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Selective antileukemia effect of stabilized nanohybrid vesicles based on cholesteryl succinyl silane

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ABSTRACT

A nanohybrid vesicle was developed from cholesteryl succinyl silane(CSS) in combination of sol–gel process and self-assembly technique. The silicalike surface adds CSS vesicles remarkably high stability against destabilization in blood or leakage of drug cargos. It was found that CSS vesicles alone exhibited selective antiproliferative effects on leukemia cells without destroying normal blood cells. In addition, they are able to encapsulate not only hydrophilic guest species inside the inner water compartment but also hydrophobic molecules in the cholesteryl succinyl bilayer membrane. More importantly, CSS vesicles loaded with doxorubicin enhanced the anticancer efficiency of cancer therapeutics greatly while minimizing the use of inactive materials and lowering the exposure of normal cells to toxic side effects. This makes CSS vesicle a promising carrier for the treatment of cancer, especially for leukemia.

1. Introduction

Leukemia is a severe cancer, which begins in specific cells responsible for the formation of blood cells. Irrespective of the age group, it is estimated that leukemia survival rate for five years is approximately 43%, enlisting it as the one of most fatal cancer forms [1]. In the objective to increase the survival rate of leukemia patients, studies are ongoing to developing the more effective therapeutic techniques.

Chemotherapy is one of the most effective treatments for leukemia. There are a number of anticancer medications that are used, such as doxorubicin(DOX) [2], daunorubicin [3] and cytarabine [4]. Despite the effectiveness of these medications for leukemia treatment, patients receiving chemotherapeutic treatment can experience severe side effects because these drugs not only inhibit the proliferation of cancer cells but also do harm to normal blood cells [5]. To improve the delivery and the effectiveness of anticancer drugs and thus reducing side effects to normal cells, various nanosized vehicles including liposomes, polymer and silica nanoparticles are used as the drug carriers [6–8]. Nevertheless, most current drug carriers are typically inert and their sole role is to operate as inert containers for drugs. Despite the attractive features of liposomes, their physical properties needed to obtain efficient drug loading and stable entrapment of cargo compounds may be in conflict with the properties of carriers that would be optimal for drug delivery. The lipid and cholesterol have no therapeutic functions merely to make the vesicles carrying drugs but they are the major component of liposomes and their contents are generally more than 90%. Accordingly, a large amount of carriers has to be used to administer a needed dose of drug. Repeated administrations of high doses of these nanocarriers may cause systemic toxicity and impose an extra burden for the patients to excrete the carriers [9]. Attacking this problem head on, active nanocarriers are much sought after in order to substantially minimize use of inactive materials, increase the drug loading content, selectively kill cancer cells while lowering the exposure of healthy tissue to toxic side effects.

Cholesterol being ubiquitous component in most of the animal cell membranes is increasingly being used as a hydrophobic segment of synthetic lipids [10–12]. It is reported that cholesteryl hemisuccinate (CS), a kind of cholesterol derivatives, can inhibit the growth of cancer cells in mice, such as C1498 (acute myeloid leukemia) and L1210 (lymphocytic leukemia) cells both *in vitro* and in *vivo* [13]. Among many structurally stable materials, silica nanoparticles with defined structures and surface properties have been widely investigated for drug delivery [14]. Nevertheless, the drawbacks of silica nanoparticles are their inherent non-biodegradability, high rigidity and mass density, as well as low biocompatibility as compared to nanoparticles comprised of naturally occurring molecules, such as liposomes or micelles that are composed of phospholipids. Liposomes have attracted considerable attention for controlled or targeted release of various drugs and

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diagnostic agents. Despite all the work done, liposomes still have not attained their full potential as drug delivery vehicles due to their insufficient morphological stability. Recently, a so-called cerasome with a liposomal bilayer structure and an atomic layer of inorganic polyorganosiloxane networks on its surface has been fabricated by molecularly designed lipidic organoalkoxysilane [15–19]. As a drug delivery system, cerasomes combine advantages of both silica nanoparticles and liposomes. The siloxane surface endows cerasomes remarkably high mechanical stability and heat resistance compared with conventional liposomes while the presence of a liposomal bilayer structure reduces the overall rigidity and density of cerasomes greatly compared to silica nanoparticles, which is expected to enhance the stability of such particles in aqueous systems against precipitation. In addition, cerasomes exhibit better biocompatibility than silica nanoparticles and can be biodegraded through the biochemical decomposition [18].

In this study, a nanohybrid vesicle with an atomic layer of inorganic polyorganosiloxane networks on its surface was developed from cholesteryl succinyl silane(CSS) in combination of sol–gel process and self-assembly technique (Fig. 1). CSS vesicles were characterized by dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM) and their encapsulation efficiency, drug content, and *in vitro* release were also analyzed. The cytotoxicity of CSS vesicles was evaluated by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay in leukemia cells (HL-60 and Jurkat), solid tumor cells (A549) as well as normal blood cells. The antiproliferative activity of CSS vesicles was compared with liposomes, cerasomes and CS vesicles. The lethal effects of DOX loaded CSS (DOX@CSS) vesicles were also investigated in comparison with free DOX in HL-60 and Jurkat cells.

