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Review

Genetic Modifications of MSCs to Improve Therapeutic Efficacy

Dai Ihara [1,2,*] and Ayano Narumoto [2]

[1] Sir William Dunn School of Pathology, University of Oxford, Oxford OX1 3RE, UK
[2] Department of Anatomy, Shiga University of Medical Science, Otsu 520-2192, Shiga, Japan
* Correspondence: dai.ihara@path.ox.ac.uk

Abstract

Human mesenchymal stem/stromal cells (MSCs) have attracted significant interest in regenerative medicine due to their self-renewal capacity, immunomodulatory functions, multipotency, and relative ease of isolation and expansion. However, several limitations restrict their clinical application, including cellular heterogeneity, challenges in large-scale expansion, and poor in vivo persistence after transplantation. Systemically administered MSCs are rapidly cleared because of limited adhesion, short survival time, and inefficient extravasation, resulting in suboptimal therapeutic efficacy. To overcome these challenges, various strategies have been developed, such as hypoxic preconditioning, biomaterial-based approaches, and genetic modification. Among these, genetic modification represents a particularly powerful and versatile strategy, as it enables targeted enhancement of specific functional properties of MSCs and even the introduction of novel therapeutic capabilities. In this review, we summarize recent advances in genetically engineered MSCs and categorize these approaches into four functional domains: migration, adhesion, secretion, and survival. We further discuss their therapeutic outcomes across diverse disease models in vivo. Collectively, genetic modification substantially enhances the intrinsic therapeutic potential of MSCs and represents a promising direction for the development of next-generation cell-based therapies.

Keywords: MSCs; genetic modification; cell therapy

1. Introduction

Approximately 50 years ago, human mesenchymal stem/stromal cells (MSCs) were first identified as fibroblast-like colony-forming cells in the bone marrow [1]. Subsequent studies demonstrated that MSCs are present not only in the bone marrow but also in various tissues, including muscle, skin, adipose tissue, umbilical cord, dental pulp, and periodontal tissue [2–5]. MSCs exhibit self-renewal capacity and multipotent differentiation potential, and are characterized by the expression of CD73, CD90, and CD105, while lacking hematopoietic markers such as CD45, CD34, CD14, CD11b, CD79, CD19, and HLA-DR [6].

MSCs have been extensively investigated in regenerative medicine owing to their ability to migrate toward damaged tissues, secrete bioactive molecules, and modulate immune responses [2,7,8]. MSCs express multiple chemokine receptors that enable them to respond to chemokines produced at sites of injury and inflammation. Although their differentiation capacity initially attracted considerable attention, accumulating evidence indicates that the therapeutic effects of MSCs are primarily mediated through paracrine secretion of growth factors and cytokines [9]. Consequently, MSCs are considered one of the most promising cell types for regenerative therapies [10].

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Despite their therapeutic potential, several limitations hinder the clinical application of MSCs. One major challenge is their limited in vivo persistence. Multiple studies have demonstrated that MSCs are rapidly eliminated following transplantation [11]. Moreover, intravenous administration often results in pulmonary entrapment, which can reduce delivery efficiency and potentially induce embolic complications. To circumvent this issue, local injection has been employed to enhance delivery to target tissues [12,13]. However, even locally administered MSCs frequently exhibit reduced viability due to hypoxic and nutrient-deprived microenvironments at the injury site [14,15]. Therefore, improving MSC survival, retention, and functional efficacy remains a critical objective in cell-based therapy.

To overcome these challenges, various strategies have been explored, including co-transplantation approaches, biomaterial-assisted delivery systems, preconditioning methods, and genetic modification [16–18]. Among these, hypoxic preconditioning has been shown to enhance migration, homing ability, and paracrine function [19–22]. However, the effects of such preconditioning strategies are often transient.

Genetic modification represents a more flexible and durable approach to enhancing MSC therapeutic efficacy. By directly modulating gene expression, specific cellular properties—including migration, adhesion, survival, and secretion—can be selectively enhanced. In addition, genetic engineering can confer novel therapeutic functions that are not inherently present in native MSCs [23]. In the following sections, we classify genetically modified MSCs according to the functional properties that are enhanced and summarize their therapeutic outcomes in various mouse disease models.

In contrast to previous reviews that broadly summarize MSC biology or various enhancement strategies, this review specifically focuses on genetic modification as a central approach to improving MSC therapeutic efficacy. By categorizing genetic modifications into four functional domains—migration, adhesion, secretion, and survival—we propose a function-oriented framework that links molecular interventions to therapeutic outcomes. This perspective enables cross-comparison of different genetic strategies and highlights shared mechanisms underlying functional improvements. Importantly, focusing specifically on genetic modification allows identification of common design principles that may not be apparent in broader MSC reviews. Furthermore, this framework may provide a basis for the rational design of next-generation engineered MSCs.

