Analytical and Bioanalytical Chemistry (2019) 411:4415–4423
https://doi.org/10.1007/s00216-019-01605-8

REVIEW

DNA-modulated photosensitization: current status and future aspects in biosensing and environmental monitoring

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Received: 9 November 2018 / Revised: 22 December 2018 / Accepted: 11 January 2019 / Published online: 8 February 2019

Abstract

Recently, photosensitized oxidation has been explored in many fields of research and applications, such as photodynamic therapy (PDT) and photodynamic antimicrobial chemotherapy (PACT). Although the photosensitized generation of ROS features emerging applications, controllable management of the photosensitization process is still sometimes problematic. DNA has long been considered the carrier for genetic information. With the in-depth study of the chemical properties of DNA, the molecular function of DNA is gradually witnessed by the scientific community. Undoubtedly, the selective recognition nature of DNA endows them excellent candidate modulators for photosensitized oxidation. According to current research, reports on DNA regulation of photosensitized oxidation can be roughly divided into two categories in principle: P-Q quenching pair-switched photosensitization and host-guest interaction-switched photosensitization. In this review, the development status of these two analytical methods will be summarized, and the future development direction of DNA-modulated photosensitization in biosensing and environmental monitoring will also be prospected.

Keywords Photosensitization · DNA · ROS · Singlet oxygen

Introduction

Photosensitization, sometimes referred to photodynamics, is a process through employing a molecule capable of absorbing light efficiently and then transferring the energy to the desired reactants. When oxygen molecule is involved as reactants, this process can be called photosensitized oxidation. In 1900, Oscar Raab firstly found that acridine could kill paramecium under visible light and defined acridine and other dyes with similar properties as photosensitizers [1]. Later in 1968, Christopher S. Foote explained the mechanism of photosensitized oxidation [1]. Due to its efficient oxidation and collaboration of naturally and widely existing light and oxygen, this process has been explored in many fields, such as photodynamic therapy (PDT) [2, 3], photodynamic antimicrobial chemotherapy (PACT) [4, 5], photoinduced organic waste decomposition [6], and organic synthesis [7, 8].

In the typical photosensitization process (Fig. 1), the photosensitizer (PS) absorbs light and is firstly excited to the excited single states (S_1). The PS (S_1) may either decay back to the ground state by emitting prompt fluorescence or undergo intersystem crossing (ISC) to activate the triple states (T_1). At this stage, the PS (T_1) molecule may interact with molecules in its immediate environment to generate reactive oxygen species (ROS) through either type I or type II pathway. In type I photosensitization, electron transfer occurs from the substrate (H_2O) to excited PS yielding anionic PS which can transfer electron to O_2 to form oxygen-containing radicals of high oxidation capacity, such as superoxide anion ($\cdot O_2^-$), hydroxyl radical ($\cdot OH$), and H_2O_2, while for type II photosensitization, energy transfer occurs from the excited PS to the ground state oxygen molecules (O_2), resulting in the generation of excited state oxygen, i.e., singlet oxygen ($^1O_2$).

Published in the topical collection *Young Investigators in (Bio-)Analytical Chemistry* with guest editors Erin Baker, Kerstin Leopold, Francesco Ricci, and Wei Wang.

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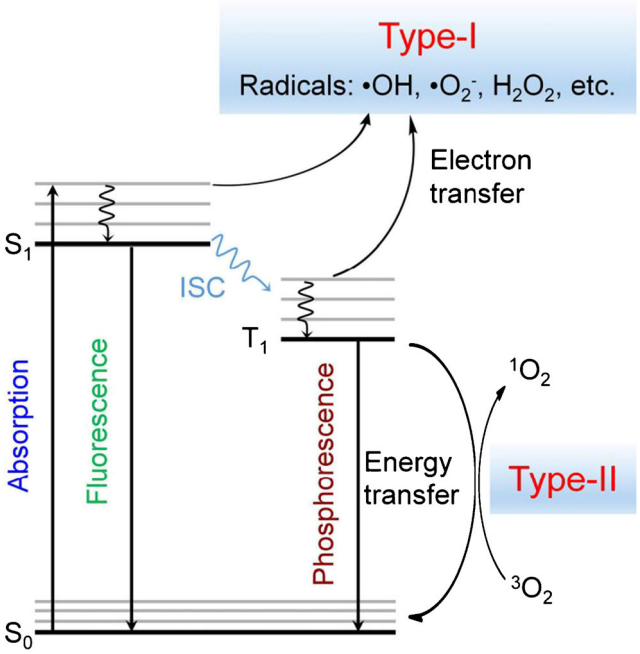

Fig. 1 Jablonski energy diagram of photosensitization

Although the photosensitized generation of ROS features emerging applications, controllable management of the photosensitization process is still sometimes problematic. On one hand, since ISC (the photophysical basis for driving photosensitization) is a spin-forbidden process in nature, the T_1 activation efficiency is thus largely restricted. On the other hand, ROS themselves possess extremely short lifetime as well as limited diffusion range in organism or liquor; it is thus necessary to control the spatial position and selective production of ROS. In this manner, a specific carrier is required for ROS initiation and transmission.

