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Multipotent Human Mesenchymal Stem/Stromal Cells: An Updated Review on Historical Background, Recent Trends and Advances in their Clinical Applications

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Abstract: Early reports demonstrated the presence of cells with stem-like properties in bone marrow, with these cells having both hematopoietic and mesenchymal lineages. Over the years, various investigations have purified and characterized mesenchymal stromal/stem cells (MSCs) from different human tissues as cells with multi-lineage differentiation potential under the appropriate conditions. Due to their appealing characteristics and potential, MSCs are leveraged in many applications including medicine, oncology, bioprinting and as recent as treatment of COVID-19. To date, reports indicate mesenchymal stromal/stem cells have varied differentiation capabilities into different cell types and demonstrate immunomodulating and anti-inflammatory properties. Reports indicate that different MSCs microenvironments or niche and the resulting heterogeneity may influence their behavior and differentiation capacity. The potential clinical applications of mesenchymal stromal/stem cells have led to an avalanche of research reports on their properties and hundreds of clinical trials being undertaken. The future looks bright and promising for mesenchymal stem cell research with many clinical trials under way to prove their utility in many applications and in the clinic. This report provides an update on the potential broader use of mesenchymal stromal/stem cells, review early observations of the presence of these cells in the bone marrow and their magnificent differentiation capabilities and immunomodulation.

Keywords: Mesenchymal stem/stromal cells, regenerative medicine, tissue engineering, Clinical Application, Differentiation Capacity, Cellular Immunomodulation, Inflammation, Signaling Cells, Transplantation, International Society for Cell and Gene Therapy.

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1.0 Introduction

Mesenchymal Stem/Stromal cells: What's in a Name?

Early reports indicated that the bone marrow contained both haematopoietic stem cells as well as mesenchymal stromal/stem cells (MSCs) [1, 2]. Classic transplantation experiments by Friedensten and colleagues demonstrated that cells from the bone marrow can create a bone marrow microenvironment in the kidney as well as formation of bone tissue [2]. This indicated that beside haematopoietic stem cells, there was an additional stem cell type, later identified as mesenchymal stromal/stem cells, a term coined by Caplan in the 1990s (Figure 1) [1-4]. Mesenchymal stem cells (MSCs) have the ability to grow in vitro, display enhanced differentiation capabilities to form the connective tissues present in different organs compared to other cells and release large amounts of biomolecules such as growth factors and cytokines [4, 5]. MSCs have been called by various names and experiments have shown that these cells demonstrate different degrees of stemness and differentiation capacities, capacities that appear to diminish with age [6-8]. In addition to mesenchymal stem cells, these cells can be referred to as mesenchymal stromal cells as well as multipotent stromal cells among many names [9-11]. Recent efforts have been made to name MSCs based on their mechanism of action, which is mainly secretion of various biological molecules including growth factors and cytokines [12-14]. In this regard, MSCs can be seen as cells involved in influencing cellular signaling [12, 13]. It is important to note that MSCs differ in their origins, differentiation ability, functions and consequently their therapeutic uses. As early as 2006, the International Society for Cellular Therapy (ISCT) defined MSCs as multipotent mesenchymal stromal cells and published a set of conditions needed to be fulfilled for cells to be called such. These conditions included the expression of several surface antigens such as cluster of differentiation 90 (CD90), CD 105 as well as being able to grow in vitro as substrate-adhering cells [9, 15, 16]. As we demonstrated in our earlier report in addition to other reports, MSCs can differentiate into adipocytes, chondroblasts and osteoblasts as well as lacking CD14, CD34 and CD45 expression [9, 16]. Additional markers also proved their utility in the isolation and identification of MSCs. For example, CD106, CD146 and stromal-1 antigen (STRO-1) are additional markers used to identify MSCs in vitro and are expressed by cells with differentiation abilities into multi-lineages [17-19].

The term 'mesenchymal' present in many of the names given to MSCs comes from the word 'mesenchyme' which is used to describe cells from the mesoderm of a developing embryo. These

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cells migrate and are distributed throughout the body of the developing embryo [4]. In adults, the mesenchymal cells forms the connective tissue including cartilage, muscle and bone marrow [20]. These cells are characterized based on their expression of markers such as fibronectin, laminin B1 and vimentin [21, 22]. It is important to note that the origin of MSCs hasn't been proven since their discovery. Several reports have shown that MSCs can also be derived from cells of the ectoderm [23-26]. Different MSC cells have been identified based on expression of markers such as Nestin as well as cell proliferation in bone marrows of developing embryos, with some cells being derived from the mesoderm whilst others are derived from the neural crest [26]. Thus the origin of MSCs is broad-based and is linked to cells of different germ layers. In summary, the germ layers from which MSCs are derived determine their final function in the adult body.

