Review Article- The Antibody Deliver System To Tumor By Combination of Nanobubbles And Ultrasound

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Abstract- *Cancer immunotherapy is a promising approach to cancer treatment that Harnesses the body's own immune system to fight cancer. Antibody-based therapies are a type of cancer immunotherapy that uses antibodies to target and destroy cancer cells. However, antibodies can have difficulty reaching Tumors, as they are often located in deep tissues and are protected by a barrier of tumor cells and stroma. Nanobubbles are a promising drug delivery system for cancer immunotherapy. nanobubbles are small gas-filled bubbles that can be loaded with drugs and targeted to tumors using ultrasound. Ultrasound is a type of sound wave that can be used to image and treat tumors. When ultrasound is applied to Nanobubbles, it causes them to vibrate and rupture. This releases the drugs that are loaded inside the nanobubbles into the tumor tissue. The combination of nanobubbles and ultrasound is a promising new approach to delivering antibodies to tumors. This approach has the potential to improve the efficacy of antibody-based therapies and to make them more accessible to Patients.*

Keywords- Cancer, Nanobubbles, Ultrasound.

I. INTRODUCTION

More than 100 antibody drugs have been approved worldwide for treating various diseases (e.g., cancer, infectious diseases, and chronic inflammatory diseases), and nearly half of these have been used in cancer therapy [1]. In addition, immune checkpoint-inhibiting antibodies and antibody–drug conjugates have ushered in remarkable progress in cancer treatment recently [2,3]. Thus, antibodies are central therapeutic agents for the treatment of cancer. The most distinctive feature of therapeutic antibodies is their high efficacy and minimal off-target toxicity (4).

Stromal tissues are mainly composed of the extracellular matrix (ECM), such as collagen and hyaluronic acid, and specialized connective tissue cells, including fibroblasts, which promote passive diffusion from tumor tissues. To overcome physiological barriers in TME, antibody therapy in combination with ECM-manipulating agents (e.g., collagenase and hyaluronidase) has been explored in preclinical studies; for chemotherapy, such combination has also been explored in clinical studies [5,6,7,8,9,10].

However, systemic injections of these agents pose the risk of unexpected side effects due to non-specific action this is a major problem to be solved [11,12]. Recently, drug-delivery systems combined with micro/nanobubbles and ultrasound have been used to enhance the localization and accumulation of drugs and gene therapeutics in target tissues without damaging normal tissues [13,14,15,16]. When micro/nanobubbles are exposed to ultrasound, they alternate symmetrically, expanding and compressing with the wave's high- and low-pressure phases. At higher ultrasound intensities, the bubbles expand rapidly and then collapse [17,18].

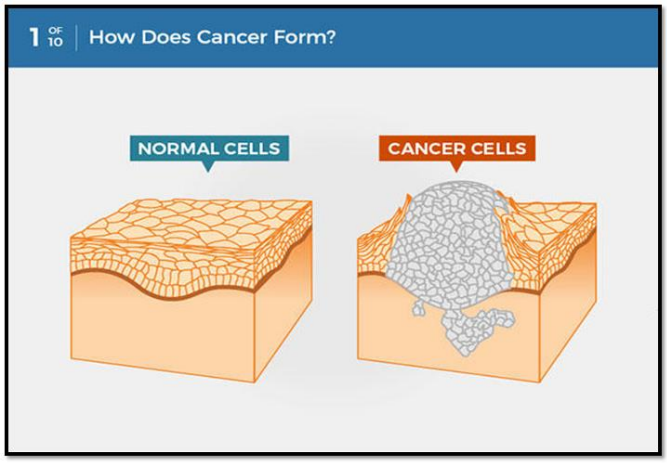
The delivery of drugs through oral and parenteral routes has enjoyed long success, but as disease treatments are refined, it is often apparent that a controlled delivery of drugs, either localized to a specific site or during a specific time, can increase efficacy and bypass problems with systemic toxicity. One approach that has increased delivery efficiency and therapeutic efficacy of drugs ranging from chemotherapeutics to antibiotics involves ultrasound technology improvements. These improvements often focus on increasing tissue sensitivity to the drug or can act as critical components of the drug delivery. In this review, we will focus on methods that allow non-invasive, spatiotemporal-specific drug delivery [19].

