Review Article

A new era of gene and cell therapy for cancer: a narrative review

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Background and Objective: With the development of cytology and genomics, genetically modified immune cells have established their role from principle to clinical applications, achieving outstanding therapeutic effects in hematologic malignancies. However, even though encouraging initial response rates, many patients experience a relapse. In addition, there are still many obstacles preventing the use of genetically modified immune cells in treating solid tumors. Nevertheless, the therapeutic effect of genetically engineered mesenchymal stem cells (EMSCs) in malignant diseases, especially solid tumors, has been widely investigated, and related clinical trials are gradually being carried out. This review aims to describe the progress of gene and cell therapy and the current status of stem cell clinical trials in China. This review focuses on the research and application prospects of genetically engineered cell therapy using chimeric antigen receptor (CAR) T cells and mesenchymal stem cells (MSCs) for cancer.

Methods: A literature search of PubMed, SpringerLink, Wiley, Web of Science, and Wanfang database was carried out for published articles on gene and cell therapy up to August 2022.

Key Content and Findings: This article reviews the development of gene and cell therapy and the current status of the development of stem cell drugs in China, with a particular focus given to the advent of the novel therapy of EMSCs.

Conclusions: Gene and cell therapies have a promising therapeutic effect on many diseases, especially recurrent and refractory cancers. Further development of gene and cell therapy is expected to promote precision medicine and individualized therapy and open a new era of therapy for human diseases.

Keywords: Gene therapy; cell therapy; chimeric antigen receptor T-cell immunotherapy; engineered mesenchymal stem cells (EMSCs); cancer treatment

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Introduction

Drugs can be generally classified into two categories: chemical small molecule drugs and biological macromolecular drugs. With the development of science and technology, cell drugs have shifted from research and development to application. In addition, artificial organ cloning is also expected to be possible in the future. As drugs became increasingly complex in structure and diverse in function, their development has also become more challenging.

In 2017, the use of genetically modified T cells, known as chimeric antigen receptor (CAR) T-cell immunotherapy, was approved by the US Food and Drug Administration (FDA), revolutionizing tumor therapy (1). CAR-T cell therapy, which includes a combination of gene and cell technology, has marked the beginning of the "new era of gene and cell therapy" (1,2). Thus far, CAR-T cell therapy has shown good application prospects in the treatment of various hematologic malignancies, such as acute lymphoblastic leukemia (ALL) (3), lymphoma (4), acute

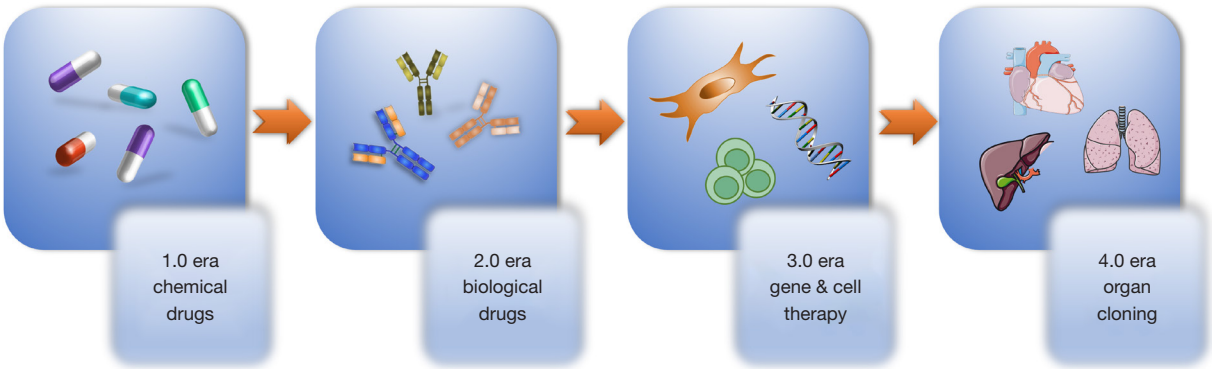

Figure 1 A map showing the development process of drugs. Chemical drugs belong to the 1.0 era, biological drugs belong to the 2.0 era, gene and cell therapy drugs belong to the 3.0 era, and tissue and organ cloning belong to the 4.0 era.

myeloid leukemia (5), and multiple myeloma (6). However, CAR-T cell therapy has been found to be less effective in the treatment of solid tumors due to the complexity of the microenvironment, heterogeneity of solid tumor antigens, diversity of immune evasion mechanisms, and difficulties in migration and permeation to solid tumors (7,8). On the other hand, genetically engineered mesenchymal stem cells (EMSCs) have shown a promising effect when treating solid malignant tumors (9-11).

