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The Impact of Mesenchymal Stem Cell Source on Proliferation, Differentiation, Immunomodulation and Therapeutic Efficacy

Hui-Yun Cheng[1], Nicolae Ghetu[2], Christopher G Wallace[3], Fu-Chan Wei[1,3] and Shuen-Kuei Liao[4,5]*

[1]*Center for Vacularized Composite Allotransplantation, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[2]*University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Romania & Plastic Surgery Unit, Regional Oncological Institute Iasi, Romania*
[3]*Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital at Linkou & School of Medicine, Chang Gung University, Kweishan, Taoyuan, Taiwan*
[4]*Graduate Institute of Cancer Biology and Drug Discovery and Center of Excellence for Cancer Research, Taipei Medical University, Taipei, Taiwan*
[5]*Vectorite Biomedica Inc., Taipei, Taiwan*

Abstract

Since their discovery almost 50 years ago, mesenchymal stem cells have shown great clinical potential in various clinical scenarios owing to their multilineage differentiation potential as well as immunomodulatory properties. However, recent studies indicate that properties of MSCs appear to be affected by factors such as their source. In this review, we focus on recent literature reporting direct comparisons of MSCs derived from different tissue sources, which include fetal MSCs from amniotic fluid, cord blood, umbilical cord and placenta, and adult MSCs from bone marrow, adipose tissue, heart, lung, synovial membrane and peripheral blood. It is demonstrated that MSCs from different sources showed variation in proliferation capacity, differentiation to various cells, immunomodulation capabilities, and efficacy of cell therapies in different scenarios. Furthermore, studies on MSCs derived from allogeneic or autologous origins revealed that allogeneic MSCs induced immunogenicity, potentially influencing their *in vivo* durability and thus efficacy when utilized as cell therapies: syngeneic (ie. autologous in inbred animals) or recipients' adipose-tissue-MSCs had better efficacy than allogeneic counterparts in inducing donor-specific tolerance in allotransplantation animal models. Therefore, careful consideration of the MSC source is recommended when a specific application is sought.

Keywords: Mesenchymal stem cell; Cell source; Differentiation; Immunomodulation; Cell therapy

Introduction

Mesenchymal stem cells (MSCs) were first isolated in 1968 by Friedenstein et al. [1] from bone marrow. It was later found that MSCs are multilineage progenitor cells with the capability to proliferate and differentiate *in vitro* [2]. The International Society for Cellular Therapy (ISCT) published minimum criteria to define MSCs, which included plastic adherence; fibroblast-like morphology; differentiation to osteoblasts, adipocytes, and chondroblasts; positive expression of CD105, CD73 and CD90; negative expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19, and HLA-DR surface molecules [3]. MSCs possess immunomodulatory properties that influence a variety of immune cell populations [4]. They have shown great potential for development in regenerative medicine, transplantation, and autoimmunity, to name only a few.

MSCs are present in all tissues [5]. They have, for example, been isolated from bone marrow, adipose tissue, periodontal ligament, synovial membrane and muscle [6], as well as fetal tissues such as placenta, amniotic fluid, umbilical cord, and Wharton's jelly. Whilst the ISCT-defined characteristics are mandatorily present, *in vitro* properties and surface molecular expressions appear to differ amongst MSCs from different origins [6,7]. This suggests that the origin of MSCs may affect cellular fates *in vivo* and/or their behavior when administered *in vivo* as therapeutic agents. Although research into MSCs is blooming, systematic investigations into how the sources of MSCs affect their behaviors are lacking. In the present paper, we review the literature that has reported side-by-side comparisons of MSCs derived from different origins, in order to help identify MSCs with specific properties for certain clinical applications.

Given the extensive literature in this field, this review has been limited principally to more recent papers and is not intended to be exhaustive. Throughout this paper, MSCs are derived from human tissues, unless otherwise specified, and MSCs will be identified with their corresponding origins as follows: AF-MSC (amniotic fluid), AM-MSC (amnion), AT-MSC (adipose tissue), BM-MSC (bone marrow), CB-MSC (cord blood), CP-MSC (chorionic plate of placenta), H-MSC (heart), I-MSC (islet-derived), L-MSC (lung), OE-MSC (olfactory ectomesenchymal), PB-MSC (peripheral blood), PL-MSC (placenta), SM-MSC (skeletal muscle), SY-MSC (synovial membrane), UC-MSC (umbilical cord), and WJ-MSC (Wharton's jelly in umbilical cord).

