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Adipose-derived stromal cells in regulation of hematopoiesis

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Abstract

Over the past decade, mesenchymal stromal cells (MSCs) found in the bone marrow microenvironment have been considered to be important candidates in cellular therapy. However, the application of MSCs in clinical settings is limited by the difficulty and low efficiency associated with the separation of MSCs from the bone marrow. Therefore, distinct sources of MSCs have been extensively explored. Adipose-derived stromal cells (ASCs), a cell line similar to MSCs, have been identified as a promising source. ASCs have become increasingly popular in many fields, as they can be conveniently extracted from fat tissue. This review focuses on the properties of ASCs in hematopoietic regulation and the underlying mechanisms, as well as the current applications and future perspectives in ASC-based therapy.

Keywords: Mesenchymal stromal cells, Hematopoiesis, Adipose-derived stromal cells, Therapy, Stem cells

Background

Hematopoiesis occurs mainly in the bone marrow (BM) of adult mice and humans [1], which makes the microenvironment indispensable for the maintenance of hematopoietic stem cells (HSCs) [2, 3]. Mesenchymal stromal cells (MSCs) have been identified as essential components of the HSC niche. MSCs are able to produce cytokines such as stem cell factor (SCF), macrophage colony-stimulating factor (M-CSF), stromal cell-derived factor 1 (SDF-1), and angiopoietin 1; and adhesion molecules and extracellular matrix (ECM) proteins such as vascular cell adhesion molecule 1 (VCAM-1), fibronectin, and various selectins, which thus provide support in the self-renewal, differentiation, and homing of HSCs [4, 5]. In addition, MSCs can differentiate into adipocytes, osteoblasts, and chondrocytes to meet the needs of tissue damage repair [6]. Although the mechanisms are not fully understood, MSC-based therapy has been applied in clinical trials, achieving curative outcomes in certain disorders [7]. However, with a relatively lower amount of MSCs being obtained from the BM, MSCs in other tissues or organs are being urgently explored.

General properties of adipose-derived stromal cells

The isolation procedure and cytological characterization of adult human adipocyte precursors from adipose tissue were studied in the early 1970s [8]. These cells were extracted from diverse anatomical sites, such as superficial abdominal areas, the upper arm, and inguinal and trochanteric areas [9, 10]. Several similar names were given to cells isolated from adipose tissue in different studies, such as adipose-derived adult stem cells, adipose stromal cells, adipose mesenchymal stem cells, preadipocytes, or processed lipoaspirate cells. In order to eliminate this discrepancy, the International Fat Applied Technology Society arrived at a consensus that any plastic-adherent, stable-doubling, and multipotent population of cells derived from lipoaspirate can be referred to as adipose-derived stromal cells (ASCs) [11]. The current procedure to isolate ASCs via liposuction surgery is well controlled and minimally invasive. The number of ASCs found in adipose tissue is notably higher than that of MSCs in bone marrow (BM-MSCs) at the same tissue volume [12]. Studies have revealed that ASCs were more easily obtainable than MSCs derived from the BM.

Zuk and colleagues first identified the multilineage differentiation character of ASCs in 2001 [13]. ASCs were characterized as one kind of adult stem cells, owing to their pluripotent but restricted differentiation ability. In general, culture expanded ASCs are positive for markers such as CD13, CD29, CD44, CD90 and CD105, while they lack hematopoiesis-related markers such as CD14, CD19, CD45, CD106 and HLA-DR [14, 15]. In addition, ASCs have the potential to secrete cytokines and chemokines, such as SCF, granulocyte colony-stimulating factor (G-CSF), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α). ASCs can give rise to multilineage descendants, including adipocytes, osteoblasts, and chondrocytes [16, 17]. Moreover, ASCs secrete adipose-specific proteins, such as leptin and adipsin [18, 19], which are not shared with BM-MSCs (Table 1).

