Nanobubbles for tumors: imaging and drug carriers

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Abstract: The development of nanobubble technology provides a good means diagnosis and treatment. In this review, the research and development progress of nanobubbles is discussed. On the one hand, they can be used as a good contrast agent for tumors and effectively visualize the shape of tumors. On the other hand, due to its good water solubility, high drug loading rate and stability, it is used for the delivery of anti-tumor drugs, m nanobubbles, which can significantly improve the efficacy of chemotherapeutic precise administration and targeted reoxygenation in the hypoxic area of the tumor; there are also vapor nanobubbles, which are formed by external forces (such as heat instantaneous stimulation of nanoparticles, destroy the structure and rele therapeutic effects. Nanobubbles can also be used in combination therapy with other drugs. It expected that this review will provide new ideas for tumor applications based technology and promote the process of tumor treatment.

Keywords: tumor, nanobubbles, ultrasound contras nanobubbles, vapor nanobubbles

1. Introduction

Cancer is one of the most important causes of human death, and its diagnosis and treatment have always been the focus of research. Contrast-enhanced ultrasound is of great significance i tumor detection and qualitative diagnosis. Compared with computed tomography and resonance imaging, ultrasound contrast agent (UCA) has more advantages, such as no radiation, no nephrotoxicity and liver toxicity [1]. The most concerned is the microbubble contrast agent used to observe the tissue perfusion state. MBs have three important characteristics such as have been well scattering properties, can produce rich harmonics, and a rupture effect under t action of sound pressure. In addition to the use of microbubble contrast agents for tissue imaging [2-4], the development of drug-carrying delivery systems has also been rapid [5-6], and targete UCA with dual roles of diagnosis and treatment is also under st (NBs) are bubbles with a smaller diameter than microbubbles, with the development of nanobubble (NB) technology, its role in the diagnosis and treatment of diseases [11-15], such as tumors (Figure 1) has become more prominent.

NBs contain a gaseous core encased in a shell of biocompatible materials such as lipids

proteins. When exposed to ultrasound, NB shrinks and expands, which may cause the ultrasound to scatter backwards, cavitation and even the shell breaks. Because of these acoustic behaviors, NBs are widely used as UCA and show increasing potential for drug delivery. Under l ultrasound irradiation, NBs can be used as contrast agents in ultrasound imaging for permeability and retention (EPR) evaluation. Throu cavitation, EPR-mediated treatment can be improved by increasing drug delivery [16-18].

With the development, the application of NBs in pharmacy has also increased. Compared with MBs, NBs exhibit unique perfusion dynamics, with higher peak intensity and slower elution rate, showing enhanced exudation and retention in tumor tissues, ultrasound molecular imaging and drug delivery beyond tumor l example, NBs can be used to enhance imaging capabilities [21-23]. Due to their good stability and high solubility, NBs also have many applications in drug delivery [24-27]. And ultras enhance drug delivery [28]. Oxygen nanobubbles (ONBs) significantly improve the eff chemotherapy drugs by improving the hypoxic area of the tumor [29-30]. When the nanoparticle is kept at a temperature higher than the critical temperature of the s nanobubbles (VNBs) will be formed. Because the bubble formation is a very short breaks in nanoseconds while mechanically destroying the cell membrane tumor cells [31]. The combined application with other drugs is also a development direct NBs. There are reports in the literature that ultrasound molecular imaging combines the advantages of ultrasound contrast and the photothermal effect of graphene oxide (RGO), and can be used as an ultrasound photothermal agent for in vitro visual photothermal therapy [32].

Here, the application progress of NBs in tumors is intr technologies optimize the methods of diagnosis and treatment. In the following descripti will describe these applications in detail, hoping to provide new ideas for later researchers, make joint efforts for the treatment of cancer.