2. Genetic Modification of MSCs

Genetic modifications of MSCs can be broadly categorized according to the cellular functions they enhance. As illustrated in Figure 1, these functional improvements can be grouped into four major domains: migration, adhesion, secretion, and survival. Each of these modifications contributes to strengthening the therapeutic performance of MSCs in distinct pathological contexts. Below, we discuss representative genetic strategies within each functional category and summarize their effects in preclinical disease models.

Despite numerous reports demonstrating improved efficacy of genetically modified MSCs, therapeutic outcomes vary depending on disease models and experimental conditions. For instance, enhanced homing is particularly critical in systemic inflammatory or ischemic diseases, whereas secretion-related modifications may play a dominant role in tissue regeneration models. In addition, most studies rely on small animal models, and validation in large animal models remains limited. Given the physiological differences between species, further investigation in clinically relevant models will be essential for translation.

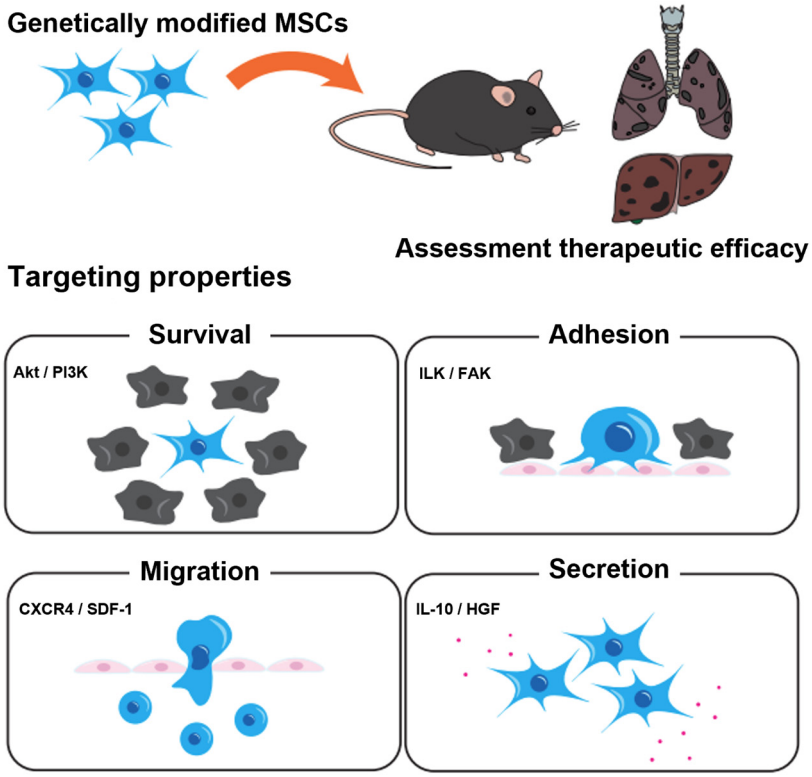

Figure 1. Therapeutic enhancement by genetic modification of MSCs. MSCs are modified during migration, adhesion, secretion, and survival, and the therapeutic effects of these modifications are examined in a pathological mouse model.

2.1. Migration

2.1.1. Migration Through Blood Circulation

Stem cell homing refers to the process by which circulating stem cells migrate toward and engraft within specific tissue niches. MSCs possess intrinsic homing capacity and are capable of migrating not only during embryogenesis but also in adult tissues. The homing process of MSCs shares mechanistic similarities with leukocyte trafficking. In inflammatory conditions, leukocytes exit the bloodstream primarily through post-capillary venules via a multistep cascade consisting of (1) rolling, (2) activation, (3) firm adhesion, and (4) transmigration across the vascular endothelium.

Compared with leukocytes, MSCs exhibit relatively low migration efficiency, largely due to reduced expression of key adhesion molecules such as selectins and integrins that are essential for extravasation. CD49d (integrin α4, ITGA4) is a critical adhesion molecule involved in leukocyte-endothelial interactions. Overexpression of CD49d in MSCs significantly enhanced their homing ability and bone marrow engraftment [24]. In a rat stroke model, transplantation of CD49d-overexpressing MSCs reduced cerebral embolism and improved functional recovery [25].

Similarly, MSCs engineered to overexpress intercellular adhesion molecule-1 (ICAM-1) demonstrated enhanced homing to the colon and spleen in a dextran sodium sulfate-induced inflammatory bowel disease model, resulting in improved tissue repair [26]. In that study, therapeutic effects were associated with immunomodulatory changes, including decreased Th1 and Th17 cell populations and increased regulatory T cells. Collectively, ectopic expression of adhesion molecules that mediate leukocyte trafficking enhances MSC extravasation and tissue targeting, thereby improving their therapeutic efficacy in inflammatory and ischemic disease models.

