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TARGETING APPROACHES FOR BRAIN TUMOR: A COMPREHENSIVE REVIEW

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ABSTRACT

The development of a drug delivery strategy that can not only cross the blood-brain barrier (BBB) rapidly, but also targets the glioma and reaches the core of glioma is essential and important for glioma treatment. Targeted drug delivery system is a unique approach for drug delivery to the appropriate site which is highly efficient, biocompatible, and non-immunogenic. The receptor-mediated endocytosis is one of the targets approaches especially for targeting anticancer drugs to cancerous sites. In brain cancer, cells have overexpressed receptors like folate, transferrin, low-density lipoprotein and hyaluronic acid receptors which can be used for effective site-specific drug delivery to cancerous cells using appropriate receptor-specific ligands. Active and passive targeting promotes tumor specificity with reduced possible side effects. Severalnanocarriers like liposomes, nanoparticles, micelles and dendrimers are used in the delivery of drugs to the target site. Thereis many transporters also involved in targeting. The targeted drug delivery system has numerous clinical and diagnostic applications. Modern approaches like ligand-mediated or stimuli-sensitive drug delivery systems have been used for the development of multifunctional nanocarriers that can effectively target cells and cellular organelles.

KEYWORDS: Targeting; Ligand; Receptors; Cancer, Nanocarriers, Blood-brain barrier.

1. INTRODUCTION

In the last many years, pharmacists and biochemicologists have been involved in research to deliver drugs to the brain at an effective concentration. The major problem with the delivery of anticancer drugs to the brain is the blood-brain barrier (BBB). The presence of a tight junction of brain capillary endothelial cells that abolishes aqueous paracellular pathways across the cerebral endothelial cells prevents the free diffusion of solute into the brain. The diffusion or permeability of a drug also depends on its lipophilicity and, therefore, practical strategies are required for the mediating of drug transport across the BBB.

A targeted drug delivery system is referred to as a system having selective and effective localization of drug molecules at the target(s) site at therapeutic concentration, but controlling its access to the non-target site leading to enhancement of therapeutic effect and reduction in toxicity. Targeted drug delivery systems describe the presence of the drug-carrier complex which delivers the drug(s) completely to the pre-identified target cell in a specific manner. Various approaches have been used either to regulate the distribution of drugs by incorporating them into a carrier system. The receptor is the main target in the case of a targeted drug delivery system which includes its interaction with ligand for site-specific drug delivery. The targeting is highly significant if the target organ has different characteristics than the other parts of the body which leads to the placement of active drugs in the vicinity of the target site and a limiting quantity of drugs in the non-target site which minimizes the toxic effects of the drug. The specific characteristic of targeting is the specific drug receptor binding and rate of controlled drug release. Targeted drug delivery system is generally used in cancer chemotherapy. The pathophysiology of the cancer cell is different from that of the normal cell which is a key point for targeting cancer cells. Cancer cells overexpress many receptors which can be used as a suitable target to deliver cytotoxic agents into tumors (Jaracz*et al*., 2005). The special characteristic of cancer cells has an enhanced permeability retention (EPR) effect which is a selection criterion for the accumulation of nanocarrier in the tumor microenvironment and delivery of the chemotherapeutic drug to the tumor site (Torchilin*et al*., 2011; Kale *et al*., 2011; Maeda *et al*., 2012). Several nanocarriers are mainly focused on targeted drug delivery approaches for the active targeting of nanocarriers to the tumor site. The endothelial gaps present between the vascular capillary play a crucial role in the accumulation of nanocarriers in cancer cells (Deshpande*et al*., 2013).

2. OVEREXPRESSED RECEPTORS ON BRAIN CANCER CELL

Many cancer cells overexpress various receptors which provide opportunities to understand cancer biology and its management. These overexpressed receptors may be

managed by using antibodies or ligands. These ligands do not deliberately interfere with receptor function but exploit receptor overexpression for the targeted delivery of suitable anticancer drugs which cannot distinguish between cancers cell and normal cells. These carrier systems containing the anticancer drugs can directly link with ligands besides such overexpressed receptors present in the cancer cell (Akhtar *et al.,* 2014). Recently various ligand conjugated novel drug delivery systems like liposomes, micelles, dendrimers, quantum dots, carbon nanotubes etc. have been synthesized for targeted drug delivery to cancer cells (Bose *et al.,* 2018).