DNA has long been considered the carrier for genetic information. With the in-depth study of the chemical properties of DNA, the molecular function of DNA is gradually witnessed by the scientific community. DNA itself possesses good biocompatibility and can be easily modified with other functional groups [9, 10]. The two single strands of DNA complement each other strictly following Watson Crick's base pairing principle [11], i.e., A-T and G-C, thus forming a well-known DNA double helix structure. Besides, DNA also features specific recognition and precise self-assembly, leading to the generation of new functional DNAs, such as aptamer [12] and DNAzyme [13]. Moreover, there are also some special structures, such as hairpin [14], G-quadruplex [15–17], and i-motif [18]. Undoubtedly, the selective recognition nature of DNA endows them excellent candidate modulators for photosensitized oxidation. In fact, such attempts have already been made during the past decades (Fig. 2) and attract special interests in biosensing, toxicological study, and potential environmental monitoring.

The involvement of DNA in photosensitization has been reported for years [29–31]. However, most of the previous works were focused on the DNA damage caused by the photosensitized generation of singlet oxygen. Herein, we summarized the recent progress in the use of DNA for modulation of photosensitization, with special emphasis on the usage of DNA as a tool for regulating $^1O_2$ generation. We believe that DNA-modulated photosensitization may be also promising in analytical biosensing and environmental monitoring applications. Therefore, the review presented here is more like a perspective, not a comprehensive review.

The roles of DNA in modulation of photosensitization

The primary structure of the DNA is a flexible linear or circular structure, in which the deoxyribonucleotides are linked by a 3′,5′-monophosphate diester bond into an unbranched single-strand DNA (ssDNA). According to Watson Crick's base pairing principle, the two deoxynucleotide chains are coiled in antiparallel to form a double helix structure, i.e., the 3′-end of one ssDNA hybridized with the 5′-end of the complementary ssDNA, which forms a secondary structure of relatively rigid double-strand DNA (dsDNA). The regular double helix is the most representative structure of dsDNA, but further distorting and folding of dsDNA into a tertiary and quaternary structure are also reported.

Labeled DNA for photosensitization switch

DNA itself possesses good biocompatibility and can be easily modified with other functional groups at 3′- and 5′-ends. Molecular beacon (MB) is the most famous technological exploration of such facile functionalization, with one end labeled with a fluorescent reporter and the other a quencher. MB allows controllable switching on/off of the fluorescence through changing the distance of the fluorophore-quencher pair, based on the principle of fluorescence resonance energy transfer (FRET) [32]. Though it is often believed that FERT only affects the first S_1 of the photosensitive molecules, similar effects are also applicable for T_1, resulting in controllable modulation of ROS. Similar to fluorescence modulation in classical molecular beacons, DNA-regulated photosensitization with labeled photosensitizer (T_1) and quencher at the two ends also permits highly selective activation of ROS (Fig. 3A).

Host-guest interaction-switched photosensitization

Besides labeling, dsDNA also offers non-covalent binding sites for a variety of guest molecules through host-guest interaction. Binding of small molecules with dsDNA can be roughly categorized into three types (Fig. 3B), namely, intercalation,

