REVIEW ARTICLE

The most commonly used cell surface markers for determining mesenchymal stromal cells in stromal vascular fraction and bone marrow autologous concentrate: a systematic review

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The use of regenerative technologies is widely spread in modern medicine. Adipose derived stem cells (ADSCs) in stromal vascular fraction (SVF) seem to be the most advantageous for use in cell therapies and in tissue engineering. The results of bone marrow autologous concentrate (BMAC) use are very promising. The purpose of this review was to analyze and summarize the available literatures that pertain to the cell surface characterization of ADSCs and bone marrow mesenchymal stromal cells (BMMSCs) from SVF and BMAC, respectively. The results found that the most commonly reported markers for mesenchymal stromal cells (MSCs) derived from adipose tissue (AT) and bone marrow (BM) were CD29, CD44, CD73, CD90, CD105, and should be defined as positive, while CD34, CD45, CD56, CD146 should be defined as negative. For additional markers such as c- Kit (CD117), SSEA-1 (CD15), PDGFR, and CCR5X (CD195), there was no single consensus, although most authors agreed on the positive expression of HLA-ABC and STRO- 1 and the negative expression of HLA -DR. The results concluded that SVF and BMAC were not only concentrates of isolated MSCs, but also containing several additional growth factors. The main regenerative function belonged to MSCs. Therefore, their qualitative and quantitative confirmations were the keys to the effectiveness of SVF and BMAC. For this purpose, it is recommended a minimum panel of positive and negative markers for identifying MSCs, which include the positive markers of CD29, CD44, CD73, CD90, CD105 and the negative markers of CD14, CD31, CD 34, CD45, CD146.

Keywords: bone marrow mesenchymal stem cells; adipose-derived stem cell; phenotypic cell surface characterization; mesenchymal stromal cell; surface markers.

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Introduction

The use of regenerative technologies is widely spread in modern medicine. The field of orthopedics has developed significantly in the last decades with the emergence of new regenerative products and surgical techniques. Research areas that have received particular attention are those employing stem cells, scaffolds, and growth factors. The use of stem cells in regenerative medicine is a particularly appealing area of research that has received a great deal of interest in recent years. Stem cells have great potential in advanced tissue engineering and cell therapies. There are four main sources of stem cells including embryonic tissues, fetal tissues, adult tissues, and differentiated somatic cells after genetically reprograming and are referred as induced pluripotent stem cells (iPSCs). Adult stem cells

are located in practically all organs and tissues of the adult organism such as skin, brain, heart, blood vessels, skeletal muscle, intestine, liver, kidneys, reproductive organs, adipose tissue, and bone marrow. Among adult stem cells, adipose derived stem cells (ADSCs) seem to be the most advantageous for use in cell therapies and in tissue engineering. It has been reported that 500 times more stem cells can be obtained from adipose tissue than that from equal amounts of bone marrow [1]. In comparison with bone marrow mesenchymal stem cells (BMMSCs) received from bone marrow autologous concentrate (BMAC) [2, 3], ADSCs can be relatively easily harvested in higher quantities with less discomfort and less damage to the donor site. ADSCs have also a higher proliferation capacity than that of BMMSCs. However, BMMSCs are known to have high osteogenic ability and anti-inflammatory effects on the injured tissue. The results of BMAC use are very promising. Although progenitor cells have been used for a long time in clinics, BMAC is not only composed by progenitor cells, but also having a large quantity of growth factors. This combination makes BMAC a powerful therapy. However, obtaining BMAC is invasive, which requires closed systems during the preparation, and the positive results are strongly correlated with the number of stem cells. Therefore, processing bone marrow (BM) by BMAC may be clinically beneficial to increase the concentration of mesenchymal stromal cells (MSCs) [4-7]. In recent years, the use of BMAC has become an increasingly popular method of augmenting bone [8] and cartilage regeneration [9] in orthopedic surgery.

