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Review Article

Multifunctional Nanoparticles In Diagnosis And Therapy Of Brain Tumor

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ABSTRACT

Brain tumors treatment is enormous challenge in neuro-oncology. Diversity in neoplasms often carry poor prognosis for patients. The prognosis of patient with malignant glioma (oligodendroglioma, ganglioglioma) is extremely poor in surgery and improvement in radiotherapy and chemotherapy. Nanotechnology protect the therapeutic agent and allow it sustain release which is very relevant for treatment of glioma therapy. This technique is tumor specific targeting and specific intertumoral distribution must be developed to target specific delivery of nanoparticles. Stem cell therapy and nanotechnology together efficiently deliver drug to brain tumor. The nanoparticles are specifically designed to identify the tumor cell.

The blood brain barrier is physiological barrier which results inadequate amassing of therapeutic agent in tumor location and avert sufficient demolition to malignant cell. Its essential requirement to improve the imaging of brain tumor for better identification, delineation and characterization of tumors, during surgery its improve visualization, taking response of chemotherapy and radiotherapy. The management of brain tumors is become very easier and more potent by the help of multifunctional nanoparticles. There is a significant improvement in the management of disease and better prognosis for a patient. we discuss the therapeutic and diagnostic application of nanoparticles in brain tumor for better approach to target the tumor for tumor imagen and delivery of therapeutic agent. We can also examine the clinically attainable nanoparticles management strategies brain tumor patient. We label the barricade towards the clinical execution of multifunctional nanoparticles for the surroundings of brain tumor administration.

INTRODUCTION:

With the expeditious maturing of nanotechnology for biomedical application, up to date evolved particle system have a thoroughgoing smash of brain cancer identification and therapy[1-2]. The nanoparticles between 1-100 nanometers for design, synthesis and application of active multifunctional nanoparticles. It contains the, magnetic, thermal and optical properties that are encouraging system which offers recently developed chance to get the better of the limitation of contemporary brain tumor management option in clinic. The major clinical protocols need enhancement to remove hurdle covering of brain tumor administration to highlight begun advancement in clinical application of nanoparticles is focusing currently:

- To improve brain tumor imaging.
- Targeted drug therapy with relevant dosage form.
- Identify most relevant route of administration of drug.
- Remove the barrier toward clinical implementation of nanoparticles.

The brain tumor refers to heterogeneous category of chief and metastatic neoplasms in the CNS. The condition is characterized by low survival rate. Twenty-four thousand cases of brain tumor are registered annually in India. 70% of new brain cancer originating from glial cells of brain. Brain metastasis are further principal class of tumor in central nervous system arising mostly from systemic cancer in breast, lung and skin. The major number of cases reported brain tumor are mainly of systemic cancer metastasis cases. The chemotherapy is mainly based on two categories namely Cytotoxic Agents and Cytostatic Agents[15]. The mechanism of these agents involves growth factor pathway disruption, direct tumor cell death, pro-differentiation, anti-angiogenesis and inhibition of tumor invasion. The initial line of systemic chemotherapy agent for patient with brain tumor are Temozolomide. Immunotherapy, gene therapy and photodynamic therapy are potential and unconventional treatments of brain tumor and are under clinical trials. These additive therapies have broadened the spectrum of threptic agents for brain tumor to photo sensitizers, genetic material and antibodies.

Obstacles In Brain Tumor Treatment

The blood brain barrier is major obstacle to deliver drug to the targeted tumor cells because of that the action towards of brain tumor continue to exist formidable provocation in meadow of neuro-oncology[10]. There is some other obstacle for successful treatment of brain tumor are as follows: -

- The Complexity in brain structure.
- Inadequate assembly of drug at the tumor location.
- Pharmacogenetics difference in individual of same species.
- Acquired drug resistance to chemotherapy.
- The nature of brain tumor is invasive and heterogeneous.

The brain is most composite system of the body, it commands multiple task and information of the body. Due to difficulty of brain function the investigation of brain tumors require highly selective elimination of cancerous tissue. Highly skilled surgeons are required for invasion far off principal tumor mass into the surrounding normal tissue[12]. There are several physiological barriers which hampered the effectiveness of systemic delivery of therapeutic agents. Unlike the alternative organs brain is safeguarded through blood-brain barrier. The BBB prevent inflex generated by drug molecules from the blood stream that's why it is crucial restricting element for anti-brain tumor therapy. Blood cerebrospinal fluid barrier is the following barrier that chunk the movement of systemically directorial therapeutic agent[25]. This barrier is composed of dense leap choroid epithelial cell which check the molecule perforate inside the interstitial fluid of the brain parenchyma. It also inhibits the macromolecule from hasting into the CSF through blood stream. Third barrier reported in treatment of brain tumor is blood tumor barrier. It is made up of tight junction of endothelial cells in the tumor. It hurdles in drug penetration from blood stream to the tumor

