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Targeted Fullerene Lysosome Nano Carrier to cross the Blood Brain Barrier as a Treatment for Brain Tumors

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ABSTRACT - *The Blood Brain Barrier has posed an issue in curing various neurological and mental diseases despite its necessity and great importance as a part of the immune system. It has been a great objective of the neuro-biological scientific community to pass this barrier using nanoparticles to cure various diseases. This paper proposes a nanoparticle structure (Nanosome with the additive of PEG and a coating of Transferrin) that crosses the BBB through RMT to5VGH1 treat Brain Tumors. [1]*

KEYWORDS-Gold Nanoparticles (AuNPs), Drug Encapsulation, Nanoparticle toxicity, Liposome-based Nanoparticles, Alkylation conjugation, Doxorubicin, Methotrexate, Dihydro folate educates (DHFR), Tetrahydro folate

1. INTRODUCTION

The Blood Brain Barrier acts as a partially permeable membrane that prevents certain particles from crossing into the cerebrospinal fluid to maintain homeostasis. This barrier has posed a problem for treating brain tumors along with other neurological diseases. One of the methods researched to cross this barrier is nanoparticles. This paper explores the possibility of using Stealth Liposomes with the additive of PEG and a coating of Transferrin to cross this barrier.

2. TYPES OF NANOPARTICLES

2.1 Metallic Nano-Particles

Metallic Nanoparticles (NP) are typically smaller than most nanoparticles (including but not limited to: Lipid NPs and Polymeric NPs). These can cross the Blood Brain Barrier (BBB) into the brain using various methods such as passive diffusion, or trans-synaptic transport. However, due to the dense nature of the metal, the drugs cannot be encased in the nanoparticle. Hence, therapeutic agents such as anticancer drugs, antibodies, and siRNA can be bonded to the nanoparticle's surface. Metallic Nanoparticles such as those made of Gold are highly toxic and their quantity must be carefully regulated. Moreover, their diameter has to be 5nm and modified with the trans-activator of transcription peptide to be enabled to cross the BBB. Moreover, as a result of their dense nature, they lack mobility. [2]

2.2 Polymeric Nanoparticles

These nanoparticles consist of relatively softer materials, hence, allowing them to be more mobile in comparison to metallic nanoparticles. Moreover, due to their less rigid nature, they can also encapsulate a contrast of drugs such as chemotherapeutic drugs and contrast agents. This means that this nanoparticle can not only deliver drugs but also assist in medical imaging. [3]

2.3 Fullerene Nanoparticles

The majority of research regarding fullerene nanoparticles has been performed on carbon-based fullerene nanoparticles. The main concern is that the majority of research performed regarding this nanoparticle is in Vitro which does not take into account the toxicity concerns that come with the incredibly tiny size of this particle.[4]

Carbon atoms form the unique form of molecules known as fullerenes, which are entirely made up of carbon. Some molecules have a closed polyhedral shape with different sizes and forms. The most common fullerene is C60 because it contains 60 carbon atoms which are connected by C5–C5 single bonds and C5 = C6 double bonds. Other types that have been found include those with 70, 76, 84, or more carbons in them. In addition to this, due to its physical properties and chemical characteristics fullerene has been under investigation for quite some time now since it acts like something that can be used for targeted drug delivery.[5]

Fullerene has lately been employed in targeting cells having a nucleic acid deficit. The mathematical representation of Fullerene is as follows: 'n' hexagons contain (20+2n) carbon atoms. C60 Fullerene molecules can produce oxygen species upon exposure to visible light. Fullerenes double bounds may be very useful during the addition reactions because the outer sphere of the carbon cage can be modified.

Fullerenes can be synthesized using various methods. The most common method involves arc discharge, where graphite electrodes are vaporized in an inert atmosphere like helium. The resulting carbon vapor condenses to form soot, which contains a mixture of fullerenes. Other methods include laser ablation, where a laser is used to vaporize graphite, and combustion, where hydrocarbons are burned in a controlled environment. The fullerenes produced by these methods are typically a mixture of different sizes and shapes. They need to be separated and purified using techniques like chromatography and

solvent extraction to obtain pure fullerenes for specific applications.