The stromal vascular fraction (SVF) freshly isolated from adipose tissue (AT) is used for tissue regeneration as it contains ADSCs. MSCs derived from both AT and BM are able to interact with their adjacent microenvironment leading to the generation of new committed progenitors and cells. At the same way, they secrete exosomes containing growth factors, cytokines, chemokines, and micro-RNA involved in restoring tissue defects and biological functions. Some literatures reported that the relative numbers of stem cells and progenitor cells in uncultured SVF were up to 3% of the total number of cells. In addition, adipose tissue provides more stem cells than that in bone marrow aspirate [10]. A bone marrow transplant contains approximately 6×10^6 nucleated cells per mL [11], of which only 0.01–0.02% are mesenchymal stromal cells [12]. In comparison, the number of SVF cells that can be isolated from subcutaneous liposuction aspirates is approximately $0.5\text{-}2.0\times10^6$ cells per gram of adipose tissue [11, 13], whereby the percentages of stem cells range from 1 to 10%, most likely depending on the donor and tissue harvesting site. Therefore, approximately 0.5×10^4 to 2×10^5 stem cells can be isolated per gram of adipose tissue, varying among patients. ADSCs are mainly separated from SVF by using a mechanical or enzymatic process, seeded facultatively in an expansion culture before being administered through autologous or allogenic transplantation. Their use in therapeutic protocols is conditioned by high cell numbering, low culturing passage, and reduced time delay before processing [14]. The efficiency of using the regenerative potential of MSCs in orthopedics directly depends on their quantity in the preparation used. Based on this, confirmation of the quality of the cell preparation (qualitative and quantitative) is fundamental in obtaining the maximum positive effect.

The purpose of this review study was to analyze and summarize the available literatures that pertained to the cell surface characterization of ADSCs and BMMSCs, and identification of common markers and specific for each type of stem cell source. The identification of a set of positive and negative cell surface markers would allow for a much more consistent and reliable method of identifying stem cell population both *in vitro* and *in vivo*.

Literature searching method

This study emphasized the search for literary sources for the period of the last 10 years. The search keywords were set as bone marrow

mesenchymal stem cells, adipose-derived stem cells, surface markers, and mesenchymal stromal cells. The literature search was conducted in the following online databases including PubMed® (https://pubmed.ncbi.nlm.nih.gov), Medline (https://www.nlm.nih.gov/medline/medline_overview.html), Zetoc electronic table of contents from the British Library (The British Library's Zetoc service has ceased), Web of Knowledge (https://www.webofscience.com), EMBASE (https://www.embase.com), Ovid® (https://ovidsp.ovid.com), and other non-indexed citations such as Research Gate (https://www.researchgate.net).

Results and discussion

ADSCs surface markers

Analyzing the literature data, it was possible to identify the most commonly used markers for determining ADSCs, which were distinguished by many authors in a minimal panel. The minimal panel for ADSC included CD105+, CD90+, CD73+, and CD45−, CD34−, CD14− or CD11b−, CD79α− or CD19−, and HLA-DR− in their surface marker expressions. Since the publication of these minimal criteria to define MSCs was in 2006 [15], the acronym and the hMSC criteria had been under debate lately [16-18], which was partially based on the inconsistent or even contradictory research results, probably due to a lack of uniformity in nomenclature, no reference cell type, and/or the lack of information on the process of generating MSCs [19].

Nowadays, the most typical categories of ADSC surface marker proteins found in the literatures were (1) surface enzymes such as CD9, CD10, CD13 (aminopeptidase), CD73 (5ecto-nucleotidase); (2) adhesion molecules such as CD29 (integrin b1) and CD49e (integrin a5); (3) intercellular adhesion molecules, CD54 (ICAM-1); (4) complement regulatory proteins such as CD55 (decay acceleration factor); (5) activated lymphocyte cell adhesion molecule such as CD166 and ALCAM; (6) receptor molecules such as CD44 (hyaluronate) and CD144 (cadherin-5); (7) extracellular matrix proteins such as CD90 (Thy-1), CD105 (endoglin), and CD146 (Muc18); (8) vascular adhesion molecules, CD106 (VCAM); (9) histocompatibility antigens such as human leukocyte antigen (HLA)-ABC [9, 22, 23] (Table 1). Markers in common with BMSCs included CD13 (aminopeptidase), CD29, CD44, CD58 (lymphocyte function associated antigen-3 (LFA-3)), CD90, CD105, and CD166 [9, 20-23]. The following markers were negative for ADSC including CD31, CD45, CD14, CD11b, CD19, CD56 and CD146 [16, 24, 25].

