Journal of
Bioresearch Communications

Grover et al., J Biomol Res Ther 2013, 2:2
DOI: 10.4172/2167-7956.1000e113

Editorial Open Access

Nanoparticle-Based Brain Targeted Delivery Systems

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Abstract

Numerous deaths are caused every year by the morbidity of brain disorders, namely gliomas. The staggering number of deaths may be contributed by the anatomic blood-brain barrier, restricting access to a number of therapeutic compounds. This article briefly describes the blood-brain barrier and the current state of nanoparticle therapeutics that aim to cross the blood-brain barrier to improve drug delivery to this highly sensitive region.

Glioblastomas

Presenting a very dismal prognosis, glioblastomas present as one of the most malignant brain tumors [1]. In addition to its low prognosis, glioblastomas account for ~70% of all astrocytic and oligodendroglial tumors, making this one of the most common types of brain tumors [1]. Through the mutations of multiple pro-oncogenic genes, primary glioblastomas develop as other neoplasms but present as "full-blown tumors" upon diagnosis, designating their development as *de novo* [1]. In contrast, because secondary glioblastomas develop through the progression of multiple low-grade and less malignant astrocytomas, they tend to differ from primary glioblastomas in development, the expression of various proteins, and responses to therapy [1]. Attempts at therapeutic intervention fall prey to blockages by the blood-brain barrier (BBB).

The Blood-Brain Barrier

The BBB is an anatomic barrier to the brain developed by the coordinated function of multiple cell types aiming to limit the penetration of harmful substances to the brain. Microvascular endothelium, basement membrane, and glial cells such as astrocytes and pericytes work together to form the BBB [2]. The tightness of the endothelial cells lining the brain capillaries forms tight junctions, limiting substances crossing this barrier into the brain [2]. However, the cytoplasm of the microvascular endothelial cells contain pinocytic vesicles and high number of mitochondria for the active transport of certain molecules between the blood and brain [2]. However, the BBB holds a number of transport proteins that are essential for the permeation of molecules essential to proper brain health. An example of this is the glucose transporter (GLUT) [2]. It is possible that therapeutic compounds can be modified to be recognized by the GLUT protein so that they can be transported into the brain endothelium. However, the compound attempting to be transported across the BBB needs to be able to bypass the multidrug resistance protein, MDR1, an efflux transporter that limits the accumulation of certain compounds in the brain [2]. Given the presence of this highly selective barrier, the development of certain therapies that can bypass the BBB and efficiently deliver drugs to affected areas would be a huge gain towards the development of effective therapies against glioblastomas and other brain disorders (Figure 1) represents a model of the BBB.

Manipulating Nanoparticles for BBB Permeability

The relatively-recent development of nanomedicines, specifically nanoparticles,provides a new platform upon which to develop potential therapies to pass through the BBB. Nanoparticles are engineered to have at least one functional dimension in the nanometer scale range (10^{-9} meter). At this size range, a number of distinct properties in the nanoparticles emerge; these properties are markedly different than those that would be apparent at a larger scale, possibly due to quantum effects at the nanoscale. The development of nanomedicine technologies opens the door to the potential delivery of a number of therapeutic compounds across the BBB by manipulating the engineered conditions of nanoparticles. However, for nanoparticle technologies to be effective in targeting brain tissue, three main criteria have to be met:

If the nanoparticle therapy is systemically administered, it would need to effectively find BBB without adversely effecting other cell types;

It would have to be able to cross the BBB; and

It would have to be able to effectively target the appropriate cells after BBB translocation to release the therapeutic compound [3].

