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Drug-Based Reversal of Drug Resistance in Hepatocellular Carcinoma (HCC) Using TPGS

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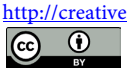

Abstract

Hepatocellular carcinoma (HCC) is a cancer with high incidence and mortality rates worldwide. In the various treatment methods for HCC, the lack of cancer cell specificity and the development of multidrug resistance (MDR) are two major obstacles in the treatment of HCC. P-glycoprotein (P-gp) is an ATP-dependent drug efflux pump that can reduce the accumulation of drugs in cells and make cancer cells acquire drug resistance. D-α-tocopheryl polyethylene glycol succinate (Vitamin E TPGS or TPGS) can inhibit the activity of ATP-dependent P-gp and serves as an effective excipient for overcoming tumor multidrug resistance (MDR). TPGS has been approved by the FDA as a safe adjuvant and is widely used in drug delivery systems. The biological and physicochemical properties of TPGS provide multiple advantages for its application in drug delivery, such as high biocompatibility, enhanced drug solubility, improved drug permeation, and selective antitumor activity. In recent years, more and more studies have found that using TPGS-modified nanomaterials to load chemotherapy drugs to treat tumors can effectively reverse the drug resistance of tumors, including HCC. This review summarizes and discusses the role of TPGS in reversing tumor drug resistance and the therapeutic effects of TPGS-based drugs on drug-resistant HCC.

Keywords

HCC, TPGS, MDR, P-gp

1. Introduction

With an annual incidence rate exceeding 660,000 cases, hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide and the third leading

cause of cancer-related deaths [1]. Over 80% of HCC patients are diagnosed at an advanced stage, where treatment options such as local ablation, surgical resection, or liver transplantation have poor outcomes [2]. Chemotherapy is an important cancer treatment strategy; however, liver cancer cells typically exhibit a poor response to systemic chemotherapy drugs [3].

Studies have shown that the low sensitivity of HCC patients to chemotherapy may be mediated by multidrug resistance (MDR), a phenomenon where cancer cells develop resistance to anticancer drugs [4] [5]. Numerous cellular and molecular changes may contribute to the development of the MDR phenotype, one of the most well-known mechanisms being the efflux pump based on the function of the ABC transporter protein P-gp, a 170-kDa plasma membrane glycoprotein encoded by the human MDR1 gene [6] [7]. Known to use ATP as an energy source, P-gp can promote the extrusion of a variety of cytotoxic drugs, including anthracyclines, vinca alkaloids, epipodophyllotoxins, and taxanes [8]. P-gp is overexpressed in many chemotherapy-resistant tumors, such as liver cancer, colorectal cancer, renal cancer, pancreatic cancer, and adrenal cancer, and is upregulated after disease progression following chemotherapy in many other cancers [7]. Moreover, HCC patients with high levels of P-gp protein detectable in tumor sections have shorter disease-free intervals and survival times [9] [10]. Therefore, the study of P-gp inhibitors is essential for improving the outcomes of chemotherapy in HCC.

TPGS1000 is the most commonly used form of TPGS in nanomedical applications. D-α-tocopheryl polyethylene glycol 1000 succinate (briefly referred to as TPGS or Vitamin E TPGS) is a water-soluble derivative of natural Vitamin E (VE), formed by the esterification of Vitamin E succinate with polyethylene glycol 1000. When the molecular weight (Mw) of PEG is 1000, the product is denoted as TPGS1000, or simply TPGS. If the Mw of PEG varies, the name should reflect the Mw, such as TPGS450 (Mw = 450) and TPGS2K (Mw = 2000). Variations in PEG are also associated with physicochemical/biological properties, including the critical micelle concentration (CMC), hydrophilic-lipophilic balance (HLB) value, P-gp inhibitory activity, and even circulation time after intravenous administration.

