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Mesenchymal Stem Cells

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Stem cells have two features: the ability to differentiate along different lineages and the ability of self-renewal. Two major types of stem cells have been described, namely, embryonic stem cells and adult stem cells. Embryonic stem cells (ESC) are obtained from the inner cell mass of the blastocyst and are associated with tumorigenesis, and the use of human ESCs involves ethical and legal considerations. The use of adult mesenchymal stem cells is less problematic with regard to these issues. Mesenchymal stem cells (MSCs) are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc. This is because the ease of harvest and quantity obtained make these sources most practical for experimental and possible clinical applications. Recently, MSCs have been found in new sources, such as menstrual blood and endometrium. There are likely more sources of MSCs waiting to be discovered, and MSCs may be a good candidate for future experimental or clinical applications. One of the major challenges is to elucidate the mechanisms of differentiation, mobilization, and homing of MSCs, which are highly complex. The multipotent properties of MSCs make them an attractive choice for possible development of clinical applications. Future studies should explore the role of MSCs in differentiation, transplantation, and immune response in various diseases.

Key words: Mesenchymal stem cells (MSCs); Differentiation; Immune; Homing

INTRODUCTON

Stem cells have two features: the ability to differentiate along different lineages and the ability to self-renew (74). Two major types of stem cells have been described, namely, embryonic stem cells (ESC) and adult stem cells. ESCs are obtained from the inner cell mass of the blastocyst and are associated with tumorigenesis (6,7,97). The use of human ESCs involves legal and ethical considerations (38). These problems are less severe in adult stem cells. Adult stem cells have multipotency, which make them an attractive choice for clinical applications. This review focuses on the new origin of mesenchymal stem cells (MSCs) and signaling pathway on differentiation.

MESENCHYMAL STEM CELLS

MSCs are stromal cells that possess the capacity to self-renew and also exibit multilineage differentiation (18,87). MSCs can be isolated from a variety of tissues, such as umbilical cord, endometrial polyps, menses blood, bone marrow, adipose tissue, etc. (23,24) (Fig. 1). This is because the ease of harvest and quantity obtained make these sources most practical for experimental and possible clinical applications. Recently, many MSCs have been derived from new sources, such as menstrual blood and endometrium.

MSCs From Menstruation

About 400 cycles of menstruation take place in a woman's reproductive years. Usually, menstrual blood is discarded. Recently, MSCs from menstrual blood were discovered (42,68,88,91). This represents a new, noninvasive, and potent source of human MSCs for regenerative medicine. Most MSCs from menstrual blood have the ability to differentiate to muscle, especially cardiac muscle cells (42,88). These cells have been shown to possess a remarkable myogenic capability enabling

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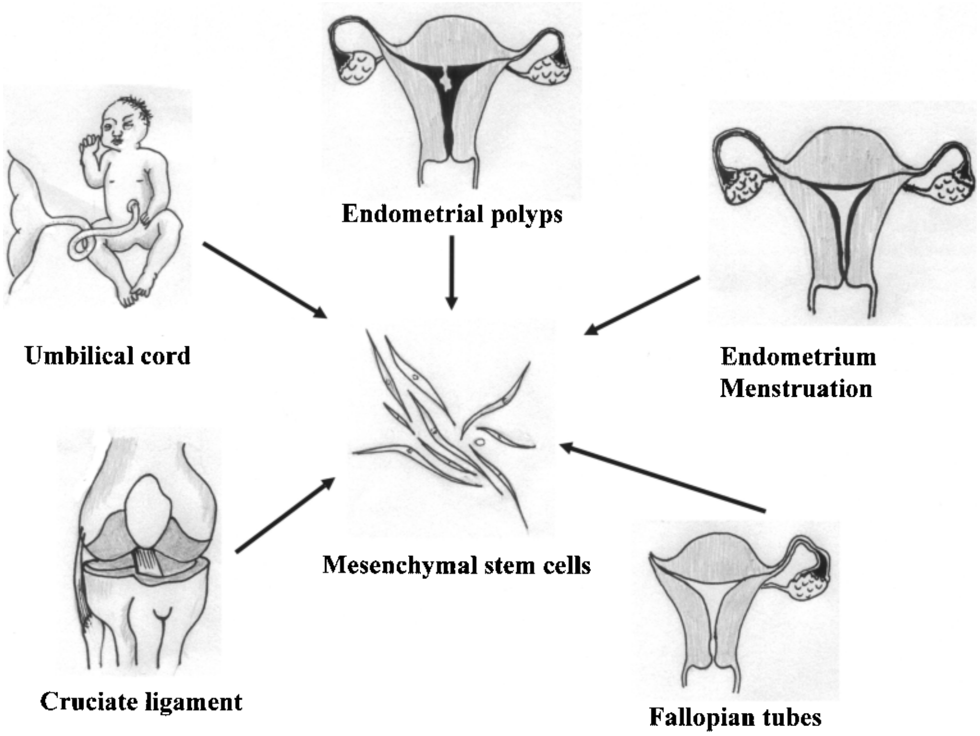