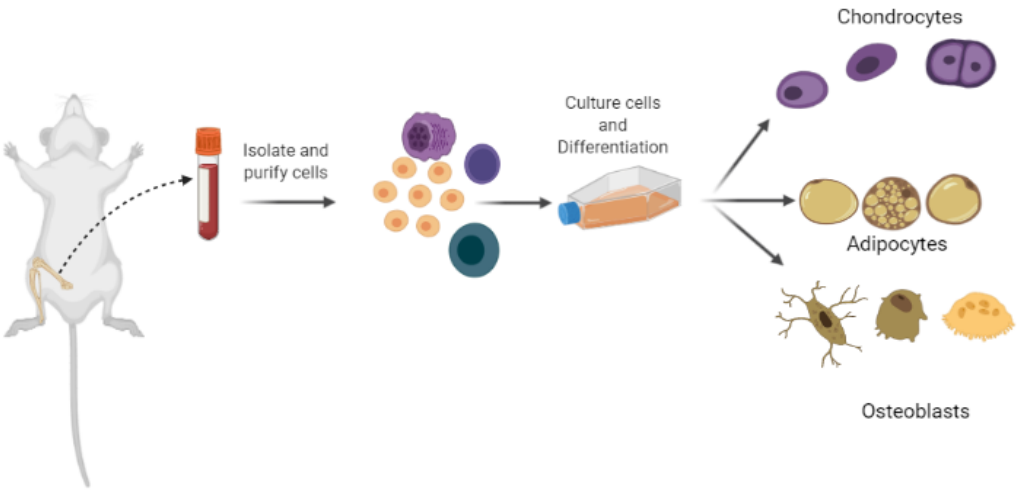

Figure 1 Historical background of Mesenchymal Stem cells. Cells isolated from the bone marrow were shown to form clonogenic colonies. Studies later showed that cells from the bone marrow can differentiate into the connective tissue.

2.0 Sources and Niche of Adult Mesenchymal Stem/Stromal Cells

Well-known sources of mesenchymal stromal/stem cells include the bone marrow, umbilical cord tissue, adipose tissue as well the placenta (Figure 2) [27, 28]. In most cases, some of these tissues do not raise ethical issues regarding harvesting of cells as they can be considered medical waste for example during liposuction and after child-birth [29-32]. Several factors such as the final use of the isolated MSCs, the differentiation potential of the MSCs and the total number of cells needed for the application can influence the source of the cells [33-35].

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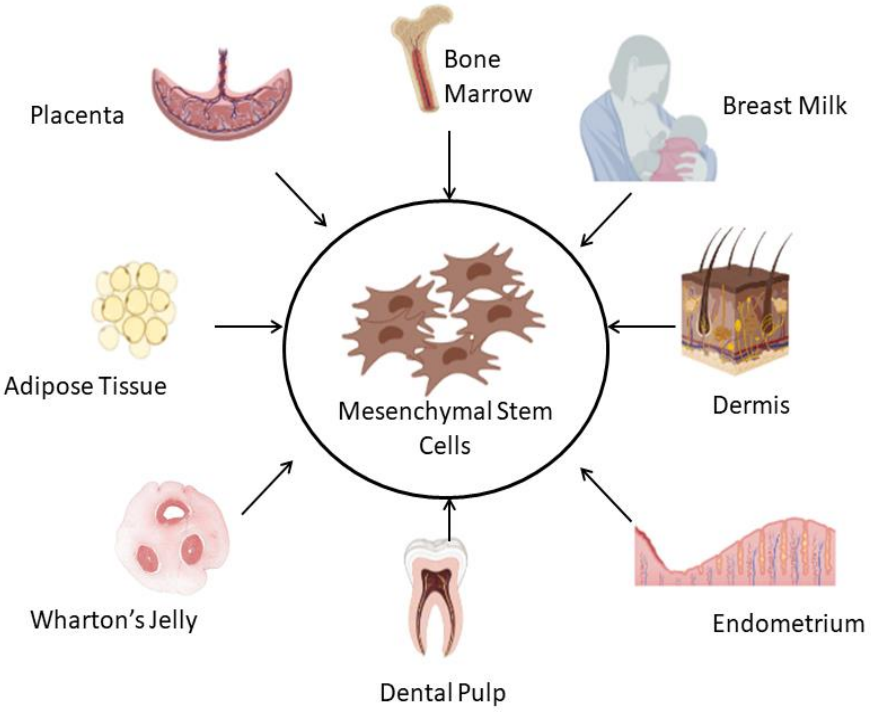

Figure 2 Sources of mesenchymal stem cells.

