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Application of Stem Cells in Disease and Gene Therapy

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ABSTRACT

Over the last two decades, a number of strategies have been devised with the aim to treat diseases with a genetic approach. Gene therapy or the genetic manipulation of nongerm line cells has emerged as one of most promising strategies for treating human diseases. There are two methods of gene therapy: direct gene therapy or in vivo and indirect gene therapy or in vitro. Both two gene transferring that are divided and are modified genetically. Stem cells have some specifications to transfer highlighted genes to patients. These include proliferation viability and renewing in long period of time and diferention to variety of host cells. The basis for gene therapy is based on treatment both genetic and multifactorial disorders like neoplasia, infectious disease and cardio-vascular disorders. Comparing to other genetics engineering fields, Stem cell gene therapy will only meet success when essential improvement developed in stem cell studies and transferred gene regulation.

Keywords: Gene Therapy, Disease, Stem Cell.

INTRODUCTION

Two basic strategies for the introduction and expression of foreign DNA into host cells are (1) gene therapy, which is based on the permanent insertion of DNA, and (2) gene medicine, which is used for transient transformation and short-term expression of a gene product [1]. Genes can be delivered by either in vivo or ex vivo approaches. In vivo techniques are based upon the direct introduction of genes to the target tissue. Ex vivo techniques rely upon the isolation and cultivation of selected cells with their transfection in vitro and a subsequent transplantation to a host. In both approaches, the selection of an appropriate vector for the introduction of genes is paramount for success [2]

Gene therapy, defined as the insertion of a gene into recipient cells, was initially considered only as a treatment option for patients with a congenital defect of a metabolic function or late-stage malignancy [3].

Gene transfer, using viral vectors, relies on the ability of viruses to carry and express their genes into host cells. Production of viral gene therapy vectors begins with the genetic modification of the virus. Deletion of the original viral genes for replication or assembling is followed by insertion of the desired therapeutic gene [2, 4]. The ability to reproduce recombinant viruses is restored by using specialized cells called “packaging cells” which are engineered to replace the function of the deleted viral gene [4]. Gene therapy vectors are developed by the modification of different types of viruses. Retroviruses and lentiviruses are non-lytic replicators produced from the cellular membrane of an infected cell which leaves the host cell relatively intact. The lytic replication method involves the release of virions with the collapse of the host cell after infection. Human adenoviruses, adeno-associated viruses and herpes simplex viruses are examples of lytic replicators.

To summarize, viral vectors are the original and most established technology for gene delivery. A wide range of applications have been developed and many virus-mediated gene transfer models are successful. The production of viral vectors, however, is time and cost consuming, transfection efficacy is variable, and the risk of local or systemic infections, leading to fatal outcomes, remains a concern.

In 1995, Hengge et al. first described the direct injection of DNA coding for interleukin-8 genes[5]. Eriksson et al. modified the direct injection technique, termed "micro-seeding", which delivers naked DNA directly into target cells via solid needles mounted on a modified tattooing machine [6]. Another technique used to penetrate the cellular membrane employs the "gene gun". In this approach, 1–5 μm gold or tungsten-coated particles carrying DNA plasmids are propelled into cells [7].

Another method receiving particular attention as a reliable and highly efficient therapy is the cutaneous gene delivery with cationic liposomes. Cationic liposomes (CL) are synthetically prepared vesicles with positively charged surfaces that form loose complexes with negatively charged DNA to protect it from degradation in the wound environment.

Another method receiving particular attention as a reliable and highly efficient therapy is the cutaneous gene delivery with cationic liposomes. Cationic liposomes (CL) are synthetically prepared vesicles with positively charged surfaces that form loose complexes with negatively charged DNA to protect it from degradation in the wound environment. The net positive charge of the complex binds readily to negatively charged cell surfaces to facilitate uptake via endocytosis [8, 9]. Genes encapsulated in CL can be applied either topically or by direct injection [8, 10]. As a positive attribute, non-viral gene therapy is performed without a viral vector, which eliminates the risk of infection and cost of vector production [11].