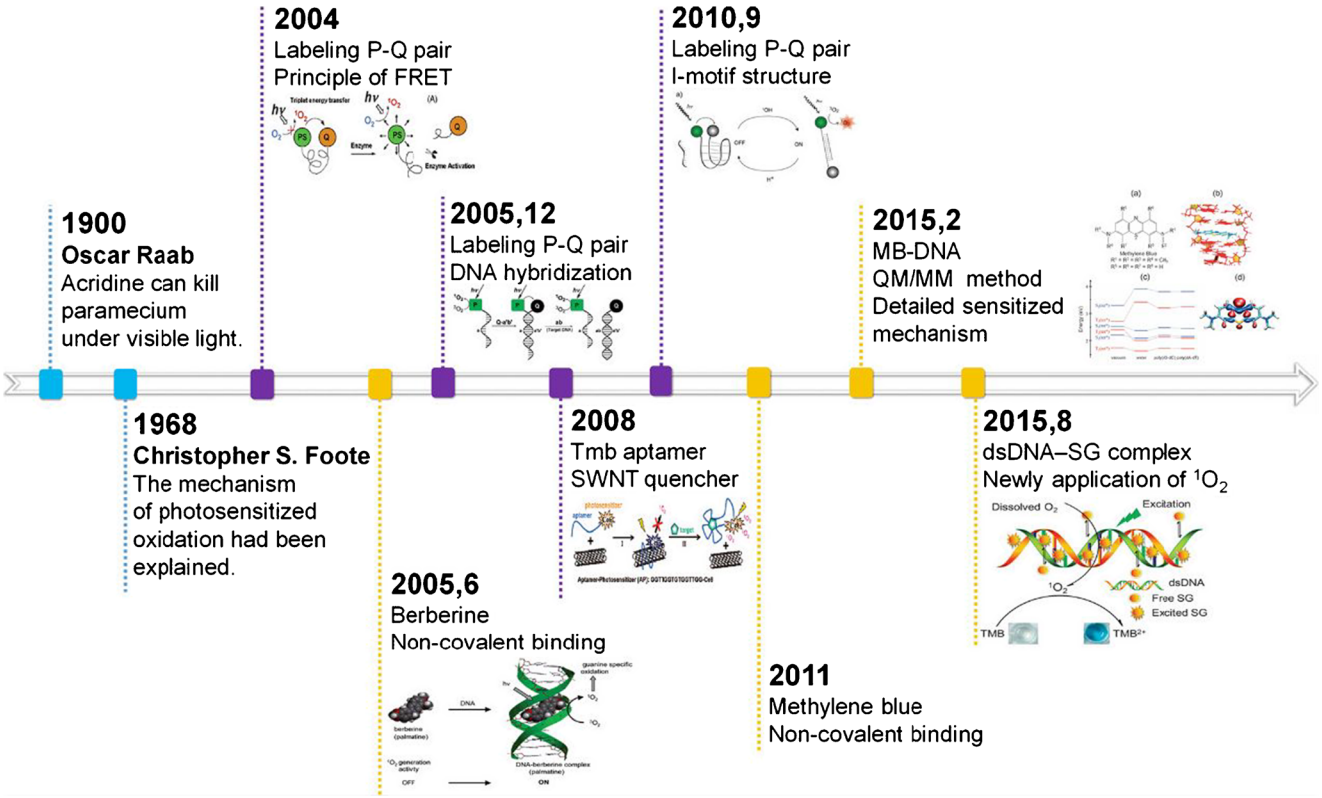

Fig. 2 A brief timeline for the developments of DNA-modulated photosensitization [19–22]. Reprinted with permission from ref. [22] (2004), Copyright 2004 American Chemical Society; ref. [23] (2005, p. 6), Copyright 2005 American Chemical Society; ref. [24] (2005, p. 12), Copyright 2006 American Chemical Society; ref. [25] (2008), Copyright 2008 American Chemical Society; ref. [26] (2010, p. 9), Copyright 2010 Wiley-VCH; ref. [27] (2015, 2), Copyright 2015 Wiley-VCH and Copyright 2010 Wiley-VCH; ref. [28] (2015, p. 8), Copyright 2015 the Royal Society of Chemistry

groove binding, and electrostatic interaction. Surprisingly, the photophysical properties of some host molecules change strikingly before and after dsDNA hosting. For example, the dsDNA-staining dyes (e.g., ethidium bromide, SYBR Green I) fluoresce brightly after binding with dsDNA, while some previous researches revealed that such dsDNA-involved host-guest interaction could also activate the ROS generation from the guest photosensitizers.

DNA-modulated photosensitization

P-Q quenching pair-switched photosensitization

Photosensitized oxidation was initially devoted to the development of photodynamic therapy. Due to the short lifetime and limited diffusion distance of $^1O_2$, a targeted biocarrier was indispensable for selective modulation of the ROS generation. Because of the excellent biocompatibility and specificity of DNA, molecular beacons involving photosensitizer-quencher pair for ROS regulation are thus expected. In fact, such attempt was first carried out by Chen et al. in 2004 [22], in which a short tumor-specific peptide containing a caspase-3 enzyme-recognition site was labeled with the photosensitizer-quencher pair at two ends. Upon enzyme (caspase-3) cleavage, photosensitized generation of $^1O_2$ was activated, leading to selective cancer cell therapy. However, the peptide linker is prone to be degraded by various proteases.

In 2006, Gothelf et al. creatively proposed the first DNA-programmed control of photosensitization [24]. As shown in Fig. 4A, the photosensitizer (pyropheophorbide-*a*) was attached to a 15-mer ssDNA and the quencher (black hole quencher 3) to a 21-mer ssDNA complementary to the P-DNA strand. Through DNA-programmed assembly, P and Q were brought close proximity, resulting in $^1O_2$ "turn-off" (Fig. 4B, revealed with the $^1O_2$-specific phosphorescence at 1270 nm). In the presence of target DNA (21-mer, specific to Q-DNA), the previous DNA (P)-DNA (Q) duplex was disassembled, leading to $^1O_2$ generation recover (Fig. 4C).

Due to high specificity and robustness of DNA hybridization, the above established $^1O_2$ on/off switching model opened a new door for selective modulation of $^1O_2$ generation [33–40]. It should be noted that although effective for the current photosensitizer (pyropheophorbide-*a*), the quenching efficiency of the "black hole quencher" to other photosensitizers lies largely uninvestigated. Besides, although the PS-quencher pair was disassembled, the quencher was still left in the homogenous solution. In fact, at least ~ 15% of the

