

Sources of Adult Mesenchymal Stem Cells Applicable for Musculoskeletal Applications - A Systematic Review of the Literature

R. Mafi¹, S. Hindocha^{*2,3}, P. Mafi¹, M. Griffin² and W.S. Khan⁴

¹The Hull York Medical School, Hertford Building, Hull, HU6 7RX, UK

²Manchester Interdisciplinary Biocentre, University of Manchester, 131 Princess Street, M17DN, UK

³Department of Plastic Surgery, Whiston General Hospital, Liverpool, L355DR, UK

⁴University College London Institute of Orthopaedics and Musculoskeletal Sciences, Royal National Orthopaedic Hospital, Stanmore, Middlesex, HA7 4LP, UK

Abstract: Mesenchymal stem cells (MSCs) were first discovered by Friedenstein and his colleagues in 1976 from bone marrow. The unique property of these cells was their potential to develop into fibroblastic colony forming cells. Since Friedenstein's discovery of these cells the interest in adult MSCs has been progressively growing. Nowadays MSCs are defined as undeveloped biological cells capable of proliferation, self renewal and regenerating tissues. All these properties of MSCs have been discovered in the past 35 years. MSCs can play a crucial role in tissue engineering, organogenesis, gene therapy, transplants as well as tissue injuries. These cells were mainly extracted from bone marrow but there have been additional sources for MSCs discovered in the laboratories including: muscle, dermis, trabecular bone, adipose tissue, periosteum, pericyte, blood, synovial membrane and so forth. The discovery of the alternative sources of MSCs helps widen the application of these cells in different areas of medicine. By way of illustration, they can be used in various therapeutic purposes such as tissue regeneration and repair in musculoskeletal diseases including osteonecrosis of femoral head, stimulating growth in children with osteogenesis imperfecta, disc regeneration, osteoarthritis and duchenne muscular dystrophy. In order to fully comprehend the characteristics and potential of MSCs future studies in this field are essential.

Keywords: Mesenchymal stem cells, muscular dystrophy, musculoskeletal applications, tissue engineering.

Thirty five years ago Friedenstein *et al.* discovered mesenchymal stem cells (MSCs) in the bone marrow where he observed a certain population of cells that developed into fibroblastic colony forming cells (CFU-F) [1]. MSCs account for a very small ratio of the bone marrow and it has been estimated that 1/10000 to 1/100000 of the bone marrow nuclear cells are MSCs [2, 3]. Since the ground breaking discovery of these cells, the interest in adult MSCs has been growing and other sources of the adult MSCs have been identified by scientists. The new sources of adult MSC can be used for various therapeutic purposes such as tissue regeneration and repair in musculoskeletal diseases [4]. Despite their therapeutic and clinical significance, there are no articles bringing together and comparing the sources of MSCs and their various applications in musculoskeletal conditions. In this systematic review, studies have been searched for different sources of adult MSCs as well as the recent musculoskeletal applications using adult MSCs. These studies were predominantly searched using AMED, CINAHL, EMBASE, Medline, PubMed and ZETOC. The aim of this study is to summarize all the available literature relating to sources of adult MSCs and their application in musculoskeletal diseases.

Stem cells are defined as undeveloped biological cells capable of proliferation, self renewal, conversion to differentiated cells, and regenerating tissues. There are two main types of stem cells in mammals [5]; embryonic stem cells (ESC) are pluripotent cells derived from the inner cell mass of blastocysts which are formed several days after an egg is fertilised, and nonembryonic stem cells (non-ESC) also known as adult stem cells as they are usually attained from the bone marrow of adults. There are two types of stem cells from this source: Haemopoietic, that differentiate into blood cells, and MSCs. Less mature tissue sources including umbilical cord blood, placenta and fetal somatic tissues are ranked among the non-ESCs. Furthermore, the fetal stem cells (FSCs) are regarded as an intermediate cell type between ESCs and adult stem cells. FSCs are obtained from the gonads in the first trimester of development [5, 6].