In the historical development of drugs, if the development of chemical drugs can be called the 1.0 era and the development of biological drugs is called the 2.0 era, then the development of gene and cell therapy drugs can be considered the 3.0 era, while tissue and organ cloning will be considered the 4.0 era (*Figure 1*). This article reviews the development of gene and cell therapy and the advent of a new era of therapy. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3882/rc).

Methods

A literature search of PubMed, SpringerLink, Wiley, Web of Science, and Wanfang database was conducted on articles on gene and cell therapy published until August 2022. The key search words and terms were as follows: "gene therapy", "cell therapy", "chimeric antigen receptor T (CART) cell immunotherapy", AND "tumor" OR "cancer", "human umbilical cord-derived mesenchymal stem cells", "engineered mesenchymal stem cells", "mesenchymal stem cells" AND "trial" AND "tumor" OR "cancer" (*Table 1*).

Discussion

The 21st century is the era of gene and cell therapy

The rise of gene therapy

According to the FDA, gene therapy is defined as products "*that mediate their effects by transcription and/or translation of transferred genetic material and/or by integrating into the host genome and that are administered as nucleic acids, viruses, or genetically engineered microorganisms*" (12). Gene therapy can be divided into *in vivo* and *ex vivo* therapy based on whether the engineering and modification of cells for therapeutic use are performed *in vivo* or *ex vivo* before being administered to the recipient (12).

Using gene therapy to treat human genetic diseases was proposed more than 50 years ago (13). Although the road from theory to clinical application has been long and challenging, gene therapy has provided new choices in therapy for multiple diseases. Successful gene therapies have been developed from the administration of viral vectors *in vivo* directly to the adoptive transfer of genetically engineered cells and genome editing (14). The first human gene therapy experiment was performed in 1970 by Stanfield Rogers, who tried to treat 2 children with hyperargininemia by injecting arginase-containing papillomavirus but failed to achieve a successful outcome (15). In 1999, Jesse Gelsinger volunteered for a gene therapy trial conducted at the University of Pennsylvania in Philadelphia for the rare genetic disease ornithine transcarbamylase deficiency, but he died shortly after the trial (16). The first successful clinical results for a gene therapy trial were published in 2000 and involved severe combined immunodeficiency (SCID)-X1, paving the

Table 1 The search strategy summary

Items	Specification
Date of search	From March 10, 2022, to August 5, 2022
Databases and other sources searched	English databases (PubMed, SpringerLink, Wiley and Web of Science) and Chinese database (Wanfang database)
Search terms used	"Gene therapy", "cell therapy", "chimeric antigen receptor T (CART) cell immunotherapy" AND "tumor" OR "cancer", "human umbilical cord-derived mesenchymal stem cells", "engineered mesenchymal stem cells", "mesenchymal stem cells" AND "trial" AND "tumor" OR "cancer"
Timeframe	March 3, 1972–August 5, 2022
Inclusion and exclusion criteria	The inclusion criteria were as follows: (I) articles written in English and Chinese; (II) articles about gene therapy and cell therapy; (III) articles related to CAR-T cell immunotherapy; (IV) articles about mesenchymal stem cells and engineered mesenchymal stem cells; and (V) articles that involved mesenchymal stem cells and clinical trials
	The exclusion criteria were as follows: (I) articles written languages other than Chinese and English; and (II) meeting abstracts, conference summaries, case reports, and letters
Selection process	Articles were independently evaluated by 3 reviewers using the same standard as above

