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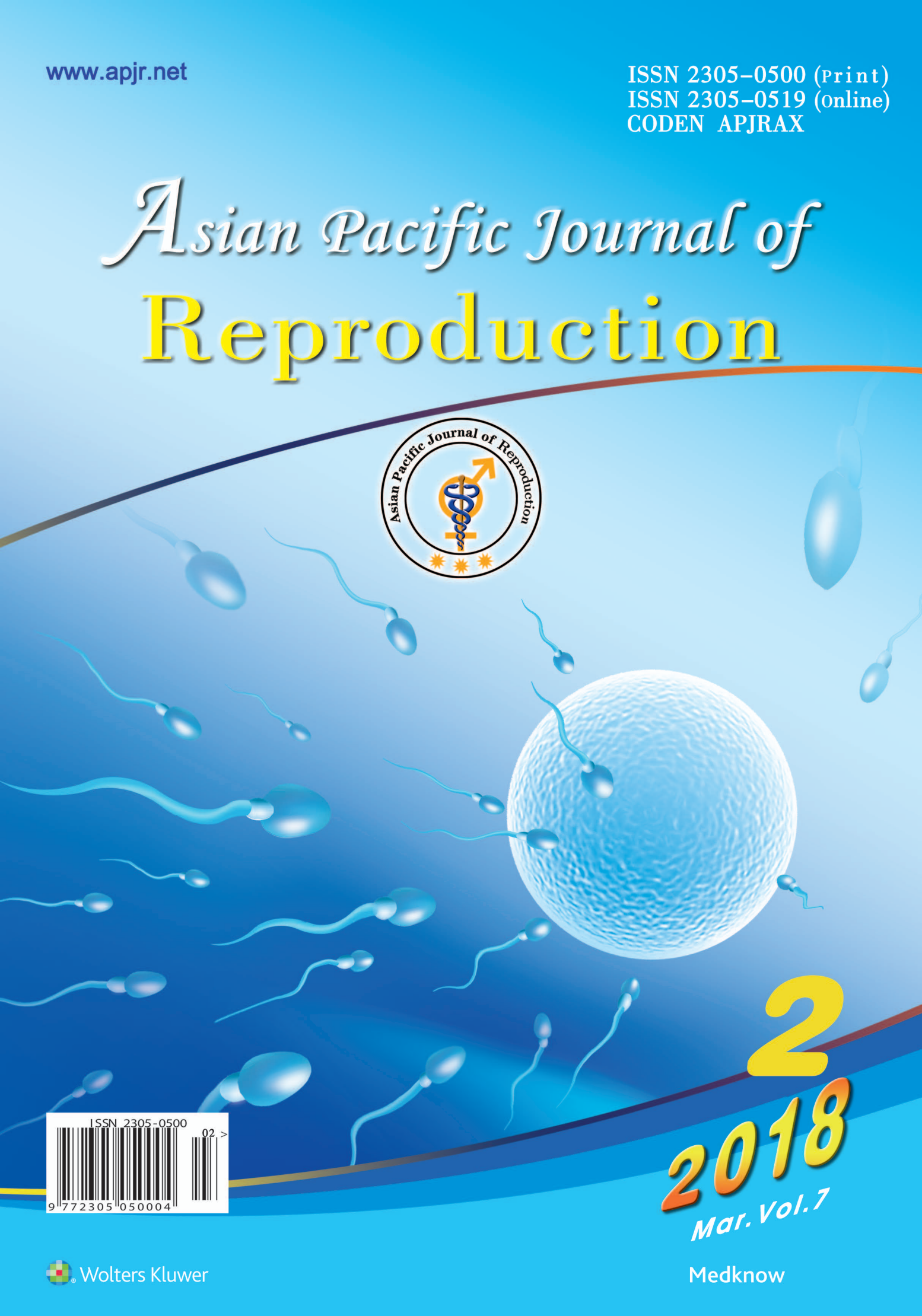

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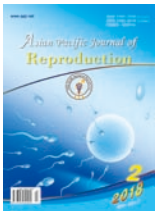

