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Ultrasound Responsive Nanoparticles in Cancer Imaging and Therapy

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Abstract

Ultrasound-responsive nanoparticle can selectively target cancer cell by applying ultrasound waves at the desired part, minimizing unwanted effect and improving the efficacy of anticancer agent. In this review we summarize the recent application of ultrasound responsive nanoparticles for imaging and therapy.

Keyword: Cancer; Ultrasound; Nanobubbles; Stimuli-responsive

Abbreviations: DPPC: Di-Palmitoylsn-Glycero-3-Phosphocholine; MPPC: Myristoyl-2-Palmitoyl-sn-Glycero-3-Phosphocholine; MSPC: Myristoyl-2-Stearoyl-sn-Glycero-3-Phosphocholin; PFC: Per Fluoro Carbon; VEGFR2: Vascular Endothelial Growth Factor Receptor 2; ERP: Enhanced Permeation and Retention Effect

Introduction

Over the years, tremendous efforts have been made to improve cancer diagnosis and treatment. Delivering anticancer agents to solid tumors has always been a major challenge. Anticancer agents have no tumor selectivity, making them potentially toxic to cancer and normal cells. Moreover, tumor tissue has abnormal vasculature and disrupted extracellular matrix which may act as a drug barrier and limit drug bioavailability [1]. Introduction of nanotechnology has shown promising results to overcome the inconsistent pharmacokinetics and distribution of anticancer agents. The use of nanoscale formulations can help to improve drug in-vivo pharmacokinetics, increase their stability and minimize degradation, thus more drug accumulation inside the tumor by the so called enhanced permeation and retention effect (ERP) [2]. Another strategy to target cancer cell is to use stimuli-responsive nanosystems. This "smart" technology is sensitive to either external stimuli, such as light, magnetic field, ultrasound, etc. or internal stimuli that take advantage of tumor microenvironment characteristics Such as lower pH value, higher temperature, etc.

External stimuli-responsive systems could be used as contrast agents to enhance nanoparticles accumulation in the target tissues, by activating the nanosystems with external triggers at the desired time. Therefore, more controlled drug release and higher potential for clinical efficiency [3]. Ultrasound technology is one of the most widely used diagnostic modalities in clinics, due to its good safety profile and relatively inexpensive application. Ultrasound-responsive nanosystems are used to control drug release and to direct it toward tumor cells upon the application of ultrasound waves.

Ultrasound-Responsive Nano-System

The drugs are released from the nanosystems through thermal and mechanical effects produced by ultrasound. Thermo responsive liposome's or polymer micelles were formulated to release their drug payload after mild application of heat (typically around 40-42 °C) on the tumor allowing rapid release of the drug and deeper penetration inside the tumor. 1,2-dipalmitoylsn-glycero-3-phosphocholine (DPPC) is the most frequently used phospholipid for thermal drug delivery. With a melting temperature just above body temperature (41.5 °C), applying mild hyperthermia on the formulation will render more flexible and permeable liposome that can release the drug. The first thermo sensitive Liposomes based on DPPC were studied by Yatvin et al. [4]. Furthermore, lysolipids such as 1-myristoyl-2-palmitoyl-sn-glycero-3-phosphocholine (MPPC) or 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholin (MSPC) can be incorporated into the conventional thermo sensitive liposomes

at different ratios to change the release rate [5]. ThermoDox® is referenced in many clinical trials uses lysolipid thermo sensitive liposome technology to encapsulate doxorubicin [6].