Mesenchymal stem cells niche is the microenvironment within which MSCs exist and can maintain their 'stem cell' status [36, 37]. In the bone marrow, MSCs released growth factors and cytokines required for the proliferation and maturation of haematopoietic cells [38, 39]. Méndez-Ferrer and colleagues demonstrated using MSCs expressing Nestin that they are part of the haematopoietic niche in the bone marrow [38]. In their study, the authors showed that MSCs expressing Nestin can form colonies with fibroblastic activity and can grow in suspension with self-renewing and expansion capabilities [38]. Several other studies have also shown that MSCs can be isolated from tissues derived from the mesoderm during embryonic development [26, 40, 41]. Several other studies have demonstrated that MSCs can be derived from different sources and therefore can exist in different niche. For example, it was shown that cells with MSC-like properties can be isolated from perivascular space of blood vessels from many tissues including pancreas and adipose tissue [22, 42-44]. The isolated cells were able to express markers such as CD146 (cluster of differentiation 146), PDGF-RB (platelet-derived growth factor receptor B) as well as alkaline phosphatase (ALP) [42]. The osteoprogenitor cells or MSCs within sinusoidal blood vessels are able to produce a haematopoietic microenvironment after transplantation [19, 45]. However, several other studies including one by Feng and colleagues demonstrated that cells that do not express CD146 but can differentiate into pericytes for example are able to meet the minimum criteria for MSCs [46-48]. Several studies have shown that MSCs and pericytes are

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functionally different although they express similar genes and have almost identical differentiation capabilities [43, 49-52]. Only pericytes are able to form fully functional blood vessels in contrast to MSCs isolated from the bone marrow [49, 53-55]. Further studies are needed to fully explain and delineate the relationship between MSCs and pericytes. In vitro assays performed by Blocki and colleagues demonstrated that not all MSCs are pericytes [49]. A study by Loibl and colleagues demonstrated that MSCs can be induced into a pericytes-like phenotype through co-culture with endothelial progenitor cells [56]. In addition, flow cytometric purification of pericytes can result in pericytes that are similar to MSCs in many growth, morphology and differentiation characteristics [57-61]. Overall, the interconnectivity between MSCs and pericytes require further investigations.

Cell-cell interactions are important within MSCs' in vivo niche for the maintenance of stem cell properties and cadherins such as N-cadherin have been shown to play key roles [62, 63]. Migration of MSCs from their niche result in new environments characterized by increased ECM molecules including collagens and proteoglycans [64-66]. To be able to interact with ECM molecules, MSCs express integrins and are able to form focal adhesions [67, 68]. Culture of MSCs in vitro induce cellular changes and influence differentiation into specific lineages. For example, culture on rigid surfaces can induce osteogenic and adipogenic differentiation [9, 69, 70]. Soft tissues and surfaces induce MSCs towards the myogenic and neurogenic lineages [71-75]. Thus the stiffness of a surface or microenvironment can influence the expression of markers and shape of MSCs both in vivo and in vitro (Figure 3) [76-78]. Generally, a stiff surface or environment tends to favour MSC differentiation into lineages associated with stiff tissues such as bones [69, 78]

Figure 3 MSCs interacts with different components of its microenvironment including cells, ECM and biomolecules. (a) On a soft surface, MSCs exhibit a round shape typical of cells interacting with cells and the ECM. (b) When cultured on a rigid surface, MSCs can take an elongated shape.

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3.0 Heterogeneity of MSCs

MSCs display great heterogeneity in terms of their functionality and consequently application despite their sharing of several characteristics. Thus, whilst MSCs from different tissues meet the minimum criteria needed for classification as MSCs, those isolated from different tissues and developmental stages, display differences that impact on their use [79-81]. Initially isolated from the bone marrow, MSCs can now be obtained from a variety of sources such as Wharton's Jelly, adipose, blood, placenta and amniotic fluid (Figure 2) [82-86]. MSCs from fetal tissues tend to proliferate at a higher rate and have longer telomeres than those from adult tissues [87, 88]. In addition, several reports also indicate that fetal MSCs have a higher differentiation potential than adult tissue-derived MSCs [89-91]. Furthermore, MSCs from fetal tissues can proliferate in vitro for a longer period of time before displaying characteristics of senescence [91]. In contrast, MSCs from the bone marrow and adult adipose tissue display a higher level of stemness as demonstrated by the formation of more colony-forming units compared to fetal tissue-derived MSCs [92-95]. In a detailed analysis of MSCs from different sources, Heo and colleagues demonstrated that MSCs from bone marrow express DLX5 and Sox2 needed for brain neuron development [96]. In addition, the authors showed that bone marrow- and adipose tissue-derived MSCs displayed similar differentiation capacities as well as gene expression. MSCs from different sources also display multi-lineage differentiation as well as immunomodulatory behaviours. Kern and colleagues demonstrated that MSCs from the bone marrow and adipose tissue can easily be isolated compared to MSCs from the umbilical cord blood [97]. In addition, the authors also demonstrated that umbilical cord blood MSCs showed no adipogenic differentiation abilities compared to those from the bone marrow and adipose tissue [97]. Several studies including our own have demonstrated that indeed, adipose-derived MSCs can undergo multi-lineage differentiation under different conditions [9, 98-100].

