Enhanced photodynamic therapy by enhancing the light energy capture efficiency of porphyrin photosensitizers

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Abstract

Photodynamic therapy (PDT) has received increasing attention in cancer treatment because of its advantages such as minimally invasive and selective destruction. With the development of PDT, impressive progress has been made in the research of preparing photosensitizers, especially porphyrin photosensitizers. However, the limited tissue penetration and light energy capture efficiency of porphyrin photosensitizers have been the two major obstacles for conventional photosensitizers. Therefore, it is necessary to enhance the tissue penetration and improve the light energy capture efficiency of porphyrin photosensitizers through structural modifications. In addition, indirect excitation of porphyrin photosensitizers using fluorescent donors (fluorescence resonance energy transfer) has been successfully used to address these issues. In this manuscript, we focus on how to enhance the photoenergy capture efficiency of porphyrin photosensitizers, aiming to improve the efficiency of singlet oxygen (1O2) production in tumor tissues and enhance the photodynamic therapy effect of photosensitizers.

1 Introduction of PDT

PDT is an emerging non-invasive cancer treatment(Kwiatkowski et al. 2018) that uses photosensitizers, light and endogenous molecular oxygen to kill cancer cells or microorganisms(Dougherty et al. 1998). Hermann von Tappeiner first proposed the "photodynamic effect", reporting that certain dyes can make microorganisms sensitive to light and that exposure to sunlight can rapidly lead to cell death(Kessel 2019). Photosensitizer is not toxic to cells before illumination. Photosensitizer forms an excited singlet state when irradiated by light at appropriate energy wavelengths and then transforms into a long-lived excited triplet state; this triplet state can undergo photochemical reactions in the presence of oxygen, transferring energy to surrounding oxygen molecules and forming reactive oxygen species (ROS), which kill cancer cells, pathogenic microorganisms and unwanted tissues(Abrahamse and Hamblin 2016; Castano et al. 2004; Josefsen and Boyle 2008; Nyman and Hynninen 2004; Weizman et al. 2000). How photosensitizers under light conditions transfer energy to oxygen molecules? And how to improve the light energy capture efficiency of photosensitizers are questions to be further explored by scientists.

2 Porphyrins and their effects

Porphyrins are macrocyclic pigments and cofactors that occur commonly in nature and are often referred to as the "pigments of life"(Battersby 2000). The word porphyrin actually comes from the Greek word "porphyra", because porphyrins are usually bright purple or red in color(Senge et al. 2021). The backbone of porphyrins is porphine (Fig. 1), an aromatic compound that contains up to 26 π-electrons, 18 of which form a continuous plane. Its role in plants and animals as a metal-binding cofactor to form biomolecules is crucial in many metabolic pathways, especially in facilitating oxygen transport in cellular respiration and

energy capture in photosynthesis(Pan et al. 2021). The insertion of metal atoms into porphyrins affects the degree of electron delocalization of the conjugated system, making their properties more diverse and further broadening the idea of the development of porphyrin-based photosensitizers(Gupta et al. 2006; Takechi et al. 2006).

Fig. 1 Structure of porphine.

2.1 Porphyrins are involved in photosynthesis in plants (excellent light-trapping properties).

Sunlight is the most abundant source of energy on Earth and is the source of various bioenergy production. Phototrophic organisms are able to access this light energy and convert it into chemical energy through the process of phototropic charge separation(Harmatys et al. 2019). In ecosystems, the chemical energy required for life is obtained mainly through the conversion of light energy by photosynthesis(Mirkovic et al. 2017), and porphyrins are essential pigments for many biological energy transfer processes in plants, algae and bacteria(Shen et al. 2015; Xie et al. 2020; Zhu et al. 2019a). Chlorophyll is a magnesium (Mg)-tetrapyrrole molecule (Fig. 2) that plays a crucial role in photosynthesis. The functions of chlorophylls include capturing light energy, transporting excitation energy down to the reaction center on a time scale of 10-100 ps, and driving charge separation reactions at the reaction center(Croce and van Amerongen 2014; Park et al. 2021). These molecules contain similar five-membered ring structures, but with different side chains or reduced states(Chen 2014). Variations in the rings or side chains in different types of chlorophyll result in different absorption properties, allowing the organism to capture different wavelengths of sunlight and enhance light energy harvesting efficiency(Chen and Scheer 2013). The ability of chlorophylls to convert light energy into chemical energy has made porphyrins popular in light energy capture research. Chlorophyll is widely found in nature and is a key substance for plants and some bacteria to capture light energy and produce organic matter, which is the basis for people's survival. For this reason, there is an urgent need to enter a new field in the study of porphyrins and expect to move to a higher level.

Fig. 2 Chemical structure of chlorophyll (Chls).

