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● *Review Article*

POLYMER-BASED MATERIALS IN CANCER TREATMENT: FROM THERAPEUTIC CARRIER AND ULTRASOUND CONTRAST AGENT TO THERANOSTIC APPLICATIONS

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Abstract—The emergence of theranostics with ultrasound technology is a promising development, as it opens pathways to providing more effective treatments for cancer. Advancements in ultrasound imaging would give a more detailed and accurate image for better diagnosis and treatment planning. Polymeric ultrasound contrast agents (UCAs) are appealing because they are stable and easily modified for active targeting. In addition, a better therapy could be achieved in conjunction with advancements in UCAs. The active targeting not only makes the precise imaging possible, but also leads to targeted delivery of active components to specific local treatment sites. A polymeric nanocarrier with surface bioconjugation is the key to prolonging the bioavailability of the encapsulated drugs or genes and the capacity to target the specific tumor site. Using ultrasound with other imaging modalities will open more precise and better ways for diagnosis and therapy and bring us a step closer to personalized medicine. This review focuses on polymer-based materials of UCAs, multimodal imaging agents and therapeutic carriers that have been currently explored for their theranostic applications involving ultrasound for cancer diagnosis and treatment. (E-mail: kamolrat@mtec.or.th) © **2016 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Cancer, Multimodal imaging, Polymeric nanocarrier, Targeted therapy, Theranostics, Ultrasound, Ultrasound contrast agent.**

INTRODUCTION

Cancer is still one of the most deadly diseases around the world. Even though it has been known to mankind for centuries, scientists are still conducting research to determine the most effective strategies for increasing the survival rate and improving the quality of patient life during treatment (Brindle 2008; Fan et al. 2014; Gao et al. 2014; Mura and Couvreur 2012; Terreno et al. 2012). The keys to reaching these goals are accurate diagnosis and localized tumor treatment. Accurate and detailed diagnosis from various imaging techniques will give physicians the best tools for planning the treatments. With these tools, effective treatment will reduce the unpleasant, sometimes deadly, side effects of chemotherapy by limiting the treatment to the tumor site, or to make therapeutic components sufficiently stable so they can be delivered specifically to cancer cells.

One of the most promising technologies in this era is theranostics, which combines both therapeutic and diagnostic strategies into one procedure. Nanocarriers are widely studied in theranostics in terms of facilitating delivery of therapeutic materials and acting as contrast agents for diagnosis. In addition to the requirements of safety and lack of toxicity, the ideal characteristics of these carriers for theranostics are: (i) stable in the body during the imaging thus enabling the best diagnostic outcome; (ii) capable of encapsulating, accumulating and releasing the treatment components at targeted tumor sites thereby minimizing the side effects and toxicity to normal tissues; and (iii) specifically tailored fabrication to make personalized treatment possible (Ahmed et al. 2012; Brindle 2008; Chatterjee et al. 2014; Fan et al. 2014; Gao et al. 2014; Lammers et al. 2011; Mura and Couvreur 2012; Sagnella et al. 2014; Terreno et al. 2012; Toy et al. 2014).

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Ultrasound imaging would be a method of choice for theranostic applications since it is non-invasive, low cost and performed in real-time. A contrast agent in conjunction with a focused ultrasound beam could be developed for molecular imaging and for targeted therapeutic delivery (Son et al. 2014). This potential for development is further supported by the flexibility of multiple functionalities of polymer-based materials such as tailorable chemistry, tailorable size, biodegradability, biocompatibility and hydrophilicity/hydrophobicity (Gao et al. 2014; Nazarenus et al. 2014), which have attracted the great attention for medically purposed theranostic uses. This review focuses on polymer-based materials of UCAs, multimodal imaging agents and therapeutic carriers that have been explored for their theranostic applications involving ultrasound for cancer diagnosis and treatment.

