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Short Review

Genetic Engineering of Mesenchymal Stem Cells to Improve Therapeutic Effects

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Abstract

Based on the therapeutic potential of MSCs, including homing to damaged sites, trans-differentiation, secretion of trophic factors, and immunomodulation, approximately 1,100 clinical studies have been registered in the ClinicalTrials.Gov, and several drugs using MSCs have been approved worldwide. However, despite their therapeutic potential, MSCs have not yet shown sufficient therapeutic effects in humans. Therefore, in order to increase the therapeutic potential of MSCs, methods such as MSC priming, genetic modification, Three-Dimensional (3-D) culture, and MSC-derived exosomes are being studied intensively. Among them, genetic modification increases the expression of therapeutic genes, leading to increased homing of MSCs to the damaged sites, increased engraftment rates, and increased survival durations of transplanted MSCs. It has been reported that genetically engineered MSCs can greatly increase their therapeutic effects. This review aims to provide an overview of the method of target gene delivery to MSCs and discuss the advantages and disadvantages of each method.

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Introduction

Mesenchymal Stem Cells (MSCs) are multipotent stromal cells that can be isolated from various tissues, including bone marrow, adipose tissue, dental pulp, amniotic fluid, and umbilical cord [1-5]. According to the International Society for Cellular Therapy (ISCT), MSCs are defined as cells that can adhere to plastic, express CD73, CD90, and CD105 as cell surface antigens (≥ 95% positive), and differentiate into adipocytes, chondroblasts, and osteoblasts under *in vitro* differentiation conditions [6]. Potential therapeutic mechanisms of MSCs for the regenerative treatment of incurable diseases have been reported. First, MSCs possess a homing property, allowing them to adhere to damaged and tumor sites [7,8]. The homing effect of MSCs theoretically implies that, in clinical applications, MSCs can be delivered to the damaged area for injury repair using only intravascular transplantation of MSCs and not surgery. Second, although it has been reported that the ratio of differentiated cells to transplanted cells is very low [9], MSCs can directly differentiate into damaged cells, facilitating repair [10]. Third, MSCs have the ability to regulate immune responses [11-13] and can promote the regeneration of damaged tissues by regulating the activity of immune cells [14-16]. Fourth, it has been reported that MSCs can express various trophic factors, which can inhibit the activity of immune cells, inhibitor delay cell death in damaged sites, and promote progenitor/stem cell proliferation and differentiation into target cells [11,12,14,16-18]. Finally, MSCs are known to be hypoimmunogenic or immune-privileged, which allows allogeneic MSC transplantation across major histocompatibility barriers and the creation of off-the-shelf therapies consisting of MSCs grown in culture [19].

Based on the therapeutic potential of MSCs, more than 1,100 clinical trials using MSCs have been registered for various diseases (https://clinicaltrials.gov). However, despite the progress in basic and clinical studies using MSCs, MSC treatment has not yet shown sufficient therapeutic effects in humans. Therefore, to improve the therapeutic potential of MSCs, MSC priming [20-22], genetic modification [23-27], Three-Dimensional (3-D) culture [28-30], and MSC-derived exosomes [31-34] have been studied. Once delivered to the damaged site, MSCs release various factors that regulate the activity of inflammatory cells after exposure to inflammatory cytokines; this is followed by treatment of the damaged area. Therefore, the therapeutic effect of MSCs can be improved by pre-exposing them to inflammatory cytokines, such as IFN-γ, TNF-α and IL-1β [22]. Three-dimensional culture of stem cells using various scaffolds has been reported to increase the proliferation and differentiation efficiencies of stem cells [28,30] and enhance their therapeutic effects in liver disease, peritonitis, kidney injury, and myocardial infarction [35-37]. Since various trophic factors secreted by MSCs exhibit therapeutic effects, their regenerative therapeutic effects can be increased by

utilizing the MSC-derived secretome or exosomes. Since exosomes can be stored, controlled qualitatively, and administered repeatedly, they are an optimal factor that can be used for the treatment of acute diseases. One way to reliably improve the therapeutic effect of MSCs is to increase the expression of the target gene, which plays an important role in tissue regeneration. Therefore, in this review, we will discuss gene delivery methods into MSCs, which are known to have low transformation efficiencies, and discuss the production of functionally enhanced MSCs and their therapeutic efficacy.

Gene Delivery into MSCs

The ability of MSCs to home to the damaged and/or tumor site makes it possible to use MSCs as a vehicle for various therapeutic agents, including genes. The method of gene delivery to MSCs depends on whether viral or non-viral vector systems are used [38]. Retrovirus, lentivirus, adenovirus, and adeno-associated virus have been extensively used as viral vectors for gene delivery into MSCs [38-40]. In non-viral vector systems, single or combinations of cationic lipids, surfactants, peptides, polysaccharides, metals (gold, magnetic iron), and synthetic polymers have been used for genetic manipulation [41-43].

