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REVIEW

Triphenylphosphine-Based Mitochondrial Targeting Nanocarriers: Advancing Cancer Therapy

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Abstract: Numerous chemotherapeutic drugs are commercially available for cancer treatment; however, their efficacy is often compromised by diminishing therapeutic effectiveness and unpredictable adverse effects. The lack of specific targeting limits their optimal therapeutic potential. Mitochondria are the primary sites of cellular energy production and play a critical role in cell survival and death. Furthermore, numerous studies have found an apparent association between mitochondrial metabolism and carcinogenesis and progression. Therefore, significant attention has been directed toward nanocarriers specifically designed for mitochondrial delivery, aiming to enhance the precision of chemotherapeutic agent transport to these critical organelles. Among these, triphenylphosphonium has emerged as a prominent mitochondrial targeting agent due to its superior targeting capabilities. This approach not only reduces the required drug dosage but also minimizes adverse effects on healthy tissues. This review provides a concise analysis of nanotechnology's contributions to cancer therapy, emphasizing its potential for targeting at both cellular and sub-cellular levels. Additionally, it delves into mitochondrial targeting, with a particular focus on nanocarriers engineered for efficient mitochondrial drug delivery. Moreover, it focuses on strategies employed by researchers to introduce TPP in nanocarrier systems for mitochondrial delivery and concludes by addressing challenges associated with TPP including hemolytic activity and how researchers mitigate this issue.

Keywords: nanomedicine, cancer, mitochondrial targeting, triphenylphosphine, nanoparticles

Introduction

Cancer stands as the primary contributor to mortality, causing the loss of over six million lives annually.[1,2] The significant percentages of cancer in men exist in the urinary bladder, rectum, colon, bronchus, lung, prostate, and blood whereas the highest cancer prevalence in women occurs in the breast, thyroid, uterine corpus, rectum, colon, bronchus, lung, and blood.[3,4] In general, breast and prostate cancer constitute a major portion of women and men.[5] Despite substantial investments in personnel and resources to investigate novel cancer treatments, existing clinical procedures have encountered restricted success due to the intricacy, variety, and heterogeneity inherent in the field of oncology.[6] The primary challenge arises from the lack of specificity in chemotherapeutic drugs, a factor that frequently limits their clinical effectiveness and gives rise to severe side effects.[2,7]

Recent progress in the field of nanocarriers enables their passive targeting and accumulation in tumor tissues via the enhanced permeability and retention (EPR) effect.[2,8–10] However, studies have shown that a very low percentage of introduced nanocarriers ultimately gather in solid tumor locations, primarily due to various complexities such as nonspecific adherence, off-target effects, and premature release.[11,12] Thus, the development of organelle-specific targeting nanocarriers has surfaced as a current focal point within contemporary targeted drug delivery research.[13–15]

The majority of eukaryotic cells possess mitochondria, crucial cellular structures that control programmed cell death and function as a vital energy reservoir for cellular metabolism.[16] Mitochondria initiate the cellular apoptosis pathway through diverse mechanisms, such as the release of cytochrome C, the translocation of apoptotic proteins, and the

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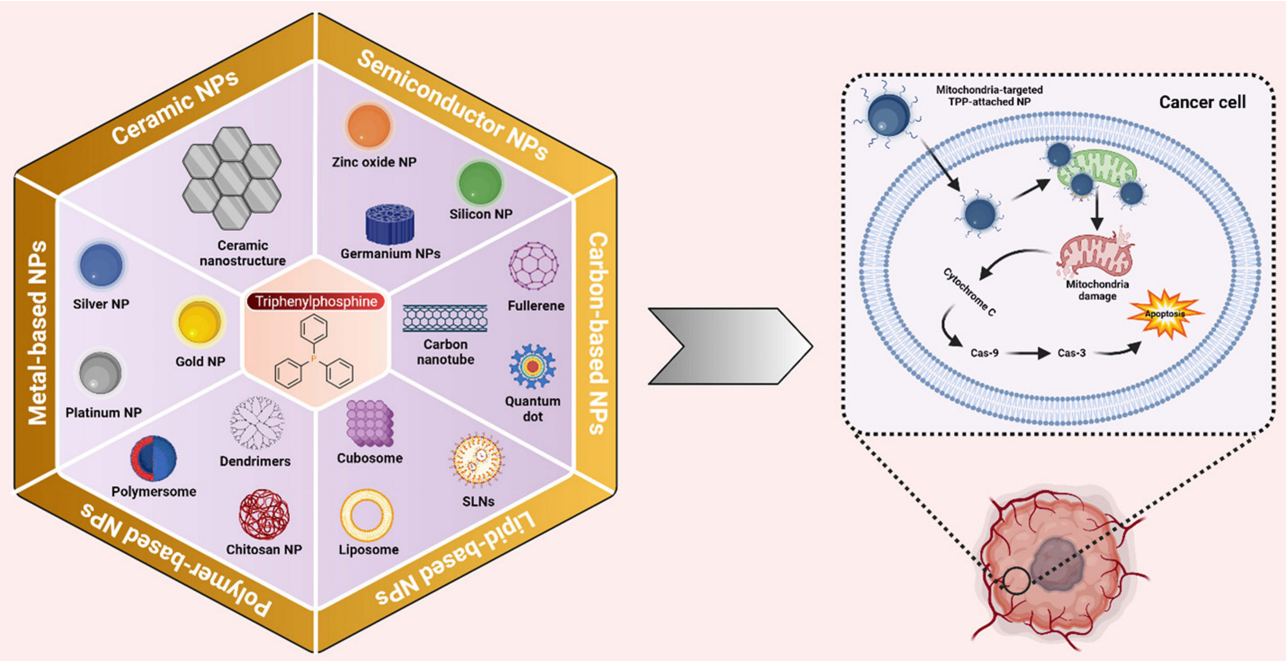
Graphical Abstract



reduction of mitochondrial membrane potential (MMP).[17] Alterations in mitochondrial structure not only disrupt the development, metabolism, and proliferation of tumors but also serve as the catalyst for inducing apoptosis in tumor cells. Nevertheless, the direct targeting of mitochondria using traditional nanocarriers proves to be difficult, majorly due to the complex structure of mitochondria and various other barriers in the tumor environment.[18,19] The frequently employed targeting moieties for mitochondria encompass cationic peptides, triphenylphosphonium (TPP), pyridinium, dequalinium (DQA), and so on.[20] However, several studies have unveiled the potential of TPP-conjugated nanocarriers as a robust mitochondria-targeted system for cancer treatment (Figure 1).[21,22]

TPP can easily accumulate in mitochondria after successfully passing through the phospholipid bilayer.[22,24] Alkylated TPP cations were initially utilized to investigate the process of linking the oxidative phosphorylation (OXPHOS) with MMP and subsequently, they were used to measure the MMP and it was also found that pharmacophores, antioxidants, and probes were also transported to mitochondria by TPP cations.[22] In this context, the present review briefly discusses the role of nanotechnology, the importance of targeted delivery, and the scope of cellular and sub-cellular targeting in cancer treatment. Furthermore, it meticulously delves into the technical aspects of mitochondrial targeting and TPP-conjugated mitochondrial targeting nanocarriers in cancer therapy.

Brief Note on Role of Nanotechnology in Cancer Therapy

Nanoparticles (NPs) have gained popularity in recent years because of their potential to solve issues with chemotherapy medications like stability, solubility, immunogenicity, blood circulation half-time, and diffusivity as well as to improve the targeted delivery of drugs to cancer cells during cancer treatment.[25–30] Additionally, NPs offer many benefits for diagnosis and treatment, including easy surface functionalization, a large surface area for carrying therapeutic and imaging payloads, the ability to solubilize hydrophobic drugs, drugs can be protected from biodegradation, and control over size and shape.[31] NPs can be developed into a variety of sha pes, including one-dimensional (1D) structures like nanowires and nanotubes, two-dimensional (2D) structures like single-layered graphene and other molecular sheets, three-dimensional (3D) structures like liposomes, micelles, and hydrogels, and zero-dimensional (0D) structures like quantum dots.[32] Nanomedicine is fueled by the synergy between NPs and their special adjustable qualities (shape, optical properties, size, surface properties, etc) in contrast to traditional

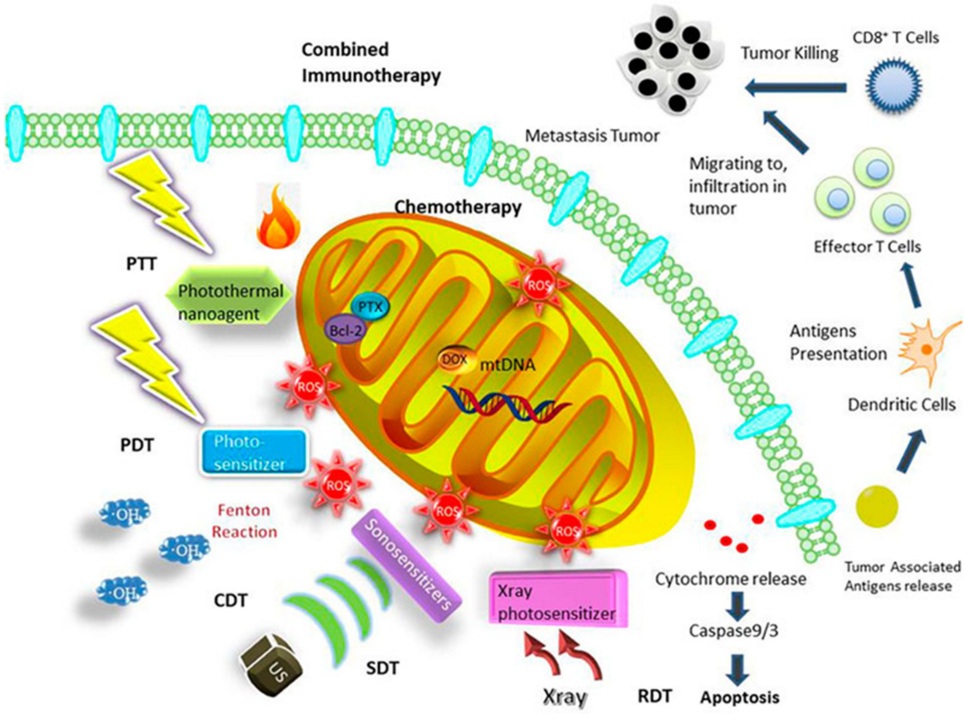


Figure 1 Mitochondria-targeted cancer therapies enabled by nanoplatforms including chemotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), chemodynamic therapy (CDT), sonodynamic therapy (SDT), radiodynamic therapy (RDT), and combined immunotherapy, reproduced from Gao Y, Tong H, Li J, et al. Mitochondria-targeted nanomedicine for enhanced efficacy of cancer therapy. Front Bioeng Biotechnol. 2021;9:720508. Copyright © 2021 Gao, Tong, Li, Li, Huang, Shi and Xia.,[23] licensed under CC BY 4.0.