BMMSCs surface markers

The CD45−CD10+, CD45−CD29+, CD45−CD90+, CD45−CD105+, CD45−CD119+ cells, and CD45dimCD90+CD271+ MSCs were significantly concentrated in BMMSCs. BM concentration also increased the numbers of CFU-F, platelet-derived growth factor, vascular endothelial growth factor, macrophage colony-stimulating factor, interleukin-1b, VCAM-1, and total protein. Neither system concentrated red blood cells, hematopoietic stem cells or bone morphogenetic proteins [7].

Surface marker expression

The inaccuracies in the literature data were partially related to the incorrect interpretation of the expression markers of the initial and after passages. Cells in the SVF (freshly isolated) and early-passage human ADSCs had relatively high expression levels of CD117 (c-kit), HLA-DR, and stem cell-associated markers such as CD34, and low levels of stromal cell markers such as CD13, CD29, CD44, CD63 (lysosome-associated membrane glycoprotein 3 (LAMP-3)), CD73, CD90, CD166, and CD105 [7, 26-28]. However, in human ADSCs, SVF (fresh), or early-passage ADSCs, the following cell markers were differentially expressed including CD14, CD31, CD34, CD105, CD106, CD117, CD166, HLA-DR, and STRO-1. Separating the initial fresh SVF, the passage and expanded human ADSCs showed that these cells appeared with stem cell markers such as CD29, CD44, CD73, CD90, CD105, and CD166 [25, 28]. When the passage number increased, the hematopoietic stem cell (HSC)

Table 1. The most typical categories of MSC surface marker proteins derived from AT and BM.

Categories of surface marker proteins	ADSC	BMMSC
surface enzymes	CD9	
	CD10	
	CD13 (aminopeptidase)	CD13 (aminopeptidase)
		CD71 (TfR1)
	CD73 (ecto-nucleotidase)	
adhesion molecules	CD29 (integrin b1)	CD29 (integrin b1)
	CD49e (integrin a5)	
		CD58 [lymphocyte function associated antigen-3 (LFA-3)]
		CD146 (MCAM)
intercellular adhesion molecules	CD54 (ICAM-1)	
complement regulatory proteins	CD 55 (decay acceleration factor)	complement regulatory proteins
activated lymphocyte cell adhesion molecule	CD166 (ALCAM)	CD166 (ALCAM)
receptor molecules	CD44 (hyaluronate)	CD44 (hyaluronate)
	CD144 (cadherin-5)	
extracellular matrix proteins	CD90 (Thy-1)	CD90 (Thy-1)
	CD105 (endoglin)	CD105 (endoglin)
	CD146 (Muc18)	
vascular adhesion molecules	CD106 (VCAM)	
histocompatibility antigens	(HLA)- ABC	

markers such as CD11, CD14, CD45, and CD34, expressed on SVF would decrease or be lost because SVF cells consisted of multiple-cell populations in comparison with ADSCs that were selected and subsequently expended from adipose tissue as a single-cell population [9, 29]. Number of literature sources stated that ADSC cultures also expressed aggrecan and Sox 9. In addition to these chondrogenic markers, ADSC pellet cultures turned positive for HLA-ABC and HLA-DR epitopes as visualized by immunohistochemistry [30, 31].

