Mesenchymal stem cell carriers enhance anti-tumor efficacy of oncolytic virotherapy (Review)

XIANYAO WANG[1-3], XING ZHAO[1-3] and ZHIXU HE[2,4]

[1]Center for Tissue Engineering and Stem Cell Research, Guizhou Medical University; [2]Key Laboratory of Adult Stem Cell Translational Research, Chinese Academy of Medical Sciences, Guiyang, Guizhou 550004; [3]Department of Immunology, Guizhou Medical University, Guiyang, Guizhou 550025; [4]Department of Pediatrics, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China

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Abstract. Oncolytic viruses (OVs) specifically infect, replicate and eventually destroy tumor cells, with no concomitant toxicity to adjacent normal cells. Furthermore, OVs can regulate tumor microenvironments and stimulate anti-tumor immune responses. Mesenchymal stem cells (MSCs) have inherent tumor tropisms and immunosuppressive functions. MSCs carrying OVs not only protect viruses from clearing by the immune system, but they also deliver the virus to tumor lesions. Equally, cytokines released by MSCs enhance anti-tumor immune responses, suggesting that MSCs carrying OVs may be considered as a promising strategy in enhancing the anti-tumor efficacies of virotherapy. In the present review, preclinical and clinical studies were evaluated and discussed, as well as the effectiveness of MSCs carrying OVs for tumor treatment.

Correspondence to: Dr Zhixu He, Key Laboratory of Adult Stem Cell Translational Research, Chinese Academy of Medical Sciences, 9 Beijing Road, Guiyang, Guizhou 550004, P.R. China
E-mail: hzx@gmc.edu.cn

Dr Xing Zhao, Center for Tissue Engineering and Stem Cell Research, Guizhou Medical University, 9 Beijing Road, Guiyang, Guizhou 550004, P.R. China
E-mail: xingzhao@gmc.edu.cn

Abbreviations: MSCs, mesenchymal stem cells; OVs, oncolytic virus; OVT, oncolytic virotherapy; TME, tumor microenvironment; TAAs, tumor-associated antigens; TANs, tumor-associated neoantigens; DAMPs, danger-associated molecular patterns; PAMPs, Pathogen-associated molecular patterns; OAD, oncolytic adenovirus; NK, natural killer; DC, dendritic cell

Key words: oncolytic virus, mesenchymal stem cells, cellular carriers, tumor tropism, immunosuppressive function, oncolytic virotherapy

Contents

1. Introduction

With the development of targeted therapies and cellular immunotherapies, such as T cell-based, natural killer (NK) cell-based and dendritic cell (DC)-based immunotherapies, the therapeutic efficacy of cancer treatment has been greatly improved (1). However, the overall remission and survival rate of patients with certain tumors has not been fundamentally addressed. In recent decades, oncolytic viruses (OVs) have generated widespread interest, and have become a major focus of interest for clinicians and scientists (2,3). These viruses include adenovirus, measles virus, reovirus, herpes simplex virus, Newcastle disease virus, vesicular stomatitis, vaccinia virus and poliovirus (4,5).

Previous preclinical and clinical studies have demonstrated that the intratumoral injection of OVs is effective, although the efficacy toward disseminated and metastatic tumors remains modest (6,7). Numerous factors can affect viral efficiency in reaching tumor tissue, including viral destruction by the immune system and viral absorption by tissues and organs (8,9). Therefore, appropriate carrier vehicles are required to deliver OVs to tumor sites in order to improve therapeutic efficacy.

In recent years, mesenchymal stem cells (MSCs) have become a promising cellular vehicle for anti-tumor drug delivery, thanks to their inherent tumor tropism (10-13). MSCs can specifically migrate to the tumor or inflammatory site. A recent review has reported that MSCs can be modified by advanced approaches to suppress tumor growth (14). Furthermore, MSCs exert immunosuppressive functions, by inhibiting NK proliferation, cytotoxicity and cytokine production (15), suppressing differentiation and function of DC (16) and inducing therefore the emergence of regulatory

T cells. These features make MSCs ideal candidates for OVs delivery. In the present review, an overview of MSC loading of OVs for oncolytic virotherapy was provided. We briefly introduced MSC characteristics for OV delivery and summarized developments in the MSC oncolytic virotherapy arena.

