Thermoactivatable polymer-grafted liposomes for low-invasive image-guided chemotherapy

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The objective of this study was to develop a thermotriggered, polymer-based liposomal drug carrier with an activatable magnetic resonance imaging (MRI) contrast property for monitoring the release of substances and for localized tumor therapy. The multimodal thermoactivatable polymer-grafted liposomes (MTPLs) were tested to investigate whether the accumulation of MTPLs in colon-26 grafted tumors could be visualized in vivo using MRI and optical imaging, whether MTPLs induce signal enhancement, reflecting the release of their contents, after triggering by short-term heating (42.5°C for 10 minutes) 9 hours after MTPL administration (late-phase triggering), and whether MTPLs can provide a sufficient antitumor effect. The imaging and therapeutic properties of MTPLs were tested both in vitro and in vivo (BALB/c nude mice: heated group with MTPLs (n = 5), nonheated group with MTPLs (n = 5), heated group with doxorubicin-free MTPLs (n = 5), nonheated group with manganese-free MTPLs (n = 5), and kinetics observation group (n = 3); N = 23). Through in vivo MRI and fluorescent imaging, the MTPLs were shown to have significantly accumulated in the grafted colon-26 tumors 8 hours after administration. Delayed thermotriggering (9 hours after administration) caused MR signal enhancement, reflecting the release of their contents, after a short exposure to tolerable heat. In addition, significant antitumor effects were observed after treatment. The proposed polymer-based activatable MTPLs with a "delayed thermotrigger" provide a promising technology for cancer theranostics that allows minimal adverse effects and rapid interactive therapy. (Translational Research 2015;166:660–673)

Abbreviations: 2D = two-dimensional; DDS = drug delivery system; DPPC = dipalmitoylphosphatidylcholine; EPR = enhanced permeability and retention; FOV = field of view; MBE = manganese-bound relaxivity enhancement; Mn = manganese; $MnSO_4$ = manganese sulfate; MRI = magnetic resonance imaging; MTPL = multimodal thermoactivatable polymer-grafted liposome; NA = number of acquisitions; PEG = polyethylene glycol; R_1 = longitudinal relaxation rate; R_2 = transverse relaxation rate; ST = slice thickness; T_1 = longitudinal relaxation time; T_2 = transverse relaxation time; TR = repetition time; TE = echo time; TPL = thermosensitive polymer-grafted liposome; TSL = temperature-sensitive liposomes

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AT A GLANCE COMMENTARY

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Background

The present study focused on thermoactivatable ''polymer-based'' liposomal drug delivery imaging and chemotherapy systems, which are currently recognized as promising technologies for providing nanopharmaceuticals. Although several lipid-based thermosensitive liposomes have been reported, we believe that the polymer-based strategy can provide lower adverse effect because of the short-term triggering.

Translational Significance

We developed a drug carrier embedded with an anticancer drug, fluorophore, and MRI contrast agent. Conformational changes triggered by a short-term heating (42.5°C for 10 minutes) provoke a rapid target-selective content release without painful hyperthermia. The MRI contrast agent could act as an activatable probe to identify disrupted liposomes in vivo. Significant antitumor effects were observed.

INTRODUCTION

Drug delivery systems (DDSs) using nanoparticles have been developed to enhance the effectiveness and minimize the adverse effects of chemotherapy by allowing sustained and controlled drug release in tumors. Liposome-based carriers offer remarkable advantages, such as the ability to load hydrophilic drugs inside them, biocompatibility, and a controllable lipid membrane. Liposome-based carrier has been approved for clinical use, such as Doxil, which consists of polyethylene glycol (PEG)-grafted doxorubicin-containing liposomes. Unfortunately, in Doxil, the release of doxorubicin cannot be controlled with an external trigger, and its distribution in a tumor is not visible using clinical in vivo 3-dimensional (3D) imaging technologies. To allow externally triggered controllable drug release, several types of stimuli-sensitive liposomes have been proposed, such as those triggered by enzymes, pH, and temperature.[1-3] Among stimuli-sensitive liposomes, temperature-sensitive liposomes (TSLs) offer excellent potential because of their tunable drug-release temperatures, flexibility in design, and synergistic effect with hyperthermia.[4-11] From the time of first report of Yatvin et al on TSLs consisting of dipalmitoylphosphatidylcholine (DPPC),[3] many different types of temperature-sensitive DPPC liposomes have been developed.[1,4,12] Using doxorubicin-containing TSLs (Dox-TSLs) composed of DPPC and palmitoyl lysophosphatidylcholine, it was demonstrated that the intratumor doxorubicin concentrations were up to 30-fold greater in mice treated with liposomes than in those administered with free doxorubicin.[13,14] In combination with hyperthermia, thermosensitive Dox-TSLs, which are designed based on the principle of the gel-to-liquid-crystalline phase transition of the liposomal membrane, are currently undergoing a clinical trial (ie, ThermoDOX; Celsion Corp).

In addition to the current success with liposomal DDS design, the in vivo visualization of liposome dynamics and drug release can further improve and optimize chemotherapy efficacy. The 3D imaging of certain in vivo traceable liposomes has been performed, using predominantly magnetic resonance imaging (MRI) (iron oxide nanoparticles,[15,16] gadolinium chelates,[17] and manganese [Mn][18]) but also nuclear imaging (positron emission tomography and single photon emission computed tomography).[19,20] MRI is widely used in the clinical field and offers many advantages, such as high spatial resolution 3D imaging, no exposure to ionized radiation, and detection with functional and physiological mapping. Thermosensitive liposomes loaded with water-soluble contrast agents (gadolinium chelates[21] or Mn^{2+}[8,22,23]) have been reported for monitoring liposome accumulation or drug-release processes. In particular, the pioneering approaches of Ponce and Viglianti allow visualization of the time course and spatial pattern of drug release using Dox-TSLs loaded with an MRI contrast agent.[8,24] However, the liposomes used in these previous approaches were heated in the early phase (0–15 minutes) after liposome administration.[8,23,24] Nanoparticles that passively accumulate in tumors are generally designed to have a long blood circulation time (4–48 hours) to maximize passive accumulation (enhanced permeability and retention [EPR] effect) and to minimize any nonspecific drug distribution in the blood or tissues.[25,26] Therefore, further development of an image-guided thermosensitive liposome that has fine temperature reactivity, high in vivo stability, and the capability for tumor-specific accumulation is still required.

A technology involving thermosensitive polymer-grafted liposomes (TPLs) has been previously reported,[27-30] which can facilitate drug release as an alternative to the gel-to-liquid-crystalline phase-transition technology.[3] These polymer-based liposomes are grafted with 2 types of polymers, a thermosensitive polymer[31] for lipid membrane destabilization and PEG for sustained blood half-life to avoid capture by the reticuloendothelial system.[25,26] These polymer-