Figure 1. Various new sources of MSCs. Cells are isolated and cultured and can differentiate to three germ layers for transplantation purpose.

the rescue of dystrophied myocyte of Duchenne muscular dystrophy or cardiac myocardial infarction models (42,88). MSCs from menstrual blood could therefore have potential as a novel, easily accessible source of materials for myogenic stem cell-based therapy. Recently, Sanberg et al. showed menstrual blood-derived stem cells can be used for brain repair (76). Menstruation-derived MSCs can differentiate into neurons in vitro. These cells were used to treat stroke animal model and improvement by a mechanism that does not appear to involve cell replacement was observed. This finding raises hope that menstrual-derived stem cells are not only myogenic but also neurogenic and may have potential for use in stroke therapy in the future.

MSCs From Endometrium

Endometrium from human uterus is a highly regenerative tissue undergoing more than 400 cycles of shedding, growth, and differentiation during a woman's reproductive years. Stem or progenitor cells may play a major role in endometrial regeneration. Gargett and colleagues found that human endometrium contains a small population of MSC-like cells, which may be responsible for its cyclical growth (34,35,77). They found CD146 is a good marker to identify these cells, which may provide a new source of MSCs for tissue engineering applications. Meng et al. also found endometrial regenerative cells were able to differentiate into nine lineages: cardiomyocytic, respiratory epithelial, neurocytic, myocytic, endothelial, pancreatic, hepatic, adipocystic, and osteogenic cells (66). They also found these cells can produce MMP3, MMP10, GM-CSF, angiopoietin-2, and PDGF-BB (66). In addition, they found these cells possess the ability to inhibit intracranial glioma growth (41). Tsuji et al. found that side population cells in human endometrium contributed to genesis of human endometrium (90). They conclude that human endometrial side population cells may contain putative stem cells.

MSCs From Endometrial Polyps

Endometrial polyps are localized hyperplastic overgrowths of endometrial glands and stroma around a vascular core that form a sessile or pedunculated projection from the surface of the endometrium. Endometrial polyps cause intermenstrual bleeding, irregular bleeding, and menorrhagia, and can be discovered by hysteroscopy (43). As endometrial polyps are benign overgrowths of endometrial tissue, they may be a rich source of MSCs. We have derived MSCs from endometrial polyps (Fig. 2A), which showed traditional MSC surface marker (Fig. 2B). MSCs can also differentiate into adipocytic, osteogenic, and neurogenic lineages (Fig. 2C, D). They also proliferate faster than endometrial stromal cells and bone marrow stromal cells. Our results indicate that endometrial polyps may have potential as a novel source of MSCs.

MSCs From Fallopian Tubes

The human fallopian tubes share the same embryologic origin as the uterus. They have the capacity to undergo dynamic endocrine-induced changes during the menstrual cycle, including cell growth and regeneration, in order to provide the unique environment required for the maintenance of male and female gamete viability, fertilization, and early embryo development as well as transport to the uterus (63). Jazedje et al. recently found MSCs derived from human fallopian tubes. These cells can differentiate into adipogenic, chondrogenic, oestogenic, and myogenic lineages (51). They conclude human tubal MSCs can be easily isolated and expanded. Furthermore, they present a mesenchymal profile and are able to differentiate.