2.2 Porphyrins promote oxygen transport in animals and humans (excellent biocompatibility)

Heme (Fe-protoporphyrin IX) is an endogenous porphyrin derivative that is an important molecule in aerobic organisms(Kabe et al. 2006). Heme (Fig. 3) is a metal compound consisting of an iron atom coordinated through its nitrogen atom to a tetrapyrrole ring system known as the protoporphyrin part. The iron in heme binds to the histidine residues of the pearlin chain to form hemoglobin. Notably, the iron in hemoglobin (the primary carrier of oxygen) is in the ferrous state (Fe^{++}), which allows for reversible binding to molecular oxygen. Hemoglobin is oxidized and converted into methemoglobin, where iron is oxidized to Fe^{+++} and its oxygen-carrying capacity changes significantly(Tsiftsoglou et al. 2006), so that hemoglobin can participate in respiration as an oxygen molecular carrier. Besides, heme is an important cofactor in mitochondrial electron transport (complexes II-IV), drug and steroid metabolism (cytochromes), signal transduction (nitric oxide synthase, soluble guanylate cyclase), transcription (N-PAS2, Bach I) and regulation of antioxidant defense enzymes(Krishnamurthy et al. 2007; Ponka 1999). The many functions of heme in animals and humans have attracted the interest of scientists. It is worth mentioning that the widespread presence of heme in animals as well as humans indicates that porphyrins are biocompatible in humans, offering the possibility of developing porphyrin-based photosensitizing drugs.

Fig. 3 Chemical structure of heme.

2.3 Application of porphyrins in PDT of cancer

Cancer has become a huge threat to human health, with millions of patients dying from cancer every year, making it the second leading cause of death in the world after cardiovascular disease(Bouramtane et al. 2019). Traditional cancer treatments are divided into three main types, surgical treatment, physical therapy and chemotherapy, but all of them have many side effects. Therefore, breakthroughs in novel cancer treatments have become the main goal of scientists. The key roles of porphyrins in light energy capture and oxygen molecule transport in the human body have been described earlier in this paper, respectively. The excellent

light trapping properties and good biocompatibility in human tissues make it possible for porphyrins to be applied as photosensitizers for cancer therapy.

As medicine continues to evolve, so do cancer treatment strategies. PDT is considered to be a safer cancer treatment with fewer side effects(Luo et al. 2017). With the development of PDT, impressive progress has been made in the research of preparing photosensitizers, especially porphyrin-based photosensitizers(Lin et al. 2020). Most of the photosensitizers used for cancer therapy have a porphyrin-based macrocyclic backbone(M. 1997; Martinez De Pinillos Bayona et al. 2017; Morgan and Oseroff 2001), and the main advantages of porphyrins in photodynamic studies include: (1) stability of aromatic compounds; (2) effective absorption of visible light; (3) high yield of reactive oxygen species; (4) easy functionalization modifications and structural diversity; (5) long triplet state lifetime and low dark toxicity(Ethirajan et al. 2011; Xiong et al. 2019). Hematoporphyrin (HPD) was first used by Dougherty in 1978 for the treatment of gastrointestinal cancers(Dougherty et al. 1978; Habermeyer and Guilard 2018). Clinical studies have shown that PDT has been increasingly used in the treatment of solid tumors, including tumors of the brain, head and neck, skin, esophagus, lung, gastrointestinal tract, pancreas, bladder, prostate, breast, cervix, and ovary, as well as basal cell carcinoma(Banerjee et al. 2017; Dobson et al. 2018; Fan and Andrén-Sandberg 2007; Felsher 2003; Li et al. 2018). Sodium porphyrin (Fig. 4) is the world's first approved photosensitizer for the treatment of cancer(Lin et al. 2020) that is not only reusable but also has virtually no side effects and does not develop resistance to the drug.

Fig. 4 Structure of sodium porphyrin.

3 Mechanism of PDT of porphyrin

The anti-tumor mechanism of PDT consists of two main phases (Fig. 5). Photosensitizer (PS) accumulates at the tumor site after intravenous injection and then irradiates the tumor tissue at a specific wavelength. In the first stage, PS changes from the ground state (single-linear state (S_0)) to the excited single-linear state (S_1) after being irradiated (nanosecond range). The excited state of the photosensitizer is very unstable and loses excess energy through non-radiative (thermal emission) or radiative (fluorescence emission) pathways(Bouramtane et al. 2019; Castano et al. 2005; Robertson et al. 2009). The excited single-linear state can produce a more stable excited trilinear state (T_1) with parallel spins (microsecond to millisecond range) by inter-system crossover. In the T_1, PS can undergo two types of reactions (Type I reactions and Type II reactions). In the first type of pathway, electron or hydrogen atom transfer occurs between the T_1 photosensitizer and the cell membrane of the biomolecule(Z. 2003). This process forms free radicals and radical ions, leading to the production of cytotoxic hydroxyl radicals (*OH), hydrogen peroxide (H_2O_2), and other ROS. The second type of reaction involves the interaction between electronically excited trilinear state photosensitizers and the ground state trilinear state molecular oxygen ($^3O_2$). The excited PS transfers energy to $^3O_2$ to form the singlet oxygen. The product$^1O_2$ can react with a variety of biomolecules and is a key factor in the induction of apoptosis and tissue destruction in cancer cells(Buytaert et al. 2007; Kessel and Oleinick 2010; Mehraban and Freeman 2015). In addition, it has been demonstrated that type I and type II reactions can occur simultaneously and independently, and that type II reactions play a more important role in PDT(Castano et al. 2004; Ethirajan et al. 2011; Gomes et al. 2018; Lin et al. 2020).