2. Mechanisms of oncolytic virotherapy

In the last decades, great progress has been made in elucidating the molecular mechanisms of OV infection. OVs can infect target cells using low-affinity binding to sialic acid residues, from where they internalize via specific high-affinity receptors (17,18). The expression of OV strain receptors on the cell surface is a crucial factor in determining viral infection (19). However, accumulating evidence from preclinical and clinical studies has indicated that growth conditions and genetic background of tumor cells can affect cell sensitivity to OVs (19). For example, cathepsin B and cathepsin L are critical for viral shelling, which is associated with the sensitivity of tumor cells to oncolytic reoviruses; however, virus shelling is also limited by low levels of cathepsin B and cathepsin L in normal cells (20). In addition, Ras mutations can increase cell sensitization to reoviruses (21,22). Following OV infection, virus progeny replicates highly in tumor cells, eventually lysing and killing infected cells. Subsequently, tumor cell lysis releases infectious viral progeny that spreads to surrounding tumor cells, causing more tumor cells to undergo oncolysis. However, OV replication is often limited in healthy cells, thus viral clearance is rapid with minimal oncolysis (23).

With expanding OV research, virotherapy has gradually changed from direct oncolysis to virus mediated anti-tumor immunity (24,25). It has been demonstrated that the immune system serves a crucial role in oncolytic virotherapy. On the one hand, inherent and adaptive immunities control viral infections, reducing or eliminating their oncolytic potential. On the other hand, viruses can trigger anti-tumor immune responses through a variety of mechanisms. Firstly, tumor-associated antigens (TAAs) and neoantigens (TANs), which are released by tumor cells, are captured by antigen-presenting cells and are ultimately activated by tumor specific T cells in order to respond to tumor antigens (26,27). Secondly, OVs can promote immunogenic cell death by cell necrosis, immunogenic apoptosis and autophagic cell death (27-30), subsequently releasing danger-associated molecular patterns (DAMPs), including ATP and high-mobility group box 1 protein (28,31,32). In addition, virus-induced tumor cell death also leads to the release of pathogen-associated molecular patterns (PAMPs), such as nucleic acids, proteins and viral capsid components (33,34). DAMPs and PAMPs are recognized by pattern recognition receptors (PRRs) on innate immune cells, such as DC and NK cells, in turn activating NF-κB signaling and releasing type I interferon (IFN), proinflammatory cytokines and chemokines (35,36). However, these molecules promote the recruitment and activation of macrophages, NK, DC and tumor specific cytotoxic T lymphocytes to the tumor microenvironment (TME), and help reverse the immunosuppressive state of TME (32,35-38). In addition, tumor cells infected with OVs express virus-specific antigens on their surface, which facilitate their destruction by anti-viral T cells (39). Therefore, OVs can induce anti-tumor immune response, even if the virus does not effectively replicate (40).

3. The main hurdles limiting OV efficacy for virotherapy

In 2015, the US Food and Drug Administration approved Amgen's talimogene laherparepvec (T-VEC or Imlygic®) for the treatment of melanoma (41), and in December of the same year, T-VEC was approved by the European Medicines Agency for the treatment of unresectable stage IIIB/C and stage IVM1a melanoma (42). The T-VEC success has significantly promoted OV research and clinical applications, and aroused great interest in the academic and industry communities (43,44). However, in most cases, the elicited immune response limits the killing effects of OVs, the efficacy remains modest, and the ultimate therapeutic efficacy of OVs as a systemic administration reagent is limited (45-47). There are four reasons that may explain this phenomenon: i) Individuals carry anti-viral antibodies, such as anti-reovirus and anti-measles virus antibodies. After systemic administration, OVs are quickly cleared by pre-existing antibodies, which hinders OV efficacy (48,49); ii) OVs are cleared by macrophages located in the liver and spleen; iii) for solid tumors, OVs must pass through the endothelial layer to reach target cells, therefore physical barriers pose a significant challenges to viral transmission; and iv) due to interactions between OVs and antigen presenting cells, extensive anti-viral immunity, pre-existing circulating antibodies and blood factors, such as coagulation factors and complement proteins, OVs are easily cleared by the host's immune system (50). Taken together, these factors suggest that it may be difficult to determine whether enough OV particles could reach the tumor site. In the following sections of this review, current strategies for OVs loading by MSCs for anti-tumor therapy will be discussed.

