Mitochondrial Dysfunction-Targeted Nanosystems for Precise Tumor Therapeutics

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Abstract. Mitochondria play critical roles in the regulation of the proliferation and apoptosis of cancerous cells. Targeted induction of mitochondrial dysfunction in cancer cells by multifunctional nanosystems for cancer treatment has attracted increasing attention in the past few years. Numerous therapeutic nanosystems have been designed for precise tumor therapy by inducing mitochondrial dysfunction, including reducing adenosine triphosphate, breaking redox homeostasis, inhibiting glycolysis, regulating proteins, membrane potential depolarization, mtDNA damage, mitophagy dysregulation and so on. Understanding the mechanisms of mitochondrial dysfunction would be helpful for efficient treatment of diseases and accelerating the translation of these therapeutic strategies into the clinic. Then, various strategies to construct mitochondria-targeted nanosystems and induce mitochondrial dysfunction are summarized, and the recent research progress regarding precise tumor therapeutics is highlighted. Finally, the major challenges and an outlook in this rapidly developing field are discussed. This review is expected to inspire further development of novel

mitochondrial dysfunction-based strategies for precise treatments of cancer and other human diseases.

1. Introduction

Cancer, one of the world's deadliest diseases, has become a serious threat to human public health [1]. In spite of the significant funding being invested in manpower and resources to explore new cancer treatments, current clinical protocols have met with limited success as a result of the complexity, diversity and heterogeneity of oncology [2, 3]. The most problematic issue is mainly due to the non-targeting nature of small molecule drugs that often restrict the clinical efficacy and cause serious side effects to patients [4, 5]. Promisingly, precise medicine could be employed for the precise diagnosis and effective treatment of cancer, as witnessed by a couple of breakthroughs in the pre-clinical and clinical exploitation [6, 7]. Fortunately, nanoscale carriers can be passively targeted and enriched in tumor tissues through enhanced permeability and retention (EPR) effect [8]. Some physical methods (e.g., magnetic field and electric field) can also assist this accumulation [9]. In addition, nanocarriers are capable of actively targeting cancer cells to enhance their internalization through surface ligand modifications owing to specific recognition between ligand and receptor [10]. Moreover, a wide variety of responsive designs including internal stimuli (e.g., pH, overexpressed enzymes, redox, and hypoxia) and external stimuli (e.g., light and ultrasound) have been applied to the invention of nanocarriers, facilitating cargo-specific controllable release [11].

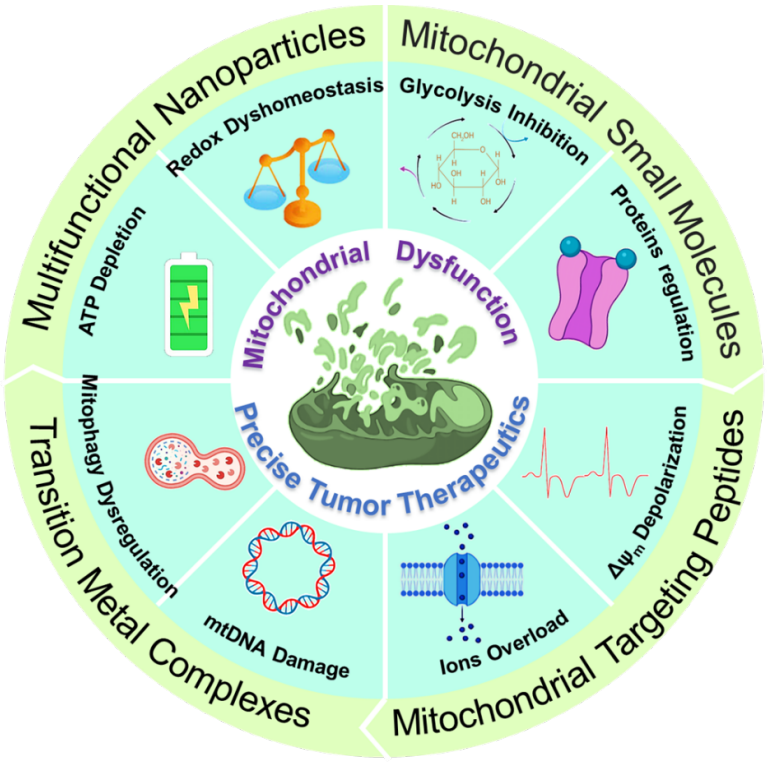
In fact, only 0.7% of administered nanocarriers eventually accumulate at solid tumor sites, mainly as a result of multifactorial interferences such as non-specific adsorption, off-targeting, and premature leakage [12, 13]. Some therapy methods require specific intracellular sites to exert their therapeutic effects, and stubborn cancer cells are also multidrug resistant, compromising the final therapeutic outcome [14, 15]. For example, genes need to reach genetic sites such as nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) to stimulate gene therapy

[16], and toxic reactive oxygen species (ROS) generated in phototherapy and chemodynamic therapy (CDT) must be in close proximity to bioactive substances such as proteins and genes for effectively killing cancer cells [17]. Meanwhile, the diffusion of drugs during transportation may cause non-specific interactions, which may affect the therapeutic effect or even result in adverse side effects. Consequently, exploring advanced drug delivery systems (DDSs) for precise delivery of drugs to the desired subcellular sites would be beneficial in improving the ultimate therapeutic efficacy and minimizing systemic side effects.

Mitochondria are one of the most important organelles in cells, playing critical roles in the regulation of cell survival and apoptosis [18]. On the one hand, mitochondria, as the “power house”, are essential to generate adenosine triphosphate (ATP) through oxidative phosphorylation for energy production, sustaining the growth and proliferation of eukaryotic cells [19]. On the other hand, mitochondria serve as “weapon store” in cellular protein biosynthesis, signaling transduction and genetic transcription, and regulate various cellular death pathways including apoptosis, necrosis, ferroptosis, pyroptosis, immunogenic cell death and autophagy [20]. It is worth mentioning that many cancer cells still use glycolysis to generate ATP even when there is sufficient oxygen. This phenomenon is called Warburg effect, which may be related to mitochondrial dysfunction [21]. In particular, a comparison of mitochondria between cancer cells and normal cells reveals significant differences in structure and function [22]. Cancer cells have more extensive metabolic reprogramming to meet immortality, making them more susceptible to mitochondrial disruption than normal cells [23]. Mitochondrial DNA mutations in cancer cells are usually frequent, which may lead to mitochondrial dysfunction and promote tumorigenesis [24]. Based on these premises, targeting the mitochondria of cancer cells becomes a means of selective tumor therapy. Thus, a variety of nanosystems have been successfully constructed for targeting mitochondria in enhancing tumor therapy, mainly due to their controlled physical (size, stiffness, morphology) and chemical (oxidability, reducibility, stability) properties [25]. For example, because of the strong transmembrane potential of

mitochondria, modification of nanocarriers with positively charged and lipophilic chemical molecules have been found to have targeting localization, preferentially to the mitochondria of cancer cells [26]. In addition, various mitochondria-targeted photosensitizers have been constructed to selectively generate large amounts of ROS at the mitochondria, which can greatly enhance the ultimate photodynamic therapy (PDT) efficacy by addressing the short life time of ROS [27]. More importantly, direct delivery of DDSs to the mitochondria and release of the loaded drugs could concentrates the localized drug contents and bypasses some subcellular barriers such as nuclear pores, thus effectively overcoming drug resistance and remarkably improving therapeutic efficacy [28, 29]. To date, many mitochondria-targeted therapeutic strategies have been proven to kill cancer cells based on different perturbation mechanisms including mitochondrial metabolism interference, information transmission interference, biosynthesis interference, redox interference, mtDNA interference, etc [30].

Based on recent advances in different mechanisms of mitochondrial disruption, we summarize effective nanotherapeutic strategies based on mitochondrial dysfunction for precise cancer therapy (**Scheme 1**). In this review, we present general strategies in the design of targeted mitochondrial nanosystems for precise cancer therapy. Specifically, therapeutic approaches based on mitochondrial dysfunction including reducing ATP, breaking redox homeostasis, inhibiting glycolysis, regulating proteins, ion overloading, membrane potential depolarization, mtDNA damage, and mitophagy dysregulation are described and classified in detail. In the end, current challenges and future opportunities about progressing clinical applications of targeted mitochondrial nanosystems are provided.



Scheme 1. Design of diverse mitochondrial dysfunctions for precise therapeutics.

2. Mitochondria-Targeting Agents

Mitochondria possess a double membrane with a diameter of approximate 1 μm, which is structurally distinct from other subcellular organelles. From outer to inner, there are the outer mitochondrial membrane (OMM), intermembrane space (IMS), inner mitochondrial membrane (IMM) and mitochondrial matrix (MM) [31]. The OMM acts as an organelle boundary membrane with abundant receptors that selectively recognize and absorb certain substances into the mitochondria. For nonspecific small molecules, they can enter the OMM through voltage-dependent anion channel because the OMM is permeable for small molecules (<≈ 5 kDa). The IMM with many inward folds has a larger specific surface area and is responsible for more biochemical reactions, such as electron transport chain (ETC). The ETC is a pathway to transfer electrons between proton pump complexes in the IMM, which plays a substantial role in promoting energy metabolism and ATP synthesis [32]. Each mitochondrial membrane hosts a

unique group of proteins participating in ion channels and metabolic pathways, which are necessary to maintain homeostasis throughout the cells [33]. Moreover, it has been reported that the mitochondria of cancer cells possess a stronger negative charge (-220 mV) relative to normal cells (-140 mV) [34]. Therefore, the uptake of lipophilic cationic complexes can reach up to 1000 times higher than that of extracellular complexes [35]. As a result, mitochondria-targeted agents make it possible to selectively target cancer cells. This selectivity would lessen the damage to normal cells and reduce the effective concentration of the drug, thus improving the corresponding bioavailability for precise tumor therapy.

2.1 Mitochondrial Small Molecules

Selective attack on cancer cells can be achieved by constructing anticancer drugs [36, 37]. However, the double-layered membrane of mitochondria, in addition to its function of regulating their metabolism, also prevents foreign substances from crossing the membrane to a certain extent, which makes penetrating mitochondria a great challenge [38]. Interestingly, the proton pump of IMM drives the protons flow from MM to IMS, enabling IMS to carry a positive charge and conversely MM a negative charge, which naturally lead to a strong mitochondrial membrane potential ($\Delta\psi_m$) [39]. Thus, lipophilic and positively charged molecules are more likely to accumulate in mitochondria with the assistance of $\Delta\psi_m$ [40]. Moreover, the membrane potential of mitochondria in cancer cells is higher than that of normal cells, which results in the accumulation of positively charged compounds in the mitochondria of cancer cells about 10 times higher [41]. Thus, cationic compounds preferentially accumulate in tumor cells, reducing the side effects on normal cells [42].

Skulachev et al. discovered the first mitochondrial targeting compound, methyl triphenylphosphine cation, in 1969 [43]. Based on their descriptions, delocalized lipophilic cations (DLCs) are widely acknowledged because they are rapidly absorbed by mitochondria without the need for specific types of transport. After that, several DLCs have been reported,

including triphenylphosphonium ion (TPP), dequalinium [44], rhodamine 123 [45], guanidine/biguanide [46, 47], and (E)-4-(1h-indole-3-ylvinyl)-n-methylpyridine iodide (F16) [48]. One of the most typical examples is TPP, which has been prevalently used to target mitochondria [49]. In addition to having a positive charge, this lipophilic cation is hydrophobic and can drive its interaction with hydrophobic IMM, thereby promoting penetration into the mitochondria. As such, the concentration of TPP ions in mitochondria can reach 100-500 times higher than in the cytoplasm. The chemical structures of some conventional mitochondria-targeted drugs have been summarized in **Fig. 1** [50].

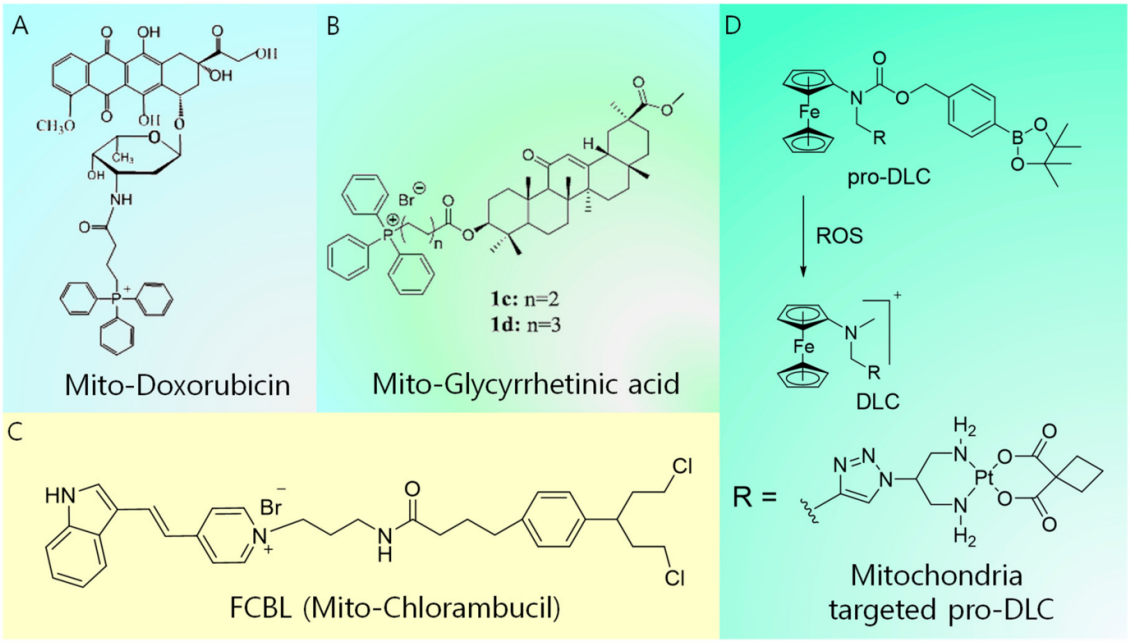


Fig. 1. Molecular design of some conventional mitochondria-targeted drugs. (A) Mitochondria targeted doxorubicin, (B) mitochondria-targeted glycyrrhetinic acid, (C) mitochondria-targeted chlorambucil, and (D) mitochondria-targeted pro-DLC. Reproduced with permission from Ref. [50]. Copyright 2019 Multidisciplinary Digital Publishing Institute.

