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## More to Explore; The Mesenchymal Stem Cells (MSCs) Major Tissue Sources, Known Surface Markers and Its Immunomodulation properties

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### ABSTRACT

Mesenchymal stem cells (MSCs) are currently available for a range of applications and have become a good material for regenerative medicine, tissue engineering, and disease therapy. MSCs are self-renewing, multipotent progenitor cells with multilineage potential to differentiate into cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes and exert potent immunosuppressive potentials. In the present review, we highlight the currently reported variations in the differentiation potential of MSCs from different tissue sources, the minimal criteria to define MSCs from various tissue environments and provide a detailed description of MSCs surface markers. Furthermore, MSCs immunomodulatory features secrete cytokines and immune receptors which regulate the microenvironment in the host tissue also revisits in detail. We propose that there are likely more sources of MSCs waiting to be discovered. We need to Standardize MSCs characterization by selecting markers for isolation, cellular and molecular mechanisms involved in MSC-mediated immune modulation, and other functionalities of MSCs should be characterized prior to use in clinical applications.

**Keywords:** Mesenchymal stem cells (MSCs), Tissue sources, Surface marker, Cytokines and Immunomodulation.

### INTRODUCTION:

Stem cells represent a novel cell type in the body. Stem cells have two features: the ability to differentiate along different lineages and the ability to self-renew and maintain tissue homeostasis. Stem cells can be multiplied in large Stem cells are broadly classified based on their source into embryonic (hESCs) and adult (ASCs) stem cells. Bhartiya, (2013) Embryonic stem cells are pluripotent in nature and can be differentiated into 200 odd cell types where as the adult stem cells are isolated from adult body tissues and are multi-to unipotent in nature (Thomson *et al.*, 1998). MSCs are adult stem cells which can be isolated from human and animal

sources with the capacity to differentiate into mesodermal lineage. MSCs and their multilineage were first found by Friedenstein via studies on the mouse bone marrow in the 1960s (Friedenstein *et al.*, 1987; Friedenstein *et al.*, 1976; Friedenstein, 1966).

The multilineage differentiation potential of adult human MSCs from bone marrow was described by Pittenger and group. They have been isolated from almost all tissues including per vascular area (Pittenger *et al.*, 1999). In view of many studies till now, neither single definition nor a quantitative assay to help in the identification of MSCs in mixed population of cells is available; some biomarkers are available for identi-

fication of human MSC (hMSC). In 2006 a set of markers and cell characteristics has been proposed by the International Society for Cellular Therapy has proposed minimum criteria to define MSCs as these cells (a) should exhibits plastic adherence; (b) possess specific set of cell surface markers, i.e. cluster of differentiation CD73, D90, CD105 and lack expression of CD14, CD34, CD45 and human leucocyte antigen-DR (HLA-DR); and (c) have the ability to differentiate *in-vitro* into adipocyte, chondrocyte and osteoblast (Crisan *et al.*, 2008). The availability and culturally expandable in vitro with special genomic stability and less ethical issues, marking these incredible cells importance in cell regenerative therapy and medicine (Dominici *et al.*, 2006; Ullah *et al.*, 2015). The resent study is the concise review article to gather available the information about stem cell sources, identification makers, Paracrine secretion, Immunomodulation by MSCs and their importance in regenerative therapies.

**Human Mesenchymal Stem Cell (hMSC) Sources:**

The bone marrow (BM) has been the prevailing source of MSCs in humans (Mushahary *et al.*, 2018). However, while BM is a rich source of hematopoietic stem cells, it constitutes only a rare MSC population (Li *et al.*, 2016) BM-derived MSC (bmMSC) supply is the painful harvesting procedure marking their application in research and in the clinical setting limited. Over time, a number of other tissues have been identified as alternative sources for hMSC. Today, MSC can be isolated from multiple tissues (Ullah *et al.*, 2015). The human MSC (hMSC) properties can vary greatly depending on multiple parameters including tissue source, isolation method and medium composition and several studies mentioned variations in the differentiation potential of MSC from different tissue sources. **Table 1** summaries some of the currently used tissue sources and the respective confirmed differentiation potentials.