4. MSC biology

MSCs are adult stem cells derived from the mesoderm that can be isolated from various tissues, including bone marrow, adipose tissue, dental pulp, placenta, amniotic fluid, umbilical cord, Wharton's jelly and umbilical cord blood (51,52) (Fig. 1). Although MSCs derived from these tissues contain diverse background genetic lineages, they can exert intrinsic and extrinsic effects, and MSCs cultured *in vitro* may share common features in agreement with the International Society of Cell Therapy (ISCT) criteria established in 2006 (53). Firstly, under *in vitro* culture conditions, MSCs exhibit spindle-shaped or fusiform morphology. Secondly, *in vitro* cultured MSCs express CD73, CD90 and CD105 markers on their surface; however, they express no monocyte markers, such as HLA-DR, CD14 or CD11b, CD79α or CD19, and no hematopoietic markers, such as CD34 and CD45 (53). In addition, MSCs can differentiate into osteoblasts, adipocytes and chondroblasts following specific *in vitro* differentiation conditions (53). Although MSCs have the potential to express surface antigens and differentiate, other characteristics of MSCs that would support anti-tumor therapeutic interests are vital. In the following section, MSC functions, including inherent tumor tropisms, as well as the immunosuppression and paracrine characteristics of anti-tumor MSC carrying OVs will therefore be discussed.

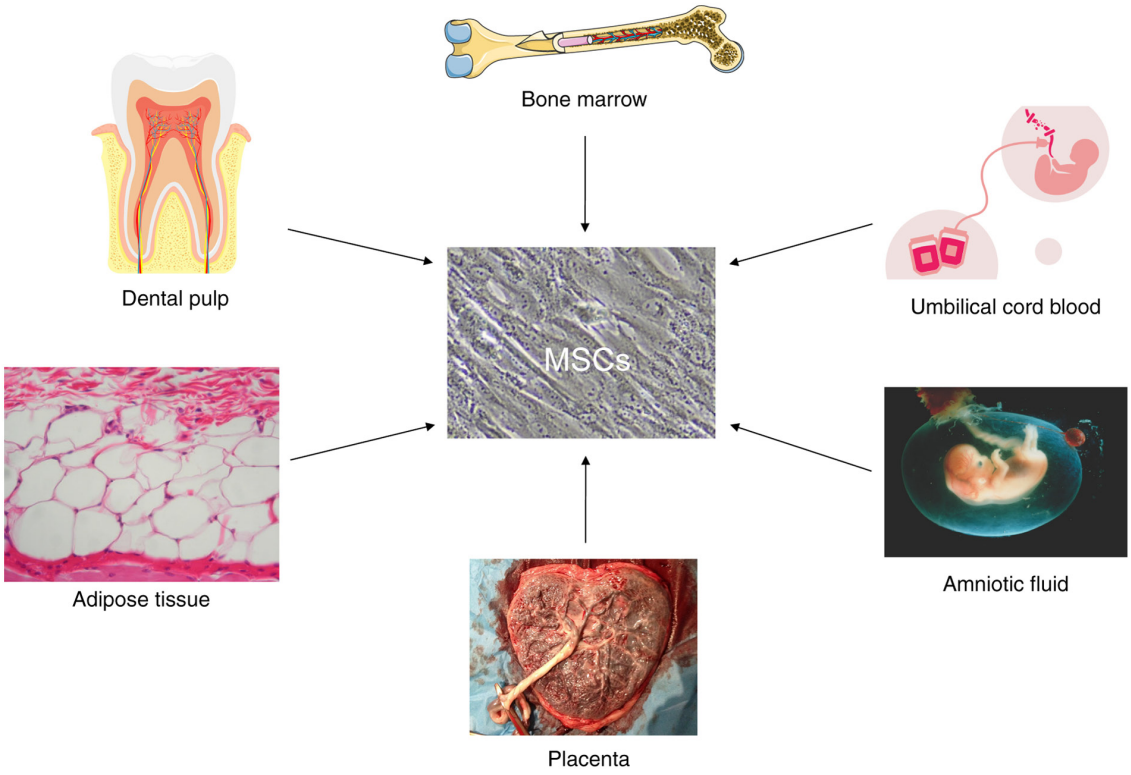

Figure 1. Different sources of MSCs in humans. MSCs, mesenchymal stem cells.