Hematopoiesis-regulating properties of ASCs

The hypothesis that ASCs regulate hematopoiesis like BM-MSCs stems from the fact that they are components of the niche. Several research groups have proved this hypothesis by conducting co-culture assays of ASCs and HSCs in vitro. Nakao et al. proposed that mouse ASCs can improve the expansion and proliferation of CD34$^+$ peripheral blood hematopoietic stem/progenitor cells (HSCs/HPCs) as a feeder layer [26]. In the ASC co-culture system, a higher population count of CD34$^+$ cells was observed, and the total number of colonies was significantly increased. Nishiwaki et al. drew a similar conclusion using human ASCs from healthy volunteers after a series of ex vivo experiments [27]. In vitro co-culture assays showed that ASCs not only promoted the frequency of CD34$^+$ cells, but also yielded more hematopoietic progenitors compared to BM-MSCs. Andreeva et al. also reported that human ASCs supported the expansion of primitive hematopoietic precursors with the CD34$^+$CD133$^-$ phenotype from the umbilical cord blood [28]. These results suggest that ASCs can act as a feeder layer in the co-culture system and promote CD34$^+$ HSC/HPC expansion ex vivo. Besides the supportive capacity of ASCs in the maintenance and proliferation of HSCs, other studies have demonstrated that ASCs help HSCs to differentiate. It was reported that ASCs showed biases in promoting differentiation of HSCs into myeloid and

Table 1 Comparison between ASCs and BM-MSCs

		ASCs	BM-MSCs	Reference
Source		Adipose tissue	Bone marrow	[20]
Surface markers	CD13	+	+	[12, 14, 15, 21, 22]
	CD14	-	-	
	CD19	-	-	
	CD29	+	+	
	CD44	+	+	
	CD45	-	-	
	CD49d	+	-	
	CD90	+	+	
	CD105	+	+	
	CD106	-	+	
	CD166	+	+	
	HLA-DR	-	-	
Cytokines, chemokines, and specific proteins	SCF	+	+	[18, 19, 23]
	G-CSF	+	+	
	GM-CSF	+	+	
	M-CSF	+	+	
	SDF-1	+	+	
	IL-1α	-	+	
	IL-6	+	+	
	IL-8	+	+	
	IL-12	-	+	
	TNF-α	+	+	
	Leptin	+	-	
	Adipsin	+	-	
Differentiation	Adipogenesis	+	+	[16, 17, 20]
	Chondrogenesis	+	+	
	Osteogenesis	+	+	
	Myogenesis	+	+	
	Angiopoiesis	+	+	
	Neurogenesis	+	+	
Cell yield		0.5×10^4 - 2×10^5 cells per gram	1×10^3 cells per mL	[12, 15]
Clinical trials		185	217	
Approved products		Alofisel	Prochymal, Stempeusel, TEMCELL, Hearticellgram-AMI	[24, 25]

The number of registered clinical trials is obtained from the website of the U.S. National Library of Medicine under the terms "adipose-derived stromal/stem cells" and "bone marrow mesenchymal stromal/stem cells" respectively (until September 2019)