General Properties Including *ex vivo* Isolation and Proliferation

Percentages of MSCs vary in different tissues. For example, the frequency of MSC in bone marrow is low (0.001%-0.01% in mononuclear fraction), whereas adipose tissue contains about 500-fold higher numbers of AT-MSCs [8,9]. The percentage of MSCs in amniotic fluid ranges from 0.9% to 1.5% [10]. Notably, however, isolation success of MSCs from bone marrow and adipose tissue was around 100% but ranged from 10% to 63% from umbilical cords [7,11,12]. Following isolation, cultured AT-MSCs reached confluence around day 15, but took 22 days for BM-MSCs to reach the same state [13]. For CB-MSCs, establishment of primary culture took approximately 30 days [14]. AT-

***Corresponding author:** Prof. Shuen-Kuei Liao, Taipei Medical University, 250 Wu-Hsing St., Taipei 11031, Taiwan; Tel: +886-912-753-715; E-mail: liaosk@h.tmu.edu.tw

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MSCs also showed higher than average metabolic activity compared with BM-MSCs [9].

MSCs derived from fetal tissues (amniotic fluid, amniotic membrane, cord blood, umbilical cord) reportedly proliferated faster than those from adult tissues (bone marrow and adipose tissue) [15-18]. The average doubling time of AF-MSCs and BM-MSCs was 1.6 and 3.75 days, respectively [10]. Interestingly, CB-MSCs showed more than a two-fold increase in proliferation at each subcultivation up to passage 14, while proliferation of BM-MSCs markedly reduced especially after the 10^{th} passage [14]. Donor age appears to impact on the growth rate of MSCs, since cells from newborn skin grew faster than those isolated from adult skin [19]. However, AT-MSCs isolated from 8-week old mice exhibited significantly shorter doubling times than their counterparts from 4-week old mice. Interestingly, this trend was the opposite of that observed for BM-MSCs [20]. Self-renewal of MSCs *in vitro* is not unlimited. AF-MSC, for example, can be maintained for 29 passages without any visible morphological changes whereas BM-MSCs could be expanded for, at most, 12 passages before showing morphological alterations consistent with aged cells [17].

Fetal tissue-derived stem cells also differ from one another. Zhu et al. demonstrated that UC-MSCs displayed higher proliferative capacity, shorter doubling time, lower rate of apoptosis, and more mitotic activity than MSCs from placenta (PL-MSCs) [21]. Transmission electron microscopy revealed that PL-MSCs may have better adhesion capability than UC-MSCs. Similarly, AF-MSCs and WJ-MSCs were found to reach adherence at 2.7 ± 1.6, and 6.5 ± 1.8 days, respectively [22]. WJ-MSCs demonstrated superior proliferation potential and required less time to double in population compared to AT-MSCs [23]. Atomic force microscopy revealed that UC-MSCs have superior mass transport and cell migration capabilities than PL-MSCs [21].

The inspection of gene expression profiles reveals that MSCs appear to be specialized, at least in part, according to their source(s). Hsieh et al. reported that WJ-MSCs expressed more angiogenesis and growth-related genes, whereas the gene expression pattern of BM-MSCs was significantly closer to that of osteoblasts [24]. Such differences appear to be reflected in the higher proliferative potential of WJ-MSCs and in the better osteogenic potential of BM-MSCs [24]. In contrast, H-MSCs (from heart) showed higher levels of cardiovascular related markers such as myosin light chain-2a, miR-126 and miR-146a [25].

Differentiation

In addition to the ability of MSCs to differentiate to other mesenchymal cell lineages, the *in vitro* capability of MSCs to trans-differentiate to endo/ectodermal lineages is important in regenerative medicine.

