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INTERACTION OF LIPOSOMES WITH CANCER CELLS: INFLUENCE OF LIPOSOME SURFACE PROPERTIES ON CELLULAR UPTAKE

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ABSTRACT

The enormous progress in understanding the basic biology of cancer cells and the rapid advancement of nanotechnology showed immense potential for improving conventional ways of treating cancer. The understanding of how liposomes interact with cancer cells in a biological environment is a serious concern and need substantial knowledge to develop novel drug delivery vehicles for cancer cell specific delivery while sparing off adjacent normal tissues. This review summarizes the scientific reports on liposome-cell interactions with a focus on the effect of liposome size, surface charge and lipid composition of liposomes on the interaction with different kinds of cancer cells.

KEY WORDS: Liposomes, Endocytosis, Polyethylene glycol (PEG), charge, drug delivery.

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INTRODUCTION

Cancer is most serious health concern worldwide and the second leading cause of death in the United States[1;2].Cancer is a complex disease in which several proliferation and survival related signaling pathways of normal cells are hijacked by cancer cell to maintain their unlimited growth[3-6]. Although, substantial progress has been made in the area of cancer biology but still current therapies such as chemotherapy, radiation and surgery are not adequate in curing this disease[7;8].The advance understanding of the complex biology of cancer cells [9-11] and the enormous progress in the field of development of novel delivery vehicles[12-16] has laid the foundation of cancer nanomedicine. Cancer nanomedicine has emerged as one of the most significant therapy to overcome the side effects of conventional chemotherapy and poor bioavailability and pharmacokinetics of drugs[17;18]. Recently, a significant progress has been made in the area of cancer nanomedicine as apparent by FDA approved nanoformulations as well as a large number of nanoformulations in the clinical trials for the treatment of various cancers[16]. However, very few formulations have been successful to come in the market in a very long time of research in the area of cancer nanomedicine (Table 1). Thus, we need to recognize the basic understanding of the interaction of nanocarrier with cancer cells to enhance their cellular uptake and ultimately delivery of drug at target site. In this review we will discuss about different kind of interactions that can occur between liposomes and the cancer cells. The interaction of the liposomes bilayer with cancer cells is very complex and need significant attention to develop novel liposome based drug delivery systems against cancer. We have reviewed a large number of studies addressing the issue of liposome-cancer cell interactions as a function of their composition, size, charge and surface properties.

Table 1
List of FDA approved liposomal formulations for the treatment of cancer

Product	Manufactured by	Drug	For the treatment of	Year of FDA approval
Doxil/Caelyx	Johnson & Johnson	Doxorubicin	Kaposi's sarcoma	1995
			Ovarian cancer	1999
			Breast cancer	2003
			Multiple myeloma	2007
DaunoXome	Galen	Daunorubicin	Kaposi's sarcoma	1996
Abraxane	Abraxis Bioscience	Nab-Paclitaxel	Various cancers	2005
Myocet	Cephalon	Doxorubicin	Breast cancer	2000
Marqibo	Talon	Vincristine	Acute lymphoblastic leukemia	2012
Lipo-Dox	Sun Pharma	Doxorubicin	Kaposi's sarcoma, Ovarian and Breast cancer	2013
Abraxane	Celgene	Nab-Paclitaxel + gemcitabine	Metastatic pancreatic cancer	2013

Nab-Paclitaxel: Nanoparticle Albumin- bound Paclitaxel

Mechanism of cellular uptake of liposomes

The one most important aspect for developing liposomal nanomedicine against cancer is to understand the biology of liposome and cancer cell interaction for their enhanced cellular uptake and target specific delivery. The interaction of liposomes with cells has been extensively studied and different mechanisms of interactions have been proposed[19-21]. The physical properties of liposomes and their interaction with biological components and cell membrane determine the mechanism of their cellular uptake to deliver their content to cells. Additionally, nature of the cell membrane such as lipid composition, fluidity, receptors etc. and the type of cell can influence liposome-cell interactions and therefore the mechanism of cellular uptake[22;23]. Liposomes can interact with cells in anyone or combination of the four ways as depicted in figure 1: (a) Adsorption, (b) Fusion, (c) Endocytosis (d) lipid exchange, depending on their surface properties[21]. However, the main pathway for internalization of liposomes in mammalian cells is endocytosis.