It has been more than 130 years that the existence of non-hematopoietic stem cells was proposed by the German pathologist Cohnheim. He suggested that bone marrow can aid the wound healing process in various peripheral tissues [7, 8]. This theory was confirmed by Friedenstein in the 1970's. He discovered that the bone marrow consisted of fibroblastoid cells with clonogenic potential *in vitro* which are capable of forming colonies (CFU-F). Furthermore, Friedenstein proved that it was achievable to regenerate heterotopic bone tissue in different transplants. This way he provided evidence in support of the self renewal potential of these cells [1]. Ever since, numerous scientists have

*Address correspondence to this author at the Department of Plastic Surgery, Whiston Hospital, Warrington Road, Liverpool, L35 5DR, UK; Tel: 01244366265; Fax: 01244366277; E-mail: hindocha2001@yahoo.com

confirmed those findings and have expanded on them by showing that the cells isolated by Friedenstein were also present in human bone marrow. Moreover, they demonstrated that these cells could be differentiated *in vitro* into cells with mesenchymal lineages such as adipocytes, chondrocytes, myoblasts and osteoblasts [9]. Therefore, cells isolated by Friedenstein were named MSCs by Caplan and colleagues [10].

After the discovery of the MSCs, it has progressively become clear that these cells could be the basis for a natural system of tissue repair [11]. In various studies MSCs have proven to be an effective therapeutic agent in experimental models of tissue injuries [12-14]. According to Prockop *et al.* in the majority of these studies there was little correlation between therapeutic efficacy and engraftment efficiency. Consequently, the ability to repair is secondary to the secretion of soluble factors by MSCs which alter the tissue microenvironment [7]. In other words, according to Caplan and colleagues MSCs may provide the so called 'trophic activity' [10]. It has been demonstrated that MSCs *in vitro* produce a variety of factors that are capable of manipulating a broad range of biological functions. Among the most important are angiogenesis, secretion of neuroregulatory peptides and cytokines that have crucial role in inflammation and repair [10].

Further investigations in the biology of MSCs in the *in vivo* setting will provide an important insight into cellular mechanisms of angiogenesis, bone development, hematopoiesis and vasculogenesis. Despite numerous studies which correlate CFU-Fs to bone mass there is still no robust evidence indicating that MSCs are the skeletal stem cells [15, 16]. Significant information is gathered concerning the use of MSCs for tissue engineering purposes. Scientists identified various modalities of expanding bone marrow as well as adipose tissue MSCs while retaining their multipotency [7, 10]. These cells have only been experimented on animal models to form tissues such as bone and cartilage at specific sites thus, there is no MSC technology for humans available [7].

According to Phinney *et al.*, if the MSCs develop into a natural system of tissue repair then it is essential to know how these cells are able to reach the site of injury. Chamberlian *et al.* point out the chemokines including SDF1 and its cognate receptor CXCR4 to have a significant role in guiding MSCs to sites of injury [17]. A more recent study by Belema-Bedada *et al.* suggests that the cytokine receptor CCR2 and the intercellular adaptor molecule FROUNT serve in a similar way to SDF1 for taking the bone marrow derived MSCs to various sites for repair [18]. Despite these studies, there is not sufficient information regarding the mobilization of the MSCs from the bone marrow. Rochefort *et al.* claim that MSCs can be perceived in circulating blood and the circulating pool can increase by exposure to chronic hypoxia [19]. However, the precise mechanism of this phenomenon remains an enigma.

MSCs can be distinguished from the hematopoietic stem cells (HSCs) by their cell surface antigens which create a phenotypic separation from HSCs. Therefore identification of cell-specific cell surface markers on MSCs is of great importance. Numerous cell-surface antigens expressed by the MSCs have been identified but only very few scientists

managed to establish a phenotypic characterization of MSCs *in vivo* [20].

In 1980's, Simmons *et al.* managed to isolate an antibody called STRO1 that could recognize the cell surface antigen in human MSCs. The cell population identified by this antibody were referred to as STRO-1 positive cells and were able to generate CFU-Fs and differentiate into multiple mesenchymal lineages *in vitro* [21]. More recently it was reported that by positive selection for VCAM/CD106 the degree of homogeneity of the STRO-1 positive cells could be more enhanced [22]. In addition to that, MCAM/CD146 positive cells isolated from BM-MSCs hold on plastic *in vitro* and are clonogenic. Other properties of these cells include self-renewal *in vitro*, generating bone and a hematopoietic supportive microenvironment in transplants done in mice [23]. The relationship between the MCAM/CD146 positive cells and the ones reported by Simmons *et al.* needs to be elucidated.

Simmons and colleagues have also identified a bone marrow pool of CD45 (-) CD31 (-) cells which appear to consist of MSCs [24, 25]. CD45 and CD31 are pan-hematopoietic and endothelial cell markers respectively and were broadly used in this study to negatively select for hematopoietic as well as endothelial cells. Interestingly, a study led by Rogers *et al.* has also shown that a subset of CD45 (+) Lin (-) bone marrow cells could differentiate *in vivo* into different cells including endothelial cells, osteoblasts, muscle cells and natural cells. This finding contradicts the nature of CD45 as a marker of hematopoietic cells and can be used to redefine the boundary between HSCs and MSCs.