**Table 1:** Summary of hMSCs tissue sources and *In-vitro* differentiation potentials.

SN	Source	In vitro differentiation	References
1.	Bone Marrow	Osteocytes, chondrocytes, adipocytes	(Li <i>et al.</i> , 2016; Mamidi <i>et al.</i> , 2012; Otsuru <i>et al.</i> , 2013; Ranera <i>et al.</i> , 2013)
		Hepatocytes	(Zhang <i>et al.</i> , 2011)
		Cardiomyocytes	(Stock <i>et al.</i> , 2014)
		Pancreatic cells	(Xu <i>et al.</i> , 2004; Tang <i>et al.</i> , 2012; Gabr <i>et al.</i> , 2013)
		Neuronal cells	(Phadnis <i>et al.</i> , 2011; Barzilay <i>et al.</i> , 2009)
2.	Adipose Tissue	Osteocytes, chondrocytes, adipocytes	(Barzilay <i>et al.</i> , 2009; Wilkins <i>et al.</i> , 2009; Pendleton <i>et al.</i> , 2013)
		Hepatocytes	(Wagner <i>et al.</i> , 2005)
		Cardiomyocytes	(Baglioni <i>et al.</i> , 2009)
		Pancreatic cells	(Wang <i>et al.</i> , 2014)
		Neuronal cells	(Choi <i>et al.</i> , 2010; Timper <i>et al.</i> , 2006)
3.	Umibical cord, Umibical cord blood	Osteocytes, chondrocytes, adipocytes	(Kang <i>et al.</i> , 2003; Miao <i>et al.</i> , 2006)
		Hepatocytes	(La Rocca <i>et al.</i> , 2009; Baek <i>et al.</i> , 2014)
		Endothelial like cell	(Wilkins <i>et al.</i> , 2009)
		Pancreatic cells	(Hang <i>et al.</i> , 2014)
		Neuronal cells	(An <i>et al.</i> , 2014)
4.	Dental Tissue	Osteocytes, chondrocytes, adipocytes	(Prabakar <i>et al.</i> , 2012; Zhao <i>et al.</i> , 2014)
		Pancreatic cells	(Huang <i>et al.</i> , 2009; Hilkens <i>et al.</i> , 2013)
		Neuronal cells	(Govindasamy <i>et al.</i> , 2011; Kanafi <i>et al.</i> , 2013)
		Melanocytes	(Zhao <i>et al.</i> , 2014)
5.	Amniotic fluid	Chondrocytes, adipocytes	(Völlner <i>et al.</i> , 2009; Wang <i>et al.</i> , 2010)
		Neuronal cells	(In't Anker <i>et al.</i> , 2003)
6.	Skin- and foreskin-derived MSCs	Osteocytes, chondrocytes, adipocytes	(Tsai <i>et al.</i> , 2004; CaiH <i>et al.</i> , 2010)
		Myocytes	(Tsai <i>et al.</i> , 2004)
7.	Limb bud-derived MSCs	Osteocytes, adipocytes	(Bartsch <i>et al.</i> , 2005)
		Hepatocytes	(Bartsch <i>et al.</i> , 2005)
		Neuronal cells	(Bartsch <i>et al.</i> , 2005)
8.	Placenta	Adipocytes, Osteocytes	(Riekstina <i>et al.</i> , 2008; Jiao <i>et al.</i> , 2012)
		Endothelial like cell	(Jiao <i>et al.</i> , 2012)

