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Review

Breaching barriers in glioblastoma. Part II: Targeted drug delivery and lipid nanoparticles

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ABSTRACT

Tailored nanocarriers have gained huge research focus for brain drug delivery, aimed at combating several neuro-oncological conditions, such as the glioblastoma multiforme (GBM). The progress of knowledge on the pathogenesis of GBM has allowed identifying the major hurdles for efficient treatment, encompassing biological interfaces (blood-brain barrier and blood–brain tumour barrier), specificities of tumour microenvironment, as well as both bulk and glioma stem cell subpopulations. These findings provided new insights into the molecular basis of GBM, being a strong driving force behind development of targeted nanomedicines in this area. Diversified nanoparticles have been designed to target GBM surface markers, overexpressed receptors, aberrant genes and signalling pathways, in addition to contemplating barriers targeting strategies. Among the nanocarriers explored, lipid nanoparticles claim important and unique features, including the versatility in promoting both passive and active drug targeting, making them excellent candidates for brain drug delivery and one of the most appealing to overcome the obstacles of the current GBM treatment.

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1. Targeted drug delivery using nanomedicines

Due to the poor prognosis of glioblastoma multiforme (GBM), nanoparticle-based carriers have been intensively explored in an attempt to improve bioavailability of therapeutic molecules for brain uptake and their targeted delivery within the tumour. Indeed, increasing the amount of the drug delivered to the target tumour cells is the greatest challenge for the development of novel cancer nanomedicines (Pourgholi et al., 2016; Kim et al., 2016). After being systemically administered, nanoparticles have to face several hurdles *in vivo* to reach their target site inside the cells. However, due to their ability of active or passive targeting, nanoparticles have been considered one of the most appealing drug delivery systems (DDS) to overcome the limitations of the current GBM treatment (Kim et al., 2015a; Karim et al., 2016).

The passive targeting drug delivery can occur through the EPR effect, which is linked to the anatomical differences between normal and tumour tissues. In other words, the passive method of targeting tumours takes advantage of the unique tumour characteristics, including the high vascular density, the leaky vasculature and the inefficient lymphatic drainage. However, some nanoparticle properties must be taken into account, including particle size, shape, and surface characteristics, as they influence the EPR effect (Yu et al., 2016; Steichen et al., 2013). To date, many approved nanoparticles for solid tumours depend on the EPR effect. However, despite passive targeting strategies may be useful in the treatment of tumours, they present some limitations. For example, the EPR effect relies on the diffusion of drugs, but not all drugs diffuse efficiently through cells. Since brain tumours present a relatively weak EPR effect due to a dense brain matrix, the diffusion of drugs is often compromised in these tumours, which results in insufficient drug concentrations at the tumour site. Furthermore, due to the inefficient lymphatic drainage in tumours, the interstitial fluid pressure increases, thereby resulting in the following situation: larger nanoparticles are able to accumulate in the tumour, while smaller ones easily diffuse. Thus, it is estimated that when administered intravenously, most of passively targeted nanoparticles (about 95%) do not reach the tumour since they accumulate non-specifically in other organs (Kim et al., 2015a; Yu et al., 2016; Danhier et al., 2010; Bae and Park, 2011).

To overcome the limitations of passive targeting, the attachment of site-specific ligands on the surface of nanoparticles can increase their uptake selectivity with the consequent cellular accumulation. Thus, active targeting takes advantage of the receptors generally overexpressed in certain tumour cells, and not expressed by healthy cells. Affinity ligands, such as antibodies, peptides, or aptamers, are capable of binding to antigens or receptors on the target cells, which lead to the internalization of nanoparticles via receptor-mediated endocytosis and thereby enhancing the therapeutic effects. However, targeting moiety of nanoparticles should be engineered without directly perturbing the receptor binding site's characteristics (Pourgholi et al., 2016; Kim et al., 2015a; Steichen et al., 2013). It has been described that nanoparticles usually form a "corona" layer after systemic administration. This phenomenon occurs because proteins, peptides and other cellular apparatus circulating in the biological fluids tend to adsorb on surface of nanoparticles, generally modifying their initial physicochemical properties. It should be noted that protein corona may confer new biological identity to the nanoparticles, therefore interfering with their cellular uptake, circulation time and bioavailability (Nguyen and Lee, 2017; Blundell et al., 2016).

Considering their potential role in GBM treatment, nanoparticle DDS have been largely developed and studied for targeting different molecular biomarkers and signalling pathways of the tumour, as shown in Table 1.

1.1. Barriers to targeted drug delivery

The blood-brain barrier (BBB) is a neuroprotective barrier, which presents different defence mechanisms to block the passage of noxious agents to the brain (Karim et al., 2016). To counteract these protective effects of BBB, alternative approaches have emerged, such as direct chemotherapy delivery to the brain as well as the passive targeting based on the EPR effect (Fig. 1**A**). However, the passive targeting strategy is not enough to reach the tumor invasive cells, once the EPR effect appears to be weak near the tumor area containing these infiltrating cells (Kim et al., 2015a; Juillerat-Jeanneret, 2008; Jue and McDonald, 2016). That is, not only the BBB, but also the blood–brain tumour barrier (BBTB), is known to prevent drugs from reaching the tumor bulk, contributing to chemotherapy resistance and recurrence of cancer. Therefore, new strategies for active targeting have been developed in order to circumvent effectively BBB/BBTB and enhance the efficacy of GBM treatment (Fig. 1**B**) (Wei et al., 2014; Hendricks et al., 2015).

1.1.1. Disruptions in tight junctions

Recently, the opening of tight junctions (TJs) in the cerebral endothelial cells (CECs) has been object of study in order to create reversible and transient disruptions between the TJs, resulting in an increased drug permeability. In line with this reasoning, when the BBB is exposed to adverse conditions, such as chemical or mechanical stress, its integrity may be disrupted. Thus, different chemical (mannitol), biological (histamine and bradykinin) and physical (ultrasound and electromagnetic waves) stimuli have demonstrated ability to alter the integrity of TJ structure. For instance, the hyperosmolar agent mannitol has shown to contract the CECs by withdrawing water from them, thereby altering their shape with the consequent opening of TJs for a few hours. In turn, bradykinin acts at the level of B2 receptors of the CECs, leading to changes in the TJ integrity and an increased drug permeability (Karim et al., 2016; Jue and McDonald, 2016; Siegal et al., 2000; Prados et al., 2003; Alyautdin et al., 2014). Some surfactants, such as polysorbate 80 and sodium dodecyl sulfate, have also shown ability to disrupt TJs (Kim et al., 2015a; Karim et al., 2016; Alyautdin et al., 2014; Peluffo et al., 2015).

Although this technique favours the entry of the drug into the brain, it is obvious that it has limited usefulness due to toxicity, since the neuroprotective function of the BBB becomes compromised. In addition, BBB disruption by itself is not enough to obtain a significant outcome in GBM patients, bearing in mind that drugs still need to overcome other physical barriers, such as brain parenchyma, to reach their target cells (Kim et al., 2015a; Woodworth et al., 2014). The complex nature of this technique, involving non-targeted and toxic side effects, due to exposition of brain cells to neurotoxins present in blood, make it less interesting for research in neurology (Karim et al., 2016).