Pharmaceutical Hypothesis

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Cell organelle-shaped liposomes: A novel approach to present the stable intracellular drug delivery systems

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Abstract

Caveolae are lipid raft-enriched flask-shaped, expose in the plasma membrane of various cell types. It has become clear now that caveolae and their caveolin "marker proteins" are associated in a several cellular procedures including endocytosis, lipid homeostasis, signal transduction, and tumorigenesis. Caveolin has been shown to have high binding affinity for cholesterol and sphingolipids. Caveolin oligomers construct filamentous networks that are believed to stabilize the membrane. Liposomes are the well-known drug delivery systems with spherical shape that can be produced from natural non-toxic phospholipids and cholesterol. Liposomes have been used as a considerable tool in biology, biochemistry, medicine, and drug delivery. The utilization of liposomes as a drug-delivery system has become more attractive in carrying systemically administered drugs with narrow therapeutic windows. The similarity between plasma membrane and liposomes from several points of view gives hope that the incorporation of caveolin in the phospholipid bilayer structures of liposomes can result in tightening and therefore stabilizing and long circulation of these structures.

Keywords: Caveolin, Liposome, Long-circulation, Phospholipid bilayer tightening.

1. Introduction

Caveolae are the small invaginations of the plasma membrane with the size of 50 to 100 nm (1). A long with the physiologic-based influential roles of these important structures, it has become clear now that caveolae and their caveolin "marker proteins" are associated in a several cellular processes including lipid homeostasis, endocytosis, signal transduction, and tumorigenesis (2) (Figure 1). The caveolin family is consisted of three definite proteins including caveolin-1, caveolin-2, and caveolin 3 (Cav-1, -2,-3) (3, 4). The caveolin proteins have a variety features which are important not only for selective localization to caveolae but also for compelling the invagination of these complexes. Cav-1 has been demonstrated to have high binding affinity for cholesterol and sphingolipids (5, 6). This property, as well as three carboxy-terminal lipid modifications (palmitoylations), stabilizes and targets Cav-1 to caveolae (7). Cav-1 oligomers form filamentous networks that are believed to stabilize the membrane and define the size and shape of caveolae (8). Caveolae can be divided from cells as cholesterol and sphingomyelin-enriched microdomains that are traditionally found decorating both apical and/or basolateral membranes in terminally differentiated cells (9). Identification and cloning of a caveolae coat-associated protein, Cav-1 is also possible (10, 11).

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Liposomes and their characterizations

Liposomes are the well-known drug delivery systems with spherical shape that can be pro-

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duced from natural non-toxic phospholipids and cholesterol. Phospholipids, triglycerides, and cholesterol are the main constituents of liposomes. In fact, liposomes are phospholipid bilayers with an entangled aqueous extent. The first suggested utilized of liposomes came from Weismann et al. in 1969 (12). Since then, liposomes have been used as a considerable tool in biology, biochemistry, medicine, and drug delivery (13). Because of their wide size range, hydrophobic/hydrophilic properties and, demonstrated biocompatibility, liposomes are considered as a hopeful system for drug delivery. Furthermore, drugs with different lipophilicities can be encapsulated into liposomes (14). The utilization of these lipid-based vesicles as a drug-delivery system has become more attractive over the last decades, because of their biocompatibility and flexibility in carrying systemically administered drugs such as chemotherapeutics and antibiotics with restricted therapeutic windows. Liposomes can be conjugated to antibodies or ligands to provide target-specific drug delivery possibility. They are classified into three categories based on their size and number of bilayers. Small unilamellar vesicles (SUV) are surrounded by a single lipid bilayer and are 25–50 nm in diameter. Large unilamellar vesicles (LUV) are a heterogeneous group of vesicles similar to SUVs but larger in size, while enclosed by a single lipid bilayer, too. Multilamellar vesicles (MLV); however, consist of several lipid bilayers separated from one another by a layer of aqueous solution (15). Moreover, liposomes are widely used as carriers for small drugs and macromolecules in drug delivery (16).