		Neuronal cells	(Jiao <i>et al.</i> , 2012)
9.	Salivary gland	Osteocytes, chondrocytes, adipocytes	(Raynaud <i>et al.</i> , 2012; Rotter <i>et al.</i> , 2008; Sato <i>et al.</i> , 2007; Baek <i>et al.</i> , 2014)
		Pancreatic cells	(Sato <i>et al.</i> , 2007; Baek <i>et al.</i> , 2014)
10.	Synovial fluid	Osteocytes, chondrocytes, adipocytes	(Sui <i>et al.</i> , 2020; Morito <i>et al.</i> , 2008)
11.	Wharton’s jelly	Osteocytes, chondrocytes, adipocytes	(Hatakeyama <i>et al.</i> , 2017; Hou <i>et al.</i> , 2009; Salehinejad <i>et al.</i> , 2012; Christodoulou <i>et al.</i> , 2013)
		Hepatocytes	(Yoon <i>et al.</i> , 2013)
		Neuronal cells	(Anzalone <i>et al.</i> , 2010)

**Markers for MSC Identification and Verification:**

The International Society for Cellular Therapy (ISCT) published the minimal criteria for defining MSCs in 2006. The ISCT proposed positive and negative markers that enabled researchers to distinguish MSCs from other cells in the bone- marrow compartment. The negative markers were selected to include surface antigens that are expressed by hematopoietic cells, while the positive markers were selected to include surface antigens that are absent from most hematopoietic cells. It is well established that cultured colonies of MSCs express CD105, CD73, and CD90, but do not express CD45, CD34, CD14 or CD11b, CD19, and HLA-DR (Datta *et al.*, 2011; Karystinou *et al.*, 2009) **Table 2.** Some labeling strategies have also been used to successfully isolate MSCs enriched for markers such as STRO-1 (Saeedi *et al.*, 2019; Gronthos *et al.*, 2003; Kuroda *et al.*, 2010; Psaltis *et al.*, 2010) CD146 (Bensidhoum *et al.*, 2004; Covas *et al.*, 2008), SSEA-4 (da Silva Meirelles *et al.*, 2015; Gang *et al.*, 2007), CD271 (NGFR) (Battula *et al.*, 2008; Vaculik *et al.*, 2012) antigen 1 (MSCA-1). ISCT acknowledges that the criteria must be met with some flexibility, particularly as they relate to expression of the negative mar-

ker, HLA Class II. Specifically, HLA Class II can be expressed by MSCs under certain conditions, such as cytokine stimulation. Therefore, cells that meet all other criteria, but are also positive for HLA Class II, can be designated as MSCs if an adjective is used to indicate that the cells were stimulated. According to the ISCT, CD34 is a negative marker of MSCs. However, some reports suggest that the CD34 negative status is an artifact of cell culture condition (Pilbauerová *et al.*, 2019). In fact, several groups have shown that MSCs isolated from adipose tissue express CD34 at the time of isolation but lose expression while in culture (Lin *et al.*, 2012; Quirici *et al.*, 2010). Expression of CD34 by MSCs is also supported by the fact that the STRO-1 antibody (Clone STRO-1), which is commonly used to identify MSCs, was developed using CD34+bone marrow as the immunogen (Pachón-Peña *et al.*, 2011). The debate over the use of CD34 as a negative marker raises the possibility that markers may vary depending on the MSC tissue source (Kim & Cho, 2013). For specific immunophenotypic patterns, the variety of tissue sources of peripheral stem cells that could be isolated by their lineage-specific surface markers are summarized in **Table 3.**

**Table 2:** Minimal criteria of mesenchymal stem cells.

Surface markers	Differentiation potential		Other characteristics
<b>Positive Marker</b>		<b>Biological Role</b>	
CD73+	Osteogenic	Catalyzes the conversion of AMP to bioactive adenosine	Adherence to plastic
CD90+	Adipogenic	Wound repair, cell-cell and cell-matrix interactions	Spindle-shape morphology
CD105+	Chondrogenic	Vascular homeostasis; modulates TGF-beta functions via interaction with TGF-beta RI and TGF-beta RI	
<b>Negative Marker</b>		<b>Used to Exclude</b>	
CD34-		Primitive hematopoietic cells and endothelial cells	
CD45-		Leukocytes	
CD11b-		Monocytes and macrophages	
CD14-		Monocytes and macrophages	
CD19-		B cells	
CD79a-		B Cells	
HLA-DR-		B cells, T cells, monocytes, macrophages	