5. MSCs loaded with OVs-the anti-tumor story

MSC tumor tropisms facilitate OV delivery to tumor sites. MSCs undergo chemotaxis and migration to tumor lesions (54). A recent study has reported that MSCs migrate and bind to the tumor matrix and target the TME (14). At these sites, the tumor oxidation state, vascularization and tumor inflammatory status can affect MSC migration efficiency (55). Furthermore, MSCs have been demonstrated to exert positive chemotactic effects on solid tumors, such as hepatocellular carcinoma (55), breast cancer (56) and glioma (57).

MSCs migrate to damaged tissue or inflammatory sites and release simultaneous secretory cytokines (58,59). In addition to tumor cells, the TME also contains immune cells, fibroblasts, vascular endothelial cells, adipocytes and tumor stromal cells, which secrete large numbers of cytokines, such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), interleukin (IL)-8, IL-6, stromal cell-derived factor-1 (SDF-1), basic fibroblast growth factor (bFGF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), hepatocyte growth factor (HGF), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), urokinase type plasminogen activator receptor, vascular cell and intercellular cell adhesion molecules (VCAM, ICAM), C-X-C motif chemokine ligand-12 (CXCL-12), C-C motif chemokine ligand-2 (CCL-2), C-C motif chemokine ligand-3 (CCL-3), C-C motif chemokine receptor 4 (CCR4) and C-X-C motif chemokine receptor 4 (CXCR4) (59-63).

Pavon *et al* (64) reported that human umbilical cord blood-derived MSCs express the chemokine receptors CCR2 and CXCR4, and demonstrated that MCP-1/CCL2 and SDF-1/CXC12 secreted by CD133-positive GBM cells can induce MSC migration *in vitro*. Furthermore, *in vivo* experiments confirmed that MSCs can cross the blood-brain barrier and migrate to glioblastoma tumor areas (64). In addition, Lejmi *et al* (63) co-cultured hepatoma cells with MSCs and demonstrated that the expression of matrix metalloproteinase-1 is significantly increased in MSCs, promoting therefore MSCs migration toward hepatoma cells. In essence, cytokines secreted by immune and tumor cells are key to inducing the chemotactic migration of MSCs and are the central theoretical tenet for MSCs as OV cellular vehicles (65,66). Therefore, when OVs are loaded onto MSCs, they exploit the inherent tumor tendency of MSCs to reach tumor sites, thereby increasing OV targeting and enhancing oncolysis.

MSC immunosuppressive functions protect OV clearance from the immune system. MSC immunological characteristics serve crucial roles in the therapeutic efficacy of MSCs loaded with OVs towards tumors. Evidence indicates that MSCs amplified *in vitro* do not express HLA-II or costimulatory molecules, such as CD40, CD80, CD83, CD86 and CD154 (67). Therefore, no additional immunosuppressants are required for autologous or allogeneic MSC transplantation. In addition, MSCs exert strong immunosuppressive functions. For example, MSCs produce and release a variety of soluble cytokines, including IL-6, IL-10, TGF-β, heme oxygenase-1, inducible nitric oxide synthase and indoleamine-2-dioxygenase-3 (68), which play major roles in immunosuppression. At present, MSCs are used for immunomodulation, mostly for immune rejection and autoimmune diseases, such as hematopoietic stem cell transplantation, organ transplantation, rheumatoid arthritis

and systemic lupus erythematosus (69,70). However, the underlying mechanisms of MSC immunosuppressive function *in vivo* remain unclear.

In recent years, increasing evidence from preclinical and clinical studies has indicated that MSCs exert immunosuppressive functions by inhibiting the activity of certain types of immune cell, including T, B lymphocytes and NKs, thereby affecting monocytes, DC and macrophage function (71-74). MSCs affect the activation, proliferation, maturation, cytokine production and cytotoxic activity of innate and adaptive immune cells (68). Indeed, MSCs can reduce cytokine secretion from helper T cells, weaken the killing effects of effector T lymphocytes (75), hinder B lymphocyte differentiation and impede their ability to secrete immunoglobulin (76,77), and inhibit INF-γ secretion by NK cells and reduce their killing effects (78). In addition, MSCs prevent $CD14^+$ monocytes and $CD34^+$ progenitor cells from differentiating into mature DC cells (79). Importantly, MSCs promote the emergence of regulatory immune subsets, including $CD8^+CD28^-$ T lymphocytes (80), $CD4^+CD25^+FOXP3^+$ T lymphocytes (81), IL-10-producing B lymphocytes (82) and IL-10-producing DCs (83). Therefore, inhibiting immune cell functions and promoting the emergence of regulatory immune cell subsets, could serve positive roles in MSC immunosuppressive functions. These functions are key MSC features in protecting OVs from immune system clearance, and a guarantee to enhance OV spread and increase viral persistence (84).