2.3.1 Crossing the BBB with Fullerene NPs

Receptor-Mediated Transcytosis: FNPs can be functionalized with ligands that bind to specific receptors on the BBB endothelial cells, triggering receptor-mediated transcytosis, which facilitates their transport into the brain. Adsorptive-Mediated Transcytosis: FNPs can interact with the BBB through adsorption, leading to their internalization and transport across the barrier. However, due to the lack of research on this nanoparticle, we have chosen to go a different route.

3. OUR NANOPARTICLE STRUCTURE

The nanoparticle that we are presenting is a bi-layer nano some. This allows for the quantity of drugs to be released per unit of time to be lower. The particle will be administered through IV directly into the bloodstream. This NP will have an additive of Polyethylene Glycol and will be coated in Transferrin. The payload will be stored inside this capsule. This particle will have a size of 65nm. This particle is a single bi-layer to ensure that the deployment of the drug is easier. We have chosen this nanoparticle as it is the easiest to modify and formulate other molecules with. An example of this would be that instead of coating the nanoparticle in transferrin we formulate the outer layer with the glycosyl derivative of cholesterol. This nanoparticle is less toxic than metal nanoparticles and is the most researched nanoparticle of all.

3.1 Lipo somes

Liposome-based nanoparticles are fairly efficient as they can carry hydrophilic, hydrophobic, and amphoteric drugs. These nanoparticles can take advantage of the negatively charged surface of the BBB and use a particle with a cationic nature to cross the blood-brain barrier (AMT). Moreover, these particles can also use Receptor-Mediated Transport, providing a more specific route through the BBB and into the CNS. The surface of this nanoparticle can also be modified to decrease particle clearance. These liposomes can also be exploited through formulation with a glycosyl derivative of cholesterol to transport the NP across the BBB by targeting Glucose receptors. These nanoparticles are mostly known to carry drugs for cancer treatment; these drugs include (but are not limited to: fluorouracil, paclitaxel, doxorubicin, and erlotinib).[6]

3.1.1 PEGylated Liposomes

Conventional liposomes are removed from the circulation too quickly; hence, the particle should be coated with Poly-Ethylene Glycol in order to increase the time duration that the liposome spends in the circulatory system. This longer circulation time ensures that the NP does not escape through any endothelial cells so that it does not suffer the “leaky endothelium” effect. This also allows the NP to release various drugs over a longer period of time rather than within several minutes. This specialized liposome is referred to as the “Stealth Liposome”. [7]

3.2 Poly-Ethylene Glycol

Modifying the particle surface and covering it with a layer of polyethylene glycol chain will increase the period of time in which the particle stays in the bloodstream. PEGylation also allows for a decreased degradation by enzymes. This chemical has proven to be non-toxic. This chemical also assists in medical imaging inside the body. Hence, this additive will help to map out more details of the Blood-Brain Barrier. This modification of the liposome nanoparticle is called a Stealth Liposome (SL) Nanoparticle.

The conjugation strategy that would be most effective for this is alkylation which assists in taking advantage of the negatively charged nature of the BBB as the coating is then positively charged. All of this research has been conducted in Vivo making it even more promising.

This alone, however, is less effective for cancer treatment as it causes less interaction with the target cells. This leads to less endocytosis conducted by the cancerous cells and causes less accumulation in the target cells with regards to Transferrin.[8]

3.3 Transferrin

Transferrin (Tf) is a glycoprotein that is responsible for the transfer of iron in blood, hence, it binds itself to the transferrin receptors in the BBB. Moreover, due to the high number of transferrin receptors in cancer cells, this has been a well-researched modification for liposome particles that can help treat Brain Cancer by traversing the Blood Brain Barrier and attaching itself to cancerous cells due to the aforementioned large number of transferrin receptors. Combining this with PEG would result in an optimal particle as it would allow for more accumulation in the target cells. This is proven by the study conducted by XueMing Li, LiYan Ding, Yuanlong Xu, Yanglu Wang, and QiNeng Ping in which doxorubicin-loaded nanoparticles were experimented on. The results of this study not only prove that this particle is effective for crossing the Blood blood-brain barrier but also effective for cerebral cancer treatment.[9]Not only will the development of this modification allow for crossing the BBB but also be a huge development in cancer treatment.