lymphoid lineages, while erythroid progenitors did not change [23]. ASCs particularly helped HSCs to expand myeloid and lymphoid progenitor numbers in vitro, especially granulocytes and their progenitors. However, Zhu et al. suggested that ASCs inhibited the proliferation of erythroleukemia K562 cells in vitro [29]. It has also been proved that ASCs can promote development of megakaryocytes and platelets [30]. The recent studies have not drawn a consistent conclusion on hematopoietic regulation biases of ASCs.
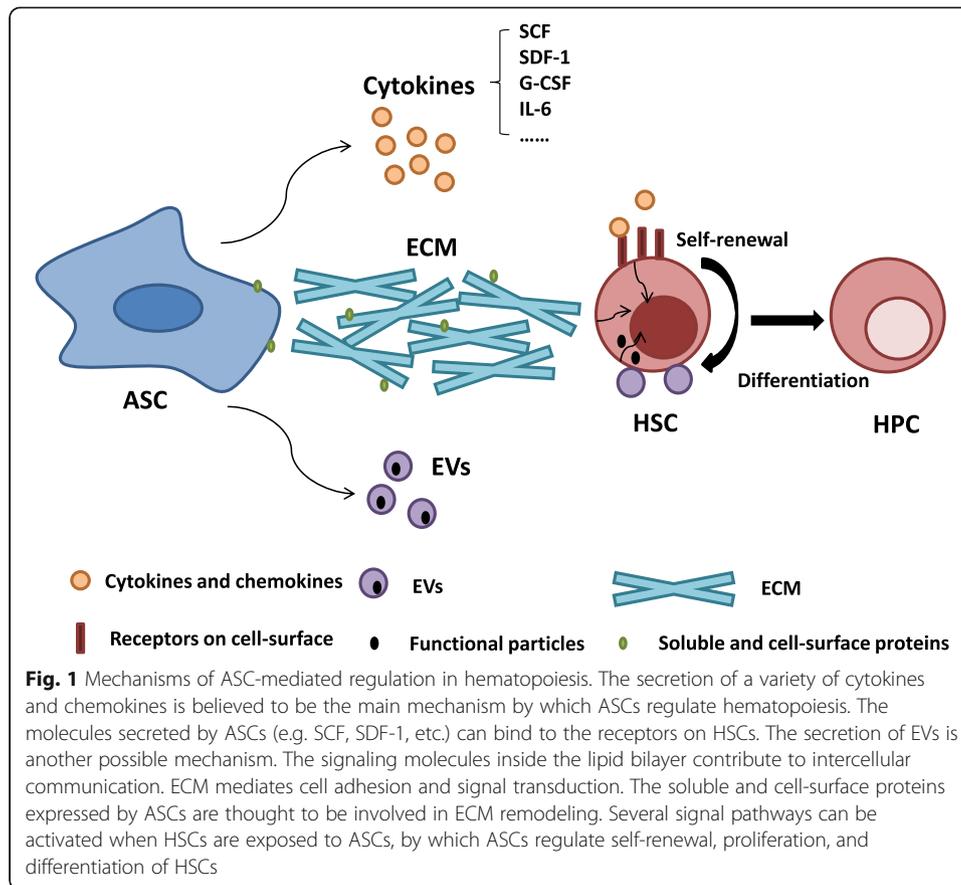
In order to further explore how ASCs support hematopoiesis in vivo, BM transplantations were performed in multiple studies. Nakao and colleagues showed that intra-bone marrow transplantation of ASCs through injection into the tibias facilitated engraftment efficiency and increased homing of donor HSCs [26]. ASCs attracted significantly more Lineage⁻Sca-1⁺c-kit⁺ cells to the BM in comparison with BM-MSCs. This supportive effect in hematopoietic recovery was a result of the dose-dependent effect of ASCs [31], but the effective ASC:HSC ratio differed among several research groups [31, 32]. ASCs were also able to help hematopoietic reconstitution when they were directly

transplanted into the BM cavity of wild type and NOD/SCID fatally irradiated mice [26, 27]. Serial transplantations were performed to further elucidate the supportive engraftment effect of ASCs. The results revealed that intravenous co-infusion of ASCs and HSCs improved engraftments in secondary and tertiary transplantation, which indicated that ASCs regulated not only short-term repopulating progenitors but also long-term HSCs [31]. Besides the supportive effect in BM transplantation, the regulatory capacity of ASCs in the differentiation of HSCs was also explored. Lee and colleagues showed that intraperitoneal co-injection with ASCs into NOD/SCID mice promoted the growth of acute lymphoblastic leukemia cells in vivo [33]. Zhang et al. demonstrated that ASCs have the potential to ameliorate platelet recovery in irradiated mice [34]. ASC administration protected BM cells from apoptosis and particularly promoted the frequency of $CD41^+$ megakaryocytes within 21 days after irradiation. Thus, these studies indicate that ASCs can support the expansion and specific differentiation of HSCs in vivo. However, the regulatory effects of ASCs on the downstream progenitors of HSCs, including common lymphoid progenitors, common myeloid progenitors, granulocyte-macrophage progenitors, and erythro-myeloid progenitors, should be explored in future studies. Overall, these results provided evidence that ASCs could facilitate hematopoietic reconstitution in vivo, which was consistent with the regulatory effects of ASCs on HSCs in vitro.