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Germline cells derived from mesenchymal stem cells, with the focus on Wharton's jelly

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ABSTRACT

Previous attempts have indicated that mesenchymal stem cells (MSCs) are a valuable source and candidate and new approach for tissue engineering and reproductive medicine. MSCs have this potential to be induced and differentiated in an appropriate *in vivo* and *in vitro* condition toward various cell lineages and then they can be applied in cell therapies and clinical applications. During recent two decades, various sources have demonstrated they are a great source for MSCs, including bone marrow, the human umbilical cord as well as Wharton's jelly. Due to discarding after birth, easily accessible cells and less ethical concerns, these cells have attracted more and more scientists' attention. Infertility and reproduction diseases have provided special opportunity to examine the efficiency of MSCs in this kind of application. Based on recent investigations, MSCs embedded in Wharton's jelly tissue are more appealing for cell therapies, especially in infertility treatment purposes. So, differentiation of MSCs embedded in Wharton's jelly tissue into germ layer cells for cell-based therapy purposes is now under intensive study.

1. Introduction

Mesenchymal stem cells (MSCs) are a valuable source for clinical application of cells and tissue engineering[1−3]. Source of variations arise from whether the cells were derived from allogeneic or autologous sources. Autologous sources are more appreciated because they eliminate issues such as contamination and risk of malignancy[4]. The allogeneic application brings some others problems such as possible ineffectiveness[5]. There is a body of reports showing that MSCs have a particular function in *in vitro* and *in vivo* condition. They display immunomodulatory functions and inhibit T-lymphocyte proliferation and activation and induced by cellular factors[6,7], and respond to injury or stress, just like the respond of immune system cells to pathogen exposure[8,9], participation in regeneration, immune cell activation

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or suppression, angiogenesis, remodeling, bactericidal activity and cellularrecruitment[10]. MSCs also can be found in different adults and birth-associated tissues. This review study focused on some of the standard features of MSCs from various sources and their differentiation capacity toward germ line cells with an emphasis on Wharton's jelly.

2. Mesenchymal stromal cells

Mesenchymal stromal cells or stem cells are a great source of multipotent stem cells with self-renewal capacity, which have the capacity of differentiation into various cell lineages and be transdifferentiated toward astrocytes-like cells, hepatocytes and neural cells *in vitro* as well[11,12]. Due to their capacities, they are always utilized in tissue regenerative medicine and transplantation studies[13–17].

MSCs are derived from various tissues including bone marrow, adipose tissue, adult and fetal tissues and Wharton's jelly of the umbilical cord (Figure 1). They are undifferentiated cells that can be mostly found in embryonic and extraembryonic tissues[18]. The embryonic tissues containing MSCs are including spleen, fetal bone marrow, pancreas, lung, liver, and peripheral blood and the extra-embryonic structures such as umbilical cord, umbilical cord blood, amniotic fluid, placenta and amnion, are containing mesenchymal stem cells[2,19].

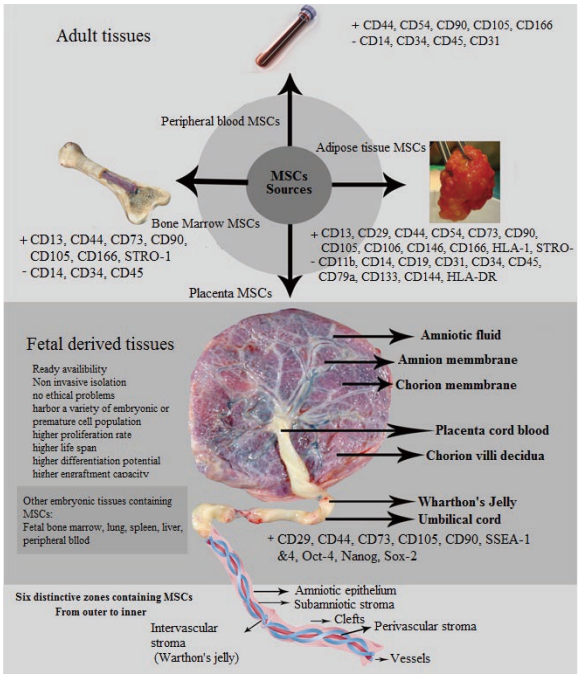

Figure 1. MSCs features from some sources and their differentiation capacity toward germline cells with an emphasis on Wharton's jelly.