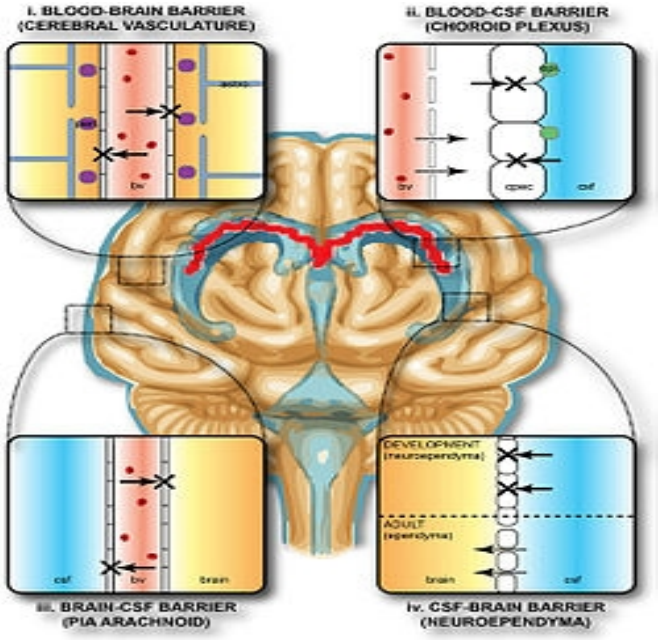


Figure:1 Depiction of Blood brain barrier

Source - https://en.wikipedia.org/wiki/Blood%E2%80%93brain_barrier

Nano particle utility

The surgeon requires high resolution image of tumor before surgery specially for the cases of glioblastoma multiform that is characteristically incursive[16]. Such incisiveness make it entirely difficult to precisely determine an understandable tumor borderline by eyes. MRI is the most advanced diagnostic tool for brain tumor.

Nanoparticle as a MRI contrast Agent

Gadolinium chelates (Gd-DAPA) are divergence agent usually used in MRI[3]. It does not commonly cross BBB but source marked signal alter in case of Brain tumor. Its having very short half-life and that's why it requires repeated injection with high dosage to achieve adequate response(*Table:1)*. The Nano particle which are used as a contrast agents having magnetic elements such as Fe, Mg and Gd are in the process of developmental phase as a contrast agent of MRI for capturing accurate image of brain tumor[27]. The Nano particles successfully show their potential to enhance quality and accuracy of image, to the enhancement of MRI signals to extent the duration of exposure and improves tumor border visualization[12]. The phase-I and phase-II trail of iron oxide had done successfully in Paris govt hospitals. The selecting peptide moderation of iron oxide is enhancing modernize of brain tumor lot following superior contrast of MRI with in tumor.

Table:1 Different Nanoparticles

Substance	Type	Structure	Size	Major component	Application	Phase
Hybrid	Fusion of nanoparticles	Tanker or Barge	Material dependent	Corona single or multilayer lipid or polymeric or core metallic	Theranostics	Pre-clinical
Organic	Micelles	Nano shell	20-180nm	Polymer	Drug carrier	Pre-clinical
Organic	Liposomes	Vesicular colloid structure	15-900nm	lipid	Drug carrier	Phase 1 and 2 clinical trial
Inorganic	Titanium dioxide crystals	Sphere	5nm	Titanium dioxide	Photodynamic therapy[11]	Pre-clinical
Inorganic	Gold nanoparticle[17]	Nano shell	1-90 nm	Gold	Drug carrier, photo chemical therapy	Pre-clinical
Inorganic	Quantum dots[8]	Nano rod	4-20 nm	Cadmium selenide	Florescence imaging	Pre - clinical

Therapeutic Nanoparticles Delivery For Brain Tumor

The nanoparticles use as therapeutic agent because its having potential to overcome many hurdles faces by conventional therapy.

- Nanoparticles improves the therapeutic agent circulation.
- Nanoparticles are responsible for targeted drug delivery.
- Nanoparticles having high loading capacity.
- Responsible for controlled drug release

Magnetic Nanoparticles-

The nanoparticles having magnetic properties or respond in presence of magnetic field are called nanomaterials which are very useful in the brain tumor as a therapeutic agent[8]. The principle of working of these nanoparticles is heat generating by the maneuver of magnetic nanomaterials in the lofty frequency make changes to field. Therapeutic efficacy of magnetic nanomaterials is depending to certain factors. SPIO nanoparticles effetely encourage glioma cell death due to that it enhances survival rate[24]. Magnetic nanomaterial has been utilized in short frequency of magnetic field in the treatment of brain tumor.