Literature search and inclusion criteria

All cited studies involved obtaining informed consent from each study participant and protocol approval by an ethics committee or institutional review board. Likewise, if animals were studied, there was the Institutional Animal Care and Use Committee approval and/or the international, national or institutional guidelines for the care and use of animals were followed. Studies not published in English and abstracts of studies published in conference or seminar proceedings were excluded from this review. The databases searched to find relevant studies for the period 1998–2015 were PubMed (Public/Publisher Medline), Science Direct, Google Scholar, Thomson Innovation patent database (1981–2015) and the ClinicalTrials.gov results database (2005–2015). The following key words were used for: (i) a published article search: "ultrasound contrast agent", "polymeric ultrasound contrast agent", "cancer drug delivery", "gene delivery", "ultrasound multimodal imaging", "photoacoustic", "photoacoustic contrast agent", "theranostic" and "polymer"; and (ii) patent and the ClinicalTrials.gov searches: "ultrasound contrast agent", "polymeric contrast agent", "polymeric ultrasound contrast agent", "cancer drug delivery" and "theranostic". Potential articles based on references identified in eligible studies were also manually searched.

POLYMERIC CARRIERS IN CANCER DRUG AND GENE DELIVERY

Drug delivery

The inception of polymeric carriers in cancer treatment began with researchers' attention to defective endothelial gaps. Due to the rapidly dividing cells of a tumor, researchers became aware that new vasculature was needed to supply it with nutrients and oxygen during tumor development. This growth process for new vessels is known as angiogenesis (Bertrand et al. 2014; Brindle 2008). One consistent difference between tumor blood vessels and normal physiologic vessels is the tendency to be "leaky" (Jain 2001). It has been reported that the pore cut-off size of several tumor models ranges between 200 and 1000 nm (Bertrand et al. 2014; Danhier et al. 2010; Fang et al. 2011; Felice et al. 2014; Sagnella et al. 2014; Taurin et al. 2012; Zhong et al. 2014), which is a lot wider than 10 nm of normal vessels. Therefore, a developed drug carrier designed to exit the bloodstream needs to be smaller than these leaky gaps. Aware of this need, researchers employed specific sized nanoparticles that could be delivered as anticancer drugs through these pores, in a process known as *enhanced permeability and retention effect*. The nanoparticles also protect the drug from inactivation during transport.

It has been known that passive targeting relied on the accumulation of drug nanocarriers in the tumor site due to the enhanced permeability and retention effect (Bertrand et al. 2014; Danhier et al. 2010; Fang et al. 2011; Felice et al. 2014; Sagnella et al. 2014; Taurin et al. 2012). Additional benefits of drug delivery could be achieved by active targeting, which is the addition of ligand onto the surface of the nanocarriers. The ligand-attached carriers could bind to cell receptors making the drug delivery system more specific (Bertrand et al. 2014; Low et al. 2008; Marelli et al. 2013; Montenegro et al. 2013; Yu et al. 2012; Zhong et al. 2014) These ligands could be antibody, protein, peptide, nucleic acid or small molecules. Each type of ligands has advantages and disadvantages, as shown in Table 1.

Polymeric nanoparticles such as poly(lactic-co-glycolic acid) (PLGA) or poly(lactic acid) (PLA) have drawn wide interest for drug delivery due to their biodegradability, biocompatibility and US Food and Drug Administration (FDA) approval for clinical applications. The PLGA or PLA particles were included in many studies for encapsulating hydrophobic and/or hydrophilic anticancer drugs and tested their efficacy for drug delivery. Docetaxel (DTX) was used as a hydrophobic anticancer drug model in a system of porous PLGA nanoparticles with D-α-tocopheryl polyethylene glycol succinate (TPGS) used as a pore-forming agent and an enhanced drug encapsulation efficiency agent (Zhu et al. 2014). The DTX-loaded nanoparticles with TPGS demonstrated significantly greater inhibition of tumor growth as opposed to DTX-loaded nanoparticles without TPGS and free DTX. The drug release could be controlled by adjusting the ratio between PLGA and TPGS, resulting in different pores in the particles (Zhu et al. 2014). A further study also showed paclitaxel (PTX) could be encapsulated in TPGS-functionalized PLGA nanoparticles. In comparison to a free drug, the drug-loaded nanoparticles showed greater effectiveness in increased intracellular uptake, inhibited human lung