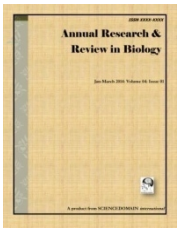

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Mesenchymal Stem Cell-based Cancer Gene Therapy: Application and Unresolved Problems

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Authors' contributions

This work was carried out in collaboration between all authors. Authors STN and VQP wrote the parts of 1, 2 and 3. Authors NKP and PVP wrote the parts of 4, 5 and edited manuscript. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

There are many barriers that have hindered the progress of clinical application of gene therapy as a potential method for treating cancer. These limitations are caused by transduction/delivery failure rates with viral vector systems and were due to the resultant non-specific targeting as well as the triggering of immune system stimulation. Recently, mesenchymal stem cells (MSCs) were found to be advantageous in improving tumor tropism as well as in providing an immune-privilege. Therefore, the combination of viral vector systems and stem cells was suggested as an attractive solution to promote targeted-delivery of anticancer therapeutics to tumor sites. In this regard, many published studies have shown that MSCs could be useful as a potential vehicle for delivering anticancer agents to tumors. In this review, the disadvantages of viral vector systems for gene therapy were analyzed, and an updated account on the role of MSCs in cancer gene therapy was presented. In addition, major safety and therapeutic unresolved problems facing this approach in clinical application were also addressed.

Keywords: Mesenchymal stem cells; gene therapy; tumor tropism; immune-privilege; cancer.

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1. INTRODUCTION

Gene therapy can be classified into two types *ex vivo* (where the cell is manipulated outside the body and transplanted back into the patient's body again) and *in vivo* (where the desired gene is transferred inside the patient's body).

Most of the current *in vivo* studies of cancer gene therapy applications state that the desired genes must enter the cancer cell and function directly or indirectly inside the patient. Transformation of genes requires a carrier vehicle called the *Vector*. Gene delivery method by vectors can be classified into two: *viral* and *non-viral vectors*. *Viral vectors* such as *Herpes Simplex Virus* have been used to successfully treat animal disease models [1-5], cancer [6-10] and chronic pain [11-13]. In the case of *adenoviral s vectors*, the first clinical trials of this virus therapy for cystic fibrosis received no evidence for clinical efficacy, but more clinical studies are committed with adenovirus vectors for the treatment of cancer, some examples include clinical trials on glioblastoma [14], breast cancer [15], gynecologic cancer [16], colorectal carcinoma [10], hepatocellular carcinoma [17] and myocardial angiogenesis [18]. However, *viral vectors* used in targeting cancer cell in the patient's body may have resulted in nonspecific genomic rearrangements in normal cells and had an impact on cell physiology at the integration site. The limitation of this vector includes the stimulation of host immune system.

In the case of *ex vivo* gene therapy, therapeutic cells are modified outside the patient's body to formulate the desired genes carriers, which are then transfected into patients. The types of therapeutic cell that were used in gene therapy treatment include hematopoietic stem cells, neural stem cells, and mesenchymal stem cells. These kinds of stem cells have been demonstrated to possess the ability to suppress host immune system with the resulting efficiency of carrying therapeutic gene to the desired site within the patient's body. Therefore, a combination of gene and stem cell therapy would be a better choice in overcoming the barriers of gene therapy for cancer treatment.

2. SHORTCOMING OF GENE THERAPY

There are two major obstacles that are known to limit the clinical efficacy of gene therapy applications: lack of vector- tumor tropism and the triggering of an immune response.

The human immune system has evolved to fight off foreign antigens that are introduced into the body. This mechanism helps to maintain genetic fidelity and stability throughout the human evolution. Therefore, innate immunity and antigen-specific adaptive immune responses against vector-derived antigens may reduce the efficacy and stability of an in vivo gene transfer. In addition, some vectors are derived from human viruses leading memory immune responses against vector antigens. Moreover, antibody and T-cell responses may be directed against therapeutic gene products that may differ from endogenous proteins [19-21]. Therefore, immune stimulation targeting viral vectors is always the main obstacle for a successful gene therapy.

The majority of gene therapy clinical trials were dependent on viral vector systems to transduce exogenous genes into target cells. The choice of viral vectors may be due to their efficient transducing powers; however, these viral vectors will transduce genes in a non-specific manner. These viral vectors will transduce therapeutic genes non- differentially into both target and non-target cells, which will induce toxicity for normal body cells. For

example, transduction of adenovirus-mediated gene therapy was based on the high-affinity binding of the knob domain of the virus fiber protein in Coxsackie-adenovirus receptor (CAR) to the membrane of the target cell [22,23], however, when the cancer cell down-regulate CAR on their membrane, the specific-transducing ability of the virus would be decreased [23]. In addition, CAR is localized to epithelial tight junctions in vivo with its responsibility in the regulation of epithelial permeability and tissue homeostasis [24], therefore, it will be non-feasible to use CAR as a specific marker to safely and efficiently deliver therapeutic genes into target cells. It was evident that receptor specificity for the efficient transduction of these therapeutic genes is lacking and constitutes a barrier for the widespread safety in the application of adenovirus vectors; hence, the binding between a virus ligand and its cellular receptor is a crucial and important step for a viral infection. Studies aimed at overcoming the safety problems caused by the failure of natural viral vector tropism would need more time to show better and safe outcomes. These unresolved application barriers have obstructed the use of current vectors as specific and efficient targeting tools/ models in cancer therapy. The major aim for future gene therapy studies is to incorporate stem cells as an attractive delivery option targeted at providing potential protection for viral vectors from immune surveillance in support of any targeted delivery of genes or therapeutic proteisn to tumor sites.