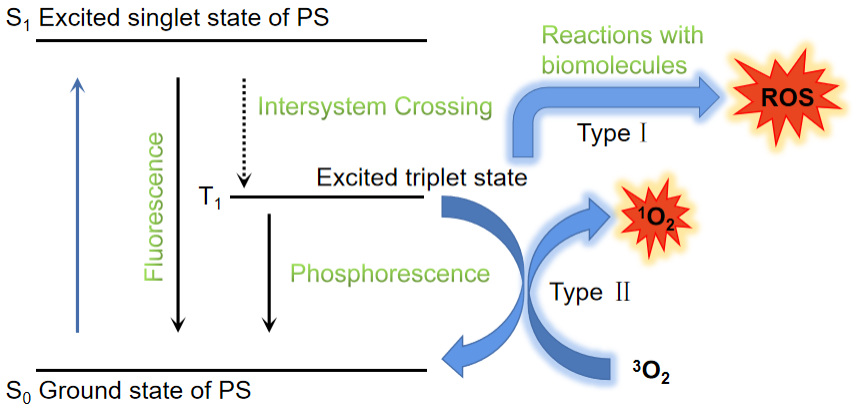

Fig. 5 Mechanism of PDT action.

4 Enhance PDT by improving the light energy capture efficiency of porphyrin photosensitizers

Porphyrins are widely used in the field of PDT because of their special photosensitive properties. However, porphyrins also have many shortcomings in cancer therapy. For example, porphyrins have low water solubility, which makes it easy for them to aggregate through buildup, leading to electronically excited state bursts, thus reducing the quantum yield of $^1O_2$ and weakening the effectiveness of PDT. In addition, longer wavelengths of red light are generally chosen in PDT, which can easily irradiate deeper tumor tissue and enable photosensitizers to produce photodynamic therapeutic effects. However, the limited tissue penetration and light energy capture efficiency of porphyrin photosensitizers have been the two major obstacles for conventional photosensitizers. Therefore, it is necessary to enhance the tissue penetration and improve the light energy capture efficiency of porphyrin photosensitizers through structural modifications. In addition, indirect excitation of porphyrin photosensitizers using fluorescent donors (fluorescence resonance energy transfer) has been successfully used to address these issues. In this manuscript, we focus on how to enhance the photoenergy capture efficiency of porphyrin photosensitizers, aiming to improve the efficiency of $^1O_2$ production in tumor tissues and enhance the PDT effect of photosensitizers.

4.1 Structural modification red-shift the spectral absorption band of porphyrin photosensitizers

In the past few years, most studies have focused on enhancing the photophysical properties of PS through different structural modifications. Such as binding with other molecules, metallization and nanotechnology applications(Lin et al. 2020). Hilmey and co-workers synthesized a series of dithioporphyrin-based photosensitizers and evaluated a series of photodynamic properties(Hilmey et al. 2002). The results showed that the different combinations of heteroatoms in the center of the porphyrin ring resulted in the I-band absorption peaks of these compounds with longer wavelengths than those of Photofrin. And the new coordination porphyrin compounds synthesized in this study efficiently generate $^1O_2$ under the irradiation of I-band. The red-shift of the I-band absorption peak can increase the effective penetration depth of light, which is of great significance for the clinical application of porphyrin-based photosensitizers (Fig. 6). Cheng and co-workers made a composite photosensitizer(Cheng et al. 2019) by simply mixing DNA G-quadruplex with hydrophilic porphyrin $(TMPipEOPP)^{4+}*4I^-$. This new photosensitizer showed a new absorption band near 700 nm. More interestingly, the absorption intensity of the new photosensitizer in the Q-band is much higher than that of the free TMPipEOPP. For example, the molar absorption coefficient at 700 nm of the complex formed by TMPipEOPP with G-tetramer AS1411 is about 47,000 $L{\cdot}mol^{-1}{\cdot}cm^{-1}$, which is 7.4 times higher than the molar absorption coefficient of free TMPipEOPP at 650 nm. Compared with the conventional porphyrin photosensitizer, the excitation wavelength of the composite photosensitizer is red-shifted by ˜50 nm (from 650 nm to 700 nm), which is favorable for light penetration. In addition, the light absorption efficiency of the composite photosensitizer was increased by ˜7.4 times, which greatly improved the $^1O_2$generation capacity and PDT effect.

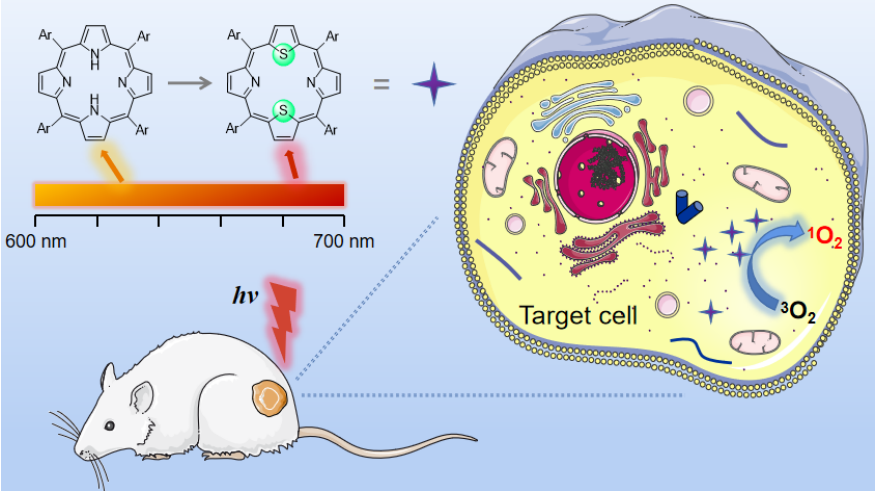

Fig. 6 Porphyrin photosensitizer structure modification to enhance PDT. The redshift of the absorption spectral region of the photosensitizer enhances the penetration of deep tissues