2. The application of NBs as UCA in tumor diagnosis

2.1 Nanobubble ultrasound contrast agent

Photoacoustic imaging combines the molecular sensitivity of optical imaging and the spatial resolution of ultrasound imaging. As a portable, non- characteristics of high molecular sensitivity, good spatial resolution, and large measurement depth. Since photoacoustic imaging is highly sensitive to light absorption, first of all, high-a

optical contrast agents can be loaded in NBs, which have strong photoacoustic contrast, non-specific molecular interactions, improve stability, and extend cycle life. Secondly, N encapsulate a variety of imaging agents for multimodal imaging of abnormal tissue structure and function. Thirdly, the surface of NBs can be PEGylated and conjugate photoacoustic imaging. Finally, a variety of imaging agents and c embedded in NBs to achieve image-guided collaborative treatment [33].

Nano-scale UCA has been proven to be a potentially accurate and visual cancer tre method [34]. Some literatures reported that the stability and nanobubble contrast agent they prepared are better than the definity microbubble used in clinical practice [35-36]. Moreover, coupling NBs with targeting ligands (such as a achieve sensitive and selective targeted ultrasound imaging (Figure 2) [37-38]. Because nano-scale UCA not only remains in the vascular system, but also exudes in tissues (for exa tissues), so when these UCAs target cancer cells, passive and active targeting strategie combined [39-41].

2.2 Tumor imaging

Based on the above, the application of NBs in anti-tumor drugs has become more and more mature. And based on simple imaging [41-45], targeted imaging strategy has been developed..

One strategy to achieve tumor selectivity is to use specific ligand- document, a biocompatible chitosan-vitamin C lipid system anthocyanin 5.5 conjugated NBs was reported as a dual ultrasound fluorescence contrast agent to achieve selective tumor imaging in a mouse tumor model. [46] discovery of nanobodies provides a promising strateg development of new ultrasound-targeted NBs because of the small size [47]. Hengli Yang et al. not only prepared uniform nanolipid NBs by controlling the thickness of the phospholipid membrane, but also successfully combined the NBs with biotinylated anti-ErbB2 Affibody® molecules. These NBs had a small, precise and robust Structure, and had high affinity and specificity for human epidermal growth factor r overexpressed in some breast cancer tumors, and was a good UCA in HER imaging [48]. Hengli Yang et al. prepared uniform nano-scale lipid IR-780-NBs (IR-780 is a near-infrared fluorescence dye). These NBs have been confirmed to have near-infrared flu imaging and ultrasound contrast imaging capabilities in vivo and in vitro, with good stability and no cytotoxicity. At the same time, it was found that IR-780-NBs can spontaneously accumulate on

female tumor cells, but cannot accumulate on normal cells [49]. There wa
reported demonstrating the application of echo lipids targeting cancer antigen 125 (CA-125) and
surfactant-stabilized NBs in standard clinical contrast harmonic ultrasound imaging for CA-125
positive OVCAR-3 rat tumors of imaging. This technique may help improve the
epithelial ovarian cancer [50].

Some of the above applications use NBs coupled with antibodies to achieve tumor selective enhancement of imaging capabilities. In addition, it can also be achieved by preparation methods. Jiaqi Zhan et al. prepared NBs under optimized centrifu characteristics of uniform bubble size, good stability, and low toxicity. Ultrasound imaging in vitro showed that NBs have the same enhancement ability as MBs [51]. Selectivity can also be achieved by modifying NBs. Sujuan Duan et al. prepared a new type of folate (FOL) targeting ultrasound NBs by connecting two FOL molecules per DSPE-PEG2000 chain, which has better tumor targeting. It not only has the function of UCA, but also has selective anti-tumor effe positive tumors (Figure 3) [52].

The targeted imaging strategy of NBs is shown in Table 1.