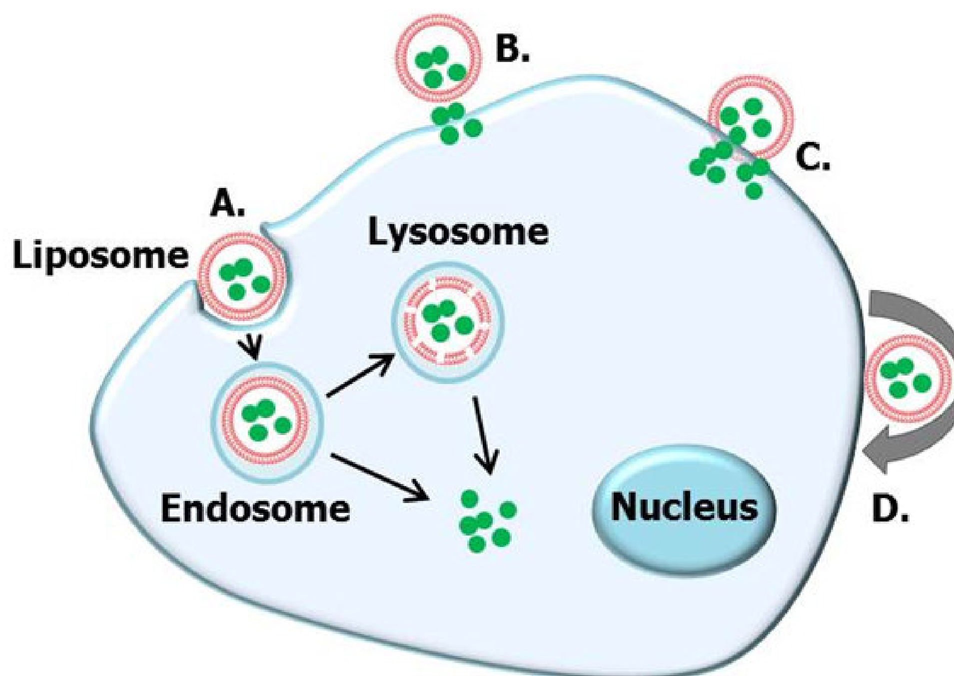

Figure 1

Mechanism of liposome-cell interaction: Liposomes can interact and delivery their cargo to cells by (A.) Endocytosis, (B.) adsorption onto the cell surface, (C.) fusion with the cell membrane or (D.) lipid mixing mechanisms. After endocytosis, liposomes are internalized into endosomes and fused with lysosomes to release the entrapped material. Liposomes can also destabilized the endosomes and drug can be release directly into cytoplasm.

Adsorption is believed to be the first step for cellular uptake of liposomes. After adsorption, liposomes release its content into extracellular environment and subsequent active and/or passive transportation of these contents occur across the cell membrane. Liposomes after adsorption can selectively exchange/transfer the lipids from liposomal bilayer to the cell membrane. Moreover, liposomes can release their content in to the cytoplasm by fusion of liposome bilayer with the cell membrane. However, in the case of endocytosis, liposomes are endocytosed in to bilayer vesicles called endosomes. The presence of liposomes in endosomes was first confirmed by electron microscopy in polymorphonuclear leukocytes isolated from a Tay-Sachs patient[24]. Straubingeret al., (1983) first demonstrated that negatively charged liposomes are internalized into CV1 cells by endocytosis via coated pits pathway[25]. Chin et al., (1989) further confirmed the involvement of the clathrin-coated vesicles in liposome endocytosis by microinjection of anti-clathrin antibody to HeLa cells[26]. Endocytosed liposomes are transported to lysosome where liposome can be degraded and content is released. In this process, liposomal phospholipids are hydrolyzed to fatty acids which can be either released outside the cell or recycled to incorporate again into cell membrane [27]. Fusion of liposomes with lysosome and lysosomal degradation of liposome contents was first demonstrated in Kuffer cells[28]. However, liposomes can also provoke endosome destabilization to release their contents into cytoplasm [29]. The physiochemical properties such as surface charge, shape and size of liposome and lipid composition and rigidity of liposome bilayer play an important role in the interaction of liposomes with cells.

