tissue (7). MSC were demonstrated to suppress T-lymphocyte proliferation, which paved the way to the application of MSC therapy for allogeneic transplantation and to its potential in immunomodulatory therapy (8). They offer the advantage that they are easily expanded and stored *ex vivo* and are considered to be "immunoprivileged". Thus, once harvested, they can safely be infused into either autologous or allogenous hosts owing to their lack of host immune reactivity (9-12). From a therapeutic perspective, and facilitated by the ease of preparation and immunologic privilege, MSC are emerging as an extremely promising therapeutic agent for tissue regeneration (1).

MSC represent a rare population (approximately 0.001-0.01% nucleated cells) of adult human bone marrow cells, but they can also be identified in other adult tissues such as muscle, periosteum, adipose and other connective tissues (13-16). Large numbers of MSC would be needed for regenerative medicine but the frequency and expansion capacity of adult MSC are limited and may decrease with age. Thus, alternative sources of MSC need to be explored (17). The recent isolation of fetal stem cells from several sources either at the early stages of development or during the later trimesters of gestation, sharing similar growth kinetics and expressing pluripotency markers, provides strong support to the notion that these cells may be biologically closer to the embryonic stem cells, actually representing intermediates between embryonic stem cells and adult mesenchymal stem cells, regarding proliferation rates and plasticity features, and thus able to confer an advantage over postnatal .

Novel Sources of Fetal Stem Cells

Human MSC have been isolated from bone marrow, adipose tissues, cord blood, amniotic fluid, amniotic membrane, placenta, and umbilical cord tissues (19-30). Bone marrow (BM) has been considered the main MSC source because of their potential to both proliferate and differentiate. However, other sources of similar cell populations are being investigated, because BM-derived MSC isolation requires a painful and invasive procedure, the frequency of MSC is low, and their ability to proliferate and differentiate declines with age (19,31-33).

Adipose tissue has recently been identified as a convenient alternative source of MSC-like cells. Adipose tissue-derived stem cells (ADSC) are available in quantities of hundreds of million cells per individual, have an extensive self-renewal capacity, are easily isolated by differential sedimentation, and can be cultured for several months *in vitro* with low level of senescence. ADSC also have the potential to differentiate into various cells, including adipocytes, osteoblasts, chondrocytes, neurons, and multinucleated myocytes in response to lineage-specific induction factors (14,34-40).

Mesenchymal stromal cells from amniotic fluid represent a relatively homogenous population of immature cells with immunosuppressive properties and extensive proliferative potential. Despite their high proliferative capacity in culture, studies have not observed any karyotypic abnormalities or transformation potential *in vitro* nor any tumorigenic effect *in vivo* (41).

Umbilical cord blood (UCB) is an easily accessible alternative source for multipotent MSC and is generally believed to provide MSC with a higher proliferative potential compared with adult bone marrow. However, reaching the estimated clinical dose of at least $2x10^6$ MSC per kilogram body weight of adult patients has been a major problem that has hampered the progress of clinical UCB MSC applications (42). Umbilical cord and amniotic membrane are attractive sources to obtain adult stem cells due to total global abundances, ease in culture, and fewer ethical concerns unlike those of embryonic stem cells. Isolated stem cells can still differentiate into many different lineages. Hence, the use of umbilical cord and amniotic membrane as sources of stem cells could be one of the answers to the upcoming application of stem cells in regenerative medicine (43).

Placental tissue draws great interest as a source of cells for regenerative medicine because of the phenotypic plasticity of many of the cell types isolated from this tissue. Furthermore, placenta, which is involved in maintaining fetal tolerance, contains cells that display immunomodulatory properties. These two features could prove useful for future cell therapy-based clinical applications. Placental tissue is readily available and easily procured without invasive procedures, and its use does not elicit ethical issue (44). More recently, some groups have reported success in isolating and establishing MSC cultures from umbilical cord (UC) vein and UC stroma, also called Wharton's jelly (45-49).