Mechanisms of ASC-mediated regulation in hematopoiesis

The inherent mechanisms by which ASCs regulate hematopoiesis attract much attention in order to better understand their properties related to hematopoietic regulation (Fig. 1). It has been widely accepted that ASCs produce a variety of cytokines with different functions that contribute to the quiescence and bias differentiation of HSCs. Retention factors such as SCF and SDF1 helped to maintain self-renewability and proliferation of HSCs, whereas growth factors such as M-CSF, G-CSF, GM-CSF and IL-6 helped progenitors to differentiate into functional blood cells [35]. SDF1, which is highly expressed by ASCs, could bind to the primary physiological receptor CXCR4 on hematopoietic progenitors. The SDF1-CXCR4 axis played an essential role in maintaining quiescence of HSCs [36]. Similarly, other cytokines could communicate with HSCs or more mature progenitors by binding to their specific receptors. Taken together, ASCs exhibited functional properties in hematopoietic regulation by paracrine action.

In addition, mechanisms and signals other than cytokines are also thought to regulate HSCs. The secretion of extracellular vesicles (EVs) is a possible mechanism for ASC-mediated regulation in hematopoiesis. EVs are functional particles with RNAs, lipids, and proteins inside them, wrapped by a lipid bilayer. These vesicle-associated RNAs are thought to be signaling molecules contributing to intercellular communication [37]. Although there is no report on the function of ASC-derived EVs in hematopoiesis, EVs secreted by MSCs have shown therapeutic effectiveness, including treatment for graft-versus-host disease (GVHD), acute kidney injury, and myocardial ischemia [38, 39]. It has also been proposed by several groups that a type of small, non-coding micro-RNA (miRNA) is involved in the post-transcriptional regulation for maintenance and differentiation of stem cells [40, 41]. ASCs could function as a feeder layer in an ex vivo culture with $CD34^+$ cells, and thus promote proliferation of HSCs via overexpression of

Fig. 1 Mechanisms of ASC-mediated regulation in hematopoiesis. The secretion of a variety of cytokines and chemokines is believed to be the main mechanism by which ASCs regulate hematopoiesis. The molecules secreted by ASCs (e.g. SCF, SDF-1, etc.) can bind to the receptors on HSCs. The secretion of EVs is another possible mechanism. The signaling molecules inside the lipid bilayer contribute to intercellular communication. ECM mediates cell adhesion and signal transduction. The soluble and cell-surface proteins expressed by ASCs are thought to be involved in ECM remodeling. Several signal pathways can be activated when HSCs are exposed to ASCs, by which ASCs regulate self-renewal, proliferation, and differentiation of HSCs

miR-33 and miR-145 and impairment of p53 function [42, 43]. These miRNAs may have an influence on cell cycle, apoptosis, and senescence of HSCs.

ECM was reported to function as a structural scaffold for cell-to-cell communication between HSCs and the microenvironment [44]. ECM mediated cell adhesion and signal transduction of the surrounding cells to provide functional and biochemical support. TGF-β secreted by ASCs was involved in ECM remodeling and collagen deposition, while CD44 expressed on ASCs affected ECM reorganization [45]. It was noted that several signaling pathways (including Notch-Jagged/Delta, MAPK, Wnt, and Jak-Stat) were activated when HSCs were exposed to MSCs [46]. For example, expression of both the Notch ligands on MSCs and the receptors on HSCs increased in the co-culture system. The activation of Notch signals inhibited the differentiation of HSCs. Wnt signals were involved in Notch activation, which made them vital in self-renewal and proliferation of HSCs as well [47, 48]. These signaling pathways on ASCs should be explored further to better understand hematopoiesis.

Application of ASCs and future perspectives

ASCs are considered to be useful for therapies in diverse diseases. Due to the paracrine function, multilineage differentiation, and immunological benefits, along with advantages of easy extraction and abundance, ASCs have become increasingly popular in cellular therapy. There are 185 clinical trials registered in the U.S. National Library of