2.1 Receptors used for brain cancer targeting

2.1.1 Folate receptor (FRs)

Folate (folic acid) is a high-affinity ligand that maintains a high affinity towards folate receptor upon derivatization through its carboxyl-terminal region due to its overexpression in tumor cells (Damiati*et al.,* 2018). The folate receptor is the most commonly overexpressed in cancer cells. The folate receptors are present in three isoforms i.e. α, β, and μ each of which has its tissue-specific distribution in the human body. Folate receptor α (FRα) is a cell surface glycosyl phosphatidylinositol anchored glycoprotein that can be bound with folates via receptor-mediated endocytosis. Most of the normal tissues lack the expression of FR-α isoforms except for certain epithelial cells of normal tissues which express FR-α where it is isolated by blood circulation. In most of the epithelial lineage of malignant cells of ovarian tumorsFR- α overexpression is observed in 90% of cases (Walters *et al.,* 2013). The FR-α and FR-β are closely associated in function and sequence but distinct in cellular specificity and tissue dissemination. Various studies have reported that FR-α was overexpressed in solid tumors such as breast cancer, ovarian cancer, renal cancer, cervical cancer, lung cancer, and endometrial cancer but FR-β was expressed predominately in hematopoietic cells rather than solid tumors (Dhanasekaran*et al*., 2018). FR-β is referred to as a pro-inflammatory monocyte marker and also termed as tumor-associated macrophages or M_2 anti-inflammatory regulatory macrophages marker.

2.1.2 Transferrin receptor (TFRs)

Mainly two types of transferrin receptors (TFR1 and TFR2 restricted to hepatocytes) are present in humans. The extracellular domain of transferrin receptor 2 (TFR2) has a 66% similarity with TFR1. The receptor for TFR1 (also known as CD71), is universally expressed at low levels in maximum normal human tissues. TFR2 is another member of the TFR family which is a protein similar to TFR1 but its expression is largely limited to hepatocytes cells. TFR1 is involved in the entry of iron-bound TF into the cell, and progressions into acidic endosome cells by clathrin-dependent endocytosis (Daniels *et al.,* 2012). In this mechanism, TRF 1 is recycled back into the cell surface and iron enters the cell. The TRF1 is a type II receptor that dominates the outer cell membrane of cancer cells. Despite its ubiquitous expression; TFR1 is located on malignant cells at levels many times higher than the normal cells and its expression can be associated with stage of cancer progression. This highly expressed receptor is involved in the uptake of iron into the malignant cells for cancer cell proliferation which makes them suitable for the targeting of cancer (Voth *et al.,* 2015).

2.1.3 Low-density lipoprotein receptor

The Low-density lipoprotein receptor-related protein LRP 1 (also known as CD91), a multifunctional endocytic and cell signaling receptor is expressed on the surface of multiple cells such as hepatocytes, fibroblasts, smooth muscle cells, astrocytes, macrophages, neurons, and malignant cells. In the emerging *in vitro* and *in vivo* studies it has been illustrated that LRP1 is mainly involved in many processes like tumor genesis and tumor progression, initiation of tumor cell migration and invasion by modifying matrix metalloproteinase (MMP)-2 and MMP-9 expression (Feng*et al*., 2017). It also inhibits cell apoptosis by regulating the insulin receptor, the serine-threonine protein kinase signaling pathway and the expression of Caspase-3. LRP1-mediated phosphorylation of the extracellular signaling kinase pathway and c-junction N-terminal kinase is involved in tumor cell proliferation and invasion (Xing *et al.,* 2016). LRP1 has been down-regulated by microRNA-205 and methylation of LRP1 CpG islands. Recently discovered novel fusion gene LRP1-SNRNP25 promotes osteosarcoma cell invasion and migration.

2.1.4 Lectin receptor

Various lectin receptors are overexpressed in cancer cells in which mannose is the most common receptor. Mannose receptors are the C- type lectin receptors that are expressed on the surface of macrophages and have carbohydrate recognition domains. The mannose receptor responsible for tumor invasion, proliferation, and metastasis in the tumor cells is overexpressed in tumor-associated macrophages. They have potential roles in both innate and adaptive immune responses and are associated with inflammatory and infectious diseases. Numerous macrophage-targeted liposomes grafted with mannose as a ligand have been developed for cancer treatment (Hagimori *et al.,* 2018).

