TOPIC HIGHLIGHT

Role of mesenchymal stem cells in cell life and their signaling

Shihori Tanabe

Shihori Tanabe, National Institute of Health Sciences, Tokyo 158-8501, Japan
Author contributions: Tanabe S solely contributed to this paper.
Correspondence to: Shihori Tanabe, PhD, National Institute of Health Sciences, 1-18-1, Kami-yoga, Setagaya-ku, Tokyo 158-8501, Japan. stanabe@nihs.go.jp
Telephone: +81-3-37001141 Fax: +81-3-37076950

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Abstract

Mesenchymal stem cells (MSCs) have various roles in the body and cellular environment, and the cellular phenotypes of MSCs changes in different conditions. MSCs support the maintenance of other cells, and the capacity of MSCs to differentiate into several cell types makes the cells unique and full of possibilities. The involvement of MSCs in the epithelial-mesenchymal transition is an important property of these cells. In this review, the role of MSCs in cell life, including their application in therapy, is first described, and the signaling mechanism of MSCs is investigated for a further understanding of these cells.

Core tip: Mesenchymal stem cells (MSCs) are important cells that have a differentiation and self-renewal capacity and an immune-modulation function. MSCs differentiate into osteogenic-, adipogenic-, chondrogenic- and other cells. The application of MSCs in many situations, such as disease treatment, is full of possibilities for future development. The gene and protein expression and cellular phenotypes of MSCs are described.

INTRODUCTION

Recent advances in stem cell research have brought about the possibility of stem cell therapies[1], and new approaches using human genetics have been developed to validate therapeutic targets[2]. Furthermore, some gene variations may be useful to detect drug effectiveness on these cells[2]. These novel technologies, when combined, demonstrate their possible application for stem-cell therapeutics. For example, human livers can now be generated from induced pluripotent stem cells (iPSCs) by the transplantation of three-dimensional liver buds that are self-organized *in vitro*[3]. Furthermore, hematopoietic stem cells can be generated from iPSCs by teratoma formation methods involving co-culturing with OP9 stromal cells, which may be useful for the treatment of hematologic and immunologic diseases[4]. Even diseased cells, such as sarcoma cells, are now being reprogrammed into stem cells with defined factors, such as Oct4, Sox2, c-Myc and Klf4, to change their cellular phenotype to lack tumorigenicity. Furthermore, sarcoma cells can dedifferentiate into mesenchymal stem cells (MSCs) and hematopoietic stem-like cells, and they can differentiate into connective tissue and erythroid cells[5,6].

The regulation of differentiation in stem cells involves the expression of several genes; for example, myogenic differentiation 1 induction in immature human iPSCs leads to the differentiation of these cells into mature myocytes[7]. In hepatic-lineage cell dedifferentiation, cell type-specific transcriptional profiles may correlate to the cell-type transition[8].

Recently, controlling stem-cell fate using chemical approaches has been implicated and could lead to new

therapies for disease through the understanding of stem cells and regenerative biology[9]. Chemical therapeutics may induce the self-renewal of cells and target an *in vitro* niche that allows the cells to progress towards cellular differentiation, proliferation, reprogramming and homing[9]. However, optimization of the chemical structures of these therapeutics is an important factor for developing appropriate cell therapies. Several compounds that regulate cell fate have been selected to bind to nuclear receptors or regulate cellular signaling[9]. The chemical approach to regulating cells and their niches may open a new door for therapeutic strategies in regenerative medicine, such as targeting self-renewal of stem and progenitor cells as well as differentiation and reprogramming[9].

Reprogramming using small molecule compounds such as Forskolin, VPA, CHIR99021, 616452, Tranylcypromine and 3-deazaneplanocin A instead of gene transduction has been successful[10]. In Oct4 promoter-driven green fluorescent protein (GFP)-expressing mouse embryonic fibroblasts, these compounds induce GFP-positive clusters expressing Cdh1 (cadherin 1) (E-cadherin)[10], which is a marker for the mesenchymal-to-epithelial transition, which has recently been revealed to be an important mechanism for the nuclear reprogramming of mouse fibroblasts[11]. Chemically iPSCs have gene expression profiles that are similar to those of embryonic stem cells (ESCs)[10]; therefore, monitoring the gene expression profiles of a variety of iPSCs may be useful for checking the quality of the cells in clinical applications. Additionally, some chemicals important for the self-renewal of ESCs have also been found through screening and may provide insights into the mechanism of stem cell maintenance[12]. For example, a newly identified small molecule maintains the self-renewal ability of mouse ESCs and functions as a dual inhibitor of a protein kinase, ERK1, and a small GTPase-activating protein, Ras GAP[12]. Surprisingly, human iPSCs have been developed into a three-dimensional miniature brain, referred to as an *in vitro* cerebral organoid, and this method forecasts the future of organ regeneration[13,14]. Of the variety of stem cells, MSCs have the potential to differentiate into multi-lineage cells and have other properties such as immunoregulatory functions, which will be discussed in the following sections[15-19].

