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REVIEW ARTICLE

Mesenchymal stromal cells for the delivery of oncolytic viruses in gliomas

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Abstract

Mesenchymal stromal cells (MSCs) are a type of adult stem cell that has been exploited for the treatment of a variety of diseases, including cancer. In particular, MSCs have been studied extensively for their ability to treat glioblastoma (GBM), the most common and deadly form of brain cancer in adults. MSCs are attractive therapeutics because they can be obtained relatively easily from patients, are capable of being expanded numerically *in vitro*, can be easily engineered and are inherently capable of homing to tumors, making them ideal vehicles for delivering biological antitumoral agents. Oncolytic viruses are promising biological therapeutic agents that have been used in the treatment of GBMs, and MSCs are currently being explored as a means of delivering these viruses. Here we review the role of MSCs in the treatment of GBMs, focusing on the intersection of MSCs and oncolytic viruses.

Key Words: *mesenchymal stem cell, gliomas, adenovirus, mesenchymal stromal cell*

Introduction

Mesenchymal stromal cells (MSCs) have gained increasing attention over the past several decades because of their potential application in the treatment of disease. The therapeutic prospect of MSCs lies primarily in their inherent capacity to home to injured or inflamed tissue, their ability to secrete anti-inflammatory, tissue-rejuvenating factors and the ease with which they can be modified or engineered to serve as delivery vehicles of exogenous biological agents. Unmodified MSCs have been used in the treatment of degenerative diseases [1,2], myocardial infarction [3], stroke [4] and trauma [5]. Engineered MSCs have been used as cellular carriers of antitumoral agents in various cancers, including glioblastoma (GBM), the most common and deadly malignant brain tumor in adults [6–11]. Multiple studies have shown that MSCs avidly home to solid tumors, including GBMs, presumably because the microenvironment or stromal milieu of cancer, particularly brain tumors, is similar to that of nonhealing wounds. Of the various anticancer cargoes that have been loaded into MSCs, oncolytic viruses are among the most promising in the treatment of brain tumors, and MSCs loaded with oncolytic viruses will soon be tested in clinical trials in patients with GBM. Oncolytic viruses are replication-competent viruses that have been genetically modified to selectively infect and replicate in tumor cells compared with normal cells. This review focuses on the recent advances in the use of MSCs in the treatment of brain tumors, emphasizing the role of MSCs as delivery vehicles for oncolytic viruses.

Therapeutic challenges of glioblastoma

GBM (World Health Organization grade IV astrocytoma) is the most common and deadly primary adult

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brain tumor. Despite aggressive microsurgery followed by concurrent radiation/chemotherapy and adjuvant chemotherapy, patients with GBM survive on average less than 15 months after diagnosis [12]. Recent clinical trials have shown that altering the dose or schedule of standard cytotoxic chemotherapy or inhibiting angiogenesis has little impact on patient survival [13–15]. Likewise, targeted therapies that have been effective in other cancers have not been effective against brain tumors. This poor outcome is due to the complex molecular and cellular biology of GBMs. GBMs are highly infiltrative as tumor cells migrate into normal brain parenchyma, which narrows the therapeutic window of most therapies. Furthermore, GBMs contain glioma stemlike cells (GSCs) that render GBMs resistant to most therapies. Finally, GBMs are very heterogeneous, containing many cellular clones, which results in outgrowth of therapeutic resistant subclones. The poor outcome is equally due to the inability to deliver therapeutic agents to the tumor because of the blood-brain barrier/tumor barrier (BBB/BTB), which functionally excludes most drugs from entering the tumor. Given these problems, there has been an urgent need to develop both novel therapies for GBM and innovative ways to deliver those therapies.

Stem cells as delivery vehicles in GBM

Recent evidence suggests that stem cells may be effective delivery vehicles for the treatment of cancer including brain tumors. Originally, stem cells, particularly hematopoietic stem cells, were used in cancer therapy to replace bone marrow containing residual tumor cells after "conditioning" with aggressive chemotherapy as part of autologous, allogeneic, or syngeneic bone marrow transplant strategies. Since then, the application of stem cells in cancer therapy has expanded to their use as biological vehicles for delivering novel antitumor therapies to solid tumors [6], especially brain tumors [7].

Neural stem cells (NSCs) were the first stem cell type to be investigated as potential cellular vehicles to deliver therapeutic agents to brain tumors. NSCs are found in specific periventricular regions of the central nervous system and are destined to become the cells comprising the brain, including neurons and glial cells (astrocytes, oligodendrocytes, and ependymal cells). Because NSCs possess an intrinsic capacity for extensive migration within the brain [16], early research investigated whether these migratory properties could allow NSCs to track down infiltrating tumor cells that reside outside of the main tumor mass. The seminal publication in 2000 by Aboody *et al.* first described the use of NSCs in the treatment of gliomas [17]. They showed that NSCs (genetically immortalized by transfection with avian myelocytomatosis viral oncogene homolog) could distribute themselves throughout the tumor and migrate to infiltrative tumor cells that extended out of the main tumor mass and dispersed into normal brain. Equally important, they showed that these immortalized NSCs could be engineered to carry the therapeutic transgene for cytosine deaminase (CD), an enzyme that converts the prodrug 5-fluorocytosine to 5-fluorouracil. This publication set the field of cell-based therapies for GBM into motion [17], and since then, multiple publications have reported the use of NSCs to deliver a variety of antiglioma agents, including interleukin (IL)-4 (IL-4) [18], IL-12 [19] and IL-23 [20]; a soluble variant of tumor necrosis factor–related apoptosis-inducing ligand [19,21–23]; the prodrug-converting enzyme cytosine deaminase [17,24,25]; antiangiogenic protein thrombospondin [26]; and oncolytic viruses [27,28].

Because the acquisition of NSCs for clinical use requires isolation of tissue from the brains of fetuses or from the periventricular zone of adult brains during surgery, alternative sources of stem cells were sought. One alternative source has been the adult human bone marrow, which is a rich reservoir of harvestable stem cells. Compared with NSCs, bone marrow stem cells are attractive because (i) they are easily acquired from patients via aspiration of the iliac crest or sternum; (ii) patients can act as their own donors, making autologous transplant possible and obviating immune-mediated rejection; and (iii) no ethical issues surround their use. Of the various stem cells within the bone marrow, MSCs are particularly attractive for clinical applications because the methods for acquiring MSCs are well established, *in vitro* culture is straightforward, and the techniques for engineering and manipulating MSCs are known [29]. MSCs also express low levels of major histocompatibility complex (MHC) class I molecules and do not express MHC class II on the cell surface, rendering allogeneic transplant feasible [30]. In fact, MSCs generated from adult human healthy donors have been approved for the treatment of acute graft versus host disease in Canada, New Zealand [31] and Japan [32].

The prospect of using MSCs for the treatment of solid tumors was revealed with the seminal publication by Studeny *et al.* in 2002 [6]. Soon thereafter, the use of MSCs for the treatment of various other types of cancers was reported, including in the treatment of lung [33], colon [8], ovarian [34], pancreatic [35], renal [11] and breast [36] cancers as well as sarcoma [9,10]. Several clinical trials are underway evaluating MSCs as delivery vehicles. For example, in a phase I trial, patients with advanced head and neck cancer received intratumoral injection of MSCs transduced with IL-12, called GX-051 (NCT 02079324). In another phase I trial, eligible ovarian cancer patients will undergo intraperitoneal infusion of MSCs