International Journal of Nanomedicine

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REVIEW

Stem Cell Mimicking Nanoencapsulation for Targeting Arthritis

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Abstract: Mesenchymal stem cells (MSCs) are considered a promising regenerative therapy due to their ability to migrate toward damaged tissues. The homing ability of MSCs is unique compared with that of non-migrating cells and MSCs are considered promising therapeutic vectors for targeting major cells in many pathophysiological sites. MSCs have many advantages in the treatment of malignant diseases, particularly rheumatoid arthritis (RA). RA is a representative autoimmune disease that primarily affects joints, and secreted chemokines in the joints are well recognized by MSCs following their migration to the joints. Furthermore, MSCs can regulate the inflammatory process and repair damaged cells in the joints. However, the functionality and migration ability of MSCs injected in vivo still show insufficient. The targeting ability and migration efficiency of MSCs can be enhanced by genetic engineering or modification, eg, overexpressing chemokine receptors or migration-related genes, thus maximizing their therapeutic effect. However, there are concerns about genetic changes due to the increased probability of oncogenesis resulting from genome integration of the viral vector, and thus, clinical application is limited. Furthermore, it is suspected that administering MSCs can promote tumor growth and metastasis in xenograft and orthotopic models. For this reason, MSC mimicking nanoencapsulations are an alternative strategy that does not involve using MSCs or bioengineered MSCs. MSC mimicking nanoencapsulations consist of MSC membrane-coated nanoparticles, MSC-derived exosomes and artificial ectosomes, and MSC membrane-fused liposomes with natural or genetically engineered MSC membranes. MSC mimicking nanoencapsulations not only retain the targeting ability of MSCs but also have many advantages in terms of targeted drug delivery. Specifically, MSC mimicking nanoencapsulations are capable of encapsulating drugs with various components, including chemotherapeutic agents, nucleic acids, and proteins. Furthermore, there are fewer concerns over safety issues on MSC mimicking nanoencapsulations associated with mutagenesis even when using genetically engineered MSCs, because MSC mimicking nanoencapsulations use only the membrane fraction of MSCs. Genetic engineering is a promising route in clinical settings, where nano-encapsulated technology strategies are combined. In this review, the mechanism underlying MSC homing and the advantages of MSC mimicking nanoencapsulations are discussed. In addition, genetic engineering of MSCs and MSC mimicking nanoencapsulation is described as a promising strategy for the treatment of immune-related diseases.

Keywords: stem cell migration, stem cell mimicking nanoencapsulations, autoimmune disease targeting strategy, exosomes, ectosomes, liposomes

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Introduction

Given the multi-lineage differentiation abilities of mesenchymal stem cells (MSCs) isolated from different tissues and organs, MSCs have been widely used in various

Received: 14 August 2021
Accepted: 5 December 2021
Published: 31 December 2021

medical fields, particularly regenerative medicine.[1–3] The representative sources of MSCs are bone marrow, adipose, periodontal, muscle, and umbilical cord blood.[4–10] Interestingly, slight differences have been reported in the characteristics of MSCs depending on the different sources, including their population in source tissues, immunosuppressive activities, proliferation, and resistance to cellular aging.[11] Bone marrow-derived MSCs (BM-MSCs) are the most intensively studied and show clinically promising results for cartilage and bone regeneration.[11] However, the isolation procedures for BM-MSCs are complicated because bone marrow contains a relatively small fraction of MSCs (0.001–0.01% of the cells in bone marrow).[12] Furthermore, bone marrow aspiration to harvest MSCs in human bones is a painful procedure and the slower proliferation rate of BM-MSCs is a clinical limitation.[13] In comparison with BM-MSCs, adipose-derived MSCs (AD-MSCs) are relatively easy to collect and can produce up to 500 times the cell population of BM-MSCs.[14] AD-MSCs showed a greater ability to regenerate damaged cartilage and bone tissues with increased immunosuppressive ability.[14,15] Umbilical cord blood-derived MSCs (UC-MSCs) proliferate faster than BM-MSCs and are resistant to significant cellular aging.[11]

MSCs have been investigated and gained worldwide attention as potential therapeutic candidates for incurable diseases such as arthritis, spinal cord injury, and cardiac disease.[3,16–23] In particular, the inherent tropism of MSCs to inflammatory sites has been thoroughly studied.[24] This inherent tropism, also known as homing ability, originates from the recognition of various chemokine sources in inflamed tissues, where profiled chemokines are continuously secreted and the MSCs migrate to the chemokines in a concentration-dependent manner.[24] Rheumatoid arthritis (RA) is a representative inflammatory disease that primarily causes inflammation in the joints, and this long-term autoimmune disorder causes worsening pain and stiffness following rest. RA affects approximately 24.5 million people as of 2015, but only symptomatic treatments such as pain medications, steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs), or slow-acting drugs that inhibit the rapid progression of RA, such as disease-modifying antirheumatic drugs (DMARDs) are currently available. However, RA drugs have adverse side effects, including hepatitis, osteoporosis, skeletal fracture, steroid-induced arthroplasty, Cushing's syndrome, gastrointestinal (GI) intolerance, and bleeding.[25–27] Thus, MSCs are rapidly emerging as the next generation of arthritis treatment because they not only recognize and migrate toward chemokines secreted in the inflamed joints but also regulate inflammatory progress and repair damaged cells.[28]

However, MSCs are associated with many challenges that need to be overcome before they can be used in clinical settings.[29–31] One of the main challenges is the selective accumulation of systemically administered MSCs in the lungs and liver when they are administered intravenously, leading to insufficient concentrations of MSCs in the target tissues.[32,33] In addition, most of the administered MSCs are typically initially captured by macrophages in the lungs, liver, and spleen.[32–34] Importantly, the viability and migration ability of MSCs injected in vivo differed from results previously reported as favorable therapeutic effects and migration efficiency in vitro.[35]

To improve the delivery of MSCs, researchers have focused on chemokines, which are responsible for MSCs' ability to move.[36] The chemokine receptors are the key proteins on MSCs that recognize chemokines, and genetic engineering of MSCs to overexpress the chemokine receptor can improve the homing ability, thus enhancing their therapeutic efficacy.[37] Genetic engineering is a convenient tool for modifying native or non-native genes, and several technologies for genetic engineering exist, including genome editing, gene knockdown, and replacement with various vectors.[38,39] However, safety issues that prevent clinical use persist, for example, genome integration, off-target effects, and induction of immune response.[40] In this regard, MSC mimicking nanoencapsulations can be an alternative strategy for maintaining the homing ability of MSCs and overcoming the current safety issues.[41–43] Nanoencapsulation involves entrapping the core nanoparticles of solids or liquids within nanometer-sized capsules of secondary materials.[44]

MSC mimicking nanoencapsulation uses the MSC membrane fraction as the capsule and targeting molecules, that is chemokine receptors, with several types of nanoparticles, as the core.[45,46] MSC mimicking nanoencapsulation consists of MSC membrane-coated nanoparticles, MSC-derived artificial ectosomes, and MSC membrane-fused liposomes. Nano drug delivery is an emerging field that has attracted significant interest due to its unique characteristics and paved the way for several unique applications that might solve many problems in medicine. In particular, the nanoscale size of nanoparticles (NPs) enhances cellular uptake and can optimize intracellular pathways due to their intrinsic physicochemical properties, and can therefore increase drug delivery to target tissues.[47,48] However, the

inherent targeting ability resulting from the physicochemical properties of NPs is not enough to target specific tissues or damaged tissues, and additional studies on additional ligands that can bind to surface receptors on target cells or tissues have been performed to improve the targeting ability of NPs.[49] Likewise, nanoencapsulation with cell membranes with targeting molecules and encapsulation of the core NPs with cell membranes confer the targeting ability of the source cell to the NPs.[50,51] Thus, MSC mimicking nanoencapsulation can mimic the superior targeting ability of MSCs and confer the advantages of each core NP. In addition, MSC mimicking nanoencapsulations have improved circulation time and camouflaging from phagocytes.[52]

This review discusses the mechanism of MSC migration to inflammatory sites, addresses the potential strategy for improving the tropism of MSCs using genetic engineering, and discusses the promising therapeutic agent, MSC mimicking nanoencapsulations.