pharmaceutical ingredients.[33] Cancers exhibit irregular cell proliferation, which is facilitated through the newly formed blood vessel networks with large gaps between the endothelial cells, making them highly permeable.[34,35] NPs are engineered to circulate in the bloodstream for extended periods and to accumulate in tumors, either through the EPR effect or as a result of the affinity between ligands attached to NPs and tumor receptors.[36] This is because tumor tissues have different anatomical and physiological features than healthy tissues.[37] Among the most crucial and promising elements of cancer treatment is drug distribution. Controlled, prolonged, and predictable release of medicines or biomolecules, external/internal stimulus-responsive site-targeted distribution, and the detection of certain biomolecules that can offer therapeutic feedback are some of the ways that NPs are used in drug delivery systems. Optimal cellular and subcellular delivery can be achieved by accurately controlling drug delivery platforms through changes in their size, shape, surface chemistry, and chemical composition. Doxorubicin-loaded liposomes were approved 25 years ago to treat Kaposi's sarcoma, and they have also been approved recently to treat ovarian and breast cancer.[38] The FDA has so far approved over 20 distinct NPs for use in therapeutic settings.[39] The therapeutic advantages of nanotechnology for the focused administration of anticancer agents, nanomedicine may help with unresolved clinical issues, lessen adverse effects, and increase a drug's bioavailability. Some of the NPs include liposomes, dendrimers, nanostructured lipid carriers, polymer NPs, micelles, gold NPs, mesoporous silica NPs, metal-organic frameworks, and so on.

Among cellular delivery, subcellular delivery gained the attention of researchers all over the world to increase the therapeutic activity of active moiety.[40] Mitochondria are essential to the production of energy which leads to the survival of eukaryotic cells. Mitochondria are essential modulators of the intrinsic apoptotic process by controlling the movement of pro-apoptotic proteins from the mitochondrial intermembrane space to the cytosol. Moreover, mitochondria are involved in several non-apoptotic cell death processes, most notably controlled necrosis, or necroptosis.[41,42] As per Otto Warburg, the mitochondria of cancerous cells were dysfunctional,[43] and due to its key role in cancerous cell progression, its target serves as a promising approach to cancer treatment. For the successful elimination of cancerous cells, therapeutic agents linked with mitochondrial targeting agents should be effectively delivered to mitochondria[44] and for that several approaches were designed by researchers for targeting the mitochondria either by small molecules, bioactive molecules, sequences, nanomaterials or mitochondrial biomarkers.

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Importance of Targeted Drug Delivery in Cancer Therapy

The goal of targeted drug delivery is to deliver drugs to their intended site of action in high concentrations, regardless of how they are administered.[45–50] Therefore, to improve the effectiveness of advanced chemotherapy, either a drug delivery system that can specifically deliver drugs to their intended site of action is needed, or a new target site should be identified.[51–54] Targeting drug delivery is preferred above traditional drug delivery systems for four reasons: unsatisfied pharmacotherapeutic (High dose, Adverse effects, Low patient compliance), pharmaceutical (Low solubility, Low stability), pharmacokinetic (Low Half-life, High Volume of Distribution), and pharmacodynamics (Low specificity, Low therapeutic index) performance.[55–59] Optimizing drug delivery strategies to target specific areas not only improves therapeutic efficacy but also reduces toxicity associated with large doses and a small therapeutic index.[12,55,60–64] Targeting is necessary to address the limits and inherent shortcomings of traditional drug delivery systems.[65–70] Furthermore, targeted drug delivery offers promising benefits such as simplified drug-administration processes, reduced drug amount which lowers therapeutic costs, and the ability to quickly boost drug concentration in target compartments without affecting non-target compartments.[71–75] In general, targeting was achieved in two ways, active targeting uses specific ligands that bind to specific receptors on cancer cells to deliver drugs more effectively.[76–78] The surface of nanocarriers can be made to specifically target cancer cells by attaching targeting ligands to them.[79] Chemotherapeutic drugs must be actively targeted by utilizing molecular ligands to increase their cellular uptake and therapeutic efficacy.[80,81] The EPR effect is caused by the leaky nature of tumor blood vessels and the poor drainage of fluids from tumors, which leads to the formation of new blood vessels in a rapid and uncontrolled manner.[58,82] So, passive targeting utilized this feature of the tumor microenvironment via nanoscale drug carriers to target tumor cells.[83] It was also observed that free drug diffuses non-specifically but due to the unique size of nanocarriers, they can penetrate the cancer cell mass with ease through the leaky vasculature via the EPR effect.[84–86]

Scope of Cellular and Sub-Cellular Targeting in Cancer Therapy

During the pathological transition of a cell from normal to diseased, several changes occur at the macromolecular and morphological levels. These changes include modifications to the cell's shape and enzymatic profile, alterations to the immediate microenvironment (such as changes in redox properties and pH), and the expression of new molecules at various cellular locations.[87,88] Overexpressed markers often require specialized or unique methods for active targeting.[64,89,90] The majority of active cellular targeting strategies rely on interactions between ligands and receptors, enzymes and substrates, or antibodies and antigens.[91–93] Some cancer cells exhibit an excess of specific surface markers, including somatostatin receptors (SSTRs), vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor 2 (HER2), folate receptor protein, myeloid antigen (CD13), cell adhesion glycoprotein (CD44), programmed death ligand-1 (CD274), myeloid antigen (CD13), and αvβ3 integrin.[94,95] The utilization of specific molecules that bind to overexpressed cellular markers has facilitated more effective drug targeting of cancer cells.[73,96,97] Cellular targeting is effective at killing cells by delivering the drug solely to the interior of the cell. In contrast, subcellular targeting directs drugs to be released at the subcellular location or targeted organelle (eg, mitochondria, nucleus, endoplasmic reticulum, lysosome, Golgi body).[98,99] This has spurred increased research efforts to develop more sophisticated nano-drug designs capable of directing internalized nano-drug complexes to their intracellular target sites.

Mitochondrial Targeting in Cancer Therapy

The energy-producing organelles known as mitochondria are essential for maintaining metabolic and cellular life functions.[100–102] They play a key role in vital physiological functions such as calcium ion control, ATP synthesis, electron transport, reactive oxygen species (ROS) formation, and the start of cell death.[103–105] The ATP synthase enzyme is responsible for producing ATP on the inner membrane of mitochondria. Complexes I, III, and IV pump protons from the mitochondrial matrix into the intermembrane gap during the synthesis of ATP.[106] The usual mitochondrial membrane potential (about 140 mV) is maintained by pumping out protons from the inner membrane using electrons supplied from reduced coenzymes via the ETC. Figure 2 demonstrates how complexes I, III, and IV are involved in ROS production and calcium ion transport, which in turn opens the mitochondrial transition pores and causes cell death. Normal cells depend on mitochondria for a variety of vital functions, such as energy provision, oxidative phosphorylation, ATP synthesis, reactive oxygen species (ROS)

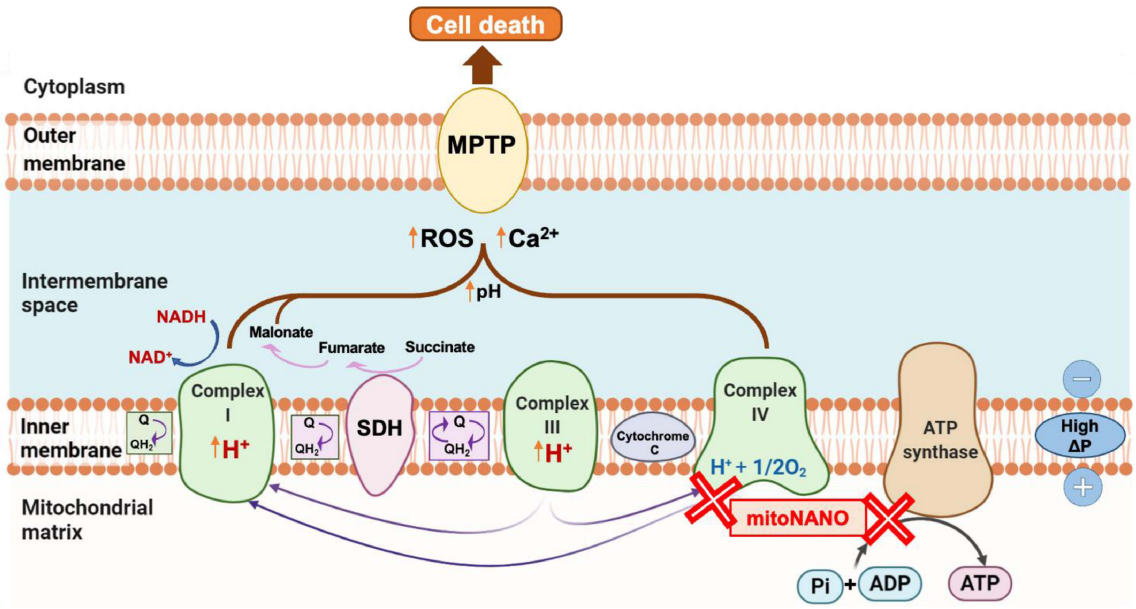

Figure 2 Schematic illustrating mitochondria as a primary driver and therapeutic target of cancer. The figure depicts the chaotic development of cell death events. The respiratory activities of complexes I, III, and IV cause proton translocation across the inner mitochondrial membrane, resulting in the production of ATP from ADP and Pi. Quinone oxidoreductase reduces coenzyme quinone (**Q**) after oxidizing the mitochondrial electron transport chain. Reduced Q produces cytochrome C (by complex III), which catalyzes the reduction of molecular oxygen to water (via complex IV). The formation of reactive oxygen species (ROS) by complex I, together with the accumulation of calcium ions, increases the opening of the mitochondrial permeability transition pore (MPTP), leading to programmed cell death, reproduced from Tabish TA, Hamblin MR. Mitochondria-targeted nanoparticles (mitoNANO): an emerging therapeutic shortcut for cancer. Biomater Biosyst. 2021;3:100023.[115] copyright 2021, Elsevier.

