Theranostics Using Indocyanine Green Lactosomes

Subjects: Others

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Lactosomes™ are biocompatible nanoparticles that can be used for cancer tissue imaging and drug delivery. Lactosomes are amphiphilic micelles in which the particle size can be controlled in the range of 20 to 100 nm. Lactosomes can also be loaded with imaging probes and anticancer agents. Indocyanine green-loaded lactosomes accumulate in cancer tissues and function as a photosensitizer, which simultaneously enables diagnosis and photodynamic therapy.

Keywords: indocyanine green lactosome ; tumor accumulation ; photodynamic diagnosis

1. Introduction

Molecular imaging and theranostic (a fusion of the words “therapy” and “diagnostic”) nanoparticles are effective for the early diagnosis and treatment of cancers. Large-scale industrial, governmental, and academic studies in the field of theranostics have been conducted worldwide. Molecular probes are the cornerstone of imaging and enable early diagnosis and treatment. Molecular probes can be delivered via the enhanced permeability and retention (EPR) effect, which occurs in inflammatory and ischemic diseases as well as in cancers [1]. The EPR effect is a phenomenon in pathological conditions in which nanoparticles with sizes of 30–100 nm accumulate in the interstitium due to vascular leakage [2]. Further, the lymph system surrounding the tumor grows too slowly to exclude nanoparticles from tumor tissues [3]. Lactosomes™ are amphipathic polymers that can be manufactured to exhibit particles of sizes in the range of 20 to 100 nm [4][5][6]. In addition, the shape of polymer micelles can be accurately controlled [7][8]. Lactosomes can be loaded with labeling agents such as indocyanine green (ICG) [9]. ICG has been approved by the Food and Drug Administration for clinical and research use in humans since 1956 [10]. ICG is widely used in ocular angiography and hepatic function assessment. Furthermore, fluorescence imaging using ICG can delineate the area of the tumor and confirm residual tumor after resection, and, subsequently, ICG can be used for photodynamic therapy (PDT). PDT after surgical removal of most of the tumor is used for “tumor bed sterilization”, that is, selective removal of the remaining tumor with minimal damaging of the essential tissue. However, ICG in the blood tends to bind to albumin, which confines most of the bolus to the intravascular space until albumin-mediated hepatic uptake and subsequent excretion into bile [11][12]. Alternatively, ICG-loaded lactosomes remain stable during long-term blood circulation and can accumulate in tumor tissues, where they can act as photosensitizers that generate reactive oxygen species upon application of light of the appropriate wavelength for ICG excitation, about 780 nm [13]. Furthermore, it is possible to label the surface of lactosomes with antibodies to selectively deliver drugs and genes to cancer cells. Thus, lactosomes may be used for both early diagnosis and subsequent treatment of cancers [14].

2. Molecular Design of Indocyanine Green-Loaded Lactosomes

Polymers formed by ICG-poly-L-lactic acid (PLLA) and AB-type polysarcosine PLLA are amphipathic [4][5][6]. PLLA has been used for therapeutic applications, such as in materials for osteosynthesis, as a highly biocompatible and biodegradable hydrophobic polymer. Polysarcosine is a highly hydrophilic polypeptide, with a base material that does not adsorb non-specifically into tissues and cells, and is also biodegradable [15][16]. This amphipathic polymer forms lactosomes in water by self-assembly of PLLA via intermolecular interaction forces. The particle size of the resultant lactosomes can also be controlled.

2.1. Accumulation of Lactosomes in Cancer Tissues

Recent research efforts have focused on the development of molecular probes based on nanoparticles that rely on the EPR effect [2][3]. Nanoparticles containing therapeutic agents such as radioactive and fluorescent agents, as well as magnetic substances, can accumulate in cancer tissues and allow for molecular imaging to sensitively track the effect of treatment. Makino et al. demonstrated the accumulation of ICG-loaded lactosomes in cancer tissue using near-infrared fluorescence imaging in various mouse transplant models of cancer (i.e., subcutaneous, liver, lung, large intestine, and brain) [4][5].

2.2. Theranostics Application with ICG-Lactosomes

Biodegradable nanoparticles (ICG-lactosomes) can carry biocompatible cyanine dyes for high biopermeability, near-infrared fluorescence, and photosensitivity, which allows for tumor selectivity and local retention. Combining ICG-lactosomes with a near-infrared light camera allows for: (1) clear delineation of the tumor area during surgery, (2) confirmation of residual tumor after resection to support additional resection if necessary, and (3) a shift to photodynamic therapy to treat only the tumor site.

Although fluorescence imaging has been used to assess the pharmacokinetics of ICG-lactosomes in vivo, this method provides no depth-resolved information.

The mechanism of the antitumor effects during PDT has previously been reported. First, the photosensitizer, which accumulates in the cancer tissue, is irradiated with a laser light. A photon of the right wavelength is absorbed by the photosensitizer, such as ICG, so that ICG passes from the singlet ground state to an excited singlet state. From there, it passes to the lowest triplet state by intersystem-crossing. The lowest triplet state can then transfer its energy to the surroundings in a collisional process involving molecular oxygen, leading to the generation of reactive oxygen species. The presence of reactive oxygen species may then lead to apoptosis as well as necrosis or other forms of cell death [17]. This system is generally applicable to solid tumors, because it relies on the EPR effect in the neovascularization but does not require a specific antibody for tumor cells. Therefore, the approach can be used to treat cancer cells in unresectable regions, such as parts of the brain in glioblastoma or the tissue near the carotid artery in head and neck cancer. Furthermore, the drug can also be manufactured at a lower cost than antibody-based therapies. This cancer treatment system using near-infrared light with ICG-lactosomes consists of the following elements: (1) a near-infrared fluorescent agent such as ICG-lactosomes, which can accumulate in the cancer and are composed of biodegradable molecules [9]; (2) a near-infrared semiconductor laser irradiator device [9]; and (3) a device that can visualize near-infrared light or a photoacoustic signal during surgery [4][13].

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