Photosensitive Nanomaterials

The photosensitive nanoparticles based on semiconductor mechanism of junction diode electrons. The semiconductors having both properties of metal and nonmetals which are very essential in treating brain tumor. Semiconductors nanoparticles for example titanium dioxide (TiO2) and the quantum dots have photosensitive properties that not long ago been evolve as light mediated glioma treatment. These molecules soak up energy coming to light and converts upon molecular oxygen. These are called ROS (reactive oxygen species) which is responsible to oxidized DNA, Ribosomes, cell organelles, protein and lipids. Gold nanoparticles are used as photosensitive nanoparticles in photothermal therapy. Gold Nano shells and nanorods can convert and absorb NIR light and heats then leads to cell death. Gold nanoparticles are used as photosensitive nanoparticles in photothermal therapy. Gold Nano shell and Nano rods can convert and absorb NRI lights and heats then lead to cell death.

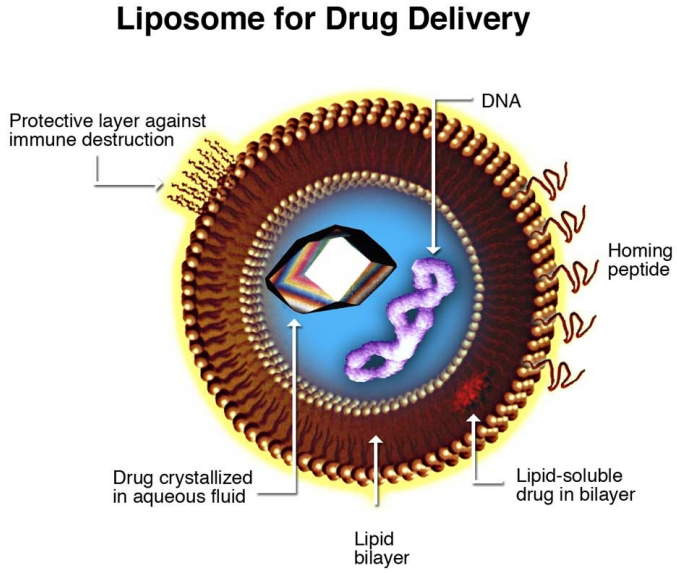


Figure:2 liposome for Drug Delivery

Source: https://en.wikipedia.org/wiki/Targeted_drug_delivery

The liposomes are spherical polymeric vesicles made up of lipid bilayer and the size range is 100nm to 4 micrometers[23]. The liposome consists of two lipid bilayers one is hydrophilic and another is hydrophobic in nature. The liposomes are very easily manipulated during their synthesis processes (Figure:2). The liposomes have very specific property of temperature sensitivity and Ph sensitivity allowing for regulating the targeted drugs approaches[19].

Nanoparticles As Chemotherapeutic Agent

Targets are Malignant brain tumor, Glioblastoma, GBM, nanoparticles enhanced chemotherapy. Only few conventional chemotherapies have been

effective in GMB, using of nanoparticles for targeted drug delivery further enhances the results[4]. Nanoparticles enhances the time of drug in blood circulation and reduces the half-life of drug this can make drug more effective[10]. By the using of nanoparticles drug can easily cross BBB because its coadded in liposomes and other structures which can pass through BBB(*Figure:3*). Polyethylene glycol coadded paclitaxel offers greater bioavailability as compare to free paclitaxel with a survival advantages shown in rodent glioma model[14]. While control release offered by nanoparticles reduces the systemic toxicity and allow drug slowly release when it reaches to the target. There is also needed that adequate dosage for better drug delivery and appropriately and adequately reaches to targeted area.