generation, cell cycle regulation, cell differentiation, and programmed cell death. Moreover, mitochondria play a key role in a variety of metabolic processes that affect cell fate, such as the citric acid cycle, gluconeogenesis, steroid production, and beta-oxidation of fatty acids.[107–109] Traditional methods that target the mitochondria of cancer cells typically try to harm or impair the function of the mitochondria.[110] The growth and survival of cancer cells are significantly influenced by mitochondria, which makes them a desirable target for cancer treatment.[111,112] Numerous investigations have demonstrated that the development of cancer cells is significantly influenced by mitochondrial building blocks.[111] ATP, ROS, and metabolites for the synthesis of macromolecules are all primarily produced by mitochondria.[112] Targeting mitochondria has therefore been shown to be a successful cancer treatment tactic. Numerous authorized medications that provide therapeutic benefits by triggering mechanisms of apoptosis by directly affecting mitochondria emphasize the significance of mitochondria in pharmacology as targets.[113,114]

Additionally, it has been observed that the mitochondria in cancerous cells exhibit structural and functional differences compared to those in normal cells (Figure 3).[116,117] The transmembrane potential (MTP), also known as the MMP, is established across the inner mitochondrial membrane through the negative charges carried by the mitochondrial membrane.[118] The variance in membrane potential between mitochondria and the plasma membrane is the basis for achieving mitochondrial targeting. Generally, the plasma membrane potential is 3- to 5-fold lower than the MMP.[22,119] Furthermore, it has been noted in several cases that the MMP of cancerous cells is higher than that of healthy cells.[120] This biological distinction has served as a basis for the development of mitochondrial targeting compounds, allowing drugs to be preferentially concentrated within the mitochondria of cancerous cells. The capacity to generate highly reactive oxygen species (ROS) and adenosine triphosphate (ATP) through aerobic glycolysis is significantly greater in the mitochondria of cancerous cells than in normal cell mitochondria. This distinction provides an alternative approach for targeting cancer cell mitochondria over normal cell mitochondria.[121] By increasing the mitochondrial accumulation of anticancer drugs, drug resistance may be addressed, and therapeutic effectiveness could be enhanced.[122] There are two well-known methods for delivering drugs to the mitochondria: the targeting ligand is directly conjugated to drugs, or the targeting ligand is attached to nanocarriers.[123] Small compounds that target the mitochondria include rhodamine 123, rhodamine 19, TPP, guanidine salt, dequalinium, tetrachlorotetraethyl benzimidazole carbocyanine iodine, and N-methylpyridineiodide Tetrachloro-1,1′,3,3′-tetraethyl-imidacarbocyanine (5,5′,6,6′) compounds (JC-1).[124–126] These

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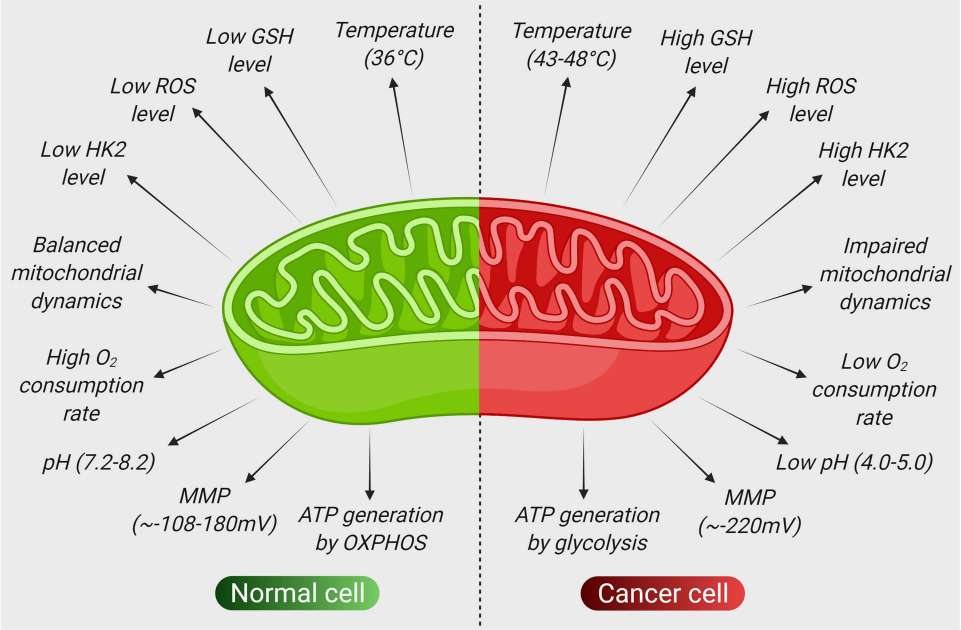

Figure 3 Important distinguishing features of mitochondria of cancer cells from mitochondria of normal cells, reproduced from Mani S, Swargiary G, Tyagi S, et al. Nanotherapeutic approaches to target mitochondria in cancer. Life Sci. 2021;281:119773.,[128] copyright 2021, Elsevier.

compounds can target mitochondria due to their lipid solubility, enabling them to enter both the cell and the mitochondria. The positive charge of these particles allows them to be drawn into the mitochondria under the influence of MMP.[127]

Mitochondrial Targeting Agents

Mitochondria targeting agents are chemicals under the special category that have a positive charge and interact with mitochondria. They can be small peptides, molecules, or metal complexes that can accumulate in mitochondria without the need for additional targeting systems. High transmembrane potential and protein import mechanism of mitochondria are the primary reasons through which mitochondria targeting agents target the mitochondria.[129–132] Some of the majorly used mitochondrial targeting agents are discussed below.

Dequalinium (DQA)

DQA, or dequalinium, is a lipophilic substance first reported by Weiss et al in 1987. It is made up of two cationic quinoline groups joined by an alkyl chain of ten carbons. It is a cationic, delocalized lipophilic chemical that targets mitochondria. According to Weiss et al, this substance prevented several cancer cell lines from proliferating in vitro and in vivo. According to studies, DQA can cause the generation of ROS by preventing ATP synthesis, which in turn causes cytochrome c expression and a decrease in mitochondrial membrane potential. Ultimately, this mechanism triggers the endogenous apoptosis pathway that is dependent on caspase-3 and 9.[133] As a result, DQA's cytotoxicity restricts its use in numerous biological investigations, including cell biology research and fluorescent probes. But because of its cytotoxicity, DQA is also a great drug delivery ligand for anti-cancer treatment. To transport Dox to mitochondria specifically, studies have coupled DQA chloride with Dox (DQA-Dox). The drug compound DQA-Dox demonstrated substantial cytotoxicity to cancer cells and was mostly observed to accumulate in the mitochondria of MCF-7/ADR cells. Despite this, the low endosome DQA capacity for escape and transfection efficiency restrict its application in delivery that targets the mitochondria.[134]

Pyridinium

Another type of often used, positively charged, lipophilic mitochondrial targeting group is pyridinium salts. Pyridine salts are frequently modified with ethylenic bonds to create big conjugated systems, in contrast to TPP, which is modified with long alkyl chain links. For the optical detection of mitochondria, the conjugated systems and electron-withdrawing

properties of pyridine salt may produce or control molecular luminescence. However, pyridine salts' lipophilicity prevents them from entering tissues in vivo. Cheng's team created a human serum albumin-facilitated pyridine salt complex to address this problem. This complex was able to target mitochondria in tumor tissue and cause tumor cell death, leading to a breakthrough in the in vivo use of pyridinium salt.[135]

Mitochondria Targeting Cationic Peptides

Another method for making mitochondrial targeting easier is a peptide. Peptide-based delivery scaffolds have appealing properties such as high absorption in cells and in vivo, tunability, biocompatibility, and ease of production. Peptide advantages make them extremely versatile for transporting a wide range of chemicals. Peptides that target mitochondria are typically lipophilic and cationic charged, enabling them to interact positively with hydrophobic mitochondrial membranes and take advantage of the negative membrane potential of mitochondria. Peptides did not induce mitochondrial depolarization at millimole concentrations like TPP and pyridinium salt. Additionally, due to their biocompatibility, peptides were better suited for treating illnesses and delivering medications to living organisms.[136]

Mitochondria Penetrating Peptides

Peptides based on cell penetrating peptide (CPP) that effectively penetrate mitochondrial double membranes are known as mitochondrial penetrating peptides (MPP). The highly negative charge of mitochondrial membranes makes it simple for positively charged peptides to enter mitochondria. However, in contrast to CPP, MPP interacts more with inner mitochondrial membrane (IMM) than plasma membrane because of more hydrophobicity exhibited by IMM. Horton et al created mitochondrial penetrating peptide (MPP) with high cellular uptake and mitochondrial matrix targeting capacity for the first time by striking a balance between cationic amino acids (arginine and lysine) and hydrophobic amino acids (cyclohexylalanine).[137] It was shown that MPP might alter the intracellular distribution of medications, causing them to mostly collect in mitochondria rather than the nucleus, when covalently conjugated with anticancer medications such as cisplatin or DOX. Additionally, research using fluorescence quenching and PCR-based assays verified that MPP transport medications to the mitochondrial matrix to harm mtDNA.[138–140] Moreover, the mitochondrial accumulation was 11.6 times greater in the connected MPP to HPMA copolymer-DOX conjugation.[141] Overall, the research suggested that MPP may be used to preferentially deliver nanosystems and chemotherapeutics to mitochondria.