Adenoviral vectors

Adenoviruses are non-enveloped viruses with icosahedral nucleocapsids, containing a double-stranded DNA genome. Adenoviruses are the most commonly used gene delivery vector because they have a wide host range and can infect both dividing and non-dividing cells [44,45]. The efficiency of gene delivery by adenoviruses is closely associated with the expression of Coxsackievirus and Adenovirus Receptors (CARs) on target cells [46]. Since MSCs express a very low level of CARs [47], gene delivery efficiency using adenovirus vectors is very low. To improve the efficiency of gene delivery by adenoviruses into MSCs, a capsid- and a fiber-modified adenovirus has been developed [46,48,49]. In addition, the initial robust expression of the newly introduced gene gradually declines in bone marrow-derived MSCs after 21 days; thus, this strategy could only be applied for the transient expression of target genes [50]. However, adenoviruses have high immunogenicity, which limits their use in gene therapy.

Lentiviral vectors

Lentiviruses are a genus of retroviruses that contain a single-stranded RNA genome. After entering cells, lentiviral RNA is reverse-transcribed into double-stranded DNA, which can be integrated into the host genome, leading to insertional mutagenesis. Recently, non-integrating lentivirus vectors have been generated through alterations in the viral integrase or long terminal repeats and have been used for stable and safe gene delivery, resulting in long-term expression of the transgene [51]. Lentiviruses are one of the most widely used vectors in MSC-based gene therapy and have benefits such as a large genome size, high infection efficiency, and stable gene transfer [39,49]. In addition, lentiviruses can be transduced into non-dividing cells and persist for several generations. MSCs engineered with HSP70 by a lentiviral vector improved the survival and resistance to apoptosis in hypoxic and ischemic conditions without affecting the morphology, viability, or differentiation abilities of MSCs [52]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-overexpressing MSCs induced apoptosis in cancer cell lines, including lung, colon, pleural mesothelioma and oral squamous cancer [53].

Retroviral vectors

Retroviruses have a lipid envelope and a double-stranded RNA genome, which is reverse-transcribed to DNA that integrates into the host genome, resulting in insertional mutations. Despite the high tropism of retroviruses to host cells, there are many difficulties in using them for gene therapy, such as the absence of long-term transgene expression, ineffective transduction of MSCs, induction of insertional mutagenesis, and the requirement for administering high loads of vectors in several rounds to transduce host cells [39,46 49].

Adeno-associated virus-based vectors

Adeno-Associated Viruses (AAV) are considered an attractive gene therapy vector for the following reasons: despite their ubiquity in the human population, they have no association with any disease; most human tissues can be infected with AAV; AAV vectors are not capable of replication without a helper adenovirus; AAVs exist in an episomal form for long-term transgene expression; and AAV vectors have been shown to be nontoxic in clinical trials in humans [54-56]. However, the clinical applicability of AAV vectors has been limited due to their low transduction efficiency in MSCs [46,49].

Non-viral vectors

Plasmids, which are non-viral vectors, have been considered as another suitable candidate for gene delivery into MSCs because they can be easily produced and have low immunogenicity [46,57,58]. Unlike viral vectors, conventional transfection methods such as lipofection, magnetofection, and electroporation are combined to deliver non-viral vectors into host cells. However, the efficiency of gene delivery into MSCs is very low compared to that of viral vectors. Moreover, transfection reagents and/or procedures can increase the cytotoxicity of MSCs, leading to cell death or senescence [58-62]. Recently, Helledie et al., reported that electroporation is a superior gene delivery method for lipofection in MSCs without causing loss of proliferation and differentiation potentials, while lipofection with Lipofectamine2000 decreased proliferation rate and increased cell death in MSCs [61]. They described a simple and reliable electroporation protocol that resulted in a transfection efficiency of up to 90% compared to most viral methods, but the absolute transfection efficiency was approximately 35%. Recently, a novel method for efficient gene delivery into MSCs has been developed based on Therapeutic Ultrasound (TUS) [63]. MSCs were transfected with plasmids encoding hemopexin-like domain fragment (PEX), an inhibitor of angiogenesis, using low intensity and moderate frequency TUS. MSCs transfected with TUS-mediated PEX expressed biologically active PEX without loss of stemness and homing capabilities and subsequently inhibited 70% of prostate tumor growth in a mouse model [63].

Conclusion

The homing effect of MSCs to the damaged and/or tumor site makes it possible to use MSCs as a transport vesicle for various therapeutic agents, including genes. MSCs equipped with these therapeutic agents not only have important therapeutic effects, but also act predominantly in only the damaged site, reducing the expected frequency of side effects resulting from the nonselective action of the drug. For gene delivery into MSCs, viral and non-viral vectors have been studied, and genetically engineered MSCs have been reported to significantly improve their therapeutic effects in regenerative

medicine and cancer treatment. Viral vectors have disadvantages such as high immunogenicity and insertional mutagenesis, but have the advantages of high transfection efficiency and long-term gene expression. Conversely, gene delivery with non-viral vectors has a low transfection efficiency and transient expression of target genes. Therefore, based on the disease being treated, different types of vectors must be used to suit the therapeutic purpose. Further, new methods must be developed to make use of the advantages of each vector and to compensate for the disadvantages. If such research is conducted in the future, it is expected that not only will the therapeutic effect of MSCs be enhanced, but the application of MSCs to various diseases can greatly improve the quality of life of patients.

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Competing Interest

The authors declare that they have no competing interests.

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