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Commentary

Mission impossible: mesenchymal stem cells delivering oncolytic viruses before self-destruction

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Oncolytic virotherapy is an emerging class of cancer therapy that selectively destroys cancer cells while sparing normal cells.[1] Systemic administration of oncolytic viruses (OVs), however, leads to sequestration by other organs and virus elimination by the immune system, which largely hamper the effectiveness of the therapy. Therefore, the development of new strategies to improve the bioavailability and tumor delivery of OVs is essential to boost antitumor efficacy. Mesenchymal stem cells (MSCs) are multipotent stem cells capable of self-renewal and differentiation into distinctive lineages to maintain key physiological roles, such as tissue repair and regeneration.[2] In recent decades, MSCs have emerged as promising candidates for the delivery of OVs due to their inherent regenerative properties, high immunomodulatory ability, and tumor tropism. Additionally, MSCs protect OVs from immune-mediated antibody neutralization and support viral replication during migration, thereby allowing successful delivery of OVs to the tumor site.[3]

In this issue of *Molecular Therapy: Oncology*, Sukegawa et al.[4] identified the importance of selecting an appropriate MSC source as OV carriers for the antitumor effect of MSC-based OV therapy. The authors highlighted the impact of human MSC (hMSC) origin on their functions as oncolytic herpes simplex virus (oHSV) carriers, including their ability to migrate, susceptibility to oHSV infection, efficiency of oHSV spread and release, and efficacy of cancer killing using a three-dimensional (3D) co-culture system.

The immortalized hMSCs used by the authors were derived from various human tissues: bone marrow (BMMSCs), adipose tissue (ADMSCs), umbilical cord blood (UCBMSCs), and endometrium (EPCMSCs). While all four types of hMSCs can migrate toward pancreatic cancer cell-conditioned medium or bile duct cancer organoids in a two-dimensional (2D) setting, BMMSCs demonstrated exceptional migration efficiency among the hMSCs tested. In support of this observation, BMMSCs rapidly migrate to form small aggregates around spheroids derived from the human pancreatic cancer cell line PANC-1 than other hMSCs in a 3D co-culture system. Minimum migration toward human dermal fibroblast-derived spheroids suggested that the migration ability of hMSCs is cancer specific. The authors further demonstrated the accumulation of BMMSCs at tumor sites in a pancreatic cancer xenograft model *in vivo*, reinforcing the high migration ability of BMMSCs toward cancer cells.

This high mobility characteristic of BMMSCs can be explained by the elevated expression of cell migration and chemokine receptor signature genes, including the interleukin (IL)-1 receptor cluster (IL-1RL1 and IL-1R2) and somatostatin receptor 1 (SSTR1). Inhibition of SSTR prevented BMMSC migration toward PANC-1 spheroids, suggesting that somatostatin signaling, at least partially, plays a role in BMMSC migration. Future studies could identify other chemoattractants released from cancer cells, such as IL-1, that drive the high mobility of BMMSCs toward cancer spheroids in the 3D co-culture system.[5]

The susceptibility of hMSCs to oHSV infection and the efficiency of oHSV release are key determinants of carrier cell selection. While no differences were observed in the infection efficiency of oHSV across all four hMSCs, they all remained sensitive to oHSV infection *in vitro*. Both BMMSCs and ADMSCs exhibited higher oHSV release efficiency, suggesting that these two types of hMSCs can be efficiently loaded with oHSV and subsequently released to adjacent cancer cells upon cell lysis.[6] Indeed, all oHSV-hMSCs exhibited a strong cytotoxic effect on PANC-1 cells, except for oHSV-EPCMSCs in a 2D setting. In addition, oHSV-BMMSCs demonstrated the highest oHSV spread efficiency via infiltration into the PANC-1 spheroids as early as 6 h post infection, resulting in strong antitumor activity against PANC-1 spheroids on day 7. Collectively, the data implicate BMMSCs as the superior oHSV carrier for enhancing viral spread and antitumor effects in a 3D co-culture model.

It is important to note that the migration capability of BMMSCs is dependent on the cancer cell type. Significant migration toward colorectal adenocarcinoma DLD-1 and urinary bladder cancer T24 spheroids were observed but not osteosarcoma U2OS spheroids. These findings further support the importance of choosing the appropriate hMSC type prior to selecting tumor types for clinical development. Examining the release of tumor type-specific chemoattractants will help distinguish the cancer cell type-dependent differences observed in hMSC migration ability.

The 3D co-culture model introduced by the authors is a powerful alternative to the 2D system that enables a time-dependent monitoring of the 3D dynamics to predict the migration of hMSCs toward tumor sites *in vivo*. Despite being an artificial system, the motility and tumor-infiltrating properties of hMSCs can be visualized and quantified with ease. This provides valuable insights for the broad array of basic and translational research as a screening tool for the preclinical evaluation of oHSV-carrying hMSCs. Future

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improvement with the addition of immune cells and cancer-associated fibroblasts to the 3D co-culture system, using patient-derived organoids or *in vivo* immunocompetent syngeneic mouse models, would help determine to what degree the hMSC source can affect the immunomodulatory properties of hMSCs as carriers and the overall antitumor effect of oHSV hMSCs.[7]

Although the findings by Sukegawa et al.[4] suggest BMMSCs as an outstanding vector for oHSV spreading and cancer killing, limitations regarding clinical application should be taken into consideration. The numbers of BMMSCs decline drastically with age, with only one in two million bone marrow cells by the age of 80.[2] In contrast, ADMSCs offer advantages over BMMSCs due to their significantly higher intrinsic yield for clinical use that requires relatively large quantities of these cells.[7] Adipose tissue is also in abundance and can be easily harvested via liposuction. The clinical feasibility of culture-expanded BMMSCs is an additional challenge to the limited intrinsic yield. Several lines of evidence have documented the accumulation of chromosomal abnormalities and neoplastic characteristics during prolonged *in vitro* culture, which may interfere with antitumor therapies that utilize hMSCs.[7] Collectively, tissue accessibility and safety should be evaluated when selecting the hMSC source as OV carriers in the clinical setting.

Overall, the work by Sukegawa et al.[4] is the first to demonstrate the impact of the hMSC source on the migration capability, viral spreading, and antitumor efficacy of oHSV-loaded hMSCs in a novel 3D co-culture system. The findings provided by the authors now add to the significance of the hMSC source as a sophisticated carrier for systemic oncolytic virotherapy. These promising preclinical studies strongly support the clinical use of hMSCs as safe and effective cell carriers of OVs to maximize delivery to the tumor bed and elicit antitumor efficacy.[7]

AUTHOR CONTRIBUTIONS

J.X.L. and J.C.W. conceived and wrote this commentary.

DECLARATION OF INTERESTS

J.X.L. and J.C.W. are employees of ALX Oncology.

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