Based on differentiation potential and proliferation capacity, there are variations between fetal and adult MSCs. Fetal MSCs have some priorities and advantages over other sources such as faster doubling time than adult MSCs, greater expansion capacity *in vitro* as well as longer telomeres[20]. Fetal MSCs don't have the properties of immune suppression, for instance, lack of class Ⅱ human leukocyte antigens (HLA Ⅱ), but they seem to synthesize HLA-G, in contrast to adult MSCs in which HLA Ⅱ is present and HLA-G is absent[21]. Overall, fetal MSCs are secreting a slightly different cocktail of cytokine than adult MSCs (Table 1)[22].

Table 1

Markers of BM-MSC, umbilical cord, and Wharton's jelly.

Marker	BM-MSC	Umbilical cord	Wharton's jelly	References
HLA-A	+	+	+	[68–70]
HLA-B	+	+	+	[68,71–73]
HLA-C	+	+	+	[68,71,74,75]
HLA-DR	-	-	-	[69,70,74,76]
HLA-G	+	-	+	[54,77,78]
CD29	+	+	+	[11,27,59,79]
CD44	+	+	+	[11,59,78]
CD73	+	+	+	[11,59,73,78]
CD105	+	+	+	[11,59,78]
CD53	+	+	+	[11,59,78]
CD54 ICAM-1	+	-/+a	*n*.a	[79–82]
CD56	-	-	-	[11,59,70]
CD58	+	-	+	[11,59]
CD106 VCAM-1	+	-/+	+	[78,80,81,83]
CD166 ALCAM	+	+	+	[69,78,81]
SSEA-1	+	-	+	[59,78]
Oct-04	+	-/+	+	[59,70,78]
Nanog	+	+	+	[59,70,84]
Sox-2	+	+	+	[59,84]

Two methods have been applied for isolation of MSCs including enzymatic digestion and tissue culture (insert method). In order to perform enzymatic digestion, after the membrane and veins have been removed, collagenase and trypsin are routinely utilized to digest the umbilical cord tissue. It has been proposed that trypsin and collagenase might damage the Wharton's jelly, however, this method has increased the outcomes of obtained cells[23]. Meanwhile, enzymatic digestion is unaffordable with a high risk of contamination and takes more time to perform and is not easy to control[24]. Mechanical digestion of the cord is an essential step before the onset of enzymatic digestion[25,26]. The common point of digestion is the use of collagenase-containing caseinase, clostripain, and tryptic activities. Type Ⅰ collagenase is routinely used for the isolation of stromal cells[27]. A combination of collagenase with hyaluronidase is critically important because it facilitates the outcomes of matrix digestion and shortens the time required for isolation process[26].

Different independent groups have reported their successful

isolated MSCs from umbilical cord using culture method[28,29]. Explant of tissue fragments is one of the most primitive techniques in cell isolation and propagation *in vitro*. This approach affects the quantity and quality of the isolated cells, but the tissue size should be small enough for freely gases and nutrients diffusion[30]. The primary explanted culture success rate is directly dependent on the migratory ability of the cell type[31].

3. MSCs derived from bone marrow

The first source which was claimed to comprise MSCs was bone marrow[32], and MSCs were obtained from bone marrow by Friedenstein's team for the first time[33]. They described these cells as a population of cells similar to fibroblast-like colonies with the capacity of differentiating toward multiple mesenchymal lineages and then Caplan *et al*[34] called these cells as "mesenchymal stem cells". Finally, Horwitz *et al*[35] recently referred these cells as "multipotent mesenchymal stromal cells".

The procedure of sampling from bone marrow is an annoying and invasive procedure[36], and along with aging and adolescence, the bone marrow-MSCs (BM-MSCs) numbered creases[20]. Meanwhile, this should be always considered in mind that the risk of viral contamination during the isolation of MSCs from bone marrow is still present[37]. Due to all of these reasons, the application of bone marrow in cell therapy procedures as a great source of MSCs has been limited. Therefore, the applications of other sources which have MSCs with a higher proliferative and differentiation potency and lower risk of viral contamination have been considered.