Triphenylphosphine

The history of triphenylphosphine targeted medication delivery dates back to 1995 when Liberman et al used alkylated TPP cations as mitochondrial probes to evaluate oxidative stress in mitochondria. Following that, Smith's team fabricated Mito-vite E in 1999, an antioxidant that efficiently protected mitochondria from oxidative stress. Other noteworthy advances included MitoQ10 (combines coenzyme Q10 with TPP) which demonstrated selective oxidative stress protection.[142–145] In 2002, Fantin et al developed F16-TPP to target mitochondria and fluoresced after aggregating in mitochondria and killing multiple-tumor cells.

Therefore, the discovery of TPP is considered one of the most successful examples of using lipophilic cations to target mitochondria.[24] TPP, a delocalized lipophilic cation, is typically employed for mitochondrial targeting because it accumulates on the negatively charged mitochondrial membrane[146,147] (Figure 4). The three lipophilic phenyl groups surround the positively charged phosphorus atom that makes up TPP, enhancing its combination.[148] This structure also allows for the addition of numerous functional molecules and the formation of a positive charge that is delocalized, enabling it to pass through the non-polar membrane of the mitochondria.[149] TPP increases the accumulation of drugs in the mitochondrial matrix by 100–500 times by reducing the activation energy during the MMP process. Additionally, TPP leads to the generation of harmful ROS and the release of apoptosis activators, ultimately resulting in mitochondria-mediated apoptotic cell death.[150–152] Drugs modified with lipophilic cations, such as TPP, can effectively accumulate in mitochondria because they can penetrate the phospholipid membrane of mitochondria due to their lipophilicity. This lipophilicity is attributed to the phenyl group and the delocalization of positive charge on the phosphorus atom.[153] Consequently, the mitochondrial targeting vector TPP group is frequently incorporated into anticancer medications to reduce their toxicity.[22,154] Many bioactive molecules have been conjugated with TPP to facilitate their mitochondrial

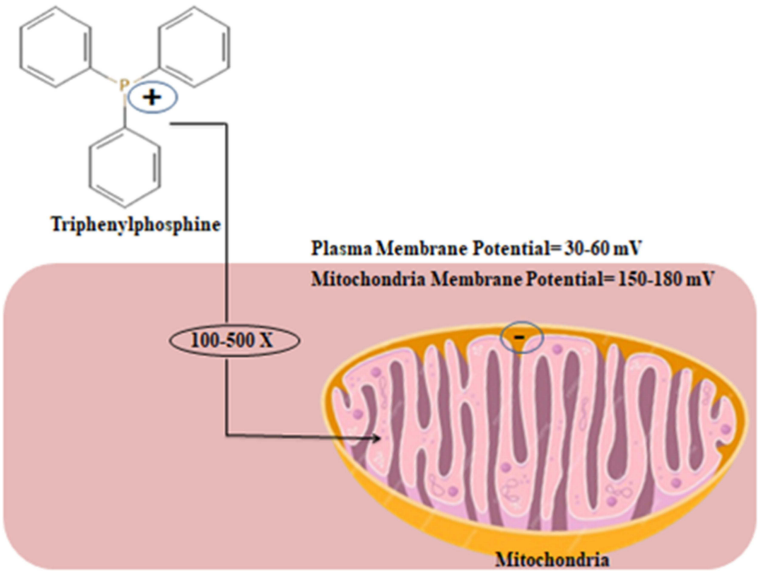

Figure 4 TPP conjugated substances are uptaken by cells via plasma and mitochondria membrane potentials. Created in BioRender. Gowda b.h., J. (2025) https://BioRender.com/ qxll1ii.

targeting. For instance, when doxorubicin (DOX) was chemically linked to TPP, it demonstrated a strong ability to target mitochondria. This led to the induction of apoptosis, or programmed cell death, in tumor cells through the mitochondrial pathway. The combination proved to be more effective in damaging mitochondria compared to using DOX alone.[149] Combining TPP with nanoformulations can also enhance mitochondrial targeting. For instance, liposomes loaded with paclitaxel (PTX) and modified with the lipophilic cation TPP can effectively target mitochondria in cancer cells[155] (Table 1). Apart from the advantages, the main disadvantage associated with TPP due to its strong positive is hemolysis. This problem was overcome by the researchers after utilizing strategies like stimuli-responsive nanocarriers which expose TPP only at the desired location. For example, TPP-DOX was specifically released only in the tumor micro-environment via pH-responsive BSA-based nanocarrier due to which premature interaction of TPP with normal cells was

Table 1 Investigations on TPP-Based Mitochondrial Targeting Nanocarriers for Cancer Therapy

Nanocarrier	Therapeutic Agent/s	Cell Line	Animal Model	Inference	Ref.
Polymer dots	Paclitaxel	HeLa, PC-3, CHO-K1	–	PTX release is controlled in cancerous cells and minimizes its undesired release in normal cells.	[157]
Carbon nanodots	Camptothecin	HeLa, A549, HepG2, 4T1, MCF-7	Mice	Higher cytotoxicity was achieved.	[158]
Liposome	Paclitaxel	4T1	Mice	Strong anti-tumor activity and considerable mitochondrial targeting were achieved.	[155]
TPP-TS-HUA based	Lapatinib	MDA-MB -231	Mice	In vivo targeting efficiency, accumulation in tumor, and anticancer activities of NPs were increased.	[159]
Lipid hybrid NPs	IR 780 and Zinc copper oxide	HT-29 and A549	Mice	Significant anti-tumor efficacy was achieved.	[160]
Photosensitizer based NPs	Pyropheophorbide a (PPa) and Diethyl maleate (DEM)	MDA-MB -231	–	Significant ROS levels were generated which leads to enhanced cell apoptosis.	[161]

(*Continued*)

Table 1 (Continued).

Nanocarrier	Therapeutic Agent/s	Cell Line	Animal Model	Inference	Ref.
Folate-cholesteryl albumin NPs.	Pheophorbide-a	HeLa	Mice	A good cellular uptake and low mitochondrial membrane potential was achieved which ultimately leads to better accumulation of drug within mitochondria.	[162]
Extracellular vesicles based nanoensitizers	Piperlonguime	MCF-7	Mice	ROS generation levels, cellular uptake, and aqueous stability of formulation were greatly enhanced by EVs.	[163]
pH-responsive NPs	Doxorubicin	MCF-7	Mice	Mitochondria of tumor cells were targeted; drug resistance cells were killed more efficiently and more OH produced by the formulation improves anti-cancer activity of formulation.	[164]
Albumin NPs	Paclitaxel	MDA-MB -435, MCF-7	–	Significant apoptotic activity was achieved	[165]
Targeted core-shell -based NPs.	Doxorubicin	MCF-7	Mice	Enhanced cellular and sub-cellular targeting levels by NPs.	[156]
NPs with positive core and negative outer layer.	Celastrol	4T1	Mice	Good cellular uptake, rapidly escaped from lysosomes and better localization within mitochondria were shown by formulation and ultimately it exerts good anti-tumor activity.	[166]
Liposomes	Glycyrrhetinic acid and Doxorubicin	HepG2	Mice	Good tumor targeting, Considerable mitochondrial damage was observed by formulated NPs.	[167]

inhibited. Similarly, chitosan nanoparticle coated by HA enables its active uptake through CD44 receptors and this coat masks the positive charge of TPP and is released in acidic tumor microenvironment.[156] Moreover, another approach was done by Zhang et al in which they embedded TPP in the lipidic bilayer of PEGylated liposomes which gives stealth behavior in the bloodstream and shows mitochondrial targeting after internalization. These strategies overcome the limitations associated with positive TPP charge which ensures safety with significant therapeutic efficacy.

Based on literature, it can be inferred that TPP is superior over DQA, pyridinium, and cationic peptides in terms of mitochondrial targeting. Despite the luminescent property of pyridinium salts, it suffers from low tumor tissue penetration due to its excessive lipophilicity. While DQA has a limitation like poor transfection efficiency and low endosomal escape. However, TPP offers significant accumulation in mitochondria due to its optimal ratio of delocalized positive charge and lipophilicity. Moreover, enzymatic degradation is the major concern associated with cationic peptides in the biological environment unlike TPP that is chemically stable, and deeply penetrates mitochondria across various cells. These properties make TPP an efficient and consistent approach for focused mitochondrial delivery.

Evaluation Methods of TPP Targeting

Here, we discussed the methods used to evaluate the mitochondrial targeting ability by TPP which is further elaborated in the next section. One of the widely used techniques is confocal laser scanning microscopy in which mitochondria specialized dyes like MitoTracker Red or Green were used which allows the researchers to visualize the accumulation of TPP-functionalized cargo or nanoparticle within subcellular organelle mitochondria. Another technique is flow cytometry which can quantitatively assess the degree of cellular and subcellular uptake of therapeutic agent or nanocarrier via fluorescence intensity. For assessment of mitochondrial uptake, researchers first performed subcellular fractionation via High-Performance Liquid Chromatography to isolate mitochondria and then analyzed the accumulation of therapeutic cargo or nanoparticle within it. Another approach is the decrement of mitochondrial membrane potential that leads to the disruption of mitochondria which implies effective mitochondrial targeting and for that confirmation stainings like Rhodamine 123 or JC-1 are employed by the researchers. For example,

after colocalized MitoTracker with TD@MB, mitochondrial delivery of DOX was validated,[164] and in another research, fluorescence intensity indicates the substantial uptake of PTX-TPP loaded HSA-Apt nanoparticle in mitochondria.[165]

Triphenylphosphine-Based Mitochondrial Targeting Nanocarriers in Cancer Therapy

TPP can be introduced into the nanoparticles either by physically or chemically on the surface of nanoparticle or it can be conjugated chemically with the therapeutic agent and then load into the nanoparticle (Table 2). This review comprehensively explores both the approaches.