MSCs from different donors and of different ages also display great heterogeneity. Phinney and colleagues demonstrated that bone marrow-derived MSCs from different donors show differences in differentiation capabilities as well as osteogenic potentials [101]. The authors showed that MSCs from different donors show different growth rates and alkaline phosphatase activity in culture [101]. In addition, the authors postulated that MSCs heterogeneity and differentiation potential were also influenced by method of harvest used. For example, Pezzi and colleagues demonstrated that oxygen levels impact on MSC heterogeneity in vitro and this has huge influence on long term culture of MSCs for therapy [102]. Other reports have postulated

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that MSCs maybe a product of long term in vitro culture [102-104]. Furthermore, other reports demonstrate bone marrow derived-MSC heterogeneity due to age of donor, with more MSCs from older donors undergoing apoptosis and having a low proliferation rate than those from younger donors [105-107]. Naïve MSCs have been shown to exhibit heterogeneity based on transcription data [108]. If MSCs are to be used for therapy there may be need to synchronise the cells via stimulation or growth in media with no growth factors [103, 109, 110]. 'Priming' of MSCs through the use of a stimulus must be done with caution as some factors can induce undesirable effects such as apoptosis and senescence [111-113]. Current data show that priming of MSCs can be done via the use of cytokines, drugs, growth factors, biomaterials and the extracellular matrix as well as hypoxia. When cultured in vitro, MSCs display three main morphologies. Colter and colleagues as well as others demonstrated that beside the fibroblastic spindle shaped cells and the large flat cells, a third type of cells characterized as small, round and having enhanced self-renewal abilities also exists in vitro [114-117]. Studies now show that cells from a single colony are not all the same and can demonstrate multipotence, dipotence or unipotence [104]. Thus, a single MSC colony can give rise to different cell types with varied differentiation potentials. With publication of different data sets, it has been theorized that even within MSC populations, cells exist in a hierarchical structure, with some remaining as unipotential or dipotential whilst others become multipotential, a characteristic which they can eventually loose [118-121]. Several pieces of evidence suggest that the transformation of MSCs may be linked to a lower proliferation rate and decreased expression of markers such as CD146 [122-124].

4.0 MSCs and the Immune System.

Reports over the years have shown that MSCs have immunomodulatory properties. MSCs were shown to influence the behaviour of cells involved in immune responses and to be able to impact a lot of cellular processes (Figure 4) [125]. MSCs achieve their immunomodulating effects via prevention of apoptosis in native and activated neutrophils, preventing the action of peripheral blood mononuclear cell proliferation, preventing the recruitment of cells at wound sites as well as preventing the interaction between neutrophils and vascular endothelial cells (Table 1) [126-129]. Several reports have shown that native or transformed MSCs release several cytokines including TGF-B, which can impact other cells such as tumor cells and neutrophils [5, 130, 131]. Furthermore, MSCs have been shown to release various chemokines involved in recruiting macrophages and neutrophils to wound areas [132-135]. Brown and colleagues

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demonstrated that MSCs prevent mast cell degranulation and limit cytokines secretion by these cells [136]. In addition, MSCs can inhibit the proliferation of natural killer cells and have been shown to suppress natural killer cell cytotoxicity [137, 138].

Several MSC-secreted factors have been shown to prevent the differentiation and maturation of blood monocytes into dendritic cells as well as preventing dendritic cells from migrating to tissues [139-141]. MSCs have been shown to induce transformation of M1 macrophages into M2 macrophages, via nuclear factor-kB (NF-kB) and signal transducer and activator of transcription 3 (STAT3) pathways, with anti-inflammatory properties [142, 143]. The resulting M2 macrophages are anti-inflammatory and release cytokines such as interleukin 10 (IL-10) that can prevent T cell proliferation [142, 144, 145]. Glennie and colleagues demonstrated that bone marrow-derived MSCs can inhibit growth of activated T cells and lymphocytes [146]. Overall, MSCs induce a reduction in synthesis and release of cytokines that promote inflammation and increase the synthesis of anti-inflammatory cytokines by T-lymphocytes [147, 148]. MSCs have also been shown to prevent the differentiation of CD4-positive T lymphocytes into T helper cells, whilst inducing differentiation of T cells into CD4-positive regulatory T cells [149, 150]. It has been shown that MSCs suppress chemokines expression by B lymphocytes and this impact the ability of the B lymphocytes to migrate [151, 152]. Finally, MSCs have been shown to inhibit the synthesis of several immunoglobulins by activated B cells and in the process prevents formation of plasma cells [153-155].