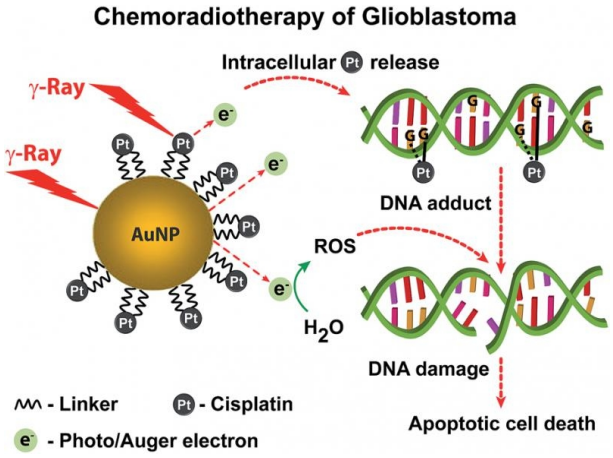
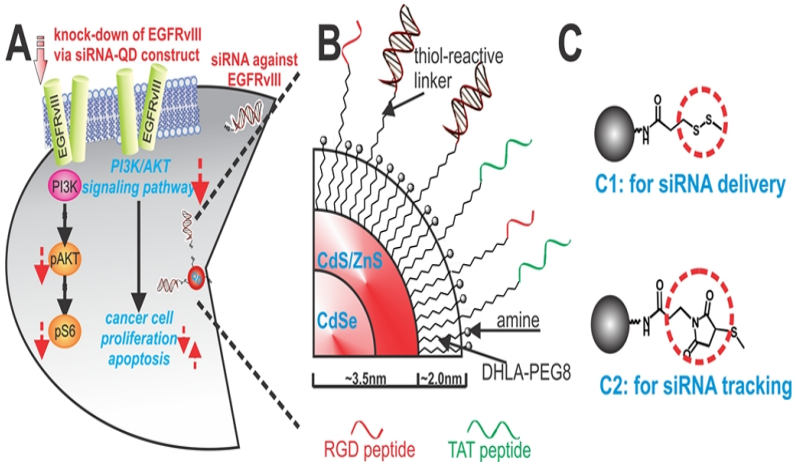


Figure:3 Chemoradiotherapy of Glioblastoma

Source: http://www.cam.ac.uk/sites/www.cam.ac.uk/files/inner-images/diagram.jpg

Nanoparticles Helpful In Gene Delivery

Cationic solid lipid nanoparticles can be conjugated to PEGylate therapeutic agent and reduces GMB tumor growth without significant toxicity[29]. Another RDG nanoparticles coadded with siRNA is a viral target its very helpful to inhibit the growth of tumor and with very less toxicity. This carrier increases the efficacy and survival rate of patient in clinical trials[14].



Source: *http://kblee.rutgers.edu/wp-content/uploads/2012/07/A1.png*

Uses Of Nanoparticles In Brachytherapy-

Nanoparticles are very useful in radiotherapy also brachytherapy is localized radiotherapy which delivered directly to the tumor cells. Fullerene nanoparticle is used in brachytherapy with radio labeled lutetium (Lu-177)[35]. This molecule guided the radiation to the tumor only and safe the adjacent cell from radiation. This kind of targeted radiotherapy is very essential to minimize the side effects of therapy[2].

Conventional Enhanced Delivery By Nanoparticles

In this type, enhanced pressure is used to delivered the drug to brain tumor cells where the BBB is bypassed by using significant measure throughout

the brain by maintain the pressure gradient. This bypass of BBB is allowing targeted delivery infuscate parenchyma in region of interest through a catheter[5]. A pump is used to maintain the gradient pressure positive during the delivery of molecule to the interstitial cells of brain. The size of nanoparticles keeping optimum to ensure the delivery through catheter and penetration of nanoparticles is possible due to large effective pores of ECM-50 micrometer[20]. It ensures the efficacy of drug in targeted tumor cell[6].

CONCLUSION-

Nanotechnology is very helpful and promising tools in ongoing clinical research of neuro-oncology. Nanotechnology gives significant result in treating patient of brain tumors by the enhancement of imaging techniques, targeted drug delivery and minimize the systemic adverse effects. Nanotechnology is very helpful in creating significant differences from past clinical techniques and evolve advance method of treatment and dealing with brain tumors. By the implementation of nanotechnological technique the rate of survival of patient enhances. Its gives new direction of thinking to doctors and researchers team for the better advancement of procedure previously used in treatment. Uses of different metals in MRI imaging is very helpful to locate the exact location, size, texture and mass of tumor cell so that it's very easy to operate without leaving little amount cancerous cells. Nanoparticles are based on advance engineering, chemical, and technological advancement in field if medical science. The size of nanoparticles is varying from 1 to 100 nm. Nanoparticles are very useful in targeted drug delivery and it's also having ability to cross blood brain barrier so by the help of it drug molecule can easily reach to the targeted area by crossing blood brain barrier and it is a very big challenge in past medical treatment of brain tumor. Nanotechnology makes revolution in the treatment of brain tumor and its imaging technique.

KEYPOINTS

- Malignant glioma is still very difficult to treat.
- Nanoparticles is very helpful to recognize the accurate size, shape, mass and location of malignant glioma.
- Uses of magnetic nanoparticles are very helpful in proper imaging of tumors cells.
- Thermosensitive nanoparticles are very relevant for targeted drug delivery.
- Better infusion technique is evolved by nanoparticles.
- Gene delivery through nanoparticles are very safe.

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