3. Application of NBs as drug carriers in tumor treatment

3.1 Nanobubble carrier

The phenomenon that NBs penetrate into the vascular system after intravenous injection (the pore size cuts off between 380 and 780 nm) and remains in the tumor tissue is called passive tumor targeting. Passive tumor targeting of NBs results in a higher local bubble concentration tumor cells, which may increase cell permeability under ultrasound irradiation. Just like MBs, NBs can also detect cavitation and sound waves under the irradiation of low-frequenc Subsequently, the therapeutic compound may enter the tumor cells near the NBs. On the contrary, the damage to normal tissue cells without passive NBs accumulation is much lower. The passive targeting and cavitation inducing ability of NBs make it an ideal non-viral vector [53].

Ultrasound stimulation may trigger the release of drugs from NBs, so the drugs promote the antiproliferative activity of NBs in tumor cells [54-55]. In the gene therapy of ultrasound-mediated nanobubble destruction (UMND) combined with NBs, the use of NBs can not only be used as a carrier to improve potential genes, but also protect genes from the degradation of DNase in serum [15, 56].

Ultrasound (US) irradiation on NBs will produce a cavitation effect similar to MBs, thereby

promoting the permeability of tumor cells, which helps drugs or genes to produce killing effects in specific areas of US irradiation [57]. Ultrasound-targeted nanobubble destructio produce cavitation, thereby promoting the release of drugs and inhibiting tumor growth [58]. In a document, a GPC3 (liver cancer homing peptide) -targeted and drug-loaded NB was develop which successfully achieved selective growth inhibition and apoptosis of liver cancer HepG2 cells in vitro, proving that UTND technology is a kind of control drug delivery and tre approa[c5h9]. Zhiping Yu et al. designed G250 antigen-targeting tems (G250-TNBs) based on the targeted drug delivery system and combined G250-TNBs with UTND, which can deliver anti-tumor drugs to local RCC cells and i concentrations in tumors, thus enhancing anti-tumor efficacy and reducing side effects o [60].

Gene therapy technology has the potential to provide novel treatments for cancer and oth diseases caused by genetic abnormalities. A safe, non-toxic and effective nano-delivery system can enhance gene transfection ability. NBs can load DNA onto their shells and have the potential maintain circulation time, accumulate in tumor tissues (through the EPR effect) and cell transport. The combination of ultrasound and DNA-bound bubbles can improve DNA transfection [61]. The androgen receptor small interfering RNA (AR siRNA) -coupled NBs prepared by Luofu Wang et al. had ideal in vivo and in vitro properties, including nanometer size, good stability, and stro ability to penetrate transplanted tumors in vivo. In vivo and in vitro studies have confirmed that it can significantly inhibit the growth of prostate cancer cells under ultrasound irradiation, confirming that NB was an effective gene carrier [62]. Bo Zhang et al. established an ultrasonic nanobubble-mediated purine nucleoside phosphorylase (PNP)/fludara treatment of human hepatocellular carcinoma (HCC), in which NBs constitute a non-toxic, stable and effective gene delivery platform [63]. Intracerebroventricular (ICV) injection has been clinically to inject anticancer drugs, Koki Ogawa et al. successfully develo response to nanobubble-mediated method, which could transfect genes into the cerebral ventricle area by ICV injection in rats. Therefore, it may be a good idea to use this method to treat tumors caused by genetic abnormalities [64]. For spinal cord injury (SCI), ultrasound-mediated destruction of NBs could also significantly improve the transfection efficiency of neurotrophic factor gene and had obvious neuroprotective effects on injured spinal cord [65-66].

NBs were stable and could be detected by magnetic resonance (MR) imaging. The

potential drug carrier for MR-guided high-intensity focused ultrasound (HIFU) ablation of tumors [67]. Not only that, NBs could enhance the effect of thermal sensitizers on radiofrequency ablation of tumors. The experimental results of Reshani H. Perera et al. proved that lipid and shelled, echogenic NBs combined with ultrasound modulation can serve as an effective theranostic method for sensitization of tumors to RF ablation [68].