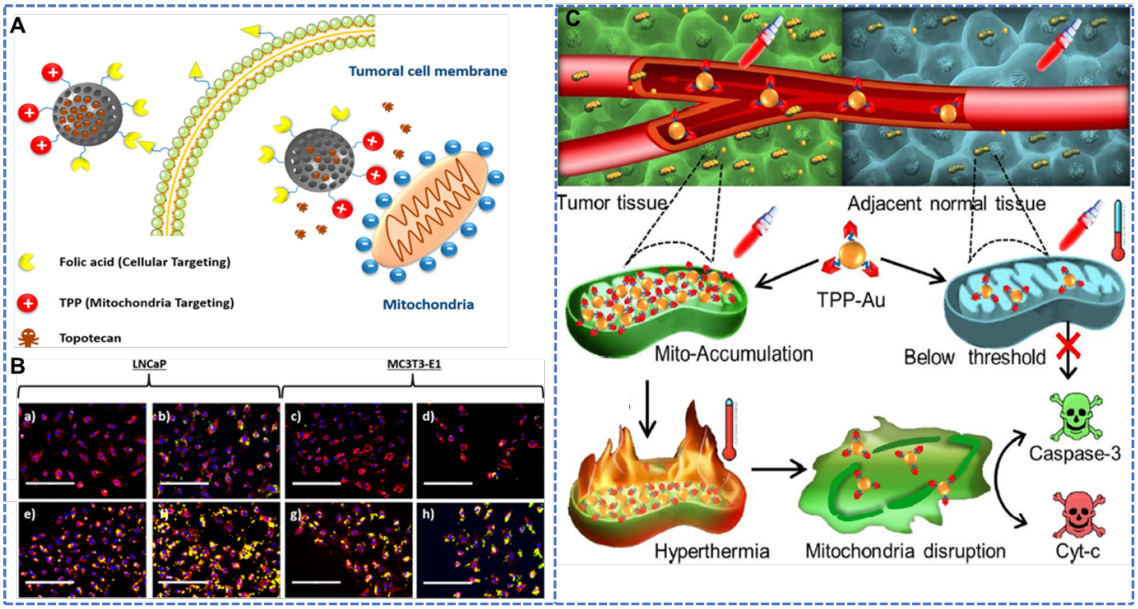


Fig. 2. (A) Mechanism of action of dual-targeted MSN: cellular and mitochondrial targeting. (B) Fluorescence microscopic images of cells exposed to a fixed concentration of the following MSN derivatives: (a, c) NH_2-MSN-CO_2H, (b, d) MSN-Fol, (e, g) MSN-TPP, and (f, h) Fol-MSN-TPP. Blue color corresponds to cell nuclei, obtained by use of blue DAPI staining agent; red corresponds to mitochondria, obtained by employing red MitoTracker; green dots correspond to MSN nanosystems due to the presence of fluorescein trapped within the silica matrix. Scale bars = 200 μm. Reproduced with permission from Ref. [51]. Copyright 2017 American Chemical Society. (C) Mechanism of mitochondria-templated gold nanoparticle accumulation for tumor-selective therapy. Reproduced with permission from Ref. [53]. Copyright 2018 American Chemical Society.

For example, Vallet-Regí et al. developed Janus mesoporous silica nanoparticles (MSN) decorated with two targeting moieties (folic acid and TPP) to achieve sequential cell to mitochondria vectorization (Fig. 2A) [51]. Subsequently, cell experiments also confirmed that dual-targeted MSN exhibited the highest accumulation and mitochondria localization (Fig. 2B), indicating the suitability of this strategy to enhance the efficacy of nanocarrier-based therapy. Mitochondrial redox homeostasis plays a key role in biosynthesis and apoptosis. Thus, Liang

and co-workers designed carbon dots (CAT-g) loading well-dispersed Au with TPP targeting and cinnamaldehyde to amplify mitochondrial oxidative stress [52]. After entering mitochondria, the increase of ROS and the consumption of glutathione (GSH) disrupted mitochondrial redox homeostasis and caused apoptotic cell death. The nanoplatform provides the potential for future precision therapy by targeting mitochondrial redox homeostasis. In addition, TPP as a lipophilic cation could drive a special function of preferentially targeting the mitochondria of cancer cells, which brings hope for minimizing damage to normal cells. We took this advantage to develop a mitochondria-templated accumulation method to precisely ablate tumors while avoiding damage to adjacent normal tissues [53]. As shown in Fig. 2C, mitochondria-targeted gold particles were driven by TPP to accumulate more heavily in tumor mitochondria. Subsequently, the interparticle plasmonic coupling effect between the accumulated gold particles induced hyperthermia under NIR light, ablating the tumor. For adjacent normal tissues, the small clusters of TPP-Au were unable to elicit the corresponding phenomena. Hence, this mitochondria-templated accumulation protected adjacent normal tissues from damage, which would provide therapeutic applications in some specific tumors, like brain tumors. Moreover, it is also a big challenge for the penetration of deep tumor tissue. Deng et al. designed a mitochondrial targeted nanostructure, consisting of poly (lactic-co-glycolic acid) (PLGA) wrapped photosensitizer and gold particles with surface modification of TPP, for X-ray-induced PDT [54]. This mitochondrial targeting formulation is therapeutically effective in deep tissues with greatly reduced radiation side effects.

Typically, most of these DLCs can be connected to nanocarriers by simple chemical binding for mitochondrial targeting [55]. However, high concentration of DLCs may destroy the mitochondrial membrane potential, leading to cell toxicity. For the effectiveness of DLCs in transportation, the delivery of large cargoes may still depend on the overall size and charge of the nanosystems [56].

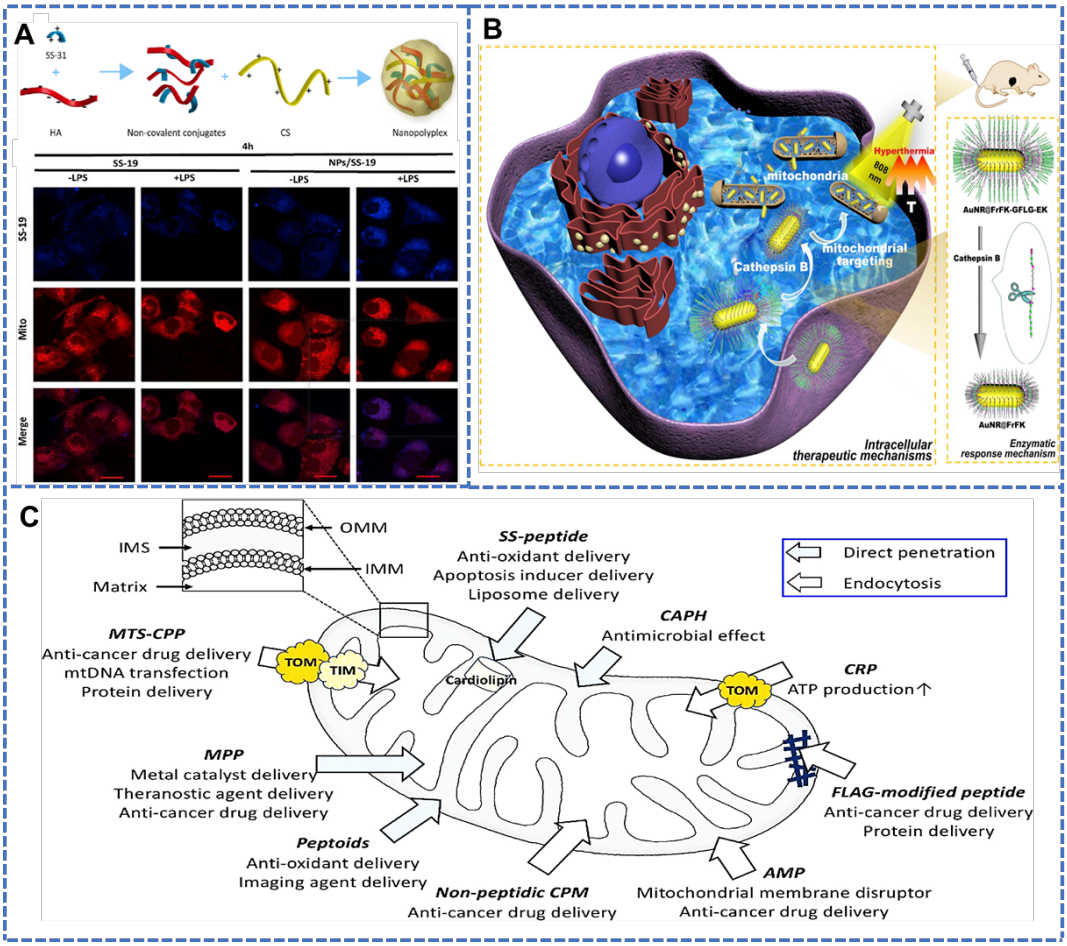


Fig. 3. (A) Preparation of nanopolyplex and its targeted uptake by LPS-stimulated cells (SS-19: the fluorescent analog of SS-31, blue). Scale bar = 10 μm. Reproduced with permission from Ref. [59]. Copyright 2019 Elsevier Ltd. (B) Cathepsin B-responsive multifunctional peptide conjugated gold nanorods for mitochondrial targeting and precise photothermal cancer therapy. Reproduced with permission from Ref. [61]. Copyright 2021 Elsevier. (C) Mitochondrion-targeting peptides and peptidomimetics based on their structural classes and reported applications. MTSCPP: MTS with cell-penetrating peptides; MPP: mitochondrion-penetrating peptides; SS-peptides: Szeto-Schiller peptides; CAPH: cationic amphiphilic polyproline helix; CRP: cysteine-rich peptides; FLAG-modified peptide: FLAG tag-based peptide that self-assembled into a nanofiber; AMP: peptides derived from antimicrobial peptides; CPM: nonpeptidic cell-penetrating motif. Reproduced with permission from Ref. [71]. Copyright 2020 American Chemical Society.

2.2 Mitochondrial Targeting Peptides

Szeto-Schiller (SS) peptides are mitochondrial targeting peptides discovered in 2004 [57]. They are small water-soluble tetrapeptides consisting of four alternating amino acids (Tyr-D-Phe-Arg-Lys-NH_2), having positive charge characteristics. These peptides were originally used as antioxidants due to their 2,4-dimethyltyrosine residues, and then selective accumulation in the IMM of mitochondria was observed. SS peptides can easily penetrate cells and their uptake does not require energy, while their definitive targeting mechanism is still unclear. After the continuous optimization, a series of SS peptides, such as SS-01 (Tyr-D-Arg-Phe-Lys-NH_2), SS-02 (Dmt-DArg-Phe-Lys-NH_2), and SS-31 (D-Arg-Dmt-Lys-Phe-NH_2), have been widely explored for the treatment of many diseases [58]. For example, Liu et al. designed a pH responsive nanopolyplex with SS-31 peptide for acute kidney injury treatment, showing mitochondrial colocalization (**Fig.** 3A) [59]. Unlike TPP, these peptides even at millimolar concentrations are not toxic to mitochondria. Therefore, SS-31 has entered phase II clinical trials for the treatment of reperfusion and microvascular injury.

Mitochondrial penetrating peptides (MPPs) as synthetic peptides were discovered to have mitochondrial localization in 2008 [60]. MPPs benefit from alternating cationic and hydrophobic residues and possess outgoing cell permeability and mitochondrial targeting. Wang and co-workers established a gold nanorods with MPPs (FrFKFrFK-$CONH_2$ (Phe-r-Phe-Lys-Phe-r-Phe-Lys-$CONH_2$, where r = D-arginine)) for mitochondrial targeting and precise photothermal cancer therapy (Fig. 3B) [61]. Meanwhile, Horton et al. pointed out that the uptake of MPPs does not seem to depend on the endocytic pathway, explaining that MMP can accumulate in mitochondria [62]. If the peptide is too short or has low hydrophobicity, it would not be enough to destroy the cell activity, but only accumulate in the mitochondrial matrix. When these peptides have very high concentrations, they can induce the release of cytochrome c by activating the permeability transition pore complex [63]. In conclusion, the increase of length and hydrophobicity for MPPs is the key factor to destroy cell activity. Apart from

targeting, some MPPs have therapeutic properties. Many therapeutic peptides are found in nature, such as from animals, plants and microorganisms [64]. For instance, the proapoptosis peptide KLAKLAKKLAKLAK (denoted as KLA) is a 14-amino-acid helical peptide, which is originally known as an antimicrobial peptide by destroying the mitochondrial membrane of eukaryotic cells, leading to apoptosis and death [65]. Later, researchers developed multifunctional nanosystems to deliver proapoptotic peptides across cell membranes for effective tumor therapy. Wu et al. summarized the latest progress in the tumor therapy of MPPs based on mitochondrial targeting [66]. The tunability and easy synthesis of MPPs are conducive to the adjustment of intracellular and *in vivo* pharmacokinetic profiles. In addition, it is concluded that the drugs combined with MPPs could target mitochondria to repair the mitochondria of cancer cells or directly provide proapoptosis to active intracellular pathway.

Mitochondrial targeting sequence (MTS) peptides usually consisting of 20-40 amino acids are recognized by receptors on the mitochondrial membrane, including translocator of the OMM and translocator of the IMM [67]. These translocators play a role in introducing MTS into mitochondria, and this entry process is mainly driven by ATP or $\Delta\psi_m$. MTS peptides have been reported to be successfully applied in the mitochondrial transport of proteins, enzymes, nucleic acids, and prodrugs [68, 69]. Bae et al. designed an MTS-based cationic oligopeptide (MTS-H3R9) for targeted delivery and cancer treatment [70]. On the other hand, MTS peptides have large structures, poor solubility and inherent low membrane permeability, which limit their applications in nanomedicine.

In addition, there are various other mitochondria-targeting peptides combined with nanosystems for targeted tumor therapy. Kim et al. classified mitochondrion-targeting peptides and peptidomimetics in terms of their structures and applications (Fig. 3C) [71]. However, each mitochondrial transporter is hindered by not only the type and size of cargos they can deliver, but also the accessibility to specific mitochondrial compartments [72]. Therefore, there is a

need to establish easily decorated multifunctional delivery systems that complement the characters of ligands and cargos for better mitochondrial uptake.