2.1.2. Chemotaxis

Chemokines are small heparin-binding proteins that regulate directional cell migration. They are broadly classified into inflammatory chemokines, which are upregulated during inflammation and promote leukocyte recruitment, and homeostatic chemokines, which are constitutively expressed to maintain tissue organization and immune surveillance [27]. These chemokines play essential roles in immune cell trafficking and tissue homeostasis [28]. Human MSCs endogenously express various chemokine receptors [29]. However, isolated and expanded MSCs often exhibit reduced chemokine receptor expression and diminished homing capacity [30,31]. To overcome this limitation, numerous studies have focused on genetically enhancing chemokine receptor expression to improve MSC migration toward inflamed or injured tissues. CCR1, whose ligand is CCL7, has been introduced into MSCs to enhance their migration. CCR1-overexpressing MSCs demonstrated increased accumulation in damaged myocardium and exerted superior therapeutic effects in a mouse model of myocardial infarction compared with control MSCs [32]. Similarly, CCR7 overexpression enhanced MSC migration to secondary lymphoid organs and prolonged survival in a graft-versus-host disease (GvHD) model [33].

CXCR family receptors have also been widely investigated. CXCR2-overexpressing MSCs significantly reduced inflammation and improved tissue repair in radiation-induced oral mucositis [34]. CXCR5 overexpression enhanced MSC migration and augmented anti-inflammatory effects in a contact hypersensitivity model [35]. The SDF-1 (CXCL12) axis is particularly important in stem cell homing. CXCR4 and CXCR7 are major receptors for SDF-1 [36–38]. Overexpression of CXCR4 or CXCR7 consistently enhanced MSC migration and tissue targeting [39–42]. CXCR4-overexpressing MSCs accumulated in breast cancer xenografts [43] and showed increased homing to injured lungs in LPS-induced acute lung injury (ALI) models [44]. Enhanced therapeutic effects of CXCR4-overexpressing MSCs have also been demonstrated in myocardial infarction [45,46], acute kidney injury [47], and colitis-associated tumorigenesis [48]. SOX10-overexpressing MSCs increase CXCR4 expression levels, and they also improve homing after myocardial infarction [49]. Likewise, CXCR7-overexpressing MSCs exhibited SDF-1–dependent hypermigration and improved therapeutic outcomes in ALI models [50].

In addition to classical chemokine receptors, nuclear receptors such as Nur77 and Nurr1 have been reported to enhance MSC chemotaxis toward SDF-1–expressing cells in a CXCR4-independent manner [51]. Taken together, genetic overexpression of chemokine receptors and migration-associated molecules represents a robust strategy to enhance MSC homing efficiency and improve therapeutic efficacy across diverse inflammatory and ischemic disease models.

Notably, many migration-enhancing strategies converge on common signaling pathways, particularly the CXCR4/SDF-1 axis, which plays a central role in MSC homing and tissue targeting. This convergence represents a key mechanistic insight of this review, suggesting that distinct genetic modifications may ultimately act through shared downstream mechanisms. Understanding such common pathways may facilitate the rational design of more efficient MSC engineering strategies.

2.1.3. Other Migratory Systems

In addition to classical chemokine receptor–mediated homing, other signaling systems have been reported to enhance the tissue-specific migratory capacity of MSCs. Hepatocyte growth factor (HGF) is highly expressed in the liver and plays a central role in tissue repair and regeneration. MSCs engineered to overexpress HGF exhibited enhanced migration and differentiation potential in a mouse model of acute liver failure (ALF) [52]. Similarly, overexpression of c-Met, the receptor tyrosine kinase for HGF, significantly improved

MSC homing and therapeutic efficacy in ALF models [53]. These findings indicate that modulation of tissue-specific growth factor signaling can augment targeted MSC migration.

Prostaglandin signaling has also been implicated in MSC trafficking. The E-prostanoid 2 (EP2) receptor is a subtype of prostaglandin E2 receptor involved in inflammatory signaling. MSCs overexpressing the EP2 receptor demonstrated increased lung accumulation and enhanced therapeutic effects in an LPS-induced acute lung injury model [54]. This suggests that prostaglandin-directed migration represents another viable strategy for improving tissue-specific homing. Collectively, beyond classical chemokine axes, growth factor– and lipid mediator–associated signaling pathways can be genetically modulated to enhance the migratory behavior of MSCs, thereby improving their therapeutic targeting efficiency.