MSCs From Human Cruciate Ligaments

Cheng et al. (14) and Ge et al. (36) found MSCs from human anterior and posterior cruciate ligaments (ACL, PCL) and found these cells can differentiate into chondrocytes, adipocytes, and osteocytes. These ligaments

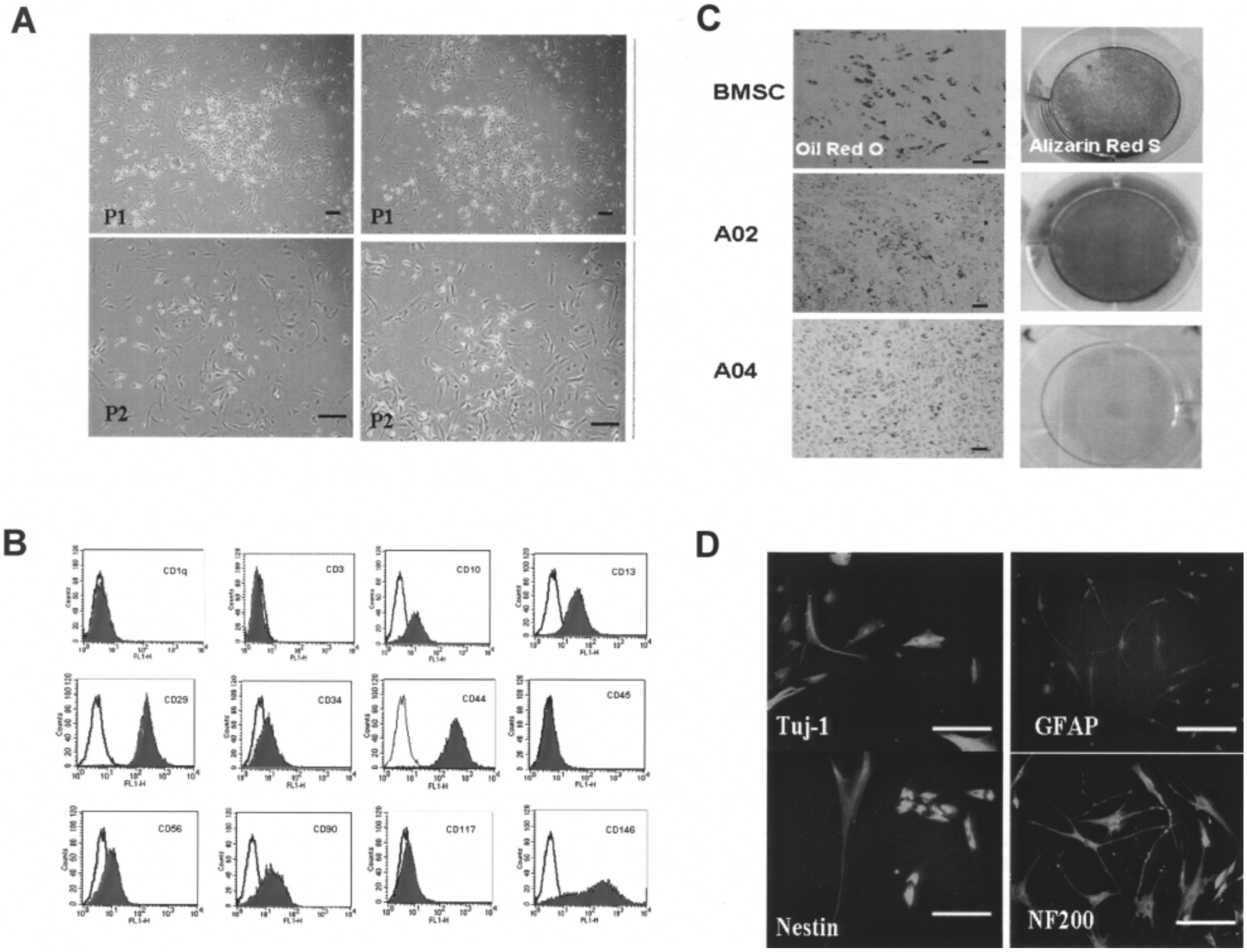

Figure 2. MSCs derived from human endometrial polyps (EPMSCs). (A) Representative photographs of endometrial polyp stem cells grown in proliferation medium. (B) Flow cytometry of endometrial polyp stem cells that express CD13, CD29, CD44, and CD90. (C) Adipogenic differentiation shows morphological changes in the formation of neutral lipid vacuoles, with almost all cells containing numerous Oil Red O-positive lipid droplets. Osteogenic differentiation shows numerous differentiated cells containing mineralized matrices, which were strongly stained by Alizarin Red S. (D) In neuro-glial differentiation, morphologies of refractile cell bodies with extended neurite-like structures were arranged into a network. EPMSCs-derived neuroglial cells were identified by immunostaining against nestin, Tuj-1, GFAP, and NF200. Scale bars: 50 μm (A, B), 100 μm (C, D).

can be easily obtained from patients following total knee or cruciate ligament reconstructive surgery. They conclude that human MSCs can be isolated and expanded from ACL and PCL and could be a viable alternative source for use in regenerative medicine.