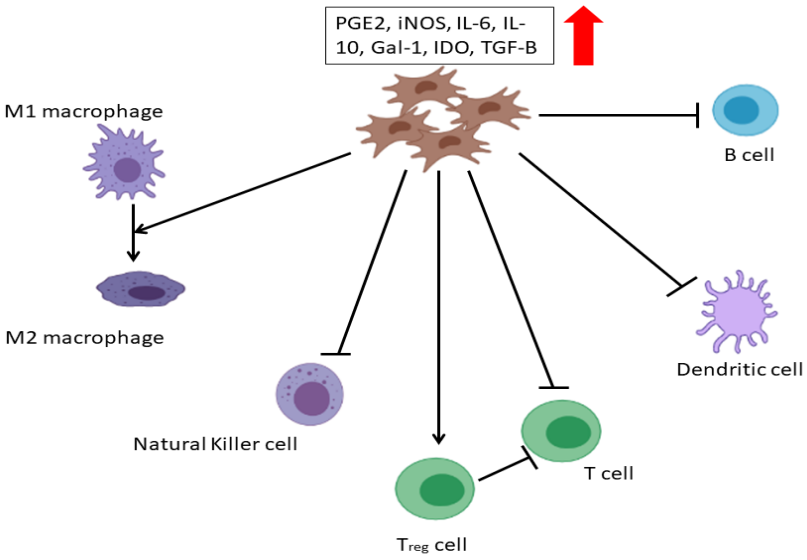

Figure 4 Interactions between MSCs and Immune cells. Through the synthesis and secretion of various factors including TGF-B, PGE2, interleukin-6, IL-10 and Gal-1, MSCs impact on the proliferation and activation of immune cells such as macrophages, dendritic cells and natural killer cells.

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Table 1 Immunomodulatory Effects of mesenchymal stem cells

Mesenchymal Stem Cells	Affected Cells	Immunomodulatory Effect	References
MSCs	Dendritic Cells	Limit recruitment of dendritic cells to tissues. Prevent transformation of naïve dendritic cells into mature cells.	[139-141, 154, 156]
MSCs	Lymphocytes	Suppress lymphocyte proliferation and expression of chemokines. Downregulate the synthesis of inflammatory cytokines by lymphocytes whilst inducing anti-inflammatory cytokine synthesis. Prevents naïve lymphocyte differentiation into T helper cells. Inhibit the synthesis of various immunoglobulins.	[146, 147, 149, 150]
MSCs	Macrophages	Conversion of M1 macrophages into M2 macrophages that synthesize IL-10, which inhibit proliferation of T-cells. Induce migration of macrophages and recruitment to injury sites. Activate macrophages to perform phagocytosis	[130, 142, 143]
MSCs	Mast cells	Prevents mast cell degranulation. Inhibit mast cell response to chemotactic factors	[136, 157-159]
MSCs	Natural Killer cells	Prevents the activation of natural killer cells. Suppress natural killer cell cytotoxicity activity.	[137, 138]
MSCs	Neutrophils	Reduce binding between neutrophils and vascular endothelial cells. Prevents neutrophils from mobilizing at injury sites. Inhibit apoptosis of neutrophils.	[126, 127, 130]

5.0 Paracrine Properties of MSCs

Recent reports show that MSCs secrete several factors that act in both autocrine and paracrine fashion. Thus, one area of MSCs being investigated thoroughly is that of provision of factors rather than the differentiation of MSCs into different lineages. If MSCs can release factors necessary for immune modulation, tissue repair and wound healing, then MSCs can be useful in various ways. One primary function of secreted factors is the regeneration of damaged or diseased tissues [11, 160-163]. Factors secreted by MSCs include growth factors, enzymes, cytokines, chemokines as well as ECM proteins [133, 161]. MSC-secreted factors act in a

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context-dependent manner. For example, secreted factors such as VEGF and TIMP-1 and TIMP-2 are known to regulate angiogenesis in opposing ways, with VEGF promoting angiogenesis whilst TIMP-1 and TIMP-2 inhibit angiogenesis [164, 165]. Additionally, VEGF secreted by MSCs is known to influence other processes such as fibrosis and apoptosis [166-168]. MSC-derived VEGF, IGF-1, IGF-2 and HGF have anti-apoptotic effects [169-173]. Thus, an increase in the expression of one factor can have multiple effects on the tissue into which it is released. Cantinieaux and colleagues demonstrated that conditioned media from bone marrow-derived MSCs can protect neurons from apoptosis as well as activates macrophages [164]. Menezes and colleagues demonstrated that MSCs can recruit pericytes and induce angiogenesis via release of factors such as VEGF during the repair of spinal cord injury in rats [174].

In classic co-culture experiments of both esophageal and breast cancer cells with Wharton Jelly-derived MSCs, we demonstrated that MSCs reduced the effects of paclitaxel and cisplatin on cancer cells [5]. One factor that was released in large quantities by both cancer cells and MSCs was TGF-B and was involved in transformation of MSCs into cancer-associated fibroblasts (CAFs) [5]. Thus MSCs protected cancer cells from drug-induced apoptosis. Several other pieces of evidence substantiated our findings [175]. For example, Eliopoulos and colleagues demonstrated that bone marrow-derived MSCs also reduce the renotoxicity of cisplatin in mice [176]. Bergfeld and colleagues showed that MSCs from the bone marrow enhances the metastatic abilities of tumor cells in addition to the promotion of drug resistance [177]. Orimo and colleagues also demonstrated that stromal cells such as MSCs promote breast carcinoma cells as well as angiogenesis through the secretion of factors including SDF-1 [178]. It appears the source of the MSCs and the cancer under study is important in determining the overall effect of MSCs on the cancer cells. For example, Khakoo and colleagues demonstrated that MSCs can exert anti-tumorigenic effects in a model of Kaposi's sarcoma [179]. In yet another study, Ohlsson and colleagues showed that mesenchymal progenitor cells can inhibit tumor growth when grown in a gelatin matrix [180]. Furthermore, Maestroni and colleagues demonstrated that factors secreted by bone marrow-derived stromal cells can inhibit the growth of Lewis lung carcinoma and B16 melanoma cells in mice [181]. The contrasting data as presented above demonstrate the importance of accurate reporting and understanding the effects of MSCs and factors they release on cancer cells [182, 183]. In addition, one of our studies showed that Wharton's Jelly-derived MSCs when cultured on an ECM activate apoptosis in in a p21-dependent mechanism in esophageal and breast cancer cells [10]. It appears the effect of MSCs

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on cancer cells is context-dependent, may depend on the paracrine factors released and requires further investigations.