Although the ability to differentiate to osteoblasts, adipocytes, and chondroblasts is a defining feature of MSCs, it is known that MSCs from different tissue sources show bias in their differentiation patterns. For example, AT-MSCs had inferior osteogenic and chondrogenic potential compared to BM-MSCs [13,26,27]. Synthesis of collagen II and proteoglycans was only found in growth factor-treated BM-MSCs but not AT-MSCs [28]. MSCs from peripheral blood displayed less osteogenic and adipogenic differentiation, in addition to a more chondrogenic capacity than BM-MSCs [29]. CB-MSCs and PL-MSCs had less adipogenic capability and produced fewer and smaller lipid vacuoles than BM-MSCs and AT-MSCs [11,30]. Some reports suggested that CB-MSCs lacked adipogenic differentiation potential [7,12]. Interestingly, although CB-MSCs displayed chondrogenic potential, they differentiated to fibrocartilage with a distinctly different morphology to that which BM-MSCs and PL-MSCs differentiated to [7]. Furthermore, MSCs from fetal lung and placenta showed lower chondrogenic potential compared to MSCs derived from fetal or adult bone marrow [31]. Diekman et al. demonstrated that BM-MSCs and AT-MSCs proceeded to differential chondrogenesis in response to differing culture parameters, such as the presence of serum, growth factors, or the composition of scaffold [32]. In terms of osteogenesis, fetal MSCs produced more calcium and showed higher levels of osteogenic-specific gene expression than adult BM-MSCs. Interestingly, a hierarchy in oeteogenesis potential was found in fetal MSCs with different sources as follows: BM>blood>liver [33].

MSCs demonstrate versatility in multilineage differentiation, implicating great clinical potential for MSCs in replacement/regeneration of diseased tissues/cells. For instance, AT-MSCs and BM-MSCs have comparable potential to differentiate towards functional hepatocytes expressing key metabolic enzymes such as cytochrome P450s [34]. Additionally, Zheng et al. reported that AF-MSCs had greater differentiation potential toward hepatocytes than BM-MSCs [17]. On the other hand, PL-MSCs produced more hepatogenic cytokines, such as HGF, than BM-MSCs and AT-MSCs [35].

For generating pancreatic islet cells *in vitro*, BM-MSCs were compared with islet-derived stem cells (I-MSCs). I-MSCs can be considered partially committed and show very low adipogenic differentiation potential. Both BM-MSCs and I-MSCs can differentiate to islet-like cells (ILCs), although glucose-induced insulin produced by BM-MSCs was significantly lower than from I-MSCs [36]. AT-MSCs may also differentiate to ILCs, but with a lower capacity compared to BM-MSCs [37]. On the other hand, primitive stromal cells from umbilical cord (UC-PSCs) formed larger ILC clusters and produced about 2.5 fold more insulin than BM-MSCs upon differentiation. Concurrently, more viable cells and less apoptosis were found in differentiated UC-PSC culture [38].

MSCs can be induced to neural stem cells (forming neurospheres, NS, in culture) and thus may have therapeutic potential to treat nerve injury or neuronal degenerative diseases. NSs derived from AF-MSCs (AF-NSs) were larger and proliferated at a higher rate than those from BM-MSCs, in addition to greater expression of neuronal stemness markers. Furthermore, AF-NSs differentiate to more neurons and glial cells upon terminal differentiation [39]. WJ-MSCs (from Wharton's jelly) were also reported to be induced to neural progenitors with better efficiency than either BM-MSCs or AT-MSCs [40]. However, Datta et al. demonstrated that WJ-MSCs and BM-MSCs had comparable potential to differentiate to dopaminergic neurons [41]. In their animal study, Zhang et al. showed that NSs derived from AT-MSCs had greater expansion and differentiation abilities than those from BM-MSCs [42].

Sources of MSCs were shown to influence differentiation potential to other lineages. UC-MSCs had significantly higher tubule length, diameter and area than BM-MSCs after endothelial differentiation [43]. AT-MSCs had better differentiation capacity to sinus-like cells than BM-MSCs from the same donor [44]. Rat MSCs from skeletal muscle (SM-MSCs) showed better myogenesis potential and higher expression of myoblast markers than AT-MSCs and BM-MSCs [45], although human AT-MSCs showed more myogenic differentiation than BM-MSCs [46]. Interestingly, choice of cell culture media also affected level of the skeletal muscle marker desmin expressed by the differentiated AT-MSCs [46]. On the other hand, fetal MSCs from umbilical cord, bone marrow, and amniotic membranes demonstrated potential to differentiate to functional cardiomyocytes, although adult counterparts from bone marrow and adipose tissue did not [47].