MSCs From Umbilical Cord Matrix

Recently, stem cells have also been derived from the umbilical cord matrix (32,67,95). Mitchell et al. proved that mesenchymal stem cells from Wharton's jelly (WJC) can differentiate into neuronal and glial cells in vitro and proved that umbilical cord Wharton's jelly could be a rich source of primitive cells (67). Fu et al. also used the same kind of cells in a neuron-conditioned medium with the addition of sonic hedgehog (Shh) and fibroblast growth factor 8 (FGF8), and found that these cells differentiated into dopaminergic neurons, which could help recover the function of 6-OHDA-treated rats (32). We have also found that stem cells derived from Wharton's jelly of the human umbilical cord can migrate to the site of injury and differentiate to neuronal and glial cells in stroke rats (22). Behavioral and functional tests showed improvement in the treated group (22). In contrast to BMSCs, WJCs have greater expansion capability, faster growth in vitro, and may synthesize different cytokines and as therapeutic cells in several preclinical models, such as neurodegenerative disease, cancer, heart disease, etc. (10,89). WJCs are considered an alternative source of MSCs and deserve to be examined in long-term clinical trials (10).

CHARACTERIZATON OF MSCs

Surface CD marker is often used to distinguish MSC from hematopoietic cells by their lack of CD34, CD45, CD14, and HLA-DR. Stro-1 is specific for clonogenic MSCs (73,81,84). These cells can differentiate to form cells with the characteristics of adipose, cartilage, and bone cells in vitro, and form human bone tissue after transplantation into immunodeficient SCID mice (39, 40). The profile of adhesion molecules is also different from donor to donor and is influenced by the serum used in the culture (87). Vimentin, laminin, fibronectin, and osteopontin can be synthesized by BMSCs (19). MSCs also express some markers, such as myofibroblasts (α-smooth muscle actin, smooth muscle myosin heavy chain), neurons (nestin, Tuj-1), and endothelial cells (CD146, CD105) transforming growth factor-β (TGF-beta) receptor, and various forms of integrin (15,28,46, 47,64,65,85).

Fibroblast colony forming units (CFU-F) were discovered by Friedenstein et al. They isolated adherent cells that were colonogenic and able to form colonies from bone marrow stroma and newborn rodents (31). Some mitogenic factors (platelet-derived growth factor, epidermal growth factor, basic fibroblast growth factor, TGF-β, and insulin growth factor) can regulate the proliferation of CFU-F (44,62,82). Most MSCs have the capacity to adhere to a plastic support. MSCs enrichment could be realized with relatively deprived medium only containing serum. CFU-F assays also show that the fraction is heterogenous with different colony sizes, cell morphologies, and differentiation potentials (30,56).

DIFFERENTIATION PATHWAYS

MSCs can differentiate into various lineages of mesodermal, ectodermal, and endoderm such as bone, fat, chondrocyte, muscle, neuron, islet cells, and liver cells under specific in vitro conditions (55,69). Differentiation is also regulated by genetic events, involving transcription factors. Differentiation to a particular phenotype pathway (Fig. 3) can controlled by some regulatory genes which can induce progenitor cells differentiation to a specific lineage (18). Besides growth factors and induction chemicals, a microenvironment built with biomaterial scaffolds can also provide MSCs with appropriate proliferation and differentiation conditions (79,93).

Mesoderm Differentiation

Theoretically, mesodermal differentiation is easily attainable for MSCs because they are the same embryonic origin. In osteogenic differentiation, a mixture of dexamethasone (Dex), β-glycerophosphate (β-GP), and ascorbic acid phosphate (aP) has been widely used for induction and is demonstrated by calcium accumulation and alkaline activity (70). In adipogenesis differentiation, Dex and isobutyl-methylxanthine (IBMX) and indomethacin (IM) are used for induction and is shown by lipid droplets in cells being stained by Oil Red O solution (46,78). In chondrogenesis differentiation, TGF-β2 and TGF-β1 are involved in differentiation (45). PPAR-γ2, C/EBP, and retinoic C receptor are involved in adipogenesis (27,86). PLZF and CBFA-1 induce osteogenesis (26,49, 53). Lastly, Smad3, CBP/p300, and SOX9 induce chondrogenesis (33). Furthermore, lineage repression can also lead to differentiation. Overexpression of the PPAR-γ2 gene encoding adipogenic factor also represses Cbfa-1 gene expression in osteogenic cells (57).