**Table 3:** Surface Marker Expression Profiles of Main MSC Types.

SN	MSCs	CD Marker Expression	Reference
1	ADSCs	CD9+, CD10+, CD13+, CD29+, CD44+, CD49D+, CD49E+, CD54+, CD55+, CD71+, CD73+, CD90+, CD105+, CD106+, CD146+, CD166+, STRO-1+ CD11B <sup>-</sup> , CD14 <sup>-</sup> , CD19 <sup>-</sup> , CD31 <sup>-</sup> , CD45 <sup>-</sup> , CD79A <sup>-</sup> , CD133 <sup>-</sup> , CD144 <sup>-</sup> , HLA-DR <sup>-</sup>	(Chan <i>et al.</i> , 2014); Vasiliki, 2016; Huang <i>et al.</i> , 2013)
2	BMMSCs	CD13+, CD33+, CD44+, CD73+, CD90+, CD105+, CD166+, CD28+, HLA class I+ CD14 <sup>-</sup> , CD34 <sup>-</sup> , CD45 <sup>-</sup>	(Dominici <i>et al.</i> , 2006; Zuk, 2010; Gauthaman <i>et al.</i> , 2010)
3	PDLSCs	STRO-1+, CD13+, CD29+, CD44+, CD59+, CD90+, CD105+	(Huang <i>et al.</i> , 2009; Boxall & Jones 2012)
4	TBMSCs	CD73+, STRO-1+, CD105+	(Pérez-Silos <i>et al.</i> , 2016)
5	SMMSCs	CD44+, CD73+, CD90+, CD105+	(Tuli <i>et al.</i> , 2003)
6	PMSCs	CD90+	(Djouad <i>et al.</i> , 2005)
7	MMSCs	CD34+, CD117+, Sca1+	(Johnstone <i>et al.</i> , 1998; Jankowski <i>et al.</i> , 2002)
8	SSCs	CD105+, CD90+, CD73+, CD29+, CD13+, CD44+, CD59+, VCAM-1+, ICAM-1+, CD49+, CD166+, SH2+, SH4+, EGFR+, PDGFRα+, CD271+, Stro-1+, CD71+, CD133+, CD166+, Keratin-19+ CD10 <sup>-</sup> , CD11b <sup>-</sup> , CD14 <sup>-</sup> , CD34 <sup>-</sup> , CD49d <sup>-</sup> and HLA-DR <sup>-</sup>	(Qu-Petersen <i>et al.</i> , 2002; Vishnubalaji <i>et al.</i> , 2012)
9	WJ-MSCs	CD13+, CD29+, CD44+, CD51+, CD73+, VCAM-1, CD166 CD90+, CD105+, SH2, SH3, SSEA-1	(Orciani <i>et al.</i> , 2010; Gauthaman <i>et al.</i> , 2010)
10	Hepatic stem cells	EpCAM+, E-cadherin+, CD133+, CD29+	(Yazdekhesti <i>et al.</i> , 2018)
11	Peripheral Blood MSC	CD44 <sup>+</sup> , CD54 <sup>+</sup> , CD90 <sup>+</sup> , CD105 <sup>+</sup> (SH2), CD166 <sup>+</sup> CD14 <sup>-</sup> , CD34 <sup>-</sup> , CD45 <sup>-</sup> , CD31 <sup>-</sup>	(Kim & Cho, 2013)
12	DPSCs	CD13 <sup>+</sup> , CD29 <sup>+</sup> , CD44 <sup>+</sup> , CD73 <sup>+</sup> , CD90 <sup>+</sup> , CD105 <sup>+</sup> , CD146 <sup>+</sup> STRO-1+ CD45 <sup>-</sup> , CD31 <sup>-</sup> , CD46 <sup>-</sup> , CD106 <sup>-</sup>	(Tosh & Strain 2005; Paduano <i>et al.</i> , 2016)