BM-MSCs have the ability of self-renewal and differentiate into connective tissues cells such as adipocytes, osteoblasts as well as chondrocytes[11,38,39]. They express various cell surface markers including CD29, CD44, CD73, CD90, CD105, CD166, CD49e, CD51, CD54, CD59, CD71 and CD200, however there are some other surface markers which BM-MSCs do not express (such as CD14, CD31, CD34, CD45, CD79, CD86, CD117 and glycophorin A) (Table 1)[11]. Characterizations of BM-MSCs and their non-tumorigenic properties have made them a suitable candidate for human therapeutic applications, particularly in degenerative diseases by autologous cell transplantation[40]. Also, they do not induce proliferation of T-lymphocyte *in vitro* and some reports have shown that they prevent the T-cell responses to mitogenic and antigenic stimuli. They don't have the capacity to stimulate B cells and are resistant to lysis which has been mediated by thenatural killer cell[41,42]. Di Nicola *et al*[6]indicated that transforming growth factor- β and hepatocyte growth factor block T-cell expansion in mixed lymphocyte reaction and T-lymphocytes are suppressed by BM-MSCs, and they couldn't enter apoptosis.

Johnson *et al*[43] reported that there is some evidence showing that oocyte might generate from bone marrow in adult mammalian ovaries. Their results revealed that bone marrow is a considerable origin of germ cells which lead to the continuation of oocyte production during adulthood. Moreover, Bukovsky *et al*[44,45] observed that new oocytes might be originated from ovarian cortical mesenchymal cells. Nayernia *et al*[46-50] assessed the capacity of BM-MSCs to produce male germ cells and claimed that there is a new aspect of germ cell development for the application of BM-MSCs in reproductive medicine. They also indicated that mouse MSCs have the ability for differentiation toward germline stem cells *in vitro* and this relieved that the differentiated cells stop progress at premeiotic stages after transplantation into the testes of matureinfertile mice[51]. In another study, Drusenheimer *et al*[52] also demonstrated that spermatozoa can be derived and differentiated from human BM-MSCs.

4. MSCs derived from umbilical cord

The umbilical cord has been located between fetus and mother during pregnancy and which is contained a mucous connective tissue, known as Wharton's jelly, between the amniotic epithelium and the umbilical vessels[53]. Human umbilical cord is a tissue which consists of at least six distinctive zones including from outside to innerside: 1) surface epithelium; 2) sub-amniotic stroma; 3) clefts; 4) intervascular stroma also known as Wharton's jelly; 5) perivascular stroma; and 6) vessels (Figure 1)[24]. MSCs have been collected from several parts of the umbilical cord including umbilicalcord blood, umbilical vein sub-endothelium, and the Wharton's jelly[24]. MSCs, which are derived from the human umbilical cord (hUC-MSCs), share many traits with BM-MSCs, for instance, they have low expression capacity for HLA major histocompatibility complex class Ⅰ, self-renewal ability and the capacity to be differentiated into various cell lineages[24], however, they don't have the capacity for expression of CD31, CD45, HLA major histocompatibility complex class Ⅰ (Table 1)[54]. They also can be frozen/thawed and extensively expanded in culture[39]. Carlin *et al*[55] was the first one who reported the expression of Oct-4, Sox-2, and Nanog markers (some of the embryonic stem cell markers) in porcine umbilical cord matrix cells. A large body of studies indicated that derived hUC-MSCs from extra-embryonic mesoderm, have differentiation potential toward osteogenic, adipogenic, chondrogenic lineages[24,56]. The hUC-MSCs are able to sustain the normal ovarian physiology and decrease the rate of apoptosis in mice model of premature ovarian failure[57].