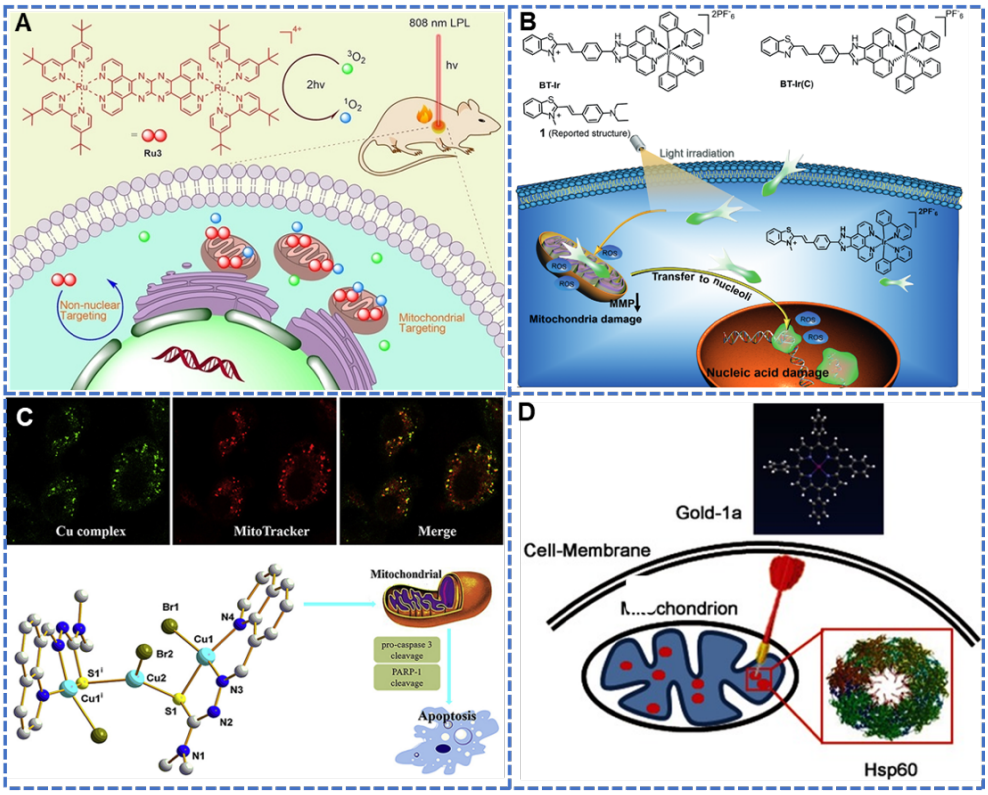


Fig. 4. (A) Illustration of dinuclear ruthenium complexes acting as the mitochondria targeted agent for dual two-photon photodynamic and photothermal therapy. Reproduced with permission from Ref. [79]. Copyright 2022 Wiley-VCH. (B) Chemical structures of Ir complexes and schematic representation of light-driven cascade mitochondria-to-nucleoli photosensitization in cell ablation. Reproduced with permission from Ref. [80]. Copyright 2021 Wiley-VCH. (C) Illustration of N-heterocyclic thiosemicarbazone copper complexes for activation of mitochondrial-mediated apoptosis pathway. Reproduced with permission from Ref. [81]. Copyright 2019 Elsevier. (D) Illustration of the anticancer compound gold(III) meso-tetraphenylporphyrin (gold-1 a) for targeting mitochondrial chaperone Hsp60. Reproduced with permission from Ref. [83]. Copyright 2015 Wiley-VCH.

2.3 Transition Metal Complexes

Metal complexes containing easily modified coordination ligands show remarkable usefulness in biological applications [73, 74]. In particular, several transition metal complexes exhibit high affinity to mitochondria [75]. These transition metal cycles usually have a high charge, so that it has an inherent high affinity for the mitochondria of cancer cells [76]. Many of these complexes present luminescence properties and high ability to produce $^1O_2$ [77]. Thus, many photodynamic agents based on transition metal complexes have been developed for PDT [78]. For example, Gao et al. developed a series of binuclear ruthenium complexes with mitochondria targeting for *in vivo* dual therapy (PDT/PTT) (**Fig.** 4A) [79]. It is possible to give higher administered dose (longer exposure time) in further human trials for larger or deeper tumors, thus becoming a potential candidate for a new generation of low-power laser driven therapy. Liu and co-workers designed a functionalized iridium complex for mitochondria-to-nucleoli photosensitization, opening new opportunities for efficient PDT (Fig. 4B) [80]. In addition, Gu et al. reported a copper complex with good mitochondrial targeting and high anti-metastatic activity (Fig. 4C) [81]. Gold (III) ion is usually unstable in solution, while employing strong σ-donor ligands can deliver stable structures for specific biomolecular interactions and targeting [82]. Che et al. developed a gold (III)-porphyrin complex through photo-affinity labeling and click chemistry capable of targeting mitochondrial chaperone Hsp60, contributing to the inhibition of Hsp60 and cell imaging (Fig. 4D) [83].

Apart from that, recent studies have demonstrated that metal complexes of europium, manganese, platinum, cobalt, nickel, zinc, rhodium, antimony and osmium could perform mitochondrial targeting ability with promising potentials for anticancer applications [84-86]]. The subcellular localization of the metal complexes can be adjusted by changing the type of ligand around the metal center. Owing to their distinctive photophysical and photothermal properties, some of them have been proven to be suitable for PDT and photothermal therapy (PTT). Although these lipophilic metal complexes are a kind of mitochondrial targeting agents, excessive cation enrichment may induce depolarization of the $\Delta\psi_m$, resulting in the cytotoxicity.

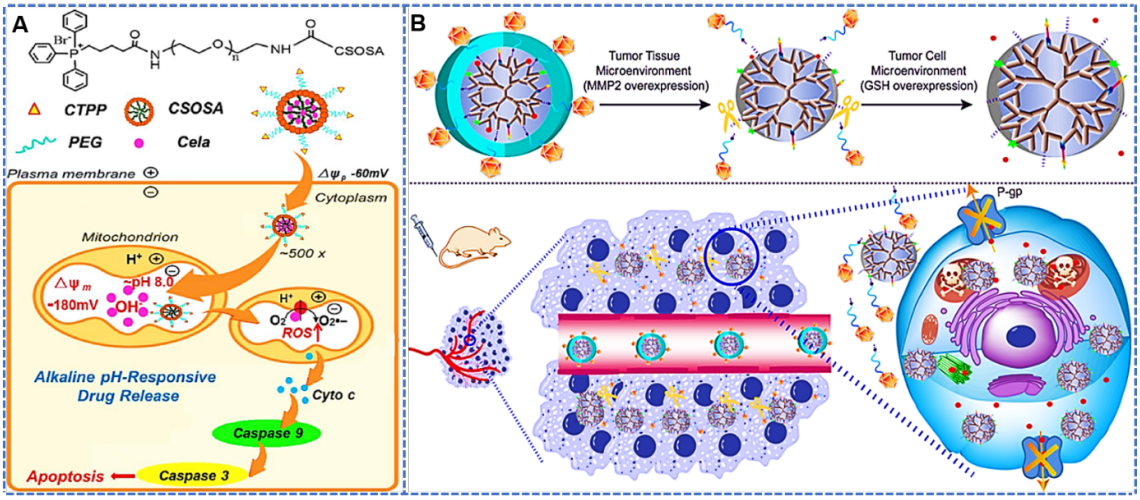


Fig. 5. (A) Schematic diagram of a drug delivery system with mitochondrial alkaline pH-responsive release. Reproduced with permission from Ref. [82]. Copyright 2018 Elsevier. (B) Schematic illustration of glucose-peptide-triphenylphosponium conjugate and its action mechanism for overcoming multidrug resistance. Reproduced with permission from Ref. [83]. Copyright (2018) American Chemical Society.

2.4 Multifunctional Nanoparticles

Mitochondrial targeting molecules have also been introduced into nanoscale DDSs for targeted cancer therapy [87, 88]. The most widely employed nanoparticles in biomedicine, such as liposomes, micelles, dendrimers, carbon nanoparticles, extracellular vesicles (EVs) and metal nanoparticles, may possess the merits of high biocompatibility, low toxicity, high drug loading capacity, and good water dispersibility [89]. Jiang et al. synthesized dendritic lipopeptide liposomes for mitochondria-targeted delivery and achieved tumor eradication by the combination of PDT and PTT [90]. Tan et al. developed mitochondrial micelles for alkaline pH-responsive drug release and enhanced tumor-targeted therapy (**Fig. 5**A) [91]. Drug resistance is considered one of the most fatal obstacles to chemotherapy. Zhang and co-workers used polyamidoamine dendrimer-linked TPP to directly act on the mitochondria for overcoming paclitaxel multidrug resistance of tumor cells (Fig. 5B) [92]. Inspired by the dual-targeting

concept, Jia and co-workers designed a nanocarrier consisting of hollow graphitic carbon nitride nanospheres, hyaluronic acid and targeting peptides, which exhibited therapeutic efficacy superior to monotherapy [93]. For biological carriers, Guan et al. developed breast cancer cell-derived EVs loaded with TPP/recombinant P53 proteins for breast cancer mitochondrial targeted delivery of therapeutic P53 [94]. Similarly, Li et al. constructed mini-sized Au@silica nanorod modified TPP to enhance tumor permeability through loose extracellular matrix [95]. Other general nanocarriers for targeting mitochondria include polymeric nanocarriers [96], silica nanoparticles [97], black phosphorus nanosheets [98], and metal-organic frameworks [99].

By skillfully integrating mitochondrial targeting molecules with nanosystems, various thorny obstacles have been solved for effective cancer treatment. Therefore, it is reasonable to conclude that the introduction of targeted mitochondrial molecules to nanoparticles can achieve optimal therapeutic efficacy and minimal systemic toxicity. Representative mitochondrial targeting agents covered in this review are listed in **Table 1**.

Table 1. Summary of various agents, targeting mechanisms, and therapeutic strategies.

Mitochondrial targeting agents	**Targeting mechanism**	**Names**	**Therapeutic strategies**	**Ref.**
Small molecules	Delocalized lipophilic cations (DLCs)	Triphenylphosphonium (TPP)	Targeting ligand	[51-54, 92-95, 201]
		Dequalinium		[44]
		Rhodamine 123		[45]
		Guanidine/Biguanide		[46, 47]
		(E)-4-(1H-Indol-3-ylvinyl)-N-methylpyridinium iodide (F16)		[48]
Peptides		FrFKFrFK		[61]

	Electrostatic attraction	KLAKLAKKLAKLAK	Targeting ligand / preapoptosis	[65, 109]
		SS peptides		[58, 59]
Transition metal complexes	Mitochondrial membrane potential (ΔΨm)	Ruthenium (II) complexes	Mitochondrial bioimaging/PDT/PTT	[79, 156]
		Iridium (III) complexes		[73, 80, 134, 146]
		Gold (III) complexes		[82, 83]
		Europium (III) complexes		[95]
Multifunctional nanoparticles	Surface modification	Liposomes	Targeting nanocarriers	[44, 90, 213]
		Micelles		[91, 192]
		Dendrimers		[92]
		Polymeric nanocarriers		[89, 96]
		Silica nanoparticles		[51, 95, 97, 174, 178]
		Carbon nanoparticles		[52, 93]
		Black phosphorus nanosheets		[98]
		Metal nanoparticles		[139, 166]
		Metal-organic frameworks		[99]
		Extracellular vesicles (EVs)		[94, 110]

3. Targeting Tumor Therapy through Mitochondrial Dysfunction

In addition to supplying energy to cells, mitochondria are involved in processes such as cell differentiation, cellular information transmission and apoptosis, and have the ability to regulate cell growth and the cell cycle. All these endow the mitochondria with five distinctive functions, i.e., energy conversion, tricarboxylic acid cycle, oxidative phosphorylation, storage of calcium

ions, regulation of membrane potential and control of programmed cell death [100]. These multifaceted functions of mitochondria make them essential for sensing cellular stress and adapting to the environment. These functions are complementary and inextricably linked to each other to determine the fate of the cells [101]. Considering that each of these functions has a systemic effect, disrupting any of them may bring about a chain reaction that threaten the survival of the cells [102, 103]. For this reason, many therapeutic strategies have been developed to achieve precise tumor treatment by inducing mitochondrial dysfunction, mainly classified as reducing ATP, breaking redox homeostasis, inhibiting glycolysis, regulating proteins, ion overloading, membrane potential depolarization, mtDNA damage, and mitophagy dysregulation. In this section, we discuss each of them in detail.

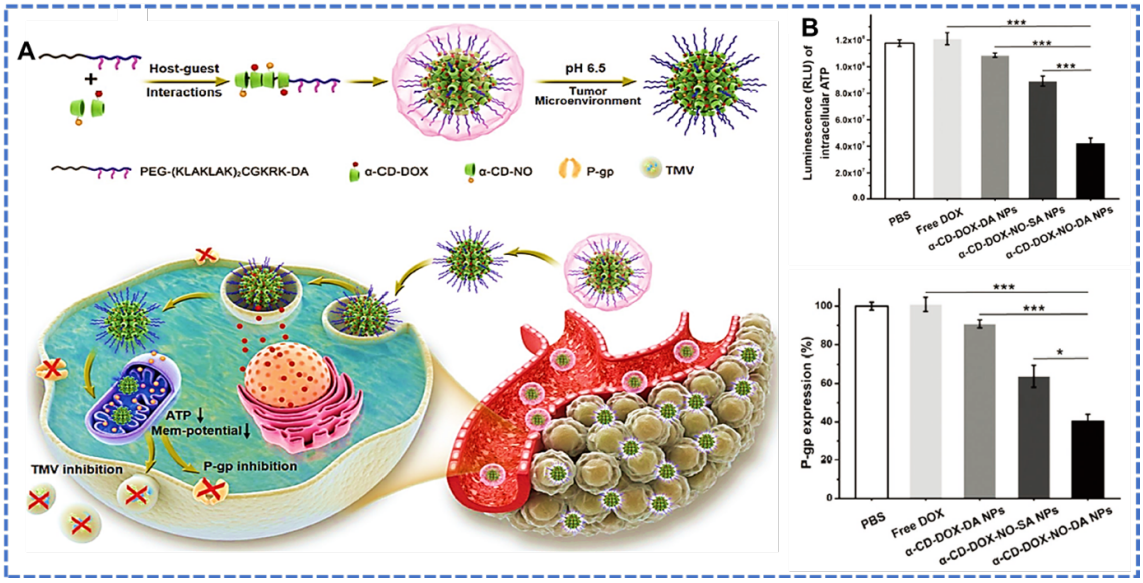


Fig. 6. (A) Synthetic scheme of α-CD-DOX-NO-DA to overcome drug resistance and cancer metastasis. (B) Intracellular ATP levels and the expression of relative P-gp in MCF-7/DOX cells after different treatments. *P < 0.05, **P < 0.01, ***P < 0.001. Reproduced with permission from Ref. [109]. Copyright 2020 Wiley-VCH.