Several MSC-derived factors including VEGF, HGF, EGF, SDF-1 and TGF-α can suppress fibrosis in many tissues [184-188]. Chemokines with opposing effects including stromal cell-derived factor 1, CCL5 and monocyte chemoattractant protein 2 are also secreted by MSCs and impact on cell chemotaxis [189-192]. Some studies have shown that MSC-secreted factors can have anti-bacterial and anti-viral activities [193, 194]. Indeed, several cytokines including IL-6, IL-10 and TNF-α have been shown to fluctuate during bacterial infection [195-199]. Meisel and colleagues demonstrated that MSCs stimulated by inflammatory cytokines display antimicrobial activities against several bacteria, protozoal parasites and viruses [193]. In addition, Li and colleagues demonstrated that MSCs can prevent inflammation and severity of Haemophilus influenza infection by recruiting CXCR3+ Tregs [200].

5.1 Mesenchymal Stem Cell-derived Extracellular Vesicles

MSCs have also been suggested to secrete extracellular vesicles (EVs), through which they can relay signals and cues to other cells. These extracellular vesicles may include apoptotic bodies, microvesicles and exosomes. The biomolecules and other factors that are carried by EVs also called cargo are largely dependent on the cell type from which they originate, although some reports indicate some processing can take place during transportation. EV cargo is composed mainly of lipids, nucleic acids, and proteins and thus mainly functions to regulate cellular processes, cellular functions, immune response and also the maintenance of homeostasis [201, 202]. Recent reports indicate that EVs isolated from MSCs can function in the same way as the MSCs [203-206]. Isolated MSC supernatants or conditioned media can perform similar action compared to the actual MSCs, demonstrating that biomolecules and factors within the MSC-derived EVs are responsible for the effects of MSCs observed in many experiments [207-210]. Patel and colleagues demonstrated that mesenchymal stem cells are protective to breast cancer cells via the release of several factors including TGF-B [211]. Tang and colleagues demonstrated that MSCs induces vascular regeneration in a model of myocardial infarction in rats via the release of various factors [212]. Mao and colleagues showed that MSC-derived EVs can alleviate myocardial ischemia in mice [213]. Ren and colleagues showed that MSC-derived EVs containing miR-29a-3p can protect against myocardial injury after severe acute pancreatitis [214]. Caution

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must be practised however, as the protection afforded to other cells by MSCs and their EVs can have a negative effect in cancer. For example, Li and colleagues showed that EVs from bone marrow-derived MSCs can enhance osteosarcoma cell proliferation, invasion and migration in a mechanism involving the Wnt-B-catenin signaling [215]. Furthermore, Guo and colleagues showed that MSC-derived EVs containing miR-130b-3p promotes the progression of lung cancer [216].

6.0 MSCs Differentiation Potential

One of the criteria used to characterize MSCs is the ability to differentiate into multi-lineages (Figure 5) [9, 11, 21, 54, 210]. Several reports including one by Dominici and colleagues spelt out the minimum criteria required for cells to be defined as MSCs as stipulated by The International Society for Cellular Therapy [16]. As we showed in our early publication, this can be achieved through culturing the MSCs in differentiation media with specific supplements and then evaluating adipogenesis markers, osteogenesis markers and chondrogenesis markers [9]. Adipogenic-inducing medium consisted of DMEM containing 10% FBS, 1% 1 µM dexamethasone, 0.5 mM 3-isobutyl-methylxanthine, 200 µM indomethacin, and 10 µg/mL insulin. We utilized both real time PCR as well as staining for lineage-specific markers. For adipogenesis, we evaluated the levels of PPARG2 and Lipoprotein lipase (LPL) using real time PCR as well as staining with Oil Red O for lipid droplets [9]. Osteogenic medium made up of DMEM with 10% FBS, 0.1 µM dexamethasone, 50 µM ascorbate-2-phosphate, and 10 mM β-glycerophosphate. To evaluate osteogenesis markers we used real time PCR to measure the levels of CBFA1 and Osteocalcin (OC) as well as staining for mineralization with Alizarin red S [9]. Chondrogenic medium made up of DMEM containing 0.1 µM dexamethasone, 50 µg/mL ascorbate-2-phosphate, 10 ng/mL TGF-β-3, 40 µg/mL proline, 100 µg/mL pyruvate, and 1% insulin, human transferrin and selenous acid premix universal culture supplement. To evaluate chondrogenesis markers we used real time PCR to measure the levels of type II collagen (COL2) and Sox9 as well as staining with Toluidine Blue O for proteoglycans that are visible as purple [9]. These conditions have been utilized by several laboratories worldwide and are the stipulated conditions for such analysis [28, 217-219]. Beside these differentiating conditions, MSCs are also characterized based on expression of several surface markers as we showed in our study. Specifically, our data show that our adipose-derived MSCs expressed markers such as CD73, CD90, and CD 105, with no expression of CD34 and CD45 [9]. In addition, we also utilized and characterized Wharton's Jelly derived MSCs [10]. Flow cytometric analysis of Wharton's Jelly-