Effect of composition and size on cellular uptake of liposomes

The size and composition of nanoparticles or liposomes greatly influence their interaction with cells [30-33]. Heath et al., (1985) have studied the effect of cholesterol and size on the liposomal endocytosis. They have reported that cholesterol is an essential component of liposome membrane and optimum liposome size for the drug delivery is 0.1μm[34]. Allen et al., have reported that size and composition of liposomes play an important role in the endocytic uptake by cultured bone marrow macrophages[35]. The percentage of cholesterol and sphingomyelin, which increase membrane rigidity, in phosphatidyl choline (PC) liposomes is inversely related with cellular uptake. Additionally, it was shown that there was an inverse correlation between size of extruded large unilamellar vesicles (LUV) and their uptake by macrophages. Yamamoto et al., (2002) have studied the effect of liposome size, dose and lipid composition on the triggered release of cytokines from peripheral blood cells. It was observed that the size of liposomes affected the degree of the cytokine release with the larger sized liposomes causing higher levels of cytokine release. Moreover, the liposomal composition had no effect on the release kinetics of cytokine[36]. The therapeutic activity of

liposomal doxorubicin of various diameters was accessed by the Charrois and Allen, (2003) in tumor bearing mice. They have reported that the liposomal formulations of 100 or 157 nm size were equally efficacious and superior over the liposomes of 255 nm to delay the tumor growth[37]. The size of the liposomes can also determine the mechanism of endocytosis. The cellular uptake of larger liposomes (97.8 nm and 162.1 nm) by Caco-2 cells was predominantly by clathrin-dependent endocytic mechanisms and the smaller sized liposomes (40.6 nm) select dynamin-dependent mechanism while medium sized liposomes (72.3 nm) enter the cells by all known pathways [38]. The size of liposome also influence the circulation time in blood. The liposomes of size >300 nm and <70 nm were preferentially accumulated in spleen and liver of mice, respectively while the medium sized liposomes (150-200 nm) exhibit longest circulation [39].

Effect of surface charge on cellular uptake of liposomes

The surface charge is the most influential factor for governing the adsorption of liposomes to cell membrane. The very first report on the effect of charge on liposome interaction suggest that uptake of negatively charged vesicles is substantially greater than the uptake of the positively charged and neutral vesicles by macrophage cells[40]. Conversely, it was reported that positively charged liposomes interact more efficiently with rat peritoneal macrophages[41]. On the other hand, rat Kupffer cells exhibit more endocytosis for negatively charged liposomes[42]. Furthermore, it was reported that the binding of negatively charged liposomes containing PS, PA or PI to the J774A.1 cells and guinea pig peritoneal macrophage is significantly inhibited by various ligands of scavenger receptor, like dextran sulphate, fucoidin, acetyl-LDL and oxidized LDL. They suggested that acidic phospholipid containing liposomes are first recognized by scavenger receptor present on the surface of macrophages and subsequently enter by endocytosis[43]. Another study indicated that liposome binding at the J774 cell surface controlled the overall rate of liposome-cell interaction. The number of high affinity sites for charged liposomes was higher for J774 cells grown in monolayer than those grown in suspension. Surface associated J774 cells are a better representative models of resident macrophages fixed in the sinusoids of the RES[44]. Further the effect of liposome surface charge on liposome binding and endocytosis was examined in two different cell lines: a human ovarian cancer cell line (HeLa cells) and a murine macrophage cell line (J774 cells). HeLa cells were found to endocytose positively charged liposomes to a greater extent in comparison to neutral or negatively charged liposomes. In contrast, the extent of endocytosis of liposome by J774 cells was greater for both positively and negatively charged liposomes than neutral liposomes. Moreover the cellular uptake of positively charged liposomes was more as compared to negatively charged liposomes[45]. Baczynska et al., 2001 have shown that electrostatic charge on liposome surfaces enhances their association with colon cancer cells (CX-1.1) regardless of the charge sign. The interaction of positively charged liposomes containing 20 mol % cationic lipids reached to maximum whereas if liposomes containing only negative charged lipids (phosphatidylserine), the association of negatively charged liposomes was most efficient[46]. He et al., (2010) studied the effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. The nanoparticles with high surface charge and large particle size were phagocytized more efficiently by murine macrophage. *In vivo* biodistribution suggested more efficient tumor accumulation of particles with slight negative charges and size of 150[47]. It is reported that cellular binding and uptake of liposomal ricin containing positive charge was more as compared to neutral and negatively charged liposomes in CHO pro− cells[48]. Similarly, ricin was entrapped into variously charged liposomal formulations and the effect of surface charge on the cellular uptake of liposomes with human epidermoid carcinoma (KB) cells was investigated. It was observed that negatively charged liposomes interact more with KB cells and showed greater cellular uptake as compared to neutral and positively charged liposomes[49].