way for the gene therapy for other diseases (17,18). Over the past decade, messenger RNA (mRNA)-based therapeutics have emerged as highly attractive novel treatments, especially for cancers, with tremendous progress being made in technologies regarding lipid nanoparticles (LNPs) within the design of nonviral vectors for gene delivery (19,20). In 2012, Glybera was approved as the first-ever gene therapy drug for treating a rare disease of lipoprotein lipase deficiency caused by a congenital gene defect (21). The success of Glybera indicated that human genetic diseases caused by congenital gene defects could be repaired with drugs. In the same year, American scientist Jennifer A. Doudna and French scientist Emmanuelle Charpentier developed the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (CAS9) gene-editing technology that revolutionized the field of gene therapy (22). In 2017, the FDA approved the listing of CAR-T cells (1), which was of epoch-making significance in the fight against cancer. The approval further increased the enthusiasm for capital investment in the gene therapy industry and advanced the development of the field. Remarkably, two LNP-based mRNA vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were granted the first historic emergency use authorization from the FDA in 2020, which was a milestone for the use of mRNA-based gene therapy and attracted extensive attention worldwide (23,24).

The advent of the era of cell therapy

The 3.0 era of gene and cell therapy drugs began with the development of gene and cell biology technologies. From the perspective of life development, diseases in a living body usually indicate problems in basic unit of life—cells. Therefore, gene or cell therapy aims to repair damaged cells or tissues rather than the disease itself. For example, to treat infectious diseases, it is necessary to eliminate pathogenic microorganisms and repair and regenerate tissues and organs damaged by disease. For the management of cancer, cancer immunotherapy is the latest treatment method (25). Although an excessive immune response kills cancer cells, it also affects the surrounding healthy tissues and organs. Thus, finding a therapy that can mediate immune responses and repair and regenerate damaged tissues is essential. Accordingly, cell therapy has become a novel strategy for treating such diseases (26).

Currently, the main focus of research and development of cell drugs includes immune and stem cells. Immune cells refer to cells that participate or assist in the process of an organism's immune response. Lymphocytes have a key role in the immune process. During the immune response, various lymphocyte groups not only restrict each other but also cooperate to collectively exert immune function. CAR-T cells, a new type of therapeutic T cell (1,27), are exemplary immune cells used for cell therapy; they express chimeric receptors that can recognize specific

Table 2 Clinical trials of MSC-related drugs that have been approved by the CDE in China

Auto-/allo-	Cell type	Source of MSCs
Auto- [3]	Autotransfusion of cells [2]	Bronchial basal layer cells [2]
	Mesenchymal progenitor cells [1]	Adipose tissue [1]
Allo- [31]	Mesenchymal stem cells [25]	Umbilical cord [18]
		Bone marrow [3]
		Adipose tissue [1]
		Dental pulp [1]
		Placenta [1]
		Uterine blood [1]
	Precursor cells [3]	Human embryogenic mesenchymal precursor cells [3]
	Progenitor cells [2]	Adipose mesenchymal progenitor cells [1]
		Vascular endothelial progenitor cells [1]
	Human embryogenic cells [1]	The ectoderm of the blastocyst stage on day 8–9 of embryonic development [1]

The numbers in square brackets represent the number of clinical trials for MSCs approved by the CDE in China. CDE, Center for Drug Evaluation; MSC, mesenchymal stem cell; auto-, autologous; allo-, allogeneic.

tumor antigens on the surface of T cells through genetic engineering (28). The expanded CAR-T cells can be reinfused into the patients to kill tumor cells (29). Stem cells, which can self-proliferate and differentiate, are another popular product for cell therapy. A large amount of quiescent stem cells are stored in tissues and organs, forming the basis for organ development and regeneration (30). The clinical application of stem cells has spawned the development of regenerative medicine, bringing hope for treating various diseases (31). One of the most representative stem cell types is mesenchymal stem cells (MSCs), a heterogeneous subset of stromal stem cells that exists in many fetal and adult tissues and can differentiate into cells of the mesodermal and other embryonic lineages (32,33). MSCs are a type of multipotent stem cell with the potential for self-renewal and multidirectional differentiation (34) as well the exertion of multidirectional anti-inflammatory (35), immunomodulation (36), tissue repair, and targeted chemotaxis functions (37), representing a wide range of clinical applications (26).

The current status of the development of stem cell drugs in China

In recent years, the Chinese government has actively promoted and regulated the development of the stem cell industry. At the time of writing, stem cell products are still in the developmental stage in China. As of June 2022, stem cell research and development enterprises have submitted 44 investigational new drug (INDs) applications for MSC-related drugs to the National Center for Drug Evaluation (CDE) in China, 34 of which have been approved thus far (*Table 2*). The MSC products approved for registered clinical trials constitute China's first echelon of stem cell drug development. MSC products that have entered the phase II clinical trial stage represent the vanguard of China's emerging stem cell drug industry and are expected to achieve future breakthroughs in new stem cell drug innovation in China.