In the previous decade, MSCs have been used by scientists for gene therapy in experimental models and to treat certain conditions including osteogenesis imperfecta in humans. In order to use MSCs as permanent therapeutic agents in the future, more research is required [26, 27].

One of the most significant features of MSCs that is worth considering is their extraordinary and unexplained immunomodulatory properties. It has been reported that the adult MSCs express intermediate levels of class I major histocompatibility complex (MHC) proteins but no class II MHC proteins. Therefore, this phenotype is classified as non-immunogenic, which indicates that no immunosuppression is required in a transplant into an allogenic host [28]. Further studies have shown that MSCs have immunosuppressive properties by modulating specific T-cell functions *in vitro* and can be translated into *in vivo* setting in experimental models [29, 30].

MATERIALS AND METHODS

The relevant articles for this review were searched primarily from the electronic data bases AMED, ASSIA (CSA Illumina), CINAHL (EBSCO), Conference Proceedings Citation Index: Science (ISI) on Web of Knowledge, EMBASE, Medline, PREMEDLINE In-Process & Non-Indexed Citations (OvidSP), PsycINFO (OvidSP), PubMed, Science Citation Index (ISI) on Web of Knowledge, Social Sciences Citation Index (ISI) on Web of Knowledge and Cochrane Library (Wiley) and ZETOC. The following key words were used for citing the appropriate articles: mesenchymal stem cells, stem cells, MSC

applications, musculoskeletal applications, tissue engineering and muscular dystrophy.

The following inclusion criteria were used to select relevant studies: A) Identified sources of MSCs in adult humans, B) Contained information about the applicability of MSCs in musculoskeletal conditions. C) Articles using animal MSCs for human applications. Articles which were excluded: A) did not include MSCs B) Involved stem cells not found in adults, e.g. embryonic stem cells, C) Failed to refer to potential uses of MSCs in musculoskeletal diseases. Out of 151 articles and studies that were viewed 78 were found relevant and suited the inclusion criteria.

RESULTS

The relevant information from the included articles is summarized in Tables 1 and 2.

As presented in Table 1, new sources for adult MSCs have been found since 1976. Adult stem cells have the ability to differentiate into more than one cell type, but unlike the embryonic stem cells they are often restricted to certain types or 'lineages' [51, 52]. MSCs have the potential to differentiate into chondrocytes, osteoblasts, adipocytes, fibroblasts, marrow stroma, and other tissues of mesenchymal origin [4]. According to the studies summarized in Table 1, the MSCs derived from the bone marrow have a higher transdifferentiation ability than Mesenchymal cells of different origin which can differentiate into 11 types of cells. The bone marrow aspirate is currently considered the most enriched and accessible

source of MSCs but according to Tuan *et al.* [4]. An alternative source such as trabecular bone could take its place, in view of recent efficient isolation of multipotential cells from this tissue [4]. A recent study by Sart *et al.* [53] argues that ear MSCs bear the characteristics of progenitor cells because of their ability to be differentiated into the three lineages of osteocytes, adipocytes and chondrocytes. Furthermore, it was found that Ear-MSCs had a threefold higher cell growth rate compared to bone marrow derived MSCs. According to Shi *et al.* [54] there are also other sources for MSCs that have been discovered such as umbilical cord blood, amniotic fluid, placenta, dental pulp, tendons, though the complete equivalency of such populations has not been formally demonstrated and it is not for certain what lineages they can differentiate into.

DISCUSSION

In this systematic review we managed to look at various studies that discussed the nature and source of the MSCs and reviewed the application of these cells for organogenesis and tissue engineering for numerous diseases. Apart from summarizing various sources of the adult MSCs their lineage differentiation potentials have been pointed out as well. With regards to studies in Table 1, MSCs derived from the bone marrow have the most differentiation potential among the rest, now the question rises whether one should only rely on bone marrow derived MSCs for therapeutic applications?