Nanoparticle Surface Modification with TPP

Polymer dots (PDs) used as nanocarriers have several advantages, such as biocompatibility and high hydrophilicity. Therefore, they can be employed to address the issue of drug hydrophobicity by increasing the solubility of drugs once they are loaded into PDs.[169,170] Due to the varying levels of ROS and glutathione (GSH), diselenide bonds can selectively target cancer cells and release chemotherapeutic drugs only in a cancerous environment. This prevents the release of chemotherapeutic drugs in normal cells, thereby reducing the side effects of cancer treatment.[171] By utilizing diselenide bonds, researchers have

Table 2 Investigation the Physicochemical Properties and TPP Incorporation Strategies of Nanoparticles

Nanocarrier	TPP Incorporation Approach	Bond Type	Particle Size	Zeta Potential	Release Behaviour	Ref.
Polymer dots	TPP attached chemically to the surface of polymer dot through NHS/EDC chemistry	Amide Bond	230.1nm	NA	GSH/ROS responsive release	[157]
Carbon nanodots	TPP attached chemically to the surface of carbon nano-dots	Disulfide Bond	152.72 nm	2.14mV	GSH responsive release	[158]
Lipid hybrid NPs	TPP attached chemically to the surface of lipid hybrid nanoparticle through NHS/EDC chemistry	Amide Bond	128.7 ± 3.2 nm	13.1 ± 3.2 mV	Stimuli responsive release through laser irradiation	[160]
Photosensitizer based NPs	TPP attached to photosensitizers via chemical conjugation	Thioketal bond	NA	NA	Stimuli responsive release through laser irradiation	[161]
Folate-cholesteryl albumin NPs.	TPP conjugates with PheoA through NHS/EDC chemistry	Amide bond	161.4 ± 14.3 nm	−18.7 ± 0.7 mV	pH responsive release	[162]
Extracellular vesicles based nanoensitizers	TPP conjugates with Ce6 through NHS/EDC chemistry	Amide bond	149.5 ± 3.0 nm	−22.8 ± 1.3 mV	Ultrasound triggered release	[163]
pH-responsive NPs	TPP conjugates with NHS/EDC chemistry.	Amide Bond	1oo nm	−12mV	pH responsive release	[164]
Albumin NPs	TPP conjugates with paclitaxel through DCC/NHS chemistry	Amide bond	139 ± 5nm	−14.1 ± 0.8mV	pH responsive release	[165]
Targeted core-shell -based NPs.	TPP conjugates with Doxorubicin through DCC/NHS chemistry	Amide Bond	NA	NA	pH responsive release	[156]
Liposome	Liposomes surface functionalized by TPP through PEG	Amide Bond	164.8 ± 45.1	1.66 ± 5.5 mV	Tumor microenvironment sensitive release	[168]
TPP-TS-HUA based	TPP attached to nanoparticle by EDC/NHS chemistry	Amide Bond	207 nm	−24.2 mV	pH responsive release	[159]

synthesized redox-responsive PDs, allowing for controlled drug release in response to redox stimuli at targeted sites.[172,173] In this lane, Kim and teammates formulated ROS and GSH-responsive PDs as a nanocarrier with TPP for mitochondrial targeting to control the release of PTX (PDs-TPP-PTX) in malignant cells as demonstrated in (Figure 5). MTT assay was done by using HeLa and PC-3 (cancerous cells) and CHO-K1 (normal cells) and the results revealed that on increasing the concentrations of PDs-TPP all three cell lines showed high cell viability which confirms that PDs-TPP is not able to kill cancer cells. When the concentration of (PDs-TPP-PTX) was increased, cell viability in HeLa and PC-3 cells decreased significantly. However, cell viability in CHO-K1 cells remained relatively high even at high concentrations of (PDs-TPP-PTX). These findings demonstrated that this approach was capable of controlling the release of PTX in cancer cells while minimizing undesired release in normal cells. A cellular uptake study showed that both HeLa and PC-3 cells exhibited bright fluorescence after 3 h of PDs-TPP uptake, which became even brighter after 6 h. In contrast, CHO-K1 cells showed low fluorescence intensity even after 6 h of uptake. It was concluded that PDs-TPP occurred more frequently in cancer cells because of the cleavage of diselenide bonds in higher levels of ROS and GSH.[157]

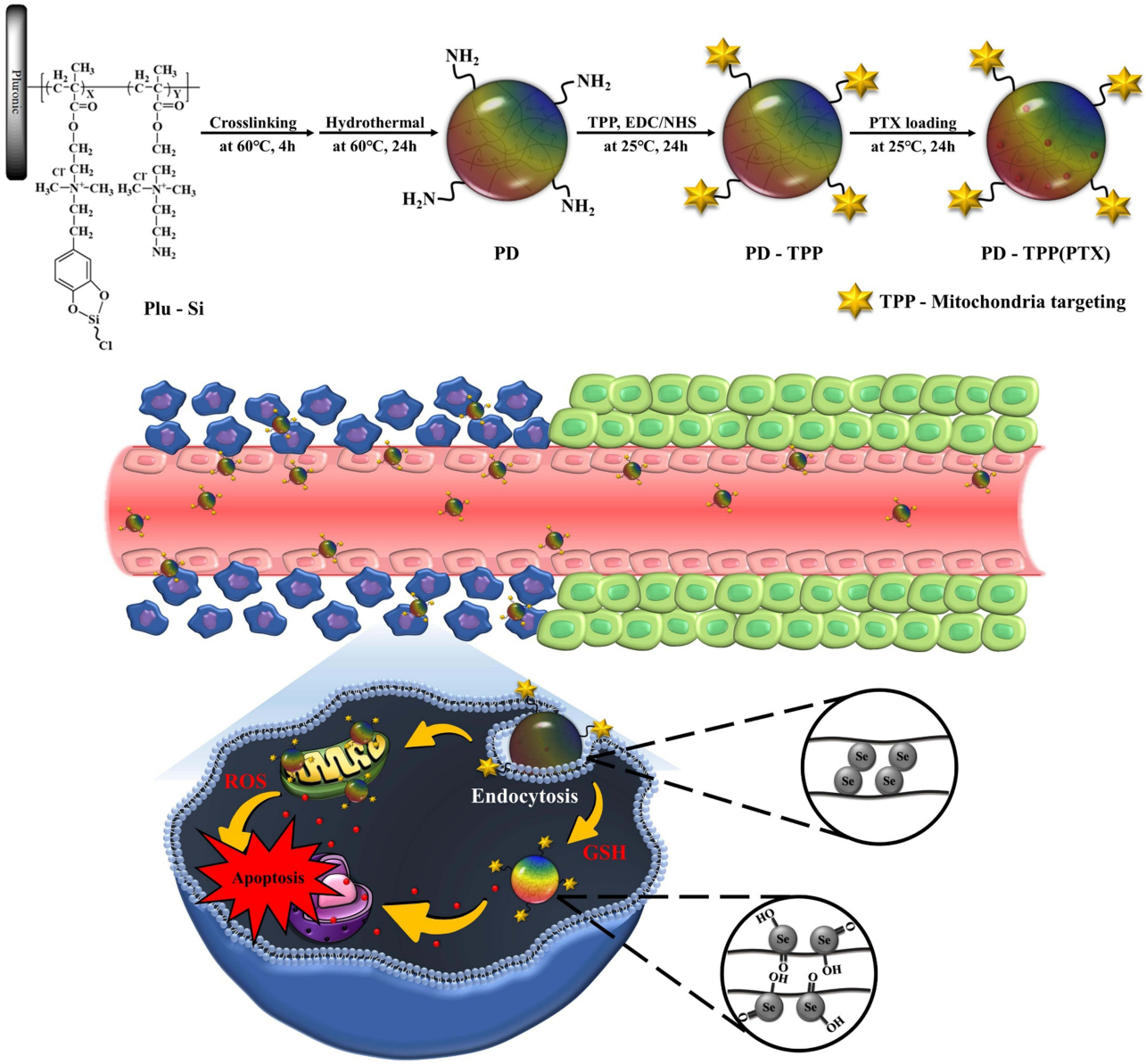

Figure 5 PDs-TPP (PTX) synthesis, the mechanism of selective PTX release, and mitochondrial targeting in cancer cells are shown schematically. Image reproduced from Kim SG, Robby AI, Lee BC, Lee G, Park SY. Mitochondria-targeted ROS- and GSH-responsive diselenide-crosslinked polymer dots for programmable paclitaxel release. J Ind Eng Chem. 2021;99:98–106. Copyright (2021), with permission from Elsevier.[157]

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A recent study conducted by Gong et al developed a nanoscale drug delivery system (DDS) targeting mitochondria and responsive to GSH stimuli. The DDS is based on a compound called TPP, which incorporates a disulfide linker ("S-S"), and fluorescent carbon nanodots (CDs). The DDS can deliver the anticancer medication camptothecin (CPTN) to mitochondria. After evaluating cytotoxicity studies on HeLa, HepG2, A549, MCF-7, and 4T1 cells it was found that TPP-CDs-S-CPTN possessed remarkable in vitro antineoplastic activity. On comparing CDs-S-CPTN and TPP-CDs-S-CPTN, the latter possessed higher cytotoxicity which makes TPP-CDs-S-CPTN a good therapeutic nano drug delivery system. This is because TPP-CDs-S-CPTN released a sufficient amount of CPTN by the breakage of disulfide linkage after being administered into cancerous cells. Moreover, prominent cytotoxicity was induced in normal LO2 cells by naked drug CPTN, whereas much lower cytotoxicity was induced in normal LO2 cells with the same drug concentration by TPP-CDs-C-CPTN, TPP-CDs-S-CPTN, and CDs-S-CPTN. This is because TPP-CDs-S-CPTN and CDs-S-CPTN released a sufficient amount of CPTN in cancerous cells rather than healthy cells. After all, cancerous cells have higher levels of intracellular GSH than normal cells and at last, it was also found that cytotoxicity in healthy as well as cancerous cells was not shown by CDs and TPP-CDs, which indicates that CDs are a good drug carrier. To assess the biological toxicity organ indices, spleen coefficient, body weight, and tissue slices were analyzed in mice 28 days after injection of TPP-CDs-S-CPTN, TPP-CDs-C-CPTN, CDs-S-CPTN, TPP-CDs-S and normal saline in the tail by intravenous injection for five times. Observed results indicate that the developed formulation has no potential biotoxicity and is a good candidate for mitochondrial-targeted drug delivery.[158]