Ectoderm Differentiation

In neuron differentiation, DMSO, BHA, KCL, forskolin, and hydrocortisone were used for induction (75). In our previous study, we used a three-stage induction protocol (25) with addition of bFGF, β-mercaptoethanol (β-ME), NT-3, NGF, and BDNF. Tuj-1, neurofilament 200, MAP-2, synaptophysin, and γ-aminobutyric acid (GABA) and GFAP were used to assess the capacity of neuronal differentiation (22). Notch-1 and protein kinase

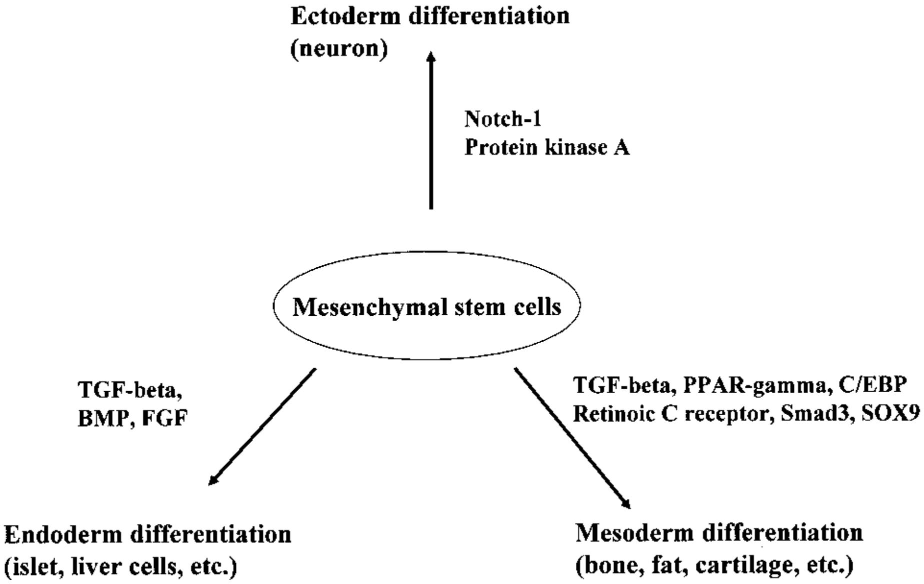

Figure 3. Effects of various pathways on MSCs differentiation. MSCs can differentiate to form various lineages through different cytokines and pathways. TGF, transforming growth factor; BMP, bone morphogenetic protein; FGF, fibroblast growth factor.

A (PKA) pathway are involved in neuron differentiation (16,96,98).

Endoderm Differentiation

In pancreatic islet β-cell differentiation, nicotinamide and β-ME were used for induction and this resulted in specific morphology, high insulin-1 mRNA content, and synthesis of insulin and nestin (13). In liver differentiation, hepatocyte growth factor and oncostatin M were used for induction and obtained cuboid cells that expressed appropriate markers (α-fetoprotein, glucose 6-phosphatase, tyrosine aminotransferase, and cytokeratin-18) and albumin production in vitro (58). Recently, murine mesenchymal stem cells can differentiate to endoderm islet cells with high efficiency. Firstly, MSCs differentiated to endoderm (expressing Sox17, Foxa2, GATA-4, and CK-19), then to pancreatic endoderm (PDX1, Ngn2, NeuroD, PAX4, and Glut-2), and finally to pancreatic hormone-expressing (insulin, glucagon, and somatostatin) cells (11). In liver maturation, mesoendodermal phenotype was genetically regulated through cytokine signaling, including TGF-β, bone morphogenetic protein, fibroblast growth factor, and other signaling pathways (50).

MOBILIZATION OF MSCs

Several growth factors, cytokines, and chemokines have been found to mediate mobilization of MSCs. In both animal and human studies, growth factors VEGF, stromal-derived factor-1 (SDF-1), granulocyte colony-stimulating factor (GCSF), granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), erythropoietin (EPO), angiopoietin-2, fibroblast growth factor, placental growth factor (PlGF), platelet-derived growth factor-CC, stem cell factor (SCF), interleukin (IL)-2, IL-3, IL-6, IL-8, and IL-1β are all known to stimulate and mobilize MSCs (5,61,92). During the process of angiogenesis and vasculogenesis, hematopoietic stem cells (HSC) and endothelial progenitor cells (EPC) from bone marrow may show concomitant mobilization due to the physiological need of synergistic interactions (48). In this respect, it is thought that VEGF-A, PlGF, and SDF-1, released by blood platelets and monocytes, activate metalloproteinase-9 (MMP-9), which mediates a joint mobilization of HSCs, EPCs, and MSCs. The interactions between these cells may contribute to the revascularization process (24).