MSC Homing, Migratory Ability, and Genetic Engineering

The MSC migration mechanism can be exploited for diverse clinical applications.[53] The MSC migration mechanism can be divided into five stages: rolling by selectin, activation of MSCs by chemokines, stopping cell rolling by integrin, transcellular migration, and migration to the damaged site (Figure 1).[54,55] Chemokines are secreted naturally by various cells such as tumor cells, stromal cells, and inflammatory cells, maintaining high chemokine concentrations in target cells at the target tissue and inducing signal cascades.[56–58] Likewise, MSCs express a variety of chemokine receptors, allowing them to migrate and be used as new targeting vectors.[59–61] MSC migration accelerates depending on the concentration of chemokines, which are the most important factors in the stem cell homing mechanism.[62,63] Chemokines consist of various cytokine subfamilies that are closely associated with the migration of immune cells. Chemokines are divided into four classes based on the locations of the two cysteine (C) residues: CC-chemokines, CXC-chemokine, C-chemokine, and CX3 Chemokine.[64,65] Each chemokine binds to various MSC receptors and the binding induces a chemokine signaling cascade (Table 1).[56,66]

Mechanisms of MSC Homing

The mechanisms underlying MSC and leukocyte migration are similar in terms of their migratory dynamics.[55] P-selectin glycoprotein ligand-1 (PSGL-1) and E-selectin ligand-1 (ESL-1) are major proteins involved in leukocyte migration that interact with P-selectin and E-selectin present in vascular endothelial cells. However, these promoters are not present in MSCs (Figure 2).[53,67]

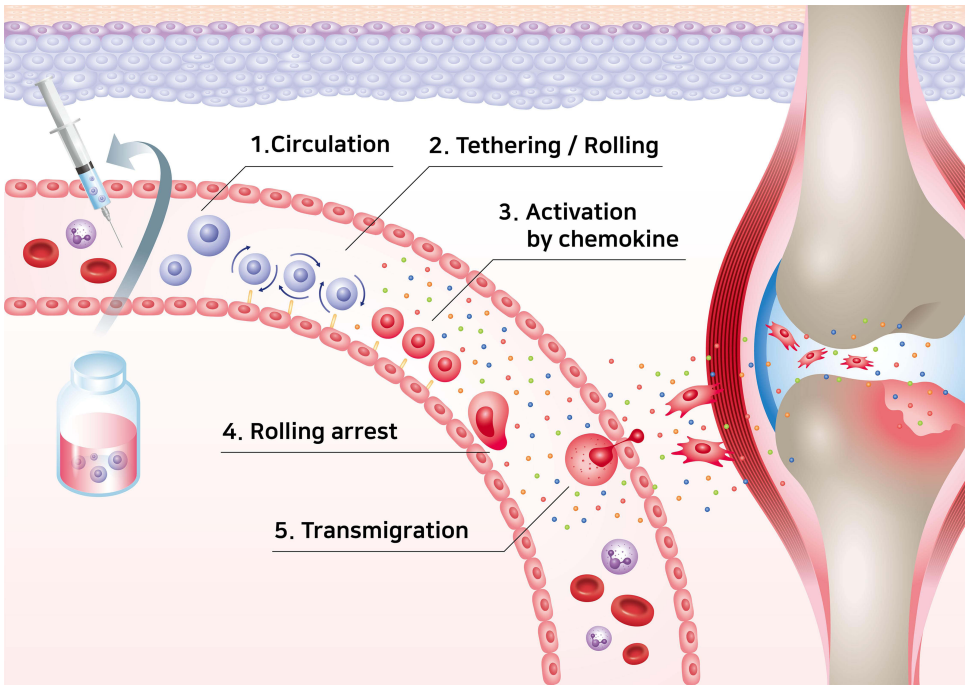

Figure 1 Representation of stem cell homing mechanism.

Table 1 Chemokine and Chemokine Receptors for Different Chemokine Families

Chemokine Family	Chemokine Receptor	Chemokine
CC-family	CCR1 (CD191)	CCL3, CCL4, CCL5, CCL7, CCL8, CCL13, CCL14, CCL15, CCL16, CCL23
	CCR2 (CD192)	CCL2, CCL7, CCL8, CCL13, CCL16
	CCR3 (CD193)	CCL4, CCL5, CCL7, CCL11, CCL24, CCL8, CCL13, CCL15, CCL16, CCL23, CCL26, CCL28
	CCR4 (CD194, CNOT6)	CCL3, CCL5, CCL17, CCL22
	CCR5 (CD195)	CCL2, CCL3, CCL4, CCL5, CCL8, CCL11, CCL13, CCL14, CCL16
	CCR6 (CD196)	CCL20
	CCR7 (CD197)	CCL19, CCL21
	CCR8 (CDw198)	CCL1, CCL4, CLL16, CCL17, CCL18
	CCR9 (CDw199)	CCL25
	CCR10 (GPR2)	CCL27, CCL28
CXC-Family	CXCR1 (CD181, IL-8RA)	CXCL1, CXCL7, CXCL8, CXCL6
	CXCR2 (IL-8RB)	CXCL1, CXCL2, CXCL3, CXCL5, CXCL7, CXCL8, CXCL6
	CXCR3 (GPR9, CD183)	CXCL9, CXCL10, CXCL11, CXCL4, CXCL13
	CXCR4 (CD184)	CXCL12
	CXCR5 (BLR1, CD185)	CXCL13
	CXCR6 (BONZO, CD186)	CXCL16
	CXCR7 (GPR159, ACKR3)	CXCL12, CXCL11
C-family	XCR1 (GPF5)	XCL1, XCL2
CX3-C-family	CX3CR1 (GPR13)	CX3CL1
	Unknow	CXCL14, CXCL17

Abbreviations: CC-family, cistain cistain chamokine structure; CXC-family, cistain one amino acid cistain chemokine structure; C-family, cistain chemokine structure; CX3-C-family, cistain three amino acid cistain structure.

The initial rolling is facilitated by selectins expressed on the surface of endothelial cells. Various glycoproteins on the surface of MSCs can bind to the selectins and continue the rolling process.[68] However, the mechanism of binding of the glycoprotein on MSCs to the selectins is still unclear.[69,70] P-selectins and E-selectins, major cell-cell adhesion molecules expressed by endothelial cells, adhere to migrated cells adjacent to endothelial cells and can trigger the rolling process.[71] For leukocyte migration, P-selectin glycoprotein ligand-1 (PSGL-1) and E-selectin ligand-1 (ESL-1) expressed on the membranes of leukocytes interact with P-selectins and E-selectins on the endothelial cells, initiating the process.[72,73] As already mentioned, MSCs express neither PSGL-1 nor ESL-1. Instead, they express galectin-1 and CD24 on their surfaces, and these bind to E-selectin or P-selectin (Figure 2).[74–76]

In the migratory activation step, MSC receptors are activated in response to inflammatory cytokines, including CXCL12, CXCL8, CXCL4, CCL2, and CCL7.[77] The corresponding activation of chemokine receptors of MSCs in response to inflammatory cytokines results in an accumulation of MSCs.[58,78] For example, inflamed tissues release inflammatory cytokines,[79] and specifically, fibroblasts release CXCL12, which further induces the accumulation of MSCs through ligand–receptor interaction after exposure to hypoxia and cytokine-rich environments in the rat model of inflammation.[79–82] Previous studies have reported that overexpressing CXCR4, which is a receptor to recognize CXCL12, in MSCs improves the homing ability of MSCs toward inflamed sites.[83,84] In short, cytokines are significantly involved in the homing mechanism of MSCs.[53]

The rolling arrest stage is facilitated by integrin α4β1 (VLA-4) on MSC.[85] VLA-4 is expressed by MSCs which are first activated by CXCL-12 and TNF-α chemokines, and activated VLA-4 binds to VCAM-1 expressed on endothelial cells to stop the rotational movement (Figure 2).[86,87]

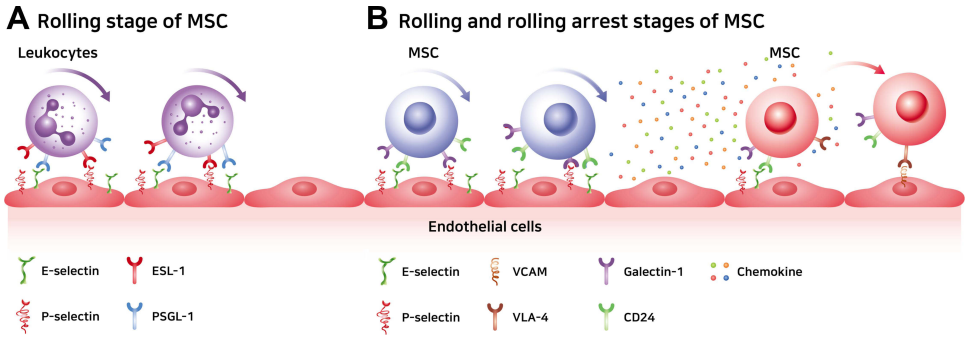

Figure 2 Differences in adhesion protein molecules between leukocytes and mesenchymal stem cells during rolling stages and rolling arrest stage of MSC. (**A**) The rolling stage of leukocytes starts with adhesion to endothelium with ESL-1 and PSGL-1 on leukocytes. (**B**) The rolling stage of MSC starts with the adhesion to endothelium with Galectin-1 and CD24 on MSC, and the rolling arrest stage was caused by chemokines that were encountered in the rolling stage and VLA-4 with a high affinity for VACM present in endothelial cells.
Abbreviations: ESL-1, E-selectin ligand-1; PSGL-1, P-selectin glycoprotein ligand-1 VLA-4, very late antigen-4; VCAM, vascular cell adhesion molecule-1.