3. STRATEGIES FOR TARGETING TO TUMOR

Targeted drug delivery may be accomplished by utilization of carrier systems and the various signaling pathways followed by these carriers which protect the drug from the bio environment. Drug targeted especially to cancer cells or specific organelles inside the cells permits the internalization of substances with low cellular permeability by endocytosis and drug release in targeted organelles (e.g., lysosomes, nucleus) (Minko *et al*., 2004). Tumor microenvironment (TME) is employed as a better target for cancer treatment due to its significant nature in tumor development, progression and metastasis and also in the development of drug resistance(Joyce *et al*., 2005; Meads *et al*., 2009). Any

modification in TME provides another strategy for the enhancement of penetration of NPs in tumor cells (Chauhan *et al*., 2013). Tumor micro-environmental conditions which are required for the metastatic cells to survive and proliferate can be exploited for the development of a new therapeutic approach for the treatment of tumors (Psaila*et al*., 2009; Shi, *et al*., 2016). Active and passive targeting of nanocarriers is shown in Figure 1. Various strategies which have been employed in the targeted delivery to the tumor are discussed below.

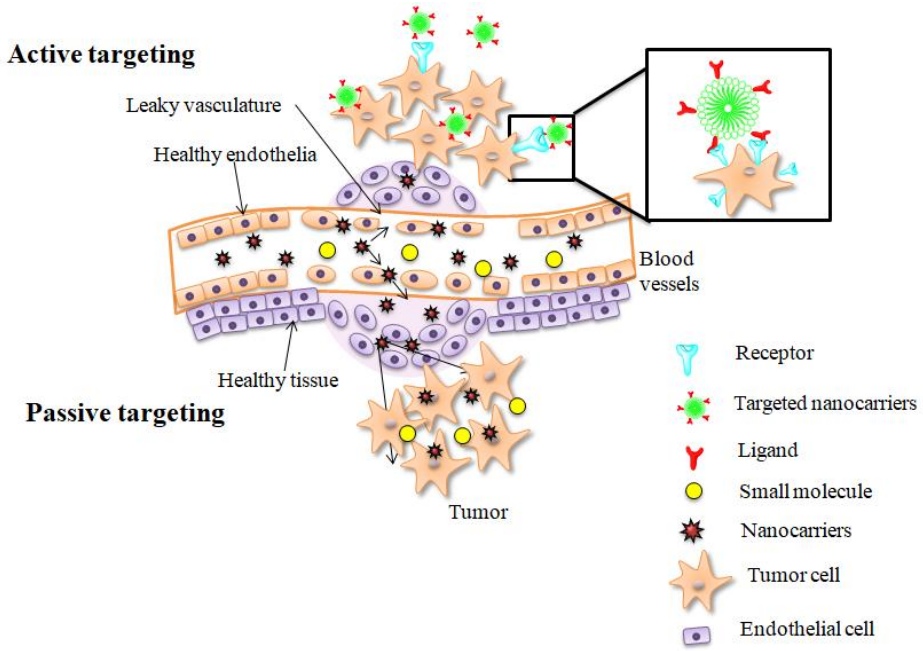

Figure 1 Schematic representation of active and passive targeting.

3.1 Passive targeting

Passive targeting is referred to as a method to deliver drugs based on the ability of the carrier to circulate for an extended period in systematic circulation (Cabral *et al*., 2011). Passive targeting occurs because of the body's natural response to the physiochemical characteristics of the drug or drug-carrier system. This type of targeting exploits the natural biodistribution of the carrier system. Passive targeting approaches mainly include the enhanced permeability and retention (EPR) effect, in tumor-bearing organs, and the topical transport of drugs directly to the tumor. Cabral *et al*. (2011) reported that macromolecules are retained easily in the tumors due to the low venous return in the tumor and reduced lymphatic clearance. In passive targeting, the coupling of low MW drugs with high MW carrier systems is inadequately removed by using the lymphatic system of the body and consequently accumulates in tumors. Various types of macromolecules which are permeated by the EPR effect depict wide application potential in cancer drug delivery (Thanou*et al*., 2003). The capability of the carrier system occupied by the RES exclusively in the spleen and liver has made them an ideal drug delivery system for hepatic targeting of drugs to these compartments. Nanocarriers are having passive target ability because of the identification of exogenous particulates either in intact or in the opsonized form, by the phagocytic cells of RES.

3.2 Active targeting

Active targeting is achieved by the modification of drug carriers by receptor-sensitive ligand, which is used for the selective targeting of tumor cells. Active targeting is also known as ligand-based targeting; it is based on ligand-receptor recognition permitting the binding between the ligand and conjugated carriers to the target site (Cabral *et al*., 2011). Targeting ligands have been introduced to improve the cell, tissue, and sub-cellular specific delivery through active targeting, as compared to its corresponding non-targeted delivery. Various cell-specific active targeting agents are used to achieve enhanced targeting of cancer-specific cells (Shi *et al*., 2011). Targeting ligands used in active targeting comprises small molecules for example folic acid (Park *et al*., 2016), peptides (e.g. RGD (Jin *et al*., 2016)), proteins (e.g. transferrin (Guo et al., 2015, Liu *et al*., 2013)), antigen binding fragments (nanobodies) (Talelli*et al*., 2013) and aptamers (Hrkach *et al*., 2013). There are three levels of targeting-

3.2.1 First order targeting

It is referred to as the selective distribution of drug from the carrier system to the desired target site i.e. tissue and organ. It is also known as organ level targeting or compartmental targeting to the peritoneal cavity, lungs, and eyes, etc.