Fetal stem cells represent a relative newcomer in the field, exhibiting unique and fascinating features, while recent studies have so far provided an impressive wealth of information and new insight into our understanding of the biology of stem cells in general and have suggested putative strategies to exploit their therapeutic potential. These cells can be derived either from the fetus proper or from the supportive extra-embryonic structures that are of

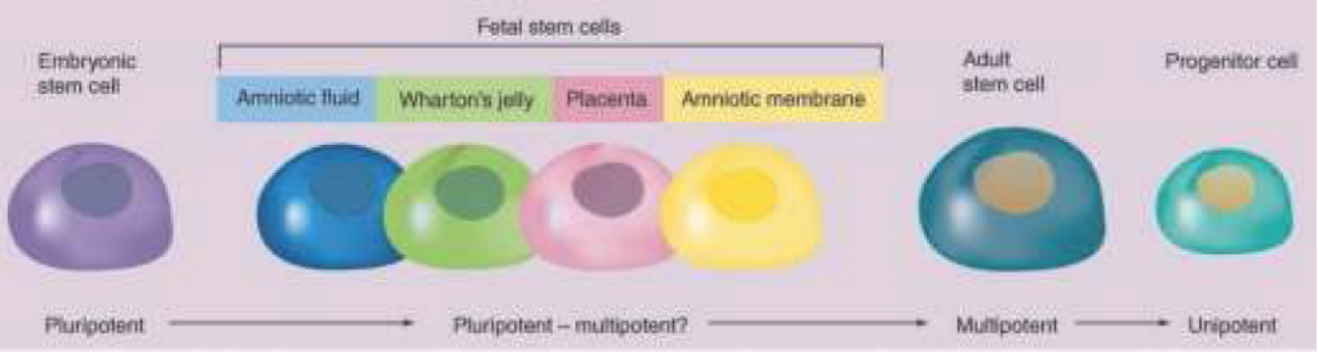

Figure 1. Current Model for the Developmental Position and Potency of the Fetal Stem Cells from Several Fetal Sources Emerging During Gestation, Such As the Amniotic Fluid, Wharton's Jelly, Placenta and Amniotic Membrane (Used with permission from American Society of Hematology. 2009).

fetal origin (50). A series of recent studies regarding the numerous novel features of fetal stem cells have reignited our interest in the field of stem-cell biology and in the possibilities for the eventual repair of damaged organs and the generation of *in vitro* tissues on biomimetic scaffolds for transplantation. These studies, employing elegant approaches and novel technologies, have provided new insight regarding the nature and the potential of fetal stem cells (18).

Amniotic Fluid Stem Cells

Traditionally, amniotic fluid (AF), via amniocentesis, has been used for decades as a consistent source for prenatal diagnosis; however, recent studies have provided important clue about the potential of AF cells to become an alternative source of stem cells (23-24,51-59). The cells are mostly of epithelial nature, derived either from the developing fetus or from the inner surface of the amniotic membrane. AF cells of earlier gestational age seem to express higher levels of endoderm and mesoderm markers compared with those of later gestational age, while ectodermal markers show no difference (57).

Human amniotic fluid has great cellular heterogeneity, the composition of which varies with gestational age and fetal development. The viable adherent cells of amniotic fluid can be classified into three large groups according to their morphologic and biologic characteristics: epitheloid (E-type) cells, with a low expansion potential; typical amniotic fluid (AF-type) cells, with a moderate expansion potential; and fibroblastoid (F-type) cells, with an enormous expansion potential. Human amniotic fluid-derived mesenchymal stromal cells (hAMSC) possess the potential to be used in regenerative medicine, given their great expansion capacity, differentiation potential and probably great undifferentiation (51,53,55,60-76). Recent study by Miranda-Sayago *et al.* showed that F-type hAMSC exhibit reproducible biologic characteristics, confirming that these cells are ideal candidates for use in regenerative medicine (77).