ORIGIN OF MSCS

MSCs, which are a type of stem cell, have the ability to differentiate into a variety of cell lineages, such as bone, cartilage, tendon, ligament and adipose tissue[15,16]. MSCs were originally found as nonhematopoietic cells in bone marrow by the observation of Cohnheim nearly 150 years ago, even before being recognized as MSCs[20,21]. Osteogenesis, one of the main characteristics of MSCs, was also observed in bone marrow transplantation before the discovery of MSCs[22,23]. MSCs began to be experimentally recognized and were studied using culture dishes in the 1970's[24], and during that time, fibroblast colonies were found in bone marrow cultures[24]. The efficacy of MSCs *in vivo* has been investigated, and MSCs were found

to suppress graft *vs* host disease[19]. Self-renewing MSCs in bone marrow are rare and are candidates for tissue engineering because of their multilineage-differentiation capacity into various cells[25]. The phenotype of MSCs is usually described as positive for many molecules, such as CD105 and CD73, and negative for other molecules, such as CD34, CD45 and CD14; however, the MSC phenotype is altered during cultivation[25-27]. MSCs are promising cells for tissue repair and immunomodulation because they have site-directed and systemic delivery functions[25]. Furthermore, MSCs have now been considered for the potential use in diabetes mellitus treatment, making the clinical application of MSCs more diverse[28]. The roles of MSCs are not restricted to disease treatment and include wound repair, as observed in their original discovery. The sources of MSCs now include bone marrow, amniotic fluid, placenta, umbilical cord blood, periosteum and adipose tissue[29-35].

The criteria for defining MSCs by the International Society for Cellular Therapy position statement are: (1) plastic adherence under standard culture conditions; (2) expression of CD105, CD73 and CD90 and no expression of CD45, CD34, CD14 or CD11b, CD79A or CD19 and HLA-DR; and (3) capacity to differentiate into osteoblasts, chondroblasts and adipocytes *in vitro*, which is termed the trilineage differentiation potential[36,37]. MSCs have been reported to be transformed into sarcomas, especially in mice, or to promote tumor growth; however, human MSCs are considered relatively safe for clinical applications[36,38]. Recently, MSCs have been used for various purposes that utilize their multi-potential abilities to treat disease, and a new cellular model using disease-derived MSCs has been developed[39]. For the application of MSCs in clinical use, the monitoring of MSC features is essential[40].

MSC APPLICATION

MSCs have been applied for various purposes, such as the clinical replacement of tissues, and as sources of cells in immune-regulation[41,42]. Recently, MSCs have been applied as vaccines[43]. To apply MSCs as a novel vaccine platform, MSCs are expanded *ex vivo* and genetically modified[43]. However, the quality control of MSCs *ex vivo* is important for the safe application of these cells; therefore, a bank of stored MSCs has been established[44]. Human iPSCs can be used as sources of MSCs[45]. The induction of human iPSCs using a small-molecule inhibitor of transforming growth factor (TGF)-β into MSCs has been successful[45]. In this section, applications of MSCs and differentiated-MSCs in therapeutics are described.

Osteogenic differentiation of MSCs

MSCs are recognized as sources of bone-related regenerative medicine because they can undergo osteogenesis. One of the mechanisms of osteoporosis has been suggested to be an inability of MSCs to differentiate into osteoblasts[46]. Therefore, a precise investigation for revealing the gene expression profile and molecular signaling

of osteogenic differentiation is needed.

Osteogenic differentiation is often induced with dexamethasone, sodium L-ascorbate, and β-glycerol phosphate[47], but the roles of microRNAs (miRNAs) in the osteogenesis of MSCs have also been investigated[48]. Gene expression studies of MSCs using genome-wide association analyses revealed that the EphrinA-EphR pathway for femoral neck bone geometry is coordinated with osteogenesis[49]. Investigation of bovine MSCs has revealed that the osteogenic differentiation of MSCs was highly induced by ascorbic acid and fetal bovine serum[50], and upon the osteogenic differentiation of MSCs, mechanical stress could induce the capacity of MSCs[51]. Hypoxia-mediated signaling in osteogenic differentiation has shown to be mediated *via* regulation of RUNX2 by TWIST[52]. Moreover, epigenetic regulation is involved in MSC differentiation, and transcription regulation by RUNX2 is important for the osteogenic differentiation capacity of MSCs[47].