HOMING OF MSCs

Recent studies have revealed that stem cells are highly migratory and seem to be attracted to areas of brain pathology, such as ischemic regions (1,12). Human MSCs transplanted into fetal sheep will be embedded into various tissues (bone marrow, spleen, thymus, liver) (3). Circulating hematopoietic cells will actively cross the endothelial vasculature of different organs and into their bone marrow niches. Homing is also a part of host defense and repair (71). Growth factors, chemokines, and adhesion molecules are signals for the direct homing effect (17,54). MSCs can migrate and home to tissues and organs (2,20,21,29). Chemokine receptors and their chemokine ligands are essential components involved in the migration of leukocytes into sites of inflammation (83). CXCL12 [stromal cell-derived factor-1 (SDF-1)] and its receptor CXCR4 are crucial for bone marrow retention, mobilization, and homing of hematopoietic stem cells (59,72,92). MSCs can express a variety of chemokine receptors, which suggests homing affinity may vary depending on the type of tissue (94). Granulocyte colony-stimulating factor causes enhanced stem cell migration towards SDF-1, which is a potential advantage in directing and amplifying the homing of endogenous stem cells (9).

IMMUNE MODULATION OF MSCs

In addition to multilineage differentiation, MSCs also have powerful immunomodulatory effects, which include inhibition of proliferation and function of T cells, B cells, and natural killer cells (8,37,52,60). Underlying the MSC-mediated immunomodulatory mechanisms is a nonspecific antiproliferative effect, which is the consequence of cyclin D2 inhibition (80). Prostaglandin E_2, nitric oxide, histocompatibility locus antigen-G, insulin-like growth factor-binding proteins, and tolerogenic antigen-presenting cells and indoleamine 2,3-dioxygenase have been reported to play a role in this mechanism (80). Although the physiologic significance of immunosuppression is unclear, the underlying mechanism could involve stromal function. It appears to exert its influence by increasing the survival and renewal of parenchymal stem cells. Understanding these mechanisms and the precise roles of the molecules involved will be of enormous help in the development of future clinical applications, such as transplantation of stem cells or experimental applications.

FUTURE PROSPECTS

The Search for Novel MSC Sources

Besides bone marrow, MSCs can be isolated from various tissues in the human body. Adipose stem cells could be a promising source of MSCs because it is present throughout the human body. However, MSCs from fetal origin, such as umbilical cord and blood, would be a good source that does not involve ethical considerations because they are discarded after the baby has been delivered. Menstruation blood and endometrial stem cells are other promising sources of MSCs because they are usually discarded after menstruation or surgery. There are numerous kinds of tissues in the human body that may be explored as potential sources of MSCs.

Study of Differentiation Pathway and Immune Modulation

Once a novel source of MSCs has been discovered, the challenge is to determine how to differentiate them so that they can be used in clinical applications. The factors that influence differentiation are of particular importance to ensure that they are safe for human use. The better the pathways are understood, the greater the possibility that MSCs can be manipulated into the required type of cells. Immune modulation is another important issue in MSC transplantation. As the mechanism is still unclear, it is worth elucidating the roles of molecules in the immune response that may dictate whether or not an engraftment is successful.

Future Research on MSC Mobilization and Homing

Currently, there are no available data from long-term clinical studies examining drug-mediated mobilization and functional modification of endogenous stem cells. One focus of future research should be the elucidation of the molecular pathways regulating stem cell levels and the function and genetic modification of stem cells leading to improved functional capacity. The development of pharmacological and genetic strategies for targeting endothelial progenitor cells will be necessary in the future (4,24).

CONCLUSION

There are likely numerous sources of human MSCs awaiting discovery. They may be good candidates for future experimental or clinical applications. The mechanisms of differentiation, mobilization, and homing of MSCs are complex. The multipotency of mesenchymal stem cells makes them an attractive choice for clinical applications. Future studies should explore the role of MSCs in differentiation, transplantation, and immune response in various diseases.

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