MSCs were originally isolated from adult bone marrow, and their other main sources include the umbilical cord, adipose tissue, muscle, and placenta (38). There are records of the umbilical cord being used as medicine in China since ancient times, which can be traced to the Tang dynasty. Recent studies have confirmed that umbilical cord tissue is rich in MSCs (39). The biological properties and functions of umbilical cord-derived MSCs (UC-MSCs) are similar to those of bone marrow-derived MSCs (BM-MSCs) and were found to have good effects in preclinical and clinical studies in the treatment of various diseases (40). The research and development of UC-MSCs in China began early; therefore,

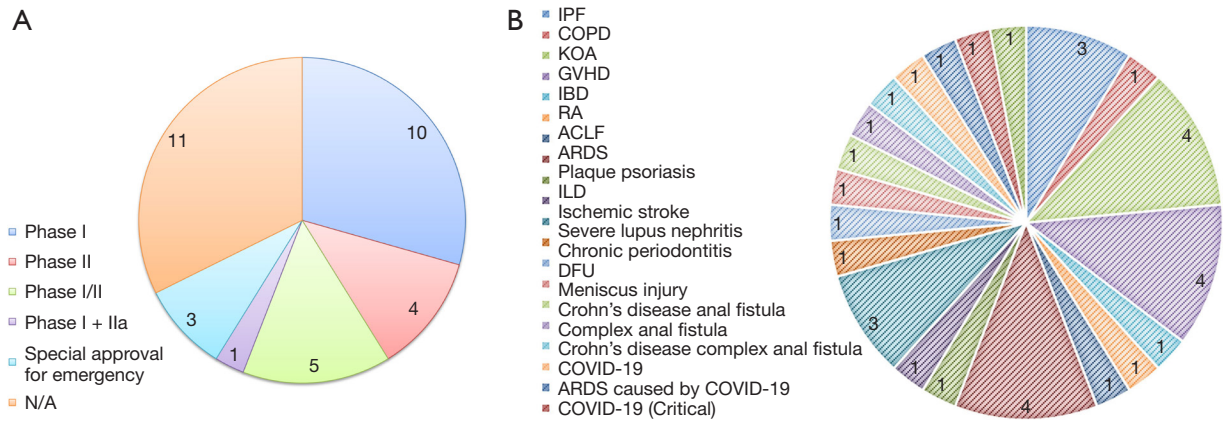

Figure 2 The progress and applications of clinical trials of MSC-related drugs approved by the CDE in China. (A) The progress is mainly in phase I and II trials. (B) There are 34 investigational new drug applications for MSCs approved by the CDE in China, with none of these cells being genetically modified. These indications of MSC therapy have been widely studied as shown in (B), including IPF, COPD, KOA, etc. N/A, not applicable; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; KOA, knee osteoarthritis; GVHD, graft-versus-host disease; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; ACLF, acute-on-chronic liver failure; ARDS, acute respiratory distress syndrome; ILD, interstitial lung disease; DFU, diabetic foot ulcer; COVID-19, coronavirus disease 2019; CDE, Center for Drug Evaluation; MSC, mesenchymal stem cell.

the processes of industrialization are relatively complete.

Moreover, many clinical studies related to the human UC-MSCs (hUC-MSCs) are underway (41-44). Compared with MSCs from other sources, hUC-MSCs have stronger immune regulation and regeneration function and are currently recognized as a stem cell type of "clinical utility". They have many major advantages (45). First, the umbilical cord is their most abundant source (46). They can be easily collected with a low risk of contamination of cells and pathogens from the maternal source (47,48). Additionally, hUC-MSCs are suitable for large-scale commercial production at a lower cost. Second, since the umbilical cord is regarded as medical waste, its use is associated with fewer ethical and moral restrictions (46). Third, hUC-MSCs have stable cells and strong biological functions. They are more primitive than BM-MSCs and have a stronger ability to proliferate and differentiate (49). Fourth, due to low immunogenicity (50), they can be used for allotransplantation. To summarize, hUC-MSCs have the characteristics of drugs, including "industrialization, scalization, and standardization" (51), and currently represent the most promising MSC drug.

hUC-MSC-related clinical trials account for more than 50% (18/34) of the MSC-related clinical trials in China and have a wide range of applications, including knee osteoarthritis, acute-on-chronic liver failure, rheumatoid arthritis, inflammatory bowel disease, graft-versus-host disease, chronic periodontitis, ischemic stroke, diabetic foot, idiopathic pulmonary fibrosis, and chronic plaque psoriasis (*Figure 2*).