4.2 Metal-modified porphyrin photosensitizers enhance light energy capture efficiency to enhance PDT

Metal-porphyrins are widely present in nature and their ability to cleave DNA nucleases has attracted significant attention in the last few years. Thus, combining porphyrins with metals not only provides additional antitumor activity and tumor selectivity, but also allows tracking the biodistribution of metals inside and outside tumor cells(Lovejoy and Lippard 2009). Due to paramagnetic effects, the photocatalytic activity of metal complexes is heavily dependent on the central metal(Zhang et al. 2019c). Therefore, many researchers have inserted metals into porphyrin rings to maintain the stability and photophysical properties of the porphyrin ring. In addition, the structure of β-substituted porphyrins is closer to that of natural porphyrins and has been widely used in biological research(Zhou et al. 1996). In these studies, some transition metal compounds, such as iridium, ruthenium, rhenium, and osmium compounds, were investigated to have good antitumor activity, especially in the field of photodynamics(Imberti et al. 2020; Xie et al. 2021; Zhang et al. 2019a; Zhu et al. 2019c). Ru is less toxic to normal cells and its use in PDT is very attractive(Schmitt et al. 2008; Schmitt et al. 2009).

Schmitt and co-workers synthesized four aromatic Ru(II) derivatives (the aromatics are C_6H_5Me or*p* -Pr^iC_6H_4Me), Mononuclear 5-(4-pyridyl)-10,15,20-triphenylporphyrin, 5-(3-pyridyl)-10,15,20-triphenylporphyrin, tetranuclear 5,10,15,20-tetra(4-pyridyl)porphyrin (tetra-4-pp), 5,10,15,20-tetra(3-pyridyl) porphyrin) (tetra-3-pp) and evaluated them as potential dual photosensitizers and chemotherapeutic agents against human melanoma cells Me300(Schmitt et al. 2009). The results showed that the uptake and high photosensitizing activity of metal Ru on human melanoma cell models were promoted under red light (652 nm) irradiation at only 5 J/cm^2. In another study, Zhang and co-workers synthesized porphyrin derivatives containing Ru(II) polypyridyl porphyrins and zinc(II) porphyrin structures and evaluated their cytotoxicity against human nasopharyngeal carcinoma HK-1 and cervical cancer HeLa cells(Zhang et al. 2011). The results showed that the porphyrins containing Ru had high$^1O_2$ quantum yields, rapid cellular uptake, low dark cytotoxicity and potent photocytotoxicity (80% of Ru-L-containing incubated HK-1 cells were killed at a concentration of 1 μM and a yellow light dose of 3 J/cm^2).

4.3 Porphyrin self-assembled nanoparticles enhance light energy capture efficiency to enhance PDT

A major drawback of porphyrin-based photosensitizers is that they easily aggregate through stacking, leading to quenching of electronic excited states, thereby reducing the quantum yield of$^1O_2$ and diminish the

effectiveness of PDT(Escudero et al. 2006; Helmich et al. 2010; Ji et al. 2018; Lee and Kopelman 2011; Liu et al. 2013). Self-assembly is a natural phenomenon and a powerful method for applying multifunctional nanomaterials to biological applications(Fan et al. 2004; Grzelczak et al. 2019; Liu et al. 2016; Wang et al. 2004; Zhang et al. 2019b). By self-assembling into nanoparticles, porphyrins can effectively address their tendency to aggregate in PDT, efficiently trapping light energy and generating $^1O_2$ (Fig. 7). Studies of meso-tetra-4-hydroxyphenylporphyrin (mTHPP) with polyethylene glycol molecules (PEG) have shown that the complexes formed improve the solubility of the porphyrin photosensitizers and reduce their aggregation in the aqueous environment, thus allowing efficient capture of light energy to produce $^1O_2$(Avci et al. 2014; Ding et al. 2011).