The physical impact (e.g, jet formation) generated at that time increases the permeability of tissues and blood vessels via perforations of membranes and vessels [20,21,22,23]. Micro/nanobubble-mediated delivery is expected to offer safe and effective antibody delivery. The size of commercial microbubbles is approximately 1–8 μm, and most of them stay in the intra-tumor vasculature because of their large size. Consequently, it is difficult for microbubble-mediated delivery to deliver drugs directly to cancer cells that are present outside of blood vessels. NBs, on the other hand, can extravasate from tumor blood vessels and penetrate deeply into tumor tissues, implying that nanobubble-mediated delivery facilitates drug

delivery to tumor tissues [24,25]. We have developed a combination system with nanobubbles (NBs) and therapeutic ultrasound (TUS) that can efficiently deliver drugs and genes to target sites [26,27,28,29].

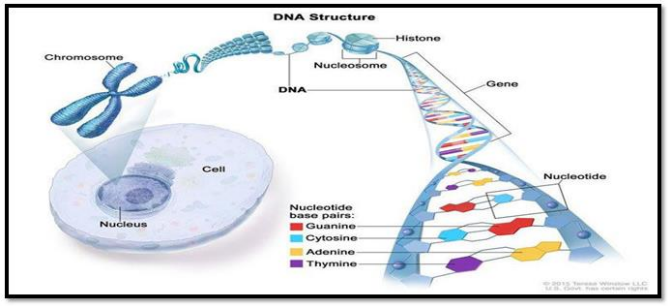
Cancer

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.



Cancer is a disease caused when cells divide uncontrollably and spread into surrounding tissues.(fig1.0)

Sometimes this orderly process breaks down, and abnormal or damaged cells grow and multiply when they shouldn't. These cells may form tumors, which are lumps of tissue. Tumors can be cancerous or not cancerous (benign). Cancerous tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (a process called metastasis). Cancerous tumors may also be called malignant tumors. Many cancers form solid tumors, but cancers of the blood, such as leukemia's, generally do not. Benign tumors do not spread into, or invade, nearby tissues. When removed, benign tumors usually don't grow back, whereas cancerous tumors sometimes do. Benign tumors can sometimes be quite large, however. Some can cause serious symptoms or be life threatening, such as benign tumors in the brain.



Cancer is caused by certain changes to genes, the basic physical units of inheritance. Genes are arranged, In long strands of tightly packed DNA called chromosomes.(fig1.1).

Earliest references to cancer

Some of the earliest evidence of cancer is found among fossilized bone tumors in human mummies in Ancient Egypt, and a reference to the same has been found in ancient manuscripts. Bony skull destruction As seen in cancer of the head and neck has been found, too. Although the word cancer was not used, the oldest description of the disease is from Egypt and dates. Back to about 3000 BC. It is called the Edwin Smith Papyrus and is a copy of part of an ancient Egyptian Textbook on trauma surgery. It describes 8 cases of tumors or ulcers of the breast that were treated by Cauterization with a tool called the fire drill. The description adds that there is not treatment for the Condition.

Between 15th and 18th centuries

During the beginning of the 15th Century scientists developed greater understanding of the workings of Human body and its disease processes.Autopsies, done by Harvey (1628), led to an understanding of the circulation of blood through the heart And body.[30,31,32]

Cancer treatment

In recent years, remarkable progress has been made towards a better understanding of cancer development, which has led to major advances in cancer treatment. However, cancer is an aggressive disease that is difficult to treat due to several reasons. These are including the major inter- and intra-tumor heterogeneity and the mutations in hundreds of different genes contributing to cancer. Further, cancer can affect a wide range of cells (e.g., epithelial, stromal, blood-based) and organs in the body. In addition, cancer is generally not a static disease, but evolves and progresses over time accumulating new mutations.[33,34]

Therefore, with cancer increasing incidence, the related clinical management continues to be a challenge in the

21st century.Traditional cancer treatment modalities as the first considered category in this study comprise of radiation therapy, surgery, chemotherapy and proton therapy. Radiation therapy despite the caused side effects remains an important component of cancer treatment for at least 50% of all cancer patients [35,36]. Chemotherapy (utilizing cytotoxic drugs) likewise inevitably damages normal tissue surrounding the tumor. Chemotherapeutic agents target cells with the high basal level of proliferation and regeneration, including tumor cells and non-tumor rapidly proliferating cells (in the skin, hair, bone marrow and epithelium of the gastrointestinal tract). This causes the high level of toxicity associated with such treatments [37,38]. Furthermore, a variety of long term complications often follow conventional cancer therapies, such as cardio toxicity, neurotoxicity, infertility, nephropathy, and chronic liver damage.[39,40,41]

On the other hand, several novel strategies have emerged showing great potential in cancer therapy, reducing suffering and cancer related death. These include photodynamic therapy (destroying tumor cells using a photosensitizing drug activated by specific wavelengths of light), Photo thermal therapy (using a photo thermal agent activated by light producing heat to damage tumor cells), Gene therapy (treating/modify tumor cells using gene materials or stimulating immune cells),and nanoparticle-drug therapy (tumor–directed drug delivery). Illumination by producing a long-lived triplet (excited states) compound Deep penetration of light into the biological tissues, low skin photo toxicity, rapid bio distribution and easy administration/ monitoring could make cyanine dyes as powerful compounds in PDT.These photosensitizers however, exhibit high plasma protein binding and rapid elimination from blood circulation [42,43,44,45,46].