3.1 ATP Decrease

Mitochondria, the main sites of oxidative phosphorylation, are responsible for aerobic respiration to produce ATP and energy [104]. Drug resistance is one of the biggest obstacles in cancer chemotherapy [105, 106]. It is mainly due to the P-glycoprotein (P-gp) and ATP binding cassette (ABC) transporters on the cell membrane, which can promote ATP-dependent drug efflux, thereby reducing intracellular drug concentrations and severely limiting cytotoxicity [107, 108]. By considering this situation, Deng et al. designed a mitochondria-targeted nitric oxide delivery nanoplatform (α-CD-DOX-NO-DA) for responsive DOX release and ATP depletion to inhibit P-gp activity, overcoming the drug resistance for enhanced chemotherapy (**Fig.** 6A) [109]. In subsequent *in vitro* studies, the α-CD-DOX-NO-DA group showed the most obvious ATP depletion and P-gp inactivation (Fig. 6B). Precise delivery of NO to deplete mitochondrial ATP levels for mitochondrial dysfunction has been proven to be critical for the ultimate therapeutic efficacy. Tumor-derived microvesicles (TMVs) play the roles of messengers and mediators in tumor growth, and can promote tumor evolution and metastasis [110]. Likewise, the production and release of TMVs requires the energy supply of ATP, which is closely related with mitochondria [111]. From this point of view, the depletion of ATP would also inhibit the TMV formation, exhibiting good anti-metastatic effect in tumors. Furthermore, the inactivation of P-gp effectively blocks drug pumping, improves chemosensitivity of tumor cells, and further restrains cancer metastasis. To this end, researchers have made efforts to develop ABC transporter protein inhibitors to reduce drug efflux and improve the efficacy of conventional chemotherapy [112]. To date, however, the US Food and Drug Administration (FDA) has not approved any ABC transporter inhibitor due to toxicity concerns.

ATP depletion not only makes chemotherapy sensitizing, but is also effective for PDT [113]. The uncontrolled and rapid multiplication of cancer cells is largely dependent on the important regulation of ATP in physiological processes such as activation of DNA repair and elevation of GSH for antioxidant defense [114]. Taking these factors into consideration, Wei et al. developed a mitochondria-targeted metal-organic framework nanocomposite (ZPCN)

composed of Cu^{2+} and carboxyl-modified ZnPc-$(COOH)_8$ that can deplete ATP in hypoxic cancer cells and sensitize PDT [115]. Upon entry into tumor cells, ATP could compete to capture Cu^{2+} for the disaggregation of ZPCN, and ZnPc-$(COOH)_8$ would be released and activated. Cu^{2+} can also activate Fenton reaction to produce hydroxyl radicals to damage ATP. The depletion of ATP not only inhibits DNA repair but also reduces GSH levels for the enhanced PDT. Finally, these synergistic effects on mitochondria lead to effective apoptosis of cancer cells even under hypoxic conditions. This research demonstrated a promising way for the ATP depletion to achieve enhanced PDT in hypoxic conditions. In different studies, Zhao et al. exploited ATP depletion for ROS-responsive theranostics to overcome the hypoxic dilemma of oxygen-dependent PDT [116].

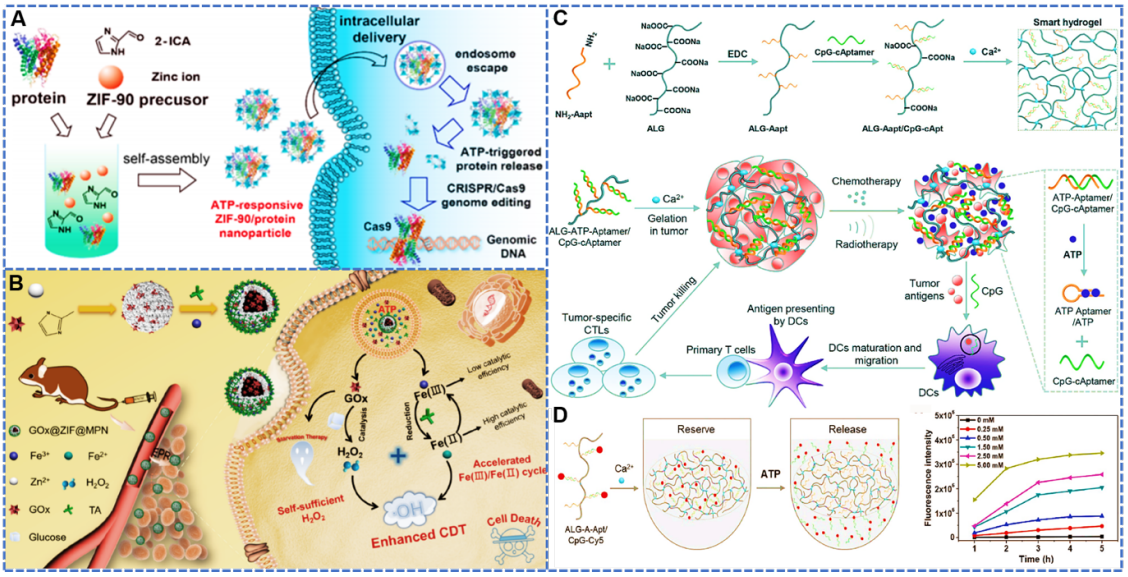


Fig. 7. (A) Schematic illustration for the self-assembly of ZIF-90/protein nanoparticles and their ATP-triggered protein release inside cells. Reproduced with permission from Ref. [121]. Copyright 2019 American Chemical Society. (B) Schematic illustration of GOx@ZIF@MPN as an ATP-responsive autocatalytic Fenton system for tumor ablation. Reproduced with permission from Ref. [122]. Copyright 2018 American Chemical Society. (C) Schematic diagram showing the construction of smart hydrogels for enabling immunoadjuvant CpG release in response to ATP released from tumor cells during chemotherapy or radiotherapy. (D)

Schematic illustration showing the release of Cy5-labeled CpG oligodeoxynucleotides from hydrogels in response to ATP, and cumulative CpG release results Reproduced with permission from Ref. [123]. Copyright 2021 Wiley-VCH.

In addition to the consumption of ATP, the production of ATP hindered at the source is another effective way to reduce intracellular ATP levels [117, 118]. Intracellular glucose metabolism produces large amounts of ATP. For this reason, some small molecule Glut1 inhibitors and glucose oxidase (GOx) have been developed to reduce intracellular glucose concentration and thus inhibit ATP production for tumor starvation therapy [119].

Due to excessive glycolysis to provide energy for rapid tumor growth, ATP is usually overexpressed (1-10×10^{-3} M) in tumor cells relative to normal cells, which provides a target for cancer therapy [120]. For example, Mao et al. employed an ATP responsive zeolitic imidazole framework-90 (ZIF-90) for tumor gene therapy (**Fig.** 7A) [121]. After entering the cells, ZIF-90 would disintegrate in the presence of overexpressed ATP, releasing cytotoxic RNase A for tumor growth inhibition. Meanwhile, Zhang and co-workers designed an ATP responsive autocatalytic Fenton system (GOx@ZIF@MPN) for enhanced CDT (Fig. 7B) [122]. The overexpressed ATP enabled the degradation of the external MPN coating to release Fe (III) and tannic acid (TA), while being exposed to GOx. The released TA reduced Fe (III) to Fe (II), and the exposed GOx consumed glucose to produce H_2O_2, which created conditions for the subsequent Fenton reaction. Therefore, the combination of enhanced CDT and starvation therapy was well realized for tumor ablation. ATP aptamers can bind specifically to ATP in forming DNA with a certain tertiary structure. Liu et al. synthesized ATP-responsive hydrogels to release the immune adjuvants for boosting cancer immunotherapy (Fig. 7C) [123]. In the presence of calcium ions, in situ formulation of the hydrogels occurred. At the end of chemotherapy and radiotherapy, the burst release of ATP from tumor cells would induce competition to capture ATP aptamers, thus resulting in the release of immune adjuvants. After

that, the maturation of dendritic cells, antigen presentation, and tumor-specific cytotoxic T lymphocytes would boost the antitumor immunity. Fig. 7D shows the disintegration and Cy5-labeled immune adjuvant release of the smart hydrogels in response to ATP. Moreover, it was found that the higher the ATP concentration (reaching the millimole level), the faster the CpG release. Such in situ ATP-responsive intelligent hydrogels are useful for improving the immune antitumor effect of low-dose (chemo)radiotherapy. Altogether, it is evident that effective inhibition of mitochondrial ATP may significantly facilitate and amplify the tumor suppressive effect.

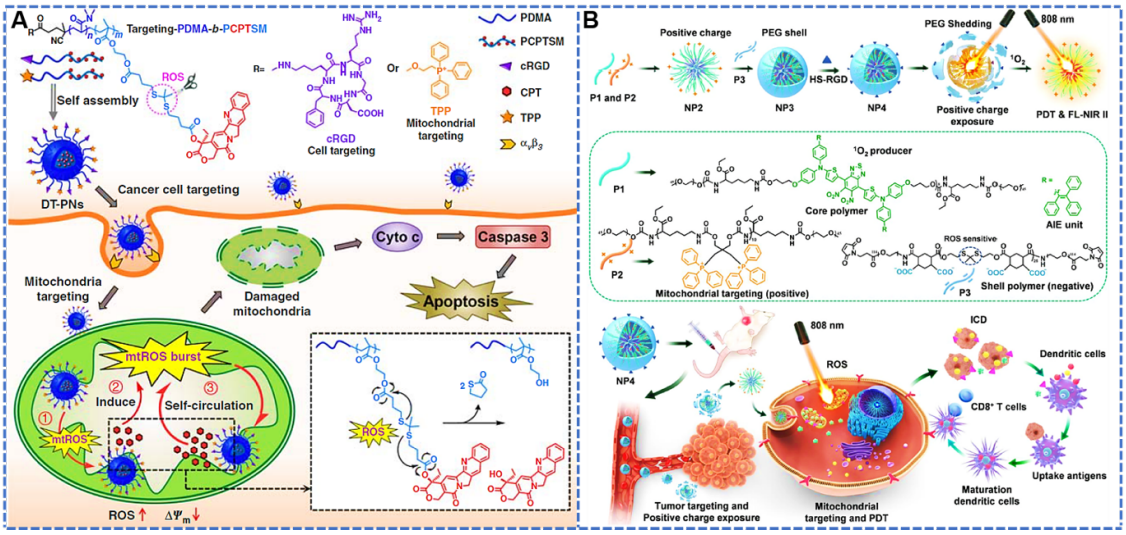


Fig. 8. (A) Mitochondria-specific polyprodrug for self-circulation drug release with ROS burst. Reproduced with permission from Ref. [130]. Copyright 2019 Nature Publishing Group. (B) Design of core-shell nanoparticles with dual-cascade targeting performance triggered by NIR light for maximizing the efficacy of PDT and cancer immunotherapy. Reproduced with permission from Ref. [131]. Copyright 2021 Elsevier.

3.2 Redox Imbalance

Mitochondrial redox homeostasis, a defense mechanism including the balance between ROS such as hydrogen peroxide and antioxidants such as GSH, is strongly associated with a multiplicity of physiological and pathological processes, and is therefore a promising target for

cancer therapy [124]. Due to oncogenic stimuli and active metabolism, most cancer cells consistently show higher levels of mitochondrial ROS relative to normal cells [125]. In response, cancer cells may increase their antioxidant ability to defend against excess ROS for having the ROS levels closer to the toxicity threshold, thus making them more sensitive to ROS than normal cells [126]. More than 90% of ROS in the normal organism are generated by the "electron leakage" of the mitochondrial oxidative respiratory chain, which is an unavoidable output of cellular metabolism [127]. Excess ROS in mitochondria usually cause irreversible damage to lipids, proteins and mtDNA, resulting in a "butterfly effect" of mitochondrial dysfunction [128, 129]. Therefore, it is possible to damage mitochondria and activate programmed cell death by increasing the level of ROS in mitochondria for the precise treatment of cancer.

For example, Zhang et al. designed a ROS-responsive polyprodrug nanoplatform to enable self-cycling mitochondrial drug release and mitochondrial ROS (mtROS) burst for intensive CDT [130]. As shown in **Fig.** 8A, mitochondria-targeted and ROS responsive polyprodrug nanoparticles were fabricated by carrying camptothecin (CPT) drug. When the polyprodrug specifically enters mitochondria, endogenous overexpression of mtROS triggers the initial CPT release. As a cellular respiration inhibitor, released CPT can further trigger significant mtROS regeneration, thus leading to subsequent release of more CPT. As such, the self-cycling CPT release and mtROS burst are favorable for long-term redox status imbalance, which in turn cause mitochondrial dysfunction and apoptosis. The initiation of endogenous mtROS eventually triggers a burst of mtROS for CDT, overcoming the drawbacks of exogenous light source in conventional PDT such as limited penetration depth and photobleaching of photosensitizers. On account of the ability to overcome the short lifetime of ROS and enhance the therapeutic effect, in addition to chemotherapy, the disruption of mitochondrial redox homeostasis has been intensively employed in PDT, PTT, radiation therapy, ultrasound therapy and immunotherapy. In particular, mtROS possesses immunogenicity that can be used to

activate immunotherapy. For example, Xiao et al. designed mitochondria-targeted core-shell nanoparticles containing a photosensitizer for PDT and ROS-activated immunotherapy (Fig. 8B) [131]. Under NIR light irradiation, mitochondrial PDT induced massive ROS production to lead to oxidative damage for the cell death. During the subsequent immunogenic cell death, ROS in turn activated CD8+ T cells in immunotherapy. Such an mtROS-induced endogenous damage-related molecular pattern to activate adaptive immunity achieved a suitable combination of PDT and immunotherapy.