3.4 Method of Crossing the BBB

This particle will cross the BBB via Receptor Mediated Transcytosis (RMT). The particle will attach itself to the Transferring Receptor (TfR) and then undergo endocytosis and cross over onto the other side. [10]

This method allows for the particle to be on the larger side of the scale without it turning into a disadvantage. This design can pass through the Blood-Brain Barrier without having to bypass it. This particle in particular will be using the TfR to traverse the BBB. [11]

Once the nanoparticle is inside the Cerebrum, the payload will be released. Due to using RMT, a larger payload than normal can be delivered as this method does not rely on the size of the nanoparticle.

3.5 Releasing the Payload / Drug

The drug will slowly be released from the nanoparticle through membrane diffusion. The small size of the nanoparticle ensures a slow release of the drug, however, the drug can be released faster if needed by adjusting the base particle to be multi-layered rather than bi-layer.

It should be noted that due to the configuration of the nanoparticle, this will not affect its efficacy nor its effectiveness due to the use of transcytosis to cross the BBB and endocytosis to enter cancerous cells which removes the reliance on just size upon which most nanoparticles are dependent.

4. BRAIN CANCER

4.1 Surgery as a method of Treatment

In the past the most commonly used method for the treatment of cancer in the brain has been surgery, however, this has proven to be too invasive. Moreover, neoplastic tissue is almost in differentiable from the normal brain making it difficult to remove the cancerous tissue without damaging nearby crucial structures.

4.2 Using Nanoparticles to penetrate cancerous cells

It is much easier to use NPs to penetrate cancerous cells as they can enter the cells through endocytosis where the membrane of the cells will naturally take up the particle as it is coated in transferrin through the cell's transferrin receptors. The cancerous cell will absorb the nanoparticle into itself. [12]

5. DRUGS

5.1 Doxorubicin

Doxorubicin is a well-researched drug and is therefore safe for usage for various cancers. Thus far, the only hurdle that has prevented it from treating tumors in the brain is the BBB. Hence, our particle allows the drug to cross that hurdle.
This drug prevents the tissue from replicating itself. The drug negatively impacts cancerous cells in 3 major ways:

1. Inserts itself between DNA pairs causing the breaking of strands. This temporarily prevents the copying of DNA.

2. It restrains topoisomerase II which is responsible for the repair of DNA strands in DNA cells. 3. Doxorubicin then generates reactive oxygen species that cause oxidative damage to the surrounding cellular components in the cancerous cell. This includes various proteins such as DNA molecules.[13]

5.2 Methotrexate

Methotrexate is a drug that is well known for its ability to disrupt the enzyme activity inside cancerous cells. This drug can cross the BBB with the nanoparticle that we have designed.

This drug affects the cancerous cells in 2 main ways: 1. This drug negatively impacts the availability of Dihydrofolate educates (DHFR) which is an enzyme that synthesizes Tetrahydrofolate which is essential for the building of nucleotides. 2. Through this, it reduces the synthesis of DNA, RNA, and other proteins.[14]

5.3 Ideal Drug

The ideal drug of all these is Doxorubicin as it is the most researched out of all of these and is the most effective at stopping the cancerous cells in their tracks. This is because it not only stops the cells from replicating but also destroys them via generating reactive oxygen species that damage the cancerous cell's proteins such as its DNA and RNA.

6. CONCLUSION

In conclusion, this nanoparticle is a revolution in treating not just brain tumors but also other neurological diseases. This nanoparticle is currently undergoing research in various parts of the world and presents a promising front for future treatment of brain tumors. The drugs that we have presented are also highly effective and highly researched. They can also be used in combination to ensure that the tumor is effectively taken care of.

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