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Chapter 9

Biomolecules Oxidation by Hydrogen Peroxide and Singlet Oxygen

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Additional information is available at the end of the chapter

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Abstract

Hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) are important reactive oxygen species (ROS) for biological and medicinal fields. Oxidation processes of chemical materials by molecular oxygen are important H_2O_2 source, whereas photochemical reaction is important for $^1O_2$ production. Reactivity and biomolecule damage by these ROS depend on the surrounding conditions and targeting molecules. In this chapter, production mechanisms of H_2O_2 and $^1O_2$, biomolecule oxidation by these ROS, their detection methods, and production control of $^1O_2$ are briefly reviewed.

Keywords: hydrogen peroxide, singlet oxygen, DNA damage, protein damage, photooxidation

1. Introduction

Biomolecule damage, for example, oxidation of DNA and/or protein, by reactive oxygen species (ROS) is closely related to carcinogenicity [1–3] and/or toxicity [4–6]. Furthermore, oxidative damage to unwanted tissue can be applied to the treatment of disease including cancer treatment [7–9], and similar reaction is applied to sterilization [10–14]. Hydrogen peroxide (H_2O_2) is a relatively long-lived ROS compared with a short-lived ROS such as superoxide anion radicals ($O_2^{\bullet-}$) [15]. One of the most important producing mechanisms of H_2O_2 is a dismutation of $O_2^{\bullet-}$, which is easily formed though oxidation of various materials by dioxygen molecule (O_2). Various carcinogenic chemical compounds produce H_2O_2 through their oxidation processes. Relationship among molecular oxygen and ROS is shown in **Figure 1**. Oxygen molecules are easily reduced by surrounding materials, and various ROS and the intermediates are formed (**Figure 1A**). In the case of photosensitized reaction, excited states of oxygen molecules are produced (**Figure 1B**). Singlet oxygen ($^1O_2$), which is also an important ROS, can

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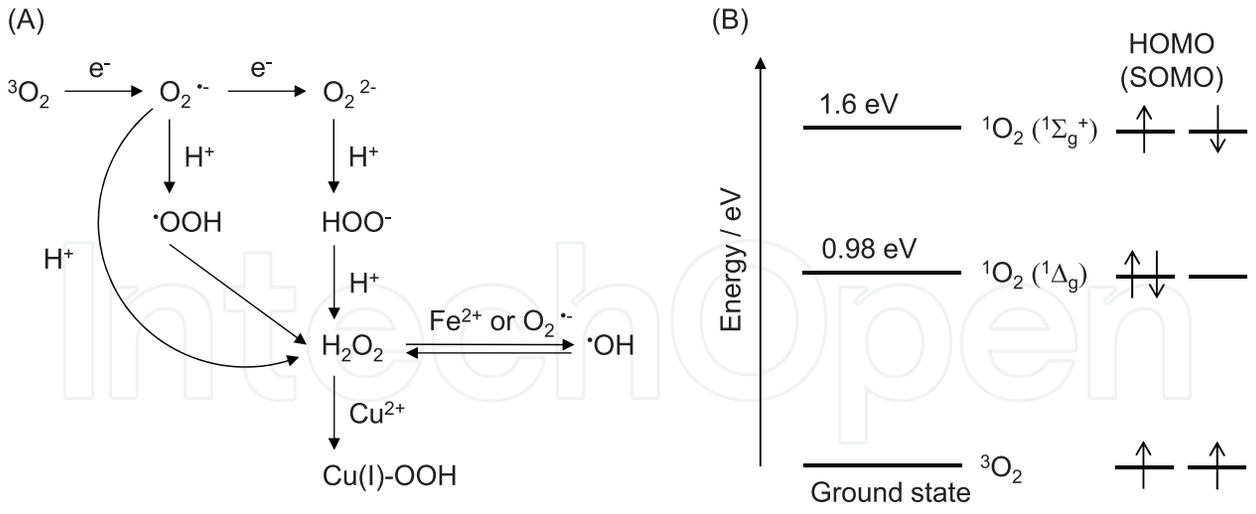

Figure 1. Relationship among ground-state oxygen molecule ($^3O_2$) and ROS (A) and the energy levels of oxygen molecule (B). HOMO and SOMO are the abbreviations of highest occupied molecular orbital and semi-occupied molecular orbital, respectively. The "arrows" in (B) indicate the electron spin.

be easily generated via photosensitized reaction [16–18]. The $^1\sum_g^+$ state ($^1O_2(^1\sum_g^+)$) is mainly produced through the excitation energy transfer from the excited state, in general triplet excited (T_1) state, of photosensitizer [16–18]. The $^1O_2(^1\sum_g^+)$ has higher energy, 1.6 eV, corresponding to the ground state of oxygen molecule ($^3O_2$). The lifetime of $^1O_2(^1\sum_g^+)$ is several picoseconds, and $^1O_2(^1\sum_g^+)$ is rapidly converted to the $^1\Delta_g$ state ($^1O_2(^1\Delta_g)$) [16–18]. Because the lifetime of $^1O_2(^1\Delta_g)$ (several microseconds) is markedly longer than that of $^1O_2(^1\sum_g^+)$, $^1O_2(^1\Delta_g)$ is a more important ROS. After that, $^1O_2$ indicates $^1O_2(^1\Delta_g)$ without explanation in this chapter. Visible light, other than ultraviolet radiation, has sufficient energy to produce $^1O_2$ from the ground state of oxygen molecule. Therefore, $^1O_2$ production is an important mechanism of phototoxicity and/or photo-carcinogenicity under strong light illumination with phototoxic materials. The purpose of this chapter is a review of the ROS-mediated biomolecule damage and the related topics.