3. MESENCHYMAL STEM CELL-BASED CANCER THERAPY

Mesenchymal stem cells are stem cells that have shown great interest due to their apparent ability to home to injury sites following their systemic delivery. It is evident that MSCs possess an inherent ability to both self-renew and differentiate into multiple lineages including osteoblasts, chondrocytes and adipocytes. These cells can easily be isolated from many sources including the stromal compartments of bone marrow, adipose tissue, trabecular bone and skeletal muscles.

Mesenchymal stem cells have the ability to migrate to a variety of organs and tissues when injected, however, localized pathogen-induced inflammatory site will elicit enhanced MSCs homing for general remodeling and repair. Recent reports have shown that MSCs preferentially migrate to sites of injury in an animal model of ischemia [25], central nervous system [26,27], lung [28], liver [29], musculoskeletal tissue[30], ischemic brain [31], kidney [32] and glioma [33].

The tumor homing ability of MSCs seems to be based on chemo-attraction. In fact, MSCs are known to express chemokine and chemokine receptors that can be up-regulated by cytokines. It have been demonstrated that MSCs express a wide range of mRNA encoding cytokines, chemokines and their receptors. Tumor products such as CXCL12/stromal cell derived factor alpha, CX3CL1/fractalkine, CXCL10/interferon-gamma inducible protein play a significant role in their migration [34]. Pro-inflammatory factor including TNF-alpha and IFN-gamma are key in regulating the expression of chemokines and their receptors in MSCs [34, 35]. Interleukin IL-1β, a representative inflammatory factor, has been demonstrated to induce the secretion of trophic factors and adhesion to extracellular matrix components such as collagen and laminin in MSCs [36] will support their adhesion and migration processes. Therefore, expressing chemokines and their receptors in MSCs is considered the key mediators that provide linkage to tumor tropism. Recently, soluble factors produced by macrophages including IL-8, CCL-2, CCL-5 were shown to impact the mobility of MSCs in response to inflammation [37]. Fibronectin-rich matrices at vascular re-modelling sites may also play a key role in their tumor tropism. In fact, adhesion of MSCs with fibronectin has been demonstrated to activate platelet-derived growth factor receptor (PDGFR-β)

phosphorylation in α5β1-integrin dependent manner, resulting in actin reorganization and MSC migration [38].

Another functional advantage of MSCs is their capacity to elicit sell-protective immunosuppressive effects upon their injection into the body. This property is due to the low expression of class II Major Histocompatibility Complex and co-stimulatory molecules on their surface throughout the different pathways of the immune response. This process is achieved by means of direct cell-to-cell interactions and soluble factors secretion, where MSCs can effectively target the main immune cell subsets to inhibit the proliferation of T-cells, B-cells, natural killer cells (NK) and dendritic cell (DC) [39,40]. It is well known that MSCs had the ability to reduce the inflammatory response of peripheral blood mononuclear cells through down-regulating the biological function of T-cell helper 17 (Th17) and inhibiting the expression of IL-7, IL-6 and TNF-alpha [41]. These Th17 cells are known to synthesize signature cytokine IL-17A to mediate localized tissue inflammation. It has been shown that MSCs inhibit Th17 differentiation from naive and memory T-cells as well as Th17 cells from the site of inflammation. The MSCs-derived prostaglandin E2 has been shown to mediate a suppressive effect on Th17 via the EP4 receptor [42]. Interestingly, this inhibitory effect of MSCs was found in inflammatory but not in healthy environments [41]. This pattern of events will support the fact that inflammatory mediators may have cause the immune regulatory property of MSCs. In fact, inflammatory cytokine-induced immunosuppression property of MSCs is manifested through adhesion molecules; MSCs were found to up-regulate the adhesive capacity of T-cells due to overexpression of ICAM-1 and VCAM-1 when co-cultured with T-cells. Hence, the more adhesion molecules that MSCs express, the more immune-suppression properties they possess [43]. Recent studies have shown that galectin-1, a protein detected intracellularly and on the cell surface of MSCs, plays an important role in inhibiting immune effector cells. Blocking of galectin-1 has led to loss of immune-regulatory ability of MSCs [44]. Moreover, MSCs-derived galectin-1 effectively regulated the release of cytokines that have influenced autoimmunity such as TNFα, IFNγ, IL-2, and IL-10. This role provides an interesting novel function for adhesion molecules in MSCs besides their original adhesive functions. In addition, MSCs that were primed with IFN-γ have induced cancer apoptosis through the tumor necrosis factor apoptosis-inducing ligand (TRAIL) [45]. This situation will provide a potential for enhancing the immune suppression ability of engineered MSCs that were primed with inflammatory agent such as IFN- γ.