2.2. Adhesion

Adhesion of MSCs to target tissues is a critical determinant of their survival and therapeutic efficacy following transplantation. Efficient adhesion to extracellular matrix (ECM) components and vascular endothelium facilitates cell retention within injured tissues and promotes tissue regeneration.

Integrins are major mediators of cell–ECM and cell–cell interactions. Upon ligand binding, integrins activate intracellular signaling pathways involving focal adhesion kinase (FAK) and integrin-linked kinase (ILK), which regulate cell survival, proliferation, and differentiation [55]. Genetic enhancement of adhesion-related signaling has therefore been explored as a strategy to improve MSC engraftment.

MSCs overexpressing ILK exhibited approximately 1.5-fold prolonged survival in vivo [56–58]. In myocardial injury models, ILK-overexpressing MSCs demonstrated improved cardiac functional recovery compared with control MSCs, suggesting that enhanced adhesion contributes to superior therapeutic outcomes. ITGB3-overexpressing MSCs demonstrated improved homing and improved atherosclerotic plaque formation [59].

MicroRNA-9-5p has also been implicated in the regulation of MSC adhesion. MicroRNA-9-5p targets CK1α and GSK3β, thereby activating β-catenin signaling. Overexpression of microRNA-9-5p promoted MSC adhesion through enhanced focal adhesion formation and F-actin reorganization [60]. These cytoskeletal changes strengthened cell–substrate interactions and improved cellular stability within damaged tissues.

Hypoxia-inducible factor-1α (HIF-1α) is a key transcription factor activated under hypoxic conditions. Hypoxic preconditioning enhances MSC adhesion and paracrine activity. Consistently, MSCs engineered to overexpress HIF-1α exhibited enhanced therapeutic efficacy in cardiac disease models, including myocardial infarction, compared with control MSCs [61,62]. Enhanced adhesion and survival under hypoxic stress likely contribute to these improved outcomes.

Collectively, genetic modulation of adhesion-related molecules and signaling pathways strengthens MSC retention within injured tissues and enhances their therapeutic persistence. Reinforcing adhesion represents a crucial complementary strategy for improving homing efficiency. It should be noted that, compared with other functional domains such as migration and secretion, genetic modification strategies specifically targeting adhesion remain relatively underexplored. Therefore, the current evidence base is more limited, which is reflected in the relatively concise nature of this section.

2.3. Secretion

The therapeutic efficacy of MSC-based cell therapy is largely attributed to their paracrine activity rather than direct differentiation. Enhancing the intrinsic secretory profile of MSCs has therefore become a major strategy for improving therapeutic outcomes in diverse disease models.

2.3.1. Anti-Inflammatory Cytokine Engineering

Several studies have focused on augmenting the anti-inflammatory capacity of MSCs through cytokine overexpression. MSCs engineered to overexpress IL-1 receptor 1, a decoy receptor for IL-33 released during inflammation, demonstrated enhanced therapeutic effects in a mouse model of acute lung injury (ALI) [63]. Similarly, IL-4-overexpressing MSCs improved disease severity in experimental autoimmune encephalomyelitis and reduced pro-inflammatory cytokines such as IFNγ and IL-6 [64]. IL-23R overexpression also enhanced therapeutic efficacy in autoimmune encephalomyelitis models [65].

IL-10, a potent anti-inflammatory cytokine, has been widely studied. MSCs overexpressing IL-10 promoted neuronal regeneration and functional recovery in spinal cord injury models through EV-mediated modulation of macrophage polarization [66]. IL-10-overexpressing MSCs also suppressed inflammatory cytokine production and improved tissue repair in myocardial infarction [67], traumatic brain injury [68], and liver fibrosis [69]. These findings highlight the importance of reinforcing immunomodulatory secretory functions. IL-10 overexpression has been widely investigated as a strategy for enhancing the anti-inflammatory properties of MSCs.

2.3.2. Growth Factor Enhancement

Growth factor overexpression further amplifies paracrine-mediated tissue repair. Keratinocyte growth factor (KGF) enhances proliferation of alveolar epithelial cells, and KGF-overexpressing MSCs significantly attenuated pulmonary edema in ALI models [70]. Hepatocyte growth factor (HGF), a key mediator of liver regeneration and anti-apoptotic signaling, has also been widely employed. HGF-overexpressing MSCs demonstrated improved therapeutic outcomes in liver injury models [71–73].

2.3.3. Engineering Extracellular Vesicles (EVs)

MSC-derived EVs are increasingly recognized as major mediators of paracrine effects. EVs contain proteins, RNAs, and lipids that modulate recipient cell behavior. However, EVs exhibit short in vivo retention times—detectable for only several hours following systemic administration [74–76]—which limits their clinical applicability.