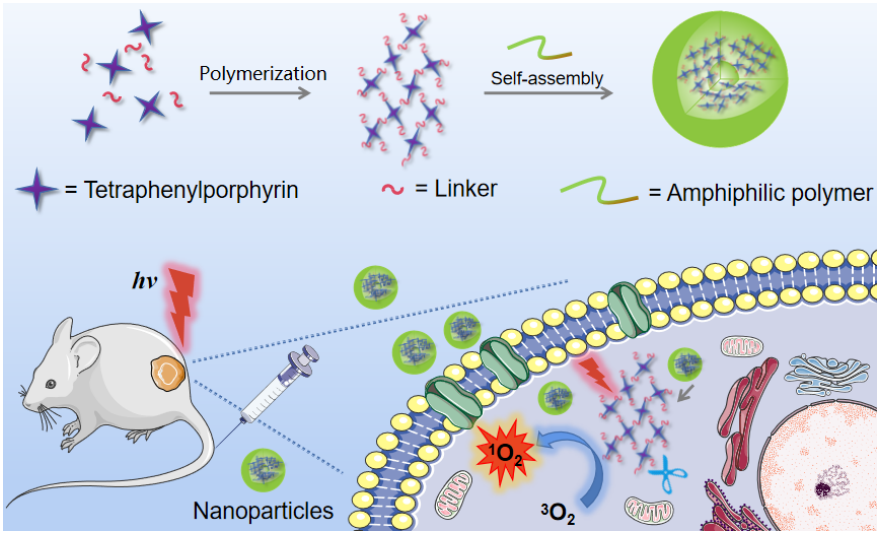

Fig. 7 Porphyrin self-assembled nanoparticles restrict porphyrin aggregation to enhance PDT. Advantages: a. Limited tetraphenylporphyrin precipitates b. High $^1O_2$ generation efficiency

On this basis, Jin and co-workers prepared alternating copolymers (P(MIPOSS-alt-VBTPP)-b-POEGMA) using 4-vinylbenzyl terminal tetraphenylporphyrin (VBTPP) and maleimide isobutyl polyhedral oligomeric sesquioxane (MIPOSS) as starting monomers by alternating reversible addition-rupture chain transfer (RAFT) polymerization(Jin et al. 2018). In which porphyrins and polyhedral oligo-sesquisiloxanes (POSS) are alternately mounted on the main chain. They self-assemble into nanoparticles in water. The aggregation-induced quenching (AIQ) phenomenon among the porphyrin units can be effectively reduced by the spatial cage structure and alternating structure of the POSS units. In vitro dark cytotoxicity and phototoxicity assays. Cells treated with 50 μg/mL of polymer nanoparticles (concentration of porphyrin) showed no significant dark cytotoxicity. At a concentration of 25 μg/mL, the phototoxicity of PM nanoparticles without POSS units (control group) was significantly lower than that of the experimental group. This result indicated that the POSS units with spatial cage structure in the block copolymer could effectively improve the photocatalytic efficiency. The group further evaluated the in vivo efficacy of PDT by intravenous injection. The results showed that the tumors of both nanoparticle-treated mice were inhibited, and the tumors of one group of experimentally treated mice were almost eradicated. This suggests that P(MIPOSS-alt-VBTPP)-b-POEGMA with a spatial cage-like structure has better PDT efficacy.

Although several approaches have been developed to reduce aggregation-induced quenching, such as using POSS units on polymer side chains to isolate tetraphenylporphyrin (TPP) or developing tree-like macromolecules around TPP, the drug loading capacity (LC) of PS is relatively low due to the additional introduction of redundant non-therapeutic groups(Ideta et al. 2005; Jin et al. 2018). zheng and co-workers developed the first poly TPP nanoparticles prepared by cross-linking degradable reactive oxygen clusters,

thiometallic linkers, and tetraphenylporphyrin derivatives, followed by co-precipitation(Zheng et al. 2019). With quantitative loading efficiency (>99%), homogeneous nanoparticles (no aggregation), and increased quantum yield of $^1O_2$ ($\Phi_\Delta = 0.79$ in dimethyl sulfoxide compared to 0.52 for the original TPP). The results of the in vivo antitumor effect study of nanoparticles showed that poly TPP nanoparticles could effectively accumulate at the tumor site after 8 h of injection. 650 nm lighted TPP nanoparticles showed significant inhibition of tumor growth, and the tumor volume was about 1/10 of that in the PBS group after 10 d. In contrast, poly TPP nanoparticles showed the best therapeutic effect and significant inhibition of tumor growth. Finally, the volume of the poly TPP nanoparticles group was almost 1/5 of the original volume and 1/50 of the PBS group. This is sufficient to demonstrate the efficient drug release and excellent in vivo antitumor effect of poly TPP nanoparticles under red light irradiation.

4.4 Nanomaterial modification of porphyrin photosensitizers to enhance light energy capture efficiency for PDT

Nanotechnology has evolved significantly in the last decade. The use of nanomaterial platforms for diagnostics and therapeutics has enabled precise drug delivery to target tissues and increased the effectiveness of anticancer treatments(Ariga et al. 2011; Shi et al. 2017). The enhancement of photodynamic activity of photosensitizers by metal nanoparticles through increased production of$^1O_2$ has attracted significant interest(Toftegaard et al. 2008; Zhang et al. 2007). Under light excitation, the surface electrons of metal nanoparticles exhibit collective oscillations (fixed-domain surface plasmon excitations) that can excite enhancement of a series of optical processes near the surface of metal nanoparticles, such as metal-enhanced singlet oxygen production, surface-enhanced Raman scattering (SERS), absorption, and fluorescence and phosphorescence emission intensity(Karolin and Geddes 2013; Zhang et al. 2006). Gold nanoparticles (Au NRs) are capable of enhancing ROS production in PDT applications due to their high biocompatibility, stability, and tunable plasmonic resonance bands(Ferreira et al. 2017; Jang et al. 2011; Schmitt and Juillerat-Jeanneret 2012; Zhao et al. 2012). (Fig. 8)

