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Antitumour treatment

Stem cell-based therapy for malignant glioma

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ABSTRACT

Stem cells have been extensively investigated as tumour-tropic vectors for gene delivery to solid tumours. In this review, we discuss the potential for using stem cells as cellular vector systems in gene therapy for malignant gliomas, with a focus on neural stem cells, and multipotent mesenchymal stromal cells. Tumour cell-derived substances and factors associated with tumour-induced inflammation and tumour neovascularisation can specifically attract stem cells to invasive gliomas. Injected stem cells engineered to produce anti-tumour substances have shown strong therapeutic effects in experimental glioma models. However, the potential caveats include the immunosuppressive functions of multipotent mesenchymal stromal cells, the contribution of stem cells to the pro-tumourigenic stroma, and the malignant transformation of implanted stem cells. In addition, it is not yet known which stem cell types and therapeutic genes will be most effective for the treatment of glioma patients. Here, we highlight the possibilities and problems for translating promising experimental findings in glioma models into the clinic.

Introduction

Glioblastoma (GBM) is the most common and severe form of malignant glioma. Despite enormous efforts, the prognosis for GBM patients is still poor. The median survival of GBM patients is 14.6 months, and around 10% of GBM patients survive more than 5 years, despite receiving surgery, radiotherapy, and chemotherapy with temozolomide (TMZ).[1,2] A major portion of treatment failure is due to the invasive growth of GBM. Microscopic tumour extensions and distant tumour microsatellites grow along white matter fibre tracts and normal brain tissue blood vessels.[3] Therefore, complete surgical resection is rarely achieved. Other GBM therapy challenges include an increased interstitial fluid pressure within the tumour, resulting in low concentrations of systemically delivered drugs, an intrinsic and acquired drug resistance of tumour cells, and treatment neurotoxicity.[4] Furthermore, although GBM presents with a dysfunctional and leaky blood–brain barrier (BBB), single infiltrative GBM cells reside deep within the normal brain parenchyma with an intact BBB; therefore, they are protected from many blood-borne drugs.[5] A successful GBM treatment requires several criteria to be fulfilled, including the targeting of invasive tumour cells, the targeting of tumour cells characterised by different genetic aberrations (including putative cancer stem cells), and the selective elimination of tumour cells while sparing normal neural cells.[6]

In this review, we present the concept of using genetically engineered stem cells in gene therapy for brain tumours. We discuss different stem cell types that are used for glioma gene therapy, mechanisms by which stem cells are attracted to tumours, and the major principles of their therapeutic functions. We also highlight critical issues for translating the experimental findings to the clinic.

Scientific rationale for stem cell-based therapy for GBM

Gene therapy using viral vectors has been explored in several clinical GBM treatment trials.[7] Proteins aimed at inhibiting tumour angiogenesis, enhancing anti-tumour immune responses, and correcting tumour-specific genetic defects have been expressed in GBM by using locally or systemically administered viral gene vectors. Viral-mediated GBM gene therapy has shown promising results in animal models.[8] However, clinical studies have had modest success at limiting tumour growth and extending patient survival.[7] Failure has been attributed mainly to difficulties in achieving the distribution of viral vectors throughout the invasive

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tumour. In addition, the viral transduction efficiency of GBM cells has been low.[7]

Implanting or injecting stem and progenitor cells that have been genetically modified to produce anti-tumour substances has several advantages over viral-vector mediated gene delivery. Initially described by Aboody et al., implanted neural stem cells (NSCs) possess the capacity to migrate to and within intracranial tumours in which the NSCs deliver a cytotoxic substance that can reduce tumour growth.[9] The tumour-tropic homing and migratory capacity has been replicated by many groups using different types of stem and progenitor cells, including multipotent mesenchymal stromal cells (MSCs)[10,11], and hematopoietic progenitor cells (HPCs)[12] in animal models. For example, a single MSC implantation into an invasive rat glioma results in MSC migration to the majority of the infiltrative tumour extensions and a fraction of distant tumour microsatellites.[13] Differentiated cells, such as fibroblasts, do not exhibit a similar tumour tropism.[9–12] In contrast to viral vectors, stem cells are attracted primarily to tumour tissue, whereas they show minimal tropism for normal neural cells. Therefore, tumour-specific gene delivery is feasible, and cerebral side effects can potentially be avoided.[9,13] Numerous studies have demonstrated the potential of stem cell vectors in the treatment of brain tumours and many other invasive solid tumour types.[14] Thus, although each tumour type may require tailor-made cellular vehicles and transgenes, the results from work with non-neural tumours may contribute to the development of a successful stem cell therapy for GBM and vice versa.