Karp et al categorized the migration of MSCs as either "systemic homing" or "non-systemic homing." Systemic homing refers to the process of migration through blood vessels and then across the vascular endothelium near the inflamed site.[67,88] The process of migration after passing through the vessels or local injection is called non-systemic homing. In non-systemic migration, stem cells migrate through a chemokine concentration gradient (Figure 3).[89] MSCs secrete matrix metalloproteinases (MMPs) during migration. The mechanism underlying MSC migration is currently undefined but MSC migration can be advanced by remodeling the matrix through the secretion of various enzymes.[90–93] The migration of MSCs to the damaged area is induced by chemokines released from the injured site, such as IL-8, TNF-α, insulin-like growth factor (IGF-1), and platelet-derived growth factors (PDGF).[94–96] MSCs migrate toward the damaged area following a chemokine concentration gradient.[87]

Migratory Ability of MSCs to Arthritis

RA is a chronic inflammatory autoimmune disease characterized by distinct painful stiff joints and movement disorders.[97] RA affects approximately 1% of the world's population.[98] RA is primarily induced by macrophages, which are involved in the innate immune response and are also involved in adaptive immune responses, together

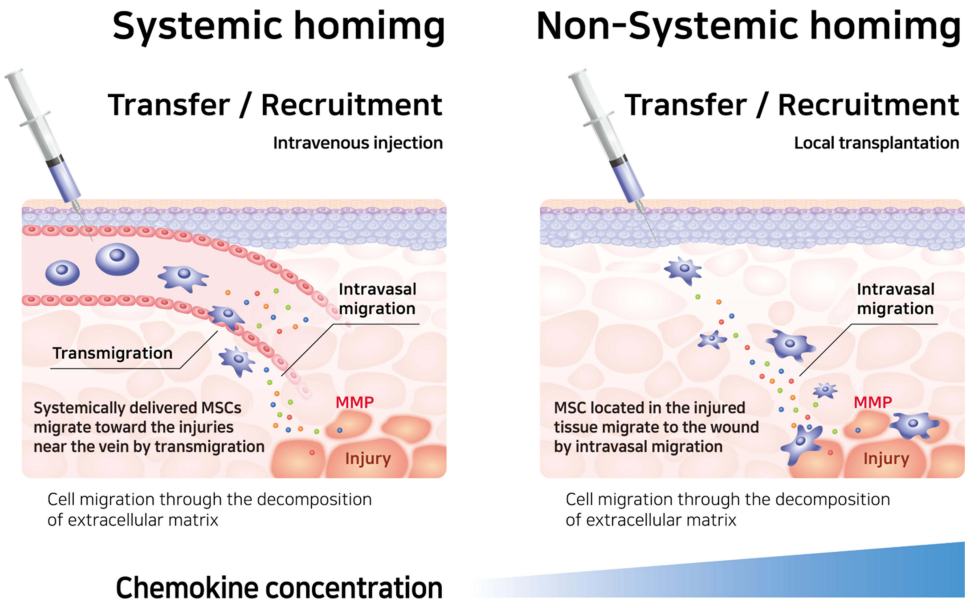

Figure 3 Differences between systemic and non-systemic homing mechanisms. Both systemic and non-systemic homing to the extracellular matrix and stem cells to their destination, MSCs secrete MMPs and remodel the extracellular matrix.
Abbreviation: MMP, matrix metalloproteinase.

with B cells and T cells.[99] Inflammatory diseases are caused by high levels of inflammatory cytokines and a hypoxic low-pH environment in the joints.[100,101] Fibroblast-like synoviocytes (FLSs) and accumulated macrophages and neutrophils in the synovium of inflamed joints also express various chemokines.[102,103] Chemokines from inflammatory reactions can induce migration of white blood cells and stem cells, which are involved in angiogenesis around joints.[101,104,105] More than 50 chemokines are present in the rheumatoid synovial membrane (Table 2). Of the chemokines in the synovium, CXCL12, MIP1-a, CXCL8, and PDGF are the main ones that attract MSCs.[106] In the RA environment, CXCL12, a ligand for CXCR4 on MSCs, had 10.71 times higher levels of chemokines than in the normal synovial cell environment. MIP-1a, a chemokine that gathers inflammatory cells, is a ligand for CCR1, which is normally expressed on MSC.[107,108] CXCL8 is a ligand for CXCR1 and CXCR2 on MSCs and induces the migration of neutrophils and macrophages, leading to ROS in synovial cells.[59] PDGF is a regulatory peptide that is upregulated in the synovial tissue of RA patients.[109] PDGF induces greater MSC migration than CXCL12.[110] Importantly, stem cells not only have the homing ability to inflamed joints but also have potential as cell therapy with the anti-apoptotic, anti-catabolic, and anti-fibrotic effect of MSC.[111] In preclinical trials, MSC treatment has been extensively investigated in collagen-induced arthritis (CIA), a common autoimmune animal model used to study RA. In the RA model, MSCs downregulated inflammatory cytokines such as IFN-γ, TNF-α, IL-4, IL-12, and IL1β, and antibodies against collagen, while anti-inflammatory cytokines, such as tumor necrosis factor-inducible gene 6 protein (TSG-6), prostaglandin E2 (PGE2), transforming growth factor-beta (TGF-β), IL-10, and IL-6, were upregulated.[112–116]

Genetically Engineered MSCs Targeting Arthritis

Genetic engineering can improve the therapeutic potential of MSCs, including long-term survival, angiogenesis, differentiation into specific lineages, anti- and pro-inflammatory activity, and migratory properties (Figure 4).[117,118] Although MSCs already have an intrinsic homing ability, the targeting ability of MSCs and their derivatives, such as membrane vesicles, which are utilized to produce MSC mimicking nanoencapsulation, can be enhanced.[118] The therapeutic potential of MSCs can be magnified by reprogramming MSCs via upregulation or downregulation of their native genes, resulting in controlled production of the target protein, or by introducing foreign genes that enable MSCs to express native or non-native products, for example, non-native soluble tumor necrosis factor (TNF) receptor 2 can inhibit TNF-alpha signaling in RA therapies.[28]

MSCs can be genetically engineered using different techniques, including by introducing particular genes into the nucleus of MSCs or editing the genome of MSCs (Figure 5).[119] Foreign genes can be transferred into

Table 2 Rheumatoid Arthritis (RA) Chemokines Present in the Pathological Environment and Chemokine Receptors Present in Mesenchymal Stem Cells

Chemokine Family	Chemokine Receptor on MSCs	Chemokine in Inflamed Joint with RA
CC-Chemokine receptor	CCR1 CCR2 CCR3 CCR4 CCR5 CCR7 CCR9	CCL3, CCL5, CCL7, CCL14, CCL15, CCL16 CCL2, CCL7, CCL16 CCL5, CCL7, CCL8, CCL15 CCL17 CCL3, CCL5, CCL8, CCL14 CCL21 x
CXC-Chemokine receptor	CXCR3 CXCR4 CXCR5 CXCR6	CXCL4, CXCL9, CXCL10 CXCL12 CXCL13 CXCL16
CX3C-chemokine receptor	CX3CR1 (GPR13)	CX3CL1
Nonbinding Chemokine	x	XCL1, CXCL8, CCL20, CXCL11, CXCL1, CXCL5, CXCL7, CXCL6

Abbreviations: CC-family, cistain cistain chemokine structure; CXC-family, cistain one amino acid cistain chemokine structure; CX3-C-family, cistain three amino acid cistain structure.