TPGS is a quintessential multifunctional material that has gained increasing attention in nanomedical applications in recent years. Benefits of TPGS explored in nanomedical science include: 1) Safety. TPGS is an excipient approved by the FDA and CFDA for medicinal use, with an oral LD50 in adult rats of over 7 g/kg. 2) Universality. As a non-ionic surfactant, TPGS can be applied to a variety of different drug delivery systems (DDSs), such as micelles, liposomes, and nanoparticles (NPs). 3) P-gp inhibitory effect. While many non-ionic surfactants (e.g. Pluronic and Tween) can inhibit P-gp activity, TPGS is reportedly one of the most effective. Due to its special properties, TPGS can be used as an oral absorption enhancer and a drug to overcome tumor multidrug resistance (MDR). 4) Tumor cell toxicity. Studies have shown that TPGS exhibits cytotoxicity to tumor cells,

potentially due to the production of reactive oxygen species (ROS) and mitochondria-related apoptosis [11]-[13].

2. P-gp Can Mediate Drug Resistance in Tumors

P-glycoprotein (P-gp), also known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette sub-family B member 1 (ABCB1), is an ATP-dependent drug efflux pump that is widely distributed and expressed in intestinal epithelium, hepatocytes, renal proximal tubular cells, adrenal glands, and capillary endothelial cells. By reducing drug accumulation within cells, P-gp can mediate the multidrug resistance phenotype of cancer cells. Many anticancer drugs, such as paclitaxel, etoposide, doxorubicin, and vincristine, are substrates for P-gp. P-gp can affect drug distribution and bioavailability, and limit drug passage through the blood-brain barrier. It also transports toxic metabolites and xenobiotics from cells into urine, bile, and the intestinal lumen [14]. In 1999, Dintaman and Silverman were the first to study the relationship between TPGS (D-alpha-tocopheryl polyethylene glycol succinate) and P-gp. They found that TPGS, at concentrations below 0.02 wt% of its critical micelle concentration (CMC), can act as an inhibitor of P-gp, suppressing the function of P-gp-mediated drug transport and multidrug resistance in tumor cells [15]-[17]. Other non-ionic surfactants, such as Tween 80, Pluronic, and Cremophor® EL, can also inhibit P-gp activity, but TPGS shows the most pronounced effect. Rhodamine 123, a P-gp-mediated transporter, exhibits concentration-dependent sensitivity to the following inhibitors: TPGS > Pluronic PE8100 > Cremophor EL > Pluronic PE6100. Moreover, these surfactants demonstrate transporter-specific interactions rather than non-specific membrane permeability [18]-[20].

3. TPGS Structure and Its Mechanism to Overcome Drug Resistance

Vitamin E D-α-tocopheryl poly (ethylene glycol) 1000 succinate (briefly referred to as Vitamin E TPGS or TPGS) is a water-soluble derivative of Vitamin E, formed by the esterification of D-α-tocopherol succinate (D-α-TOS) with polyethylene glycol 1000 (PEG1000) [12]. It is an amphiphilic agent that, due to its excellent hydrophilic-lipophilic balance (HLB) value, can be used as a superior solubilizer, emulsifier, permeation, and absorption enhancer for hydrophobic drugs [13]. TPGS can self-assemble into micelles in aqueous solutions and serve as a drug carrier to reduce particle size and increase the solubility and availability of poorly soluble drugs, thereby enhancing the therapeutic efficacy against multidrug-resistant cells.

Poor aqueous solubility and/or permeability remain key barriers to therapeutic drugs achieving maximum activity. TPGS can be used in drug delivery as a solubilizer, absorption and permeation enhancer, emulsifier, and surface stabilizer. It has been widely applied in the preparation of nanomedicines or other formulations for many poorly soluble or poorly permeable drugs, especially for class II

and IV drugs in the biopharmaceutics classification system (BCS) [12] [13]. Moreover, it has been reported that TPGS strongly enhances the secretion of chylomicrons at low concentrations and enhances intestinal lymphatic transport [21], which will further improve drug absorption capabilities. As a surfactant, TPGS demonstrates an excellent ability to increase drug absorption rates through different biological barriers. For instance, TPGS was used to prepare repaglinide nanocrystals, and compared with the free drug, its saturated solubility and oral bioavailability were increased by 25.7 and 15.0 times, respectively [22]. In the Bittner *et al.*'s chamber transport study, TPGS could enhance the permeation of drugs in colonic tissues [23]. Additionally, the impact of TPGS on the intestinal absorption of icariin II was observed in the Caco-2 monolayer model and the four-point rat intestinal perfusion model. In the Caco-2 monolayer model, the apparent permeability coefficient value of icariin II was increased, and the efflux rate was significantly reduced due to the action of TPGS. The four-point rat intestinal perfusion model study further showed a significant increase in the permeability of icariin II in the ileum and colon [24]. Similar results were also found in the Caco-2 monolayer model using Rhodamine 123 (Rh123) in the presence of TPGS [25]. Interestingly, TPGS can also act as a pore-forming agent in the manufacture of nanoparticles, with high drug encapsulation efficiency, small particle size, and rapid drug release [26]. Furthermore, TPGS can be used as an emulsifier or surface stabilizer in the preparation of drug formulations because its hydrophobic part can capture hydrophobic drugs, while the hydrophilic part can stabilize the formulation.