**Note:** MSCs: mesenchymal stem cells; CD: cluster of differentiation; ADSCs: adipose-derived stem cells; BMMSCs: bone marrow-derived mesenchymal stem cells; HLA: human leukocyte antigen; PDLSCs: periodontal ligament-derived stem cells; TBMSCs: trabecular bone-derived mesenchymal stem cells; SMMSCs: synovial membrane-derived mesenchymal stem cells; PMSCs: periosteum-derived mesenchymal stem cells; MMSCs: muscle-derived mesenchymal stem cells and satellite cells; Sca1: stem cell antigen 1; VCAM: vascular cell adhesion molecule; ICAM: inter-cellular adhesion molecule; SSCs: skin stem cells; SH2: CD105 antibody; SH4: CD73 antibody; EGFR: epidermal growth factor receptor; PDGFRα: platelet-derived growth factor receptor α ; WJ-MSCs: Wharton’s jelly mesenchymal stem cells; SH3: CD73 antibody; EpCAM: epithelial cell adhesion molecule; DPSCs: dental pulp stem cells.

**Mesenchymal Stem Cell Markers Co-expression:**

The purity of MSCs can be increased by using more than one MSC marker for positive selection. As an example, a recent publication demonstrated that selection of mesenchymal stem cells using CD271/NGF R, CD90/Thy1, and CD106/VCAM-1 resulted in a highly clonogenic population of cells (Simmons & Torok-Storb, 1991). Specifically, the addition of CD106 as a marker for positive selection led to isolation of cells with five times greater clonogenic potential compared to the cells isolated with CD271/and CD90 alone. The degree of co expression of surface markers on MSCs also studied (Rasmusson *et al.*, 2003). The cells subsets detected for the presence of MSCA-1/TNAP, CD271/NGF R and CD56/NCAM from whole cell population of Human BM-MNCs were analyzed and reported that the CD271 expression detected and CD56

expression not detected cells expressed CD106 and CD146 whereas, CD271 and CD56 presences detected cells exclusively expressed CD166 (Mabuchi *et al.*, 2013) CD271 and CD56 double positivity enriched SSEA-4 expression and MSCA-1 expression. The study conducted by Vaculik *et al.* (2012), explains the expression pattern of SSEA-4 in dermis was analogous to CD271. CD271 and SSEA-4 both co expressed with CD45 detected cells, in human dermis where as CD73 and CD105 are co expressed. The human dermis minor population of CD73 detected cells are not expressed CD90 (Battula *et al.*, 2008). Dermis CD271 positive cells were also positive for CD73and CD105, whereas the majority of CD271 positive cells are CD90 negative (Battula *et al.*, 2008). Several other studies have been performed recently aimed at achieving high-purity BM MSCs using a combination of CD271 and markers

other than CD73, CD105, or CD90 (Pérez-Silos *et al.*, 2016) for example, CD146 has attracted a lot of interest recently, by linking CD146 expression on MSCs with their pericyte topography and function (Battula *et al.*, 2009; Pittenger *et al.*, 1999). It was also reported that CD146 expression on CD271 positive MSCs correlates more with their in situ localization (Sacchetti *et al.*, 2007). Maijenburg further reported that the distribution of CD271 and CD146 and subsets correlates with donor age. The main subset in pediatric and fetal BM was reported to be CD271 expression and CD146 expression, whereas the subset of CD271 expression and CD146 not expression detected population was dominant in adult marrow (Tormin *et al.*, 2011). The endometrial MSC-like cells (eMSCs) can be purified on the basis of their co expression of two per vascular markers, CD140b/platelet-derived growth factor receptor  $\beta$  (PDGFR $\beta$ ) and CD146 (Maijenburg *et al.*, 2012). The first novel single marker, W5C5 for isolation of endometrial MSC-like cells (eMSCs) (Schwab & Gargett *et al.*, 2007; Masuda *et al.*, 2012)

#### **Immunomodulatory Properties of MSCs:**

One of the main advantages of MSCs is their immunomodulatory properties. MSCs grown in vitro have the ability to interact and regulate the function of the majority of effectors cells involved in the processes of primary and acquired immune response. Due to low expression of MHC I and lack expression of MHC class II along with co-stimulatory molecules, like CD80, CD40 and CD86, MSCs are unable to bring substantial all reactivity and these features protects MSCs from natural killer (NK) cells lysis (Masuda *et al.*, 2012).