2. Hydrogen peroxide

Hydrogen peroxide itself is not strongly ROS. However, other ROS including hydroxyl radicals (•OH) are produced from H_2O_2. In general, H_2O_2 is produced from the dismutation of $O_2^{\bullet-}$, and, in vivo, production of H_2O_2 and $O_2^{\bullet-}$ occurs in mitochondria [19]. In this section, H_2O_2 formation from compounds, specifically artificial materials, is introduced.

2.1. Hydrogen peroxide formation through oxidation of chemical compounds

One of the most important processes of H_2O_2 production is a dismutation of $O_2^{\bullet-}$. Various chemical compounds or metals can be oxidized by oxygen molecules. In the case of a simple electron transfer-mediated oxidation, $O_2^{\bullet-}$ is produced by the electron extraction from chemical compounds or metals. The lifetime of $O_2^{\bullet-}$ in aqueous solution is about several milliseconds [15]. The produced $O_2^{\bullet-}$ in aqueous media is converted to H_2O_2 through the dismutation by proton (H^+) as follows:

$$2O_2^{\bullet-} + 2H^+ \rightarrow H_2O_2 + O_2 \quad (1)$$

For example, hydroquinone, which is one of the metabolites of benzene, can produce H_2O_2 through the autoxidation process (**Figure 2**) [20]. This process is markedly enhanced by the presence of metal ions, specifically Cu^{2+} ions [20]. In the presence of sacrificial reductants, for example, nicotinamide adenine dinucleotide (NADH), the oxidized form of hydroquinone, *p*-benzoquinone, is reduced to the parent hydroquinone. Consequently, the redox cycle is formed, leading to the production of H_2O_2 abundantly. It has been also reported that hydrazine analogues produce H_2O_2 through their autoxidation processes (**Figure 3**) [21–23].

2.2. Hydrogen peroxide production through photochemical processes

Photochemical processes also contribute to the formation of H_2O_2. Because the reorganization energy of the reduction of small molecule, such as O_2 molecules, through electron transfer becomes large due to the Marcus theory [24, 25], the $O_2^{\bullet-}$ production through photoinduced electron transfer is energetically difficult [26, 27]. However, ultraviolet radiation to reductive photosensitizer, such as NADH (**Figure 4**), can produce $O_2^{\bullet-}$ as follows [28]:

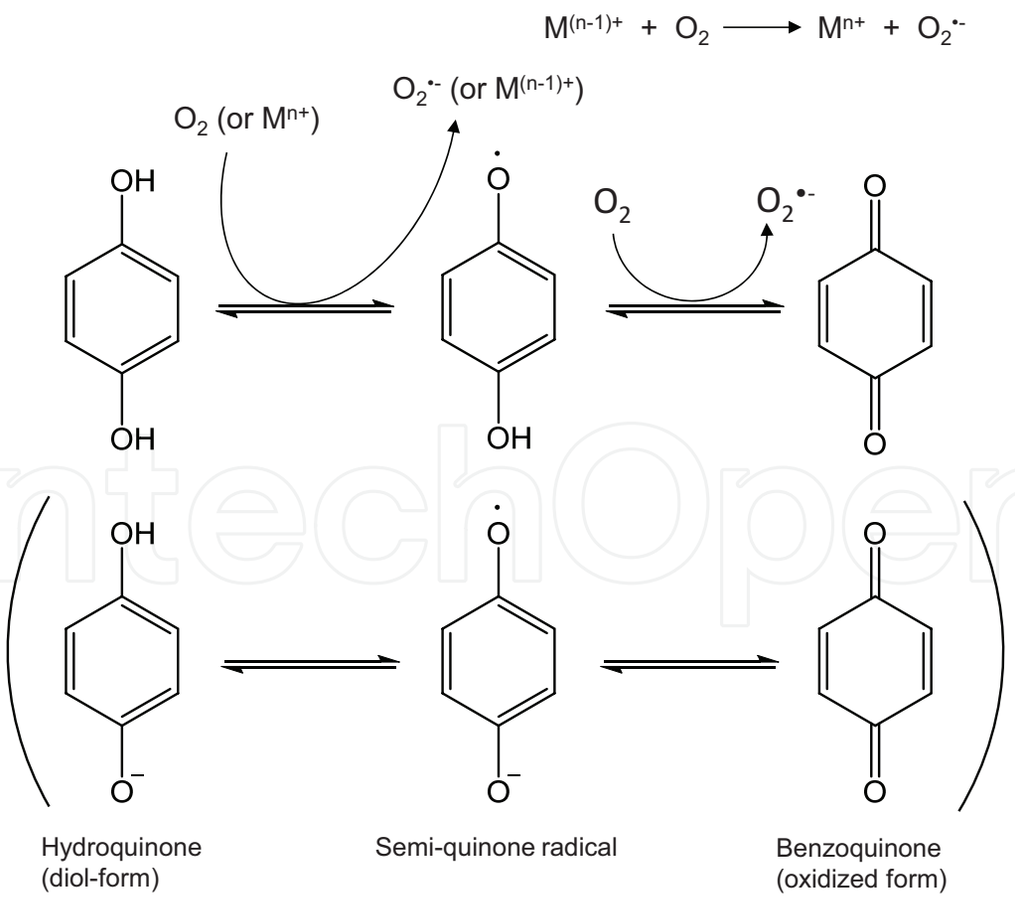

Figure 2. Autoxidation process of hydroquinone and ROS production.