3.2.2 Second order targeting

It is defined as the delivery of a drug to specific cells of the body. Targeting tumor cells rather than the normal

cell is referred to as second-order targeting. For example the selective targeting of drugs to the buffer cells of the liver.

3.2.3 Third order targeting

It is referred to as the delivery of drugs within the cell component of target cells. The lysosomal degradation of the carrier system is followed by the release of drug intracellularly through receptor-mediated endocytosis which is an example of third-order targeting. Chromatin is a new target and is an area of interest as it provides opportunities for cancer treatment which can show less toxicity than traditional treatments and affects the transcription factor by interfering with the transcription process which is usually a difficult target (Jones *et al*., 2016).

3.3 Inverse targeting

It is a specific type of targeting where the natural RES blockage phenomenon of the body is used. It avoids the passive uptake of the carrier's system by the reticuloendothelial system (RES) which leads to the reversion of biodistribution of the carrier hence the process is called inverse targeting. This is based on the suppression of the function of RES by pre-injecting the large amount of blank carrier(s) or macromolecules like dextran sulfate. This leads to the blockage of RES and causes significant impairment of the host defense system (Vyas *et al*., 2004).

3.4 Dual targeting

The standard method of drug targeting works on carrier molecules, where the carrier molecules have their intrinsic activity which synergies the pharmacological effects of the loaded drug.

3.5 Double targeting

In this targeting, the specific drug delivery is achieved by a combination of temporal control and spatial control of drug delivery which leads to a controlled rate of drug release and improved therapeutic effect.

Two main transporters responsible for brain cancer

Monocarboxylate transporter

Monocarboxylate transporters (MCTs) constitute a family of 14 members among which MCT1–4 facilitate the passive transport of monocarboxylates such as lactate, pyruvate, and ketone bodies together with protons across cell membranes. Their anchorage and activity at the plasma membrane require interaction with chaperon proteins such as basigin/CD147 and embigin/gp70.MCT1–4 are expressed in different tissueswhere they play important roles in physiological and pathological processes. This review focuses on the brain and on cancer. In the brain, MCTs control the delivery of lactate, produced by astrocytes, to neurons, where it is used as an oxidative fuel. Consequently, MCT dysfunctions are associated with pathologies of the central nervous system encompassing neuro degeneration and cognitive defects, epilepsy and metabolic disorders (congo et al., 2015). In tumors, MCTs control the exchange of lactate and other monocarboxylates between glycolytic and oxidative cancer cells, between stromal and cancer cells and between glycolytic cells and endothelial cells. Lactate is not only a metabolic waste for glycolytic cells and a metabolic fuel for oxidative cells, but it also behaves as a signaling agent that promotes angiogenesis and as an immunosuppressive metabolite (Kuo et al., 2015). Because MCTs gate the activities of lactate, drugs targeting these transporters have been developed that could constitute new anticancer treatments.

Ion transporter

Ion transporters are important in the regulation of ionic homeostasis, cell volume, and cellular signal transduction under physiological conditions. They have recently emerged as important players in cancer progression (Perez et al.,). In this review, we discussed two important ion transporter proteins, sodium-potassium-chloride cotransporter isoform 1 (NKCC-1) and sodium-hydrogen exchanger isoform 1 (NHE-1) in Glioblastomamultiforme (GBM) and other malignant tumors. NKCC-1 is a Na+-dependent Cl− transporter that mediates the movement of Na+, K+, and Cl− ions across the plasma membrane and maintains cell volume and intracellular K+ and Cl− homeostasis. NHE-1 is a ubiquitously expressed cell membrane protein that regulates intracellular pH (pHi) and extracellular microdomain pH (pHe) homeostasis and cell volume. Here, we summarized recent pre-clinical experimental studies on NKCC-1 and NHE-1 in GBM and other malignant tumors, such as breast cancer, hepatocellular carcinoma, and lung cancer. These studies illustrated that pharmacological inhibition or down-regulation of these ion transporter proteins reduces proliferation, increases apoptosis, and suppresses migration and invasion of cancer cells. These new findings reveal the potential of these ion transporters as new targets for cancer diagnosis and/or treatment (Krick et al., 2000)

4. NANOCARRIERS USED IN CANCER TARGETING

Variousnanocarriers have been explored in cancer chemotherapy. Lipid-based nanocarriers and polymeric carriers are extensively employed for targeting cancer cells.