Moreover, it is observed that human BM-MSCs were not recognized by NK cells, as they expressed HLA-DR molecules (Rasmusson *et al.*, 2003) MSCs exert immunomodulatory effects by inhibiting the complement-mediated effects of peripheral blood mononuclear cell proliferation (Spaggiari *et al.*, 2006; Tu *et al.*, 2010) blocking apoptosis of native and activated neutrophils, as well as reducing the number of neutrophils binding to vascular endothelial cells, limiting the mobilization of these cells to the area of damage (Moll *et al.*, 2011; Cassatella *et al.*, 2011). In response to inflammatory molecules such as interleukin-1 (IL-1), IL-2, IL-12, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interferon-gamma (INF- $\gamma$ ), MSCs secrete an array of growth

factors and anti-inflammatory proteins with complex feedback mechanisms among the many types of immune cells summarize in **Table 4** (Munir *et al.*, 2015; Shi *et al.*, 2015; Cagliani *et al.*, 2017; Weiss & Dahlke, 2019; Maria *et al.*, 2017; Zhao *et al.*, 2016).

The key immunomodulatory cytokines include prostaglandin 2, TGF- $\beta$ 1, HGF, SDF-1, nitrous oxide, indoleamine 2,3-dioxygenase, IL-4, IL-6, IL-10,IL-1 receptor antagonist and soluble tumor necrosis factor- $\alpha$  receptor (Murphy *et al.*, 2013). MSCs prevent proliferation and function of many inflammatory immune cells, including T cells, natural killer cells, B cells, monocytes, macrophages and dendritic cells. MSCs can block the differentiation of CD34+ cells isolated from the bone marrow or blood monocytes into mature dendritic cells both by direct contact as well as by secreted paracrine factors (Nauta *et al.*, 2006; Jiang *et al.*, 2005). They inhibit the transformation of immature dendritic cells into mature forms and limit the mobilization of dendritic cells to the tissues. (Su *et al.*, 2011) Due to the influence of MSCs, M1 (pro-inflammatory) macrophages are transformed into M2 type cells with an anti-inflammatory phenol-type, and the interleukin (IL)-10 secreted by them inhibits T-cell proliferation (Chen *et al.*, 2014; Gao *et al.*, 2014).

In vitro studies have demonstrated a direct immunomodulatory effect of MSCs on lymphocytes by suppression of activated CD4+ and CD8+ T cells and B-lymphocytes was observed (Sharif *et al.*, 2019; Glennie *et al.*, 2005). In addition, MSCs reduce the level of pro-inflammatory cytokines synthesized by T-lymphocytes, such as tumor necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\gamma$  (Yañez *et al.*, 2006) and increase synthesis of anti-inflammatory cytokines, for example, IL-4. MSCs also have the ability to limit the synthesis of immunoglobulins like immunoglobulin (Ig) M, IgG, and IgA classes secreted by activated B cells, thereby blocking the differentiation of these cells to plasma cells (Corcione *et al.*, 2006). MHC class I chain-like gene A (MICA) together with TLR3 ligand and other immunoregulatory proteins kept the MSCs safe from NKs invasion (Giuliani *et al.*, 2014). Together with other properties, these immunomodulatory features makes MSCs one of the feasible stem-cells sources for performing cell transplantation experiments.