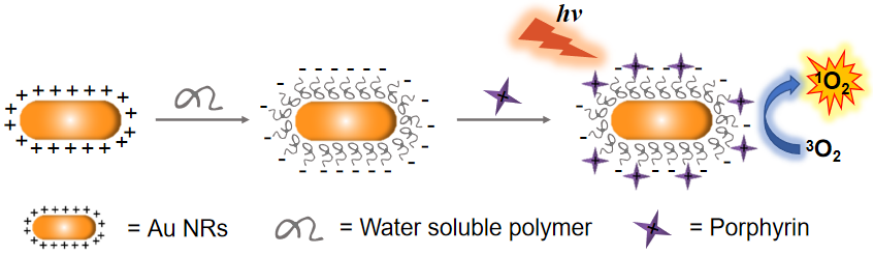

Fig. 8 Nanomaterials modified with porphyrin photosensitizers to enhance PDT. Enhanced light capture efficiency increases$^1O_2$ production

Ferreira and co-workers synthesized two different shapes of gold nanostructures (spherical and rod-like) and formed colloidal hybrid systems with 5,10,15,20-tetrakis(N-methylpyridinium-4-yl) porphyrin tosylate salt($H_2TM4PyP(OTs)_4$) (POR) that should be used in the visible light range for photodynamic therapy(Ferreira et al. 2017). Electron paramagnetic resonance (EPR) experiments combined with spin trapping were used to detect the production of reactive oxygen species and to evaluate the efficiency of these novel hybrid systems as photosensitizers. The results show that the hybrid systems composed of Au NRs and POR have a higher efficiency of $^1O_2$ production relative to the other components by about one order of magnitude. This effect is due to the enhanced local electric field around the Au NRs, which leads to an increase in light absorption by the photosensitizer, resulting in an effective energy transfer to the oxygen molecules forming$^1O_2$. On this basis, Duman and co-workers investigated nanocomposites of 5,10,15,20-tetrakis(1-methyl 4-pyridinio) porphyrin tetra(*p* -toluenesulfonate) (TMPyP) with Au NRs as nanocarrier systems for PDT and fluorescence imaging(Demir Duman et al. 2020). To confer biocompatibility and promote cellular uptake, NRs were wrapped with polyacrylic acid (PAA) and effectively loaded with cationic porphyrins

by electrostatic interaction. The nanocomposites were tested in 2D monolayer culture and 3D compressed head and neck squamous cell carcinoma (HNSCC) collagen structures after incubation in light. The results showed that loading TMPyP onto Au NRs under in vitro cell culture conditions increased the absorption and emission intensity of the photosensitizer and promoted the production of $^1O_2$ under light irradiation. Under short-term light exposure, the TMPyP-loaded NRs exhibited higher phototoxicity compared with the same concentration of free photosensitizer.

4.5 Fluorescence resonance energy transfer system enhances light energy capture efficiency to enhance PDT

Fluorescence resonance energy transfer (FRET)-based drug delivery systems for indirect activation of PS drugs via donor fluorophores have been extensively investigated in the field of PDT. The transfer of excitation energy from the donor to the PS drug can significantly improve its light capture efficiency and expand the range of light sources. Thus, the efficiency of $^1O_2$production of PS is greatly improved, which ultimately improves the photodynamic therapy effect of photosensitizers(Cao et al. 2018; Huang et al. 2020; Lovell et al. 2011). (Fig. 9)

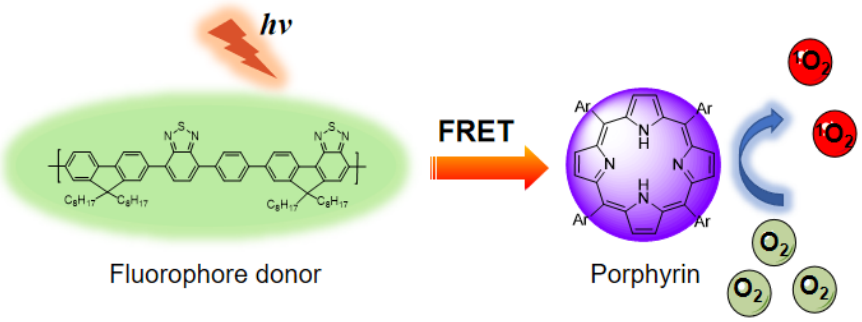

Fig. 9 FRET system enhances PDT by improving the efficiency of light energy capture

4.5.1 Single photon excitation donor type

In the past few years, a large number of fluorescent materials have been developed as donors to transfer energy to PS via photonic excitation of the donors to enhance the production of$^1O_2$. Due to the good light trapping ability of conjugated polymers, the transfer of excitation energy to the acceptor PS drug along its backbone can lead to a high amplification of the PS signal(Li et al. 2016; Liu et al. 2015; Shen et al. 2011; Yuan et al. 2014). On this basis, Chang and co-workers developed an efficient polymer-dot (Pdots) photosensitizer(Chang et al. 2016) by covalently doping porphyrins on the polymer backbone, in which the PS drug of tetraphenylporphyrin is covalently bound into the p-conjugated backbone of [(9,9-dioctylfluorenyl-2,7-diyl)-alt-co-(1,4-benzo-2,1,3-thiadiazole)] (PFBT). The resulting Pdots have excellent stability and solve the problem of photosensitizer leaching encountered in the photosensitizer-doped Pdots. Compared with the pure PFBT Pdots, the fluorescent PFBT-TPPx Pdots were significantly quenched due to the introduction of TPP, and the light-trapping polymer backbone mainly transferred the excitation energy to the TPP unit. At the same time, the Pdots exhibited excellent performance including high$^1O_2$ quantum yield (35%) and low dark toxicity. The cytotoxic effects and photodynamic effects of Pdots on MCF-7 cells were determined by colorimetric assay with tetramethylazole salts. The results showed that Pdots could efficiently kill cancer cells and produce large amounts of $^1O_2$. The therapeutic effects of PFBT-TPP Pdots were further investigated in tumor-bearing mice. The results showed that in some cases, PFBT-TPP Pdots significantly inhibited or eradicated the transplanted tumors.