In the United States, the development of drugs based on MSCs mainly derives from bone marrow and adipose sources, and there is less drug development for hUC-MSCs. China will likely be the first to approve hUC-MSCs as drugs for clinical use. In addition, the application of genetic EMSCs against cancer has also received extensive attention.

The 3.0 era of gene and cell drugs in cancer therapy

The development of CAR-T cells

The successful development of CAR-T cells heralds the arrival of the era of gene and cell drugs and tumor cures (52,53). CAR-T cell therapy has produced noteworthy results in treating certain hematologic malignancies (54). The first patients with relapsed or refractory B-cell leukemia treated with CD19-targeted CAR-T cells showed favorable responses (3,55,56). Thus, CAR-T cell therapy is a cause for optimism in some patients with relapsed and refractory hematologic malignancies. CAR-T cell therapy was approved by the FDA in 2017 for the treatment of ALL (56-59) and to treat diffuse large B-cell lymphoma in the United States (56,60). FDA approvals were also

obtained for the use of CAR-T cell therapy to treat mantle cell lymphoma in 2020 (61) and multiple myeloma in 2021 (62,63). However, most patients with B-cell malignancies were found to relapse within 1 to 2 years after CAR-T cell treatment (56). For example, even though the initial complete response rates of patients with ALL were greater than 80% after treatment with CAR-T19 cell therapy, nearly 50% of patients were found to relapse within the first year (56,59,64). The common mechanisms associated with relapse after CAR-T cell therapy include loss of the tumor antigen, T-cell exhaustion, and immunosuppression of the tumor microenvironment (TME) (52). Moreover, many obstacles prevent the use of CAR-T cell immunotherapy in the treatment of solid tumors (7).

The microenvironment of solid tumors is a decisive factor in the proliferation, metastasis, chemotherapy resistance, and immune escape of tumor cells (65,66). There are a large number of matrix and immunosuppressive components that have important roles in this process (67). A physical barrier prevents the infiltration of CAR-T cells (68). Immunosuppressive cells, such as myeloid-derived suppressor cells, regulatory T cells (Tregs), and tumor-associated macrophages (68,69) as well as their secreted inhibitory factors, such as interleukin (IL)-10 and IL-4, inhibit the connection, dampening the effect of CAR-T cells on tumor cells through a complex signaling network (70). Furthermore, solid tumors are often accompanied by aberrant vasculature and dense fibrogenic extracellular matrix, forming a hypoxic, acidic microenvironment that lowers the survival and activation of infiltrating T cells (71-73). Due to the heterogeneity between various malignant tumor tissues and patients, CAR-T cell therapy is only effective on one part of tumor cells and can sometimes increase the risk of tumor recurrence and metastasis (74,75). Therefore, research for more effective gene and cell drugs for cancer therapy, particularly for solid tumors, is urgently required, and MSCs may be an ideal choice.

The development of EMSCs

Treating tumors with naïve MSCs is a double-edged sword (76). Naïve MSCs are recruited to tumor sites by tumor cells where they can inhibit or promote tumor proliferation and development, depending on the different cytokine profiles released. Thus, MSCs can both suppress and promote cancer cells (10,77,78). Cancer cells can trigger an inflammatory response within the tumor, thereby establishing a tumor-promoting microenvironment (79).

Inflammation is a common feature of the TME, and infiltration of immune cells into tumors has a dual role: it can lead to antitumor responses or suppress immune responses to promote malignant progression (79-81). Furthermore, given the repeated alternation of tissue damage and regeneration due to the constant inflammation in tumors (65), tumors are considered "wounds that do not heal" (82).

