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Review

Liposomal delivery systems for anti-cancer analogues of vitamin E

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ABSTRACT

Pro-apoptotic analogues of vitamin E (VE) exert selective anti-cancer effect on various animal cancer models. Neither suitable formulation of α-tocopheryl succinate (α-TOS), representative semi-synthetic VE analogue ester, nor suitable formulations of the other VE analogues for clinical application have been reported yet. The major factor limiting the use of VE analogues is their low solubility in aqueous solvents. Due to the hydrophobic character of VE analogues, liposomes are predetermined as suitable delivery system. Liposomal formulation prevents undesirable side effects of the drug, enhances the drug biocompatibility, and improves the drug therapeutic index. Liposomal formulations of VE analogues especially of α-TOS and α-tocopheryl ether linked acetic acid (α-TEA) have been developed. The anti-cancer effect of these liposomal VE analogues has been successfully demonstrated in pre-clinical models in vivo. Present achievements in: (i) preparation of liposomal formulations of VE analogues, (ii) physico-chemical characterization of these developed systems and (iii) testing of their biological activity such as induction of apoptosis and evaluation of anti-cancer effect are discussed in this review.

Contents

Abbreviations: ABC, ATP binding cassette; DCs, dendritic cells; DMSO, dimethylsulfoxide; DLPC, dilauroyl phosphatidylcholine; DOPE, dioleoyl phosphatidylethanolamine; EPC, egg phosphatidylcholine; EPR, enhanced permeability and retention; ETP, etoposide; FBS, fetal bovine serum; FDA, Food and Drug Administration; GFP, green fluorescent protein; GIT, gastro-intestinal tract; GTH, glutathione; HSPC, hydrogenated soy phosphatidylcholine; IC_{50}, the half inhibitory concentration; i.m, intramuscular; INF- , interferon-gamma; i.p, intraperitoneal; i.t, intratumoral; i.v, intravenous; mitoVES, mitochondrially-targeted vitamin E succinate; MLVs, multilamellar vesicles; MRP1, multidrug resistance protein 1; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PE-PEG, phosphatidylethanolamine-polyethylene glycol; PEG, polyethylene glycol; PL, phospholipid; PSVs, pH-sensitive vesicles; RES, reticulo-endothelial system; s.c, subcutaneous; SPC, soy phosphatidylcholine; SUVs, small unilamellar vesicles; α-TAM, α-tocopheryl maleamide; α-TEA, α-tocopheryl ether linked acetic acid; α-TOA, α-tocopheryl acetate; α-TOG, α-tocopheryl glucopyranoside; α-TOH, α-tocopherol; α-TOM, α-tocopheryl maleate; α-TOS, α-tocopheryl succinate; α-TPGS, α-tocopheryl polyethylene glycol succinate; TPP, triphenyl phosphonium; VE, vitamin E; VES, vitamin E succinate; VLDL, very low density lipoprotein.

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1. Introduction

Vitamin E (VE) is a generic term used for a lipid-soluble group of the related compounds of tocopherols and tocotrienols. Their molecules share common structure composed of chromanol head and phytyl tail. Owing to its character, VE tends to associate with hydrophobic domains of various structures like biomembranes and proteins. A major biological function of VE is to protect polyunsaturated lipids of membranes against oxidation [1]. It has been reported that products of phospholipid (PL) hydrolysis such as lysoPLs together with VE form complexes. The formed complexes tend to stabilize PL bilayers and prevent membrane disintegration by detergent-like actions of lysoPLs [2]. The isomers of biological importance are tocopherols of which α-tocopherol (α-TOH) is the most potent vitamin. α-Tocopheryl succinate (α-TOS) is a semi-synthetic prototype of α-TOH representing the most developed VE analogue. α-TOS is extensively studied as the model agent used in various biological and physico-chemical experiments.

Pro-apoptotic VE analogues were found to induce cell apoptosis and demonstrated anti-proliferative activity in vitro [3–5]. It has been reported that pro-apoptotic VE analogues exert selective toxicity towards the cancer cells with low toxicity to the non-cancer cells [6–9]. Recent studies documented the cytotoxic effects of α-TOS in various experimental models against broad spectrum of cancer including breast, lung, prostate and colon cancer as well as mesothelioma, neuroblastoma and melanoma [10–16]. Higher selectivity of α-TOS toxicity to various cancer cells in vitro and the more effective prevention of tumor growth prolonging survival in vivo contribute to attractive employment of α-TOS as novel type of anti-cancer agent.

It has been also reviewed that VE analogues could be applicable for the delivery of other anti-cancer drugs. α-Tocopheryl polyethylene glycol succinate (α-TPGS), α-TOS and α-TOH were used as solubilization excipients, prodrug conjugates or carriers for paclitaxel, topotecan, doxorubicin and docetaxel delivery [17].

2. Alpha-tocopheryl succinate and vitamin E analogues

The structural molecule of α-TOH and its analogues can be divided into several functionally different domains. Each domain is responsible for individual function of particular VE analogue [18] (Fig. 1).