MSC carriers induce systemic anti-tumor immune responses. It has been reported that MSCs promote tumorigenesis through various mechanisms, such as inhibition of local immune responses (51), stimulation of epithelial-mesenchymal transformation, inhibition of tumor cell apoptosis and promotion of angiogenesis and tumor metastasis (85). Previous studies have demonstrated that MSCs, in contrast to their tumorigenic functions, can inhibit tumor growth by inhibiting angiogenesis (86), inducing cell cycle arrest (14,87), enhancing inflammatory infiltration (88) and inhibiting proliferation-associated signaling pathways (14).

Although there is some controversy over whether MSCs inhibit or promote tumor growth, emerging evidence indicates that oncolytic adenovirus (OAD)-infected MSCs induce anti-tumor immune responses and increase leukocyte infiltration into tumor lesions (89). Similarly, Mahasa *et al* (10) predicted the therapeutic efficacy of MSCs loaded with OAD in a Hep3B cell tumor model using an integrated mathematical-experimental model, and demonstrated that MSCs loaded with OAD can promote tumor therapeutic efficacy. In addition, a phase I clinical trial (NCT01844661) of bone marrow-derived MSCs carrying Celyvir for the treatment of metastatic or refractory tumors was completed and reported that the combination of MSCs and Celyvir is safe (90). Following treatment with MSCs carrying Celyvir, except for the increase in the amount of oncolytic virus administered to patients, minimizing toxicities and avoiding direct tumor injections, no grades 2-5 toxicities were reported (90). However, the safety and efficacy of MSCs carrying Celyvir require further evaluation in a phase II setting.

Mechanically, after MSC infection with the human OAD icovir-5 *in vitro*, the NF-κB signaling pathway is activated and releases large numbers of cytokines, such as IL-6, CXCL2, CXCL10 and CCL5 (91). These cytokines facilitate the migration of NK and T cells, amongst others, to the TME (Fig. 2). Indeed, 48 h following Celyvir transplantation, the levels of peripheral blood monocytes, NK cells and neutrophils are increased (89). Furthermore, the first-in-child trial of autologous MSCs infected with the human OAD icovir-5 (Celyvir) demonstrated that the number of circulating B-lymphocytes and dendritic cells is significantly higher in pediatric patients, and that CD4 and CD8 T lymphocytes are also higher in children at most time points, compared with adult cohorts (90). These preclinical data illustrate that MSCs can release cytokines that might promote anti-tumor immune responses mediated by OVs. These data are instrumental in encouraging more virotherapy preclinical and clinical studies, investigating the utility of MSCs as OV carriers for patients with advanced cancer.

MSCs as carriers for delivering OVs. The majority of preclinical studies indicate efficacy factors for MSCs as carriers for OV delivery (92-94). Du *et al* (95) used MSCs as cellular carriers for oncolytic herpes simplex virus (HSV) in order to assess efficacy in immune-deficient and immune-competent mouse melanoma metastasis models. The results demonstrated that transplanted MSCs carrying HSV could migrate to the tumor site and significantly prolong mouse survival. Furthermore, in immune-competent mice, the combination of MSC-HSV and the anti-programmed death ligand 1 (anti-PD-L1) immune checkpoint inhibitor could increase $CD8^+$ T lymphocyte infiltration, leading to the production of IFN-γ and significant prolongation of mouse survival.