Effect of amount and length of polymer coating on cellular uptake

On the basis of reports discussed above, the liposome surface modified by type and quantity of charge can be used to enhance its association with cells but the major difficulty with such an approach is that electrostatic surface charge alone is a potent biological signal and causes rapid elimination *in vivo*[50;51]. It has been shown that the incorporation of 5-7.5 mole % of PEG-PE polymer on the surface of liposomes substantially reduce their uptake by RES and increase plasma circulation time [52;53]. However, there are a number of reports in literature suggesting that incorporation of polymer on the surface of liposomes inhibit adsorption of liposomes to the surface of cells and subsequent endocytosis[45;54;55] compromising the carrier's capability to deliver its cargo. However, introduction of surface charge onto the surface along with the polymer coating will enhance liposome association with cells. Zeisiget, al., determined the uptake of HPC-liposomes by cells with regard to size, time and steric stabilization. Both the uptake and internalization were clearly reduced for PEG-liposomes (5 mol% DSPE-PEG-2000) compared to plain liposomes[56]. However, the uptake and internalization of positively charged PEGylated as well as non-PEGylated was more a human ovarian carcinoma (HeLa) cells as compared to neutral and negatively charged liposomes[45]. The effect of polyvinyl alcohol (PVA-R) polymer coating on the surface of liposomes was investigated on the interaction with macrophage cells (J774 cells) under *in vitro* conditions[57]. The interaction of PVA-R-coated EPC: Chol (5:5) liposomes with J774 cells were higher (74.2 %) than that of non- or PVA-R-coated EPC: Chol (9:1) liposomes (32.6 %). They explained that this result would be due to the excess amount of cholesterol in a liposomal formulation of EPC: Chol (5:5) liposomes because the excess amount of cholesterol formulated to the liposomes might form clusters in the resultant liposomes.

So, it was important to achieve a homogeneous polymer coating to avoid the uptake of the PVA-R-coated liposomes by macrophage cells. They observed minimum binding of liposomes with cells when concentration of PVA-R was 2 mol% as compared to 1 and 0.5 mol %. Therefore, the lipid composition and PVA-R amount on the liposomal surface were important factors for controlling the interaction with macrophage cells. Present results suggested that introduction of a PVA-R layer on the liposomal surface could inhibit the liposome-cell interactions in the same manner as occurs with PEG-coated liposomes[57]. The combined effect of electrostatic charge along with the amount and length of polymer coating was investigated on liposome-cell interaction in colon carcinoma (CX 1.1) cells[58]. It was observed that liposome-colon cancer cell interaction is highly dependent on the surface charge as well as the amount and chain length of the polymer (PEG)[57;58]. Furthermore, it was suggested that the liposome-cancer cell interaction can be altered by proper adjustment of surface electrostatics and the density and chain length of PEG. Not only has the density but chain length of polymers also influenced the interaction of liposomes with cancer cells[59-61]. It was reported that the effect of polyethyleneglycol (PEG) chain length and anchor length on cell uptake of PEG-modified liposomes and suggested that the length of PEG chain was more important than the length of the anchor for cell uptake. Additionally, inclusion of PEG on the surface of liposomes did not prevented the uptake into the Ehrlich ascites carcinoma cells rather enhanced the cellular uptake of liposomes into these cells[59]. The effect of inclusion of PEG density and the chain length of polymer on cellular uptake of liposomes was also studied in human epidermoid carcinoma (KB) cells. It was observed that plant protein ricin encapsulating liposomes showed greater interaction and cellular uptake when 5 mole % PEG of chain length 2000 was present on their surface[60]. Similarly, monensin containing liposomes exhibit greater interaction with cancer cells and subsequent their uptake when the amount of PEG polymer on their surface was 5 mole % with 2000 length of polymer[61].

CONCLUSION

The central goal of cancer nanomedicine is to target specific or selective subpopulation of cells and/ or subcellular locations. The understanding the interaction of nanocarriers like liposomes with cancer cells can help in achieving the central goal of nanomedicine. Despite huge reports on liposome-cell interaction, it is difficult to make a general statement on liposomes-cell interactions, however, some general trends can be assumed from earlier studies like there is an optimal charge and size for efficient delivery of liposomes to cancer cells. The interaction and uptake of liposomes are not only governed by the surface properties of liposomes but the type of cancer cells and the biological environment greatly influence their interaction. Further research is desired on liposome-cell interactions to develop effective and efficient cancer cell targeting delivery systems.

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