Embryonic and adult stem cells have a prolonged self-renewal capacity with the ability to differentiate into various tissue types. A variety of sources, such as bone marrow, peripheral blood, umbilical cord blood, adipose tissue, skin and hair follicles, have been utilized to isolate stem cells to accelerate the healing response of disease. Recently, the combination of gene and stem cell therapy has emerged as a promising approach for treatment of disease [11].

Cell and gene therapy using mesenchymal stem cells

In bone marrow, there are different types of tissue stem cells (adult stem cells); i.e. hematopoietic stem cells and mesenchymal stem cells (MSCs). MSCs account for a small population of cells in bone marrow as a non-hematopoietic component with the capacity to differentiate into a variety of cell lineages, including adipocytes, osteocytes, chondrocytes, muscles, and stromal cells [12]. Recent studies demonstrated that MSCs are capable of supporting hematopoiesis and of regulating immune response [13]. In addition, since MSCs can be readily isolated and expanded in vitro, they are expected to be a source of cell therapy. Interestingly, MSCs have the ability to accumulate at the site of: i) tissue/organ damage; ii) inflammation; and iii) cancer when administered in vivo. Therefore, MSCs can be utilized for: i) regenerative therapy; ii) treatment of graft-versus-host disease (GVHD) and Crohn disease; and iii) platform of cancer gene therapy (targeted delivery of anti-cancer agents). Another unique feature of MSCs is little or low immunogenicity due to the lack of expression of co-stimulatory molecules. This phenomenon makes it possible to administer MSCs without HLA matching for cell therapy. A single lot of expanded MSCs from one healthy donor can be utilized for treatment of many patients. Although clinical applications of MSCs have been conducted for the suppression of severe acute GVHD in allogeneic stem cell transplantation [14] and [15] and for regenerative therapy [16] and [17], molecular mechanisms underlying the biological effects of MSCs remains obscure. Finding key molecules for differentiation, immunosuppression, and hematopoietic support of MSCs would be valuable for further augmenting the efficacy of MSCs in a wide range of clinical applications. In this regard, development of the technology for genetic manipulation of MSCs is also important research project. Site-specific integration of a therapeutic gene into a safe locus in the genome should be investigated from the safety standpoint.

MSCs are known to have a tendency to accumulate at the site of tumors, and therefore can be utilized as a platform for targeted delivery of anti-cancer agents [18,19 and 20]. The MSC-based targeted cancer gene therapy can enhance the therapeutic efficacy, because MSCs are considered to reach tumors including metastatic lesions and to deliver therapeutic molecules in a concentrated fashion. This targeted therapy can also reduce systemic adverse side effects, because the anti-cancer agents act locally at the site of tumors without elevating their systemic concentrations. Ozawa et al [21] developed genetically-modified MSCs that produce retroviral vectors encoding HSVtk, aiming at

augmenting therapeutic efficacy of systemic suicide cancer gene therapy (Fig. 1). The tumor tropism and anti-tumor effects of vector-producing MSCs (VP-MSCs) were examined by intravascular injection in tumor-bearing nude mice. MSCs isolated from the bone marrow of SD rats were transfected with plasmid DNA expressing luciferase alone (=non-VP-MSCs) or whole retroviral vector components (LTR-Luc or LTR-HSVtk with Gag-pol and VSV-G) (=VP-MSCs) by nucleofection. To assess tumor tropism of MSCs, nude mice were subcutaneously inoculated with 9 L rat glioma cells or Rat-1 fibroblasts, and were subsequently injected with luciferase-expressing MSCs through the left ventricular cavity. The transgene expression was periodically traced by using an in vivo imaging system. As a result, the transgene expression accumulated at the site of subcutaneous 9 L tumors, but undetectable at the site of Rat-1 fibroblasts. In addition, the injection of luciferase-expressing VP-MSCs caused much stronger signal of bioluminescence at the site of 9 L tumors compared with luciferease-expressing non-VP-MSCs. Immunostaining study showed that luciferase-positive cells (injected MSCs and transduced glioma cells) were detected at the periphery of tumors. To evaluate the therapeutic efficacy, tumor-bearing nude mice were treated with non-VP-MSCs or VP-MSCs combined with HSVtk/GCV system and then the size of subcutaneous tumors was periodically measured. In this model experiments, tumor growth was more efficiently suppressed by injecting VP-MSCs compared with non-VP-MSCs. This study suggests the effectiveness of VP-MSCs in suicide cancer gene therapy. The therapeutic benefit of this strategy should be further examined in orthotopic and metastatic tumor models [21].