The applications of NBs as anti-tumor drug carriers is shown in Table 2.

Based on the natural affinity between source cells and tumor cells, nanocarriers that mim cells tend to actively recognize and adhere to tumor cells in a ligand-receptor mann addition to passive targeting, most of the NBs prepared in the above experiments were co with antigens/antibodies or aptamers. In this way, dual targeting effects be selectivity. Therefore, NBs as an anti-tumor drug carrier is a good strategy.

3.2 Oxygen nanobubbles

3.2.1 The impact of hypoxic environment on tumors

Oxygen is a key element of cell metabolism, and its concentration important role in the efficiency of many biochemical reactions. As we all know, aerobic metabolism is the main mechanism for providing energy to cells. The decrease in oxygen supply from arterial blood to biological tissue cells substantially reduces the effectiveness of drug treatment, increases the risk of infection and scar formation, and ultimately leads to tissue necrosis [70].

Hypoxia is a low level of oxygen, which is a common feature of most cancers. In tumors, the uncontrolled proliferation of cell clusters without a sustainable rate of angiogenesis leads development of hypoxic conditions within the tumor (Figure 4) [71]. The pathogenesis of tumor hypoxia is one of the molecular bases of carcinogenesis [72]. Many litera hypoxia contributes to poor prognosis, chemotherapy resistance, radiation r changes, blood flow disorder and genome instability. Therefore, ONBs play an important role in preventing tumor progression and changing the cell dynamics of tumor cells and the proce hypoxia adaptation. They are an important means of anti-cancer treatment.

3.2.2 The application of ONBs in the delivery of anti-tumor drugs

The non-uniformity of the refractive index caused by the core-shell structure of the NB will force the light to deviate from its linear trajectory to produce light scattering, which supports the recognition and tracking capabilities of the optical scattering method. Single NB tracking in field of nanoparticle positioning and targeting in single cells was demonstrated, which cou

used for clinical diagnosis and targeted therapy [73]. Because of these properties, ONBs are mainly used in medicines by improving the hypoxic environment in tumor tissues, and can be diagnose and treat tumors.

One possible way to deliver oxygen to the ischemic area is to use chemical oxygen carriers such as perfluorocarbons (PFC) [74]. PFC are highly inert compounds. Studies have shown th PFC have good oxygen-carrying capacity, which helps to maintain a high pa oxygen for a long time and relieve hypoxia [75-79]. PFC have the potential to d amounts of oxygen due to van der Waals forces. The high temperature-indu conversion of PFC can quickly release and distribute a large amount of oxygen through tumor, which is of great help in saving the tumor from hypoxia [80]. ONBs with PFC as the core were easily internalized by tumor cells, thereby releasing oxygen with continuous kinetics Bisazza et al. prepared dextran NBs that could be used for oxygen transport. The C prepared using a dextran shell and a core of perfluoropentane in which oxygen was stored. The NB preparation showed a size of about 500 nm, negative surface charge and good oxygen-ca capacity, and had no hemolytic activity or toxic effect on the cell line. The effect of NB waves under 2.5 MHz ultrasound could enhance the oxygen release kinetics. Targeted delivery of oxygen could be carried out by ultrasound, which could be used to deliver oxygen inside cells to achieve reoxygenation or to deliver cancer drugs carried by NBs to treat tumors [82].

The hypoxic tumor microenvironment has a wide range of effects in cancer epigenetics and therapeutics. In order to alleviate the hypoxic area of the tumor, weaken the path of hypoxia and inhibit the growth of the tumor, Pushpak N. Bhandari et al. developed an oxygen-coated carboxymethyl cellulose NB as an ultrasound contrast agent for methylation to reverse hypoxia. It was expected to have a significant impact in epigenetic programming and as an adjuvant to cancer treatment [71].