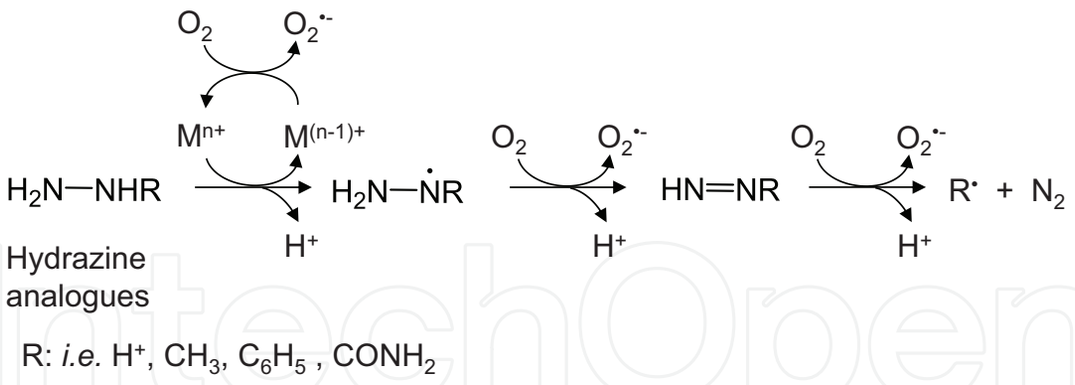

Figure 3. Autoxidation process of hydrazine analogues and ROS production.

$$NADH + h\nu \rightarrow NADH^{*} \tag{2}$$

$$NADH^{*} + O_2 \rightarrow NAD^{\bullet} + H^{+} + O_2^{\bullet -} \tag{3}$$

where NADH* is the photoexcited state of NADH and $NAD^{\bullet}$ is the radical form. $NAD^{\bullet}$ undergoes further oxidation by oxygen molecules to NAD^{+}, the final oxidized product. The formed $O_2^{\bullet -}$ is also converted to H_2O_2 through the dismutation process of Eq. (1).

Photocatalytic reaction can also produce H_2O_2 [29–34]. For example, the surface of titanium dioxide (TiO_2) can reduce relatively oxidative molecules under ultraviolet A (UVA; wavelength, 315–400 nm) irradiation [29–32]. Two crystalline forms of TiO_2, anatase and rutile with band gap energies of 3.26 and 3.06 eV, respectively, are well-known semiconducting photocatalyst [29–32]. The adsorbed oxygen molecules on the TiO_2 surface is reduced to $O_2^{\bullet -}$ by the electron of conduction band, which is excited from the valence band by UVA energy (**Figure 5**).

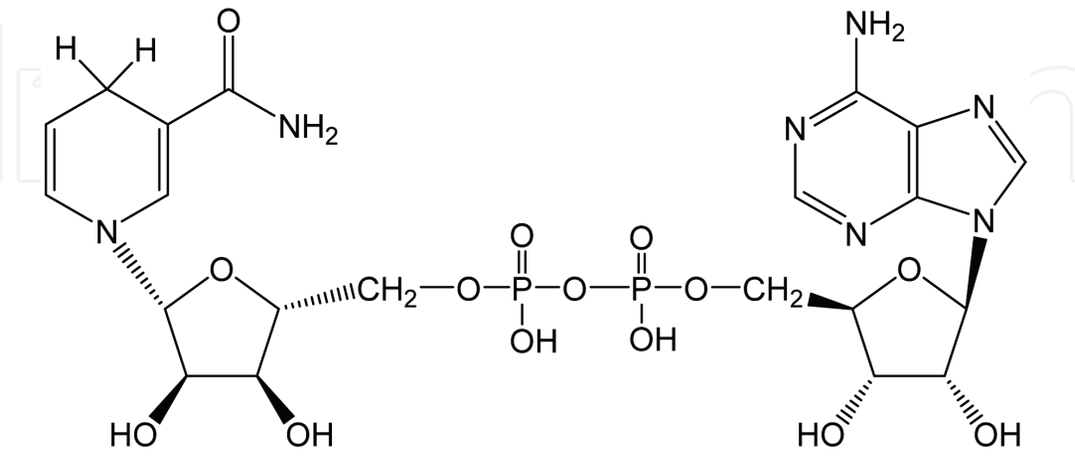

Figure 4. Structure of NADH.

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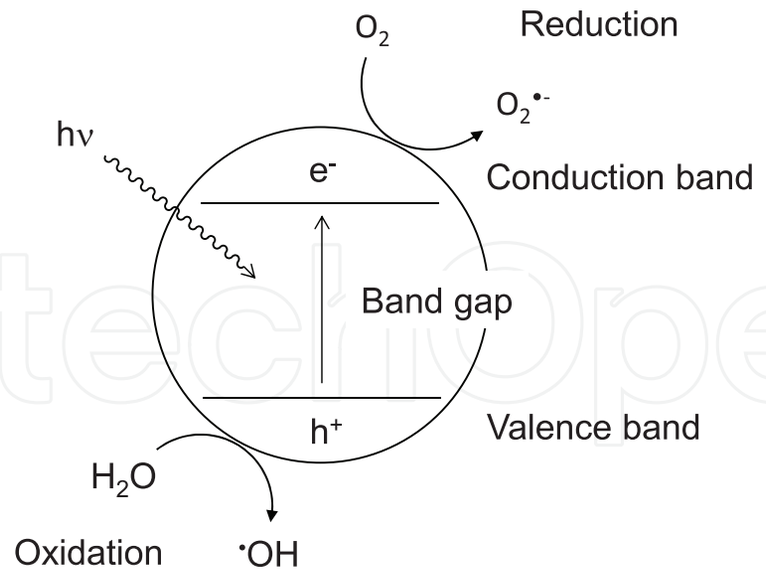

Figure 5. Photocatalytic production of ROS by TiO_2.