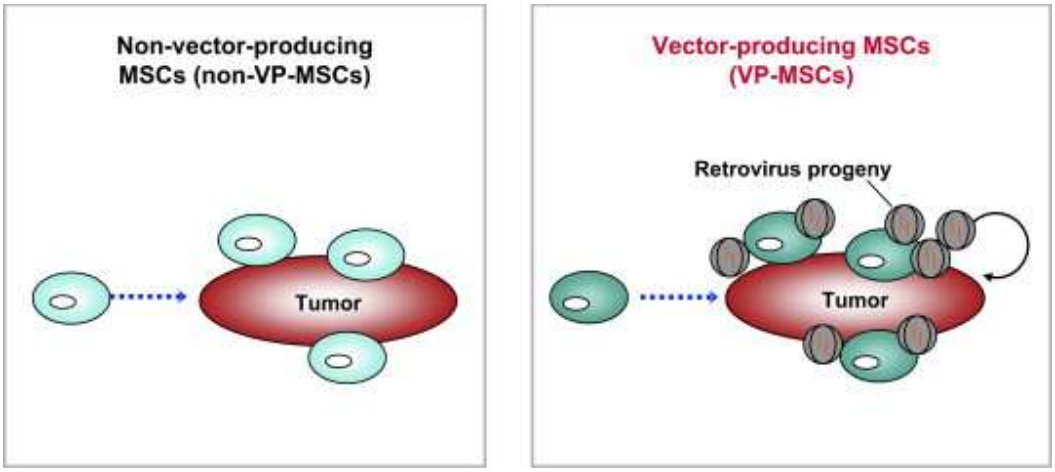

Fig. 1. Development of vector-producing tumor-tracking MSCs to augment suicide cancer gene therapy.

Stem cell-based anti-HIV gene therapy

The current HIV therapy using combinations of antiretroviral drugs termed highly active antiretroviral therapy (HAART) has decreased the morbidity and mortality of HIV infected patients [22, 23]. Although HAART has dramatically improved the patient's quality of life, HAART requires continuous drug administration to suppress virus production from HIV reservoirs [24]. The lifelong treatment creates complications such as drug toxicities and side effects, adherence difficulties, and drug resistance. In addition, lifelong treatment costs can be expensive. Even under HAART, ongoing low level viremia is evident in patients [25], potentially contributing to chronic inflammation, immune dysfunction and accelerated aging [26]. Long-term HIV control and elimination of latently infected cells have become major challenges in the HAART era [27]. Despite extensive efforts to purge residential HIV from reservoirs, existing drug therapies do not eliminate HIV reservoirs even by drug intensification [25]. In contrast, a hematopoietic stem/progenitor cell (HSC)-based gene therapy approach would offer continuous, long-term production of genetically engineered HIV resistant or HIV-targeted cells and a potential to provide stable control or eradication of HIV by a one time or minimal treatment.

Substantial progress has been made in developing a new therapeutic approach using gene therapy through HSCs to attempt to confer long-term resistance against HIV (Fig. 2). HSCs are capable of self-renewal and differentiation into all hematopoietic lineages. In theory, gene therapy approaches that introduce protective genes against HIV via HSCs can continuously produce their anti-HIV genes in all differentiated cells, including HIV target cells such as CD4+ T lymphocytes and macrophages. Successful replacement of a patient's immune system by gene modified HIV protected cells may have the potential to minimize viral loads as well as reduce reservoirs of infected and latently infected cells. Newly differentiated protected cells may prevent viral production and spread from

persistently infected cells and may allow the functional restoration of the damaged immune system. Currently, a significant clinical benefit by HSC-based gene therapy approaches for HIV diseases has not been achieved; however, this approach has the potential to provide long-term control of HIV through a single treatment. If successful, gene therapy through stem cells could free patients from lifelong daily medications and significantly impact their quality of life.