Systematic studies on the yield of AF-MSC have disclosed that these cells proliferate rapidly greater than ninefold logarithmic cell expansion within a mean period of 32.9 days, regardless of the serum type or the gestational age. This implies that as little as 5 mL of AF can readily produce more than $100x10^6$ cells required to engineer a surgically implantable construct (59). The *in vivo* applications of AF-MSC are still at an early stage (18). Amniotic fluid stem (AFS) cells might represent a novel source for cell therapy and cell transplantation strategies in repair following ischemic heart disease, with a possible paracrine mechanism of action and a potential molecular candidate for acute cardioprotection (75).

Recent studies support cell-based therapies for cancer treatment. An advantageous cell types for such therapeutic schemes are the mesenchymal stem cells (MSC) that can be easily propagated in culture, genetically modified to express therapeutic proteins, and exhibit an innate tropism to solid tumors *in vivo*. The AF-MSC tropism and capability to transport interferon beta (IFNβ) to the region of neoplasia in a bladder tumor. Study showed significant inhibition of tumor growth as well as prolonged survival of mice were observed in the presence of IFNβ-AF-MSC. Collectively, these results document the great potential of AF-MSC as anti-cancer vehicles, implemented by the targeting of the tumor site and further facilitated by their high proliferation rate and expansion efficiency in culture (76).

Umbilical Cord Blood Stem Cells

During the last 23 years, umbilical cord blood (UCB) has been exploited as a rich source of hematopoietic and progenitor stem cells to establish therapeutically effective hemopoiesis, both for malignant and non-malignant disorders (77). Approximately 1% of the mononuclear cord blood cells express the CD34 antigen, which represents the cardinal marker for hematopoietic stem cells (HSC). The capacity of $CD34^+$ stem cells for self-renewal and differentiation to several cell lineages has been convincingly established by employing a series of *in vitro* and *in vivo* assays (18,77).

UCB-MSC, representing the second major cell population of cord blood, are unique since they possess an intermediate phenotype that more closely resembles embryonic stem cells (ESC). Beside the typical markers for MSC (i.e SH2 or CD105, SH3 or CD73 and CD44), UCB-MSC also express markers for ESC such as Oct-4 that is essential for inhibiting tissue-specific genes and thus enhancing self-renewal and pluripotency. Further studies have extended the embryonic profile of the UCB-MSC by documenting significant expression of additional ESC markers including SSEA-3, SSEA-4, Tra 1-60, Tra 1-81 and Nanog. Furthermore, their multipotency and differentiation capacity to cell lineages derived from all three germ layers has been documented (77-83).

UCB MSC with retained differentiation potential can be expanded to a clinical quantity of more than $1x10^8$ cells with approximately 7 weeks. The rapid generation of large quantities of MSC from human UCB may ease the analysis of the biology and function of UCB MSC in various experimental models (42).

Wharton's Jelly Stem Cells

The umbilical cord connects the fetus to the placenta. In addition to its essential role in prenatal development, the human umbilical cord has now been recognized as an ethically acceptable, safe and sustainable source of stem cells (49,85). The umbilical cord contains one vein and two arteries which are surrounded by mucoid connective tissue, and this is called the Wharton's jelly. The cord is covered by an epithelium derived from the enveloping amnion. The network of glycoprotein microfibrils and collagen fibrils in the Wharton's jelly has been previously studied. In the Wharton's jelly, the most abundant glycosaminoglycan is hyaluronic acid which forms a hydrated gel around the fibroblasts and collagen fibrils and maintains the tissue architecture of the umbilical cord by protecting it from pressure. The phenotypic stromal cells in the Wharton's jelly are fibroblast-like cells. Mesenchymal cells isolated from the umbilical cord express matrix receptors (CD44, CD105) and integrin markers (CD29, CD51), but not hematopoietic lineage markers (CD34, CD45). Interestingly, these cells also express significant amounts of mesenchymal stem cell markers (SH2, SH3) (86-89).