Similarly to the abovementioned reaction, $O_2^{\bullet -}$ is also converted to H_2O_2 through the dismutation process of Eq. (1). In addition, oxidation reaction of TiO_2 photocatalyst also produces H_2O_2. The formed hole (h^+) in the valence band by UVA irradiation oxidizes water molecules on the surface of TiO_2 to $^{\bullet}OH$. The reaction of two $^{\bullet}OH$ species can produce H_2O_2 as follows:

$$2^{\bullet}OH \rightarrow H_2O_2 \tag{4}$$

Although TiO_2 particles are barely incorporated into cell nucleus [35], cellular DNA damage was reported [36–39]. Because H_2O_2 has a transparency for nuclear membrane, the cellular DNA damage can be explained by H_2O_2-mediated mechanism [32]. The activation of H_2O_2 and DNA damage by H_2O_2 are described later.

2.3. Secondary formation of hydrogen peroxide through photocatalytic reaction

Photocatalytic reaction can produce oxidized intermediates other than final oxidized products of chemical compounds. For example, photooxidized amino acids [40] and sugars [41] by TiO_2 photocatalyst produce H_2O_2 through secondary oxidation reaction in the presence of metal ions (**Figure 6**). Titanium dioxide can photocatalyze the production of $^{\bullet}OH$, a strong oxidant, through the decomposition of H_2O. The formed h^+ in the valence band by UVA irradiation can also oxidize various materials adsorbed on TiO_2 surface. Hydroxyl radicals and h^+ can oxidize these biomolecules, resulting in the production of oxidized intermediates. The formation of partly oxidized molecules leads to the secondary H_2O_2 production in the presence of metal ions. This H_2O_2 production process may cause a remote H_2O_2 generation in cells.

It has been reported that the photooxidized phenylalanine and tyrosine by TiO_2 produce H_2O_2 in the presence of copper(II) ion [40]. Since TiO_2 photocatalysis induces a hydroxylation of

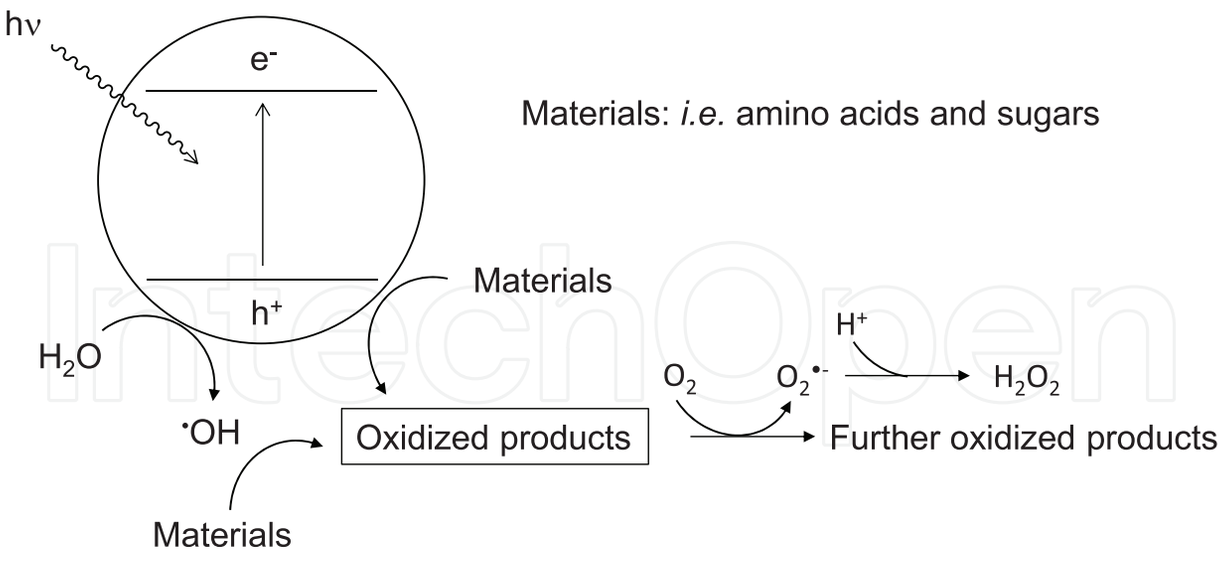

Figure 6. The secondary production of ROS by TiO_2 photocatalysis.

aromatic compounds [42], the formation of benzenediol derivatives from these aromatic amino acids is possible (**Figure 7**). As mentioned above, hydroquinone can produce H_2O_2 through the autoxidation (**Figure 2**) [20, 43]. The amount of H_2O_2 production from the photooxidized phenylalanine is significantly larger than that from tyrosine [40]. The difference of their autoxidation rates should affect the H_2O_2 production. It has been reported that the autoxidation rate of 1,4-form of benzenediol is markedly faster than that of 1,2-form [20]. Phenylalanine can be oxidized into various types of benzenediol, including the 1,4-form; however, tyrosine cannot be converted to the 1,4-form. Consequently, phenylalanine can produce relatively large amount of secondary H_2O_2 through the photocatalysis of TiO_2. Furthermore, other amino acids can be also oxidized by TiO_2 photocatalyst and induce the secondary ROS production. Specifically, photocatalyzed cysteine by anatase form produces significantly large amount of secondary H_2O_2. In the case of sugar oxidation by TiO_2 photocatalyst, the activity of secondary H_2O_2 production by anatase form TiO_2 is larger than that of rutile form [41].