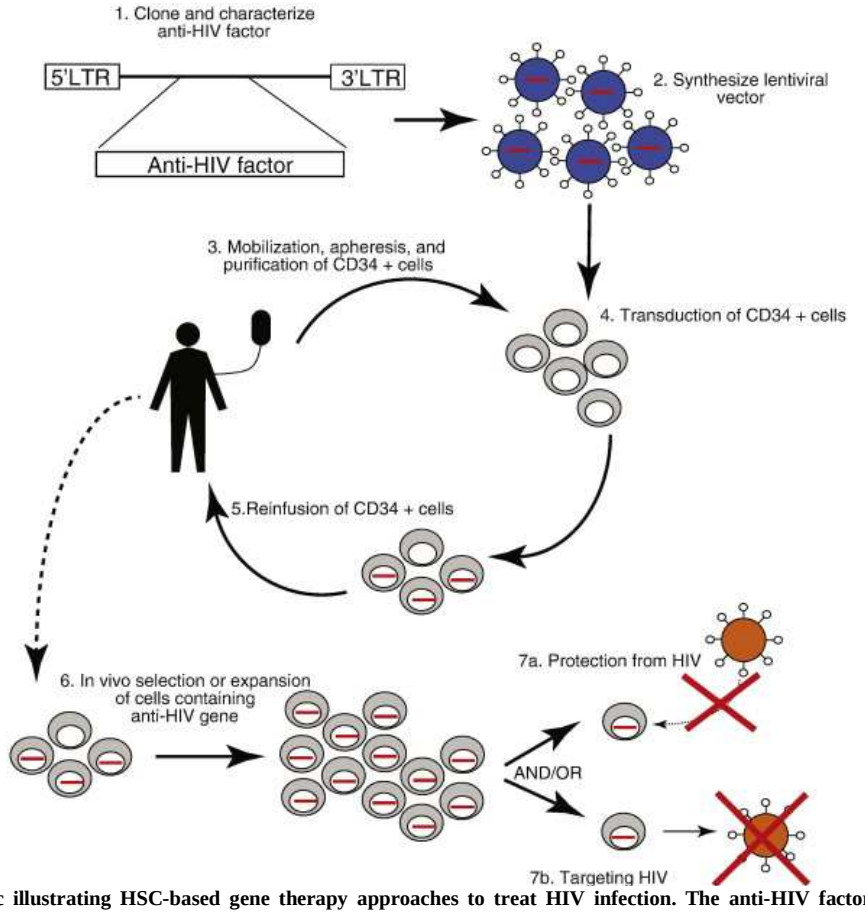

Fig. 2. Schematic illustrating HSC-based gene therapy approaches to treat HIV infection. The anti-HIV factor (such as a siRNA to CCR5 or a molecularly cloned anti-HIV TCR) is cloned and characterized (1) and made into lentiviral vector (or other form enabling genetic transduction of target cells) (2). HSCs are mobilized from the bone marrow of HIV infected individuals and peripheral blood mobilized CD34+ cells are obtained by apheresis and cell sorting (3). CD34+ cells enriched with HSCs are then genetically transduced with the anti-HIV factor (4), and the cells are then reinfused back into the individual (5). Following infusion, the anti-HIV gene containing HSCs should migrate to the bone marrow where they take up residence as long-term hematopoietic progenitors. Anti-HIV gene containing cells protected from infection should undergo selection by HIV in the body and/or cells engineered to target HIV should respond to the virus and proliferate (6). The effects of this are protection of anti-HIV gene containing cells (7a) or directed targeting of HIV or HIV infected cells by anti-HIV gene expressing cells (7b), resulting in the regeneration of antiviral immune responses and targeted eradication of HIV.

Cancer gene therapy using Mesenchymal stem cells

Recent studies have shown the ability of MSCs to migrate to and incorporate within the connective tissue stroma of tumors [28,[29]. This property of MSCs can be used to achieve targeting anti-tumor agents to tumor cells and their micro-metastases with an improvement in murine tumor models of glioma [28,30], melanoma [31], and breast [32] and colon [33] cancers.