Genetic modification provides a strategy to enhance EV stability and function. Forced expression of therapeutic growth factors and cytokines enriches EV cargo and augments their regenerative capacity [77,78]. Notably, CD47-overexpressing MSCs generate EVs expressing CD47 on their surface, enabling interaction with SIRPα on macrophages and reducing phagocytic clearance. This modification prolonged EV circulation and enhanced therapeutic effects in myocardial infarction models [79]. Furthermore, ILK-overexpressing MSCs exhibited increased IL-6 secretion under hypoxic conditions, activating STAT3 and Wnt signaling pathways in surrounding cells and promoting survival and self-renewal [80]. These findings illustrate how genetic engineering can reshape both soluble factor secretion and EV-mediated communication.

Collectively, genetic enhancement of MSC secretory functions—whether through cytokine overexpression, growth factor augmentation, or EV engineering—substantially amplifies their paracrine therapeutic mechanisms. Modulation of the secretome represents a central pillar in next-generation MSC-based regenerative strategies. In addition to cargo modification, recent studies have explored engineering of EV surface properties to enhance tissue targeting and cellular uptake. More recently, a 2024 review highlighted targeted drug delivery strategies for engineered mesenchymal stem/stromal-cell-derived exosomes, underscoring the translational value of surface engineering and cargo-loading approaches [81]. For example, incorporation of targeting peptides or ligand molecules onto EV membranes has been shown to improve delivery efficiency to specific tissues. Further-

more, advances in RNA loading technologies enable selective enrichment of therapeutic microRNAs and mRNAs within EVs, allowing more precise modulation of recipient cell behavior. These strategies highlight the growing potential of "designer EVs" as a cell-free therapeutic platform.

2.4. Survival

Following transplantation, MSCs migrate to inflamed or ischemic tissues where they encounter hostile microenvironments characterized by hypoxia, oxidative stress, inflammatory cytokines, and nutrient deprivation. Under these conditions, MSC survival is markedly reduced, limiting their long-term therapeutic efficacy. Accordingly, genetic strategies aimed at enhancing cell survival have become a major focus in MSC engineering.

2.4.1. Akt/PI3K Signaling Pathway

The Akt signaling pathway is a central regulator of cell survival and anti-apoptotic signaling. Overexpression of Akt in MSCs significantly reduced infarct size and improved cardiac function in a mouse model of myocardial infarction compared with control MSCs [82]. Indirect activation of Akt signaling through integrin-linked kinase (ILK) overexpression similarly enhanced MSC survival and promoted angiogenesis via Akt and mTOR pathways [83]. ILK-overexpressing MSCs also demonstrated improved survival mediated by enhanced IL-6 paracrine signaling [80]. In addition, protein kinase Cε overexpression activated Akt signaling and improved MSC retention and survival in ischemic myocardium [84]. Gremlin1, an angiogenic factor involved in development and tissue remodeling [85], has also been shown to activate PI3K/Akt-dependent anti-apoptotic signaling. Gremlin1-overexpressing MSCs exhibited enhanced survival and improved functional recovery in hindlimb ischemia models [86].

2.4.2. Growth Factor-Mediated Survival Enhancement

Hepatocyte growth factor (HGF) plays a multifunctional role in angiogenesis, anti-apoptosis, and tissue regeneration. HGF-overexpressing MSCs demonstrated enhanced survival and therapeutic efficacy in multiple disease models [87]. Mechanistically, HGF overexpression upregulated the anti-apoptotic protein Mcl-1, contributing to increased MSC viability [88]. Enhanced cardioprotective effects of HGF-overexpressing MSCs have also been demonstrated in myocardial infarction models [89]. Brain-derived neurotrophic factor (BDNF) further supports MSC survival. Forskolin-induced upregulation of TrkB, the receptor for BDNF, combined with BDNF overexpression, promoted MSC survival and functional recovery in experimental models [90].

2.4.3. Anti-Apoptotic Gene Overexpression

Direct overexpression of anti-apoptotic proteins has also been explored. B-cell lymphoma-2 (Bcl-2), a mitochondrial membrane protein that inhibits pro-apoptotic signaling, prolonged MSC survival and enhanced therapeutic effects [91,92]. Co-expression of Bcl-2 and vascular endothelial growth factor (VEGF) further strengthened survival and paracrine activity [93]. Tumor necrosis factor receptor (TNFR) overexpression enhanced MSC resistance to TNF-α–induced apoptosis and improved cardiac repair in myocardial infarction models [94].