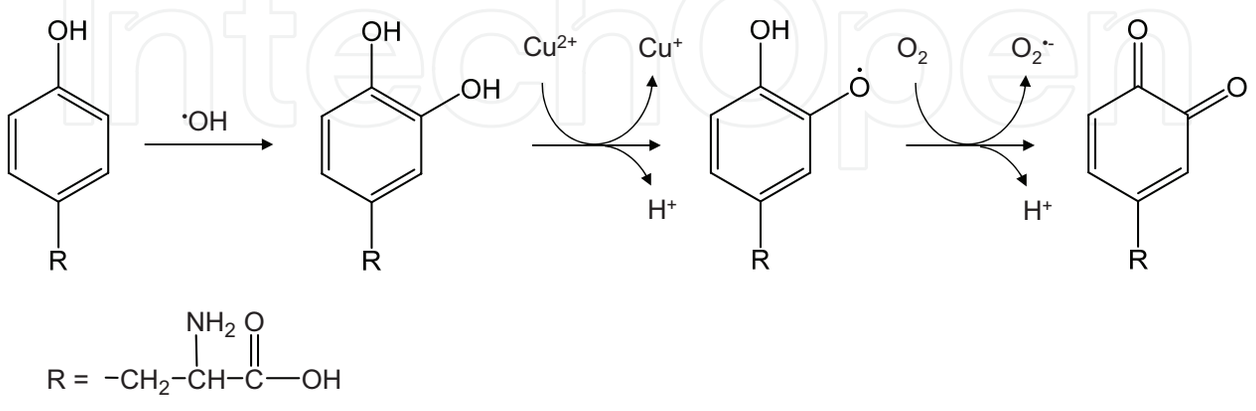

Figure 7. Tyrosine oxidation by TiO_2 photocatalysis and the copper ion mediated ROS production. Phenylalanine is also oxidized by the similar processes, leading to the secondary ROS production.

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3. DNA damage by hydrogen peroxide

Hydrogen peroxide itself barely induces DNA damage; however, it can oxidize nucleobases and cleave sugar-phosphate backbone in the presence of metal ions. In this section, the sequence-specific DNA damage by the H_2O_2-derived ROS and its biological effect are briefly introduced.

3.1. Sequence-specific DNA damage by hydrogen peroxide

Hydrogen peroxide causes alkali-labile products at guanine, thymine, and cytosine in the presence of cupper ion (Cu^{2+}) [44]. Since copper ions are associated with chromatin [45] to form stable complexes with DNA [46–49], Cu^{2+} can play an important role in the activation of H_2O_2 in cell nucleus. Polyacrylamide gel electrophoresis studies demonstrated that H_2O_2 itself cannot cleave and oxidize DNA [44]. However, the incubation of DNA with H_2O_2 and Cu^{2+} induce base modifications at guanine, thymine, and cytosine residues. These base modification sites can be cleaved by hot piperidine treatment [20–22, 44]. The derived reactive species from H_2O_2, for example, copper-peroxyl species (Cu(I)-OOH), are responsible for this DNA damage:

$$H_2O_2 + Cu^+ \rightarrow Cu(I) - OOH + H^+ \tag{5}$$

Cu(I)-OOH is not strongly reactive compared with $^{\bullet}OH$; however, its lifetime is relatively long to induce DNA base modification. Single-stranded DNA is easier oxidized by these ROS. Therefore, DNA damage by H_2O_2 is enhanced by denaturation of DNA [44]. Abovementioned chemical compounds, benzenediol [20] and hydrazine [21], induce these base modification in the presence of Cu^{2+}. In the case of relatively low concentration of TiO_2 particles, similar sequence-specific DNA damage was observed after UVA irradiation with Cu^{2+} [32]. DNA damage mediated by H_2O_2 is effectively inhibited by catalase [50], which is an enzyme to decompose H_2O_2 to H_2O and O_2. Chelating molecules for copper ions also effectively suppress this DNA damage. In addition, 3-methylthiopropanal (methional) is an effective inhibitor of Cu(I)-OOH [20, 32, 44]. Cu(I)-OOH cannot be scavenged by free $^{\bullet}OH$ scavengers, such as sugars and alcohols [20, 22, 32, 44]. In the presence of Cu^{2+}, UVA-irradiated NADH also induces DNA damage by the similar process through H_2O_2 production [28]. In general, photosensitized DNA damage could be explained by $^1O_2$ formation mechanism or electron transfer-mediated oxidation [51]. The H_2O_2-mediated DNA is a rare case in the photochemical DNA damage.

Hydrogen peroxide and Cu^{2+} can induce tandem lesion at guanine and thymine residues [32]. Clustered DNA lesions including tandem damage have important mutagenic potential [52–54]. Furthermore, the repair of such DNA damage is more difficult than single-base damage [55–60]. Therefore, oxidative DNA damage through H_2O_2 production may play an important role in carcinogenesis.

In the presence of iron ions (Fe^{2+}), •OH is formed as follows:

$$H_2O_2 + Fe^{2+} \rightarrow {}^{\bullet}OH + OH^- + Fe^{3+} \quad (6)$$

Formed •OH induces base oxidation with non-sequence specificity, because •OH can oxidize all nucleobases [44, 61]. In addition, direct cleavage of sugar-phosphate backbone is caused by •OH. Hydroxyl radical-mediated DNA damage was reported by the case of ascorbate with Cu^{2+} [62]. As mentioned above, in the case of TiO_2 photocatalysis, •OH is directly produced from water decomposition [29–32], and DNA damage without sequence specificity can be induced in the absence of metal ions [32]. Relatively high concentration of anatase form of TiO_2 induce non-sequence-specific DNA damage under UVA irradiation without metal ions through •OH production [32]. DNA damage by •OH is effectively inhibited by sugars and alcohols [32, 44]. However, in the presence of metal ions, the addition of •OH scavengers rather enhances DNA damage through the secondary generation of H_2O_2 from the oxidized products of scavengers themselves by •OH [32, 41]. Base modifications can cause carcinogenesis. Because H_2O_2 can penetrate into nuclear membrane, DNA modification can be induced by H_2O_2 originally formed in the sphere of outer cell nucleus through the assistance of metal ions.