A study conducted by Biswas et al developed a novel approach using polyethylene glycol-phosphatidylethanolamine (PEG-PEA) conjugated with TPP (TPP-PEG-PEA) and subsequently incorporated it into the liposomal lipid bilayer for the delivery of PTX. Mitochondrial targeting was investigated by Rhodamine-PE-tagged liposomes and MTG-stained mitochondria. It was found that TPP-PEG-PEA modified liposomes (TPP-PEG-PEA-L) have significantly more Rhodamine-PE fluorescence colocalization within the mitochondria than plain liposomes. A cytotoxicity study was done on 4T1 cells and it was found (TPP-PEG-PEA-L-PTX) significantly reduced the viability of cell than plain liposomal PTX. Similar results were obtained after evaluating the efficacy of anti-tumor that TPP-PEG-PEA-L-PTX induced a much more inhibitory growth than plain liposomal PTX.[155]

TPP bromide, hyaluronic acid-d-α-tocopherol succinate-(4-carboxymethyl) (TPP-TS-HUA) NPs designed by Lee et al were employed for the administration of lapatinib (LAP) in the management of triple-negative breast cancer (TNBC). Designed NPs were examined using a mouse model with MDA-MB-231 tumors for determining its tumor targeting capability which demonstrated that Cy5.5-HUA-TS-TPP/LAP NPs exhibited higher fluorescence signal than Cy5.5-HUA-TS/LAP NPs in the image obtained through ex-vivo scanning of excised tumor. The possible reason could be that HUA-TS-TPP/LAP NPs appear to have smaller particle size and unimodal size distribution over HUA-TS/LAP NPs which contribute to the enhancing the accumulation of NPs in the tumor. The results from the cellular uptake study which was done on MDA-MB-231 cells and determined by fluorescence detector Cy5.5 found that the fluorescence intensity on an average of Cy5.5-TPP-TS-HUA/LAP is greater than Cy5.5-TS-HUA/LAP NPs. The possible reason could be the presence of TPP on the exterior facade of TS-HUA/LAP NPs which seems to enhance the efficiency of cellular accumulation of TPP-TS-HUA/LAP NPs over TS-HA/LAP NPs. The effectiveness of LAP NPs in combating tumors was evaluated using an MDA-MB-231 tumor xenograft mouse model. After H&E staining of tissue removed from a tumor, it was found that HUA-TS-TPP/LAP NPs induced a higher degree of apoptosis within a significant portion of the tumor mass compared to HUA-TS/LAP NPs. The possible reason could be a combination of factors, including the passive targeting strategy of the EPR effect, the active targeting approach involving interactions with HUA-CD44 receptors, the influence of TPP and TS on mitochondrial targeting and disruption, and the pharmacological effects of LAP.[159]

Photodynamic therapy (PDT) uses a photosensitizer (PS) molecule that is activated by near-infrared (NIR) light to generate ROS which ultimately damages mitochondria, leading to cell death.[174,175] IR780 is a lipophilic dye that can generate oxygen when exposed to NIR laser light and it also preferentially accumulates in tumors, making it a potential therapeutic agent for cancer. Photothermal therapy (PTT) converts light radiation directly into heat energy that can kill cells, even without the need for oxygen. This makes it a promising new treatment for cancer and other diseases.[176,177] In this context, Ruttala et al, after combining PTT and PDT, developed a robust nano-platform system consisting of the TPP moiety for the mitochondrial targeting of cancerous cells. They developed a new type of NP that is made up of a polymer lipid hybrid core, a zinc-copper oxide NP shell, and TPP molecules (TPP-Z-I-PNPs) as demonstrated in (Figure 6). Flow cytometry study showed that TPP-Z-I-PNPs notably uptake by HT-29 and A549 cells but TPP-Z-I-PNPs showed good

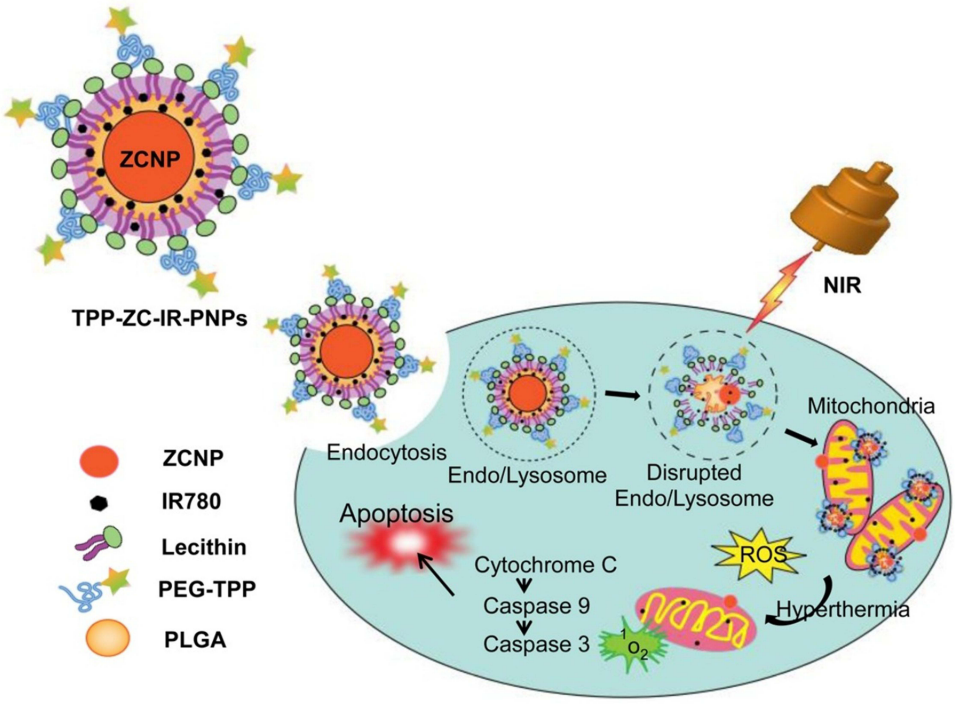

Figure 6 TPP-conjugated-ZnCuO NPs (ZNP) and IR780-loaded polymer-lipid hybrid NPs (TPP-Z-I-PNPs), which target mitochondria, are shown schematically. Image reproduced from Ruttala HB, Ramasamy T, Ruttala RRT, et al. Mitochondria-targeting multi-metallic ZnCuO nanoparticles and IR780 for efficient photodynamic and photothermal cancer treatments. J Mater Sci Technol. 2021;86:139–150, Copyright (2021), with permission from Elsevier.[160]

uptake than Z-I-PNPs. This is because TPP-conjugated NP systems have good interaction with the cell membrane as it is negatively charged. In determining the mitochondrial targeting ability of TPP-loaded nanosystems, it was found that malignant cells' mitochondria have a high concentration of nanosystems. Phototherapy of TPP-Z-I-PNPs was evaluated after evaluating the photothermal effect of zinc copper oxide NPs and the photodynamic effect of IR780 and they were determined after exposure to NIR laser. The analysis demonstrates that after 5 min of NIR irradiation, the temperature of zinc copper oxide NPs increased from 25° C to 56.8° C, and similarly after a short exposure of NIR IR780 temperature increased to 54.9° C. There is also a temperature that rises rapidly to 61.8° C by TPP-Z-I-PNPs due to the photodynamic and photothermal nature of IR780 and zinc-copper oxide NPs. It was concluded that the death of cells happened solely in the region that was irradiated, whereas cells beyond the laser region continued alive. An HT-29-bearing xenograft model was used to assess anticancer effectiveness in vivo by using ZNP (+NIR), ZNP (-NIR), Z-I-PNPs, TPP-Z-I-PNPs (+NIR), and TPP-Z-I-PNPs (-NIR) and it was found that maximum tumor regression showed by TPP-ZC-PNPs (+NIR) because of the synergistic potential of PTT and PDT.[160]

TPP-Conjugated Therapeutics

Through conjugation of the PS pyropheophorbide-a (PPa) with the mitochondrial targeting group TPP via a biodegradable ROS-responsive thioketal linkage, Huang et al developed and synthesized a PS (TPP-TKl-PPa). TPP-TKl-PPa can self-assemble into NPs because of its amphiphilic nature. These NPs can then further incorporate GSH-depleting agents (DEM) to create co-administration nanoplatforms for highly efficacious PDT. To investigate the TPP-modified nanomaterials may target mitochondria or not MitoTracker Green and Hoechst 33342 were used to stain mitochondria and cell nuclei. The results indicate that MDA-MB-231 cells treated with TPP-TKl-PPa/DEM NPs and TPP-TKl-PPa NPs showed abundant colocalization yellow fluorescent signals which indicates that preferably targeting mitochondria was achieved by using TPP. After being treated with various samples, the ability of MDA-MB-231 breast cancer cells to produce intracellular ROS was assessed by measuring the DCF fluorescence intensity of the DCFH-DA fluorescent probe. It was found that in MDA-MB-231 cells (control), PPa-treated, and DEM-treated cells negligible green

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fluorescence was observed which indicates that PPa or DEM alone might not have a therapeutic effect without PDT whereas green fluorescence was observed in TPP-TKl-PPa/DEM NPs and TPP-TKl-PPa NPs which indicates that under the exposure of light irradiation, a considerable amount of ROS was produced. A study on MDA-MB-231 cells treated with various samples both with and without light irradiation was conducted to ascertain cell apoptosis and findings suggest that apoptosis was negligible in the case of without light irradiation whereas for 2 min with light irradiation, the highest (94.4%) apoptosis rate was observed in case of TPP-TKl-PPa/DEM NPs. This is because of the presence of PPa and DEM which exhibited greater phototoxicity due to oxidative stress and PDT working together.[161]