Chondrogenic differentiation of MSCs

One application of MSCs is their use in cartilage repair[53]. MSCs from adipose tissue have been chondrogenic-differentiated in 3D culture with hydrogel[53]. Chondrogenic differentiation can be induced by insulin, transferrin, sodium selenite, sodium L-ascorbate, dexamethasone and TGF-β1[54]. In some cases, the modulation of MSCs with chemically oversulfated polysaccharide of marine origin up-regulates the TGF-β-dependent chondrogenesis of MSCs[54]. During chondrogenic differentiation, epigenetic changes have been observed using genome-wide analysis[55], and the expression of several chondrogenic signature genes were found to be up-regulated. For example, it is known that the trimethylation of lysine 4 of histone 3 (H3K4me3) is up-regulated during chondrogenesis[55].

Adipogenic differentiation of MSCs

The adipogenesis of MSCs is usually induced by 3-isobutyl-1-methylxanthine, dexamethasone, indomethacin and insulin, but a mechanically induced signal transduction using the depolymerizing drug cytochalasin D has been shown in adipogenesis[56]. Cytoskeletal mechanisms and signaling molecules such as ERK and AKT are involved in this process[56]. MSCs have been clinically applied in several situations[41]. Adipogenesis-related factors may be used for the treatment of obesity and other related disorders[41]. Importantly, upon adipogenesis of MSCs, the adipogenic differentiation capacity was decreased during *in vitro*, long-term culture[57]. It is also known that miRNA expression changes upon *in vitro* senescence of MSCs, which suggests that differential miRNA expression might be useful for distinguishing between MSC phenotypes[57].

Trans-differentiation of MSCs

MSCs also trans-differentiate into non-mesoderm lineages, such as Schwann-like cells which play roles for development, myelination and regeneration in the peripheral nervous system[58-63]. Adipose-derived stem cells can be differentiated into cells with glial phenotype expressing

GFAP[58]. Another study has also reported that adipose-derived stem cells can be induced into cells showing neural and glial cell phenotype[59]. MSCs derived from bone marrow and adipose are shown to express mRNAs and proteins of myelin that is formed by Schwann cells[64]. MSCs are also suggested to differentiate into myoblast[65]. On the other hand, MSCs are also used for various diseases including kidney injury, diabetes and brain tumors, although it needs to be elucidated whether the anti-disease effect of MSCs arise from trans-differentiation or other paracrine effects of MSCs[66-70]. The effect of MSCs for treatment of brain tumors is suggested to be caused by paracrine effect of MSCs towards cancer cells[70].

MSC effects in the immune response

MSCs are known to be involved in the immune response during circumstances such as the allogenic transplantation of bone marrow, which mainly causes an immuno-suppressive effect. A MSC-induced immunosuppressive effect might be caused by the down-regulation of T-cell differentiation into T helper 17 (Th17) cells and of the function of mature Th17 cells[71]. This inhibition of mature Th17 cells could occur *via* the cell-to-cell contact mechanism of MSCs and may be mediated by the programmed death-1 pathway[71]. Allogenic MSCs have also been demonstrated to regulate the function of Th17 cells derived from rheumatoid arthritis patients[72]. Co-cultures of MSCs with peripheral blood mononuclear cells (PBMCs) cause a decrease in orphan nuclear receptor gamma (ROR-γ), which is involved in Th17 differentiation and is expressed in PBMCs[72]. MSCs produce TGF-β and interleukin-6 (IL-6) and regulate the differentiation of T cells into regulatory T cells or Th17 cells[73]. Therefore, the immune response may be regulated by MSCs *via* Th17 signaling.

MSCs have also been applied as novel vaccine platforms[43]. MSC vaccination strategies include the modified application of MSCs in anti-microbial or cancer immunization[43]. Genetically modified MSCs may act as antigen presenters or mediators as well as suppliers of immune-related cytokines[43]. MSCs from the placenta are known to suppress allogeneic umbilical cord blood lymphocyte proliferation[74], and it has been suggested that placenta-derived MSCs may be applied in allograft transplantations[74]. The immunomodulatory properties of equine adult-derived MSCs derived from bone marrow, adipose tissue, umbilical cord blood and umbilical cord tissue have been compared, and it was revealed that lymphocyte proliferation is suppressed by MSCs and secretion of prostaglandin E2 and IL-6 is increased upon allogenic PBMC or phytohemagglutinin stimulation[75]. MSCs also decrease the production of tumor necrosis factor-α and interferon-γ[75]. The immunomodulatory effect of MSCs on B and T cells have also been studied[76]. One of the main roles of MSCs on B cells is the inhibition of B cell proliferation, but their effects on B cells are still controversial[76]. The MSC-induced regulation of the proliferative response of lymphocytes has been reported to be independent of the major histocompatibility complex,

although MSCs mainly induce inhibition and sometimes cause enhancement of the mixed-lymphocyte reaction[77].