Hypothesis: Caveolin can act as a stabilizing and long circulating agent in liposomes

The similarity between plasma membrane and liposomes from the view point of lipid combination, bilayer structure, and the possibility of the insertion of various ligands in these structures, along with high binding affinity of Cav-1 for cholesterol is an optimistic sign that the incorporation of Cav-1 in the phospholipid bilayer structures of liposomes-similar to what is naturally observed in the lipid rafts of plasma membrane – can result in

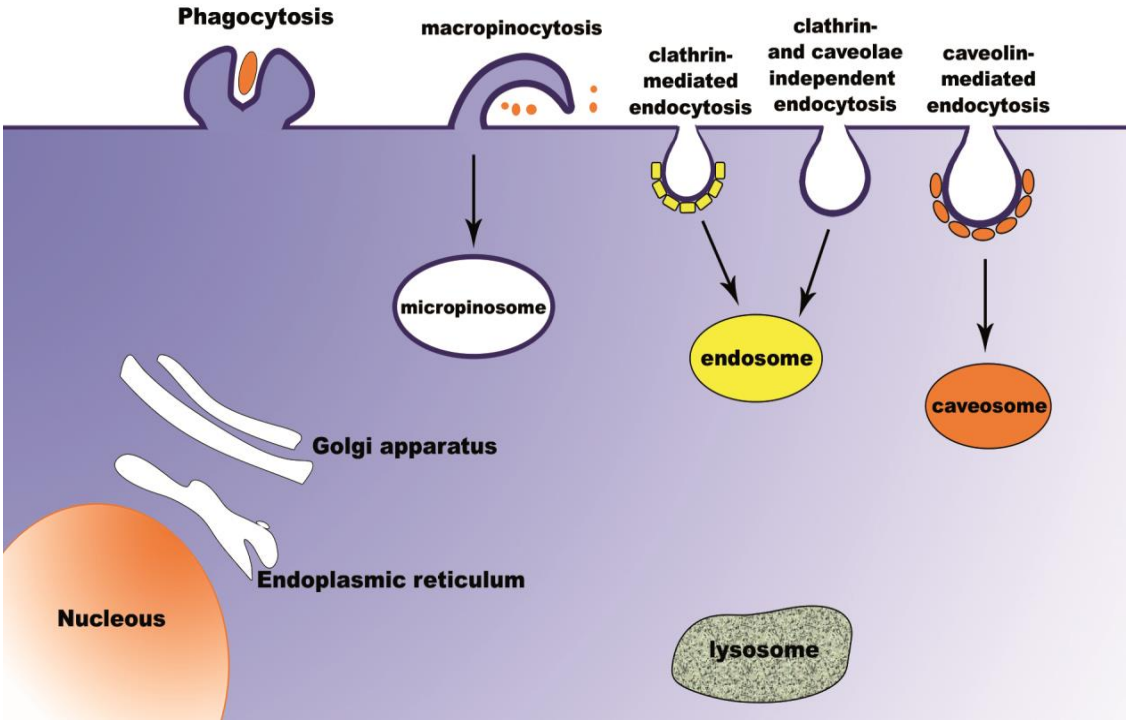

Figure 1. A schematic view of plasma membrane endocytosis processes.

tightening and therefore stabilizing of these structures. This tight and stabilized bilayer can decrease insertion of plasma proteins and also reduce reticuloendothelial system (RES) clearance of the liposomes. The stabilized liposomes can passively accumulate inside other tissues and/or organs. This aspect, named passive targeting, is especially apparent in solid tumors enduring angiogenesis. The existence of a disconnected endothelial lining in the tumor vasculature during angiogenesis promotes extravasation of liposomal formulations into the interstitial space, where they accumulate due to the lack of efficient lymphatic effluent of the tumor, and function as a controlled drug-release system. This causes the preferential accumulation of liposomes in the tumor area (a process known as enhanced permeation and retention effect EPR). Therefore, this type of liposomal drug delivery system can especially be appropriate for chemotherapeutic agent delivery and targeting.

Incorporation of the caveolin can be accomplished during liposome formation by detergent dialysis or post liposome formation by conjugation to reactive lipids. Such strategies are usual for the incorporation of the targeting moieties (13, 17). In addition to stabilizing-which in turn causes long circulation-and its consequences, Cav-1 may, this time, play its routine role of signal transduction for liposomes instead of natural cells, the revolutionary effects of which goes without saying.

Concluding remarks

The most significant properties of caveolin-modified liposomes can strongly be prolonged blood circulation and thus improved distribution in perfused tissues. Taking into account these considerations and the great advantages of caveolin-modified liposomes in decreasing specific drug toxicity and in passively targeting the incorporated molecules to the site of action, new and "improved" liposomal formulations designed for different therapeutic and diagnostic areas may be expected to arrive on the pharmaceutical research.

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Conflict of Interest

None declared.

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