Basics of Ultrasound Physics

UltrasoundImaging is characterized by the transmission of a short cyclic pressure wave (sound) (420 kHz) from a transducer through the body. When transmitted waves passing through the tissues reach a boundary with an impedance mismatch, some of the energy (typically o1%) is reflected back to the transducer, while the remaining energy continues to pass through the tissue until it encounters another boundary or is absorbed by the body. Reflected waves are used to generate images. Some characteristics used to describe an acoustic signal/sound wave include its center frequency in MHz, acoustic pressure amplitude or peak negative (rare factional) pressure in Pascal's (Pa), pulse length in seconds, pulse repetition frequency in Hz, duty cycle, (percentage of time acoustic energy is actually being transmitted), and intensity in W cm-2clinical ultrasound, administered to patients, is also described by the mechanical index (MI), a safety index which relates to the risk of non-thermal damage to the tissue.[47,48]

The physiological effects induced by ultrasound insonation have been used in a variety of ways for targeted drug delivery. Studies of mechanical means for improving drug delivery (i.e.,Ultrasound pressure waves) have demonstrated increased cyto-toxicity and drug retention at the tumor site when exposed to therapeutic ultrasound in vitro (up to a 3-fold increase for Doxorubicin (DOX)) compared to cells that were not insonated.[49,50]

Drug Delivery

Nanobubbles drug delivery is potentially being exploited in the delivery of anticancer drugs like doxorubicin in both in vitro and in vivo. These NBs reach and get assembled at the site of a tumor followed by their amalgamation to form microbubbles. Further, these microbubbles undergo distortion at the target site with intense ultrasound and hence release of the drug is achieved which results in accumulating the higher proportion of drug within the targeted cells with increased efficacy and reduced toxicity. Further exploration is necessary for these method's utility while treating various malignancies.

A polymeric nanobubble system to increase the doxorubicin sensitivity of cancer cells associated with US. The systems developed include perfluorocarbon nanodroplets stabilized by a biodegradable block copolymer wall (PEG-PLLA or PEG-PCL). With increase in temperature at about to physiological temperatures, The nanodroplets get converted into nano/microbubbles. As per the received sonic wave signals by tumor-directed ultrasound, cavitations occurs in doxorubicin-loaded nanobubbles and finally get collapse, to release the encapsulated drug and increasing the effectiveness in tumor chemotherapy in vivo [51].

Nanobubbles have also been used for treatment of Parkinson's disease. The authors demonstrated that nanobubbles can be used to delivery apomorphine, a particularly beneficial but unstable drug for treating Parkinson's disease, through the blood barrier [52].

The approach like 'Photoablation technique' can be used to promote the influx of various macromolecules that are too large to migrate passively through the NE. Thus, by providing unprecedented control over nuclear compartmentalization, nuclear photoporation offers a powerful tool over nanobubble based drug delivery applications [53].

Another approach viz. Sonoporation technology is having an application in the transfer of drug or gene into the cell or tissue in the targeted region [54]. Presently, they are also under investigations in relation with gene and gas along with drug delivery reported on the use of nanobubbles combined with US to permeabilise four types cancer cells and potentiate the cytotoxic effect of anticancer drugs (cisplatin and 5-FU). Cell sensitivity to cisplatin and 5-FU was effectively increased with Nanobubbles and ultrasound. [55,56,57]

Advantages of Nanobubbles

Till the date, chemotherapy is routinely being used as the prime modality in treatment of malignant neoplasms and substantial therapy in improving the rate of survival in case of cancer patients. In spite of that, further assessment is absolutely required to determine the efficacy of chemotherapeutic drugs to maximize drug toxicity in treating the cancer cells. The frequently found the associated adverse effect in such case is systemic toxicity. Moreover, the local delivery of chemotherapeutic drugs may minimise toxicity with increasing therapeutic dose at targeted sites and by lowering the plasma levels of circulating drugs. Ultrasound-targeted nano/microbubble destruction (UTN/MD) therapy has been widely used due to its Non-invasiveness and targetability, as an effective drug Delivery system [58].