2. Materials and methods

2.1. Materials

Cholesteryl was obtained from Avanti Polar Lipids, Inc. Triton-X 100, and MTT were purchased from Sigma. Aminopropyltriethoxysilane (APTES, 99.9%) was from Aldrich. Doxorubicin hydrochloride (DOX•HCl) was obtained from Beijing Huafeng United Technology. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) was purchased from Shanghai Medpep Co., Ltd. All chemicals are of analytical grade and used directly without further purification. RPMI1640 cell culture medium (GIBCO) was supplemented with 10% fetal bovine serum, L-glutamine (0.29 mg/ml), 100 IU/ml penicillin and 100 μg/ml streptomycin. Millipore

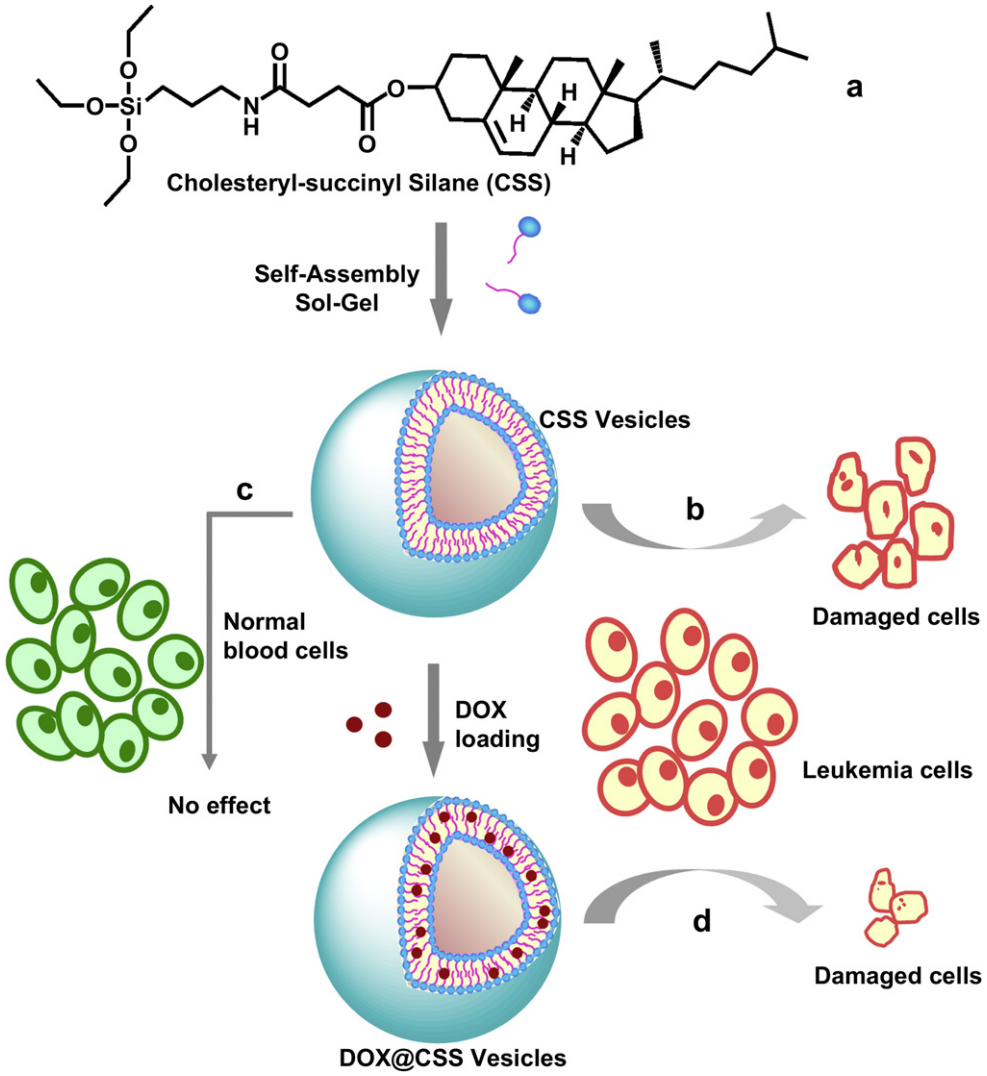

Fig. 1. Schematic antiproliferative effects of nanohybrid vesicles of CSS toward leukemia cells: (a) Chemical structure of CSS compound; (b) CSS vesicles alone could selectively inhibit growth of leukemia cells; (c) CSS vesicles do almost no harm to normal blood cells; (d) CSS vesicles in combination with DOX significantly enhanced DOX-induced death of leukemia cells.