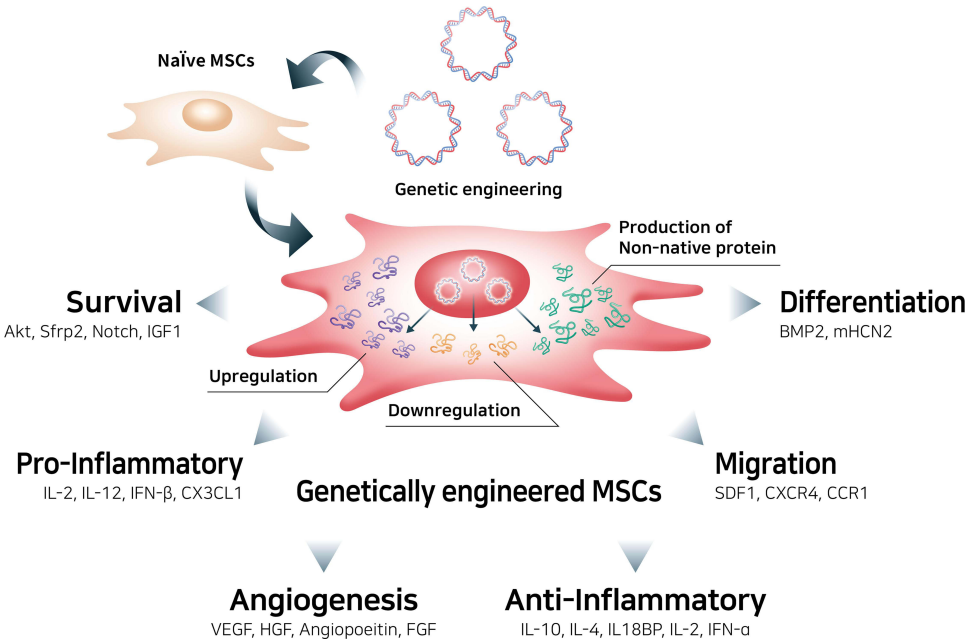

Figure 4 Genetic engineering of mesenchymal stem cells to enhance therapeutic efficacy.
Abbreviations: Sfrp2, secreted frizzled-related protein 2; IGF1, insulin-like growth factor 1; IL-2, interleukin-2; IL-12, interleukin-12; IFN-β, interferon-beta; CX3CL1, C-X3-C motif chemokine ligand 1; VEGF, vascular endothelial growth factor; HGF, human growth factor; FGF, fibroblast growth factor; IL-10, interleukin-10; IL-4, interleukin-4; IL18BP, interleukin-18-binding protein; IFN-α, interferon-alpha; SDF1, stromal cell-derived factor 1; CXCR4, C-X-C motif chemokine receptor 4; CCR1, C-C motif chemokine receptor 1; BMP2, bone morphogenetic protein 2; mHCN2, mouse hyperpolarization-activated cyclic nucleotide-gated.

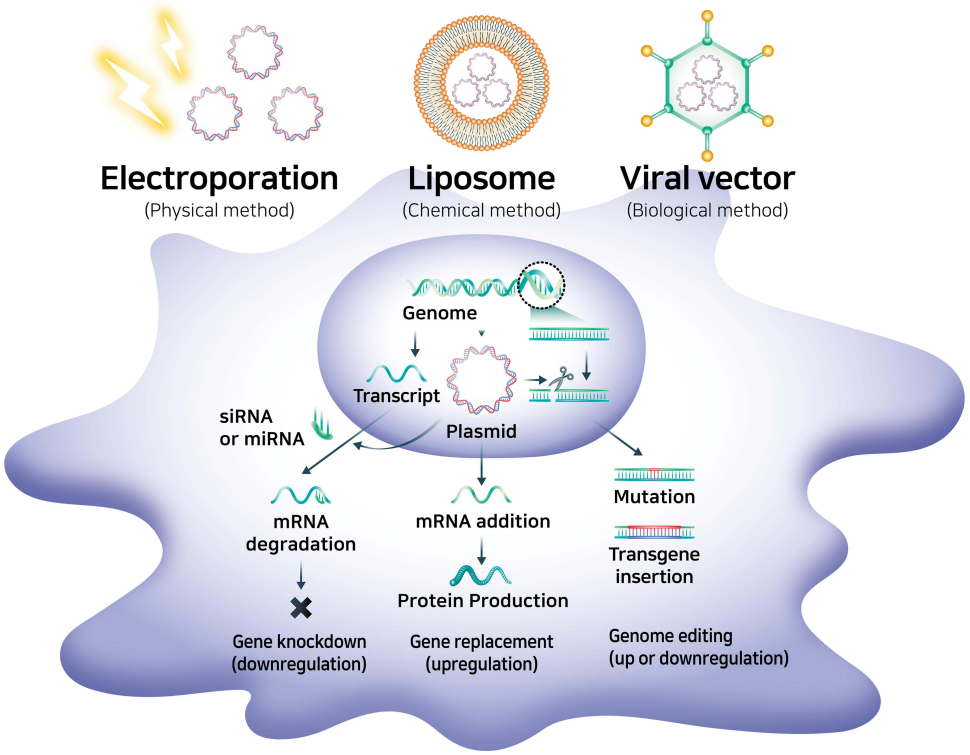

Figure 5 Genetic engineering techniques used in the production of bioengineered mesenchymal stem cells.

MSCs using liposomes (chemical method), electroporation (physical method), or viral delivery (biological method). Cationic liposomes, also known as lipoplexes, can stably compact negatively charged nucleic acids, leading to the formation of nanomeric vesicular structure.[120] Cationic liposomes are commonly produced with a combination of a cationic lipid such as DOTAP, DOTMA, DOGS, DOSPA, and neutral lipids, such as DOPE and cholesterol.[121] These liposomes are stable enough to protect their bound nucleic acids from degradation and are competent to enter cells via endocytosis.[120] Electroporation briefly creates holes in the cell membrane using an electric field of 10–20 kV/cm, and the holes are then rapidly closed by the cell's membrane repair mechanism.[122] Even though the electric shock induces irreversible cell damage and non-specific transport into the cytoplasm leads to cell death, electroporation ensures successful gene delivery regardless of the target cell or organism. Viral vectors, which are derived from adenovirus, adeno-associated virus (AAV), or lentivirus (LV), have been used to introduce specific genes into MSCs. Recombinant lentiviral vectors are the most widely used systems due to their high tropism to dividing and non-dividing cells, transduction efficiency, and stable expression of transgenes in MSCs, but the random genome integration of transgenes can be an obstacle in clinical applications.[123] Adenovirus and AAV systems are appropriate alternative strategies because currently available strains do not have broad genome integration and a strong immune response, unlike LV, thus increasing success and safety in clinical trials.[124] As a representative, the Oxford-AstraZeneca COVID-19 vaccine, which has been authorized in 71 countries as a vaccine for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which spread globally and led to the current pandemic, transfers the spike protein gene using an adenovirus-based viral vector.[125] Furthermore, there are two AAV-based gene therapies: Luxturna for rare inherited retinal dystrophy and Zolgensma for spinal muscular atrophy.[126]

Clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 were recently used for genome editing and modification because of their simpler design and higher efficiency for genome editing, however, there are safety issues such as off-target effects that induce mutations at sites other than the intended target site.[127] The foreign gene is then commonly transferred into non-integrating forms such as plasmid DNA and messenger RNA (mRNA).[128]

The gene expression machinery can also be manipulated at the cytoplasmic level through RNA interference (RNAi) technology, inhibition of gene expression, or translation using neutralizing targeted mRNA molecules with sequence-specific small RNA molecules such as small interfering RNA (siRNA) or microRNA (miRNA).[129] These small RNAs can form enzyme complexes that degrade mRNA molecules and thus decrease their activity by inhibiting translation. Moreover, the pre-transcriptional silencing mechanism of RNAi can induce DNA methylation at genomic positions complementary to siRNA or miRNA with enzyme complexes.