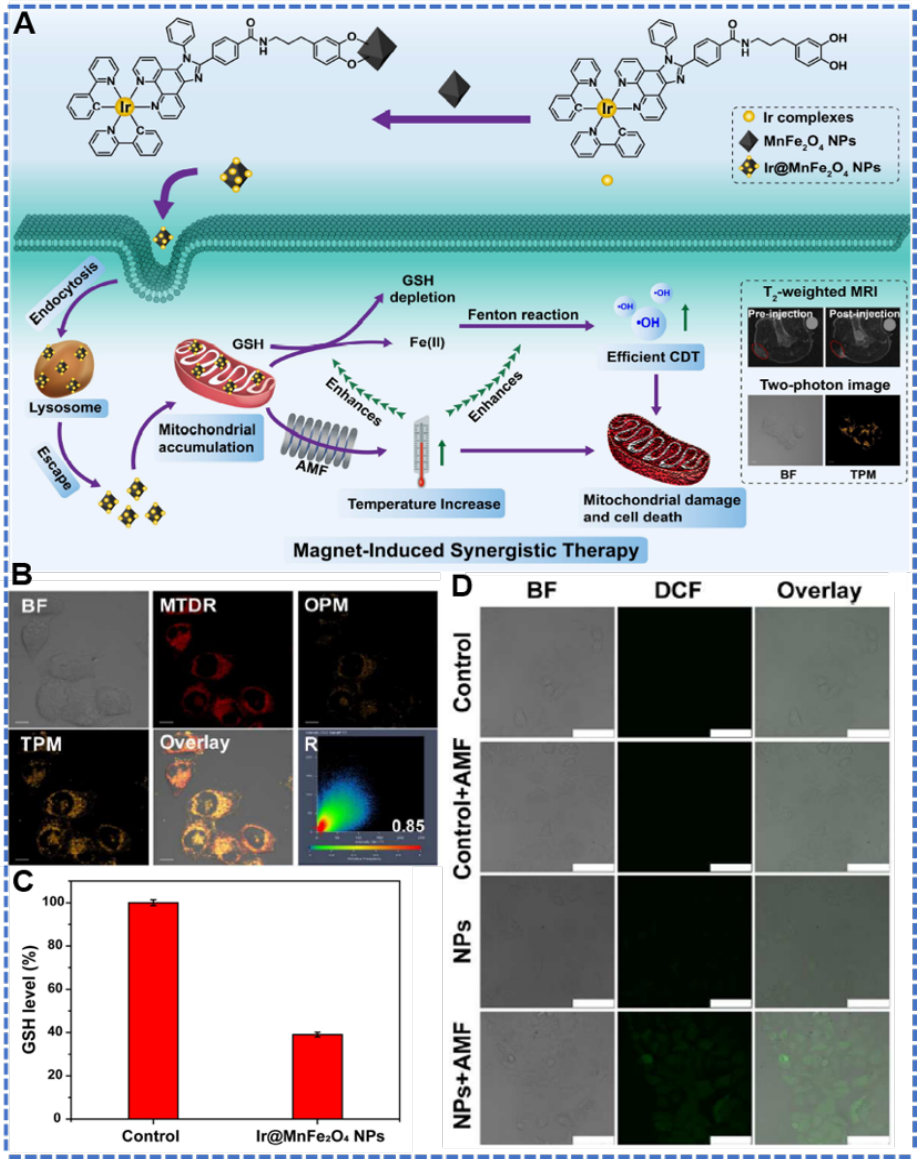


Fig. 9. (A) Synthesis of Ir@$MnFe_2O_4$ as a mitochondria-targeting magnetothermogenic nanozyme for magnet-induced synergistic therapy. (B) Colocalization images of Ir@$MnFe_2O_4$

with Mito Tracker Deep Red in HeLa cells, along with the colocalization coefficient (R). Scale bar = 10 μm. (C) GSH level of HeLa cells after incubation with Ir@$MnFe_2O_4$ (0.4 mg mL^{-1}) for 24 h. (D) Fluorescence images of HeLa cells stained with 2',7'-dichlorofluorescin diacetate (DCFH-DA) after various treatments as indicated. Scale bar = 75 μm. Reproduced with permission from Ref. [134]. Copyright 2020 Elsevier.

Free GSH in mitochondria accounts for the majority of intracellular antioxidant small molecules, producing highly reducing microenvironment and protecting cells from free radical-induced oxidative damage [132]. If GSH is not depleted in a timely manner, the effectiveness of ROS-based therapy would be largely compromised. Several strategies have been explored to reduce GSH levels within mitochondria for enhancing tumor-specific therapy [133]. Recently, Shen et al. established a mitochondrial targeted magnetothermogenic nanozyme for enhanced CDT and magnetic hyperthermia therapy (MHT) of GSH consumption [134]. As shown in **Fig.** 9A, $MnFe_2O_4$ nanoparticles decorated with mitochondria-targeting iridium (III) complex (Ir@$MnFe_2O_4$) reached mitochondria and were reduced by GSH to produce Fe^{2+}, followed by Fenton reaction to catalyze H_2O_2 into •OH. Meanwhile, the depletion of GSH would strengthen the CDT effect. When exposed to alternating magnetic field (AMF), Ir@$MnFe_2O_4$ would produce magnetic hyperthermia, accelerating mitochondrial damage for enhanced CDT. Ir@$MnFe_2O_4$ showed good mitochondrial co-localization (Fig. 9B). After 24 h of Ir@$MnFe_2O_4$ treatment, the GSH level of HeLa cells decreased significantly (Fig. 9C). For ROS detection experiments, the most pronounced green fluorescence was observed in HeLa cells after co-treatment with Ir@$MnFe_2O_4$ and AMF (Fig. 9D), indicating that GSH depletion and magnetic heat would jointly facilitate the treatment. This GSH-depleted nanoplatform not only shows ROS-based CDT, but also increases the sensitivity of cells to MHT. Another strategy is delivering GSH inhibitors to hinder the synthesis of GSH, such as L-buthionine sulfoximine [135]. Therefore, GSH depletion improves the efficiency of ROS-based therapy.

3.3 Glycolysis Inhibition

Although many different metabolic pathways can provide energy to maintain cell survival, the fact is that tumor cells preferentially derive energy from aerobic glycolysis [136]. Therefore, the inhibition of glycolysis to cut off the energy supply of tumor cells is an efficacious strategy to interfere with cellular activity and thus starve cancer cells [137, 138]. GOx has been receiving tremendous attention as a glucose depleting agent in tumor starvation therapy. Hence, Zhang et al. designed the mineralized metal nanoparticles loaded with GOx (LMGC), and the fabrication process and antitumor synergistic therapy are shown in **Fig.** 10A [139]. Upon release, GOx oxidized glucose to generate H_2O_2 and gluconic acid, accelerating the degradation of LMGC and the release of Ca^{2+} for inhibiting the tumor glycolysis. Gluconic acid produced from glucose metabolism could facilitate a significant decrease in solution pH, which subsequently resulted in the cleavage of LMGC and the release of Ca^{2+} (Fig. 10B, C). In addition, the inhibition of glycolysis could reduce ATP production and down-regulate HSP expression (Fig. 10D, E), which would enhance the efficacy of PTT by improving the tumor heat sensitivity.

Another method of inhibiting glycolysis is the targeted delivery of glycolysis inhibitors. For example, lonidamine (LND), a commonly used glycolysis inhibitor, not only impedes tumor glycolysis by inhibiting hexokinase II (HK II) activity [140], but also disrupts mitochondrial respiration [141]. Therefore, Tang and co-workers synthesized a GSH-responsive nanoprodrug (LSN), a F127-coated drug dimer of LND and NLG919, for glycolysis inhibition and attenuation of the tumor immunosuppressive microenvironment [142]. The schematic diagram of the synthetic route and antitumor treatment is shown in Fig. 10F. As compared to the control group, HK II levels were significantly reduced in the LSN group and LND group due to the release of LND (Fig. 10G). In contrast, for the LCN group, no significant reduction in HK II expression was found, mainly due to the low decomposition. Subsequently, LSN showed the best cancer cell inhibition both *in vitro* and *in vivo*, which was attributed to the inhibition of

glycolysis for limiting the metabolic activity of cancer cells (Fig. 10H, I). Therefore, the inhibition of mitochondrial glycolysis to block the metabolism of cancer cells is an effective strategy to interfere cellular activity for inducing the tumor cell death.

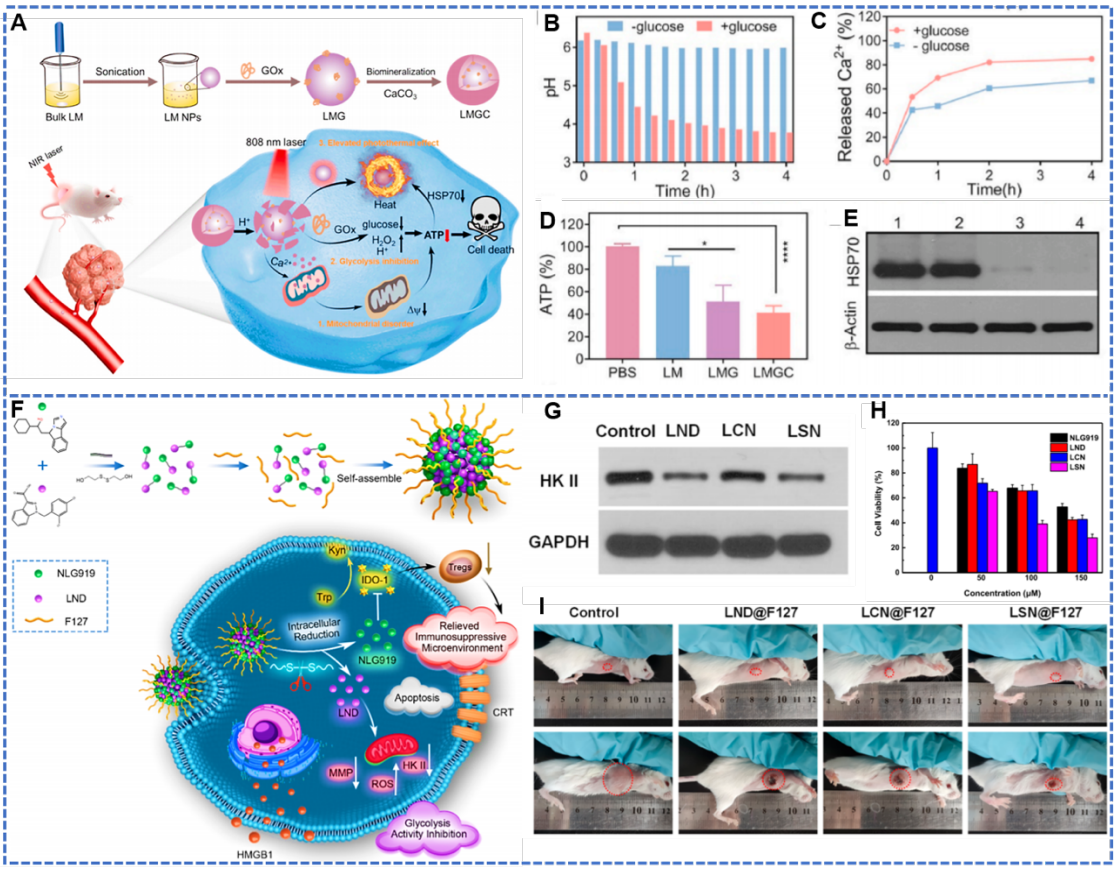


Fig. 10. (A) Schematic illustration for the fabrication of LMGC and its antitumor therapy by combining ATP inhibition and PTT. (B) pH values and (C) Ca^{2+} release of LMGC solution after 4 h of incubation in the presence and absence of glucose. (D) ATP level in CT26 cells treated with LMGC and control groups. *P < 0.05, ****P < 0.0001. (E) HSP70 expression in CT26 cells after various treatments (4: LMGC). Reproduced with permission from Ref. [139]. Copyright 2022 Elsevier. (F) Schematic illustration of GSH-responsive dimeric prodrug and the mechanism to restrain glycolysis of cancer cells and destruct the immunosuppressive microenvironment for inhibiting the tumor growth. (G) Expression of HK II in 4T1 cells with different treatments by Western blotting assays. (H) Cell viability of 4T1 cells evaluated by

MTT assay. (I) Photographs of the mice before (day 0) and after (day 14) different treatments. Reproduced with permission from Ref. [142]. Copyright 2021 American Chemical Society.

3.4 Protein Regulation

Although most of the proteins in mitochondria are derived from the cytoplasm, the unique mtDNA encodes 13 key proteins that are essential for the regulation of oxidative stress, energy metabolism, ion homeostasis, and a variety of other cellular activities [143-145]. This fact provides the opportunity to trigger cell death by adjusting mitochondrial proteins. Since mitochondria play an important role in biosynthesis, preventing mitochondrial protein synthesis in cancer cells is lethal for cell proliferation [146, 147]. Although an increasing number of targeted drugs that inhibit mitochondrial metabolism have been investigated, it remains a great challenge to specifically target the mitochondria of cancer cells without affecting the mitochondria of normal cells [32, 148]. The difference in energy metabolism between normal cells and cancer cells provides an important biochemical basis for the development of new strategies and new drugs targeting cancer cells selectively. Considering that cancer cells are more dependent on glycolysis, key enzymes in this pathway are potential therapeutic targets [149]. Recently, Xu et al. designed peptide-lipid nanoparticles (Flag-$(C16)_2$) for selective targeting of liver cancer cells over normal liver cells and for sensitizing cancer cells to cisplatin by inhibiting mitochondrial protein synthesis in liver cancer cells [150]. As shown in **Fig.** 11A, the nanoparticles, being a substrate of enterokinase (ENTK) for delivering chloramphenicol (CLRP) to the mitochondria of cancer cells, lead to the inhibition of mitochondrial protein synthesis and induce the release of cytochrome c for causing cancer cell death. To demonstrate the inhibition of mitochondrial protein synthesis, the intracellular levels of the mitochondrial cytochrome c oxidase subunit I (MT-COX-1) were evaluated after different treatments. As shown in Fig. 11B, a comparative analysis exhibited that the combination of CLRP and Flag-$(C16)_2$ did significantly reduce synthesis of MT-COX-1. In addition, the cytochrome c

expression in the cytosols of HepG2 increased upon increasing the Flag-$(C16)_2$ concentrations, alluding to the mitochondrial dysfunction (Fig. 11C). Moreover, the inhibition of mitochondrial protein synthesis subsequently sensitized cancer cells to cisplatin (Fig. 11D). This work provides an approach to repurpose other clinically approved ribosomal inhibitors to target and regulate mitochondrial protein synthesis for overcoming the tumor resistance.

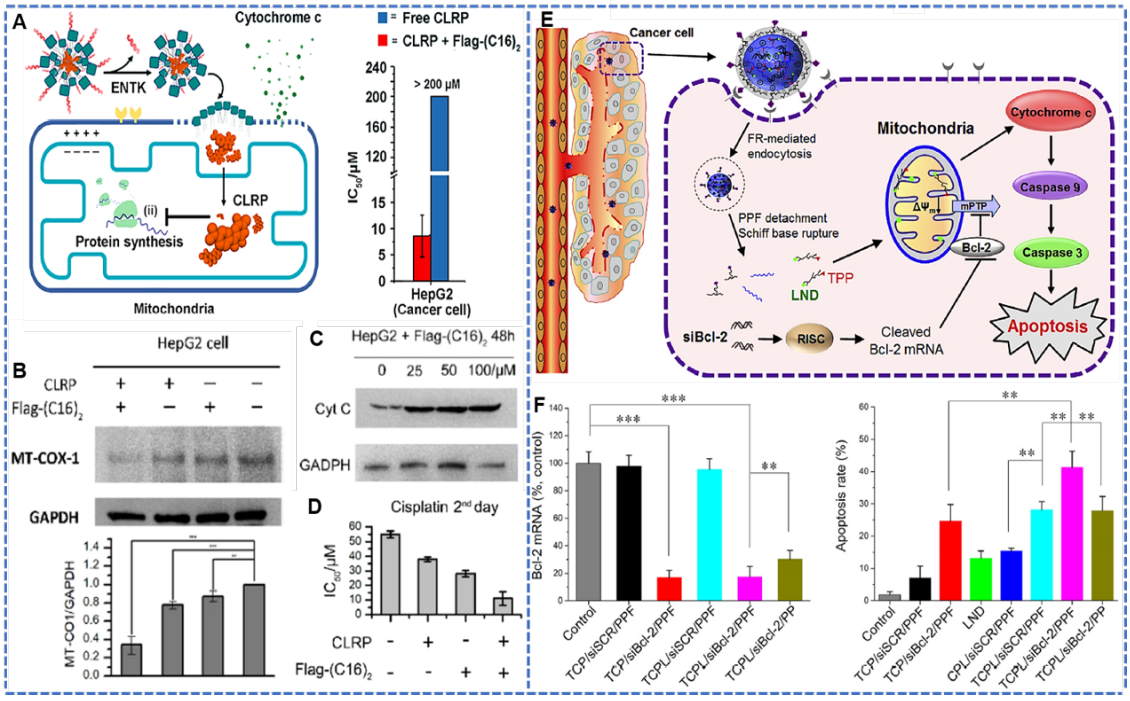


Fig. 11. (A) Multiple functions of Flag-$(C16)_2$: (i) perimitochondrial accumulation, (ii) mitochondria-targeting drug delivery, and (iii) mitochondrial outer membrane permeabilization. (B) Western blot analysis of MT-COX-1 levels in HepG2 cells treated by solvent control (PBS), Flag-$(C16)_2$, free CLRP, and the mixture of CLRP (100 μM) and Flag-$(C16)_2$. **$p < 0.01$, ***$p < 0.001$. (C) Western blot analysis of cytochrome c in the cytosol fraction from HepG2 cells incubated with Flag-$(C16)_2$ for 48 h. (D) Second day IC_{50} of cisplatin for HepG2 pretreated by solvent control (PBS), Flag-$(C16)_2$, free CLRP, and the mixture of CLRP and Flag-$(C16)_2$. Flag-$(C16)_2$ and CLRP were removed after the pretreatment, immediately followed by the addition of cisplatin. Reproduced with permission from Ref. [150]. Copyright 2020 American Chemical Society. (E) Schematic illustration for the proposed mechanism of mitochondria apoptosis

pathway synergistically motivated by siBcl-2 and LND. (F) Expression of Bcl-2 mRNA determined by qPCR and induction of apoptosis on HeLa cells by different formulations. *p < 0.05, **p < 0.01, ***p < 0.001. Reproduced with permission from Ref. [153]. Copyright 2015 Elsevier.