Another interesting investigation by Battogtokh and teammates used PDT for the development of a mitochondrial-targeted PS. They used pheophorbide-a (PheA) as a porphyrin-derivative PS and carboxybutyl TPP for mitochondrial targeting, both are conjugated via carbodiimide linkage and then further TPP-PheA compound was added to folate-cholesteryl albumin (FA-cho-BSA) NPs to improve biocompatibility. TPP-PheA@FA-cho-BSA NP and TPP-PheA showed stronger fluorescence intensity than free PheA and TPP-PheA@cho-BSA NPs in cellular uptake study and further this red and green fluorescence overlapped, and turned into yellow which indicates that TPP-PheA after passed through the cells, localized on the mitochondria. After performing ROS quantity and mitochondrial membrane disruption, it was found that on Hela cells TPP-PheA@cho-BSA produced 1.5, TPP- PheA@FA-cho-BSA produced 2.7 and TPP-PheA produced 3.6 folds more than that of PheA. On determining mitochondrial membrane disruption, it was found that PheA-treated cells and control cells showed red fluorescence signals but TPP-PheA and TPP-PheA@FA-cho-BSA NP showed green fluorescence. Based on fluorescence, it was concluded that PheA-treated cells and control cells have greater MMP whereas, low MMP was seen in TPP-PheA@FA-cho-BSA NP and TPP-PheA-treated cells. In vitro phototoxicity of TPP-PheA@FA-cho-BSA NP and TPP-PheA was performed against HeLa cells and it was found that both of them are significantly much more than free PheA and PheA@FA-chol-BSA. This is because of the presence of TPP with mitochondrial localization. In vivo imaging and biodistribution study was done with the help of fluorescence microscopy sections of frozen tumor and it was found that low fluorescence intensity from PheA after intravenously administered PheA@FA-cho-BSA whereas red fluorescence signals of PheA obtained from TPP-PheA@FA-chol-BSA which indicates greater intracellular uptake of TPP-PheA. Antitumor efficacy in vivo was determined by calculating the therapeutic effectiveness from the tumor mass in formulation-injected mice and control mice on day 14 and it was found that TPP-PheA@FA-chol-BSA NP showed the highest tumor Inhibition (82.9%), PheA@FA-chol-BSA-NP group showed 45% tumor inhibition value and lastly, PheA treated showed only 30% tumor inhibition value.[162]

In a non-invasive procedure called sonodynamic therapy (SDT), fatal ROS are created using ultrasound (US) and sonosensitizers.[178,179] It has many advantages such as good therapeutic accuracy, deeper tissue penetration, and minimal skin damage.[180,181] A study conducted by Cao et al used SDT to treat breast cancer. They developed extracellular vesicles (EVs) based nano sensitizers by using Chlorin e6 (Che6) as a sonosensitizer, linked to TPP moiety that targets the mitochondria and for achieving effective and focused anticancer activity piperlonguime (PL) which is cancer-specific chemotherapeutic and pro-oxidant was further co-encapsulated into EVs as demonstrated in (Figure 7). After performing cellular uptake studies on MC-7 cells good cellular intake levels of both TPP-Che6 and EV (TPP-Che6) was observed but comparatively EV (TPP-Che6) is better than TPP-Che6 because it facilitated cellular internalization via ligand-receptor connections or EV fusion directly with cell membranes. To determine the mitochondrial absorption of TPP-Che6, Che6, and EV (TPP-Che6), Mander's overlap coefficient was calculated and more Mander's overlap coefficient of TPP-Che6 and EV (TPP-Che6) than the Che6 group was observed. This is because of the mitochondria-targeting properties of TPP and it is also clear from these data that TPP-Che6 effectively targeted MCF-7 cells mitochondria. To exhibit ROS production from TPP-Che6 by US exposure, ROS production levels in EV (TPP-Che6/PL), EV (TPP-Che6), TPP-Che6, and free Che6 were determined in a system without cells. The US irradiation significantly raised the ROS production levels of EV (TPP-Che6/PL), EV (TPP-Che6), and TPP-Che6 demonstrating the sonodynamic action of TPP-Che6. Upon US exposure, EV (TPP-Che6/PL) and EV (TPP-Che6) both generated much more ROS than TPP-Ce6. This was because entrapped TPP-Ce6 in EVs protects it from degradation, which allows it to generate more ROS. Intracellular ROS levels in MCF-7 cells treated with TPP-Che6-loaded EV samples after exposure to the US were measured using DCF-DA dye. TPP-Che6 was capable of producing more ROS than Ce6. The possible reason could be that TPP-Che6 has a higher rate of mitochondrial absorption than Che6. In vivo, tumor accumulation efficiency was

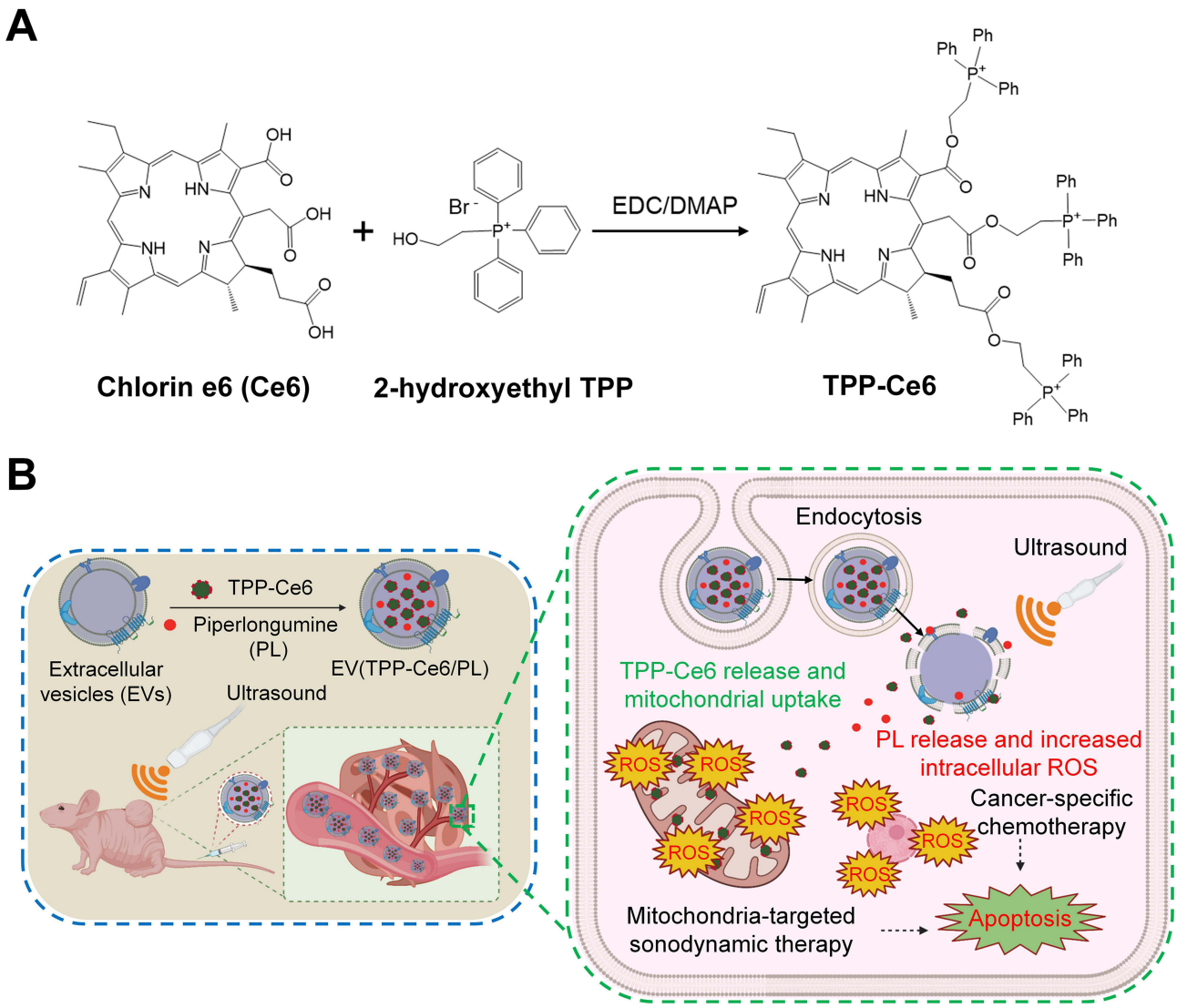

Figure 7 (**A**) TPP-Che6 synthetic scheme. (**B**) Schematic representation of combination chemo-sonodynamic therapy (chemo-SDT) employing biocompatible extracellular vesicles (EVs) containing pro-oxidant piperlongumine (PL) and mitochondria-targeting TPP-Che6. The release of TPP-Che6 and PL from the EVs was activated by ultrasonic (US) irradiation after EV (TPP-Che6/PL) was internalized into breast cancer cells by endocytosis. Under US irradiation, the released TPP-Che6 effectively builds up in the mitochondria and produces reactive oxygen species (ROS). The ROS causes mitochondrial damage, which leads to apoptosis. Through the excessive production of intracellular ROS caused by the released PL, mitochondria-targeted sonodynamic cancer therapy in conjunction with chemotherapy is made possible. Image reproduced from Nguyen Cao TG, Truong Hoang Q, Hong EJ, et al. Mitochondria-targeting sonosensitizer-loaded extracellular vesicles for chemo-sonodynamic therapy. J Control Release. 2023;354:651–663, Copyright (2023), with permission from Elsevier.[163]

evaluated by real-time fluorescence imaging after samples were injected intravenously into mice having MCF-7 tumors. EV (TPP-Che6/PL)-administered mice's tumors exhibited fluorescence till 24 h after intravenous administration. However, TPP-Che6 treated mice's tumors fluorescence almost vanished after 24 h of intravenous administration. This is because TPP-Che6 encapsulation in Evs enhanced TPP-Che6 accumulation within the tumor through EPR effects. To evaluate the in vivo toxicity, the chief organs of mice given TPP-Che6, EV (TPP-Che6), and EV (TPP-Che6/PL) did not show any significant pathological changes when exposed to US radiation on H&E staining images which indicates the high biosafety of EV loaded with TPP-Ce6.[163]

Chemotherapy medications can be used as neoadjuvant and adjuvant therapy for the management of certain cancers to slow tumor growth and trigger apoptosis in tumor cells.[182] Chemodynamic therapy amplifies the anti-tumor effect by using the Fenton reaction to produce the "OH" group highly in tumors.[183] Generally, this nanomaterial liberates metal ions (like vanadium ion, copper ion, manganese ion, ferrous ion, chromium ion, and so on), which convert hydrogen