Clinically, about 90% of patients with cancer die of tumor metastasis. Thus, the prevention of metastasis is essential for prolonging the survival of patients (83). Preventing tumor occurrence and metastasis is the most economical and effective strategy. Inflammation has an important role in the different stages of tumor development, including the initiation stage, development stage, tumor transformation stage, and infiltration and metastasis stage of tumorigenesis (84). Additionally, inflammation affects immune surveillance and response to tumor therapy (85). The anti-inflammatory effect of MSCs suggests their potential to prevent tumorigenesis and metastasis (86,87). hUC-MSCs have been reported to inhibit tumorigenesis by reducing the proportion of macrophages in mice with colon cancer (88). MSCs injected intravenously can be detected in the tumor tissue, revealing inhibited lung metastasis formation in mice, and the possible mechanism may be direct interaction between MSCs and cancer cells through soluble factors (89). However, for patients with some advanced tumors, naïve MSCs cannot achieve meaningful therapeutic effect, and the immunosuppression effects of MSCs may even have a role in promoting tumor development (86).

Since MSCs can enter the sites of tumors and metastasis, they can be used as "Trojan horses of cells" to transport antitumor factors into the TME at sites of tumors and metastasis (*Figure 3*) (90). Furthermore, MSCs can be genetically modified, and components expressed by EMSCs can exert effects of antiproliferation, proapoptosis, and antiangiogenesis (90,91). Besides these effects, MSCs can be modified to express the cytokines (i.e., tumor necrosis factor superfamily, interferons, and, interleukins) that can increase endogenous tumor immunity and effectively inhibit tumor growth, development, and metastasis (92-94). In addition, by coating or via genetic engineering antibodies, MSCs can stably and constantly express antibodies against tumor-specific ligands to tumor loci, which can inhibit tumor growth and kill tumor cells (95,96). Moreover, MSCs can also be engineered to carry suicide genes to produce toxic substances that specifically inhibit tumor growth while sparing normal tissue surrounding the tumor (97).