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derived MSCs using antibodies against CD44, CD45, CD73, CD90 and CD105, showed that our MSCs fulfilled the minimum requirements for MSCs as stipulated by the ISCT [10]. Cells characterized in our laboratory demonstrated the classical MSC phenotype of CD44+CD73+CD90+CD105+CD45- cell population [10]. Furthermore, lineage specific differentiation capacity of Wharton's jelly-derived MSCs fulfilled stipulated criteria by the ISCT.

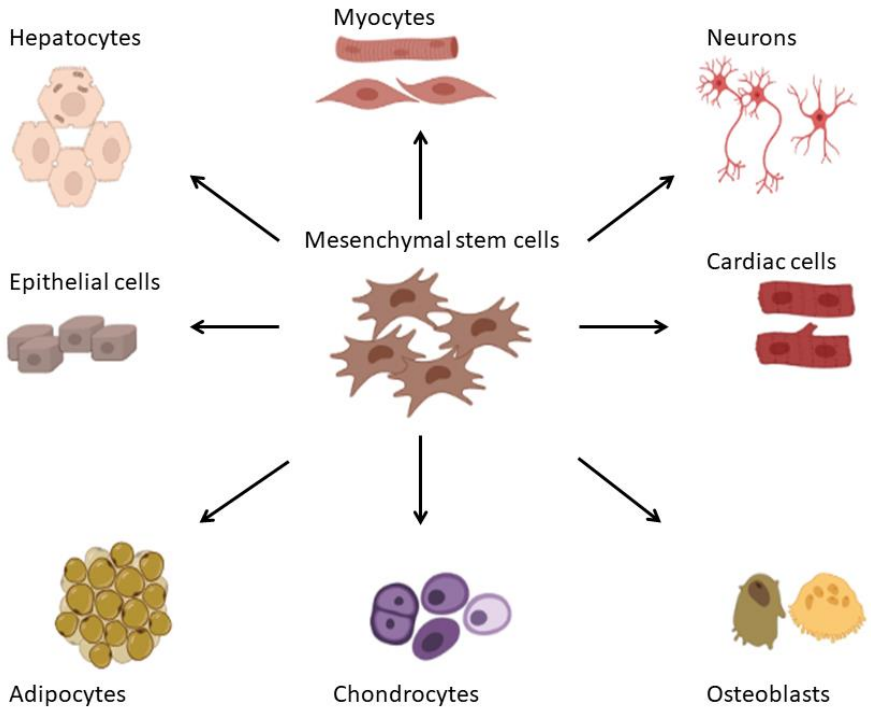

Figure 5 The differentiation potential of mesenchymal stem cells.

In addition to having multi-lineage differentiation potential, MSCs have been shown to transform to other cell types, given the right cues or signal. As reviewed elsewhere, MSCs can be a source of fibroblasts, other stromal cells and progenitors for cells making the body ligaments and connective tissue [28, 220]. Xu and colleagues demonstrated that bone marrow-derived MSCs can differentiate into cells with a cardiomyocyte phenotype [221]. It is also possible to obtain liver cells including hepatocytes as well as B-cells of pancreatic islets from MSCs provided the right supplements such as EGF, nicotinamide, dexamethasone, insulin, transferrin and oncostatin are added to the culture media [222]. Indeed, MSCs from different sources have been shown to differentiate and to mature into pancreatic islets of B-cells with the ability to produce insulin [223, 224]. Naghdi and colleagues were able to differentiate MSCs from the bone marrow into cholinergic neurons in rats, clearly demonstrating the utility of MSCs for the treatment of spinal cord injury [225]. Other cues necessary for the differentiation of MSCs into neurons

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include retinoic acid, valproic acid, EGF, hydrocortisol and 5-azacytidine [226, 227]. The resulting neurons are able to express several markers of mature neurons such as neuron-specific enolase and Nestin. Dzobo and colleagues demonstrated that MSCs cultured on a 3D cell-derived matrix, to recapitulate in vivo physiological microenvironment, showed reduced expression of integrins α2 and β1 and subsequently differentiated towards the chondrogenic phenotype as evidenced by the loss of SOX2, and NANOG gene expression as well as increase in markers such as Runx2, osteopontin, p-TGFB-RII [9]. Furthermore, our study showed that the use of siRNA and a mutant Notch1 construct showed that the mechanism through which MSCs differentiated towards chondrogenic phenotype involved Notch1 and β-catenin signaling [9]. Overall, these and other studies indicate that Cs, given the right cues and signaling molecules, can differentiate into multi-lineage cells and form several tissues of the human body.