Different types of cell vectors

Neural stem cells

NSCs can give rise to neurons, astrocytes, and oligodendrocytes. In the adult rodent brain, NSCs are located mainly within two neurogenic zones: the subependymal zone lining the lateral ventricles and the dentate gyrus of the hippocampus.[15] *In vitro*, NSCs are cultured and expanded as floating cellular aggregates called neurospheres (Fig. 1A). Initial findings demonstrated a tumour-tropic migration of the immortalised murine NSC line C17.2, following implantation into, or at a distance from, the experimental gliomas.[9] Subsequently, immortalised murine or human NSC lines and primary NSCs have been widely used for their tumour-tropic capacity and potential to deliver anti-tumour substances to gliomas[16–23] (Fig. 1B). An advantage of immortalised NSC lines (Fig. 1A) is that they are readily available. A well-characterised NSC line can be cultured and expanded *in vitro* to obtain high numbers of cells ready for transplantation within a short period. In contrast, although it is possible to harvest autologous neural precursor cells from the adult human brain,[24] it could take too long to expand, modify, and characterise these cells to prepare them for implantation into GBM patients. Furthermore, grafting immortalised NSC lines into the brain is associated with two main problems: immunogenicity and tumourigenicity. Immunogenicity implies that the immune system may attack and neutralise the grafted non-autologous cells. This could impair NSC survival and migration to the infiltrative

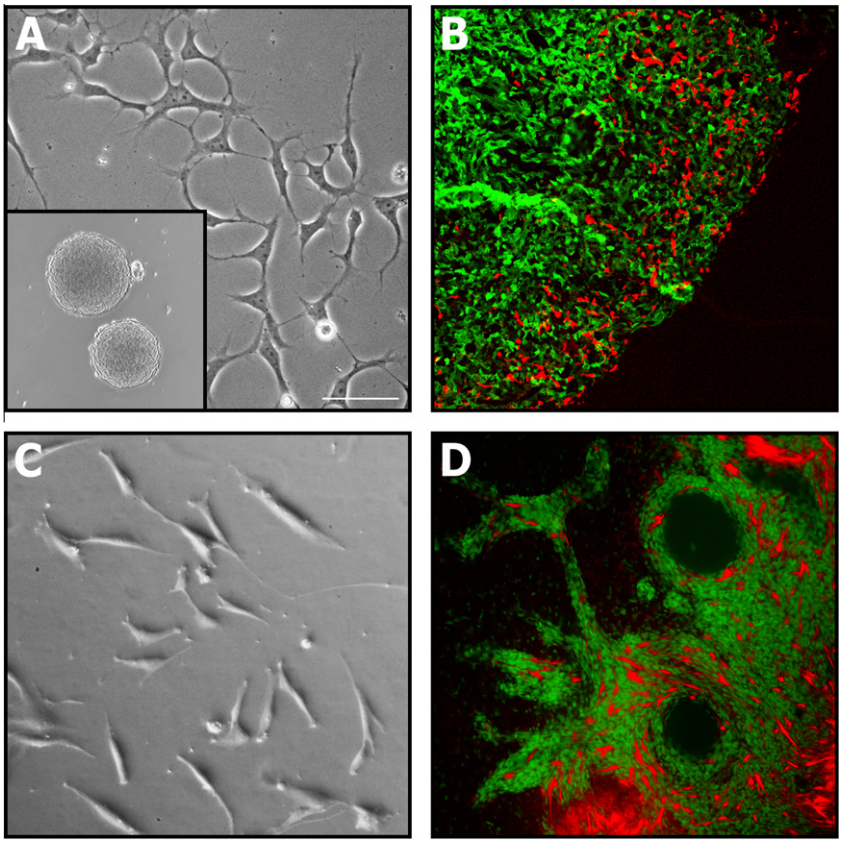

Fig. 1. (A) Phase-contrast micrograph of immortalised human NSCs after being subjected to cell culture conditions supporting neuronal differentiation. Insert in (A) Human NSCs grown as free-floating spheres in cell culture medium stimulating proliferation. (B) Immunofluorescent photomicrograph of human NSCs (red) infiltrating a human glioma (green) implanted into the immunocompromised mouse brain. (C) Phase-contrast photomicrograph of human MSCs growing adherently on a plastic surface *in vitro*. (D) Rat MSCs (red) infiltrating an invasively growing rat glioma (green) *in vivo*. Scale bar: 60 μm in A (250 μm in inflicted neurosphere photograph), 150 μm in B, 100 μm in C, and 120 μm in D. Fig. 1B is reproduced by permission of the publisher and the author.[23]