3.2. Mutagenicity and cytotoxicity caused by hydrogen peroxide production

As oxidized products of nucleobases by the H_2O_2-mediated mechanism, 8-oxo-7,8-dihydroguanine (8-oxo-G; oxidized guanine, **Figure 8**) [63–65]; 5,6-dihydroxy-5,6-dihydrothymine (OH-thy; oxidized thymine, **Figure 9**) [58, 66, 67]; 5-hydroxyuracil (OH-Ura; oxidized cytosine, **Figure 9**) [67, 68]; 5-hydroxyhydantoin (OH-Hyd; oxidized cytosine, **Figure 9**) [68], and 5-hydroxycytosine (OH-Cys; oxidized cytosine, **Figure 9**) [67] are well-known compounds.

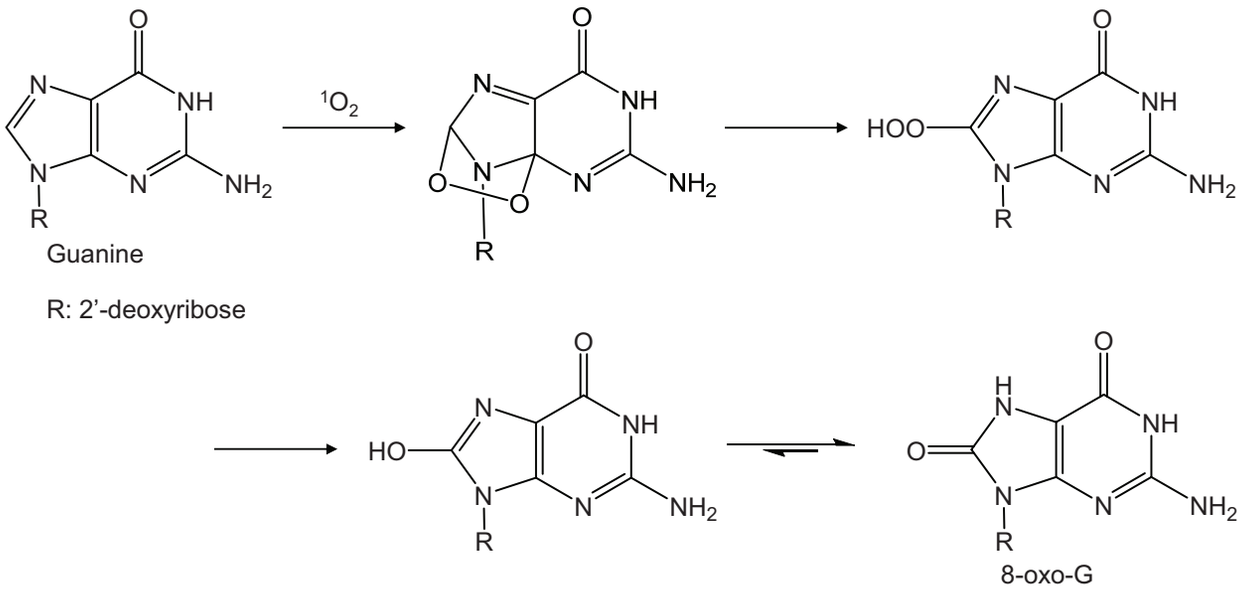

Figure 8. Guanine oxidation by ROS. This scheme is an example of the guanine oxidation by $^1O_2$ to 8-oxo-G. Other H_2O_2-derived ROS, •OH and Cu(I))-OOH, also produce 8-oxo-G through the oxidation of guanine.

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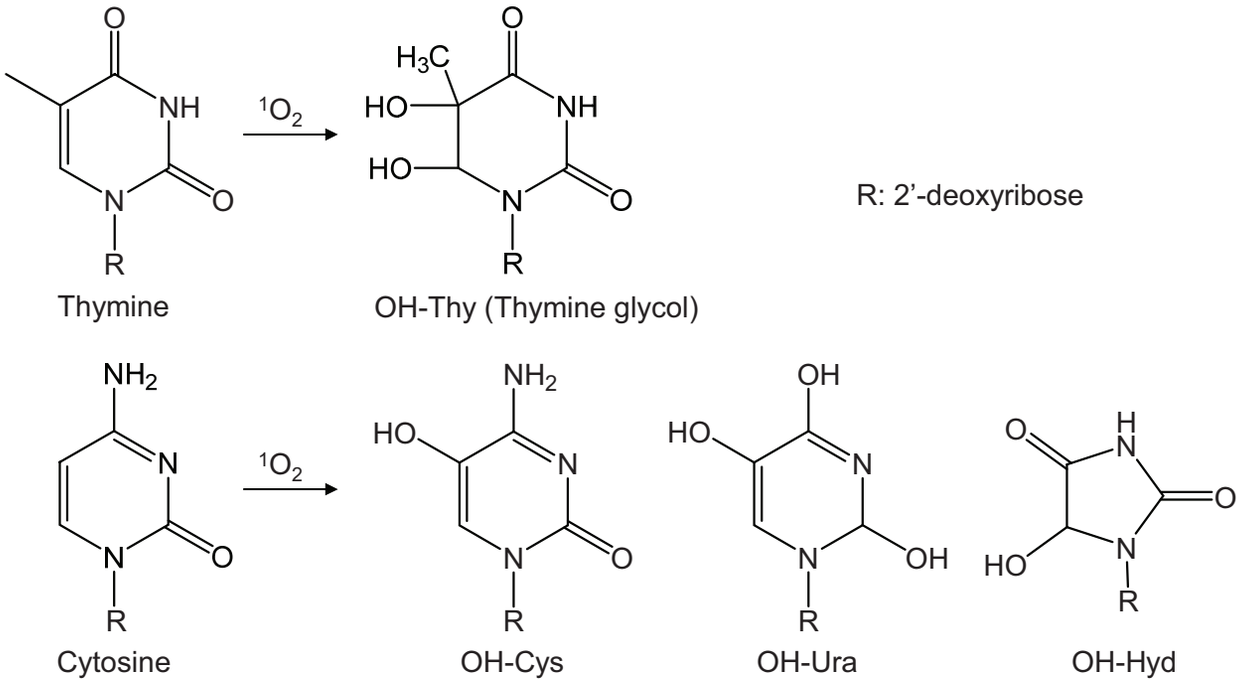

Figure 9. Oxidized products of thymine and cytosine by $^1O_2$.