7.0 Challenges, Prospects and Conclusion

The discovery that the bone marrow contained more than just hematopoietic stem cells, initiated a frantic study of these cells, resulting in the realisation that some cells within the bone marrow can form the connective tissue of the body. Mesenchymal stem cell research entered an exciting period mainly due to their appealing properties including the easy accessibility and multi-lineage differentiation. Further studies revealed that MSCs have immunomodulatory properties and can be a source of many difficult-to-repair cells and tissues, astounding many scientists in the process. Ever since the discovery of MSCs, these cells have been receiving great attention in different fields of biology from regenerative medicine, cancer research and even the treatment of infectious diseases [10, 228]. It is important that MSCs prepared for therapy are properly 'synchronized' or 'tuned' in order to provide optimum effect. Factors such as MSC isolation method, culture method, metabolic state and doses used must be carefully considered during treatment. Thus, MSCs intended for different applications must be prepared differently to increase 'therapeutic effect'. Knowledge of the 'microenvironments' that MSCs are likely to encounter when in vivo, means that the MSCs can be subjected to the same treatments or conditions during preparation time. To overcome challenges such as donor differences in MSCs characteristics, longitudinal culture analysis can be done together with genetic tagging. In addition, MSCs intended for tissue repair may benefit from 'priming' for certain environments, can be grown on specific surfaces such as the ECM as we have done previously [9]. MSCs can be 'tuned' for specific therapeutic use or they can be used to provide extracellular vesicles with a specific biological factor(s) 'package'. Furthermore, cells do not perform tissue repair in isolation.

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If MSCs are intended for tissue repair or regenerative purposes, co-culture or co-transplantation with other cells may increase 'therapeutic effect' or engraftment and differentiation. Based on our studies and those by others, the use of decellularized extracellular matrices and other scaffolds may increase both MSCs differentiation and engraftment [9, 10, 51, 176, 184, 229].

Although MSCs can be isolated and purified effectively, they comprise a very small fraction of cells in tissues. Once isolated, MSCs will therefore require in vitro expansion, a process called Biobanking. In most cases Good Manufacturing Practises are adopted and the isolated and expanded MSCs can be used in Clinical Trials or for patients' treatment in the clinic. Many clinical trials show that a specific number of cells are needed for effective stem cell therapies. Higher and lower cell numbers may not be optimal. To date several MSC preparations have been approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) for the treatment of various ailments. Efforts are underway to perfect the in vitro expansion of MSCs for the best therapeutic effect in vivo. The process of preparing different MSCs for therapeutic use must be defined for each and every application for reproducibility purposes. One popular route for delivery of therapeutic MSCs is intravascular infusion as shown in many clinical trials. Whilst studies show that infusion of bone marrow-derived MSC is safe, the same cannot be said about other MSC products from other sources. One major problem is the varied levels of pro-coagulant tissue factor (TF) which can result in an inflammatory reaction.

In order to curtail the mushrooming of unapproved MSC treatment, new and strict regulatory practices are now in place. New rules require that any medical product preparation with living cells must first seek 'investigational new drug' status before being used in clinical trials for example. The EMA has the Centralized Marketing Authorization, a series of steps involving quality checks, safety checks and final approval before any MSC-containing product can be released to the market. Based on current trajectory, the MSC products market is set for a boom. Soon it appears many MSC products will be available in the market for the treatment of various conditions. Many global health challenges including disease like cancer, HIV/AIDS, TB and degenerative diseases still remain with modern medicine and drugs unable to provide cure for [230-232]. Hence the search for solutions continues and MSCs may offer a new and untried way to treat these conditions. It is our belief that advances in the MSC industry and products will transform medicine and provide innovative strategies for different conditions.

Whilst many clinical trials are underway to evaluate the utility of MSCs in different applications, the mushrooming of scientifically unproven stem cell therapies calls for caution of what these cells can do. As wound healing demonstrate that it is a complex process, MSCs should not be used willy nilly and with little knowledge of their function and capabilities. In many cases, the bludgeoning of stem cell therapies is actually a hindrance to proper stem cell research and can cause public distrust in the effectiveness of this therapy. Importantly, all stem cell products must be thoroughly characterized with traceable records on its preparation. Scientists researching on stem cell for therapeutic use must provide accurate records and evaluate each product at several stages of preparation.

Lastly, this article provides an update on the biology and therapeutic use of MSCs and their associated cells and new strategies being devised to utilize these cells in treating various human pathological conditions. Whilst many clinical trials are underway, it is important that research into the various MSCs continue to enhance our understanding of these cells. MSCs are an appealing type of cell(s) via their differentiation potential, immunomodulatory activities, paracrine effects as well as interactions with other cells. MSCs thus provide exciting and innovative way to treat the many diseases afflicting humans.

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