The ability of MSCs to migrate toward gliomas has been assessed both in vitro and in vivo [28,34]. In vitro Matrigel invasion assays demonstrated that the MSCs derived from human bone marrow (hMSCs) have the capacity of migration towards gliomas. Furthermore, the tropism of these hMSCs for gliomas may be mediated by specific growth factors/chemokines. It was also observed that murine MSCs transfected with epidermal growth factor

receptor (EGFR) could enhance migratory responses toward glioma-conditioned media in comparison to primary MSCs in vitro. Enhanced migration of EGFR-MSC may be partially dependent on EGF–EGFR, PI3-, MAP kinase, MAP kinases, protein kinase C, and actin polymerization [34]. Another in vivo test indicated that MSCs can localize to human gliomas either after regional intra-arterial delivery or after local intracranial delivery [28]. It was also reported that intravenous injection of MSC-IFN-beta cells into mice with established MDA 231 or A375SM pulmonary metastases led to the incorporation of MSC in the tumor architecture [32]. However, in the healthy organs examined, no engraftment of intravenously administered MSCs was observed [32], indicating MSCs themselves may not cause side effects on the health organs.

As compared with the tumor-targeted nanocarrier systems, which simply involves the ligand–receptor interaction, more factors were implicated in the homing of MSCs to sites of tumor, and therefore, a higher tumor target efficiency of MSCs would be expected (Fig. 3). However, the processes and factors underling the migration of MSC to tumors sites have not been well characterized. Till now, two possible mechanisms have been proposed (Fig. 3). (1) Secretion of chemokines/cytokines from tumors tissues increases the migration of MSCs. The tumor tropism of MSCs might be mediated by several receptor–ligand combinations [35]. Cytokines, such as vascular endothelial cell growth factors, transforming growth factors (TGFs), fibroblast growth factors (FGFs), platelet-derived growth factors, monocyte chemo-attractant, protein-1, and IL-8 released from the neoplasm or inflammatory tissue are possible factors that mediate the activation of MSC migration [34] and [36]. It is already known that these factors released from cancer cells promote the migration of endothelial cell and stromal cell progenitors from the bone marrow towards the cancer bed [37,38] or tissues surrounding the tumor, therefore enhancing the formation of tumor-stroma [39]. Similar mechanisms would be anticipated for tumor-stromal formation in glioma, and the migration of implanted MSCs. Additionally, adhesion molecules, such as b1- and b2-integrins and L-selectin, may also play a significant role in the mobilization and homing of MSCs to gliomas [40,41]. MSCs injected intratumorally are mostly distributed at the border zone between tumor and normal parenchyma. They develop a capsule-like structure, and also infiltrate into the tumor bed relatively uniformly [42]. Tissue repair is a balance between damage and repair. When the balance is broken, the injured vessel requires the recruitment of more progenitor cells which contribute to lesion formation. MSCs exhibit multipotent differentiation potential, and have been shown to give rise to different mesodermal cell lineages, including osteoblasts, chondroblasts, and adipocytes under proper experimental conditions both in vitro and in vivo[43]. Therefore, MSCs could migrate towards the tumor site and participate in the formation of tumor stroma, which provides a new strategy for tumor therapy. Using MSCs as a tumor-targeted vehicle for the delivery of tumor therapeutic gene may decrease the side effects of these genes. For example, Studeny et al. [31] demonstrated that bone marrow-derived mesenchymal stem cells (MSCs) transducted with an adenoviral vector carrying the human β-IFN gene can produce biological agents locally at tumor sites. They also showed that MSCs with enhanced expression of IFN-beta inhibited the growth of malignant cells in vivo. Importantly, this effect required the integration of MSCs into the tumors, and therefore could not be achieved by systemically delivered IFN-beta or by IFN-beta produced by MSCs at a site distant from the tumors. These results indicated that MSCs may serve as a platform for delivering biological agents into tumors. The successful engraftment of MSC in tissues would most likely triggered by tissue damage or tumor growth, which makes MSC excellent candidates for the cell-based delivery of therapeutics to tumor sites [44]. (2) The interaction of the cytokines or chemokines with its corresponding receptors would induce the migration of MSCs towards tumor microenvironment. These receptors, such as CXCR4, CX3CRl, CXCR6, CCRI, CCR7 etc., were expressed on MSCs, and could interact with their respective ligands CXCLl2, CX3CLl, CXCLl6, CCL3 or CCLl9 [45]. Currently, CXCR4 and its receptor, stromal cell-derived factor-1 (SDF-1), are thought to be the most import pair cytokines in attracting of MSCs to migrate to the tumor, as CXCR4-SDF-1α interaction plays an important role in inflammation, tumor tropism of stem cells and the pathology of gliomas [46]. Therefore, the microenvironment of the tumor site plays an important role in the migration of MSCs [47]. Also, a better understanding of the signaling transduction pathways associated with the tropism of these MSCs to gliomas will help to elucidate the role of MSCs in tumor growth and may permit more efficient targeted delivery of MSCs to desired sites for therapeutic purposes [48].