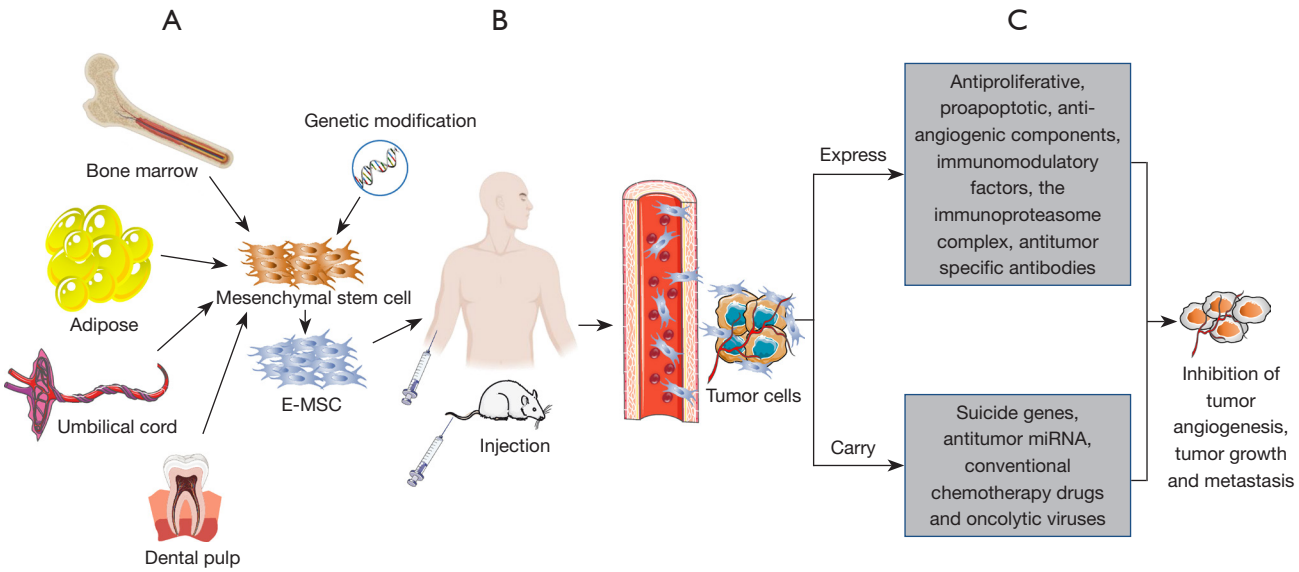

Figure 3 A schematic diagram of the source, engineering modification, and antitumor mechanisms of mesenchymal stem cells. (A) MSCs can be derived from bone marrow, adipose, umbilical cord, dental pulp, placenta, and other tissues (38). (B) EMSCs can be administered via intravenous injection, intraperitoneal injection, intrathecal injection, etc. (76). (C) Once inside the body, MSCs migrate to sites of tumor and metastasis, and then express antiproliferative, proapoptotic, and antiangiogenic components (9) and immune regulators or immunoproteasome complex to increase tumor immunity, effectively inhibiting tumor growth, development, and metastasis. Furthermore, EMSCs can exert an antitumor function by secreting antibodies against tumor-specific ligands to tumor loci. Moreover, MSCs can be used as carriers for suicide genes, antitumor microRNA, the conventional chemotherapy drugs and oncolytic viruses, which could selectively kill cancer cells. MSC, mesenchymal stem cell; EMSC, engineered mesenchymal stem cell; miRNA, microRNA.

Furthermore, MSCs can deliver therapeutic antitumor microRNA (miRNA) to inhibit tumor angiogenesis, growth, migration, and chemotherapy resistance (98-100). Additionally, MSCs can be used as delivery vehicles for conventional chemotherapy drugs with antitumor effects (101) and oncolytic viruses that can selectively kill cancer cells (102). More importantly, MSCs can be converted into potent antigen-presenting cells (APCs) by either genetically engineering them to express the immunoproteasome complex (103,104) or by pharmacological means using UM171A (105) or tranylcypromine, which can inhibit the lysine-specific demethylase 1 (LSD1) in MSCs (106). These factors promote APC-like properties that may be conducive to designing universal MSC-based anticancer vaccines (103).

Moreover, MSCs can promote tissue and organ repair (107), improve the local microenvironment of the tumor (108), and prevent tumor recurrence (109), which can overcome some obstacles of CAR-T cell therapy in the treatment of solid tumors. Consequently, EMSCs have great potential for clinical applications in treating cancer.

Clinical studies of EMSCs

Thus far, few clinical trials on EMSCs modified by viruses or nonviruses have been conducted for different diseases. The first clinical study on the use of EMSCs in treating solid tumors, reported in 2010, used the systemic oncolytic virus provided by autologous bone marrow MSCs to treat metastatic neuroblastoma. One-quarter of patients achieved a complete response more than 4 years after diagnosis (36 months after the first treatment), which was the first time a patient with stage IV neuroblastoma achieved a complete response in the investigator's 20 years of experience with neuroblastoma (110). In 2019, another clinical trial, the phase I–II treatment of advanced tumors with mesenchymal cells 1 (TREAT-ME-1) trial, which was focused on herpes simplex virus thymidine kinase (HSV-TK) -modified MSCs against advanced gastrointestinal tumors with suicide gene therapy system, evaluated the safety and tolerability of transgenic autologous MSCs combined

with ganciclovir against advanced gastrointestinal adenocarcinoma and showed preliminary efficacy of the therapy in clinical stabilization of the disease (111). In the latest clinical trial, published in 2020, autologous MSCs carrying the oncolytic virus Icovir-5 called Celyvir, an advanced therapy medicine for patients with advanced tumors, were used to treat malignant diseases. The study found no grade 2 to 5 toxicities, which suggested the combination of MSCs and oncolytic adenovirus was safe. Furthermore, the disease was stabilized in 2 patients with neuroblastoma (112). Although further phases of clinical trials are needed, EMSCs provide a valuable option for some incurable diseases in clinical practice.

Conclusions

Gene and cell therapies have broad application prospects in treating human diseases, especially autoimmune diseases and malignant tumors. These may further promote the development of precision medicine and bring changes to traditional medicine. According to patients' genes, environment, and lifestyle, an individualized treatment plan can be systematically formulated by considering the optimal treatment effect and the optimal medical cost-benefit ratio. Among the different cell types, MSCs are emerging as a potential and valuable cellular drug that can be successfully applied in cancer, autoimmune diseases and various tissue or organ abnormalities (e.g., neurodegenerative diseases, cardiovascular diseases and bone tissue fractures) in the future (9,76,113-117). Although further clinical practice is required, we believe that naïve MSCs and EMSCs will eventually open a new era of human disease prevention and treatment in the near future.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3882/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3882/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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