Furthermore, TPGS can overcome multidrug resistance (MDR) by inhibiting P-gp and modulating efflux pump activity [11] [27]. As a result, an increasing number of TPGS-based nano-delivery systems have garnered more attention and are being studied for reversing P-gp-mediated MDR.

Various TPGS-based formulations, such as tumor microenvironment-responsive nanoplatforms and therapeutic combination formulations, have been applied to overcome MDR. Jiang *et al.* [28] developed a novel pH-responsive hybrid drug delivery system by conjugating TPGS on the surface of laponite nanodiscs to overcome MDR. The prepared nanoparticles exhibited excellent colloidal stability, high encapsulation efficiency of doxorubicin (DOX), and a pH-responsive drug release profile. *In vivo* and *in vitro* results showed that DOX-loaded TPGS-modified laponite nanodiscs (LM-TPGS/DOX) had an excellent inhibitory effect on MCF-7/ADR tumors with minimal side effects. Wu *et al.* [29] prepared temoporfin-loaded RGD-nanoparticles using vitamin E succinate-grafted oligosaccharides and TPGS, combining chemotherapy and photodynamic therapy. These particles could easily target tumors rich in integrins, greatly enhancing therapeutic efficacy. Similarly, core-matched nano-assemblies were prepared for the targeted co-delivery of chemotherapeutic drugs and photosensitizers to treat drug-resistant cancers [30]. Poly(lactic acid)-D-α-tocopheryl polyethylene glycol 1000 succinate (PLA-b-TPGS), with its good biocompatibility, high loading capacity for chemotherapeutic drugs, high stability in bodily fluids, and P-gp inhibitory capability, was

developed as a matrix material for photochemical therapy. The targeting and penetration efficiency of the nano-assembly was improved by utilizing tumor vascular system-recognizing and tumor-penetrating peptide iNGR. Through the aforementioned strategies, the nano-assembly showed excellent therapeutic effects on drug-resistant tumor cells *in vitro* and *in vivo*. In addition, TPGS has good biocompatibility and is safe for living organisms. In the study by Li *et al.* [31], TPGS blank micelles exhibited no cytotoxicity to cancer cells. The cell viability of A549 and MDA-MB-231 cells was higher than that of drug-loaded carriers, proving that TPGS is a safe carrier material. In the study by Li *et al.* [32], H&E staining results showed significant differences in the histological morphology of tumors treated with Bcl-2 siRNA/DOX-TPGS-LPs compared to other groups. H&E staining of the heart indicated cardiotoxicity damage in animals of the free DOX group, which was not observed in animals treated with Bcl-2 siRNA/Dox-TPGS-LPs. H&E staining results of other tissues (such as kidneys, lungs, spleen, and liver) showed no significant differences among various formulations. This indicates that TPGS is a safe carrier with low toxicity.

4. TPGS Reverses P-gp-Mediated MDR

Drug resistance in cancer cells limits the therapeutic effectiveness of chemotherapy. As an ATP-dependent membrane transporter, P-gp has long been one of the main causes of MDR (multidrug resistance). It can pump out P-gp substrate drugs, reducing the intracellular accumulation of drugs, thereby diminishing the cytotoxic effects of chemotherapy drugs in the treatment of resistant cancers. For the past few decades, there has been ongoing research into formulations that combine P-gp substrate drugs with inhibitors or polymers that possess P-gp inhibitory capabilities to overcome MDR [33]. Rh123, a P-gp substrate, is commonly used as a model drug to study the intracellular retention of drugs in MDR tumor cells. Compared with free Rh123, TPGS can significantly increase the intracellular accumulation of Rh123 in resistant tumor cells, which has been confirmed by flow cytometry and confocal microscopy analysis [34]. TPGS appears to effectively inhibit the activity of P-gp, thereby overcoming MDR.