In a certain case, oxidative DNA damage induces cell death [69, 70]. As a minor oxidized product of guanine, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (Fapy-G, **Figure 10**) can be formed by H_2O_2 and metal ions [63, 71]. Mutagenicity of Fapy-G is low [72]; however, a related product, methyl-Fapy-G formation, is a lethal lesion [73]. Furthermore, a theoretical study suggested that the formation of Fapy-G contributes to mutation [74]. Cytotoxicity of TiO_2 photocatalyst can be explained by oxidative damage of membrane protein [75–77]. In addition, cellular DNA damage was also reported [78, 79]. Because H_2O_2 has a transparency for nuclear membrane, the cellular DNA damage by TiO_2 photocatalysis can be explained by H_2O_2 production. The formed H_2O_2 through TiO_2 photocatalysis is incorporated into cell nucleus and activated by endogenous metal ions, leading to oxidative DNA damage [32]. Examples of the mutations caused by the oxidized guanines are described in Section 4.

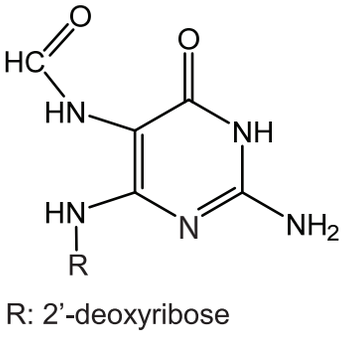

Figure 10. Structure of Fapy-G.

4. Singlet oxygen

In general, the production mechanism of $^1O_2$ involves photochemical processes. Various photooxidation processes can be explained by $^1O_2$ production. In this section, the production mechanism of $^1O_2$, its application, and biomolecule oxidation by $^1O_2$ are briefly introduced.

4.1. General property of singlet oxygen

Singlet oxygen is an excited state of $^3O_2$, ground triplet state of molecular oxygen [16–18]. In general, singlet excited (S_1) states of O_2 are $^1\Delta_g$ and $^1\sum_g^+$; they have excitation energy of 0.98 eV and 1.63 eV above $^3O_2$, respectively [16–18]. Because of the short lifetime of $^1\sum_g^+$ (a few picoseconds), $^1\Delta_g$, the lower S_1 state of O_2, plays an important role in various oxidation reactions. In this chapter, $^1\Delta_g$ is denoted throughout as $^1O_2$. The highest occupied molecular orbital (HOMO) of $^3O_2$ is a semi-occupied molecular orbital (SOMO), whereas this molecular orbital of $^1O_2$ becomes the lowest unoccupied molecular orbital (LUMO) (**Figure 1B**). The oxidative activity of $^1O_2$ is stronger than that of $^3O_2$ due to the vacant molecular orbital. Commonly, $^1O_2$ is produced through photosensitized reaction. Since the excitation energy of $^1O_2$ is relatively small, which corresponds to the energy of photon with the wavelength of 1270 nm (smaller than that of visible light photon), photoexcited states of various dyes can sensitize the generation of $^1O_2$ under visible light or ultraviolet irradiation. Various molecules become photosensitizer (PST) to generate $^1O_2$. In general, the photosensitized reaction of $^1O_2$ generation is an electron exchange energy transfer (the Dexter mechanism) [80]. These processes are presented as follows:

$$PST + h\nu \rightarrow PST^*(S_1) \tag{7}$$

$$PST^*(S_1) \rightarrow PST + \text{fluorescence} \tag{8}$$

$$PST^*(S_1) \rightarrow PST^*(T_1) \tag{9}$$

$$PST^*(T_1) + {}^3O_2 \rightarrow PST + {}^1O_2 \tag{10}$$

where PST*(S_1) and PST*(T_1) are the S_1 and T_1 states of PST, respectively. In general, since the lifetime of PST*(T_1) is markedly longer (several microseconds) than that of PST*(S_1) (several nanoseconds), $^1O_2$ is produced by PST*(T_1). However, the formation of $^1O_2$ by PST*(S_1) is not impossible. The lifetime of $^1O_2$ (τ_Δ) is relatively long (**Table 1**). Generated $^1O_2$ can oxidize various materials, including biomolecules, within its long lifetime. The τ_Δ strongly depends on the surroundings, and a solvent deuterium effect on the reactivity of $^1O_2$ is significant (**Table 1**). For example, the τ_Δ in deuterium oxide (D_2O) is markedly longer than that in H_2O, and the biomolecule oxidation by $^1O_2$ is significantly enhanced in D_2O compared with that in H_2O.

Solvent	Photosensitizer	τ_Δ/μs	Reference
Water (H_2O)	Cationic porphyrin	3.5	[81]
	Rose bengal	3.77	[82]
Phosphate buffer (pH 7.6)	P(V) porphyrin	3.5	[83]
Ethanol (C_2H_5OH)	Rose bengal	15.4	[82]
Ethanol/H_2O (1/1)	Rose bengal	6.37	[82]
Water (D_2O)	Berberine with DNA	72	[84]
	Methylene blue	32	[85]
	Phenalenone	64.4	[86]
	Tris(bipyridine)Ru(II)	59.47	[82]
Chloroform ($CHCl_3$)	Phenalenone	232	[86]
Tetrachloromethane (CCl_4)	Phenalenone	34,000	[86]

Table 1. Solvent dependence of the lifetime of singlet oxygen.