MSC GENE EXPRESSION

MSCs have a variety of gene expression profiles during their developmental stages. Gene expression of MSCs differentiating into adipocytes has been investigated and adenomatosis polyposis coli down-regulated-1 (*APCDD1*), chitinase 3-like 1 (cartilage glycoprotein-39) (*CHI3L1*), retinoic acid receptor responder (tazarotene induced 1) (*RARRES1*) and sema domain, immunoglobulin domain (*Ig*), short basic domain, secreted, (semaphorin) 3G (*SEMA3G*) have been identified as potential adipogenic-specific genes[78]. The expression of these genes is regulated in a time-dependent manner during adipogenesis[78]. During *in vitro* adipogenic and osteogenic differentiation of MSCs, various genes alter their mRNA expression[79]. Genes related to cell proliferation and cytoskeleton organization are activated during the osteogenic differentiation of MSCs, whereas genes in PPAR signaling are regulated during the adipogenic differentiation of MSCs[79].

The gene expression signature is used for the prediction of disease progression or cancer phenotype. The gene expression of patients with breast cancer has been analyzed, and the disease outcomes of young patients have been profiled using predictors[80]. In anticancer drug discovery, gene expression profiling has been performed on colon cancer cell lines[81]. MSCs with migration capacity have been used in anti-tumor therapy and must be examined carefully for safety and efficacy[82]. The gene expression of pluripotency-related genes have been examined in MSCs derived from bone marrow, adipocytes, amniotic membrane and epithelial endometrium-derived stem cells and stroma endometrium-derived stem cells, and these studies suggest that pluripotency-related gene expression varies in different tissues[82]. Xenograft imaging of mice differentiates between the gene expression patterns of human MSCs and human iPSCs, and the tumor sizes of tumor xenografts of iPSCs are larger than those of MSCs, indicating differences in the migration capacity of MSCs and iPSCs[82]. Comparison of phenotypic markers and the neural differentiation capacity of MSCs and multipotent adult progenitor cells has been analyzed, and MSCs expressing CD44, CD73 and CD105 have a higher differentiation capacity into neuro-ectodermal lineages than multipotent adult progenitor cells[83].

The miRNA expression in adipose-derived MSCs has been analyzed, and miR-27b has been identified to be involved in the tolerogenic response[84]; moreover, it was stated that miR-27b is associated with cell differentiation function[84]. Another study has revealed that miR-574-3p, which is regulated with Sox9, inhibits the chondrogenic differentiation of MSCs[85]. The expression of miRNAs, such as the miR-30 family, let-7 family, miR-21, miR-16, miR-155, miR-322 and Snord85, is regulated during the osteoblastic and osteocytic differentiation of MSCs[86]. These miRNAs are thought to target osteogenic differentiation-, stemness-, epigenetics- and cell cycle-related mRNAs[86]. The effects of the mechanical stimulation of MSCs that are seeded on calcium phosphate cement have been analyzed, and it was found that a small number of immediate-early response genes that were associated with transcription were activated[87].