For enveloped OVs, MSCs can deliver viruses to tumor sites via hetero-cellular fusion. Ong *et al* (96) loaded bone marrow-derived MSCs with oncolytic measles virus, and co-cultured them with human hepatocellular carcinoma cells *in vitro*. The results demonstrated that syncytia number increases when MSCs carries the measles virus, which is not the case with non-enveloped virus. Furthermore, in the presence of high titer anti-measles virus antibodies, virus-infected MSCs significantly induce heterocellular formation when compared with naked virus. In addition, MSCs precisely deliver the measles virus to tumor lesions in a patient-derived hepatocellular carcinoma model (96). These results were consistent with Castleton *et al* (97) who reported MSC delivery of the measles virus in a model for acute lymphoblastic leukemia, suggesting that OV infected MSCs could significantly prolong survival and improve anti-tumor efficacy when compared with the naked virus.

In addition, genetic engineering improves MSC delivery efficiency, enhances viral oncolytic activity and reduces virotherapy side effects. Yoon *et al* (55) reported that the OAD infection capability of MSCs is enhanced after modification of the fiber domain of OADs, allowing the virus to replicate efficiently in MSCs. These MSCs infected with OADs could effectively lyse hepatocellular carcinoma cells *in vitro*. Importantly, following MSC-OAD transplantation, MSCs home to the tumor site, facilitating a high accumulation of virions at the site, and ultimately leading to tumor growth inhibition. In another study, Kaczorowski *et al* (66) deleted the anti-apoptotic gene E1B19K from OAD and inserted the