Immunomodulation

A prominent feature of MSCs is their ability to immunomodulate various immune cells, including T cells, B cells, dendritic cells, NK cells and macrophages. This research area has been reviewed extensively [4]; only reports that have focused on comparing MSCs from different origins are included in this section.

Melief et al. systematically compared AT-MSCs and BM-MSCs from age-matched donors [8]. It was found that AT-MSCs have stronger immunosuppressive effects than BM-MSCs on anti-CD3/CD28-induced peripheral PBMC proliferation. An equivalent suppressive effect induced by BM-MSCs could be achieved by just one third of the number of AT-MSCs. Similarly, AT-MSCs were more suppressive than BM-MSCs on differentiation of monocytes to dendritic cells. Such differences correlated well with cytokine profiles. The presence of AT-MSCs led to less production of IFN-γ and higher levels of IL-10 in anti-CD3/CD28-stimulated PBMCs and stimulated monocyte culture, respectively. MSCs also attenuated the expression of the costimulatory molecule CD86 in stimulated monocyte culture [48]. Furthermore, mitogen-stimulated immunoglobulin production in PBMCs was suppressed more by AT-MSCs than BM-MSCs [13]. MSCs from other adult tissues, such as olfactory ectomesenchymal (OE-MSCs), heart (H-MSCs), and lung (L-MSCs) have been demonstrated to have *in vitro* immunosuppressive functions [49]. Compared to BM-MSCs, H-MSCs and L-MSCs preferentially suppressed T cell proliferation, whereas OE-MSCs had stronger effects on both T cell and NK cell proliferation. Interestingly, suppression on B cell proliferation was much more evident when the MSCs were primed with the inflammatory cytokines IFN-γ and TNF-α. Primed OE-MSCs and L-MSCs showed stronger B cell suppression than BM-MSCs with priming [49]. These immunomodulatory functions were found to be sustained for BM-MSCs and AT-MSCs, even with differentiation [50].

Fetal MSCs shared similar immunosuppressive functions with adult MSCs. Mitogen-stimulated PBMC proliferation can be suppressed by CB-MSCs and WJ-MSCs to a level comparable to that by adult BM-MSCs [51]. Anti-CD3/CD28-stimulated $CD4^+$ and $CD8^+$ T cell proliferation was also suppressed by BM-MSCs and CB-MSCs to a similar level, which was lower than that achieved by PL-MSCs. Such effects were correlated with increases in levels of IL-10, IFN-γ, and generation of cell subsets with $CD4^+CD25^+CTLA\text{-}4^+$ regulatory phenotype [52]. Lee et al. demonstrated that although MSCs derived from chorionic placenta (CP-MSCs) showed similar capability in suppression of T cell proliferation to BM-MSCs, higher expression level of HLA-G along with anti-inflammatory cytokines such as IL-4 and IL-13 may provide CP-MSCs with additional immunomodulatory advantages [53]. It is thought that the immunomodulatory functions of MSCs may directly relate to levels of prostaglandin-2 (PGE2) [54,55]. For example, MSCs derived from amniotic fetal membranes displayed more suppression of T-lymphocyte proliferation and higher levels of PGE-2 than counterparts from chorion [56]. Additionally, WJ-MSCs were found by Najar et al. to display suppressive effects on mitogen-stimulated T cell proliferation when the cell number was 1/40 of T cells [57]. However, significant suppression was achieved at 1/20 and 1/8 of T cells for AT-MSCs and BM-MSCs, respectively. Elevated expression of leukemia inhibitory factor (LIF) may have a causative relationship to suppression of T cell proliferation, since addition of LIF antibody abolished the effects [57].

Anti-inflammatory effects were evaluated with coculturing of MSCs with LPS-treated alveolar macrophages. It was found CB-MSCs expressed lower level of proinflammatory cytokines IL-1β, IL-6 and IL-8 than BM-MSCs and AT-MSCs. Higher expression of the upstream angiopoietin-1 in CB-MSCs was demonstrated to be critical [58].