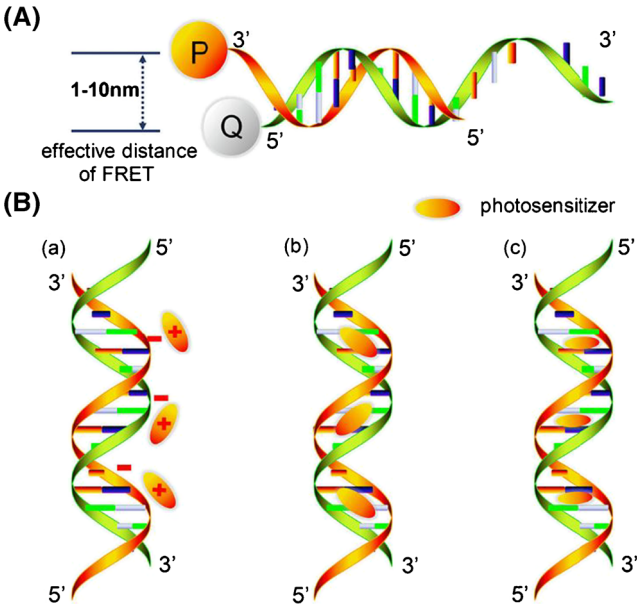

Fig. 3 **A** A model of molecular beacon, the orange ball represents the PS and the gray ball represents the quencher. **B** Three type of DNA-binding mode: (a) Electrostatic interaction: the surface of the phosphate group of DNA is negatively charged, and electrostatic interaction will happen when a positively charged cationic molecule approaches; (b) Minor or major groove binding: small molecules which are relatively flexible structure may bind to major groove or minor groove of DNA; (c) Intercalation: The intercalation means a small molecule that owns plane or an almost planar aromatic ring can insert between the base pairs of DNA

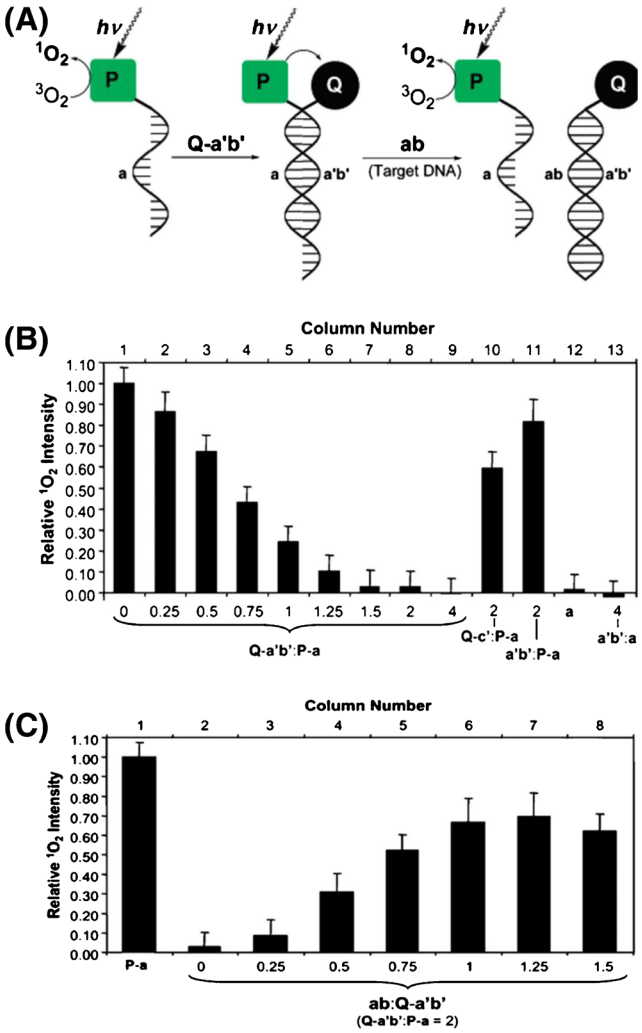

Fig. 4 **A** The scheme of DNA hybridization modulated $^1O_2$ generation, **B** monitoring the change of $^1O_2$ phosphorescence at 1270 nm in the presence of various P-Q ratios (column 1 represents P-a reference; columns 2–9 represent titration with Q-a′b′; column 10 represents non-complementary Q-c′; column 11 represents P-a + a′b′; columns 12–13 represent the blank of a and a + a′b′), and **C** efficiency of $^1O_2$ generation upon competitive release of P-a by addition of a target DNA sequence (column 1 represents P-a; column 2 represents Q-a′b′,P-a (2:1); columns 3–8 represent titration of Q-a′b′). Reprinted with permission from ref. [24]. Copyright 2006 American Chemical Society

$^1O_2$ generation efficiency could not be restored, indicating potential extra quenching effect from the quencher in the solution.

It is well known that carbon-based nanomaterials (e.g., carbon nanotube, graphene oxide, fullerene) are excellent broadband fluorescence quenchers. Moreover, these carbon-based nanomaterials are also efficient carriers for cancer cells. Therefore in 2008, Tan et al. [25] employed single-walled carbon nanotube (SWNT) to replace the classical FRET quencher for DNA-modulation photosensitization. As shown in Fig. 5A, since SWNT possesses high affinity towards ssDNA [41], assembling Ce6-labeled thrombin aptamer with SWNT resulted in efficient quenching of the $^1O_2$ generation (Fig. 5B). Upon competition with thrombin via aptamer-target specific interaction, the Ce6-tagged oligonucleotide was stripped from the SWNT, resulting in photosensitization recover ($^1O_2$ "turn-on", Fig. 5B). Therefore, changing the type of quencher largely broadens the design flexibility of this model. In fact, except SWNT, many nanomaterials are also excellent broadband quencher, such as metal nanoparticles [42] and graphene oxide [43]. These nanoquenchers and their DNA affinity provide new ideas for the designing of hybridization-switched photosensitization in the future.