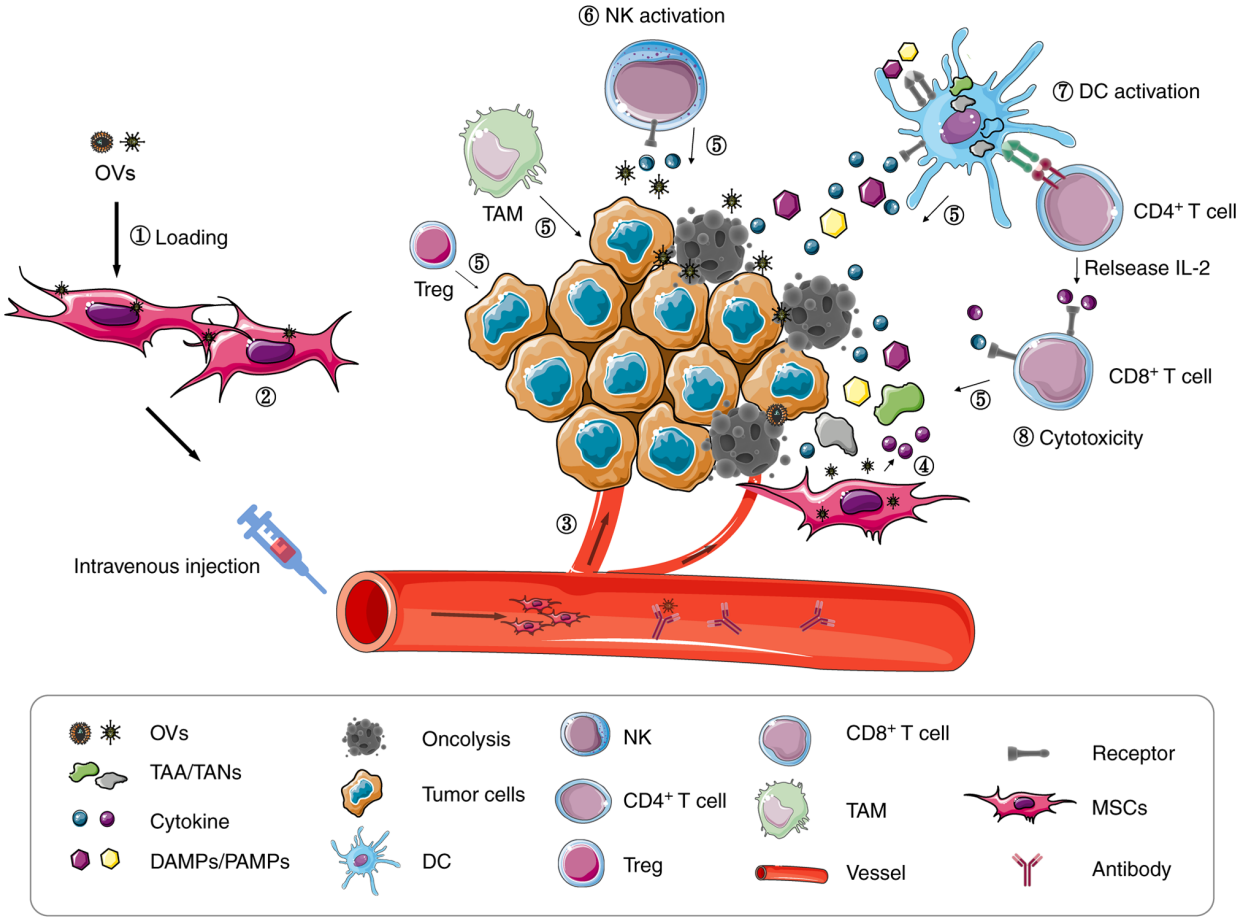

Figure 2. MSC carriers enhance anti-tumor efficacy of oncolytic virotherapy. (1) MSCs loaded with OVs. (2) MSCs provide a replication locale for OVs to produce more virus particles. (3) Tumor tropisms and immunosuppressive MSC functions facilitate precise OV targeting to tumor lesions. OVs infect tumor cells and release 'dangerous' signals. (4) OVs alter MSC cytokine profiles. (5) Cytokines induce immune cell migration to the TME. (6) NK activation. (7) DCs activation. (8) Tumor antigen specific T cell activation. OVs, oncolytic virus; DC, dendritic cell; MSCs, mesenchymal stem cells; DAMPs, danger-associated molecular patterns; PAMPs, Pathogen-associated molecular patterns; TAAs, tumor-associated antigens; TANs, tumor-associated neoantigens; NK, natural killer; TAM, tumor-associated macrophage; TME, tumor microenvironment.

cell death ligand TRAIL gene of OAD. After intravenous injection of virally infected MSCs, adenovirus capsid protein is detected in tumor xenografts established by cancer stem cell of pancreatic ductal adenocarcinoma. Similarly, following viral MSC treatment, the tumor size decreases significantly, the tumor cell proliferation-associated Ki67 and CD24 expression decreases and the tumor cell apoptosis-associated caspase-3 activity increases (66). In addition, OADs significantly increase virus release from MSCs following the deletion of the anti-apoptotic virus gene E1B19K, or the overexpression of the cell death ligand TRAIL, while MSC migration ability remains unaffected (98). These data suggest that genetic modification of OADs can induce effective oncolysis, which may represent a promising strategy for OVs in clinical applications. Similarly, MSCs as carriers for the delivery of genetically modified OVs may be considered as a useful method for improving oncolytic virotherapy efficacy (Table I)(99-106). However, MSCs can also be modified by genetic modification or preconditioned to modification in order to improve their inherent properties, such as enhanced migration, adhesion and survival, and reduced premature senescence (107). OV delivery and virotherapy efficacy may therefore be improved.

6. Conclusions and perspectives

In summary, MSCs enhance the anti-tumor efficacy of virotherapy through numerous factors. Firstly, MSCs provide a replication location for OVs, facilitating the production of more virus particles, which is beneficial for virotherapy. Secondly, the tumor tropism and immunosuppression function of MSCs allow the virus to accurately reach the tumor site and enhance the transmission and persistence of the virus. Thirdly, oncolysis leads to the release of 'dangerous' signals, such as TAAs/TANs and DAMPs/PAMPs, activating local anti-tumor immune responses, and converting the TME from an immunosuppressive to an immunostimulatory environment (93,103). However, cytokines released by MSCs recruit immune cells to the TME, further enhancing the anti-tumor immune response. Therefore, MSC carriers are considered as promising cellular vehicles for OV delivery. Assuming the high quality of MSCs and appropriate conditions of MSCs loading the virus, it is worth treating malignant tumors with such therapy, which could lead to a restrain of tumor growth progression in patients. However, further investigation is required to evaluate the effects of MSC loading viruses and explore the immune regulation mechanisms of MSCs on anti-viral and anti-tumor immune responses.

Table I. MSCs as carriers for OV delivery.