Chan et al. adopted microarray analysis to compare gene expression in fetal versus adult MSCs [15]. Functional network analysis of 950 out of 31099 genes showed eight immune response pathways were differentially regulated, including Th17 differentiation, CD40 signaling, macrophage migration inhibitory factor, and histamine H1 receptor signaling. As IL-6 participated in all eight pathways, the level of IL-6 was monitored for *in vitro* MSC and phytohaemagglutinin (PHA)-stimulated PBMC coculture. Significantly higher increases of IL-6 level following PHA stimulation was found in fetal MSC compared to adult MSC cocultures, corresponding to the suppressive potential on PHA-stimulated PBMC proliferation [15]. This highlights the importance of the role of IL-6 in regulating the immunosuppressive functions of MSCs.

PHA induced phenotypic changes upon immune cells in PBMCs in addition to influencing proliferation. It was demonstrated that AT-MSCs had stronger effects on T cell activation than WJ-MSCs and BM-MSCs, such that most T cells remained inactivated when cocultured with AT-MSC even with PHA stimulation. For B cells, acquisition of lymphoblast phenotype was inhibited by BM-MSCs and AT-MSCs whereas WJ-MSCs had no effects [59]. Furthermore, activation of NK cells was strongly inhibited by all three of these MSCs. It is therefore clear that MSCs derived from different tissues may inflict distinct functions on specific cell types.

Cell Therapy

MSCs have been applied as cell-based therapies for different disease conditions such as graft versus host disease, bone defects and myocardial infarction, to name a few [60]. Sources of MSCs have been found to correlate with therapeutic efficiency. For example, Zhou et al. demonstrated that xenotransplantation of human AT-MSCs to rats with spinal cord injury enhanced more angiogenesis and axonal regeneration in addition to better functional recovery than BM-MSCs [61]. The significantly higher levels of neurotropic factors that AT-MSCs induced, including BDNF, VEGF, and HGF, may play a role. Dogs that had MSCs administered at 1 week after spinal cord injury showed significant improvement in functional recovery, although no differences were found among AT-MSCs, BM-MSCs, WJ-MSCs, and CB-MSCs [62]. Results from a mouse stroke model *in vivo* showed that AT-MSCs significantly reduced volume of infarction and swelling, in addition to improving neurological function compared to BM-MSCs [20].

MSCs have been explored as a therapeutic approach for cancers of poor prognosis, such as glioblastoma multiforme (GBM) [63]. In a mouse xenotransplantation model, co-transplanted CB-MSCs inhibited GBM growth, whereas AT-MSCs promoted tumor growth. AT-MSCs enhanced vessel formation and suppressed apoptosis compared to CB-MSCs. Whilst higher expression of endogenous CXCL12 in AT-MSCs was shown to play a significant role, higher expressions of angiogenic factors such as VEGF, angiopoietin-1, PDGF, IGF-1 in AT-MSCs may also be relevant [64].

MSCs have been shown to promote wound healing as well [65]. Comparison of human AT-MSCs, BM-MSCs and AM-MSCs on repairing mouse wounds showed that AT-MSCs had the most pronounced effects on wound healing. More migration of dermal fibroblasts and higher expression of growth factors induced by AT-MSCs were observed [66].

The *in vivo* oseteogenesis potential of human MSCs was evaluated in a rat critical-sized femoral defect model and it was found that fetal UC-MSCs and CB-MSCs, and adult AT-MSCs and BM-MSCs, showed comparable osteogenesis potential [67]. Similar potential for *in vivo* osteogenesis was also found for canine AT-MSCs, BM-MSCs, CB-MSCs, and WJ-MSCs [68].

Infused MSCs in *in vivo* disease/injury models may not necessarily repair damage by regeneration. De Coppi et al. evaluated *in vivo* myogenesis following bladder injury and found that both BM- and AF-MSCs engaged significantly in preventing cryo-injury induced hypertrophy of surviving muscle cells [69]. This was supported by data showing that AT-MSCs and BM-MSCs protected cardiomyoblasts from cell death induced by ischemia-reperfusion to a similar degree *in vitro* [70]. Additionally, MSCs from cardiac tissues were proven to show higher cardiomyogenic differentiation *in vivo* than BM-MSCs following injection to infarcted left ventricle [25]. BM-MSCs were shown to differentiate preferentially to smooth muscle cells, in contrast to AT-MSCs, which differentiated preferentially to endothelial cells and cardiomyocytes in a rat cardiac injury model [71]. In contrast, human AT-MSCs were shown to have better myoregeneration potential than BM- and SY- counterparts when treating cardiotoxin-damaged tibialis anterior muscle [72]. These results suggest that the intrinsic properties of MSCs interact with the microenvironment *in vivo* and lead to different outcomes following cell therapy.