The cellular response induced by hypoxia increases blood vessel formation, i metastasis and resistance to treatment. Azita Mahjour et al. believed that the inhibitory effec ONB water on tumor growth might be to provide effective oxygen and reduce hypoxia to regulate the expression of HIF, VEGF and p53 genes in cancer cells, thereby inhibiting angiogenesis and inducing cell apoptosis, leading to carrying tumor growth in mice with 4T reduced [83]. Tumor hypoxia can lead to resistance to radiotherapy in cancer patients. Therefore, reversing hypoxia before radiotherapy has become a strategy to overcome the resistance of cancer

cells to radiation. Takehiko Yokobori et al. also verified that ONB wat
resistance of cancer cells to radiation by inhibiting hypoxia-inducible factor 1-α (HIF-1α) subunits [84].

Since dark-field imaging technology could be used to visualize and quantify ONBs cultured in vitro, and Pushpak Bhandari et al. have developed an oxygen-encapsulated cellulose NB used to enhance the treatment of bladder cancer, which could be propelled by ultrasound beams (up to 40 mm/s) and be accurately guided to the tumor in the body, so it could be used as a new imaging and ultrasound-guided drug delivery strategy to improve the microenvironmen regions(Figure5) [29]. Ultrasound treatment could also further enhance oxygen transmission by promoting cavitation and ultrasound, and improve the hypoxia in the tumor area [30].

In summary, ONB therapy is a safe and inexpensive method that can be used to hypoxia in the tumor area. The methods include: 1) The core of the NBs was perfluoropentane that stored oxygen; 2) The oxygen-encapsulated NBs restored hypoxia through methylation procedures to regulate epigenetic programming; 3) It might be by regulating the expression of certain growth factors in cancer cells to inhibit angiogenesis and induce cell apoptosis or as a radiosensitizer t inhibit tumor growth; 4) Precise ultrasound-guided oxygen-encapsulated NBs could enhance efficacy of chemical drugs, and significantly reduced the tumor progression rate while reducing the concentration of chemical drugs.

3.3 Vapor nanobubbles

3.3.1 The role of VNBs in drug delivery

The accurate delivery of diagnostic and therapeutic drugs is one of the biggest ch faced by chemotherapy and general drugs. Generally, the drug concentration r target cells is toxic to normal tissues because the selectivity and effectiveness of delivery are very low. Many release technologies (thermal, chemical, and biological) can also be harmful to healthy cells because they cannot provide reliable protection against accidental triggering of release. This presents the challenges of improving the control of the release process. These challenges have been solved by developing release methods that do not rely on biochemical and physiological processes, but instead use remote thermal or acoustic release activation [85]. VNB induced by Laser is also a good method.

VNBs are also called plasma nanobubbles (PNBs) [31]. When the laser pov reached the flux threshold, bubbles were formed [86-87]. After the laser pulse is absorbed, the gold

nanoparticles (AuNPs) (presumably trapped in liposomes) quickly evaporate the surrounding liquid medium. The evaporated medium forms a vapor nanobubble. The VNBs expand to their maximum diameter, then collapse and disappear. The rapidly expanding bubbles mechanically des liposomes, pushing out the molecular load. The plasma nanobubble release method has unique features: 1) The release mechanism is mechanical, non-thermal, rapid (millisecond range), local (can be activated in individual liposomes) and adjustable (to control the an released); 2) The release agent is not a particle, but a transient on-demand event, which combines mechanical and optical properties in a relatively safe gold nanoparticle-related reag release mechanism does not depend on biochemical and physiological factors that r accidental release. In addition, this mechanism is not limited to liposomes or any specific capsules. Drugs (or other molecular loads) can be delivered to specific target cel nanobubble methods [85].

In addition to mechanically destroying the drug-encapsulating carrier and the membrane layer in the cell to deliver the drug, the VNB also had high selectivity, only destroying environment around the gold nanoparticle, and would not cause damage to cells without diseas characteristics. It had low toxicity, could provide minimal biological damage, and was sa reliable [88]. Therefore, it can serve as a very good drug delivery mechanism.