The ultrasound (US)-targeted nanobubble destruction (UTND) method has become a new trend as targeted drug delivery system to solid tumors which imminently lowers systemic drug exposure and enhances therapeutic efficacy. Thus, UTND has multiple significant advantages when compared with other drug delivery systems, Nanobubbles can be formulated easily by modified emulsification processes and employed as US contrast agents in visualising tumors [59].

Nanobubbles being the contrast agents may disrupt blood vessels and thus enhances the site-specific delivery of drugs. This could be the most effective approach employing the EPR effect in passive targeting of tumors.

Moreover, NBs in combination with US could promote acoustic cavitation, improving cell membrane stimulation and ultimately permeabilization in drug uptake by tumor cells. The extensive use of the retention (EPR) effect with enhanced permeability in delivering drug at target tumor site is the motto that drug delivery by theranostics therapy involves. The EPR effect reasonably makes accumulate various types of nanomedicines in solid tumors, demonstrated by different studies. However, EPR is blamed as phenomenon with high variation due to tumor heterogeneity that ultimately results in delivering low drugs in clinical trials [60].

The earlier studies have thrown light on nontargeted NBs that are easily accumulated in the reticulo-endothelial system, causing lower drug concentration at the tumor site. To reduce systemic toxicity and increase therapeutic efficacy, it is crucial to construct drug-loaded and targeted NBs, carrying antibodies and peptides as tumor-specific ligands [59].

The formulations with echogenic bubble have wide applications in diagnosis of disease and as therapeutics. Therefore, nanobubbles were formulated and the evaluation of contrast agent was performed in determining property of nanosized bubble in ultrasonic imaging. Drug loaded NBs exhibit excellent ability to achieve ultrasound enhancement and effective drug loading/targeting. The release of drug from drug loaded-NBs at targeted site assure better efficacy with promotion of Ultrasound irradiation. The drug-loaded NBs could promote drug delivery to cells significantly and the process be analyzed with sigmoidal type pharmacokinetic curve. It further can be concluded that the formulation of nanobubble is most promising approach for both drug delivery enhancing. As well as ultrasound imaging [61].

Disadvantages of Nanobubbles

The major drawback of the lipid-encapsulated NBs is a drug delivery vehicle is its low payload efficacy. To combat this, an oil shell can be incorporated to the interior of the lipid monolayer to enhance payload efficacy. The shell ingredients of NBs such as polydimethylsiloxane, Tween 80, polyethylene glycol stearate or polyvinyl pyrrolidone that were commonly added, reinforce the shell avoiding any gas escape and thus prolonging the liposome gas bubbles lifetime in the bloodstream. The avidin–biotin interaction method is frequently used to tether antibodies to micro/ nanobubbles, leading to the development of a molecular targeting US imaging agent. However, avidin still has limitations due to its strong immunogenic character [62].

Biological effects and interactions on combining NBs with ultrasound

With the development of ultrasonic medicine, biotechnology, And nanobubble contrast agents, ultrasound irradiation Combined with NBs has attracted wide interest in clinical cancer Treatment, where the biological effects and interactions on Combining NBs with ultrasound in tumors have become problems to be investigated.

Biological alterations in tumor tissue play a vital role in The efficiency of NBs

The microvascular endothelial gap is dense and the structure of endothelial cells is complete in normal tissue, whereas in solid Tumor tissues, the endovascular endothelial pores are between 380 nm and 780 nm, and the structural integrity of endothelial Cells is poor. Therefore molecules or particles of certain sizesTend to gather in tumor tissues more than in normal tissue. This phenomenon is called the enhanced Permeability and retention (EPR) effect, which is considered to Be the mechanism of completing passive targeted therapy of Tumor tissues. In preclinical trials, drugs or gene delivery-targeted Systems based on EPR have shown significant progress in anticancer Efficacy compared with traditional chemotherapy. A variety of Nanomaterials based on the EPR effect have been applied in the past Few years, where the sizes of the nanobubbles at the nanoscale can Be transformed on account of the sizes of the pores in tumor vessels.Given that different gap sizes exist in endothelial cells for differentCategories of tumors, a suitable size nanomaterial must be estab-Lished based on the category of the tumor. Also, the obstruction Generated by biological barriers when nanoparticles reach the blood Circulation system requires high attention.Thus, considering these Challenges, to better take advantage of the EPR effect in nano-Material delivery, various means of treatment have been designed.EPR-based nanoparticle-targeting strategies are primarily Committed to adjusting the size of drugs or vectors and/or utilizing Ligands that link molecules involving the EPR effect[63,64,65,66,67].