Proper homing of MSCs to the site of interest is critical following administration. Direct comparison between WJ-MSCs and BM-MSCs showed that WJ-MSCs expressed higher levels of angiogenic chemokines such as CXCL1, CXCL, CXCL5, CXCL6, and CXCL8; and angiogenic growth factors like VEGF-D, PDGF-AA, TGF-β2, bFGF and HGF [73]. In light of these findings, WJ-MSC may be a better choice to prevent or reduce fibrosis and scarring in tissue injury.

MSCs have been shown to prolong allograft survival in the setting of solid organ transplantation (SOT) [74]. Furthermore, when allografts containing multiple types of tissues, termed vascularized composite allotransplant (VCA such as face transplants or limb transplants), were transplanted, MSCs were shown to induce donor-specific tolerance and prolong VCA survival [75-79]. BM-MSCs and AT-MSCs were the two types that were mostly utilized, although they have not yet been compared side-by-side in terms of influencing VCA survival. Interestingly, Saka et al. showed that AT-MSCs, especially when intravenously administered, induced a lower level of IgG antibodies against xenoantigens compared to BM-MSCs *in vivo* [80].

Allogeneic *versus* Autologous Sources of MSCs

There appears to be potential for allogeneic MSCs (allo-MSCs) to serve as an "off the shelf" therapeutic option, since these cells may be isolated and cultured from healthy donors in advance. This is in contrast to autologous MSCs (auto-MSCs), which need to be prepared per individual and may not be suitable or available for some acute conditions. Furthermore, MSCs with certain origins, such as fetal tissues like amniotic fluid and umbilical cord, are most likely allogeneic. Previously, all MSCs were regarded as having low immunogenicity, since they all expressed only low levels of MHC class I and II, and exerted immunosuppressive functions *in vitro* and *in vivo*. However, recent studies have suggested that allo-MSCs may not be as immunoprivileged as previously suggested. Schu et al. showed in rats that allo-MSCs induced alloantibodies with the potential to activate complement-mediated lysis *in vivo* [81]. Intra-striatal administration of allo-MSCs elicited a cellular immune response; this was, however, not strong enough to clear the administered cells [82]. Differentiation may elicit immunogenicity by increasing expression of MHC I and MHC II, and stimulating lymphocyte proliferation [83,84]. Allo-MSCs are also able to educate $CD8^+$ T cells with cytotoxicity against themselves. Interestingly, BM-MSCs elicited a higher level of lysis than AT-MSCs [9]. It seems that different factors such as the disease model, route of administration, and experimental species have effects on the immunogenicity of allo-MSCs *in vivo* [85]. Interestingly, a randomized clinical trial comparing allo-MSCs and auto-MSCs for treatment of ischemic cardiomyopathy showed low immunogenicity of allo-MSCs in addition to comparable efficacies of both cell populations [86].

MSCs have been shown to target primary and metastatic tumors. Hung et al. showed with SCID mice subcutaneously transplanted with human colon cancer cells that intravenously infused MSCs migrated and engrafted to microscopic tumor lesions [87]. By taking advantage of such an unique feature in addition to relatively low immunogenicity, allogeneic MSCs may therefore be used as a novel, universal delivery vehicle of cytokine genes such as IFN-γ or drugs to induce tumor dormancy or other antitumor therapeutic effects [88,89].