Besides the classical ssDNA and dsDNA, recently, some new conformations of DNA are also emerged, such as G-quadruplex (G4) [44] and i-motif [45]. For example, under the weak acid condition (pH ≈ 4), the oligonucleotide with C-rich sequence can form a special tetraplex structure, which consists of two parallel duplexes maintained by C·CH$^+$ pairs intercalated with each other in an antiparallel orientation, namely, the i-motif structure [18]. The Gothelf group integrated i-motif structure switching with photosensitization for pH-regulated generation of $^1O_2$ (Fig. 6) [26], in which the photosensitizer (PPa) and the quencher (BHQ-2) were labeled at the 3′- and 5′-ends of a C-rich oligonucleotide, respectively. Under acidic condition, folding of the C-rich oligonucleotide into the i-motif structure triggered energy transfer from P to Q, leading to shuttled $^1O_2$ generation. Upon alkalization of the solution,

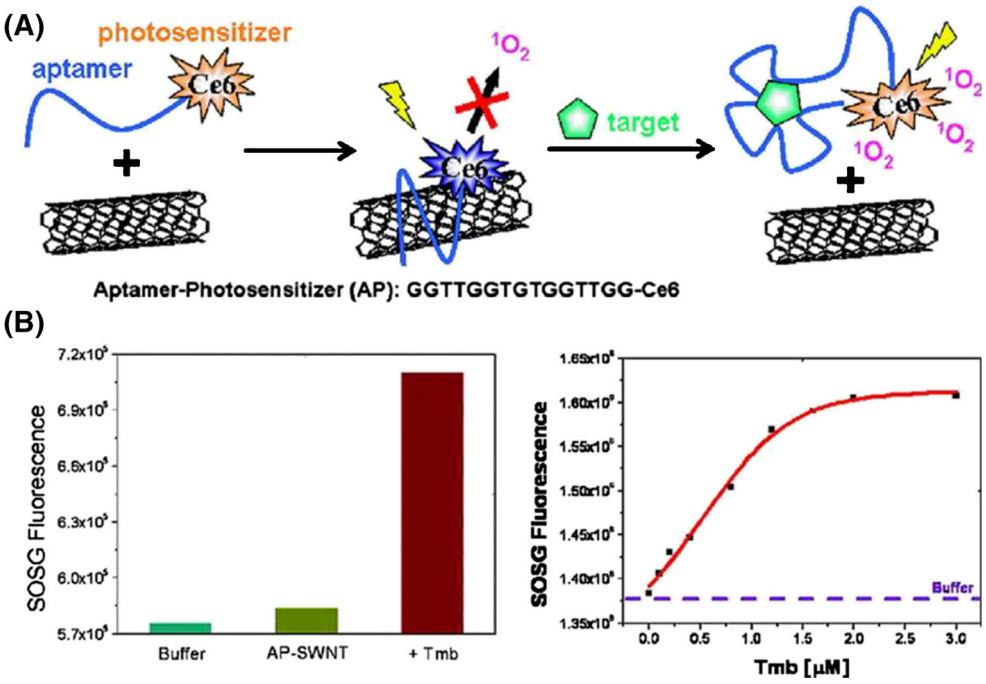

Fig. 5 **A** Schematic of aptamer-PS-SWNT complex and the regulation of $^1O_2$ upon target binding and **B** quantitative evaluation of the $^1O_2$ regulation performance (represented by the SOSG signal, a specific fluorescent $^1O_2$ trap). The left picture of **B** showed the SOSG signal of Ce6-SWNT representing great quenching of SWNT for $^1O_2$. After introduction of 2.0 μM thrombin, the signal was increased significantly. The right picture of **B** showed thrombin concentration–dependent SOSG signal (the purple line indicates the buffer's SOSG signal). Reprinted with permission from ref. [25]. Copyright 2008 American Chemical Society

