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Drug and cell encapsulation: Alternative delivery options for the treatment of malignant brain tumors ☆

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ABSTRACT

Malignant brain tumors including glioblastoma are incurable cancers. Over the last years a number of promising novel treatment approaches have been investigated including the application of inhibitors of receptor tyrosine kinases and downstream targets, immune-based therapies and anti-angiogenic agents. Unfortunately so far the major clinical trials in glioblastoma patients did not deliver clear clinical benefits. Systemic brain tumor therapy is seriously hampered by poor drug delivery to the brain. Although in glioblastoma, the blood brain barrier is disrupted in the tumor core, the major part of the tumor is largely protected by an intact blood brain barrier. Active cytotoxic compounds encapsulated into liposomes, micelles, and nanoparticles constitute novel treatment options because they can be designed to facilitate entry into the brain parenchyma. In the case of biological therapeutics, encapsulation of therapeutic cells and their implantation into the surgical cavity represents another promising approach. This technology provides long term release of the active compound at the tumor site and reduces side effects associated with systemic delivery. The proof of principle of encapsulated cell factories has been successfully demonstrated in experimental animal models and should pave the way for clinical application. Here we review the challenges associated with the treatment of brain tumors and the different encapsulation options available for drugs and living cells, with an emphasis on alginate based cell encapsulation technology.

Contents

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1. Introduction to brain tumors

Malignant brain cancer is a devastating disease and associated with very poor prognosis [1]. With an incidence of about 10 in 100,000 people, brain cancer is considered a rare disease but the mortality is very high with half of the patients presenting an incurable tumor type [1]. Pediatric brain tumors are the second leading cause of cancer-related deaths in children under the age of twenty [2]. Tumors of the central nervous system (CNS) are classified based on the presumed tissue of origin, i.e. tumors of neuroepithelial origin, tumors of cranial and paraspinal nerves, tumors of the meninges, lymphomas and hematopoietic neoplasms, germ cell tumors, tumor of the sellar region and metastatic brain tumors [3]. The majority of malignant brain tumors in adults are of neuroepithelial origin and belong to the group of gliomas, based on their resemblance to glial support cells of the brain, astrocytes and oligodendrocytes. Glial tumors are further classified in grades (I to IV) according to their clinical manifestation and malignancy. Except for grade I pilocytic astrocytomas, all other glial tumors eventually develop into a fatal tumor albeit with different incubation times. All these tumors are thus considered malignant. Diffusely infiltrating gliomas (grade II) mostly affect young adults with a high degree of cellular differentiation and slow growth. Over time these tumors evolve to anaplastic astrocytomas or oligodendrogliomas (grade III) or to glioblastomas (GBM). Grade IV astrocytoma or GBM represents the most malignant type of brain tumor in adults and is also the most frequently occurring primary brain tumor. Despite an aggressive treatment regimen, the median time from diagnosis to death for GBM patients is only 14 months [4]. Histopathological features include nuclear atypia, high cellularity, cellular pleomorphism and high mitotic activity. Prominent microvascular proliferation and/or necrosis represent essential diagnostic features. By magnetic resonance imaging (MRI), GBMs display areas of contrast enhancement indicating a disrupted blood brain barrier and neovascularization. Although most GBMs appear de novo as primary GBMs, some evolve from lower grade astrocytomas as secondary GBMs. Due to their strong infiltrative capacity they cannot be effectively removed by neurosurgical resection, and recurrence is inevitable. Invading cells can reside several centimeters outside the contrast enhancing rim and even reach the contralateral hemisphere.

In recent years extensive molecular characterization of gliomas using next generation sequencing, gene expression, copy number alterations and DNA methylation analysis has allowed an improved subgrouping based on genetic features [5–7]. This has e.g. led to the identification of a novel mutation in a gene coding for isocitrate dehydrogenase (IDH) in a subgroup of GBM samples [6]. Later it was found that mutations in IDH1 or IDH2 appear early in the disease course and are characteristic of grade II and III gliomas and secondary GBMs. More than 80% of these tumors carry the mutation, while less than 5% of primary GBMs do so [8,9]. Thus primary and secondary GBMs appear to be different biological entities, although histopathologically they are indistinguishable. In primary GBMs three important signaling pathways are consistently altered, these include receptor tyrosine kinase (RTK) signaling leading to increased cell proliferation, the p53 pathway involved in cell survival and metabolism, and the retinoblastoma (Rb) pathway regulating cell cycle activity [5]. The majority of primary GBMs display an amplification of the epidermal growth factor receptor (EGFR) gene, and additionally often express a truncated version of the receptor (EGFR variant III) which is constitutively active and is associated with increased aggressiveness [10]. These studies also highlighted the remarkable degree of genetic heterogeneity between GBMs and the close correlation between molecular markers and patient outcome.