Since the efflux transporter P-gp is ATP-dependent, the consumption of ATP plays a very important role in overcoming MDR. The MDR reversal effect of TPGS is mainly attributed to its dual function: inhibiting mitochondrial respiratory complex II to short-circuit ATP supply and inhibiting substrate-induced P-gp ATPase activity to block ATP utilization [35]-[38].

Mitochondrial respiratory complex II, also known as succinate dehydrogenase, plays an important role in mitochondrial electron transport, which is an essential component of the citric acid cycle and the mitochondrial respiratory chain [39]. TPGS can bind to mitochondrial respiratory complex II, inducing subsequent mitochondrial dysfunction and leading to a significant consumption of intracellular energy [37] [40]. TPGS can accumulate in the mitochondria and inhibit the activity of complex II, disrupting electron transfer and activating calcium channels,

resulting in calcium overload and the ensuing mitochondrial dysfunction. The characteristics of mitochondrial dysfunction include dissipation of mitochondrial membrane potential, reduced ATP levels, and increased production of reactive oxygen species (ROS) [41]. Moreover, TPGS's mitochondrial targeting ability may accelerate mitochondrial dysfunction [35] [42]. Inhibition of substrate-induced P-gp ATPase activity is another mechanism by which TPGS reduces drug efflux [38]. ATPase activity can be stimulated by the binding of substrates to the transmembrane domains of P-gp [43]. Subsequently, ATP is converted into adenosine diphosphate (ADP), which supplies the energy for drug efflux. Unlike the classic P-gp inhibitor verapamil, TPGS is not a substrate of P-gp and does not show competitive inhibition by substrate binding. The inhibition mechanism of ATPase may involve spatial blocking of binding sites and/or allosteric modulation of P-gp.

5. Drugs Based on TPGS for Anti-HCC Drug Delivery

TPGS demonstrates promising potential in anti-HCC drug delivery due to its multifaceted properties. Not only does TPGS exhibit selective cytotoxicity against cancer cells and induce apoptosis, but it also acts as a potent P-gp inhibitor, effectively reversing multidrug resistance (MDR). Furthermore, TPGS enhances the therapeutic efficacy of chemotherapeutic agents through various unique mechanisms.

Several studies highlight the benefits of TPGS in HCC treatment. For instance, Chen *et al.* [44] assessed the cytotoxicity of TPGS on human liver cancer cell lines (HepG2, Hep3B, Huh7, and Bel7402) *in vitro* and evaluated the inhibition of xenograft tumor progression by TPGS through direct delivery or administration routes *in vivo*. The results showed that TPGS treatment dose-dependently inhibited the proliferation of HCC cells by arresting the cell cycle at the G0/G1 phase and inducing apoptosis. Furthermore, due to its amphiphilic structure and enhanced permeability and retention effect, TPGS significantly inhibited the migration and invasion of HCC cells, with cytotoxicity, indicating that TPGS could serve as a promising drug for preventing liver cancer metastasis.

Beyond its inherent properties, TPGS serves as a valuable component in nanocarrier drug delivery systems. Tsend-Ayush *et al.* [45] designed and synthesized a nano-drug loaded with ETO (Etoposide, an anticancer chemotherapeutic drug). The nano-carrier used TPGS-LA (TPGS-LA conjugate) as the active targeting part of galactosylated nanoparticles, targeting the binding site of ASGPR on the surface of tumor cells, effectively inhibiting P-gp-mediated ETO efflux. Subsequently, it was internalized into the cells through receptor-mediated endocytosis (II), and degraded into bioactive TPGS-LA and ETO (III) in the cytoplasm of tumor cells, leading to cancer cell death by inhibiting topoisomerase in the nucleus. Tao *et al.* developed a BA-C60(OH)n-GBP-TPGS-NPs delivery system that can effectively inhibit the deterioration of HCC. This nano-carrier is modified with TPGS and GBP (ginkgolic acid), both of which can increase the accumulation

of chemotherapeutic drugs in tumor cells. It is loaded with Betulinic acid (BA) and Fullerene (C60(OH)n), where C60(OH)n can effectively inhibit the growth and metastasis of transplantable malignant tumors, and BA can induce apoptosis of tumor cells [46].