In particular, cancer cells can gain the ability to evade apoptosis by disrupting the balance of pro-apoptotic and pro-survival mitochondrial proteins, making mitochondrial apoptotic signals insensitive to cell death [151]. For example, anti-apoptotic proteins are usually overexpressed in many cancer cells, such as Bcl-2 protein, which may allow cancer cells to escape apoptosis, thus greatly compromising the anticancer effect [152]. To address this issue, Zhang et al. designed a graded delivery system (LND) using siRNA and therapeutic drug, where siRNA was used to suppress the expression of anti-apoptotic Bcl-2 for activating mitochondria-mediated apoptosis (Fig. 11E) [153]. After various treatments, the suppression of Bcl-2 gene expression in HeLa cells and their apoptotic profile were evaluated (Fig. 11F), indicating that the combination of Bcl-2 inhibition and chemotherapeutic agents exhibited better anticancer effects relative to their monotherapy. Overall, this work demonstrates a method for cancer chemotherapy through targeted regulation of mitochondrial proteins.

3.5 $\Delta\psi_m$ Depolarization

The mitochondrial membrane potential ($\Delta\psi_m$) is the key bioenergetic indicator that regulates respiration, ATP synthesis and ROS production, as well as the driving force for ion (beyond H^+) and protein transport, which are essential for healthy mitochondria [154]. Depolarization, meaning a decrease in mitochondrial membrane potential, would stimulate a series of cascade reactions, such as opening of mitochondrial membrane permeability, impaired oxidative phosphorylation, and release of various regulatory factors leading to progressive apoptosis [155]. Depolarization of $\Delta\psi_m$ has been widely reported as a hallmark event of mitochondrial

dysfunction for cell death [156]. In view of this, Zhang et al. employed a natural product from *Glycyrrhiza glabra* (GA) for mitochondria-targeting ligands, leading to $\Delta\psi_m$ depolarization and a series of mitochondria-mediated apoptosis [157]. The preparation of GA-functionalized graphene oxide as nanocarriers for delivery of DOX (GA-GO@DOX) through mitochondria-mediated apoptosis pathways is shown in **Fig.** 12A. After treatment with HepG2 cells, GA-GO@DOX significantly reduced $\Delta\psi_m$, indicating an opening of membrane permeability contributed to mitochondrial drug uptake (Fig. 12B). Further study was carried out on the mitochondria-mediated apoptotic pathways, where the key cascade proteins of cytochrome c, Bax/Bcl-2, caspase-9/-7/-3, and PARP were activated proportionately. GA-GO@DOX displayed the most remarkable apoptotic effect among the groups (Fig. 12C). In this work, mitochondria-mediated apoptosis mechanism was studied to show a decrease in mitochondrial membrane potential, which complementarily reinforced the targeted mitochondrial chemotherapy.

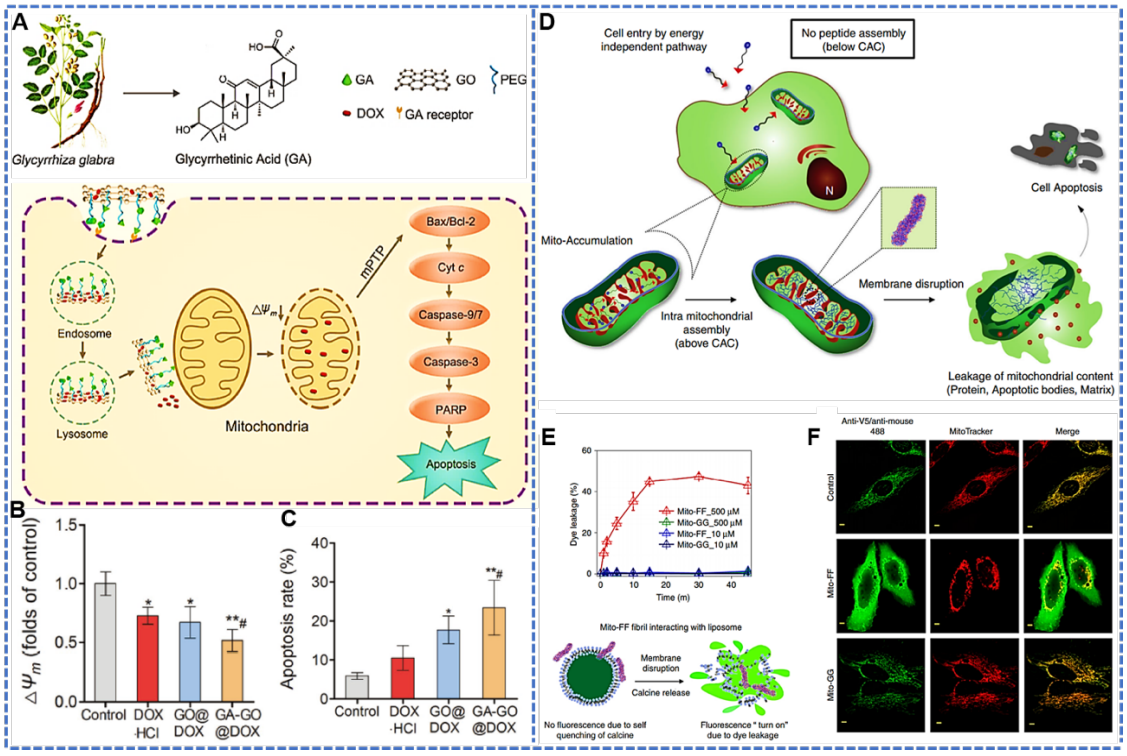


Fig. 12. (A) Natural product from Glycyrrhiza glabra used as an efficient mitochondrial targeting ligand and schematic illustration of the proposed pathway of GA-GO@DOX. (B) $\Delta\psi_m$

and (C) apoptosis rate of HepG2 cells after incubation with DOX·HCl, GO@DOX, GA-GO@DOX, and control at an equivalent DOX dose of 0.5 μg mL^{-1} for 24 h. *$p < 0.05$, **$p < 0.01$. Reproduced with permission from Ref. [157]. Copyright 2018 Wiley-VCH. (D) Stiff Mito-FF fibrils destroyed the mitochondrial membrane and activated the intrinsic apoptotic pathway against cancer cells. (E) Membrane disruption ability of Mito-FF fibrils monitored using calcein encapsulated in a model liposome. (F) Leakage of mitochondrial proteins to the cytosol monitored using APEX labeling (scale bar = 2 μm). Reproduced with permission from Ref. [160]. Copyright 2017 Nature Publishing Group.

Violent mitochondrial membrane disruption can directly induce and activate the intrinsic apoptotic pathway against cancer cells. Once the mitochondrial membrane is severely disrupted, the pro-apoptotic proteins Bax and Bak would penetrate the outer mitochondrial membrane, and cystathionases including initiating cystathionases (e.g., caspase-8 and caspase-9) and effector cystathionases (e.g. caspase-3 and caspase-7) can be activated [158]. Subsequently, apoptotic factors such as cytochrome c, Smac/Diablo and Omi/HtrA2 would be released from the mitochondria to the cytoplasm, thus stimulating apoptosis [159]. Accordingly, a mitochondria-targeted self-assembly of a peptide amphiphile (Mito-FF) was used as a powerful membrane disruptor to control the fate of cancer cells (Fig. 12D) [160]. Under mitochondrial targeting, the dipeptides were preferentially enriched in mitochondria and reached a critical concentration for self-assembly to form fibrillar nanostructures, which eventually induced severe breakage of mitochondrial membranes for apoptosis. To verify that fibril assembly could result in membrane rupture, a self-quenching liposome model encapsulated with calcein was used to perform dye leakage experiments. The addition of 500 μM Mito-FF fibrils rapidly led to the loss of membrane integrity in liposomes and the release of this calcein for restoring the fluorescence (Fig. 12E). However, the induction of liposome cleavage and fluorescence recovery were failed for self-assembled spherical counterpart. To study the mitochondrial

membrane disruption followed by induction of protein translocation or release, immunofluorescence imaging was employed to determine the location of fluorescently labeled mitochondrial proteins. As shown in Fig. 12F, the incubation with Mito-FF induced mitochondrial protein release to the cytosol, suggesting that in situ fibril formation could disrupt the mitochondrial membrane. In subsequent toxicity experiments, the membrane breakage led to mitochondrial dysfunction and apoptosis. This mitochondrial membrane disruption system offers new opportunities for in-depth studies of therapeutics and cellular function. Overall, $\Delta\psi_m$ plays a key role in intra-mitochondrial homeostasis and its depolarization would be a fatal blow against cancer cells.

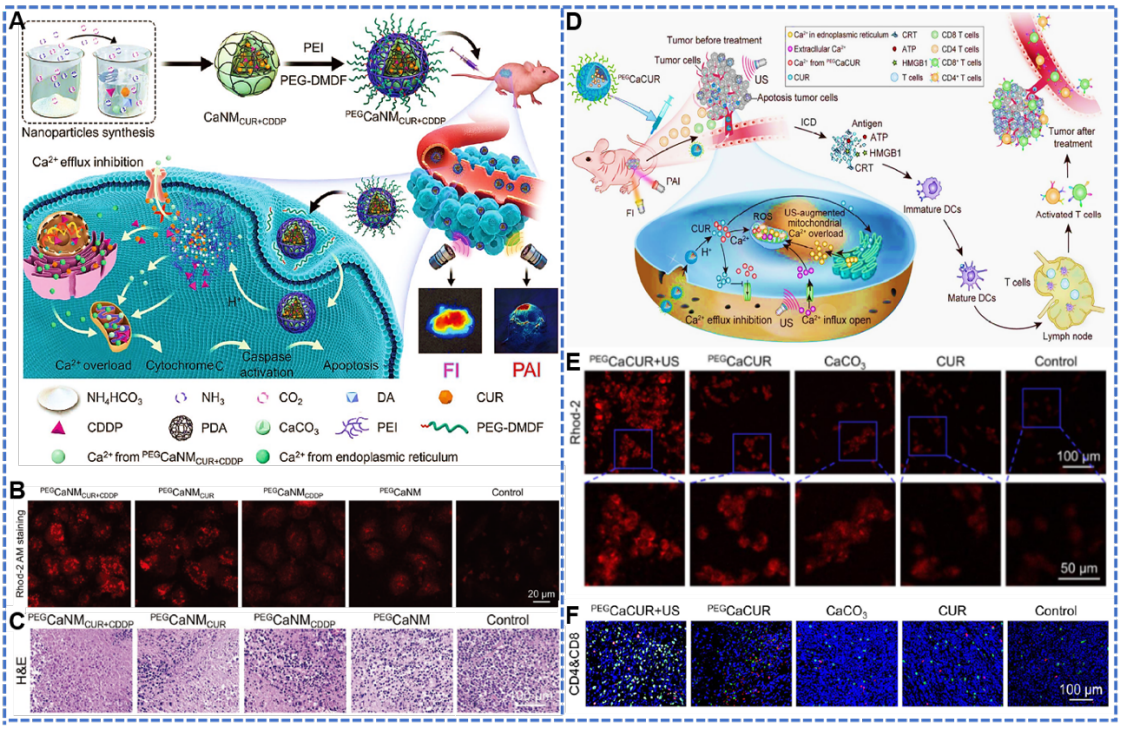


Fig. 13. (A) Schematic representation about functional pattern of multifunctional Ca^{2+} nanomodulator $^{PEG}CaNM_{CUR+CDDP}$. (B) Microimages of intracellular Ca^{2+} production after treatments with various Ca^{2+} nanomodulators for 4 h. (C) H&E-stained tumor biopsies collected from MCF-7-tumor-bearing nude mice at the end of treatment. Reproduced with permission from Ref. [169]. Copyright 2021 Wiley-VCH. (D) Schematic illustration of photoacoustic/fluorescence dual-mode imaging-guided synergistic cancer therapy through

ultrasound-augmented mitochondrial Ca^{2+} overload induced by calcium nanomodulator ^{PEG}CaCURa. (E) Microimages of mitochondrial Ca^{2+} production in 4T1 cells. (F) CD4 (red fluorescence) and CD8 (green fluorescence) T cells in tumor tissues after different treatments. Reproduced with permission from Ref. [172]. Copyright 2021 American Chemical Society.