Technical procedures to isolate MSC from the Wharton's jelly are poorly investigated and vary dramatically depending on the authors. Although the enzymatic treatment with collagenase is the most widely used technique for isolating stromal cells, this treatment varies in the literature. Trypsin or other enzymes such as hyaluronidase have been frequently but not systematically added to the collagenase, and the incubation time also varies from 4 to > 24 hours. Moreover, some authors have removed the cord vessels by stripping them manually before enzymatic treatment. Recently, a simplified protocol based uniquely on the capacities of MSC to adhere to a plastic surface without enzymatic treatment or dissection. Using this method, MSC can be isolated from all human umbilical cords and obtain a mean of $1.4x10^8$ cells at the second passage and > $7x10^9$ cells at the third. The expanded cells express characteristic markers and presented typical functional properties of MSC such as differentiation capacities, immunologic properties, and hematopoietic supportive functions (45,48,90-94).

Compared to BM-MSC, Wharthon's Jelly-MSC had higher expression of undifferentiated human embryonic stem cell (hES) markers like NANOG, DNMT3B, and GABRB3, pluripotent/stem cell markers, as well as some early endodermal markers both at early and late passages. Wharton's Jelly-MSC possess properties of true stem cells, which they retain even after extended *in vitro* culture (93). Since Wharton's jelly cells (WJC) expand faster and to a greater extent than adult-derived MSC, these finding suggest that WJC are a primitive stromal cell population with therapeutic potential. The preclinical work suggests that the WJC are therapeutic via trophic rescue and immune modulation (95). Several attempts have been initiated recently regarding the *in vivo* assessment of differentiated cells derived from Wharton's jelly MSC as a basis for cell therapy. Enhanced muscle regeneration has recently been documented following transplantation of umbilical cord matrix stem cell (UCMSC) in a mouse model of severe muscle damage (96).

Human UCMSC may have the ability to differentiate along several cell lineages of mesodermal or ectodermal origin (45,95,97-100). Furthermore, recent studies reported that hUCMSC were able to differentiate both *in vivo* and *in vitro* into hepatocyte-like cells and pancreatic islet precursors of endodermal origin (95,101). Exposed to a hepatogenic culture medium, hUCMSC expressed hepatic markers including albumin, α-fetoprotein, cytokeratin-19, connexin-32 and dipeptidyl peptidase IV (95). This study provided the foundation for the application of hUCMSC for liver regeneration. Like other MSC, hUCMSC are able to differentiate along a chondrogenic lineage under the stimulation of TGF-β in 3D cell pellets and poly-glygolic acid (PGA) scaffolds (45,89,102-104). A further modified chondrogenic environment, perhaps including the investigation of factors such as bioactive chemical signals (e.g. growth factors and aggrecan), oxygen tension, coculture, mechanical stimulation and/or *in vivo* regulation, will be needed to enhance chondrogenesis to apply hUCMSC in hyaline cartilage tissue engineering (105).

hUCMSC can differentiate into neuron-like cells when cultured with neuronal-conditioned medium (NCM) for 6 days (106). Moreover, transplantation of dopaminergic neurons derived from hUCMSC into the striatum of parkinsonian rats alleviates lesion-induced, amphetamine-evoked rotation behavior (107). The therapeutic benefits of hUCMSC transplantation for ischemic stroke are likely due to the ability of the cell to produce growth-promoting factors. Thus, hUCMSC transplantation may be an effective therapy in the future (108).

Amniotic Membrane Stem Cells

Amniotic membrane, or amnion, has recently emerged as another novel and alternative fetal source of stem cell population. Specifically, amniotic membrane, lacking any vasculature, is derived from the epiblast by day 8, comprising three layers. The three layers are an inner epithelial layer consisting of epithelial cells termed amniotic epithelial cells (AEC), an intermediate basement membrane lacking any cellular component and an outer layer juxtaposed to the chorion consisting of mesenchymal stem cells calles amniotic mesenchymal or amniotic membrane mesenchymal stromal cells (AM-MSC). Since these amnion cells, often called amnion-derived stem cells, originate from epiblast cells, it is conceivable that they might retain, and eventually portray, several stem cell features through gestation and are associated with a low percentage of HLA antigen-expressing cells (18).