Author, year	Strategies	Results	(Refs.)
Yoon *et al*, 2019, Cancer Res	MSCs loading OADs	MSCs cells locate to the tumor site and lead to the accumulation of high virion levels in the tumor tissue, which eventually led to the inhibition of tumor growth.	(55)
Du *et al*, 2017, Proc Natl Acad Sci USA	MSCs loading OHSV	Combination of MSCs-OHSV and an anti-PD-L1 immune checkpoint inhibitor increases the number of $CD8^+$ tumor infiltrating T lymphocytes and significantly prolonges mice survival.	(95)
Kazimirsky *et al*, 2016, Stem Cell Res Ther	MSCs loading NDV	Factors secreted by MSCs infected with virus make glioma cells sensitive to the cytotoxicity. of NDV TRAIL and NDV have synergistic effect in inducing glioma cell death.	(99)
Kaczorowski *et al*, 2016, Oncotarget	MSCs loading E1B19K deleted or TRAIL inserted OADs	After treatment, the tumor volume decreased significantly, Ki67 and CD24 expression is decreased and caspase-3 activity is increased.	(66)
Melen *et al*, 2016, Cancer Lett	MSCs loading genetically modified OADs	Clinical trials confirm the safety of MSCs loading genetically modified OADs.	(100)
Leoni *et al*, 2015, Oncotarget	MSCs loading OHSV	MSCs-OHSV significantly inhibit the brain metastasis of breast cancer in NSG mice.	(101)
Hoyos *et al*, 2015, Mol Ther	MSCs loading ICOVIR15 and Inducible Caspase 9 suicide gene (iC9) inserted OADs	MSCs loading ICOVIR15 increase the control of tumor growth and prolonge the survival of tumor-bearing mice.	(102)
Franco-Luzon *et al*, 2020, Oncotarget Morales-Molina *et al*, 2020, Cancers (Basel)	MSCs loading ICOVIR5	MSCs carrying ICOVIR5 enhance anti-tumor. effects	(103,104)
Hammer *et al*, 2015, Int J Cancer	MSCs loading E1B19K deleted or TRAIL inserted OADs	This strategy increases the release of the OADs from MSCs, while MSC migration ability is not affected.	(98)
Ong *et al*, 2013, J Hepatol Castleton *et al*, 2014, Blood Mader *et al*, 2009, Clin Cancer Res	MSCs loading MV	In the presence of high titer anti-measles virus antibodies, measles virus-infected MSCs can significantly induce heterocellular formation when compared with naked virus alone. In addition, MSCs accurately deliver measles virus to tumor lesions and prolong mice survival.	(96,97,105)
Hai *et al*, 2012, Chin J Cancer	MSCs loading genetically modified OADs	MSCs carrying replicable adenovirus can significantly inhibit tumor growth *in vivo*.	(94)
Ahmed *et al*, 2010, Mol Ther	MSCs loading OADs	MSCs carrying OADs enhance the spread and persistence of OADs.	(84)
Hakkarainen *et al*, 2007, Hum Gene Ther	MSCs loading infectious enhanced OADs	Intravenously transplanted MSCs are mainly located in the lung, and the virus is released to advanced orthotopic breast and lung tumors to improve the efficacy.	(106)

OADs, Oncolytic Adenovirus; OHSV, Oncolytic Herpes Simplex Virus; NDV, Newcastle Disease Virus; MV, Measles Virus; MSCs, mesenchymal stem cells; MSCs-OHSV, mesenchymal stem cells loading Oncolytic Herpes Simplex Virus.

In TME, cancer-associated fibroblasts, adipocytes, Tregs, mesenchymal stromal cells and tumor-associated macrophages release numerous cytokines, such as IL-10, which support immune evasion and tumor growth (108). In recent years, oncolytic virotherapy (OVT) has been demonstrated to relieve the tumor immunosuppressive environments, and enhance anti-tumor

immune responses (109,110). OVs stimulate anti-tumor immune responses which in turn, enhance the efficacy of immune checkpoint inhibitors (ICIs) (111). For this reason, emerging evidence from preclinical and clinical trials has indicated that combined OVT and ICIs could improve the anti-tumor therapeutic efficacy (112-114). In view of the contribution of MSCs to the activation of immune responses in virotherapy, combined MSC loading OVs with ICIs could be considered as a major therapeutic area for future anti-tumor research.

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Availability of data and materials

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Authors' contributions

XW and ZH conceived the review. XW wrote the review. ZH and XZ revised the review. XW, XZ and ZH proofread the manuscript and revised the manuscript for intellectual content. All authors read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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