CXC chemokine receptor 4 (CXCR4) is one of the most potent chemokine receptors that is genetically engineered to enhance the migratory properties of MSCs.[130] CXCR4 is a chemokine receptor specific for stromal-derived factor-1 (SDF-1), also known as CXC motif chemokine 12 (CXCL12), which is produced by damaged tissues, such as the area of inflammatory bone destruction.[131] Several studies on engineering MSCs to increase the expression of the CXCR4 gene have reported a higher density of the CXCR4 receptor on their outer cell membrane and effectively increased the migration of MSCs toward SDF-1.[83,132,133] CXC chemokine receptor 7 (CXCR7) also had a high affinity for SDF-1, thus the SDF-1/CXCR7 signaling axis was used to engineer the MSCs.[134] CXCR7-overexpressing MSCs in a cerebral ischemia-reperfusion rat hippocampus model promoted migration based on an SDF-1 gradient, cooperating with the SDF-1/CXCR4 signaling axis (Figure 6).[37]

CXC chemokine receptor 1 (CXCR1) enhances MSC migratory properties.[59] CXCR1 is a receptor for IL-8, which is the primary cytokine involved in the recruitment of neutrophils to the site of damage or infection.[135] In particular, the IL-8/CXCR1 axis is a key factor for the migration of MSCs toward human glioma cell lines, such as U-87 MG, LN18, U138, and U251, and CXCR1-overexpressing MSCs showed a superior capacity to migrate toward glioma cells and tumors in mice bearing intracranial human gliomas.[136]

The migratory properties of MSCs were also controlled via aquaporin-1 (Aqp1), which is a water channel molecule that transports water across the cell membrane and regulates endothelial cell migration.[137] Aqp1-overexpressing MSCs showed enhanced migration to fracture gap of a rat fracture model with upregulated focal

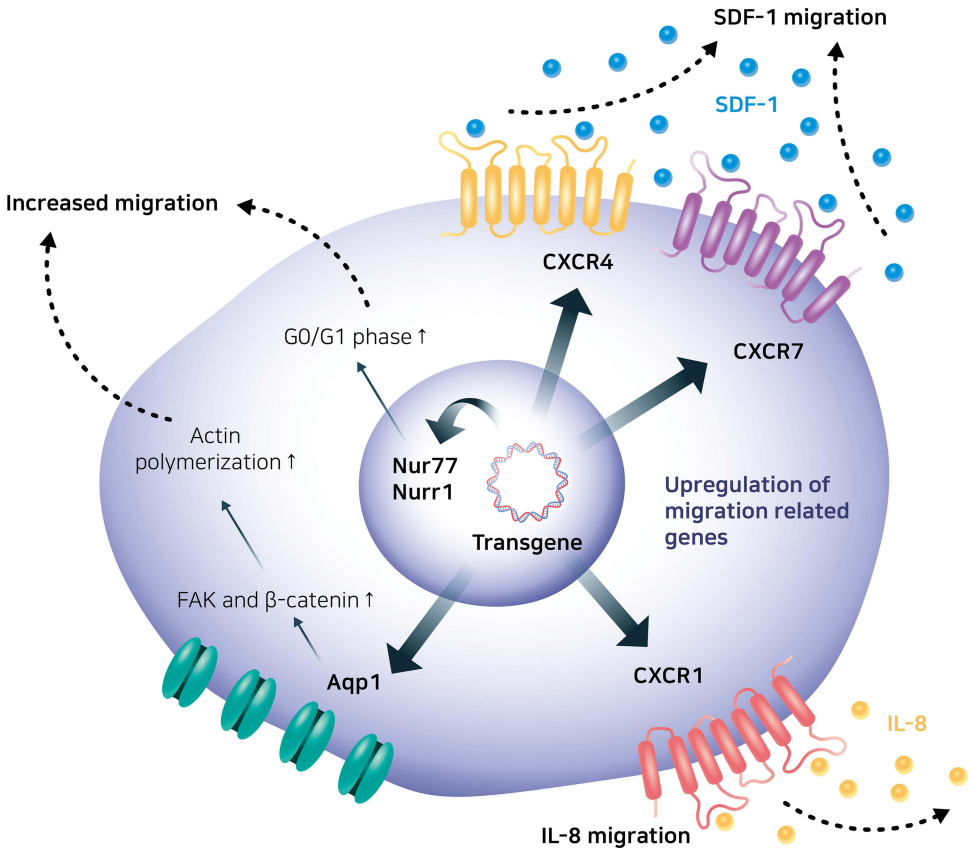

Figure 6 Engineered mesenchymal stem cells with enhanced migratory abilities.
Abbreviations: CXCR4, C-X-C motif chemokine receptor 4; CXCR7, C-X-C motif chemokine receptor 7; SDF1, stromal cell-derived factor 1; CXCR1, C-X-C motif chemokine receptor 1; IL-8, interleukin-8; Aqp1, aquaporin 1; FAK, focal adhesion kinase.

adhesion kinase (FAK) and β-catenin, which are important regulators of cell migration.[138]

Nur77, also known as nerve growth factor IB or NR4A1, and nuclear receptor-related 1 (Nurr1), can play a role in improving the migratory capabilities of MSCs.[139,140] The migrating MSCs expressed higher levels of Nur77 and Nurr1 than the non-migrating MSCs, and overexpression of these two nuclear receptors functioning as transcription factors enhanced the migration of MSCs toward SDF-1. The migration of cells is closely related to the cell cycle, and normally, cells in the late S or G2/M phase do not migrate.[141] The overexpression of Nur77 and Nurr1 increased the proportion of MSCs in the G0/G1-phase similar to the results of migrating MSCs had more cells in the G1-phase.

MSC Mimicking Nanoencapsulation Targeting Arthritis

MSC mimicking nanoencapsulations are nanoparticles combined with MSC membrane vesicles and these NPs have the greatest advantages as drug delivery systems due to the sustained homing ability of MSCs as well as the advantages of NPs. Particles sized 10–150 nm have great advantages in drug delivery systems because they can pass more freely through the cell membrane by the interaction with biomolecules, such as clathrin and caveolin, to facilitate uptake across the cell membrane compared with micron-sized materials.[142,143] Various materials have been used to formulate NPs, including silica, polymers, metals, and lipids.[144,145] NPs have an inherent ability, called "passive targeting," to accumulate at specific sites based on their physicochemical properties such as size, surface charge, surface hydrophilicity, and geometry.[146–148] However, physicochemical properties are not enough to target specific tissues or damaged tissues, and thus "active targeting" is a clinically approved strategy involving the addition of ligands that can bind to surface receptors on target cells or tissues.[149,150] MSC mimicking nanoencapsulation uses natural or genetically engineered MSC membranes to coat synthetic NPs, producing artificial ectosomes and fusing them with liposomes to increase their targeting ability

(Figure 7).[151] Especially, MSCs have been studied for targeting inflammation and regenerative drugs, and the mechanism and efficacy of migration toward inflamed tissues have been actively investigated.[152] MSC mimicking nanoencapsulation can mimic the well-known migration ability of MSCs and can be equally utilized without safety issues from the direct application of using MSCs. Furthermore, cell membrane encapsulations have a wide range of functions, including prolonged blood circulation time and increased active targeting efficacy from the source cells.[153,154] MSC mimicking encapsulations enter recipient cells using multiple pathways.[155] MSC mimicking encapsulations can fuse directly with the plasma membrane and can also be taken up through phagocytosis, micropinocytosis, and endocytosis mediated by caveolin or clathrin.[156] MSC mimicking encapsulations can be internalized in a highly cell type-specific manner that depends on the recognition of membrane surface molecules by the cell or tissue.[157] For example, endothelial colony-forming cell (ECFC)-derived exosomes were shown CXCR4/SDF-1α interaction and enhanced delivery toward the ischemic kidney, and Tspan8-alpha4 complex on lymph node stroma derived extracellular vesicles induced selective uptake by endothelial cells or pancreatic cells with CD54, serving as a major ligand.[158,159] Therefore, different source cells may contain protein signals that serve as ligands for other cells, and these receptor–ligand interactions maximized targeted delivery of NPs.[160] This natural mechanism inspired the application of MSC membranes to confer active targeting to NPs.