Current Nanoparticle-Based Strategies for Brain-Targeted Deliveries

PEG-coated nanoparticles

Poly(ethylene glycol) (PEG) (Figure 1A) acts as a potential hydrophilic cover for hydrophobic nanoparticles to increase particles' aqueous solubility and systemic retention in a nontoxic way [4]. By being complexed with nanoparticle carriers, PEG allows the nanoparticles to cross the BBB through interacting with microvascular transport proteins such as apolipoproteinE and utilizing the low-density lipoprotein (LDL) receptor-mediated pathway [5,6]. PEG may be complexed with PLGA nanoparticles to act as a cover to the hydrophobic PLGA core [6]. The hydrophilic surface of the PEG-PLGA nanoparticles reduces its clearance from the blood and significantly enhances its circulation rate by eluding opsonization and phagocytosis [6]. PEGylatingliposome vectors that target the brain's insulin receptor shows promising results for gene therapies [7], as studies in human and rat glioma cells have shown that targeting the insulin receptor yields 100-200 fold higher levels of gene expression as compared to targeting the human epidermal growth factor receptor (EGFR) or the rat transferrin

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Received August 22, 2013; **Accepted** August 23, 2013; **Published** August 27, 2013

Citation: Grover A, Hirani A, Sutariya V (2013) Nanoparticle-Based Brain Targeted Delivery Systems. J Biomol Res Ther 2: e113. doi:10.4172/2167-7956.1000e113

receptor [8]. In addition, hexadecylcyanoacrylate nanoparticles coated with PEG were shown to target rat gliosarcoma cells and accumulate within the cells [9]. PEGylated micelles were shown to accumulate into rat brain glioma models [10].Furthermore, PEG-complexed nanoparticles were shown to permeate the BBB to therapeutically effect models of multiple sclerosis [3,11] and Parkinson's disease [12] among other diseases. (Figure 2) presents an example of a PEGylated PLGA nanoparticle ready to be used for therapeutic studies.

Albumin-coated nanoparticles

Human serum albumin is one of the most common proteins found in the blood. Nanoparticles, when entering systemic circulation, are commonly surrounded by a protein "coat," known as a corona, most commonly composed of albumin [13]. Studies have shown that albumin- and albumin-coated nanoparticles (Figure 1B) are able to cross the BBB [14,15] and are able to release doxorubicin in *in* vitro neuroblastoma cell models [15].

Transferrin-coated nanoparticles

The cells lining the BBB express transferrin-receptors, making these types of nanoparticles very appealing in delivering drugs across the BBB [16]. PLGA nanoparticles coated with transferring (Figure 1C) and loaded with doxorubicin and paclitaxel were evaluated in *in vitro*- and *in vivo*-glimoa models to show enhanced inhibition of tumor growth [16].

Glutathione-coated nanoparticles

Glutathione is an antioxidant that protects cells from toxins created through oxidative stresses [17]. PLGA nanoparticles, coated with glutathione (Figure 1D) and loaded with paclitaxel, were shown to inhibit the growth of an *in vitro* rat glioma cell model (RG-2) as well as translocate the BBB in *in vivo* models to inhibit glioma cell growth [17]. (Figure 3) shows a TEM image of the cellular uptake of glutathione-coated PLGA nanoparticles in a RG-2 cell model. The nanoparticles release the drug once they are incorporated into the cell, inducing cytotoxicity in the glioma model.

Thiamine-coated nanoparticles

Thiamine is a compound required by cells for proper function, growth, and development [18]. Because all eukaryotic cells have receptors for the uptake of thiamine, the association of thiamine ligands on nanoparticles make for a suitable candidate for the development of therapies that cross the BBB [18]. Studies show that thiamine-coated nanoparticles (Figure 1E) show specificity for endothelial cells and accumulate at the BBB, diffusing across in a time-dependent manner [18]. The encapsulation of drugs within the nanoparticle could enhance the delivery of drugs across the BBB. However, because the uptake of the thiamine-coated nanoparticles is dependent on the thiamine receptor, the presence of thiamine in systemic circulation presents as a possible source of competitive inhibition in the uptake of thamine-coated nanoparticles [18].

Polysorbate-80-coated nanoparticles

Coating nanoparticles with Polysorbate-80 (PS80) (Figure 1F) is a highly popular method to induce its transport across the BBB. Mechanistic studies with PS80 show that its transport across the BBB is due to its interactions with apolipoproteins B, E, and possibly A-1 to be transported into endothelial cells by receptor-mediated endocytosis [2,3]. Studies with temozolomide-loaded, PS80-coated, PLGA nanoparticles in an *in vitro* rat glioma (C6) cell model showed a decreased cell viability in the presence of the nanoparticles [19]. In addition, *in vivo* studies have also shown the effectiveness of PS80 coatings on the BBB transport of drug-loaded nanoparticles. Gulyaev