2.4.4. Protection Against Oxidative Stress

Reactive oxygen species (ROS) significantly impair MSC survival after transplantation. Genetic enhancement of antioxidant defenses represents an effective strategy to mitigate oxidative damage. Manganese superoxide dismutase (MnSOD)-overexpressing MSCs were protected from ROS-dependent injury [95]. Similarly, heme oxygenase-1 (HO-1),

an enzyme induced by oxidative stress, conferred cytoprotective and antioxidant effects, leading to improved MSC survival. More recently, genetic overexpression of FOXO3a has been shown to enhance antioxidant defenses and improve MSC survival under oxidative stress conditions, leading to improved therapeutic outcomes in preclinical models [96].

2.4.5. Maintenance of Stemness and Proliferative Capacity

Overexpression of pluripotency-associated genes such as Oct4 and Nanog enhanced MSC proliferation and delayed cellular senescence [97]. Maintenance of stem-like characteristics may contribute to prolonged persistence and functional stability in vivo. Collectively, genetic strategies that activate pro-survival signaling pathways, inhibit apoptosis, enhance antioxidant capacity, and maintain stemness significantly improve MSC persistence in hostile microenvironments. Reinforcing survival mechanisms not only prolongs MSC retention but also amplifies their downstream paracrine and regenerative effects, thereby enhancing overall therapeutic efficacy.

2.5. Source-Dependent Heterogeneity of MSCs and Implications for Genetic Engineering

MSCs derived from different tissue sources, including bone marrow, adipose tissue, umbilical cord, and dental pulp, exhibit substantial heterogeneity in their biological properties. Transcriptomic analyses have revealed distinct gene expression profiles depending on the tissue of origin, which in turn influence proliferation capacity, differentiation potential, and immunomodulatory function. Importantly, these source-dependent differences also affect the therapeutic effect of MSCs. For example, adipose-derived MSCs often demonstrate higher proliferative capacity, whereas bone marrow-derived MSCs may exhibit stronger osteogenic potential. Furthermore, differences in chemokine receptor expression and adhesion molecule profiles can lead to variability in homing efficiency and tissue targeting.

Such heterogeneity has critical implications for genetic engineering strategies. The efficacy of gene overexpression or editing approaches may depend on the baseline characteristics of the MSC population. For instance, enhancing CXCR4 expression may yield different magnitudes of improvement depending on the endogenous expression level in the original MSC source. Similarly, immunomodulatory gene modifications may interact with intrinsic cytokine secretion profiles.

Therefore, careful consideration of MSC source is essential when designing genetically modified MSC therapies. In addition, there is a growing need for standardized criteria regarding cell source selection, culture conditions, and functional evaluation. Establishing such standards will be crucial for ensuring reproducibility, optimizing therapeutic outcomes, and facilitating clinical translation.

2.6. Clinical Application

To date, only a limited number of clinical studies have evaluated genetically modified MSCs. For example, early-phase trials investigating MSCs engineered to express therapeutic genes such as TRAIL or interferon-β have been registered (e.g., ClinicalTrials.gov identifiers NCT03298763 and NCT02530047). These studies primarily focus on safety and feasibility rather than efficacy. In contrast, the number of registered trials using unmodified MSCs is substantially larger, highlighting the relative immaturity of the clinical landscape for genetically engineered MSC therapies. However, their therapeutic efficacy has often been inconsistent or modest compared to preclinical results. This discrepancy highlights a critical translational gap and underscores the need for improved strategies, including genetic modification. Several factors contribute to the limited clinical translation of genetically engineered MSCs. These include challenges in large-scale manufacturing under GMP conditions, safety concerns related to gene delivery methods (particularly viral vectors), and stringent regulatory requirements for gene-modified advanced therapy medicinal

products (ATMPs). Furthermore, differences between controlled animal models and heterogeneous human patient populations—such as immune variability, disease complexity, and microenvironmental conditions—may significantly affect therapeutic outcomes. Future clinical studies will be essential to determine whether genetically modified MSCs can overcome the limitations observed in conventional MSC therapies and achieve consistent therapeutic benefits in human patients.

3. Conclusions

In this review, we comprehensively summarized recent advances in genetic modification strategies aimed at enhancing the therapeutic efficacy of MSCs (Table 1). Specifically, we categorized these approaches into four functional domains—migration, adhesion, secretion, and survival—and highlighted their effects in various preclinical disease models. These studies collectively demonstrate that targeted genetic enhancement can substantially improve MSC homing efficiency, retention, paracrine activity, and resistance to hostile microenvironments. Importantly, not all genetic modifications confer universal therapeutic benefits across different pathological contexts. The functional requirements of MSCs vary depending on disease type, route of administration, and tissue microenvironment. Therefore, rational selection and disease-specific customization of genetic modifications are essential for maximizing therapeutic outcomes.