Li *et al.* [33] further demonstrated the versatility of TPGS by developing cationic liposomes coated with TPGS and carrying Bcl-2 siRNA and Doxorubicin (Dox). This Bcl-2 siRNA/Dox-TPGS-LPs system enhanced Dox retention within cells and improved internalization, ultimately augmenting the anticancer effect of Dox in HCC-MDR.

Du *et al.* [47] engineered a multi-polysaccharide-modified nanoparticle drug delivery system (NO-DOX@PDA-TPGS-Gal) with multimodal synergistic therapy. This system targeted the asialoglycoprotein receptor (ASGPR) on hepatocytes and utilized the photothermal properties of PDA to enhance drug release and trigger NO generation, resulting in significant cytotoxic effects and MDR reversal [47].

Finally, Anwer *et al.* used the thin-film hydration method to develop liposomes coated with TPGS on the surface, which are loaded with VEGF (vascular endothelial growth factor) inhibitor analogs to exert antitumor effects [48]. Importantly, this new type of TPGS-modified liposome can be orally targeted to HCC tissue in the body and release drugs to exert antitumor effects [48].

These examples collectively illustrate the extensive use of TPGS in modifying nanocarriers and enhancing the efficacy of traditional chemotherapeutic drugs, particularly in reversing P-gp-mediated drug resistance in HCC.

6. Discussion

The advantages of TPGS in drug delivery are as follows: 1) TPGS has been approved by the FDA as a safe pharmaceutical excipient with high biocompatibility. 2) TPGS can act as an effective P-gp inhibitor to overcome MDR. 3) TPGS itself can act as an anticancer agent with selective toxicity to tumor cells. 4) TPGS can be easily combined with nanotechnology to develop nano-drugs, increasing the solubility and stability of therapeutic agents, improving therapeutic efficiency, and reducing side effects. We discussed many examples of TPGS-based nano-drugs, including TPGS-based prodrugs, NO donors, and polymers, which utilize the characteristics of TPGS in drug delivery, especially its effective role in overcoming MDR. These examples clearly illustrate the potential and promising applications of TPGS in overcoming MDR, improving oral bioavailability, and promoting drug penetration.

P-gp inhibition is widely recognized as the main mechanism by which TPGS overcomes MDR. Although the mechanism of inhibiting the mitochondrial-dependent P-gp pump has been well characterized, there are no clues about the exact mechanism by which TPGS inhibits ATPase. It is currently unclear whether ATPase inhibition is achieved by spatial blocking in the form of substrate binding, and whether it is achieved by direct interaction of TPGS with the nucleotide-binding

domain of P-gp or by indirect effects on P-gp function through allosteric modulation [36]. In addition, TPGS may not be able to cope with the drug resistance caused by tumor heterogeneity during tumor progression. It has been reported that TPGS can prevent tumor invasion and metastasis, and the potential mechanism is not yet clear. More comprehensive research is still needed on the application of TPGS in tumor metastasis. Moreover, since TPGS can be used as an adjuvant for the development of cancer immunotherapy vaccines, the impact of TPGS on the immune system needs to be studied.

7. Future Outlook

For TPGS-based formulations, achieving precise stimulus-responsive characteristics and deep penetration limitations in the tumor microenvironment of nano-formulations remain barriers to the widespread application of these nano-drugs. More effective strategies should be adopted to improve targeted delivery efficiency, achieve controlled drug release, and increase the penetration of therapeutic drugs in tumors. Clinical translation is the ultimate goal of nano-drug development, and attention should be paid to simple structure and multifunctionality. Leveraging the biocompatibility and multifunctionality of TPGS, TPGS-based nano-drugs may have great prospects in pharmacy due to their "molecular economy" characteristics. However, the preparation of TPGS nano-drugs is still at the laboratory scale, and the development of new nano-drugs is relatively slow, which hinders the successful clinical translation of TPGS-based nano-drugs.

8. Conclusion

In summary, TPGS-modified drugs, in combination with other therapies, show good application prospects in the treatment of drug-resistant HCC.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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