On the other hand, autologous BM-MSCs were found to have better efficacy in improving acute kidney injury [90]. Both auto- and allo- MSCs have been applied in transplantation studies with promising results [91-93]. We have employed syngeneic (identical to autologous from inbred animals) AT-MSCs in conjunction with anti-lymphocyte serum and short-term cyclosporin in rat osteomyocutaneous VCA and successfully induced donor-specific tolerance [76,94]. A side-by-side comparison with the same animal model and immunosuppression regimen showed that syngeneic or recipient AT-MSCs had superior efficacy with 66% tolerance rate as compared to their allogeneic counterparts with 33% (Figure 1). Auto-MSCs have been applied to a clinical VCA case and enabled minimal maintenance levels of immunosuppressants without acute rejection at twenty months after transplantation [95]. Given that the presence of a variety of diseases may not affect the efficacy of MSCs [96-100], more potential clinical applications with autologous MSCs are no doubt underway.

Conclusions and Perspectives

MSCs have great clinical potential for treating various disease conditions. Although MSCs derived from different tissues may have a common origin, they appear to have acquired specific characteristics due to interactions with the microenvironment of various tissues. This article has reviewed recent knowledge of the influence of MSC sources on their properties in proliferation, differentiation, immunomodulation, and cell therapy efficacy. As shown in Table 1, the general trend regarding MSC sources and their properties may be summarized as follows:

(1) Fetal MSCs in general have better proliferation capability than adult MSCs.

(2) MSCs derived from a specific tissue are better suited to differentiate to cells of that tissue. For example, BM-MSCs have better osteogenesis capability than other MSCs in comparison. Similar trends are found in I-MSCs for islet differentiation and SM-MSCs for myogenesis.

(3) Fetal MSCs or AT-MSCs are better choices than BM-MSCs if immunomodulatory function is important.

(4) AT-MSCs showed great potential as a cell therapy agent *in vivo* in general. Further studies are warranted to analyze the feasibility of AT-MSC as a treatment option for carcinomas.

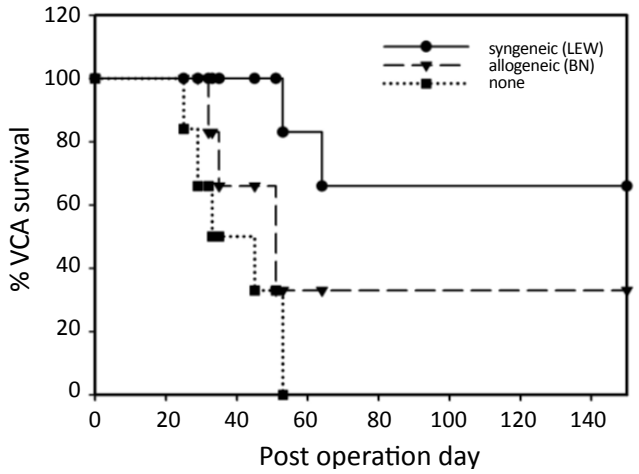

Figure 1: Syngeneic AT-MSCs prolongs survival of vascularized composite allotransplants (VCA) more than allogeneic AT-MSCs. The experimental model was rat osteomyocutaneous flap allotransplantation from BN rat to LEW rat as described in [76]. The immunosuppression regimen included antilymphocyte serum at post-operation day (POD) -1, 10, cyclosporine 16 mg/kg from day 0-10, in addition to AT-MSCs at POD 1. It was demonstrated that donor-specific tolerance developed in the recipients with long-term surviving VCA. The Kaplan-Meier survival analysis showed the median survival time for syngeneic and allogeneic AT-MSC groups was >150 and 51 days, respectively.