4.1 Nanoparticles

Nanoparticles (NPs) are a class of materials that include particulate substances which have a particle size less than 100 nm. NPs are not simple molecules and are composed of mainly three layers (i) The surface layer which may be functionalized with a variety of small molecules, metal ions, surfactants and polymers (ii) The shell layer which is a chemically different material from the core in all parts (iii) The core which is essentially the central portion of the NP. Due to such unique characteristics, these materials have the immense interest of researchers in multidisciplinary fields (Shin *et al*.,

2016). The pH-responsive multifunctional nanoparticles containing doxorubicin were developed to improve nanoparticle accumulation and drug release in cancer cells by preventing anticancer drug efflux activity. In which conjugation of DOX to the surface of nanoparticles via acid-sensitive Schiff-base lead to approximately 6.5-fold improved release at pH 5 versus pH 7.4 in the first 4 h. (Daglioglu *et al*., 2018).

4.2 Liposomes

Liposomes are vesicular systems mainly composed of phospholipids in which an aqueous core is surrounded by lipid bilayers. It can incorporate both hydrophilic and hydrophobic drugs (Torchilin *et al*., 2006). A pH-sensitive liposomal system containing tariquidar (QTR); a P-gp inhibitor and doxorubicin (DOX) was developed to overcome multidrug resistance. It depicted good stability at pH 7.4 and remarkable sensitivity at acidic pH for easier delivery of TQR and DOX. The cellular uptake study evidenced that the liposomal formulations efficiently increased the accumulation of DOX in the nuclei which could be because of raised cellular uptake by P-gp inhibitor TQR.The outcomes revealed that the developed system depicted good potential in the treatment of multidrug-resistant ovarian cancer cells (Xia *et al*., 2017).

4.3 Dendrimers

Dendrimers are monodispersed macromolecules with regular and highly branched three-dimensional structures. Doxorubicin encapsulated PAMAM dendrimers were surface modified with LFC131 peptide which recognized CXCR4 expressed on the surface of breast cancer cells. LFC131-DOX-D4 system improved cytotoxic effect as compared to untargeted DOX-D4 (Chittasupho *et al*., 2017).

4.4 Niosome

Niosomes are non-ionic surfactant-based vesicles in which an aqueous core is encapsulated by a nonionic surfactant and cholesterol-assembled bilayer (Moghassemi *et al*., 2014)). Tamoxifen Citrate (TMC) encapsulated liposomes were developed as an injectable delivery system for breast cancer therapy. The alteration in the alkyl chain of Spans and the molar ratio of cholesterol controlled the rate of drug release. The results of the *In-vitro* release study demonstrated prolonged release of drug from niosomes over 7 days. The analysis of cellular uptake and cytotoxic activity was performed in the MCF-7 breast cancer cell line. The results revealed 2.8-fold increment in cellular uptake (Shaker *et al*., 2015).

4.5 Micelles

Micelles are an aggregate of surfactant molecules dispersed in a liquid with a size range of about 5–100 nm (Oerlemans *et al*., 2010). The Poly (Histidine)-based micelles were synthesized for the delivery of Piperlongumine (PL) and estimated for pro-oxidant anticancer therapy. The PEG-poly(His) micelles improved the loading efficiency of poor water-soluble drugs (PL). These micelles stimulated the apoptosis process by generation and accumulation of reactive oxygen species and enhanced the cytotoxicity in cancer cells. The folate conjugated micelles selectively delivered the drug into cancer cells and improved the therapeutic efficacy (Hong *et al*., 2018).

5. CONCLUSION AND FUTURE PROSPECTS

A targeted drug delivery system is an inherent technique for the delivery of drugs to the appropriate sites for effective treatment. Apart from these, it also includes various ligand-mediated drugs targeting with the help of varieties of nanocarriers like liposomes, niosomes, nanoparticles, micelles, and dendrimers which increase the therapeutic effect on the target site with fewer side effects. The lack of thoroughly validated predictive biomarkers has been one of the major hurdles to stratifying cancer patients and monitoring tumor progression and response to the therapy. Investigations in the clinic and preclinical models have provided some molecular and cellular mechanisms for the above challenges.

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