MSC PROTEIN EXPRESSION

Protein expression in MSCs has been investigated in various experimental systems. Rat oligodendroglial cell maturation is promoted by MSC-derived soluble factors and induces an increase in myelin expression and a decrease in glial fibrillary acidic protein expression[88]. In thyroid hormone-induced hypertrophy in MSC chondrogenesis, bone morphogenetic protein-4 (BMP4) is up-regulated; therefore, BMP4 signaling is suggested to be involved[89]. These investigations may provide useful insights into the application of chondrogenic-differentiated MSCs[90]. MSCs exhibit biocompatibility and favorable responses towards the fibronectin-gold nanocomposite film coating that is used in cardiovascular devices[90]. MSCs on fibronectin-gold nanocomposites increase the protein expression levels of matrix metalloproteinase-9 and endothelial nitric oxide synthase[90]. Fibronectin expression has also been linked to MSC lung adherence[91]. In breast and prostate tumors, MSCs promote the growth and angiogenesis of tumors *via* the expression of pro-angiogenic factors associated with neovascularization, such as macrophage inflammatory protein-2, vascular endothelial growth factor, TGF-β and IL-6[92]. In the tissue engineering of articular cartilage, chondrocytes from healthy-donor-derived MSCs exhibit similar properties to those of osteoarthritis joints[93]. Specifically, chondrocytes from MSCs and osteoarthritis joints contain hyaline cartilage-specific type II and fibrocartilage-specific type I collagen[93]. Differentiated MSCs have increased chitinase family glycoprotein YKL-40 protein levels, and considering that the mRNA of YKL-40 is expressed in undifferentiated MSCs, the regulation between the mRNA and protein levels would be interesting to investigate[94]. The Fas ligand (FasL) plays an important role in regulating the determination of MSC fates into proliferation or adipogenic differentiation[95]. Low levels of FasL induce proliferation, whereas high levels inhibit adipogenic differentiation[95]. Adhesion and osteogenic differentiation of animal, serum-free, expanded MSCs are promoted by laminin-5 and type I collagen[96]; therefore, these proteins may be considered for the application of the *in vitro* proliferation of MSCs in animal serum-free conditions[96]. MSCs are committed to adipogenic differentiation under protein malnutrition conditions when PPAR-γ protein and mRNA levels increase[97]. Furthermore, MSCs decrease the levels of TGF-β1 in microglia/macrophages after stroke, and this is followed by a decrease in the levels of plasminogen activator inhibitor 1 in astrocytes[98].

Upon the isolation of MSCs from bone marrow, surface antigens, such as CD10, CD73, CD140b, CD146, GD2 and CD271, can be used as MSC markers[99]. In

addition to those antigens, pluripotency-related proteins, such as Oct4, Nanog and SSEA-4, have been identified to distinguish cellular populations in the human trabecular bone and bone marrow[99]. Another report has shown that the transcription factor Ebf2 in adult bone marrow is useful for distinguishing between MSC or mesenchymal progenitor-like cell phenotypes[100].

CANCER SIGNALING IN MSCS

Cancer is maintained by cancer stem cells (CSCs), which emphasizes the importance of the identification, targeting and elimination of these types of cells[101]. The initiation of cancer is thought to occur by the activation of self-renewal mechanisms that are usually restricted to stem cells[101]. Cancer cells showing CSC-like phenotypes may remain in the stem-cell state and tend to avoid cancer differentiation. Cancers exhibiting epithelial CSC-like phenotypes have an increased probability of migration and death, which indicates the possibility of epithelial CSC-like phenotypes as diagnosis predictors for cancer. This phenotype factor is shown to be independent from usual cancer diagnosis factors, such as patient age, cancer diameter, cancer progression, estrogen receptor status, lymphoid node status and blood vessel infiltration. A portion of these cells in cancer may be involved in initiation and infinite cancer proliferation[101].

CD44, which is proposed to be a tumor-initiating marker for glioma sphere cultures, has been shown to be a mesenchymal signature because mesenchymal-differentiated glioma sphere cultures have radiation resistance and include a CD44 subpopulation[102]. Recent studies demonstrate that MSCs play an important role in the formation of CSCs[103].

It is known that subunits of the polycomb repressor complex (PRC), such as BMI1 polycomb ring finger oncogene, are associated with the epithelial-mesenchymal transition, cancer progression and stem-like expression profile[104-106]. PRC2 is involved in the regulation of gene repression through chromatin modifications and is thought to be important in stem cells[107-109]. A recent study in *Drosophila* has shown that a mutation in lysine 27 of histone H3 causes the same phenotype as flies, with a loss of PRC2, which indicates that the methylation of lysine 27 of histone H3 is important for PRC function[110]. The role of chromatin regulation in CSCs will be investigated in the future.

Great efforts to understand CSCs have revealed the feature of CSCs as specific cell populations in brain, skin and intestinal tumors and the possibility of effective treatments by targeting these cells[111-114]. The markers for CSCs have been identified and include aldehyde dehydrogenase 1 (ALDH1), CD24, CD44, CD90, CD133, Hedgehog-Gli activity and α6-integrin in breast cancer as well as ABCB5, ALDH1, β-catenin activity, CD24, CD26, CD29, CD44, CD133, CD166 and leucine-rich repeat containing G protein-coupled receptor 5 in colon cancer[115].

CONCLUSION

In summary, MSCs play important roles in cell life. MSCs differentiate into various cell types, and their many applications, such as for disease treatment, are being studied. Further investigation of the MSC phenotypes is needed for the development of the safe and effective application of MSCs.

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