It is of utmost interest to emphasize that MSCs have the ability to carry their immune-modulating factors throughout the immune system while reaching for tumor sites. It has been shown that MSCs expressing LIGH; a member of TNF family as well as an immune stimulator, will eventually home to the tumor site and reverse the immune-suppressive microenvironment with the activation of CD4 and CD8 T cell response [46]. It is through the exploitation of these advantages, that MSCs were used to target tumors by carrying genes encoding IL-12 [47-49], IL-21 [50,51] in ovarian and retinal cancers. Another interleukin being suggested as an effective anti-tumor agent, IL-24 has been carried effectively by MSCs to target lung cancer sites. The interleukin transduced-MSCs were found to induce apoptosis and cell cycle arrest in cancer cells. The angiogenesis inhibitor PEDF-transduced MSCs were used to inhibit angiogenesis in gliomas [52] as well as Lewis lung cancer [53].

The tumor tropism and immune regulatory role of MSCs provides the perfect vehicle for carrying therapeutic gene to tumor sites without exposing them to the immune system. The transport of suicide genes has been associated with stem cells and has served as a potential for targeted cancer therapy. In this therapy, with the advantages of MSCs, suicide genes were carried to tumor sites by MSCs and the treatment activated pro-drugs into drugs that

killed the tumor cells. Recently, many studies have experimented with MSCs transduced with suicide genes from herpes simplex virus-thymidine kinase [54-56], and cytosine deaminase [57-62] to activate the pro-drug ganciclovir at the tumor site in attempting to reduce tumor size; for example, suicide gene transduced-MSCs associated with adjuvants such as valproic acid have enhanced their killing effects and has induced significantly tumor inhibition [63]. Recent studies that have experimented with MSCs in the delivery of therapeutic gene to treat multiple diseases including cancer by incorporation with lentivirus-mediated [56,64-70], retrovirus-mediated [71-74], plasmid mediated [75,76] and adenovirus mediated transduction [48,77,78]. Almost all the results in animal trials were found to prolong animal survival, reduce complications, and/or lower tumor volume.

4. FUTURE OF STEM CELL-BASED CANCER GENE THERAPY

In contrast to the above exciting news, recent studies have shown that MSCs may enhance the risk of tumor progression. The data in these studies showed that IL1 secreted from cancer cell promoted prostaglandin E of MSCs resulting in the secretion of proteins that have played a role in the inhibition of Th17. These interactions have led to the activation of beta-catenin signaling in cancer cell, resulting in the formation of a cancer stem cell niche via epithelial-mesenchymal transition [79,80]. In addition, MSCs may have provided a source of tumor-supporting microenvironment for osteosarcoma cells enhancing their ability for settlement and colonization that have resulted in tumor growth and metastasis and as well, served as a negative outcome in a rat model [81]. The functional interaction of cytokines and their receptors with extracellular matrix-receptors such as ICAM and VCAM have been suggested to play a positive role in tumor enhancement [81]. Moreover, galactin-1, the molecules expressed by MSCs and provides a role in the immune modulation property of MSCs, has been shown to be a critical factor for tumor promotion relating to the neo-vascularization process [82].

Furthermore, the metastasis of neuroblastoma is arguably caused by MSCs via the secretion of SDF-1 signaling [83] and the role of MSCs in enhancing the initiation of lung cancer also was also discussed [84,85]. The presence of MSCs in primary breast cancer tissues was confirmed and they were suggested to provide a favorable microenvironment for tumor cell growth [86]. Nonetheless, the immune-suppressive property of MSCs was demonstrated to favor tumor growth in allogeneic animal models [87]. These findings confirm that MSCs play a critical role in promoting cancer progression and therefore, the strategies of cancer gene therapy based on MSCs must raise a series of the question about the safety and counter productivity of the use of MSCs in cancer therapy.

5. CONCLUSION

The studies presented in this review have shown that stem cell-based gene therapy has a very promising potential for targeted cancer therapy. These cell-based applications have implicated interesting properties to overcome problems that were encountered with the use of conventional gene therapy. However, the above listed contrasting views and findings that relate to the use of MSC-based models of gene delivery in cancer therapy in connection with the stated problems in their application need to be underscored and thoroughly researched in the near future. These endeavors should attempt to provide extensive efforts to understand the underlying phenomenon and present research solutions in regard to the safety of biological applications of stem cell-based cancer gene therapy. This can be

achieved through in-depth preclinical studies that would maximize potential benefits while reducing the safety risks of these bio therapeutic applications in cancer.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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