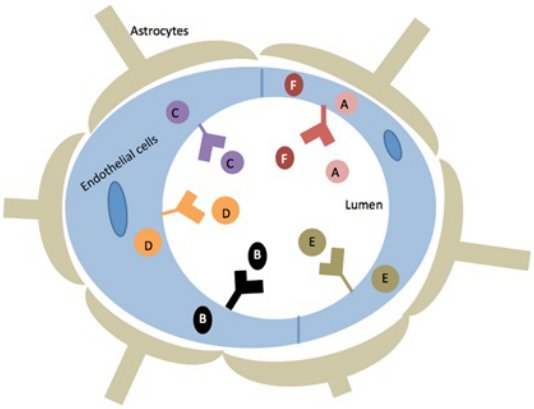

Figure 1: A model of the BBB comprised of the lumen of the blood capillaries, endothelial cells, and astrocytes. (A) represents PEG-coated nanoparticles, (B) represents albumin-coated nanoparticles, (C) represents transferring-coated nanoparticles, (D) represents glutathione-coated nanoparticles, (E) represents thiamine-coated nanoparticles, and (F) represents PS80-coated nanoparticles. Each of these has receptors that recognizes their presence and takes the respective nanoparticles up.

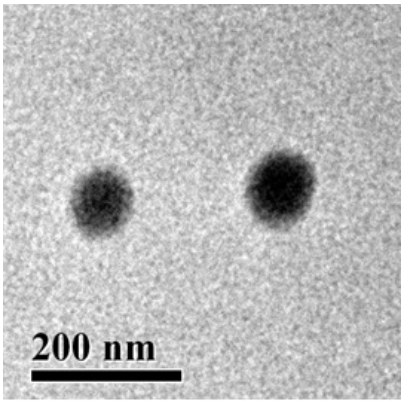

Figure 2: TEM image of drug-loaded PEGylated PLGA nanoparticles.

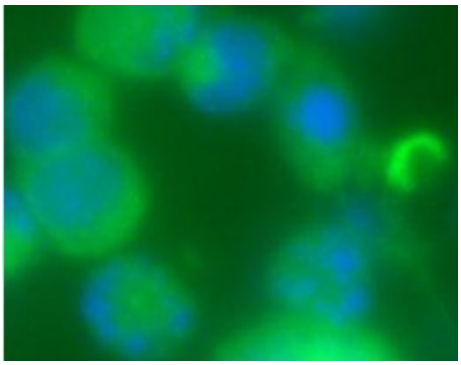

Figure 3: TEM image (Magnified 20X) of coumarin-6-loaded glutathione-coated PLGA nanoparticles in a rat glioma (RG-2) cell model. Nuclei (blue) were stained with DAPI and the nanoparticles can be seen in green.

et al. showed that carotid intravenous injections of doxorubicin-loaded, PS80-coated nanoparticles were found to be present in the brain two hours after injection, showing their ability to translocate the BBB into the brain in an *in vivo* rat model [20]. Many such studies have led to the popularity of PS80 as a nanoparticle-modifying agent, making it a "gold standard" in brain drug delivery [6].

Conclusion and Future Considerations

The development of biodegradable, nanoparticle drug-vectors is essential for brain therapies to prevent the toxic effects of non-biodegradable nanoparticles such as quantum dots and carbon nanotubes [6]. As previously mentioned, there are a number of different, modified-nanoparticle vectors that are able to translocate into the BBB to deliver their drugs in a localized way to the effected tissues. Of the mentioned brain delivery systems, the glutathione- and thiamine-coated methods seem the most promising. PS80 tends to produce cytotoxic effects in treated cells, and albumin- and transferrin-coated nanoparticles show less efficient BBB translocation as compared to glutathione- and thiamine-coated nanoparticles. The unique properties of each nanoparticle carrier, along with the drug it encapsulate and its surface modification with PEG to induce BBB permeability, has the potential to expand current brain therapeutics. Further work using *in vitro* and *in vivo* models will help advance the science of brain therapy and help the scientific community in reducing the staggering number of deaths brought about each year by gliomas and other degenerative brain disorders.

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