Biological effects by ultrasonic exposure combined withNBs

Ultrasonic delivery technology is based on the biophysical process of cell poration by ultrasound combined with NBs and this process is known as sonoporation. Compared with other nanoparticles, NBs have the special property of “collapsing” under insonation by ultrasound energy, resulting in the implosion of NBs and changes in the permeability of the cell membrane.[68]

When the ultrasonic energy is sufficiently increased, the effect of “ultrasonic cavitation” occurs, that is the bubbles (cavitation nuclei) in the liquid vibrate and grow. Constantly accumulating energy from the acoustic field and collapsing until the energy reaches a certain threshold. Ultra-sonic irradiation causes ultrasonic cavitation, leading to gaps in the cell membrane with a diameter of about 300 nm, and stable cavitation is characterized by repetitive, non-collapsing oscillations of nanobubbles, resulting in local Fow and shear stress on nearby cells, thus increasing the permeability of blood vessels.[69]

Furthermore, ultrasonic irradiation is capable of producing thermal and mechanical therapeutic effects. Heating is generated by the mechanical friction of the tissues moving with the passing of the ultrasonic wave. As early as 1987, Dyson noted that tissue must reach a certain temperature from 40 C to 45 C for more than 5 min to have a therapeutic effect in nature. The study conducted with nonperfused tissues illustrated that ultrasound irradiation increased the tissue temperature at a rate of 0.86 C min^{-1} (1MHz,1 W cm^{-2}).[70]

Nevertheless, numerous questions remain unanswered about the thermal effects of ultra-sound and its role in drug delivery. The biological effect of ultra- sound irradiation can increase the permeability of the cell membrane, induce gene transfer, improve the intracellular drug concentration, embolize tumors, nourish vessels, and overcome tissue barriers, developing a crucial targeting role. Moreover, there are numerous other biological interactions that need to be considered for modulating NBs and US for therapeutic delivery to tumors.[71]

Formulation of targeted ultrasound Combined NBs for targeted cancer therapy

Recently, specific nanocarriers have gained enormous popularity as an important means of drug and gene distribution owing to their properties. Further, they are capable of attaining the maximum concentration of cytotoxic agents in a site-specific manner. Improving the biodistribution and pharma-Cokinetics of pharmaceutical drugs through targeted delivery via nanocarriers has resulted in improved therapeutic efficacy and less adverse effects on other healthy and non-targeted tissues.[72,73]Currently, various targeting strategies are being exploited for the targeted delivery of antitumor medication through nanocarriers. For example, the use of different antibody-conjugated NBs that bind ligands in cancer cells and tissues has been a highly effective anticancer drug-targeted delivery approach. NBs may be combined with Affibody® as a directed probe in the manufacture of nano-sized ultrasonic contrast agents. In another case, a method of thin-film Hydration used to control the thickness of phospholipid □lms was employed to prepare normal phospholipid-shelled and gas-coded NBs on the nanoscale. Subsequently, the NBs were combined with biotinylated anti-ErbB2 molecules, a developed strong affinity shape, ultra-small protein, and exhibiting tumor sensitivity for over-expressed human epidermal growth factor receptor type 2 (HER2) cells. In both the in vivo and in vitro tests,The strong speci□city of the NB Affibody ligands for HER2-Overexpressing cells was observed, and the successful US improvement in HER2-positive cancer imaging was achieved.Ultrasonic NBs equipped with unique anti-PSMA

(prostate Antigen) nanobodies were fabricated to promote the imaging of prostate cancer through a biotin–streptavidin system.[74,75,76]

Challenges and future directions

One of the challenges of using nanobubbles and ultrasound to deliver Antibodies to tumors is that the nanobubbles can be destroyed by the Ultrasound waves before they reach the tumor. Researchers are working on developing nanobubbles that are more resistant to ultrasound waves.

Another challenge is that ultrasound can damage healthy tissues. Researchers Are working on developing ultrasound techniques that are more targeted and Less damaging to healthy tissues.

Despite these challenges, the combination of nanobubbles and ultrasound has The potential to revolutionize cancer immunotherapy. Researchers are conducting clinical trials to test the safety and efficacy of this approach in Patients with cancer.

II. CONCLUSION

The combination of nanobubbles and ultrasound is a promising new approach To delivering antibodies to tumors. This approach has the potential to improve the efficacy of antibody-based therapies and to make them more accessible to Patients. Researchers are working on overcoming the challenges of this Approach, and clinical trials are underway to test the safety and efficacy of this Approach in patients with cancer.

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