5. MSCs derived from Wharton's jelly

The primary role of Wharton's jelly is the suppression of compression and torsion and then support of bidirectional blood flow between fetal and maternal circulation and also help the function of adventitia[23,58]. Wharton's jelly is a potential source to be applied in

clinical applications due to their lower risk of viral contamination. MSCs have been isolated from various zones of Wharton's jelly, sub-amnion region, perivascular zone and the intervascularzone (Figure 1). Wharton's jelly-MSCs (WJ-MSCs) have the ability to differentiate toward all three cell lineages. They have the expression profile as same as other MSCs (CD29, CD44, CD73, CD105, CD73,and CD90) and as embryonic stem cell markers such as SSEA-1 and 4, Oct-4, Nanog and Sox-2 (Table 1)[59].

The higher telomerase activity, the higher proliferative potential, shorter expansion doubling times with maintenance of stem cell properties that present in WJ-MSCs in compared with MSCs derived from adult tissues, indicate that WJ-MSCs are in more primitive stage and using them in regenerative medicine has higher privileges[55]. The ability of WJ-MSCs to differentiate toward particular cell lineage depends partially on secreted growth and differentiation factors that are secreted in an environment of a particular cell lineage. Bone morphogenetic protein 4 (BMP4) and retinoic acid (RA) are two other vital factors which their role in differentiation induction has been proved[60]. *In vitro* studies showed that BMP4 induces differentiation of BM-MSCs into primordial germ cells[60]. Moreover, Ohta *et al*[61] have claimed that fetal male germ cells have the machinery to respond RA signals and be differentiated into germ line cells. Appling co-culture system is another safe approach for inducing differentiation of stem cells into specific cell lineage and using them for clinical trial purposes[62].

Deferent studies revealed that WJ-MSCs have the innate capacity, due to an enhanced proliferation potential and a higher rate of colony formation, to be used as an allogeneic cell therapy for diseases treatment[63]. Tamura *et al*[64] indicated that these cells produce several secretory proteins which increase the cancer cells death and stop the cell cycle as well as are markable decrease in the liver fibrosis. There is some evidence that confirms the supportive function of WJ-MSCs for other stem cells. For instance, WJ-MSCs support embryonic germ cell migration by secretion of glial-derived neurotrophic factor, an essential factor to keep the undifferentiated status of spermatogonial stem cells[65].

Asgari *et al*[66] indicated that human WJ-MSCs have the gene expression profile as same as primitive genes in oocyte developmentafter co-culture with placental cells. They reported that supplemented placental cell with transforming growth factor- α and β and basic fibroblast growth factor in a co-culture systemis an optimal condition which stimulates hUMSCs to be differentiated toward primordial germ cells and expresses oocyte-like genes. Amidi *et al*[67] reported that in a co-culture system between WJ-MSCs and placenta cells, differentiation potential of MSCs toward male germ-like cell improved when RA and BMP4 were present.

6. MSCs derived from adipose tissue

Just like bone marrow, adipose tissue has been originated from the mesenchyme and this great source of MSCs has a stroma which can be easily isolated[85]. Adipose tissue is another useful source of multipotent MSCs which called adipose tissue-derived stromal cells (ADSCs). In order to isolate ADSCs, after vigorous digestion and following multiple centrifugation steps, the stromal vascular are isolated[86]. Zuk *et al*[87] reported that ADSCs are similar to BM-MSCs in both differentiation capacities and gene expression[87]. They also reported that ADSCs expression levels of CD49d, CD34, and CD54 are high; however, the expression of CD106 is much higher in BM-MSCs.

7. Conclusion

Wharton's jelly, umbilical cord, and bone marrow are rich sources of MSCs for investigations and presumptive clinical usages. MSCs are ethically reliable, and have a high rate of proliferation and sufficient plasticity for such clinical applications. New progress in cryopreservation methods will open up recent great achievements in MSCs banking and further possibilities for application of cells in regenerative medicine. Meanwhile, Wharton's jelly can be applied in regenerative medicine of some reproductive diseases. These cells have a considerable potency to be differentiated toward germ-like cell lines in appropriate culture condition using BMP4 and RA. Therefore, clinical application of Wharton's jelly has been kept in mind as a promising source for regenerative medicine.

Conflict of interest statement

There is no conflict of interest in the current study.

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