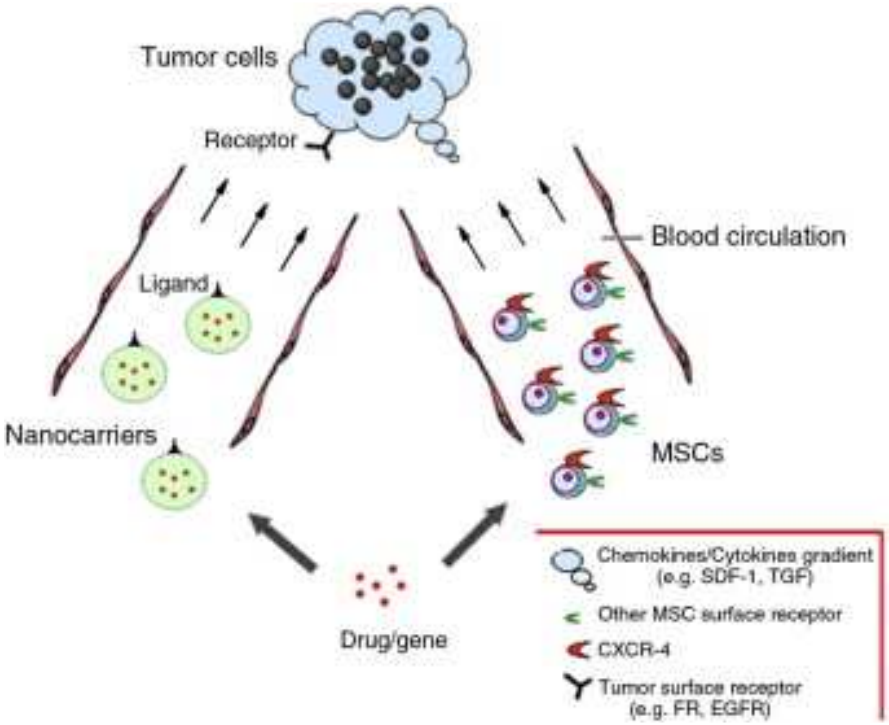

Fig. 3. Schematic of nanocarrier systems and MSCs for site-targeted drug/gene delivery (modified from 48). FR: Folate receptor; EGFR: Epidermal growth factor receptor.

CONCLUSION

Gene therapy and stem cell research have become areas of great importance. Gene therapy has evolved from a purely experimental scientific endeavor to a clinically pertinent treatment for many organ systems. In disease healing, there still remain challenges in the selection of optimal target cells, development of sequential therapeutic methods, and identification of factors which may be detrimental to the introduction of genes. Stem cell research has made a significant contribution to the study of basic mechanisms of cell proliferation and differentiation and has proven essential in the development of cellular therapy. It is evident that the plasticity of the different types of stem cells, both in vitro and in vivo, will have clinical applicability in the future, however, further research is needed on the intrinsic molecular mechanisms that keep stem cells pluripotent or direct them along particular differentiation pathways.

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