Plasma nanoparticles can be used as intracellular nanomechanical transducers to enhance the permeability of the nuclear membrane, and can promote the general absorption of macromolecules into the nucleus, including those big molecules that larger than the nuclear pore complex and will not enter the interior of the nucleus. This novel nanomechanical transduction has increased the size range and is widely applicable to the transport of macromolecules to the nucleus. Moreover, this nanomechanical transduction technology is highly localized, does not rely on specific function ligands, and is expected to be used nuclear transmission of many biomolecules, especially DN and anticancer drugs [89-90].

3.3.2 Application of VNBs in the delivery of anti-tumor drugs

When the VNBs rapidly expand and collapse, the mechanical shock wave formed will destroy nearby biological structures, causing instantaneous permeability and can control the entry and exit of substances. Therefore, some macromolecules such as proteins can be delivered to the dise site for treatment. Gaëlle Houthaeve et al. developed a method based on photoperforation mediated by VNBs to deliberately induce nuclear envelope (NE) rupture in a controlled time and space. This

method relied on the laser irradiation of AuNPs around the core, which led to the format short-lived VNBs, causing minor mechanical damage to NE, thereby forming small holes technology not only promoted nuclear transport, but also retained its proliferatio nuclear photoperforation, providing a powerful tool for basic cell biolog delivery applications [91]. Lien Van Hoecke et al. also used this technology to deli lineage kinase domain-like proteins to induce cell death in rat B16 tumor cells, thus proving that tumor cell death type can be controlled by directly transducing effector proteins involved in execution stage of apoptosis or necrosis (Figure 6) [92].

Since endosomal escape is still the most prominent bottleneck at the intracellul controlled delivery strategy for therapeutic drugs into living cells is highly needed. From chemical-based methods with low endosomal escape efficiency to physical metho concentrations (usually in the micromolar range) of cargo molecules to deliver therapeutic drug directly to the cytoplasm. Now as a trade-off, drug delivery systems (DDS) has been considered to be still taken up by endocytosis, but can induce endosomal escape based on physical triggers. This method combines the advantages of these two fields, that is, due to the efficient DDS endocytosis in the cell, the required amount of cargo is low (nanomol range), a controllability of physical stimulation, it can effectively in photothermal properties of AuNP can overcome the membrane barrier unde through two mechanisms: the inner membrane is ruptured by the mechanical energy of VNBs, or the inner membrane is permeated by thermal diffusion. Juan C. Fraire et al. evaluated these tw mechanisms, and the results showed that the VNB-mediated endosomal escape strategy was a more reproducible method for endosomal escape and gene silencing without compromising cell viability or long-term cell homeostasis [93]. A few years earlier, Ekaterina Y. Lukianova-Hleb et al reported a novel PNB-enhanced endosomal escape encapsulated technology. This technology combined acoustic diagnosis and guided intracellular delivery of anti-tumor drugs. This was a rapid process, namely plasma nanobubbles activated by pulsed lasers. The therapeutic mechanism of PNBs was based on active intracellular drug delivery th mechanical, non-thermal, drug carrier and endosome destruction and local injection of drugs to the cytoplasm (Figure 7) [94].

Because of the instantaneous mechanical destruction of PNBs, it can play a greater ro combination with other drugs and methods. Ekaterina Y Lukianova-Hleb et al. developed a ne

therapy using four clinically proven ingredients that worked together in cells: encapsulated drugs, colloidal gold nanoparticles (GNP), near-infrared short l fundamentally accelerate the effect of chemoradiation and increase it by 17 times. In this method, PNBs produced the lowest threshold flux, thus producing the largest PNB, which led to the largest therapeutic expansion. Cancer diagnosis and treatment were integrated into a s method. Its speed, sensitivity, specificity and efficacy enabled real-time intraoperative d and treatment of microscopic residual disease (MRD) in head and neck can effective dose of encapsulated drugs and X-rays, Simplifing treatment and minimizing non-specific toxicity [95].