In addition to primary brain tumors, metastatic brain tumors represent a major clinical challenge since they always constitute a fatal disease progression. Brain metastases are 2–3 times more frequent than primary brain tumors and like these are notoriously difficult to treat because the systemically delivered drugs affecting the primary tumor often do not reach the metastatic sites in the brain. Particularly lung, breast, colorectal cancer and melanoma have a tendency to metastasize to the brain.

2. Opportunities and challenges in brain tumor treatment

At present the standard treatment of GBMs is multimodal and includes surgical resection followed by radiation therapy (RT) and temozolomide (TMZ) based chemotherapy [4]. Despite this intensive treatment regimen the five year survival rate of GBM patients is below 10% [11]. Many alternative therapies are actively being tested that go beyond unspecific cytotoxic agents and aim towards a more tumor specific approach. These include targeted molecular therapies with RTK inhibitors, immune-based therapies and anti-angiogenic treatments [12,13].

Unfortunately small molecule inhibitors targeting RTKs, including the EGFR inhibitors erlotinib, gefitinib and lapatinib, have shown limited efficacy in GBM patients, although pre-clinical studies often produced promising results. Promising downstream targets of RTK signaling involve mTor, protein kinase C, Akt and PI3 kinase [13]. Currently antibodies against EGFR and vaccine strategies including EGFR and EGFRvIII are being explored. Additional promising avenues involving the immune response are dendritic cell, T cell and natural killer cell-based therapies [14]. A recent successful strategy in mice using intracerebral injection of EGFRvIII-specific chimeric antigen receptor transduced T cells holds promise for application in patients with EGFRvIII-expressing brain tumors [15].

As aberrant angiogenesis represents a major pathological feature in GBMs, multiple therapeutic strategies have been developed to target this process. Hope was put into bevavizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), the major pro-angiogenic molecule produced by GBM. Although initial small scale clinical trials indicated a strong increase in progression free survival [16–18], the clinical benefit from this remained unclear, since progression is based on imaging parameters directly affected by anti-angiogenic agents which interfere with adequate quantification of tumor growth [19]. Two recent phase 3 clinical trials comparing bevacizumab to standard of care treatment in newly diagnosed GBM (AVAglio and RTOG 0825) unfortunately did not report any positive effect on overall patient survival [20,21]. Although it remains to be seen whether a subpopulation of patients may benefit from bevacizumab treatment, it is unlikely that bevacizumab will play a major role in the management of GBM. Nevertheless combination therapies with anti-angiogenic agents remain possible. In order to counteract the metabolic adaptation of tumor cells under hypoxia, the combined targeting of angiogenesis and metabolic pathways remains an interesting avenue that awaits further exploration [7].

3. Circumventing the blood brain barrier in brain tumor treatment

In addition to the low efficacy of current drugs, drug delivery from the circulation to the brain is seriously hampered by the blood brain barrier (BBB). The BBB is composed of specialized brain endothelial cells, pericytes and astrocytic endfeet and strictly regulates the passage of large and small molecules between the blood and the brain parenchyma [22]. This structure is essential to protect the healthy brain from blood derived noxious factors, but strongly impairs drug delivery in the diseased brain. Several pre-clinical studies have convincingly shown that the inefficacy of many clinical trials for brain tumors may be partially explained by limited drug availability at the tumor site. E.g. systemic administration of monoclonal antibodies to EGFRvIII led to tumor shrinkage in subcutaneous melanomas but not in intracranial brain metastases [23]. Similarly the anti-EGFR antibody Cetuximab was ineffective in orthotopic human GBM xenografts when delivered systemically, but potently blocked tumor growth in the brain when applied via an osmotic minipump [24]. There is also convincing