Unlike other mesenchymal cells, only human amniotic membrane-derived mesenchymal stem cells (hAMS) express no major histocompatibility complex (MHC) class I molecule and may be expected to show immunologic tolerance. Because hAMC have a high ability to transdifferentiate into cardiomyocyte and to acquire immunologic tolerance *in vivo*, they can be a promising cellular source for allograftable stem cells for cardiac regenerative medicine (109).

The plasticity of amnion-derived stem cells has also been recently tested in cultures at the clonal level, where long-term self-renewal and multidifferentiation capacity have been documented (110). The proliferation rate of AM-MSC was found to lead to an approximately 300-fold expansion in 21 days, yielding 2.9×10^6 cells (111).

Placenta-Derived Stem Cells

As a unique and transient fetomaternal organ, the placenta represents a significant, valuable and promising source of stem cells with variable potency (18). The placenta is a fetomaternal organ consisting of 2 components: the maternal component, termed the deciduas, originating from the endometrium; and the fetal component, including the fetal membranes—amnion and chorion—as well as the chorionic plate, from which chorionic villi extend and make intimate contact with the uterine decidua during pregnancy (112). The pure stem cells populations derived from human placental tissues are the chorionic mesenchymal stromal cells and the chorionic trophoblastic cells, both demonstrating variable plasticity (44,50).

International Workshop on Placenta-Derived Stem Cells saw the following nomenclature proposed: human amniotic epithelial cells (hAEC), human amniotic mesenchymal stromal cells (hAMSC), human chorionic mesenchymal stromal cells (hCMSC), and human chorionic trophoblastic cells (hCTC). Furthermore, isolation protocols, phenotypic markers, and *in vitro* differentiation potential have been described for hAEC, hAMSC and hCMSC (44).

The placental tissues harbor different cell types that may complement each other in a clinical setting (i.e amniotic epithelial cells of early embryological origin with multilineage differentiation potential, as well as cells with immunomodulatory properties (44). It is tempting to speculate that placenta-derived cells may also be preferable

from an immunological point of view, given the unique role of this tissue in maintaining fetomaternal tolerance throughout pregnancy, and supported by the finding that placental cells show a greater capacity to down-regulate T-cell proliferation *in vitro* compared to bone marrow-derived cells (112).

The large number of hepatic genes and functions identified in human amniotic epithelium (hAE) suggest that if effective and efficient methods were developed to induce complete hepatic differentiation, hAE could be a useful source of cells for transplant procedures. Preclinical investigations with hepatic differentiation of hAEC have been promising (44). Human AEC have shown particular potential for treating central nervous system disorders. Since the discovery that hAEC have stem cell properties, express neural and glial markers and neural specific proteins, and also have the capacity to produce and secrete neurotransmitters, cell therapy with these cells has been considered (113-116). Successful transplants of hAEC into caudate nucleus, hippocampus and spinal cord have been reported (117-121). Transplantation of hAEC in a rat model of Parkinson's disease reversed the condition and prevented neuronal death (117-118).

hAEC transplants produce beneficial results in animal models of spinal cord injury. They were found to exhibit neuroprotection in acute phases of injury and facilitate regeneration of long tracts in long-term phases of recovery, as measured by behavioral assessment. The beneficial effect may be mediated through the secretion of novel neurotrophic factors. The preclinical studies reported strongly support the hypothesis that placenta hold much promise for the development of cell-based therapies for clinical application in the near future (44).

Summary

Recent studies on the various types of fetal stem cells have suggested that they represent a new class of stem cells developmentally and operationally located between the state of ESC and adult stem cells, sharing and exhibiting features of pluripotency and multipotency, without implying that they can generate every tissue. Stem cells derived from these fetal extra-embryonic sources, mostly of the mesenchymal type, have the advantage that they rapidly expand to adequate numbers required for clinical applications, and display negligible immunogenicity and demonstrate no evidence for teratoma formation, while presenting no ethical concerns. The fascinating features and the potential therapeutic properties of fetal stem cells from the various fetal sources described here are expected to be gradually implemented at the clinical level, through the establishment of comprehensive international guidelines for the clinical translation of stem cells and their direct derivatives (18,122).

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