In summary, the applications of VNBs in the delivery of anti-tumor drugs are refle three aspects: 1) Based on the VNB-mediated photoperforation method, some large molecules such as proteins can be delivered to the disease site for treatment; 2) VNBs enhence, induce endosome escape; 3) Combined therapy, transforming standard large-scale therapy into an intracellular demand micro-therapy, enhancing therapeutic efficacy and specificity.

3.4 The application of NBs as ultrasound contrast agents and drug carriers in anti-tumo drugs

Ultrasound imaging combined with drug-loaded targeted nanobubble delivery tumor site is a promising treatment technology. It can not only deliver drugs to the tumor site, but also visualize the tumor shape, adjuvant therapy, and can both diagnose and treat. This has bee proved by many experiments [96-98].

Zhonggao Gaoet al. developed ultrasound-sensitive multifunctional nanoparticles composed of nanoscale polymeric micelles that function as drug carriers and nano- or microscale echogenic bubbles that combine the properties of drug carriers, enhancers of the ultrasound-mediated d delivery, and long-lasting UCA drug carrying, tumor-targeting, and retention in the tumor volume are functions of the micelles, and ultrasound contrast properties are provided NBs MBs formed in a tumor volume by the coalescence of NBs [99]. A literature reported that a NB could be used as an UCA or as a drug delivery carrier. Researchers believed that the addition o Tween 80 was crucial in this dual-function NB [100]. In the study of Hsin-Yang Huang et al., a NB containing superparamagnetic iron oxide (SPIO) was synthesized. The concentration of SPIO the NB could be controlled to optimize the imaging contrast and the efficiency of HIFU to trigger drug release [101]. The doxorubicin nanobubble (DOX-NB) wrapping carbon tetrafluoride gas was

prepared by Mingming Meng et al., which has been developed as ultrasound imagin
agents, doxorubicin carriers, and enhancers of ultrasound-mediated dr
researchers reported a nanobubble-paclitaxel liposome (NB-PTXLp) co
imaging and ultrasound responsive drug (Figure 3) [103]. In the
experiment of Yongjing Li et al., by loading DOX as an anti-cancer drug and perfluorohexane as an
ultrasound probe, the resulting glycine/PEG/RGD-modified NBs
therapeutic efficacy and high quality of ultrasonic imaging. B
therapeutic functions into a single NB, the new type of theranostic NBs offe
strategy to monitor the therapeutic effects, giving important insights into ultrasound-
enhanced targeting drug delivery in biomedical applications [104].

The dual-function applications of NBs as imaging contrast agents and anti-tumor drug carriers are shown in Table 3.

4. Conclusion

In this review, we summarized NBs used in tu
drug carriers (including ONBs and VNBs). Due to the small size of NBs, strong penetrating power
and stable performance, they can enter tumor tissues through tumor blood v
induced by external stimuli to induce cavitation, stimulate cell meml
improve tumor cell uptake. Therefore, NBs can be used not only as ultrasound contrast agents, but
also as carriers for drugs and oxygen to deliver them to the local tumor sit
microenvironment around tumor cells without affecting normal
treatment technology. However, this technology also has limitations. For example, when it used as
an ultrasound contrast agent alone, the image resolution is still insuff
detection systems. Therefore, the development of multiple imaging can simultaneously comb
two or more imaging modes to minimize the shortcomings of each method. As a carrier, if it can
encapsulate some substances such as photosensitizers, it can also achieve a variety of combi
treatments such as photodynamic therapy to achieve better results. Finally, most of t
experiments have achieved therapeutic effects on animals, and clinical tests and applications a
obviously insufficient. Therefore, we hope that future research will be more clinically developed,
so that this technology can truly contribute to human tumor treatment.

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