According to the literature reviewed, it can be deduced that there is great discrepancy whether bone marrow derived

Table 1. The Various Sources of Adult MSCS as well as their Multilineage Differentiation

Adult MSCs Sources	Multilineage Differentiation Potential	Authors
Bone marrow	Adipocyte Astrocyte Cardiocyte Chondrocyte Hepatocyte Mesangial cell Muscle Neuron Osteoblast Stromal cell Embryonic tissue	Pittenger <i>et al.</i> [31] Kopen <i>et al.</i> [32] Fukuda <i>et al.</i> [33] Johnstone <i>et al.</i> [34] Petersen <i>et al.</i> [35] Ito <i>et al.</i> [32] Ferrari <i>et al.</i> [36] Azizi <i>et al.</i> [37] Pittenger <i>et al.</i> [31] Majumdar <i>et al.</i> [38] Jiang <i>et al.</i> [39]
Muscle	Adipocyte, Myotubes Endothelial Cell, neuron Chondrocyte Osteocyte	Wada <i>et al.</i> [40] Qu-Petersen <i>et al.</i> [35] Adachi <i>et al.</i> [41] Bosch <i>et al.</i> [42]
Dermis	Adipocyte, chondrocyte, osteoblast	Young <i>et al.</i> [43]
Trabecular bone	Adipocyte, chondrocyte, muscle, osteoblast	Noth <i>et al.</i> [44]
Adipose tissue	Chondrocyte, muscle Osteoblast, Stromal cell	Zuk <i>et al.</i> [45] Gronthos <i>et al.</i> [46]
Periosteum	Chondrocyte, osteoblast	Nakahara <i>et al.</i> [47]
Pericyte	Chondrocyte	Diefenderfer <i>et al.</i> [48]
Blood	Adipocyte, fibroblast, osteoblast, osteoclast	Zvaifler <i>et al.</i> [49]
Synovial membrane	Adipocyte, chondrocyte, muscle, osteoblast	De Bari <i>et al.</i> [50]

Table 2. The Use of Different Sources of MSCs in Musculoskeletal Applications

Author	Source of MSC	Musculoskeletal Application
Cenni <i>et al.</i> [55]	BM (bone marrow)	Treatment of orthopaedic conditions characterized by large bone defects
Getgood <i>et al.</i> [56]	Joint/synovium	Simultaneous use of material scaffolds, cells and signalling molecules to attempt to modulate the regenerative tissue
Tuan <i>et al.</i> [4]	Synovium	Adult MSCs as cell source for articular cartilage tissue engineering
Mitchell <i>et al.</i> [57]	Muscle	PW1+/Pax7- interstitial cells efficiently contribute to skeletal muscle regeneration <i>in vivo</i> as well as generating satellite cells and PICs
Deans <i>et al.</i> [58]	BM, adipose tissue, umbilical cord blood, and amniotic fluid	Enhancing stem cell differentiation for improving tissue regeneration in musculoskeletal diseases such as osteoarthritis
Qu <i>et al.</i> [59]	Umbilical cord	Healing of non-unions significantly quicker than auto-iliac bone transplantation
Lee <i>et al.</i> [60]	Muscle	mc13 is capable of differentiating into both myogenic and osteogenic lineage <i>in vitro</i> and <i>in vivo</i> thus capable of improving muscle and bone regeneration. Theoretic option for duchenne muscular dystrophy treatment
Scotti <i>et al.</i> [61]	BM	MSCs developed <i>in vitro</i> hypertrophic tissue structures resulted in accelerated formation of larger bony tissues
Dezawa <i>et al.</i> [62]	BM and muscle	Pax7-positive cells are more ready supply of myogenic cells than the rare myogenic stem cells normally found in muscle and bone marrow. Theoretic option for Duchenne muscular dystrophy treatment
Tapp <i>et al.</i> [63]	Adipose tissue	AD-MSCs have potential in cell-based therapy for disc degeneration
Nöth <i>et al.</i> [64]	BM	Osteoarthritis, Rheumatoid arthritis, articular cartilage repair and meniscus repair
Quarto <i>et al.</i> [65]	BM	Could treat ulna, humerus and tibia non-unions
Gangji <i>et al.</i> [66]	BM	Osteonecrosis of femoral head
Horwitz <i>et al.</i> [26]	BM	Stimulate growth in children with osteogenesis imperfecta
Funk <i>et al.</i> [67]	Periosteum	Healing non-union of the distal femur using a 3D matrix

MSCs is the best available source to be used or other sources of adult MSCs are as good or even better. By taking the information of Table 2 into consideration it can be deduced that mainly muscle derived MSC's are used for muscle related applications and bone marrow derived MSC are the preferred choice for degenerative bone diseases.