Medicine thus far (September 2019), which have been conducted in the treatment of cardiovascular diseases, neurological disorders, skeletal and muscle damage, etc. Among the laboratory studies and clinical trials, the most promising utilization of ASCs was in wound healing and tissue repair [49]. It was reported that direct injection of ASCs into the tissue was effective to cure patients with acute myocardial infarction [50], perianal fistula [51], and chronic injury [52], and combining them with bio-materials showed favorable prognosis for bone defects [53, 54]. A new ASC medicine to treat perianal fistulas in patients with Crohn's disease has been approved by the European Medicines Agency, indicating that ASC products have moved one step forward in clinical application [55]. Moreover, ASC-based therapy has been shown to be effective in the treatment of GVHD [56] and knee osteoarthritis [57] when administered intravenously. The mechanisms underlying these therapeutic effects include the capability of ASCs to differentiate into mesodermal lineages and secrete soluble factors (TGF-β, VEGF, bFGF), which could enhance tissue regeneration or down-regulate the inflammatory response [58, 59].

MSCs can be obtained mainly from adult tissues including BM, adipose tissue, dental pulp, peripheral blood, muscle and skin; and neonatal sources such as umbilical cord blood (UCB), Wharton's jelly and placenta [20]. Among the various sources, UCB-MSCs and BM-MSCs are more applied in BM transplantation due to their comparative capacity to regulate hematopoiesis. UCB-MSCs are of higher stemness than other types of adult stem cells with a low immune response. The intravenous administration of UCB-MSCs has been used to treat GVHD in clinical settings [60]. It has been reported that UCB-MSCs helped HSC expansion ex vivo and enhanced the engraftment of HSCs as effectively as BM-MSCs in a murine model [61]. These studies indicated that UCB-MSCs can be used as an alternative source from birth-derived tissues in BM transplantation. As reported previously, ASCs share many features with BM-MSCs, but differ in immunophenotype, differentiation potential, transcriptome, proteome, and immuno-modulatory activity [62], which may lead to heterogeneity in functions. Accordingly, ASCs promoted engraftment of HSCs more rapidly than BM-MSCs in murine models [26, 27]. Moreover, among MSCs from all other alternative sources, ASCs exhibited stronger immunosuppressive capabilities than BM-MSCs [63–65]. Research from our and other laboratories has shown that MSCs could facilitate engraftment of HSCs and treat steroid-resistant acute GVHD as well [66, 67]. Both BM-MSCs and ASCs have proved to be effective for the prevention and treatment of GVHD, according to the preliminary phase I/II clinical studies [68–70]. These advantages mentioned above make ASCs a promising candidate to promote hematopoietic reconstitution. The BM contains less than 1×10^3 stromal cells per mL, while there are 0.5×10^4–2×10^5 stromal cells per gram of adipose tissue, which indicates an MSC yield of at least 50-fold more cells from fat tissue than from the BM [12]. These readily accessible and abundant cells perfectly meet the requirement for clinical applications in terms of manipulation.

Meanwhile, scientists have explored new frontiers to extend our knowledge on ASC application. A Japanese group applied a specific culture of ASCs with endogenous TPO to obtain platelets [30], which might be a new technology to address platelet shortage if well controlled and fully developed. ASCs have been used in organ reproduction (e.g. cardiac valves, blood vessels, and bones) in combination with 3D printing. This technology has been successful after transplantation in mammals [71–74], which made this

extremely promising to repair damaged organs. ASCs are expected to contribute immensely to cell engineering in future and become one of the main sources of MSCs for clinical application in coming decades.

Although the accumulated studies suggest a potential future for the clinical application of ASCs, several questions need to be answered, with regard to donor and tissue selection, as well as the manner of isolation, expansion, preservation, and infusion of ASCs. It is important to determine whether the biological properties of ASCs are dependent on the donor's age, gender, body mass index (BMI) and health status. A negative correlation was found between BMI of donor and the yield of ASCs per gram [75]. The harvesting site is also believed to affect properties and yield of cells (Table 2). ASCs from the subcutaneous and omental adipose tissue depot showed differences in cell number and proliferation, but the in vitro differentiation capacity was not different [80, 81]. Other studies provided opposite evidence that cells from subcutaneous depots differentiate faster into adipocytes and osteoblasts than those from visceral depots [78, 79]. Studies have demonstrated that ASCs extracted from superficial abdominal areas were advantageous in senescence over the cells from the upper arm and inguinal and trochanteric areas [9, 10]. It has also been reported that ASC yields are much higher from abdominal subcutaneous tissue than hips and thighs [83]. The above observations indicated that ASCs from different sources might have diverse features, and abdomen could be a preferable tissue for harvesting ASCs in clinical trials.