3.6 Ion Interference

Metal ions with a variety of cell biological effects can play more important roles than expected in cell metabolism and proliferation, including osmolarity and acid-base homeostasis maintenance, catalytic and signaling pathway activation, protein and enzyme composition, and biomolecular targeting [161]. Overload of ions in mitochondria can lead to a series of disorders ranging from mitochondrial membrane depolarization, decreased ATP levels, changed mitochondrial morphology, to disturbed mitochondrial respiration and even cell death. As a result, ions can be applied to treat a wide diversity of cancers efficiently and without resistance, recently named ion-interference therapy [162]. In particular, calcium overload, characterized by an abnormal mitochondria accumulation of free calcium ion (Ca^{2+}) to induce intramitochondrial Ca^{2+} imbalance and cancer cell apoptosis, has attracted widespread attention in cancer theranostics [163]. In addition, cancer cells are more sensitive to Ca^{2+} overload than healthy cells, given the reported susceptibility of the Ca^{2+} signaling pathway in cancer cells to some stimuli [164]. Thus, various responsive Ca^{2+} nanoreactors based on calcium carbonate, calcium peroxide, calcium phosphate and calcium hydride have been widely developed for Ca^{2+} overload tumor therapy *via* disrupting mitochondrial Ca^{2+} homeostasis [165-167]. Due to the natural excretion of Ca^{2+} channels, however, the mitochondrial Ca^{2+} concentration would be immediately regulated to normal levels, resulting in a poorer anticancer effect [168]. To address the issue, Chen and co-workers reported a multichannel Ca^{2+} nanomodulator (^{PEG}CaNM$_{CUR+CDDP}$) consisting of calcium carbonate loaded with cisplatin (CDDP) and curcumin (CUR), polydopamine and surface PEGylation for Ca^{2+}-overload-dominated cancer

therapy, as depicted in **Fig.** 13A [169]. As shown in Fig. 13B, MCF-7 cells in $^{PEG}CaNM_{CUR+CDDP}$ group presented the highest fluorescence intensity as compared to the other groups, indicating the highest levels of free Ca^{2+} in the mitochondria. To further confirm the enhanced therapeutic effect of Ca^{2+} overload, hematoxylin and eosin (H&E) staining was performed on tumor tissue sections. As expected, $^{PEG}CaNM_{CUR+CDDP}$ exhibited the most apoptotic cells identified by extensive chromatin condensation and cell shrinkage (Fig. 13C). This multifunctional Ca^{2+} nanoreactor shows a promising potential for mitochondria-targeted cancer therapy.

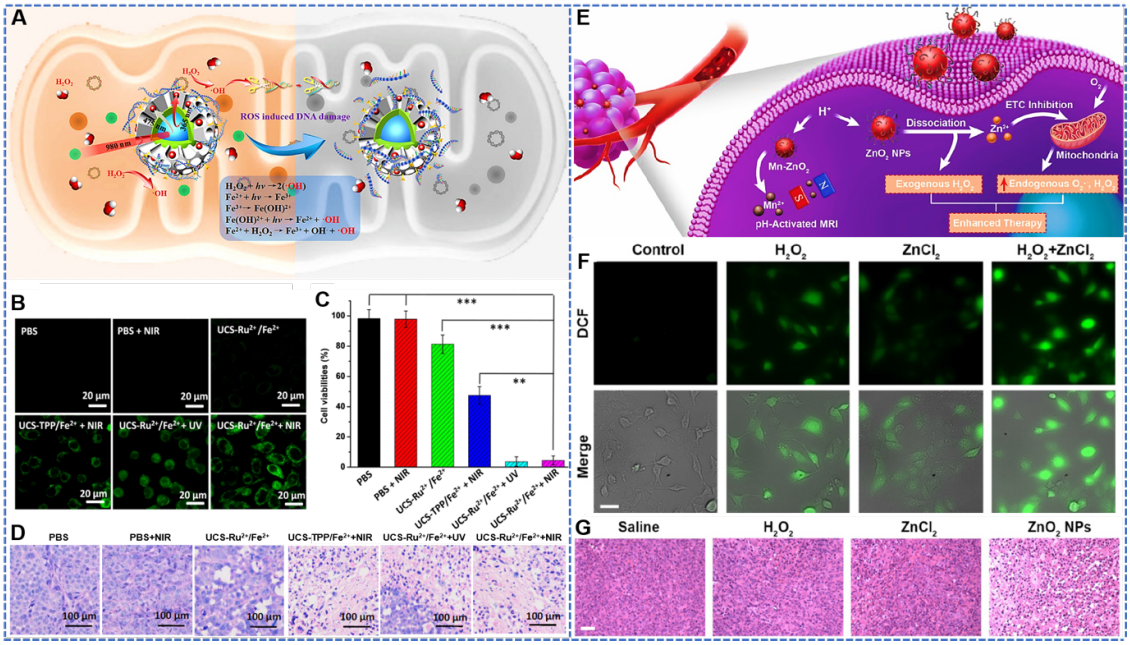


Fig. 14. (A) Schematic illustrations for the accumulated H_2O_2 in mitochondrion to react with Fe^{2+} based on a photo-Fenton for tumor-specific photochemotherapy. (B) Green fluorescence of DCF indicating the generation of •OH in HepG2 cells. (C) *In vitro* viability of HepG2 cells after different treatments (**P < 0.01 and ***P < 0.001). The power density and irradiation duration of 980 nm laser were 1.0 W/cm^2 and 20 min unless otherwise marked. (D) H&E-staining of the tumor tissue section harvested from different groups of mice in 3 days post irradiation. Reproduced with permission from Ref. [174]. Copyright 2017 Elsevier. (E) Schematic illustration of theranostic ZnO_2 nanoparticles for magnetic resonance imaging and enhanced oxidative stress-based cancer therapy. (F) DCF fluorescence of U87MG cells after

different treatments. Scale bar = 50 μm. (G) H&E staining of tumor tissues derived from different groups. Scale bar = 50 μm. Reproduced with permission from Ref. [175]. Copyright 2019 Ivyspring International Publisher.

In addition to tumor-microenvironment-responsive Ca^{2+} nanoreactors, exogenous stimuli, such as near-infrared laser and ultrasound (US), can also lead to Ca^{2+} overload in mitochondria by promoting Ca^{2+} influx from the extracellular fluid into the cytoplasm [170, 171]. Thus, an ultrasound-augmented Ca^{2+} nanomodulator (^{PEG}CaCUR) was developed by a simple one-pot strategy for mitochondrial Ca^{2+} overload and enhanced immunogenic cell death (Fig. 13D) [172]. Prior to assessing cytotoxicity, intramitochondrial Ca^{2+} levels were detected by confocal imaging (Fig. 13E). The mitochondrial Ca^{2+} concentration in the ^{PEG}CaCUR+US group was the highest among all groups, indicating that ultrasound effectively promoted Ca^{2+} influx into the cells. Furthermore, immune activation was evaluated by observing activated T cells (CD4 and CD8) in tumor tissues after different treatments. As shown in Fig. 13F, the ^{PEG}CaCUR+US group exhibited the highest number of activated T cells, indicating the sufficient immune activation *in vivo*. The authors proposed that mitochondrial Ca^{2+} overload with ultrasound could reinforce immunogenic cell death.

The overexpressed H_2O_2 in mitochondria can react with Fe^{2+} to produce strongly oxidizing and toxic hydroxyl radicals (•OH), named Fenton reaction, which has been extensively applied in tumor treatment [173]. Recently, Shi et al. construct upconversion nanoparticle/mesoporous silica nanostructures to deliver Fe^{3+}/Fe^{2+} for in situ mitochondrial Fenton reaction-assisted photochemotherapy (**Fig.** 14A) [174]. For intracellular ROS, the nanostructures carrying Fe^{2+} exhibited a strong green fluorescent signal under light exposure, indicating a large amount of ROS production (Fig. 14B). Both *in vitro* and *in vivo* anticancer experiments confirmed that the nanostructures had the best therapeutic effect among these groups (Fig. 14C, D), mainly attributed to mitochondrial Fenton reaction-assisted photochemotherapy based on Fe^{2+}.

Similarly, Chen et al. demonstrated that Zn^{2+} can exert antitumor effects by inhibiting the mitochondrial ETC [175]. At first, the modified ZnO_2 nanoparticles delivered exogenous H_2O_2 and large amounts of Zn^{2+} in the acidic tumor microenvironment (Fig. 14E). Then, Zn^{2+} acted on the mitochondrial ETC, leading to additional endogenous ROS production. To verify the synergistic anticancer effect of H_2O_2 and Zn^{2+}, intracellular ROS production was tested by 2',7'-dichlorofluorescin diacetate (DCFH-DA), an ROS probe. As shown in Fig. 14F, although U87MG cells incubated with H_2O_2 or Zn^{2+} alone exhibited obvious green fluorescence, H_2O_2 + $ZnCl_2$ group showed the most pronounced green DCF fluorescence, revealing the synergistically enhanced oxidative stress by H_2O_2 and Zn^{2+}. In addition, the mice injected with ZnO_2 nanoparticles exhibited severe damage as observed from H&E staining (Fig. 14G), attributed to endogenous and exogenous ROS. Compared with other therapeutic methods, ion interfering therapy shows lower side effects, but is limited by insufficient ion supply and incomplete elimination of tumor.

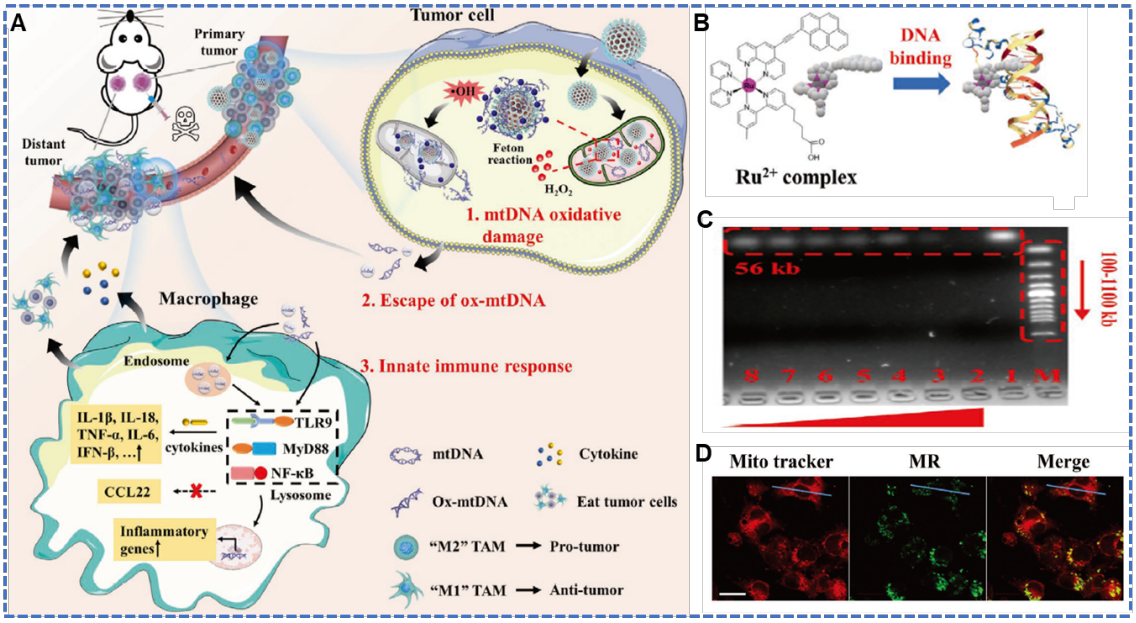


Fig. 15. (A) Schematic illustrations of MRF nanoparticles and proposed innate immunotherapy strategy for primary and distant tumor inhibition by oxidatively damaged mtDNA (ox-mtDNA) escaping from the primary tumor cells. (B) Schematic illustration of the simulated interaction

between dsDNA. (C) Ru^{2+} complex and agarose gel electrophoresis assay showing the binding of MRF nanoparticles to dsDNA (D-Loop sequence) and consequent helix structure damage at sequentially elevated MRF concentrations from group 8 to group 2. Group 1: 0 μg mL^{-1}. (D) Fluorescent fusion proteins used to examine the escape of mtDNA from mitochondria into the cytoplasm. Scale bar = 30 μm. Reproduced with permission from Ref. [178]. Copyright 2021 Wiley-VCH.

3.7 mtDNA Damage

Mitochondrial DNA (mtDNA), owning 16.5 kb base pairs and encoding 13 complexes, is essential for the oxidative phosphorylation bioenergetic mechanisms required for tumor initiation, proliferation and metastasis. In the absence of histone protection, mtDNA is more susceptible to ROS-induced DNA damage as compared to nDNA. Thus, mtDNA has become a new target for targeted tumor therapy [176]. Moreover, mtDNA containing inflammatory non-methylated CpG motifs similar to bacterial DNA makes it more like to "exogenous" rather than "endogenous" DNA [177]. By considering these properties, Shi et al. proposed a strategy to reactivate immunoresponse of macrophages based on mtDNA oxidative damage for specific tumor therapy [178]. The designed MRF nanoparticles (Fe^{2+}/Ru^{2+}-loaded mesoporous silica nanoparticles) were able to bind mtDNA, inducing oxidative damage of mtDNA by triggering the Fenton reaction in situ (**Fig.** 15A). Subsequently, the oxidatively damaged mtDNA (ox-mtDNA) would escape from the cells under an immunogenic damage-associated molecular pattern to innate immune response for releasing proinflammatory cytokines. As a result, macrophages performed pro-inflammatory M1-type polarization to recognize and phagocytose tumor cells. Ru^{2+} complexes can tightly join double-stranded DNA (dsDNA) binding by inserting into the main groove of DNA, as schematically shown in Fig. 15B. In agarose gel electrophoresis analysis, the dsDNA strips gradually became brighter upon decreasing the MRF concentrations (from right to left), indicating that the insertion of MRF nanoparticles into DNA

would lead to the fragmentation and dysfunction of dsDNA (Fig. 15C). In the co-localization assay, Ru^{2+}-loaded nanoparticles (MR) could enrich within the mitochondria. More interestingly, after 36 h of MRF treatment, the ox-mtDNA was observed to escape from the cells (Fig. 15D). Such an oxidative mtDNA for immunity activation is promising to be a natural immunotherapy method for the tumor treatment.

In addition, there are also targeted mtDNA oxidative damages associated with PDT, PTT and radiation therapy [179-181]. Recently, various approaches such as plasmids *via* hydrodynamic injection, fusogenic lipids, and cationic micelles have been developed for gene therapy of mitochondrial DNA transfection [182]. Overall, this targeted mtDNA damage in cancer cells is a feasible cancer treatment strategy.

3.8 Mitophagy Dysregulation

Mitochondrial autophagy (Mitophagy) is the targeted phagocytosis and destruction of mitochondria by the cellular autophagic apparatus and is often considered the primary mechanism of mitochondrial quality control [183]. Lysosome-mediated autophagy selectively degrades dysfunctional mitochondria to maintain the stability of the intracellular environment [184]. Mitophagy is induced by stress signals such as mitochondrial depolarization and hypoxia, and has been found to be more frequent in cancer cells than in normal cells [185]. Depending on the cancer type and stage, mitophagy fulfils different roles. Overall, phagocytosis as a form of self-protection can encourage cancer cells to gradually adapt to mitochondrial-targeted therapy and is therefore detrimental to cancer treatment [186]. For example, Cheng et al. found that effective inhibition of autophagy by bismuth embedded silica nanoparticles could enhance PTT *in vitro* and *in vivo* [187]. Ma et al. also reported that upregulated autophagy *via* gold nanospikes made cancer cells more resistant to radiation therapy [188]. To some extent, this is a stress response of mitochondrial autophagy to mitochondrial dysfunction.