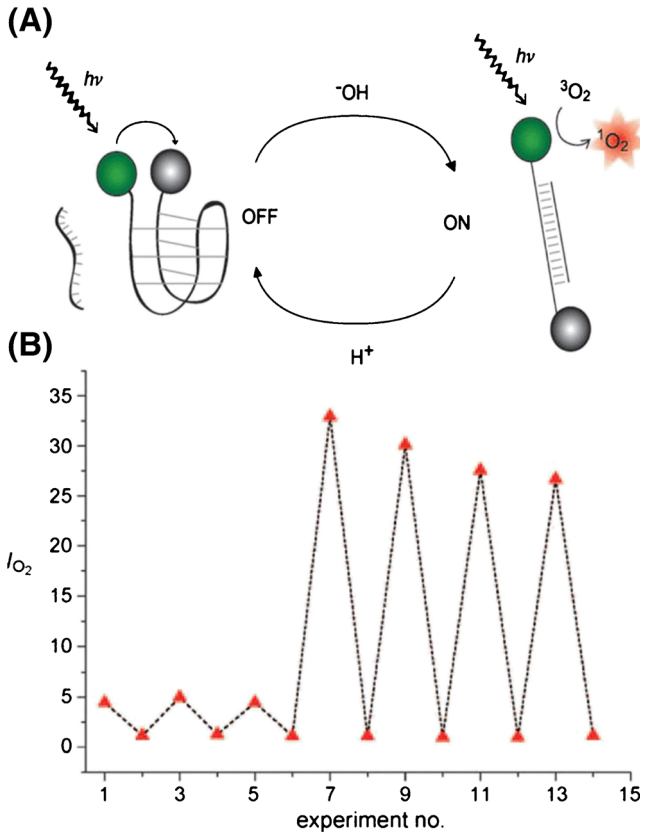

Fig. 6 **A** The scheme of i-motif-switched photosensitization by a pH-dependent change in the distance between the sensitizer (green) and the quencher (gray) and **B** intensity of the $^1O_2$ phosphorescence signal when the pH is alternated between high (ca. 8.7, odd-numbered experiments) and low (ca. 4.3, even-numbered experiments) values. Points 1–6 and 7–14 show data recorded in the absence and presence of a complementary DNA strand, respectively. Reprinted with permission from ref. [26]. Copyright 2010 Wiley-VCH

the specific i-motif structure was collapsed. Further rigidifying of the C-rich oligonucleotide with the target DNA resulted in the recovery of $^1O_2$. Therefore, the introduction of the newly discovered DNA conformations added more versatility to the photosensitization modulation. The formation rationale of the G-quadruplex is similar to that of i-motif, namely, from a G-rich oligonucleotide to two parallel duplexes. Considering that the G-quadruplex structure can be derived from the telomerase substrates [5] and that discovery of endogenous G-quadruplex from human cells was recently reported [22, 46], use of the G-quadruplex for switching photosensitization is highly expected.

Clearly, the specificity and selectivity of DNA recognition (hybridization, aptamer-target interaction, environmental responsiveness of the novel DNA secondary conformations) endow facile modulation of the photosensitizer-quencher unit, which promotes the PDT development. However, the molecular labeling process is cumbersome and sometimes time consuming, and the stability of the labeled products needs to be clarified. Besides, tagged DNAs may behavior differently from their untagged counterparts, thus experiencing biocompatibility problems in some cases. Therefore, new or improved regulation method needs to be developed further.

Host-guest interaction-switched photosensitization

Besides labeling DNA with the photosensitizer-quencher pair, another modulation strategy, namely, using the host effect of dsDNA (Fig. 3B), was also reported. DsDNA offers non-covalent binding sites for a variety of guest molecules through host-guest interaction. Such modulation strategy was first reported by Hirakawa et al. in 2005 [23]. They found upon

binding of berberine and palmatine (drugs for skin diseases) with dsDNA; not only the fluorescence, but also the photosensitized generation of $^1O_2$ were enhanced greatly (Fig. 7A). Free berberine and palmatine bear quenched S_1 state due to the intramolecular charge transfer, but such quenching was alleviated upon electrostatic binding with DNA [47, 48]. Presumably, photosensitization may also experience the same effect. Moreover, through confirmation with NMR, the generated $^1O_2$ caused selective DNA lesion, i.e., selective oxidation of guanine base into 8-oxo-7,8-dihydro-2¢-deoxyguanosine (8-oxodGuo). By comparing the fluorescence and $^1O_2$ quantum yields of different sequences of AATT and AGTC, it was found that berberine and palmatine tended to bound to the AT-rich sulcus region. Therefore, the photosensitized DNA damage by berberine and palmatine contributed to the phototoxicity of these alkaloids, which may be a new target for PDT.

Although potentially useful, alkaloids are only slightly water-soluble, which may hinder their applications in DNA-targeted PDT. Besides, the absorption of these drugs locates nearly in the UV region. Therefore, the Hirakawa group further synthesized a series of water-soluble porphyrin derivatives (AnTPyP [49], PyTMPyP [50], AnTMPyP [51], NapTMPyP, and TMPyP [52], with structures showing in Fig. 7B) that could also target DNA. Besides $^1O_2$, these photosensitization processes could also generate other ROS. Both type I and type II photosensitization processes could occur, depending on the mode that the photosensitizer is bound to DNA, i.e., the distance between the photosensitizers and base pairs. For example, when Nile blue was intercalated into DNA, predominately, type I photosensitization proceeded [53].

Besides oxidation of guanine base, the generation of $^1O_2$ from dsDNA-hosted photosensitizers could also be explored for oxidation of chromogenic substrates, such as 3,3′,5,5′-