2.1. Biological activity of alpha-tocopheryl succinate

The biological activity of α-TOS is encountered with pro-vitamin/vitamin effect. After entering the bloodstream, α-TOS is associated with lipoproteins and transported into tumor microvasculature [19]. In the tumor, α-TOS exerts pro-apoptotic activity resulting in tumor growth inhibition. Lipoproteins carrying α-TOS are also cleared during passage through the liver where α-TOS is hydrolyzed by competent esterases. The cleavage product, α-TOH, is partially excreted in bile and partially shuttled into nascent lipoproteins. The nascent lipoproteins enriched with α-TOH are then re-secreted into the bloodstream. The system with additional α-TOH promotes anti-inflammatory and anti-oxidant defenses [20,21].

The anti-oxidant activity of α-TOH is eliminated by esterification with succinic acid. The presence of succinate group endows α-TOS with apoptogenic activity. The lack or low activity of specific esterases essential for hydrolysis of α-TOS in cancer cells results in inhibition of cell proliferation. α-TOS induces the release and relocation of pro-apoptotic signals yielding mitochondrial destabilization and dysfunction leading to programmed cell death [22,23]. On the contrary, esterase activity was observed in non-cancer cells [24]. Agents bearing esteric bond are specific for cancer cells, while non-cancer cells become relatively intact. Over 60 compounds analogous to α-TOS have been synthesized. These analogues were tested for induction of apoptosis in various cancer cells to find the more efficient pro-apoptotic drugs. Some of the novel VE analogues exhibited IC_{50} in low micromolar range. The serious problem encountered when the apoptogenic activity was maximized by structure modification resulted in the loss of selectivity for cancer cells in vitro or cancer tissue in pre-clinical models [25]. For example, the highly apoptogenic α-tocopheryl oxalate was toxic to immuno-compromised mice and α-tocopheryl maleamide (α-TAM) was toxic to non-cancer cells in vitro [26,27].

2.1.1. Apoptogenic activity of alpha-tocopheryl succinate and other vitamin E analogues

It has been reported that α-TOS induces significant apoptotic activity in about 50 cancer cell lines [8]. For B16 murine melanoma, about 50% growth inhibition without any cell death for 9.4 μM of α-TOS was observed, while almost 100% lethality was caused by 18.8 μM of α-TOS [28]. Apoptogenic activity of free and vesiculated α-TOS was tested on murine Lewis lung 3LL cells. The IC_{50} of 34 and 56 μM was determined for vesiculated and free α-TOS, respectively. Cells exposed to vesiculated α-TOS underwent apoptosis earlier probably due to enhanced interaction of cancer cells with particles formed by α-TOS vesiculation [14]. α-Tocopheryl maleate ester (α-TOM) was found to exhibit far more efficient apoptogenic activity than its α-TOS counterpart in vitro [29]. A novel class of VE amide analogues with amide bond linking the functional domain to the chromanol head was synthesized. Owing to the non-hydrolysable amide bond, α-tocopheryl amides were more efficient in apoptosis induction than the corresponding α-tocopheryl esters [30]. For example, observed IC_{50} for Jurkat T lymphoma cells was 2 μM for α-TAM, while for α-TOM it was 10-fold higher [31]. In vitro cytotoxic effect of VE analogues on various cancer cells followed the order of α-TAM > α-TOM > α-TOS ≫ α-TOH. For human Meso-2 mesothelioma, human breast MCF-7 carcinoma and B16F10 murine melanoma, the corresponding IC_{50} were found to be 2, 5 and 13 μM for α-TAM, 22, 27 and 35 μM for α-TOM, and 43, 61 and 64 μM for α-TOS, respectively. Any cytotoxicity for the redox-active α-TOH was not observed [27,31]. Replacement of hydroxyl group by acetate group generates α-tocopheryl acetate (α-TOA) analogue. However, any apoptogenic activity for α-TOA was not observed as well [5]. α-Tocopheryl ether-linked acetic acid (α-TEA) represents synthetic VE analogue with non-hydrolysable acetic acid moiety attached to the chromanol head by ether linkage. Like α-TOS, α-TEA is capable to induce apoptosis in various human cancer including breast, cervical, ovarian, prostate, colon and lung cells. For ovarian cancer cells, the IC_{50} of 5–20 μM was determined [32]. Mitochondrially-targeted VE succinate (mitoVES) represents mitochondrially-targeted version of VES with cytotoxic activity enhancing the selectivity for cancer cells as well as the efficacy to reduce tumors in pre-clinical models. MitoVES was synthesized by its tagging with the delocalized cationic group triphenyl phosphonium (TPP), as pioneered for redox-active substances [33]. MitoVES was found 40-fold more apoptogenic efficient than α-TOS un-targeted. The corresponding IC_{50} of 0.5 and 20 μM in Jurkat T lymphoma cells was assessed for mitoVES and α-TOS, respectively [34].