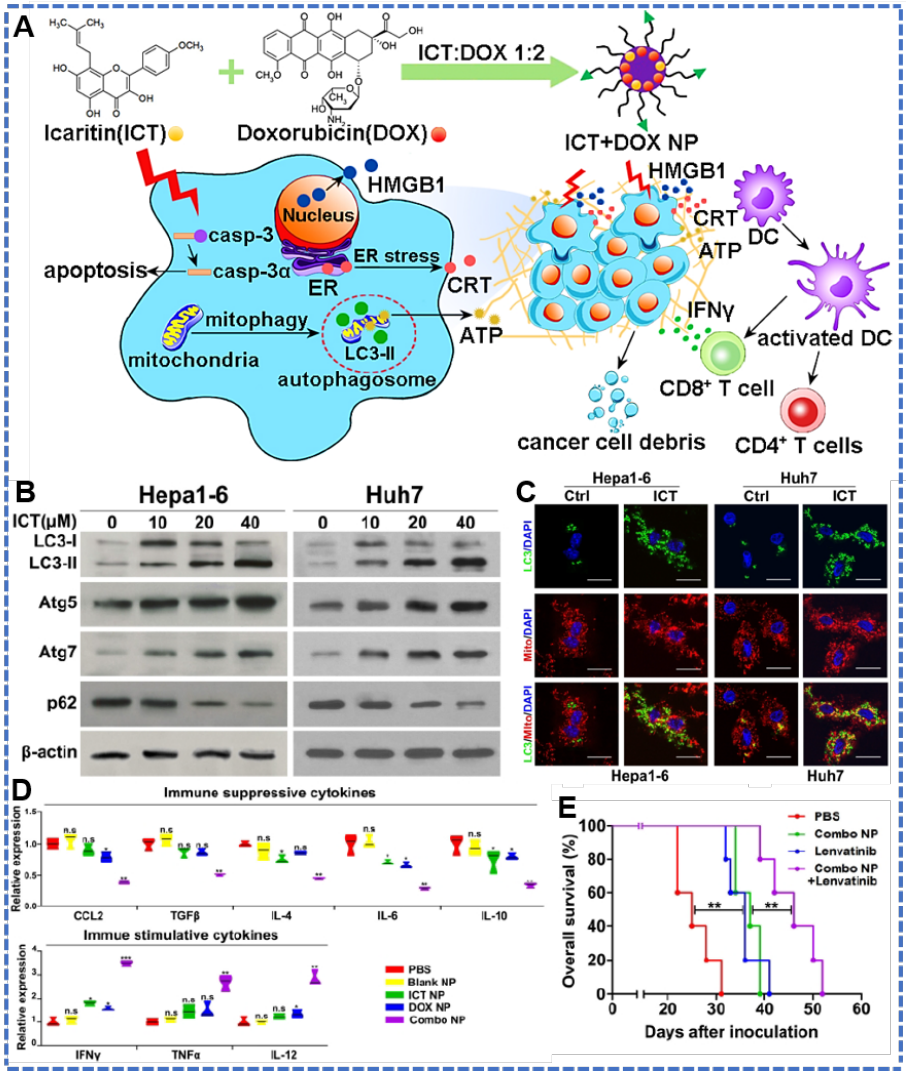


Fig. 16. (A) Schematic illustrations of icaritin for exacerbating mitophagy and synergizing with DOX to induce immunogenic cell death in hepatocellular carcinoma. (B) Immunoblotting of LC3, Atg5, Atg7, and p62 in HCC cells treated with icaritin for 24 h. β-actin acts as the loading control. (C) Cells treated with or without 20 μM icaritin for 24 h stained with MitoTracker Deep Red, and immunofluorescence stained with LC3. Scale bar = 10 μm. (D) mRNA expression of chemokines and cytokines detected by real-time PCR in tumors in various treatment groups. (E) survival curves of Hep1-6 tumor bearing mice in various treatment groups. *p<0.05, **p<0.01, ***p<0.001. Reproduced with permission from Ref. [191]. Copyright 2020 American Chemical Society.

In contrast, chronic or excessive autophagy has been reported to trigger various cell death programs [189]. However, it remains a challenge how to artificially tune autophagy, especially mitophagy, to be able to enhance cancer therapeutic effects [190]. Considering the ability of autophagy activators to induce immunogenic cell death, Yu et al. combined icaritin (autophagy activators) and DOX to remodel immunosuppressive microenvironment for an effective immunotherapy of hepatocellular carcinoma [191]. In this study, they used polylactic-co-glycolic acid-polyethylene glycol-aminoethyl anisamide nanoparticles to encapsulate icaritin and DOX with 1:2 molar ratio (**Fig.** 16A). Upon entry into the cells, the induced mitophagy activated the immune response and exhibited satisfied therapeutic effects. Icaritin induced intracellular autophagy was examined *via* immunoblotting of autophagy biomarkers. As shown in Fig. 16B, an increase in icaritin concentration promoted the conversion of LC3-I to LC3-II, the upregulation of Atg5,7 and the downregulation of p62, implying that icaritin did induce autophagy. To verify whether mitochondria were engulfed by autophagosomes, the co-localization of autophagosomes and mitochondria was demonstrated in Fig. 16C. It could be noticed that the co-localization of mitochondria and autophagosomes was significantly elevated both in Hepa1-6 and Huh7 cells after icaritin treatment. In subsequent *in vivo* immune studies, the nanoparticles exhibited a significant increase in immunostimulatory cytokines including IFNγ, TNFα and IL-12, and a decrease in immunosuppressive cytokines including CCL2, TGFβ, IL-4, IL-6 and IL-10, demonstrating the ability to reshape the immune microenvironment (Fig. 16D). After the combination of the nanoparticles with lenvatinib (a newly approved hepatocellular carcinoma inhibitor), this survival time was extended by 2 times relative to the PBS group (Fig. 16E). Recently, Wu and co-workers also reported an energy-depletion-based anticancer strategy *via* selectively activating excessive mitophagy in cancer cells [192]. Therefore, appropriately targeted tuning of mitophagy should be a promising option for the cancer treatment.

4. Conclusions and Future Perspectives

As the energy factory and suicidal weapon market of cancer cells, mitochondria have gained much awareness as a promising target for tumor therapy. In this review, we have summarized up-to-date research progress in constructing various mitochondria-targeted nanocomplexes and mitochondrial dysfunction for precision oncology therapy. Primarily, these approaches for mitochondria-targeted nanocomplex-induced mitochondrial dysfunction in cancer therapy are highlighted, categorized, compared and objectively discussed. It is expected that this review provides a wealth of inspiration on how to construct integrated nanosystems to interfere with various processes in mitochondria of cancer cells for tumor therapy, showing important implications for nanomedicine in the prevention, diagnosis, and treatment of various human diseases. In particular, mitochondrial dysfunction is thought to be a critical step in early cell death and even central to the apoptotic pathway. Based on these premises, the induction of mitochondrial dysfunction of tumor cells would have a great potential in tumor therapy. Similar effects of mitochondrial dysfunction underlie the pathology of many common diseases, and hence "mitochondrial therapy" can be applied to a wide range of diseases. With an increasingly aging world population, these common diseases become more prominent. Enormous human, economic, and medical resources would be expended on the development of advanced treatment technologies. Targeting mitochondria and developing new drugs for mitochondrial dysfunction will continue to be an area of need. Looking ahead, there are still many known and unknown challenges to the application of mitochondrial dysfunction-based nanosystems for future clinical applications.

(1) Improving biosafety: biosafety refers to the level of tolerance of ''foreign objects'' by the organism once they have entered the body, mostly depending on the size, charge, solubility and stability of nanosystems [193]. There is no doubt that biosafety is the guarantee for nanosystems to be put into clinical translation [194]. As discussed above, most of the mitochondria-targeted molecules have a strong positive charge, which may be toxic to normal

cells in the blood circulation. Currently, more and more studies are focused on using natural biomaterials to construct highly biocompatible nanosystems for cancer therapy, such as exosomes, cell membranes, bacteria, phages, red blood cells, and lymphocytes [195]. The integration of biomaterials and nanotechnology enables the construction of bio-activated, biocompatible and negligibly immunogenic nanosystems for precision nanomedicine. For example, Zhang and co-workers designed the bacteria-based bioreactor for tumor inhibition with negligible toxicity [196]. In addition, many mitochondria-targeting transition metal complexes possess photosensitive properties and are widely applied in PDT, while their phototoxicity and photobleaching issues should not be ignored [73, 197]. Since there is often no obvious boundary at the tumor site, light irradiation may result in the damage to the adjacent normal tissues. For example, our team previously used the mitochondrial template method to control the threshold value of surface plasmon resonance effect and photothermal ablation of tumors in order to avoid damage to adjacent normal tissues [50]. Thus, future studies should aim to explore intelligent biomimetic nanosystems to distinguish cancerous and normal cells for improving their biosafety.

(2) Improving targeting ability: the complexity and heterogeneity of the tumor microenvironment may affect the sensitivity and accuracy of mitochondrial targeting [198]. Therefore, to avoid non-specific targeting, improving specific identification is a prerequisite for precise treatment. The use of multi-responsive strategies to form logic gates to identify tumor cells followed by mitochondrial targeting delivery would be a useful approach to achieve the specificity. For example, we previously employed tumor overexpression of matrix metalloproteinase and low pH as dual responses to form a logic gate peptide for precise photosensitizer delivery to tumors [199]. In addition, external physical effects, such as magnetic fields, electronic fields and ultrasound, can also be utilized to facilitate the enrichment of nanosystems at the tumor site during blood circulation, which would be useful for the next mitochondrial targeting [200]. Wang et al. designed mitochondrial-targeted magnetic core-shell

nanoparticles for hierarchical targeting, with magnetic field-assisted first-stage tumor enrichment and TPP-guided second-stage mitochondrial targeting, leading to synergistic PTT and chemotherapy of cancer [201]. In addition, rational molecular simulations should be carried out to analyze the effects of structure and surface charge of nanosystems, ambient temperature and pH on "protein corona" formation during systemic delivery, possible off-target localization, and undesired toxicity for mitochondria targeting [202]. Furthermore, before targeting mitochondria, lipophilic cations may be captured by endosomes/lysosomes first, where there may be a risk of degradation by proteases. Even if they can escape, it usually takes several hours [14]. Therefore, there is also a need to develop more specific mitochondria-targeting molecules and systems for subsequent mitochondrial dysfunction.

(3) Improving stability: prior to clinical applications, nanomedicine may need to undergo long-term storage and transportation, and their stability is key to ensuring the biosafety and efficacy [203]. In addition, the surrounding environment such as high pressure and high temperature during mass production may lead to crystallization, agglomeration, and precipitation of nanoparticles [204]. When injected intravenously, the agglomeration of nanoparticles in the blood circulation can lead to blockage of capillaries with the risk of thrombosis [205]. Therefore, the stability issues of nanosystems deserve attention before being put into clinical trials. It is generally believed that small nanoparticles tend to stay in suspension longer due to their low settling rate. However, ultra-small nanoparticles are easily excreted through renal metabolism, reducing the time of blood circulation [206, 207]. For this reason, it is necessary to regulate the nanoparticles to the appropriate size. Such a demanding requirement adds to the complexity of the manufacturing process. Currently, the addition of stabilizers is usually used to improve the stability of nanosystems [208]. Self-stabilized nanosystem suspensions also gain attention [209]. A deeper understanding of the particle-particle interaction mechanism is essential for the design of efficient stabilizers. Moreover, the development of

advanced high-throughput screening techniques is also indispensable for the selection of efficient stabilizers.

(4) Combination therapy: although inducing mitochondrial dysfunction in cancer cells is an effective therapeutic strategy, it is difficult to completely eliminate stubborn tumors only by relying on mitochondrial dysfunction. Combination therapy is usually more effective than monotherapy [210]. Mitochondrial ATP inhibition is often combined with chemotherapy for drug-resistant tumors, which can effectively block the pumping out of drugs for intensifying chemotherapy and alleviating drug resistance [211]. For mitochondrial redox imbalance, it is often combined with PDT to reduce mitochondrial redox regulation while overcoming the short lifespan of ROS that compromises PDT [212]. For mitochondrial glycolysis inhibition, it is often combined with hypoxia-activated prodrug therapy, where glucose catabolism exacerbates the hypoxia, so as to further activate prodrug therapy [213]. In this case, mitochondrial dysfunction can serve as a powerful aid to enhance therapeutic efficacy and reduce effective drug concentrations through skillful coordination with other therapeutic approaches. Often, single treatment modality has been found to be difficult to completely eliminate entire tumors, mainly attributed to the resistance of complex tumors to monotherapy. For example, in radiotherapy, severe hypoxia limits the effectiveness of treatment for deep tumor cells [214]. Thus, overcoming the dilemma of monotherapy requires two or more treatment modalities to work cooperatively. Thus, the combination of mitochondrial dysfunction with other therapeutic approaches can achieve "multimodal synergistic therapy" with "1 + 1 > 2" therapeutic effects.

(5) Exploring mitochondrial functions: It is undeniable that some malignancies develop mtDNA mutations, and in some types of cancers, these mutations are the main causative factors. However, their causal relationship has still not been fully understood [173]. For example, the KRAS gene is responsible for pancreatic cancer [215], while the deletion of PTEN and TP53 is the cause of prostate cancer [216]. Both of these conditions can lead to mitochondrial dysfunction, but the mechanisms are fundamentally different. On the one hand, severe

mitochondrial dysfunction leads to the inhibition of cancer cell growth. On the other hand, appropriate stimulation of mitochondrial dysfunction can enhance mitochondrial redox homeostasis, thereby promoting cancer cell proliferation [217]. Moreover, a better understanding of the differences in mitochondrial function between cancer cells and normal cells would improve the selectivity of mitochondria targeting in cancer cells. Thereby, highly specific targeting nanosystems should be developed to trigger the death mechanism only in the mitochondria of cancer cells. Deeper understanding of the basic biology in mitochondrial dysfunction from different cancer types is essential for mitochondrial targeting and sensitivity.

In conclusion, mitochondrial dysfunction plays an important role in intensive tumor therapy, as well as other mitochondria-related diseases. The development of nanosystems based on mitochondrial dysfunction involves multidisciplinary fields such as advanced materials, biochemistry, and cell biology. Therefore, there is still an important need to investigate the applications of mitochondrial dysfunction in cancer therapy, not only to lay the foundation for the development of novel targeted drugs, but also to deepen the understanding of the pathogenesis of cancer cells.

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