Table 1. Summary of functions enhanced by genetic modification of MSCs and their investigation into pathological models.

Modified Target Gene	Effect	Target Disease	References
CD49d	Enhancement of homing to bone marrow in vivo and extravasation	Stroke	[24]
CD49d	Enhancement of transendothelial migration	Cerebral Embolism	[25]
ICAM-1	Enhancement of homing to the colon and spleen and increase the number of Tregs	Inflammatory bowel disease (IBD)	[26]
CCR1	Enhancement of homing to infarction site	Myocardial infarction	[32]
CCR7	Enhancement of migration to secondary lymphoid organs (SLOs)	GvHD	[33]
CXCR2	Reduction of inflammation	Oral mucositis	[34]
CXCR5	Enhancement of migration to inflammatory sites and reduction of inflammation	Contact Hypersensitivity	[35]
CXCR4	Enhancement of migration to the tumor site	Breast Cancer	[43]
CXCR4	Enhancement of migration to the lung	Acute lung injury (ALI)	[44]
CXCR4	Enhancement of invasion efficiency	Colitis associated tumorigenesis	[44]
CXCR4	Upregulation of BMP-7, HGF, and IL-10 expression	Acute kidney injury	[47]
CXCR4	Enhancement of migration capacity	myocardial infarction	[45,46]
CXCR7	Enhancement of migration to the tumor site	Breast cancer	[43]
CXCR7	Enhancement of migration activity against SDF-1	Acute lung injury (ALI)	[50]
Nur77	Enhancement of migration activity against SDF-1	-	[51]

Table 1. *Cont.*

Modified Target Gene	Effect	Target Disease	References
Nurr1	Enhancement of migration activity against SDF-1	-	[51]
HGF	Enhancement of migration and hepatic differentiation in vivo.	Acute liver failure	[52]
c-Met	Enhancement of migration and hepatic differentiation in vivo.	Acute liver failure	[53]
EP2	Enhancement of migration to the lung	Lung injury	[54]
ILK	Increase in survival and adhesion	Myocardial injury	[56–58]
mir9-5p	Inhibition CK1αand GSK3β expression and activation of B-catenin signaling	-	[60]
Hif-1α	Induction of angiogenesis	Myocardial infarction	[62]
ST2	Inhibition of IL-33 function	Acute lung injury (ALI)	[63]
IL-4	Suppression of IFNγ and IL-6 expression	Multiple Sclerosis	[64]
KGF	Enhancement of proliferation of alveolar type 2 cells	Pulmonary edema	[70]
HGF	Promotion of proliferation and regeneration of hepatocyte	Liver fibrosis	[71–73]
CD47	Prolongation of extracellular vesicle circulation time	Myocardial infarction	[79]
ILK	Increase secretion of interleukin-6 (IL-6)	-	[80]
IL-23R	Incorporation of exogenous IL-23R into Evs	Encephalomyelitis	[65]
IL-10	Induction of type 2 macrophages after they reach the injury site	SCI	[66]
IL-10	Decreased expression of cell death markers such as Bax, cytochrome c, caspase 3, and p53	Traumatic brain injury (TBI)	[68]
IL-10	Inhibition of the activation of HSC and TNF-α expression of T cells derived from fibrotic liver	Liver fibrosis	[69]
Akt	Improvement of MSC survival	-	[82]
ILK	Activation of AKT and mTOR signaling pathways	Myocardial infarction	[83]
HGF	Increases the expression of the anti-apoptotic protein Mcl-1	cardiovascular disease, liver injury, Parkinson's disease	[87–89]
Gremlin1	Activation of AKT signaling pathways	-	[86]
Bcl-2	Inhibition apoptotic process	-	[91,92]
VEGF	Enhancement of survival and stronger paracrine effects	-	[93]
BDNF	Improvement of MSC survival	-	[90]
TNF-α	Regulation of apoptosis	myocardial infarction	[94]
MnSOD	Protection from ROS	-	[95]
HO-1	Protection from ROS	-	[95]
Oct4 Nanog	Promotion of proliferative potential	-	[97]

Various gene delivery methods have been employed for the genetic modification of MSCs, broadly categorized into viral and non-viral approaches. Viral vectors, such as lentiviruses and adenoviruses, offer high transduction efficiency and stable gene expression, but raise safety concerns including insertional mutagenesis and immunogenicity. In contrast, non-viral methods, including plasmid-based transfection and nanoparticle-mediated delivery systems, provide improved safety profiles but generally suffer from lower efficiency and transient expression. Therefore, careful selection and optimization of gene delivery strategies are essential for balancing efficiency, safety, and clinical applicability.