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peroxide into high OH in the slightly acidic environment of the tumor. Ultimately, it leads to cell death and the inhibition of tumor growth.[184] By combining chemotherapy and chemodynamic therapy, Zhong et al prepared a pH-responsive nanoformulation TPP-DOX@MnBSA (TD@MnB) by using albumin from bovine serum (BSA) as a carrier and co-loading TPP-doxorubicin (TPP-DOX), and manganese ions (Mn). The results obtained from cytotoxicity assay in vitro showed that TPP-DOX can efficiently eliminate MCF-7/ADR cells that are more resistant to DOX than DOX alone. Additionally, the fact that TD@MnB is capable of killing drug-sensitive and drug-resistant MCF-7 cells indicates that it has a greater ability to eliminate actual heterogeneous tumors. After performing a cellular uptake study, it was concluded that DOX@MnB and TD@MnB cellular uptake are remarkably more than free DOX. This is because of the presence of albumin which can be more effectively absorbed by tumor cells, which demand large amounts of nutrients. TPP-DOX is more widely uptaken by the tumor cells than DOX because the positive charge of the lipophilic cation TPP in TPP-DOX interacts with the negatively charged cell membranes to facilitate TPP-DOX uptake. The results obtained from the transwell experiment which was done to calculate the inhibition of cell migration are that TD@MnB, TPP-DOX, DOX@MnB, and DOX all are suitable for inhibiting tumor cell migration, but still, TD@MnB and TPP-DOX are much more efficient than free DOX and DOX@MnB. This is due to the reason that the capacity of free DOX to prevent tumor metastasis is less than that of mitochondrial targeting TPP-DOX. After performing in vivo biodistribution of TD@MnB, TPP-DOX, and DOX on tumor-bearing mouse model by injecting an equivalent dose of DOX, the drug distribution in the kidney, lung, spleen, liver, heart, and tumor tissues was examined at 12 and 24 h, and it was concluded that the final formulation TD@MnB which consists of TPP has relative enrichment of tumor locations and longer system circulation time compared to free DOX.[164]

An investigation by Manesh and teammates involved the conjugation of the PTX molecule to TPP through a pH-sensitive ester bond for the delivery of anticancer drugs to mitochondria. The Hydroxyl group of PTX and the carboxylic group of TPP are responsible for the formation of Prodrug (PTX-TPP). Further, human serum albumin (HSAb) NPs modified with Aptamer (Ap) MUC1 were loaded with the PTX-TPP prodrug to create a selective multi-targeting system that is targeted specifically to mitochondria. To determine the cellular uptake and mitochondrial targeting, FITC-labeled samples have been applied to MCF-7 cells (FITC-TPP, FITC-HSAb NPs, FITC-TPP-HSAb NPs, and FITC-TPP-HSAb-Ap NP) then continued to be treated by DNA stain DAPI and MTred. Results showed that FITC-TPP-HSAb-Ap NPs are highly cellularly absorbed and localized in the mitochondria. The potential cause could be that the TPP lipophilic cation causes mitochondrial localization and cellular absorption could be improved by modifying HSAb-NPs with an Ap targeting agent. On determining apoptotic activity, results revealed that the apoptotic rate induced by PTX-TPP-HSAb-Ap NPs is higher as compared to PTX-TPP-HSAb NPs, TPP-HSAb, PTX-TPP, PTX, and Ap NPs (blank targeting NPs). The possible reason could be that aptamer-modified NPs with PTX-TPP can give MCF-7 cells sufficient PTX concentration at the mitochondrial site. The results from the cytotoxicity study when performed on MUC1 under expressing MDA-MB-435 cells and MUC1 overexpressing MCF-7 cell revealed more cytotoxicity of PTX-TPP with IC50 value 60.4 nmol when compared to plain PTX. This is because plasma membrane potential allows TPP-conjugated PTX to accumulate in the cytoplasm through the extracellular environment. The final formulation TPP-HSAb-Ap NPs demonstrated greater cytotoxicity in MCF-7 cells which is due to overexpressing of MUC1 that resulted in higher cellular uptake via receptor-mediated endocytotic pathway whereas in contrast, MDA-MB-435 cells do not express MUC1.[165]

Another interesting investigation by Arafa et al utilized a core-shell nanoparticulate system that targeted sequentially for the management of breast cancer. At first, cellular level targeting by the nanoparticulate system and then further subcellular level targeting was achieved. Cellular-level targeting is made possible by using hyaluronic acid (HUA), a specific CD44 receptor ligand, and with the help of TPP subcellular mitochondrial targeting was achieved. DOX-loaded NPs, DOX-TPP conjugate-loaded NPs, and free DOX were used in MCF-7 breast cancer cells to examine the cytotoxicity concentration of HUA-coated core-shell NPs. The analysis demonstrates that the cytotoxicity of NPs was considerably increased by increasing the HUA content. This is because of the improved cellular uptake based on CD-44 receptors. On further comparison, it was confirmed that after TPP conjugation, cell viability was significantly reduced due to the ability to target the mitochondria of tumor cells. Solid Ehrlich carcinoma (SEC) bearing mice were used to evaluate the anti-tumor efficacy of DOX-TPP and their loaded NPs, and the result was that both DOX-TPP and their loaded NPs significantly reduced the volume of the tumor. Based on the above experiments and results, it was concluded

that the core-shell NPs developed for treating MCF-7 breast cancer cell lines exhibited potent anti-tumor activity, leading to apoptosis and cell cycle arrest.[156]

Different research studies have been explored based on mitochondrial-targeted drug delivery by TPP and they all have shown promising therapeutic outcomes in cancer treatment. Although all these researches aim is to kill cancerous cells by damaging their mitochondria, they used different materials, methods, and targeting approaches. For instance, EV(TPP-Ce6/PL) utilized extracellular vesicles to co-administer pro-oxidant and sonosensitizer to enhance chemotherapy and sonodynamic therapy by synergistic generation of ROS. On the contrary, another system is TD@MB nanoparticles which enhance ROS levels through a Fenton-like reaction which is catalyzed by manganese and its incorporated chemotherapeutic drug was released in a pH-responsive manner. On the other hand, a dual-targeting strategy was employed by another nanosystem (PTX-TPP-HSA-Apt NPs) through MUC1 aptamer for cancerous cells and TPP for mitochondria. Due to this cytotoxicity was enhanced by 18 times than free paclitaxel. Similarly, chitosan nanoparticles coated by HUA utilized CD44 receptors to target breast cancerous cells in a controlled and pH-sensitive release. Furthermore, triple-negative breast cancer which is very hard to treat was treated by nanosystem HUA-TS-TPP/LPT NPS. Another prominent example is TPP-PEG-modified liposomes which demonstrate significant antitumor activity and considerable mitochondrial accumulation. Conclusively, all the strategies signify the potential of mitochondrial targeting through TPP. Moreover, treatment effectiveness was significantly enhanced after combining it with different approaches as we have discussed like aptamer guided, ROS amplification, and so on. This comparative evaluation highlights the therapeutic advantages, targeting mechanisms, and different design strategies which provide us a comprehensive insight into how these studies differ and complement one another.

Conclusion

Recently, there has been increased focus on employing nanocarriers tailored for mitochondria to deliver chemotherapeutic agents with precision to these cellular organelles. Triphenylphosphonium stands out among these carriers for its remarkable targeting prowess, promising precise delivery. This approach not only reduces drug dosage but also mitigates the indiscriminate side effects on normal tissue. Hence, this review succinctly examines the pivotal role of nanotechnology, underscores the importance of targeted delivery, and explores the potential benefits of targeting at both cellular and sub-cellular levels in cancer treatment. Furthermore, it delves deeply into mitochondrial targeting, particularly emphasizing nanocarriers engineered for mitochondrial delivery, especially those coupled with triphenylphosphonium, within the realm of cancer therapy.

Mitochondrial targeting with TPP is emerging as an innovative approach in cancer management. This review describes various types of TPP-conjugated NPs developed by numerous researchers like polymer lipid nanoparticles, carbon nanodots, extracellular vesicles, and albumin-based nanoparticles. Intracellular uptake and mitochondrial accumulation were enhanced by these TPP-functionalized nanosystems and induced apoptosis by the formation of ROS and disruption of the mitochondrial membrane. One of the major concerns associated with TPP is its cytotoxicity but this happens only at high doses, it was evident from in-vivo results after animal models being tested by TPP-derivative Mito-VitE, TPMP, and MitoQ and it was further proved by the commercial availability of MitoQ. The other challenge with TPP is hemolysis because of its positive charge and researchers mitigate this issue by encapsulating it into nanocarriers, because of which it only interacts with mitochondria after reaches to desired location. It was found that the non-specificity of cells by chemotherapeutic agents was overcome by using the targeting moiety, which enhances the accumulation of the NPs on tumor cells and decreases the dose, ultimately reducing the adverse effects associated with the drug. Ultra-high cytotoxicity in cancer cell lines was achieved by using mitochondrial-targeted NPs rather than non-targeted NPs. In vivo studies also confirmed that tumor growth inhibition is greater in the case of mitochondrial-targeted NPs than in non-targeted NPs. Hence, it can be inferred that NPs utilizing TPP for mitochondrial targeting hold significant promise in treating diverse cancer types. Their notable attributes include forming connections with chemotherapy drugs, displaying responsiveness to pH changes, supporting PTT, and ensuring targeted drug delivery to combat MDR. This review furnishes an up-to-date and comprehensive understanding of mitochondrial targeting using TPP-conjugated NPs for cancer treatment, serving as a valuable resource for scientists and researchers in this domain.

Research should be advanced in the future by focusing on developing novel derivatives of TPP and multifunctional nanocarriers that respond to cancerous microenvironments more efficiently and integrate both therapeutic and diagnostic. Moreover, it is imperative to emphasize the necessity for additional clinical evidence and research before these interventions can be introduced into the market. Conclusively, TPP-based mitochondrial targeting offers a promising approach to next-generation cancer treatment.

Disclosure

There is no conflict of interest and disclosures associated with the work.

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