VEGFR2 is a type V receptor tyrosine kinase mainly known to be expressed in vascular endothelial cells and encoded by the KDR gene. VEGFR2 protein is also known as KDR (kinase insert domain receptor), Flk-1 (fetal liver kinase 1), or CD309 in the cluster of differentiation terminology of hematopoietic antigens. Immunocytochemistry results showed that ADSC also expressed endothelial specific markers CD31, vWF, and eNOS [5]. Widely expressed in stem cells, ABCG2 was also found to confer the side population phenotype and was recognized as a universal marker of stem cells. The expression of ABCG2 was restricted to the most immature hematopoietic progenitors in human bone marrow, ADSC, and was sharply downregulated at the committed progenitor level [14].

CD9 was one of the most ubiquitously expressed protein on the surface of exosomes that was expressed on a fraction of CD105+ cells that enriched for MSCs that exhibited marked expression of osteochondral-lineage genes and were capable of robust bone formation when transplanted *in vivo* [32]. Flow cytometry analysis demonstrated that the most common markers currently used to define MSCs including CD9 were also expressed on human skin or lung fibroblasts. However, the level of expression of CD9 was significantly lower in MSCs than that in

fibroblasts. It should also be mentioned that CD9 was upregulated in MSCs cultures of passage 2nd and passage 6th [33].

CD10 is a cell-surface neutral endopeptidase. More recently, it has been investigated in a large number of normal tissues and tumors such as acute lymphoblastic leukemia, renal glomerular and tubular cells, renal cell carcinomas, salivary gland, breast myoepithelial cells, endometrial stroma, and various mesonephric and trophoblastic tumors. CD10 is highly expressed in malignant tumors, while only a small part of the literature data indicated its expression in MSCs derived from adipose tissue, which was more likely due to its binding to lymphoid tissue since it was expressed by lymphoid precursor cells, B-lymphoid cells of germinal center origin, and tumors [25, 34-36].

One of the frequently identified markers was the multifunctional cell surface peptidase, CD13, that had been shown to be expressed on human MSCs from many tissues [7, 37]. Except CD13, the most prominent markers were CD29, CD44 (a surface marker and collagen receptor), CD90, and CD105 (an essential glycoprotein with substantial importance in cell adhesion) [4, 22, 38]. In the literature, the most common combination of markers expressed in MSCs derived from adipose tissue was also typical for stromal cells derived from bone marrow including CD13, CD29, CD44, CD 73, CD90, CD105, CD29, CD44, CD90, and CD105 [6, 7, 16, 22, 24, 39, 40].

CD13 is a type II zinc-dependent metallopeptidase (also known as aminopeptidase N), which is found on the surface of all myeloid cells in addition to pericytes, activated endothelial cells, and subsets of organ-specific epithelial cells [5]. It is a multifunctional protein with both enzyme-dependent and independent functions that contribute to adhesion, cell migration, angiogenesis, inflammatory trafficking, adhesion, antigen presentation, and endocytosis.

CD29 has been reported to be widely expressed on different cell types including stem cells, in tissues like blood, skin, and especially in glandular organs like mammary glands or salivary glands as well in fat tissue [38]. The detected stem cell markers CD29 and CD44 were expressed at different stages of osteoblast differentiation. CD44 was expressed by undifferentiated MSCs and characterizes the first stage of regeneration, accompanied by active proliferation of cellular elements [35]. Determinate MSCs with osteogenic potential were labeled with CD29 (integrin β-1), a cell surface receptor involved in the interaction of cells with extracellular matrix proteins such as collagen, laminin, and fibronectin. Integrin family members are membrane receptors involved in cell adhesion and recognition in a variety of processes including embryogenesis, hemostasis, tissue repair, immune response, and metastatic diffusion of tumor cells. Among all, it had been shown that CD29 was strongly expressed by adipocyte progenitors [9, 41]. In addition, CD44 and CD29 were surface receptors through which extracellular matrix proteins realized their regulatory effects [35, 42].