MSC Membrane-Coated Nanoparticles Targeting Arthritis

Cell membrane-coated NPs (CMCNPs) are biomimetic strategies developed to mimic the properties of cell membranes derived from natural cells such as erythrocytes, white blood cells, cancer cells, stem cells, platelets, or bacterial cells with an NP core.[161] Core NPs made of polymer, silica, and metal have been evaluated in attempts to overcome the limitations of conventional drug delivery systems but there are also issues of toxicity and reduced biocompatibility associated with the surface properties of NPs.[162,163] Therefore, only a small number of NPs have been approved for medical application by the FDA.[164] Coating with cell membrane can enhance the biocompatibility of NPs by improving immune evasion, enhancing circulation time, reducing RES clearance, preventing serum protein adsorption by mimicking cell glycocalyx, which are chemical determinants of "self" at the surfaces of cells.[151,165] Furthermore, the migratory properties of MSCs can also be transferred to NPs by coating them with the cell membrane.[45] Coating NPs with MSC membranes not only enhances biocompatibility but also maximizes the therapeutic effect of NPs by mimicking the targeting ability of MSCs.[166] Cell membrane-coated NPs are prepared in three steps: extraction of cell membrane

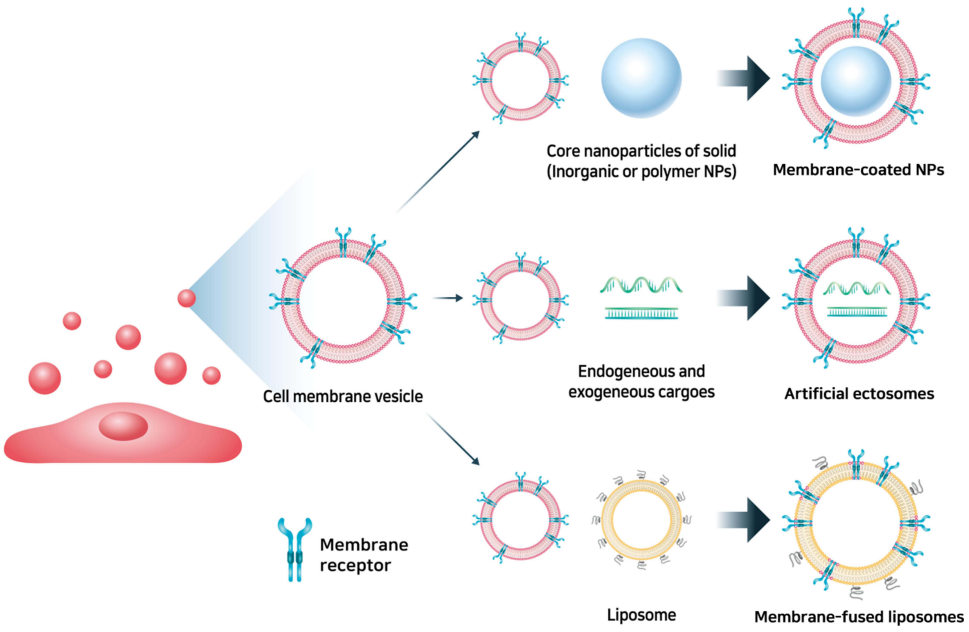

Figure 7 Mesenchymal stem cell mimicking nanoencapsulation.

vesicles from the source cells, synthesis of the core NPs, and fusion of the membrane vesicles and core NPs to produce cell membrane-coated NPs (Figure 8).[167] Cell membrane vesicles, including extracellular vesicles (EVs), can be harvested through cell lysis, mechanical disruption, and centrifugation to isolate, purify the cell membrane vesicles, and remove intracellular components.[168] All the processes must be conducted under cold conditions, with protease inhibitors to minimize the denaturation of integral membrane proteins. Cell lysis, which is classically performed using mechanical lysis, including homogenization, sonication, or extrusion followed by differential velocity centrifugation, is necessary to remove intracellular components. Cytochalasin B (CB), a drug that affects cytoskeleton–membrane interactions, induces secretion of membrane vesicles from source cells and has been used to extract the cell membrane.[169] The membrane functions of the source cells are preserved in CB-induced vesicles, forming biologically active surface receptors and ion pumps.[170] Furthermore, CB-induced vesicles can encapsulate drugs and NPs successfully, and the vesicles can be harvested by centrifugation without a purification step to remove nuclei and cytoplasm.[171] Clinically translatable membrane vesicles require scalable production of high volumes of homogeneous vesicles within a short period. Although mechanical methods (eg, shear stress, ultrasonication, or extrusion) are utilized, CB-induced vesicles have shown potential for generating membrane encapsulation for nano-vectors.[168] The advantages of CB-induced vesicles versus other methods are compared in Table 3.

After extracting cell membrane vesicles, synthesized core NPs are coated with cell membranes, including surface proteins.[172] Polymer NPs and inorganic NPs are adopted as materials for the core NPs of CMCNPs, and generally, polylactic-co-glycolic acid (PLGA), polylactic acid (PLA), chitosan, and gelatin are used. PLGA has been approved by FDA is the most common polymer of NPs.[173] Biodegradable polymer NPs have gained considerable attention in nanomedicine due to their biocompatibility, nontoxic properties, and the ability to modify their surface as a drug carrier.[174] Inorganic NPs are composed of gold, iron, copper, and silicon, which have hydrophilic, biocompatible, and highly stable properties compared with organic materials.[175] Furthermore, some photosensitive inorganic NPs have the potential for use in photothermal therapy (PTT) and photodynamic therapy (PDT).[176] The fusion of cell membrane vesicles and core NPs is primarily achieved via extrusion or sonication.[165] Cell membrane coating of NPs using mechanical extrusion is based on a different-sized porous membrane where core NPs and vesicles are forced to generate vesicle-particle fusion.[177]

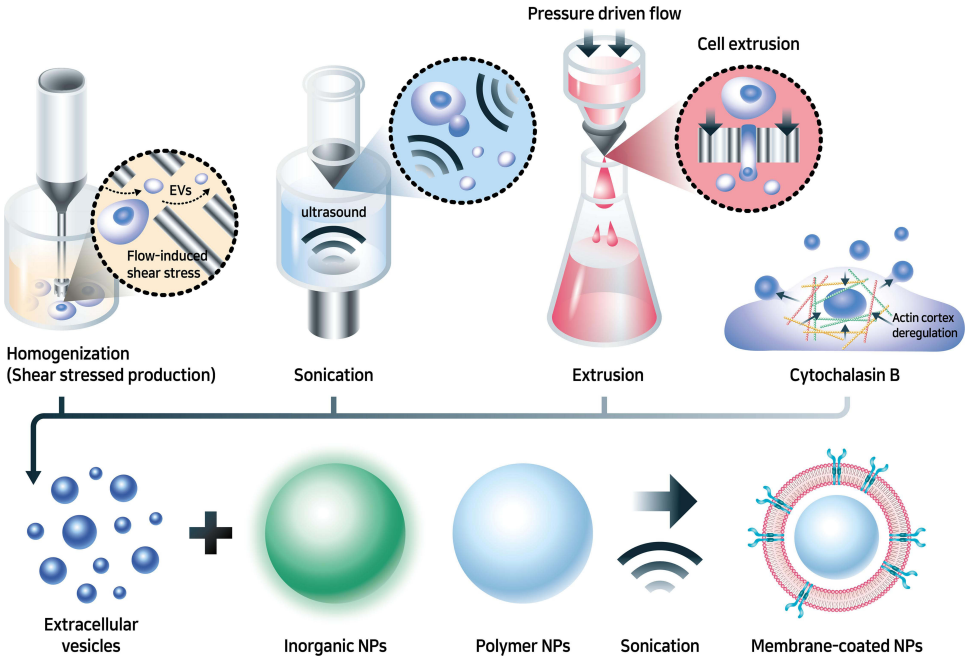

Figure 8 MSC membrane-coated nanoparticles.
Abbreviations: EVs, extracellular vesicles; NPs, nanoparticles.

Table 3 Comparison of Membrane Vesicle Production Methods

Production Criteria for Clinical Translation	Shear Stressed Production	Ultrasonication	Cell Extrusion	CB-Induced Vesicles
Clinically feasible yield	√	√	√	√
Large-scale production	√	√	√	√
Time-effective process			√	√
Structural/functional homogeneity			√	√
Consistent contents				√
Reference	[228]	[229]	[230]	[168]

Abbreviation: CB, cytochalasin B.