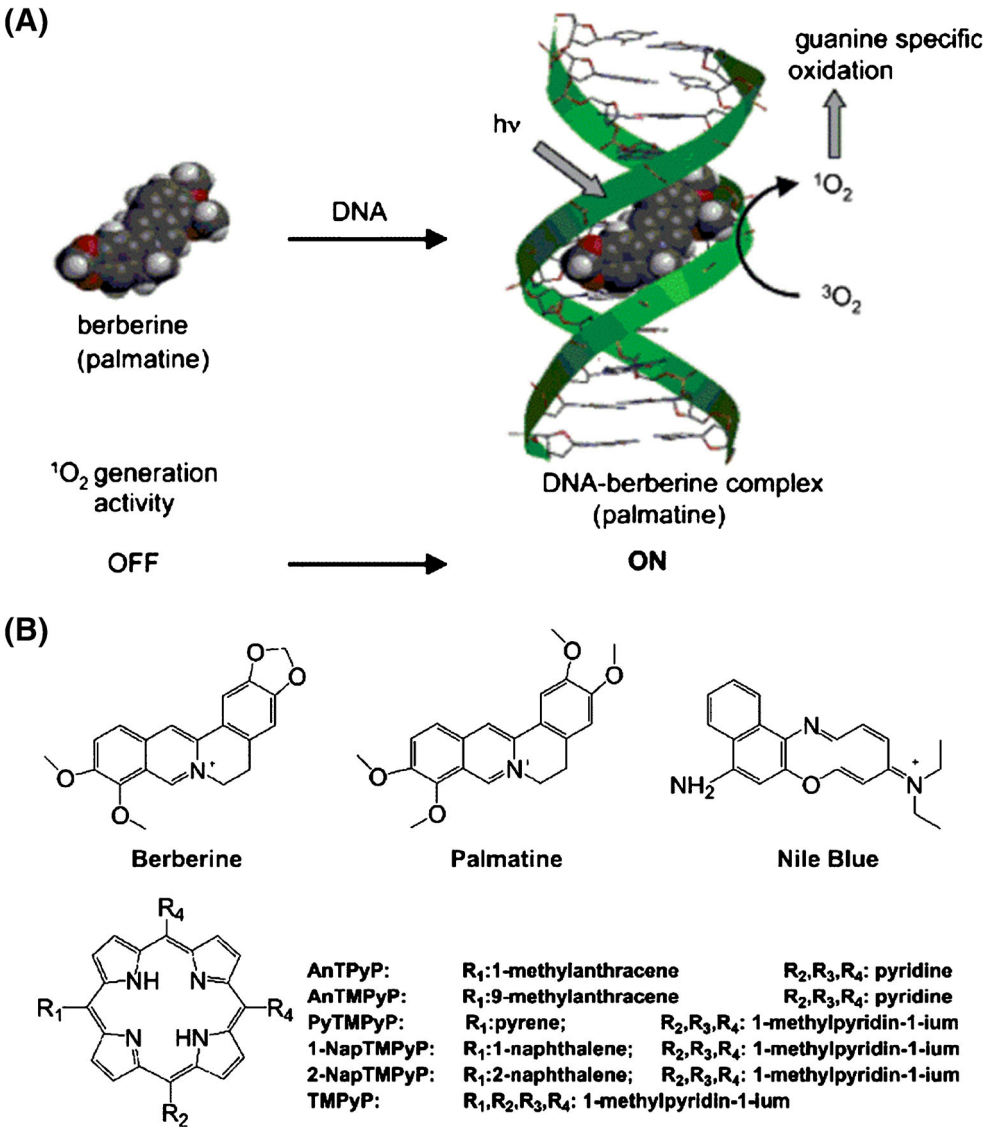

Fig. 7 **A** Proposed DNA-hosted berberine or palmatine for photosensitization turn-on (including the subsequent photodamage of guanine) and **B** the structures of the photosensitizers studied by Hirakawa et al. through DNA hosting. **a** is reprinted with permission from ref. [23]. Copyright 2005 American Chemical Society

tetramethylbenzidine dihydrochloride (TMB) and 3,3′-diaminobenzidine (DAB). As shown in Fig. 8A, our group first found SYBR Green I (SG, a well-known DNA-staining dye widely used in real time-PCR [54]) could be also photosensitized upon binding with dsDNA as berberine and palmatine, resulting in turning the colorless TMB to a blue color (Fig. 8A) [28]. In this regard, in combination with DNA hybridization and aptamer-target recognition, the dsDNA host switched photosensitization could thus be engineered into a sensitive colorimetric assay platform, for example, exploring the dsDNA-assisted color development with DNA hybridization yielding a sensitive colorimetric DNA detection scheme, with limit of detection of ~ 0.02 nM (Fig. 8B). We also demonstrated that dsDNA-switched photosensitization could be explored for sensitive colorimetric detection of melamine in milk powder [55] and uranyl cation in seawater [56], showing the analytical potential of this detection scheme in future biosensing as well as in environmental monitoring.

The $^1O_2$-assisted TMB chromogenic reaction could be further explored for potential ELSIA assays, since TMB is by far