**Table 4:** Anti-inflammatory mechanisms of MSCs.

Mechanism	Effects	Target cell
PGE2/direct contact	↓TNF- $\alpha$ , IL-12, differentiation and activation, Impairs effect on resting NK cell and ↑IL-23	Dendritic cells
PGE2, IL-6, IL-8 and SDF-1	↑ IL-10	Immature Dendritic cells
PGE2, IDO, HGF, TGF- $\beta$ 1 and NO IL-10 IL-17 FOXP3-Treg Gal-1	↓CD4+T-cell proliferation by S-phase entry block and Go/G1 phase arrest Inhibits T-cell function, ↓IL-12 Inactivate TH-1 cells ↓TH 17-cells proliferation ↑IL-10, IL-13 Antiproliferative effects on activated T cells, supports the survival of naïve T cells	T cells (CD4 +, helper T cells)
sHLA-G5 IL-10,	↓cytotoxicity ↑T-reg production and ↓ TH-1, TH-2, TH-17 Cells	T cells (CD8 +, cytotoxic T cells) T-reg cells
sHLA-G5 PGE2, HGF, TGF- $\beta$ 1, IDO, NO and PD-L1	↓Treg differentiation ↓Ig antibody production by B cell ↓B-cell proliferation by Go/G1 phase arrest ↓B-cell chemotaxis	B cells
PGE2, IDO, sHLA-G5, HGF, TGF- $\beta$ 1 IL-15	↓INF- $\gamma$ and IL-2 ↓NK cell proliferation ↓cytotoxicity	NK cells
PGE2	↓Monocyte proliferation by Go/G1 phase arrest ↓Monocyte difference to DC	Monocytes
IL-6 TSG-6 PGE2, IL-1RA, Phagocytosis	↓TNF- $\alpha$ ↓NF- $\kappa$ B and IL-10 Converts M1 (pro-inflammatory) type to M2 (anti-inflammatory) type macrophages	Macrophages
IL-8, IL-6	↓ f-MLP- respiratory burst ↓apoptosis	Neutrophils
VEGF IL-1R $\alpha$ sTNF-R	Pro-angiogenic, Increased nutrient, O <sub>2</sub> and waste transport Antagonizes IL-1 Inhibits TNF- $\alpha$ production	No specific target

**Note:** HGF, hepatocyte growth factor; HLA, human leukocyte antigen; IDO, indoleamine 2,3-dioxy-genase; IL-1Ra, IL-1 receptor antagonist; INF, interferon; MMP, matrix metalloproteinase; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cell; NK, natural killer; NO, nitrous oxide; PD-L1, programmed cell death ligand-1; PGE2, prostaglandin 2; SDF-1, stromal cell-derived factor-1; sTNF-R, soluble TNF-areceptor; TGF, transforming growth factor; TNF, tumor necrosis factor; TSG, tumor necrosis alpha-stimulating gene; VEGF, vascular endothelial growth factor; Gal-1, Galectin-1; FOXP, Forkhead box (FOX) protein; f-MLP, N-formyl-l-methionin-l-leucyl-l-phenylalanine.

Furthermore, it is also important to note that MSCs from different sources may differ in their mechanisms and capacities for immune-modulation (Mattar & Bieback, 2015). Because of their trophic and immunomodulatory functions, MSCs are generally considered to possess greater advantages in cell-based regenerative medicine, MSCs an important regulator of the immune tolerance and attractive therapeutic target for limiting autoimmune inflammation.

**CONCLUSION:**

Mesenchymal stem cells have been isolated from a wide range of species and tissues using several tech-

niques. MSCs are isolated as a heterogeneous population of cells that differ in growth kinetics and differentiation potentials. A large number of markers have been brought forward to facilitate the isolation of MSCs from their surrounding environment or the selection of MSCs with high stemness. With their ability to differentiate into multiple lineages, secrete factors related to immune regulation, and migrate to-ward sites of inflammation, All these properties of MSCs make them distinct from other stem cells and can be used in future cell replacement therapy and many other clinical implications. In this review, we concisely bring up the current data available for MSCs isolation sources,

characterization markers and its immunomodulatory properties. The future MSCs research should focus on finding more suitable markers to isolate the source-specific MSCs, basic understanding of growth regulators in differentiation and trans-differentiation and its immunomodulatory properties to modify the host immune environment.

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