In addition, Zhou and co-workers designed and synthesized a poly (metallocene) hyperbranched conjugated polyelectrolyte containing a platinum (II) porphyrin complex, which was used to efficiently generate$^1O_2$ for PDT(Zhou et al. 2016). Based on the overlap between the luminescence band of Pdots at 420 nm and

the Soret and Q absorption bands, a Förster radius of 6.6 nm was calculated, indicating that the FRET from poly(furan) to platinum (II) porphyrins is effective. The FRET process was further investigated and determined to exist in Pdots. Furthermore, the good ability of Pdots to kill cancer cells was confirmed by tetramethylazole salt colorimetry, flow cytometry analysis and real-time fluorescence imaging of photogenic cell death in situ, which was attributed to its high $^1O_2$ quantum yield (80%) by the introduction of oxygen-sensitive phosphorescent platinum (II) porphyrin complexes.

In recent years, water-soluble conjugated oligomers, including oligo-(phenylene vinylene) (OPV), oligo- (phenylene ethynylene), and oligo-(thiophene ethynylene), have attracted a lot of extensive attention due to their good molecular structures and tunable optical properties(Wang et al. 2019). In 2019, Zhao and co-workers designed and synthesized a novel donor-acceptor porphyrin PS in the form of covalent bonds through condensation reactions with cationically conjugated oligo-(thiophene ethynylene) as the donor and 5,10,15,20-4 (4-aminophenyl) porphyrins (TPP) as the acceptor(Zhao et al. 2019). The positively charged OPV plays the role of an "antenna" by its excellent light trapping ability. Under white light irradiation, the OPV overlaps strongly with the porphyrins spectrally at very short distances, and good FRET (99%) occurs, which greatly improves the$^1O_2$ yield of the porphyrins. Under white light irradiation at 5 mW/cm^2, the energy transfer from the two-armed OPV to the TPP core increased the$^1O_2$ yield of OPV-modified porphyrins by about 54-fold. On this basis, the toxic effects of OPV-C_3-TPP, OPV-C_6-TPP and TPP on MCF-7 cells were studied by colorimetric method using tetramethylazole salt. Under light irradiation conditions, the cell viability of OPV-modified porphyrins decreased with increasing concentration after incubation with cells. At a concentration of 5 μM, cell mortality reached more than 98%.

4.5.2 Two-photon excitation donor type

Some two-photon absorbing fluorescent dyes can also be used to construct energy transfer systems in photodynamic therapy. In the two-photon excited FRET system, the combination of existing photosensitizers with two-photon absorbing (TPA) dyes is utilized. Here, the photosensitizer unit (energy acceptor) is indirectly excited by the fluorescence resonance energy transfer of the two-photon absorbing dye unit (energy donor). Energy capture by the TPA donor strongly enhances the two-photon excitation efficiency of the photosensitizer, which in turn generates$^1O_2$ more efficiently(Bhawalkar et al. 1997; Dichtel et al. 2004). Since the two-photon absorbing donor can be excited by near-infrared (NIR) light during this process, deeper tissue penetration will be obtained compared to conventional PDT(Ogawa and Kobuke 2008).

Kim and co-workers prepared organically modified silica nanoparticles with 2-desethylene-2-(1-hexyloxyethyl) pyromellitic chlorophyll acid (HPPH) as an energy acceptor and 9,10-bis(4'-(4"-aminostyryl)styryl)anthracene dye with a severely distorted geometry (BDSA) as a two-photon energy donor(Kim et al. 2007). The two-photon absorption is enhanced by the partial flattening of the aggregation geometry and the resulting loose stacking of molecules in the aggregated state. At an excitation wavelength of 425 nm, the fluorescence intensity of the co-wrapped nanoparticles is quenched by about 70% for BDSA emission and amplified by about 5 times for HPPH emission compared to the fluorescence intensity of nanoparticles containing equal amounts of dye, respectively. It indicates that FRET occurs between BDSA and HPPH, which enhances the production of$^1O_2$. Hammerer and co-workers attached triethylene glycol ($P_{TEG}TP$) or diethylene glycol-α-mannosyl groups ($P_{Man}TP$) to meso-phenyl moieties of porphyrins to obtain a series of porphyrin-triphenylamine hybridized photosensitizers(Hammerer et al. 2018). These new photosensitizers have a cationic charge in them and thus are extremely water-soluble, thus improving cell penetration. Under 500 nm laser irradiation, there is an energy transfer process from TP to porphyrin. In addition, the new compounds were found to be localized in mitochondria, the preferred target organelle for PDT. In conclusion, the powerfully improved properties of the new photosensitizer significantly increase the efficiency of two-photon activated PDT.