Protocols for isolation procedures and methods varied across institutions and laboratories. It has been reported that separation methods (mechanical or enzymatic) played an important role in cell number counts, heterogeneity, and differentiation capacity of ASCs. Higher numbers of ASCs can be obtained via a combination of mechanical and enzymatic procedures [84, 85]. There is a lack of standardized protocols currently; hence, ASCs isolated by various research groups may have different characteristics. More evidence should be provided on the evaluation of cell yield, quality, characteristics, and functions of ASCs from different liposuction studies. Meanwhile, it is important to develop methods to improve the quality and quantity of ASCs.

An ex vivo culture is usually needed for most clinical trials and fundamental studies with ASCs. However, the lack of standardized culture conditions may affect the

Table 2 Comparison between ASCs from subcutaneous and visceral adipose tissues

Harvesting sites		Subcutaneous depots	Visceral depots	Reference
Source		Abdomen, hips, thighs, knees	Intestines, omentum, perirenal region	[76, 77]
Homogeneity		High	Low	[78]
Surface markers	CD13	+	+	[78]
	CD44	+	+	
	CD90	+	+	
Differentiation	Adipogenesis	+	+	[78, 79]
	Chondrogenesis	+	+	
	Osteogenesis	+	+	
Proliferation		+	+	[80, 81]
Cell yield		High	Low	[81, 82]

High homogeneity indicates that ASCs isolated from subcutaneous depots have spindle-like morphology and uphold their homogeneity in future passages. Both ASCs from subcutaneous and visceral depots can proliferate and give rise to adipocytes, chondrocytes and osteoblasts, but the capacity of proliferation and differentiation might be different. High cell yield indicates that more ASCs can be obtained from subcutaneous adipose tissues, compared to visceral adipose tissues

regeneration, proliferation, and differentiation abilities of ASCs. The freshly isolated and expanded ASCs displayed several distinctions in biomarkers, gene expression, and biological properties (e.g. secretion of cytokines) [86]. Previous studies have shown that the expression of cell markers (e.g. CD105) increased during long-term culture, while others (e.g. CD34) decreased [11]. The genetic integrity was preserved with minimal alteration up to five passages [87]. It is vital to obtain primary cells or cultured cells with fewer passages owing to the dynamic phenotype of ASCs in vitro. Although the selection of optimal passages has also been studied [87, 88], the researchers did not report a consistent conclusion. Future studies need to investigate how to isolate, purify, and characterize ASCs in vitro. Standard protocols, dosage, and manner of administration must be established to apply ASC-based therapies to clinical trials.

Conclusions

ASCs exhibit properties similar to those of BM-MSCs, including secretion of cytokines, multi-differentiation, and immunological benefits, which confer great potential in therapy. Thus, an in-depth investigation of heterogenicity of MSCs revealed that ASCs can be considered as a competitive candidate. Many previous studies have provided evidence on properties of ASCs in hematopoietic regulation; however, there are unresolved issues that need to be addressed before they can be widely utilized in clinical applications.

Abbreviations
ASCs: adipose-derived stromal cells; bFGF: basic fibroblast growth factor; BM: bone marrow; BMI: body mass index; CXCR4: C-X-C chemokine receptor type 4; ECM: extracellular matrix; EVs: extracellular vesicles; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; GVHD: graft-versus-host disease; HLA-DR: human leukocyte antigen-antigen D related; HSCs: hematopoietic stem cells; HSCs/HPCs: hematopoietic stem/ progenitor cells; IL-6: interleukin 6; M-CSF: macrophage colony-stimulating factor; miRNAs: micro-RNAs; MSCs: mesenchymal stromal cells; SCF: stem cell factor; SDF-1: stromal cell-derived factor 1; TGF-β: transforming growth factor beta; TNF-α: tumor necrosis factor alpha; TPO: thrombopoietin; UCB: umbilical cord blood; VCAM-1: vascular cell adhesion molecule 1; VEGF: vascular endothelial growth factor

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