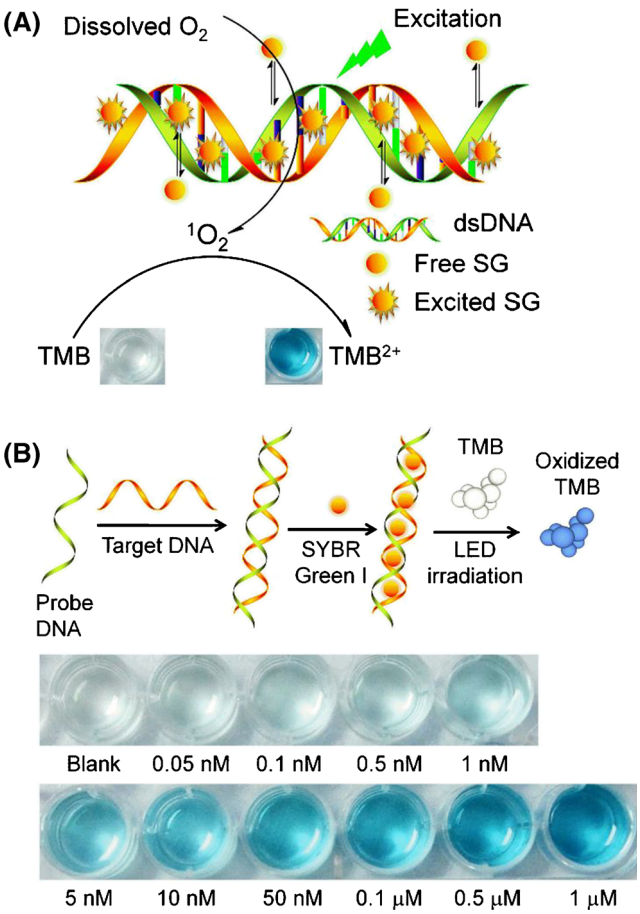

Fig. 8 **A** Scheme of the photosensitization of dsDNA-SG for TMB oxidation and **B** design and performance of the colorimetric analysis based on photosensitization of the dsDNA-SG complex for DNA detection. Reprinted with permission from ref. [28]. Copyright 2015 the Royal Society of Chemistry

the most popular chromogenic substrates in commercial ELISA kits [57]. Since SG molecules permit efficient $^1O_2$ generation after non-contently binding with dsDNA, such SG-dsDNA system may replace the classical TMB oxidation system, i.e., the H_2O_2/HRP (horseradish peroxidase) system [58], to achieve colorimetric and even electrochemical analysis [46]. For example, this method could be explored to detect DNA-involving targets through colorimetric [28] or electrical signals [59]. Thus, future exploration of this method for immunoassay and DNA amplification–based assay is highly expected.

To illustrate the photophysical mechanism of enhanced photosensitization upon dsDNA hosting, González et al. proposed the use of quantum mechanics/molecular mechanics (QM/MM) calculations to study the change of MB molecules after combining with DNA [27]. The enhanced photosensitization could be primarily ascribed to enhance intersystem crossing driven by electronic spin-orbit coupling in the dsDNA microenvironment. Moreover, in-depth study concluded apart from inhibiting the charge transfer process through electrostatic interaction with DNA, the advanced ISC process caused a suitable optimization of MB's structure for better photosensitization. However, for a given photosensitizer, the detailed mechanism may vary from molecule to molecule. It is thus expected that combination of theoretical and experimental investigations may be advantageous for illustrating the photosensitization mechanisms.

Conclusion and outlook

In summary, this review summarizes the recent progress in using DNA for controllable photosensitization. Although the photosensitized generation of ROS features emerging applications, such as photodynamic therapy (PDT), photodynamic antimicrobial chemotherapy (PACT), and organic synthesis, controllable management of the photosensitization process is still sometimes problematic. By combining labeling technique and DNA hybridization, efficient and highly specific DNA-regulated photosensitized oxidation has been already realized. The advances in DNA conjugation chemistry provide facile labeling of photosensitizer-quencher pair, which can be switched via further DNA hybridization. Moreover, some photosensitizers bearing inherent quenching unit (such as drugs and DNA-staining dyes) can be hosted by the double helix of dsDNA, providing another modulation strategy of non-covalent binding. Although the latter one is not as specific as the former P-Q quenching pair-switched photosensitization, non-covalent binding of photosensitizers avoids complicated molecular labeling process.

Originally, the DNA-labeled photosensitizer-quencher pair is inherited from the well-known molecular beacon technology. Considering the popularity of current molecular beacon

schemes [9, 60], further learning can also be expected for future developments of the photosensitizer-quencher pair. For example, it has already been evidenced that the use of SWNT quencher allowed labeling of only one oligonucleotide [25]. Besides, some nanoquenchers (such as graphene oxide) permit efficient in vivo delivering of DNA. Further combination of the quenching talent and the delivering property of the nanoquenchers may pave the way for their in vivo PDT applications.

For the dsDNA-host drug photosensitizers, the added photosensitization may endow these drugs extra in vivo therapeutic effects, but currently only berberine and palmatine were found to be effective. Therefore, more drugs are left to be investigated in this regime. Besides, the major UV absorption of these drugs limited their potential in vivo applications. Accordingly, extending their absorption to the visible and even near-infrared region should be the prerequisite, which demands more synthetic, photophysical, and medicinal efforts.

Last but not least, the photosensitization-induced chromogenic coloration allowed translation of various DNA recognition events into colorimetric signals, but the analytical and environmental monitoring potential of this method has not yet been well explored. Besides, the mechanism of the current chromogenic reaction can be extended to many classic oxidation systems, such as luminol-Fe^{2+}/H_2O_2 system and current ELISA and CLIA (chemiluminescence immunoassay) systems, which require HRP (horse radish peroxidase) and H_2O_2 for signaling. Therefore, we believe photosensitization-induced chromogenic coloration (or even chemiluminescence) may be promising for future analytical and environmental monitoring applications.

Funding information The authors received a financial support from the National Natural Science Foundation of China (Nos. 21874093 and 21522505), the Sichuan Youth Science and Technology Foundation (2016JQ0019), and the Fundamental Research Funds for the Central Universities (2018SCUH0075).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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