Despite encouraging results in animal models, translation to clinical application remains limited. One major barrier is the safety and regulatory concerns associated with viral gene delivery systems. Strict regulatory requirements for genetically modified products may restrict the widespread clinical implementation of virus-based MSC therapies. Recent progress in non-viral delivery platforms, including lipid nanoparticles and polymer-based systems, has improved gene transfer efficiency while maintaining favorable safety profiles [98,99]. These approaches are particularly promising for clinical-grade MSC engineering, as they avoid risks associated with viral vectors and are more amenable to large-scale manufacturing under GMP conditions. In parallel, advances in precision genome editing technologies, such as base editing and prime editing, offer new opportunities for engineering MSCs with improved safety profiles. Unlike conventional CR approaches that rely on double-strand breaks, these methods enable precise nucleotide modifications with reduced risk of genomic instability. Although their application to MSCs remains in an early phase, they hold considerable potential for fine-tuning gene expression without compromising cell viability. Together, these technological developments, combined with improved GMP-compliant manufacturing processes [100], may accelerate the clinical translation of next-generation MSC-based therapies.

In addition to biological efficacy, manufacturing and scalability represent critical challenges for clinical translation. The source of MSCs, culture conditions, and genetic modification methods can all influence product consistency and safety. Viral vectors offer high efficiency but raise safety and regulatory concerns, whereas non-viral approaches may improve safety but often suffer from lower transfection efficiency.

Establishing standardized protocols for cell expansion, genetic modification, and quality control will be essential for clinical application. Moreover, batch-to-batch variability remains a major obstacle, particularly given the intrinsic heterogeneity of MSCs. Addressing these issues will be crucial for translating promising preclinical findings into reproducible clinical therapies.

Future studies should focus not only on improving the efficiency and safety of genetic modification techniques but also on establishing standardized evaluation criteria for functional enhancement and long-term safety. Integration of genome biotechnology with cell engineering strategies holds significant promise for tailoring MSC therapies to specific disease conditions. With continued technological refinement and rigorous translational research, genetically engineered MSCs may represent a pivotal platform for precision regenerative medicine. Future studies should use genetic modification methods to overcome these limitations.

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Abbreviations

The following abbreviations are used in this manuscript:

ALI	acute lung injury
ALF	acute liver failure
Bcl-2	B-cell lymphoma-2
BDNF	brain-derived neurotrophic factor
CCL7	C-C motif chemokine ligand 7
CCR1	C-C chemokine receptor type 1
CCR7	C-C chemokine receptor type 7
CD47	cluster of differentiation 47
CD49d	integrin α4 (ITGA4)
CK1α	casein kinase 1 alpha
c-Met	hepatocyte growth factor receptor
CXCL12	stromal cell-derived factor-1 (SDF-1)
CXCR2	C-X-C chemokine receptor type 2
CXCR4	C-X-C chemokine receptor type 4
CXCR5	C-X-C chemokine receptor type 5
CXCR7	C-X-C chemokine receptor type 7
ECM	extracellular matrix
EP2	E-prostanoid receptor 2
EV	extracellular vesicle
FAK	focal adhesion kinase
Fsk	forskolin
GFAP	glial fibrillary acidic protein
GMP	good manufacturing practice
GSK3β	glycogen synthase kinase 3 beta
GvHD	graft-versus-host disease
HGF	hepatocyte growth factor
HIF-1α	hypoxia-inducible factor-1 alpha
HO-1	heme oxygenase-1
ICAM-1	intercellular adhesion molecule-1
IFNγ	interferon gamma
IL-1β	interleukin-1 beta
IL-4	interleukin-4
IL-6	interleukin-6
IL-10	interleukin-10
IL-23R	interleukin-23 receptor
ILK	integrin-linked kinase
ITGA4	integrin alpha 4
KGF	keratinocyte growth factor
LPS	lipopolysaccharide
Mcl-1	myeloid cell leukemia-1
miR-9-5p	microRNA-9-5p
MnSOD	manganese superoxide dismutase
mTOR	mechanistic target of rapamycin
MSCs	mesenchymal stem/stromal cells
Nanog	homeobox transcription factor Nanog
Nur77	nuclear receptor subfamily 4 group A member 1
Nurr1	nuclear receptor subfamily 4 group A member 2
Oct4	octamer-binding transcription factor 4
PDL1	programmed death-ligand 1

PI3K	phosphoinositide 3-kinase
ROS	reactive oxygen species
SDF-1	stromal cell-derived factor-1
SIRPα	signal regulatory protein alpha
STAT3	signal transducer and activator of transcription 3
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TrkB	tropomyosin receptor kinase B
VEGF	vascular endothelial growth factor

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