Semiconductor quantum dots are nanomaterials that hold great promise for PDT applications. The size of quantum dots (QDs) gives them unique optical properties that can be precisely tuned from the UV region to the IR region by varying their size and composition. Due to the ability to absorb in the near-infrared region of the spectrum, low intensity light can be used to penetrate tissues, thus allowing access to deep tumors. In

addition, due to their large leap dipole moments, quantum dots are excellent absorbing materials, making them ideal donors for activating photosensitizers in PDT(Larson et al. 2003; Pu et al. 2006; Samia et al. 2003). (Fig. 10)

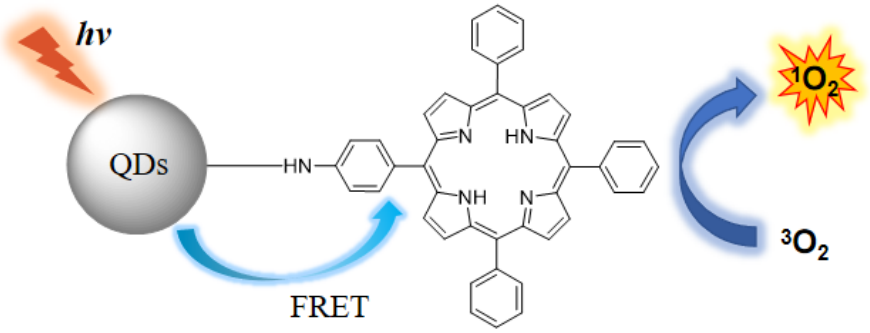

Fig. 10 Two-photon excited quantum dots FRET system enhanced PDT. Large two-photon absorption cross section and deep tissue penetration

Chou and co-workers coupled aluminum sulfonated phthalocyanine (AlPcS) to two-photon excited (TPE) quantum dots (QDs) to form QD-AlPcS couples for PDT(Chou et al. 2013). Because the quantum dots have a high two-photon absorption cross section (TPACS), the quantum dots can be excited by a low-power-density 800 nm unfocused femtosecond laser and then transfer the energy to the conjugated AlPcS via FRET. The QD-AlPcS coupling has a FRET efficiency of up to 90% in water. The FRET process of cellular QD-AlPcS was also observed in KB and HeLa cells under the action of two-photon excitation by 800 nm femtosecond laser, and effectively produced $^1O_2$ which finally succeeded in killing cancer cells. Fowley and co-workers designed a carbon quantum dot (CQD)-protoporphyrin (IX) sensitizer coupling(Fowley et al. 2013). Under 800 nm laser irradiation, the large two-photon absorption cross section of CQDs was used to indirectly excite protoporphyrin (IX) by FRET to produce large amounts of singlet oxygen, which resulted in an 82% decrease in HeLa cell viability. In addition, mice treated with intratumoral injection of CQD-protoporphyrin (IX) conjugate showed 60% tumor suppression after 800 nm laser irradiation in a fibrosarcoma tumor-bearing mice model.

5 Conclusions and perspectives

Research on porphyrin photosensitizers has made great progress in overcoming the problems of insufficient water solubility, limited tissue penetration and low light energy capture efficiency in traditional porphyrin photosensitizers. Porphyrin photosensitizers with red-shifted spectral absorption bands, metal-modified porphyrins, nanoparticle-modified porphyrins or self-assembled nanoparticles have solved the problem that photosensitizers can easily lead to electronic excited state is quenched through aggregation in living organisms while enhancing the light energy capture efficiency of porphyrin photosensitizers. In PDT of tumors, a fluorescent donor is used to indirectly activate the photosensitizer by FRET to porphyrins under light irradiation conditions. The introduction of the donor fluorescent group is able to red-shift the absorption spectral region of the porphyrin photosensitizer, which makes PDT of tumors in the near-infrared spectral region possible. Near-infrared light is more penetrating, thus enabling PDT of deep tumor tissues. In addition, the larger photon absorption cross-section of the two-photon excited donor enables efficient light energy capture, which ultimately leads to the production of large amounts of $^1O_2$ and enhances the PDT effect. However, it should be noted that the study of FRET with porphyrin photosensitizers in tumor PDT is still in its infancy, and many problems remain to be explored and solved.

Avoiding or minimizing toxicity to normal tissues is extremely important in tumor PDT. It has been shown that some nanoscale photosensitizers, such as Au NRs and silica nanoparticles, have high redox reactivity on their surfaces, which may generate unnecessary$^1O_2$ to be toxic to normal cells(Guo et al. 2015). Some

nanoparticles containing heavy metals have been shown to cause damage to normal cells(Khalil et al. 2011; Tsoi et al. 2013; Yu et al. 2017). In addition, photosensitizing drugs can be quickly cleared in the human body, resulting in low drug concentration in tumor tissue and unable to exert a good PDT effect(Wang et al. 2015; Zhu et al. 2019b). Therefore, the development of biocompatible materials in the porphyrin photosensitizer PDT to reduce the toxic and side effects of photosensitizers on normal cells is more important.

In conclusion, there has been a growing interest in developing novel porphyrin photosensitizers for PDT in recent years. Although the application of PDT technology to the clinic still needs further efforts. However, with the rapid development of optical technology and nanotechnology, it is believed that safer and more effective photosensitizers will be developed in the future.

Declarations

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