CD44 is a transmembrane glycoprotein that has various functions in cell division, migration, adhesion, and signaling. CD44 as an adhesion molecule is enables cell communication by cell-cell signal transduction [43, 44] CD44 is another marker involved in migration and adhesion. It is a glycoprotein widely expressed on the surface endothelial cells, epithelial cells, fibroblasts, keratinocytes, and leukocytes. CD44 has important functions in cell–cell and cell-matrix interactions including proliferation, hematopoiesis, and lymphocyte activation, homing, extravasation [14]. CD44 is essential for maintaining cartilage homeostasis, influences the production of collagen II and aggrecan, and influences the chondrodifferentiation of amniotic MSCs [38]. CD44 family members play important roles in physiological processes such as hematopoiesis, limb development, and lymphocyte homing. CD44 is a well-known marker for stem cells and cancer stem cells, and its profound role in tumor progression,

metastasis, and chemoresistance may also be linked to a function in these stem cells [45, 46].

CD73 (ecto-5-nucleotidase) is a membrane protein that dephosphorylates extracellular AMP to bioactive adenosine [47, 48]. CD73 expression is heterogeneous in MSCs derived from various sources with the MSCs from human umbilical cord blood at the highest level and bone-marrow-derived MSCs at the lowest level, which suggested that nonuniform expression of CD73 is a ubiquitous phenomenon in the MSC pool [38]. One important feature of CD73-positive cells is their ability to modulate the immune response. hAMSCs showed a larger population of cells (70-97%) with CD73 and more promising [16, 48-51].

Currently, there is no unique cell marker capable of solely isolating and defining MSCs, but CD90, a glycoprotein present in the MSC membranes, is related to the state of cellular undifferentiation [52, 53]. Flow cytometry showed 66% and 78% CD29+/CD90+ positivity within passage 1 of adipose and bone marrow cultures, respectively [54]. CD90, also known as thymocyte antigen 1 (Thy-1), represents a 25- to 37-kDa glycosylphosphatidylinositol (GPI)-linked membrane protein commonly associated with osteoprogenitor cells [55]. CD90 expression has been identified in endothelial cells, hematopoietic stem cells, lymphocytes, fibroblasts, and neurons [16, 49, 56-58]. In addition to this lack of cell type-specificity, another potential limitation for CD90 as an MSC marker is that this molecule appears not to be well conserved evolutionarily, and as a result commonly used anti-CD90 antibodies may not be able to react with MSCs of certain species [59]. Thus, although recommended as a positive marker, CD90 appears not to be a useful marker for *in vivo* MSC detection [29, 60].

CD105, also known as endoglin, is a type I membrane glycoprotein that functions as an accessory receptor for TGF-beta superfamily ligands. As its name suggests, endoglin is highly expressed in vascular endothelial cells [52]. Interestingly, MSCs from the adipose tissue had shown to express CD105 at low levels when freshly isolated but became increasingly CD105+ upon culture passages [27, 28]. As MSCs from other tissues cannot be isolated in sufficient quantities without culture passages, whether they also express CD105 at low levels when freshly isolated is presently unknown.

According to the International Society of Cellular Therapy (ISCT) guidelines for MSC and ADSC, ADSCs that are characterized by ≥ 95% of the MSC population must express CD105, CD73, and CD90 as measured by flow cytometry. Additionally, these cells must lack expression (≤ 2% positive) of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA class II [24]. International Federation for Adipose Therapeutics and Science (IFATS) also recommends the following criteria for primary stable positive markers in stromal cells, which includes CD13, CD29, CD44, CD73, CD90 (> 40%), CD34 (> 20%); and criteria for primary negative markers in stromal cells as CD31 (< 50%). The guidelines recommend the surface antigens used to characterize the MSCs during the analysis as CD73 and CD90, while including CD13 as an alternative or supplement to CD105. However, it is still possible that there is added value in distinguishment between the properties of CD105- and CD105+ ASC subpopulations [61]. The similar results have been reported by many authors with the average number of 88.0% cells expressing CD105, 73.7% expressing CD90, 71.9% expressing CD73, and 87.6% not expressing CD45. Moreover, flow cytometry analysis revealed that, when cells were triply labeled with CD105, CD45, and CD90 antibodies, 62.7% of cells were simultaneously expressing CD105+ CD45- CD90+, i.e., 62.7% of cells expressing MSC marker proteins and did not express hematopoietic marker protein, which indicated that majority cells in culture derived from adipose tissue could simultaneously express MSC marker proteins [9].