Liposomes have also been used for ultrasound imaging by enclosing air within the phospholipid bilayer. When ultrasound was applied the Liposomes, structure was fragmented and the entrapped gas bubbles diffused out of the phospholipid [7]. Nanobubbles are gas in liquid emulsions with polylactic acid shell to stabilize the Nanobubbles. While Per fluorocarbon (PFC) nanodroplets are liquid in liquid emulsions that under sufficient ultrasound pressures can be vaporized in situ to produce gas bubbles. The liquid to gas transition results in an immediate 3 to 5 times diameter expansion [8]. Chen et al. formulated ligand directed camptothecin loaded acoustic nanodroplets in mouse xenograft tumor models; the nanodroplets successfully enhanced antitumor effect and ultrasound imaging [9]. Another strategy to design nanoscale bubble is to use solid nanoparticles. Amorphous hydrophobic solid substances can entrap gas in their pores. Jin et al. prepared mesoporous silica nanoparticles with different levels of hydrophobicity and large surface areas; super hydrophobic mesoporous silica nanoparticles were able to generate micro bubbles in situ [10].

Targeting Techniques

Targeted delivery with ultrasound responsive nanoparticles can deliver chemotherapeutic agent or gene therapy specifically to tumor cells with the aid of different targeting ligands conjugated to the surface of the nanoparticles. This ligand can be attached covalently or non-covalently to the surface of the ultrasound responsive nanoparticles. In ultrasound imaging, many experimental studies employ streptavidin/biotin non-covalent interaction for binding the shell of the Nanobubbles with targeting ligand. This conjugation cannot be employed in human since streptavidin is immunogenic. Willmann et al. have developed a dual-targeted ultrasound imaging agent with attaching anti-VEGFR2, anti-αvβ3 integrin to Nanobubbles by streptavidin/biotin interaction, the signal intensity noticeably improved in-vivo imaging of tumor angiogenesis in a human ovarian cancer xenografting [11]. Covalent binding targeting methods depend on the type of functional groups exposed on the surface of the ultrasound responsive nanocarriers. The BR55 compound (Bracco) is an ultrasound contrast agent that does not rely on biotin/streptavidin binding approach or an antibody for binding. BR55 is a vascular endothelial growth factor receptor 2 (VEGFR2) targeted ultrasound contrast agent for molecular imaging. It's currently in phase 0 clinical exploratory study to test its safety and possibility to be used for the detection of prostate cancer [12].

For therapeutic effect, ultrasound contrast agents are either destroyed by cavitation or thermally heated in order to release the drug or gene payload. VanOsdol et al. formulated Nanobubbles encapsulated thermo sensitive Liposomes loaded with doxorubicin. With regional administration of HIFU for short duration, doxorubicin delivery into solid tumors from thermo sensitive liposome's was improved, and gas encapsulation allowed Dox to penetrate the tumor core, and the mechanisms controlling such transport involve the synergistic effect of reduced tissue barriers and hyperthermia [13]. Gene delivery approach is recently employed in many preclinical studies. Xie et al. [14] developed Cell-penetrating peptide siRNA conjugate entrapped in an ephrin mimetic peptide modified Nanobubbles. An ephrin mimetic peptide (YSA peptide) was used due to its high efficiency in targeting EphA 2 positive tumor cells. The entrapped CPP-siRNA was released after Nanobubbles shell fragmentation by the effect of ultrasound cavitation [14].

Ultrasound-Induced Drug Delivery

Encapsulation of nanoparticle with gas renders the particles acoustically active. Ultrasound responsive particles are either grow and collapse by high-pressure ultrasound to release drug payload through microjet or expand and contract by lower pressure ultrasound pulse, massaging the vascular wall. Thus increasing the blood vessel permeability and improving the extravasation of coadministered drugs [15]. A phase 1 clinical trial utilized the commercially available phospholipid micro bubble (SonoVue®) to enhance the therapeutic efficacy of chemotherapeutic agent gemcitabine. Application of ultrasound allows direct contact between endothelial cells and the micro bubbles, increasing intracellular stress signaling and drug sensitivity, which resulted in improved gemcitabine response in cancer patient [16].

Conclusion

Application of ultrasound wave on biological tissue can produce mechanical effect or thermal effect that can be utilized in deferent ways. Many preclinical studies have shown that ultrasound responsive nanoparticles could play an important role in early cancer detection and continuous cancer assessment. Moreover, the use of targeted and non-targeted ultrasound responsive nanoparticle for drug and gene delivery is expected to find its clinical application.

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