Superior	Inferior	Parameter in comparison	Reference
Basic Properties *(in vitro)*			
AT-	BM-	MSC frequency	[8,9]
AT-	BM-	metabolic activity	[8]
AF-	BM-	proliferation	[10]
WJ	AT	proliferation	[23]
UC-	PL-	proliferation	[21]
WJ-	BM-	proliferation	[24]
PL-	UC-	adhesion capability	[21]
AF-	WJ-	adhesion capability	[22]
UC-	PL-	mass transport and cell migration	[21]
Differentiation *(in vitro)*			
BM-	WJ-	osteogenesis	[24]
BM-	AT-	osteogenesis, chondrogenesis	[13,26,27]
BM-	PB-	osteogenesis, adipogenesis	[29]
BM-, AT-	CB-, PL-	adipogenesis	[11,30]
PB-	BM-	chondrogenesis	[29]
BM (fetal and adult)	L (fetal), PL-	chondrogeneisis	[31]
AF-	BM-	hepatocyte differentiation	[17]
I-	BM-	islet differentation	[36]
UC-PSC	BM-	islet differentation	[38]
BM-	AT-	islet differentation	[37]
AF-	BM-	neural stem cell differentiation	[39]
WJ-	BM- or AT-	neural progenitor cell differentiation	[40]
AT-	BM-	neural stem cell differentiation	[42]
UC-	BM-	endothelial differentiation	[43]
AT-	BM-	sinus-like cell differentiation	[44]
SM-	AT-, or BM-	myogenesis (rat)	[45]
AT-	BM-	myogenesis	[46]
Immunomodulatory *(in vitro)*			
AT-	BM-	suppressing -CD3/CD28 induced PBMC proliferation	[8]
AT-	BM-	suppressing dendritic cell differentiation	[48]
AT-	BM-	suppressing mitogen-stimulated Ig production	[13]
H-, L- OE-	BM-	suppressing T cell activation	[49]
OE-	BM-	suppressing NK cell activation	[49]
OE-, L- (primed)	BM- (primed)	suppressing B cell activation	[49]
CB, WJ-, BM-	--	suppressing mitogen-stimulated PBMC proliferation	[51]
PL-	BM-, CB-	suppressing α-CD3/CD28 induced T cell proliferation	[52]
CP-, BM-	--	suppressing T cell activation	[53]
WJ-	BM-, AT-	suppressing mitogen-stimulated T cell proliferation	[57]
CB-	BM-, AT-	anti-inflammatory effects	[58]
AT-	WJ-, BM-	suppressing PHA-induced T cell activation	[59]
AT-, WJ-, BM-	--	suppressing NK cell activation	[59]
Cell Therapy *(in vivo)*			
AT-	BM-	regeneration following spinal cord injury (rat)	[61]
AT-, BM-, WJ-, CB-	--	early recovery from spinal cord injury (canine)	[62]
AT-	BM-	improvement from stroke (mouse)	[20]
CB-	AT-	inhibit GBM growth (mouse)	[63]
AT-	BM-, AM-	wound closure (mouse)	[66]
UC-, CB-, AT-, BM-	--	osteogenesis following bone defect(rat)	[67]
CB-, WJ-, AT-, BM-	--	*in vivo* osteogenesis (canine)	[68]
H-	BM-	cardiomyogenesis (rat)	[25]
AT-	BM-, SY-	skeletal muscle regeneration (mouse)	[72]
AT-	BM-	xeno-antibody production (rat)	[80]

Note: The comparison demonstrated in the indicated reference is shown. The one with stronger effect on the specific parameter is listed at the column of "Superior". If all MSCs had comparable effects, they are all listed in the column of "Superior". Abbreviation of MSCs (source): AF-MSC (amniotic fluid), AM-MSC (amnion), AT-MSC (adipose tissue), BM-MSC (bone marrow), CB-MSC (cord blood), CP-MSC (chorionic plate of placenta), H-MSC (heart), I-MSC (islet-derived), L-MSC (lung), OE-MSC (olfactory ectomesenchymal), PB-MSC (peripheral blood), PL-MSC (placenta), SM-MSC (skeletal muscle), SY-MSC (synovial membrane), UC-MSC (umbilical cord), and WJ-MSC (Wharton's jelly in umbilical cord).

Table 1: Summary of the effects of MSC source on different parameters.

Furthermore, comparison of MSCs derived from allogeneic or autologous origins revealed that allo-MSCs may be immunogenic and cell therapy efficacies may be affected. This was illustrated by our results that syngeneic AT-MSCs had better efficacy than allogeneic AT-MSCs in inducing donor-specific tolerance to a VCAs in rats [76] (Figure 1). The wide range of biological properties of MSCs has shown great clinical potential. However, their properties can be influenced by factors such as their origins. Studies of detailed molecular events governing the variations in MSC properties are in need to decipher how environmental cues affect MSC behaviors, including the physiological and/or pathological milieu that MSCs reside in, physical and/or chemical stresses, and *in vitro* culture conditions. Our review has shown MSCs derived from various tissue origins have their own advantages/disadvantages in different aspects. Careful consideration of MSC sources with regard to specific applications is warranted.

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