A small number of literature references described the expression of CD166 as a surface gene of ADSC. CD166 (activated leukocyte cell adhesion molecule (ALCAM)) is a member of the

Table 2. The most typical surface marker proteins of ADSC and BMMSC found in the literature.

ADSC-positive cellular markers and genes	ADSC-negative cellular markers and genes	BMMSC-positive cellular markers and genes	BMMSC-negative cellular markers and genes
CD9	CD11b	CD29	CD14
CD10	CD14	CD44	CD34
CD13	CD19	CD71	CD11b
CD29	CD31	CD73	
CD44	CD34	CD90	
CD49	CD45	CD105	
CD54	CD79α	CD106	
CD55	CD80	CD140b	
CD73	CD117	CD146	
CD90	CD133	CD166	
CD105	CD144	CD340	
CD106	HLA-DR	CD349	
CD144	c-kit	STRO-1	
CD146	MyD88	Oct4	
CD166	Lin	SSEA4	
Fibronectin	HLA II	VEGF2	
aSMA			
Vimentin			
Collagen-1			

immunoglobulin superfamily, which is expressed by various cells in several tissues including fat tissue [36, 59]. As a minimal prerequisite, based on flow cytometry data analysis, ADSCs did not express hematopoietic antigens such as CD34, CD45, and HLA-DR, a profile also found in MSC [41]. In addition, the positive expressions of HLA-ABC and STRO- 1 were seen in ADSCs. However, a number of disagreements over the expression and existence of various markers, namely CD31, CD34, c- Kit (CD117), and STRO-1 was found in literature [54].

CD34 has long been regarded as a reliable marker for hematopoietic stem cells (HSC). Recent studies have demonstrated the existence of CD34- HSC and that the two populations of HSC (CD34+ and CD34-) can differentiate into one another. Several papers have shown that CD34 was highly expressed in freshly isolated ADSC (SVF cells) but was quickly lost in cultured ADSC (within 3 passages) [62].

Should keep in mind that BMAC also serves as a rich source of factors like platelet-derived growth factor (PDGF), TGF-β, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor I (IGF-I), granulocyte-macrophage colony-stimulating factor (GMCSF), bone morphogenetic protein (BMP-2 and 7), and interleukins (IL-1β, 6, 8) [62, 63] that can influence the healing responses by decrease in cell apoptosis and inflammation, and by activation of cell proliferation, differentiation, and angiogenesis *via* paracrine and autocrine pathways [50].

Conclusion

It can be argued that the phenotypic characteristics of the surface markers of MSCs obtained from both adipose tissue and bone marrow do not have difference. To confirm the qualitative presence of MSCs, the following markers should be defined as positive: CD10, CD13, CD29, CD44, CD49e, CD59, CD73, CD90, CD105 and CD166, while the another group of markers should be defined as negative: CD31, CD45, CD14, CD11b, CD19, CD56 and CD146. For

additional markers such as HLA-DR, STRO- 1, HLA-ABC and STRO- 1, c-Kit (CD117), SH2, SH3, vWF, VEGF2, ABCG2, SSEA-1 (CD15), PDGFR, alpha-SMA, OCT4+, and CCR5X (CD195), there is no single consensus although most authors agreed on the positive expression of HLA-ABC and STRO-1 and the negative expression of HLA-DR (Table 2). Moreover, it should be remembered that SVF and BMAC are not concentrates of isolated MSCs but contain a large number of additional factors in their composition. It is precisely in the composition of additional cellular elements and growth factors that they differ from each other, which is also reflected in various points of application and clinical effect such as osteogenic for BMAC and chondrogenic for SVF. It should be noted that studies in the investigation of MSCs, methods for their isolation and cultivation, as well as clinical applications are ongoing, which requires further analysis.

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