Ultrasonic waves are applied to induce the fusion of vesicles and NPs. However, ultrasonic frequencies need to be optimized to improve fusion efficiency and minimize drug loss and protein degradation.[178]

CMCNPs have extensively employed to target and treat cancer using the membranes obtained from red blood cell (RBC), platelet and cancer cell.[165] In addition, membrane from MSC also utilized to target tumor and ischemia with various types of core NPs, such as MSC membrane coated PLGA NPs targeting liver tumors, MSC membrane coated gelatin nanogels targeting HeLa cell, MSC membrane coated silica NPs targeting HeLa cell, MSC membrane coated PLGA NPs targeting hindlimb ischemia, and MSC membrane coated iron oxide NPs for targeting the ischemic brain.[179–183] However, there are few studies on CMCNPs using stem cells for the treatment of arthritis. Increased targeting ability to arthritis was introduced using MSC-derived EVs and NPs.[184,185] MSC membrane-coated NPs are proming strategy for clearing raised concerns from direct use of MSC (with or without NPs) in terms of toxicity, reduced biocompatibility, and poor targeting ability of NPs for the treatment of arthritis.

MSC Derived Exosomes and Artificial Ectosomes Targeting Arthritis

Exosomes are natural NPs that range in size from 40 nm to 120 nm and are derived from the multivesicular body (MVB), which is an endosome defined by intraluminal vesicles (ILVs) that bud inward into the endosomal lumen, fuse with the cell surface, and are then released as exosomes.[186] Because of their ability to express receptors on their surfaces, MSC-derived exosomes are also considered potential candidates for targeting.[187] Exosomes are commonly referred to as intracellular communication molecules that transfer various compounds through physiological mechanisms such as immune response, neural communication, and antigen presentation in diseases such as cancer, cardiovascular disease, diabetes, and inflammation.[188]

However, there are several limitations to the application of exosomes as targeted therapeutic carriers. First, the limited reproducibility of exosomes is a major challenge. In this field, the standardized techniques for isolation and purification of exosomes are lacking, and conventional methods containing multi-step ultracentrifugation often lead to contamination of other types of EVs. Furthermore, exosomes extracted from cell cultures can vary and display inconsistent properties even when the same type of donor cells were used.[189] Second, precise characterization studies of exosomes are needed. Unknown properties of exosomes can hinder therapeutic efficiencies, for example, when using exosomes as cancer therapeutics, the use of cancer cell-derived exosomes should be avoided because cancer cell-derived exosomes may contain oncogenic factors that may contribute to cancer progression.[190] Finally, cost-effective methods for the large-scale production of exosomes are needed for clinical application. The yield of exosomes is much lower than EVs. Depending on the exosome secretion capacity of donor cells, the yield of exosomes is restricted, and large-scale cell culture technology for the production of exosomes is high difficulty and costly and isolation of exosomes is the time-consuming and low-efficient method.[156]

Ectosome is an EV generated by outward budding from the plasma membrane followed by pinching off and release to the extracellular parts. Recently, artificially produced ectosome utilized as an alternative to exosomes in targeted therapeutics due to stable productivity regardless of cell type compared with conventional exosome. Artificial ectosomes, containing modified cargo and targeting molecules have recently been introduced for specific purposes (Figure 9).[191,192] Artificial ectosomes are

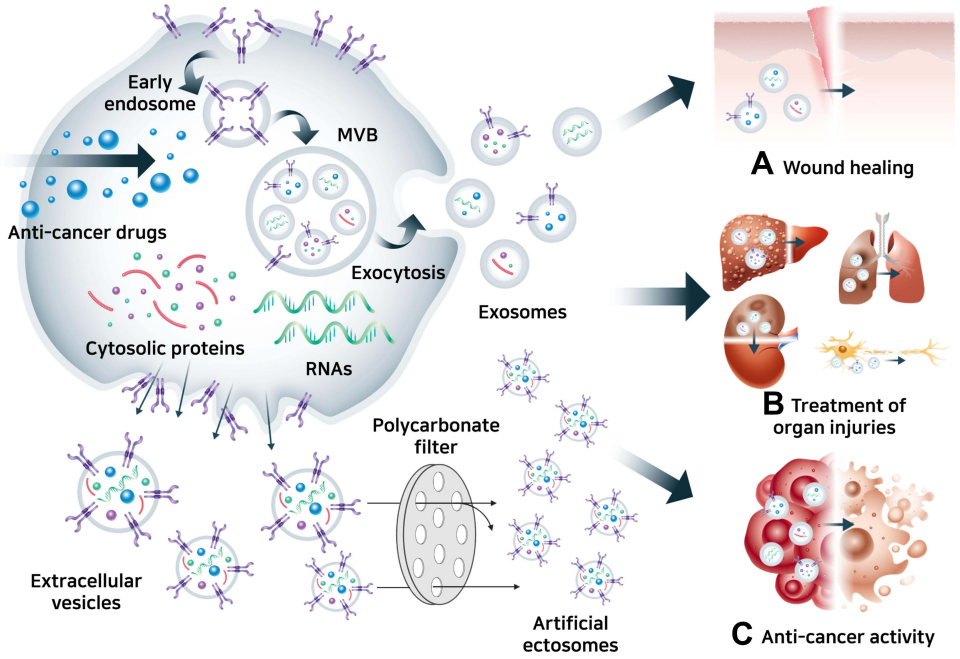

Figure 9 Mesenchymal stem cell-derived exosomes and artificial ectosomes. (**A**) Wound healing effect of MSC-derived exosomes and artificial ectosomes,[231] (**B**) treatment of organ injuries by MSC-derived exosomes and artificial ectosomes,[42,232–234] (**C**) anti-cancer activity of MSC-derived exosomes and artificial ectosomes.[200,202,235]

typically prepared by breaking bigger cells or cell membrane fractions into smaller ectosomes, similar size to natural exosomes, containing modified cargo such as RNA molecules, which control specific genes, and chemical drugs such as anticancer drugs.[193] Naturally secreted exosomes in conditioned media from modified source cells can be harvested by differential ultracentrifugation, density gradients, precipitation, filtration, and size exclusion chromatography for exosome separation.[194] Even though there are several commercial kits for isolating exosomes simply and easily, challenges in compliant scalable production on a large scale, including purity, homogeneity, and reproducibility, have made it difficult to use naturally secreted exosomes in clinical settings.[195] Therefore, artificially produced ectosomes are appropriate for use in clinical applications, with novel production methods that can meet clinical production criteria. Production of artificially produced ectosomes begins by breaking the cell membrane fraction of cultured cells and then using them to produce cell membrane vesicles to form ectosomes. As mentioned above, cell membrane vesicles are extracted from source cells in several ways, and cell membrane vesicles are extracted through polycarbonate membrane filters to reduce the mean size to a size similar to that of natural exosomes.[196] Furthermore, specific microfluidic devices mounted on microblades (fabricated in silicon nitride) enable direct slicing of living cells as they flow through the hydrophilic microchannels of the device.[197] The sliced cell fraction reassembles and forms ectosomes. There are several strategies for loading exogenous therapeutic cargos such as drugs, DNA, RNA, lipids, metabolites, and proteins, into exosomes or artificial ectosomes in vitro: electroporation, incubation for passive loading of cargo or active loading with membrane permeabilizer, freeze and thaw cycles, sonication, and extrusion.[198] In addition, protein or RNA molecules can be loaded by co-expressing them in source cells via bio-engineering, and proteins designed to interact with the protein inside the cell membrane can be loaded actively into exosomes or artificial ectosomes.[157] Targeting molecules at the surface of exosomes or artificial ectosomes can also be engineered in a manner similar to the genetic engineering of MSCs.