When comparing different sources of MSCs, each source has its advantages and draw backs. By the way of illustration, bone marrow derived stem cells have high multilineage differentiation but do not have the greatest cell growth rate as Sart *et al.* [53] in his recent study shows that ear derived MSCs have a threefold higher cell growth rate compared to bone marrow derived MSCs. MSCs from umbilical cord blood have fewest colonies after they have been isolated, but they showed a much higher proliferation capacity compared to bone marrow derived MSCs. In addition to that, adipose tissue derived MSCs showed to have greater number of colonies to bone marrow derived MSC [58]. Even though bone marrow is easily accessible for musculoskeletal applications some studies used other sources of adult MSCs. For instance Qu *et al.* demonstrated that MSCs extracted from human umbilical cord healed non-union significantly quicker than auto-iliac bone transplantation [59]. In addition to that Funk *et al.* states that periosteum derived stem cells can aid to heal non-union of the distal femur using a 3D matrix. Despite being the first MSCs discovered, bone marrow derived MSCs might not be the most suitable sources of MSCs for musculoskeletal applications. Furthermore, It is interesting to note that in

Tuan *et al.* review [4] and shi *et al.* [54] they did not consider umbilical cord blood, amniotic fluid, placenta, dental pulp and tendons as sources of adult MSCs even though MSCs can be extracted from them, due to the lack of robust scientific evidence [4].

Numerous studies over the years have shown that MSCs could potentially become the basis for a powerful 'natural system of tissue repair' [68]. MSCs have demonstrated their ability to serve as effective therapeutic agents in variety of experimental models of different tissue injuries [13]. Horwitz *et al.* [26], Gangji *et al.* [66] and Quarto *et al.* [65] managed to use bone marrow derived MSCs for aiding osteonecrosis of femoral head and stimulating growth in children with osteogenesis imperfecta. Other studies [60, 62] suggest that BM-MSCs as well as muscle derived MSCs can be used to regenerate bone and muscle in Duchenne muscular dystrophy. One should not overlook the fact that these studies have been successful on animals such as rats and dogs but no trials on humans have been done. A further study combines sand rat AD-MSCs with human annulus cells as possible option for cell-based autologous disc regeneration [63].

For future advances in MSCs in the field of regeneration and tissue engineering it is important to know the exact nature of these cells. Therefore, focusing on the cellular and genetic signature of MSCs is required. One way to achieve this is by investigating other populations of stem cells and techniques such as flow cytometry to analyze specific cell-

surface markers [4]. Furthermore, more specific information is required concerning the endogenous function in the adult MSCs' tissues to give a better understanding of their true potential for clinical uses. Learning about the role of these cells in organogenesis is required in order to adjust *in vivo* repair and regeneration processes without the necessity for *in vitro* expansion.

Developing a model that tests for the ability of MSCs to self-renew, proliferate and differentiate *in vivo* could aid to investigate more in characterization of the MSCs. By way of illustration, a test that is becoming more popular is the murine intratibial injection of MSCs and characterization of their role in bone homeostasis and fracture repair [69].

An additional achievement in this field would be to identify certain pharmacological tools in order to expand *in vivo* and *in vitro* the mesenchymal stem cell pool. There have been investigations in this field and tools such as proteasome inhibitor Velcade have been reported to expand the MSC pool in a murine model *in vivo* [70, 71].

In order to identify the appropriate pharmacological tools detailed analysis of the complex network of signalling pathways and regulatory cells that control the ability of MDCs for self-renewal, proliferation and predominantly differentiation is required. The identification of this network should not be underestimated as it will reveal the rules that govern the size of the MSC pool *in vivo*. This will eventually allow appropriate pharmacological interventions which would assist in the different applications of the MSCs in various diseases. To gain insight into the molecular mechanisms of the MSCs a global gene expression profiling approach could prove of great assistance [72-77].

Eventually, it is not for certain how valuable the *in vivo* analysis of genetically modified experimental models could be for humans. According Riminucci *et al.* human diseases such as fibrous dysplasia can broaden our understanding of MSCs, for instance analysis of Gs[alpha] signalling pathway in this disease, which involves early cells of osteoblast lineage in mosaic individuals, can be a model worth considering [78].

CONCLUSION

Adult MSCs have various sources and present an exciting progenitor cell source for applications of tissue engineering and regenerative medicine. Bone marrow was the first source of adult MSC but in recent years other sources have been identified. Among the most significant are muscle, skin, adipose tissue, synovial membrane, dermis, trabecular bone, periosteum, pericyte and blood. There is also potential evidence that MSCs derived from adult tissues can aid certain musculoskeletal diseases such as osteonecrosis of femoral head, stimulating growth in children with osteogenesis imperfecta, disc regeneration, osteoarthritis and duchenne muscular dystrophy. In order to fully understand the potential of these cells future studies should be directed to ascertain their cellular characteristics and the endogenous function of MSCs in normal and abnormal tissues.

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CONFLICT OF INTEREST

None declared.

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