Most of the exosomes derived from MSCs for drug delivery have employed miRNAs or siRNAs, inhibiting translation of specific mRNA, with anticancer activity, for example, miR-146b, miR-122, and miR-379, which are used for cancer targeting by membrane surface molecules on MSC-derived exosomes.[199–201] Drugs such as doxorubicin, paclitaxel, and curcumin were also loaded into MSC-derived exosomes to target cancer.[202–204] However, artificial ectosomes derived from MSCs as

arthritis therapeutics remains largely unexplored area, while EVs, mixtures of natural ectosomes and exosomes, derived from MSCs have studied in the treatment of arthritis.[184] Artificial ectosomes with intrinsic tropism from MSCs plus additional targeting ability with engineering increase the chances of ectosomes reaching target tissues with ligand–receptor interactions before being taken up by macrophages.[205] Eventually, this will decrease off-target binding and side effects, leading to lower therapeutic dosages while maintaining therapeutic efficacy.[206,207]

MSC Membrane-Fused Liposomes Targeting Arthritis

Liposomes are spherical vesicles that are artificially synthesized through the hydration of dry phospholipids.[208] The clinically available liposome is a lipid bilayer surrounding a hollow core with a diameter of 50–150 nm. Therapeutic molecules, such as anticancer drugs (doxorubicin and daunorubicin citrate) or nucleic acids, can be loaded into this hollow core for delivery.[209] Due to their amphipathic nature, liposomes can load both hydrophilic (polar) molecules in an aqueous interior and hydrophobic (nonpolar) molecules in the lipid membrane. They are well-established biomedical applications and are the most common nanostructures used in advanced drug delivery.[210] Furthermore, liposomes have several advantages, including versatile structure, biocompatibility, low toxicity, non-immunogenicity, biodegradability, and synergy with drugs: targeted drug delivery, reduction of the toxic effect of drugs, protection against drug degradation, and enhanced circulation half-life.[211] Moreover, surfaces can be modified by either coating them with a functionalized polymer or PEG chains to improve targeted delivery and increase their circulation time in biological systems.[212] Liposomes have been investigated for use in a wide variety of therapeutic applications, including cancer diagnostics and therapy, vaccines, brain-targeted drug delivery, and anti-microbial therapy. A new approach was recently proposed for providing targeting features to liposomes by fusing them with cell membrane vesicles, generating molecules called membrane-fused liposomes (Figure 10).[213] Cell membrane vesicles retain the surface membrane molecules from source cells, which are responsible for efficient tissue targeting and cellular uptake by target cells.[214] However, the immunogenicity of cell membrane vesicles leads to their rapid clearance by macrophages in the body and their low drug loading efficiencies present challenges for their use as drug delivery systems.[156] However, membrane-fused liposomes have advantages of stability, long half-life in circulation, and low immunogenicity due to the liposome, and the targeting feature of cell membrane vesicles is completely transferred to the liposome.[215] Furthermore, the encapsulation efficiencies of doxorubicin were similar when liposomes and membrane-fused liposomes were used, indicating that the relatively high drug encapsulation capacity of liposomes was maintained during the fusion process.[216] Combining

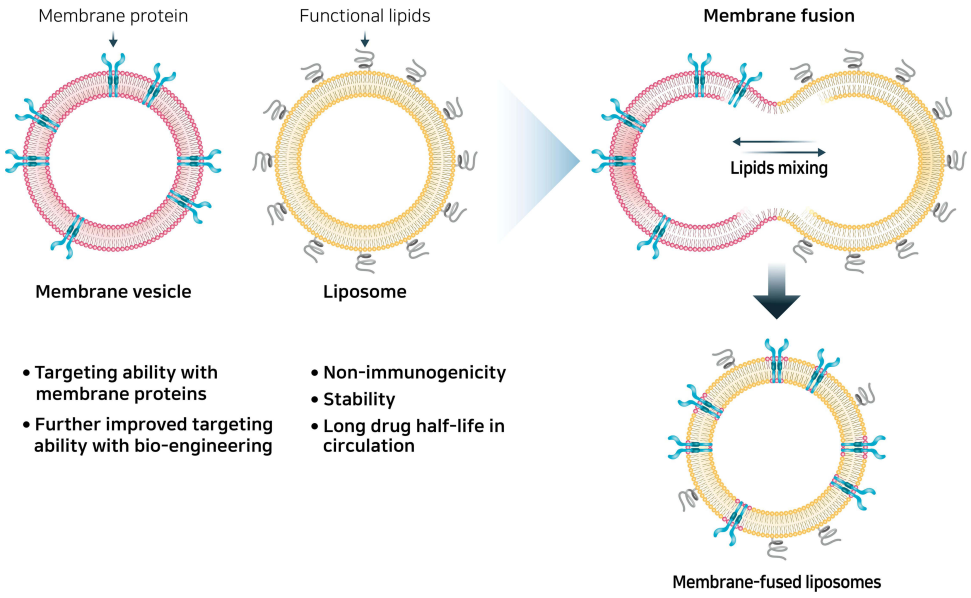

Figure 10 Mesenchymal stem cell membrane-fused liposomes.

membrane-fused liposomes with macrophage-derived membrane vesicles showed differential targeting and cytotoxicity against normal and cancerous cells.[217] Although only a few studies have been conducted, these results corroborate that membrane-fused liposomes are a potentially promising future drug delivery system with increased targeting ability. MSCs show intrinsic tropism toward arthritis, and further engineering and modification to enhance their targeting ability make them attractive candidates for the development of drug delivery systems. Fusing MSC exosomes with liposomes, taking advantage of both membrane vesicles and liposomes, is a promising technique for future drug delivery systems.

Discussion and Conclusion

MSCs have great potential as targeted therapies due to their greater ability to home to targeted pathophysiological sites. The intrinsic ability to home to wounds or to the tumor microenvironment secreting inflammatory mediators make MSCs and their derivatives targeting strategies for cancer and inflammatory disease.[218,219] Contrary to the well-known homing mechanisms of various blood cells, it is still not clear how homing occurs in MSCs. So far, the mechanism of MSC tethering, which connects long, thin cell membrane cylinders called tethers to the adherent area for migration, has not been clarified. Recent studies have shown that galectin-1, VCAM-1, and ICAM are associated with MSC tethering,[53,220] but more research is needed to accurately elucidate the tethering mechanism of MSCs. MSC chemotaxis is well defined and there is strong evidence relating it to the homing ability of MSCs.[53] Chemotaxis involves recognizing chemokines through chemokine receptors on MSCs and migrating to chemokines in a gradient-dependent manner.[221] RA, a representative inflammatory disease, is associated with well-profiled chemokines such as CXCR1, CXCR4, and CXCR7, which are recognized by chemokine receptors on MSCs. In addition, damaged joints in RA continuously secrete cytokines until they are treated, giving MSCs an advantage as future therapeutic agents for RA.[222] However, there are several obstacles to utilizing MSCs as RA therapeutics. In clinical settings, the functional capability of MSCs is significantly affected by the health status of the donor patient.[223] MSC yield is significantly reduced in patients undergoing steroid-based treatment and the quality of MSCs is dependent on the donor's age and environment.[35] In addition, when MSCs are used clinically, cryopreservation and defrosting are necessary, but these procedures shorten the life span of MSCs.[224] Therefore, NPs mimicking MSCs are an alternative strategy for overcoming the limitations of MSCs. Additionally, further engineering and modification of MSCs can enhance the therapeutic effect by changing the targeting molecules and loaded drugs. In particular, upregulation of receptors associated with chemotaxis through genetic engineering can confer the additional ability of MSCs to home to specific sites, while the increase in engraftment maximizes the therapeutic effect of MSCs.[36,225]

Furthermore, there are several methods that can be used to exploit the targeting ability of MSCs as drug delivery systems. MSCs mimicking nanoencapsulation, which consists of MSC membrane-coated NPs, MSC-derived artificial ectosomes, and MSC membrane-fused liposomes, can mimic the targeting ability of MSCs while retaining the advantages of NPs. MSC-membrane-coated NPs are synthesized using inorganic or polymer NPs and membranes from MSCs to coat inner nanosized structures. Because they mimic the biological characteristics of MSC membranes, MSC-membrane-coated NPs can not only escape from immune surveillance but also effectively improve targeting ability, with combined functions of the unique properties of core NPs and MSC membranes.[226] Exosomes are also an appropriate candidate for use in MSC membranes, utilizing these targeting abilities. However, natural exosomes lack reproducibility and stable productivity, thus artificial ectosomes with targeting ability produced via synthetic routes can increase the local concentration of ectosomes at the targeted site, thereby reducing toxicity and side effects and maximizing therapeutic efficacy.[156] MSC membrane-fused liposomes, a novel system, can also transfer the targeting molecules on the surface of MSCs to liposomes; thus, the advantages of liposomes are retained, but with targeting ability. With advancements in nanotechnology of drug delivery systems, the research in cell-mimicking nanoencapsulation will be very useful. Efficient drug delivery systems fundamentally improve the quality of life of patients with a low dose of medication, low side effects, and subsequent treatment of diseases.[227] However, research on cell-mimicking nanoencapsulation is at an early stage, and several problems need to be addressed. To predict the nanotoxicity of artificially synthesized MSC mimicking nanoencapsulations, interactions between lipids and drugs, drug release mechanisms near the targeted site, in vivo compatibility, and immunological physiological studies must be conducted before clinical application.

Acknowledgments

This work was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF-2019M3A9H1103690), by the Gachon University Gil Medical Center (FRD2021-03), and by the Gachon University research fund of 2020 (GGU-202008430004).

Disclosure

The authors report no conflicts of interest in this work.

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