4.2. Photodynamic therapy

One of the most important medicinal applications of $^1O_2$ is photodynamic therapy (PDT) (**Figure 11**) [7–9]. Photodynamic therapy is a promising and less invasive treatment for cancer [7–9] and photosterilization [10–14]. For cancer PDT, in general, porphyrins are used for photosensitizers, for example, porfimer sodium [87] and talaporfin sodium [88]. Photosterilization, antimicrobial PDT, is also carried out using dyes, for example, methylene blue (MB) [11, 14, 89]. The important mechanism of PDT processes including photosterilization is oxidation of biomolecules of cancer cell or bacteria through $^1O_2$ production under visible light irradiation. Visible light, especially longer wavelength visible light (wavelength > 650 nm), is less harmful for the human body and can penetrate into the tissue deeply. As mentioned above, $^1O_2$ can be generated by longer wavelength visible light. Administered photosensitizers, porphyrins, or other dyes produce $^1O_2$ through energy transfer to oxygen molecules with relatively large quantum yield (Φ_Δ).

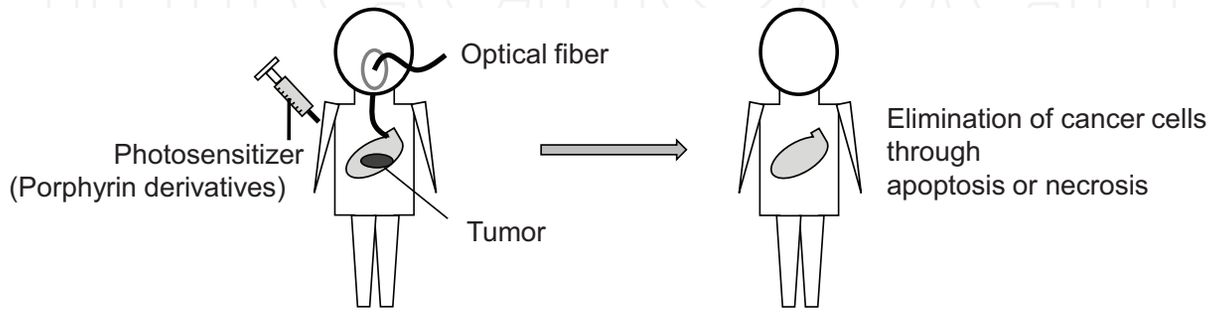

Figure 11. Scheme of the general procedure of PDT.

4.3. Photocatalytic singlet oxygen generation

As mentioned above, TiO_2 photocatalyzes the generation of various ROS. Singlet oxygen can be also produced through the photocatalysis of TiO_2 [31, 90–96]. In general, photogenerated electron in the conduction band reduces the surface-adsorbed oxygen molecules to $O_2^{\bullet-}$. Through the reoxidation of $O_2^{\bullet-}$, $^1O_2$ is formed. The possible reactions of photocatalytic $^1O_2$ productions are as follows:

$$O_2^{\bullet-} + h^+ \rightarrow {}^1O_2 \tag{11}$$

and

$$O_2^{\bullet-} + {}^{\bullet}OH \rightarrow {}^1O_2 + OH^- \tag{12}$$

The photogenerated h^+ in the valence band and $^{\bullet}OH$ can act as the oxidants to produce $^1O_2$. In addition, hydroperoxyl radical ($^{\bullet}OOH$) generated from $O_2^{\bullet-}$ and H^+ also produces $^1O_2$ as follows:

$$O_2^{\bullet-} + {}^{\bullet}OOH + H^+ \rightarrow {}^1O_2 + H_2O_2 \tag{13}$$

The reported values of Φ_Δ are depending on the experimental condition, for example, around 0.2 (0.2, Degussa P25 in water [92], and 0.22, rutile particle in chloroform [95]). Other cases reported relatively small values, for example, 0.003 [96] and 0.02 [94]. In the cases of airborne $^1O_2$, quite small value (10^{-8}–10^{-9}) was reported [93]. It has been reported that the τ_Δ value of $^1O_2$ produced by Degussa P25 aqueous suspension is 5 μs [92]. Other photocatalytic materials, for example, zinc oxide (ZnO) can photocatalyze $^1O_2$ production through the similar reaction of TiO_2 photocatalysis [97]. Recently, carbon quantum dots, which have been paid attention as interesting nano-materials, also photocatalyze $^1O_2$ production [33].

Singlet oxygen is an important ROS for PDT. Other than $^1O_2$, H_2O_2 production can be also applied for PDT mechanism. Photocatalytic materials can produce these ROS under photoirradiation. Therefore, application of photocatalysts, specifically TiO_2 nanoparticles, for PDT has been also studied [29, 98–101]. To realize the TiO_2-utilized PDT, direct administration of small TiO_2 powders into tumor assisted with an optical fiber was proposed [29]. In addition, it was reported that oral-administrated TiO_2 nanoparticles are transported into the tumor of nude mouse skin transplanted from a human prostate cancer cell line [98]. As mentioned above, in general, TiO_2 nanoparticles can be excited by UVA irradiation. To utilize visible light for TiO_2 excitation, upconversion technique was also studied [100].

4.4. DNA oxidation by $^1O_2$ and mutation

Singlet oxygen can oxidize only guanines without sequence specificity; however, it does not have the ability to induce the oxidation of other nucleobases or to cleave the sugar-phosphate backbone [44]. The main oxidized product of guanine by $^1O_2$ is 8-oxo-G (**Figure 8**) [63–65]. Guanines undergo the Diels-Alder reaction by photoproduced $^1O_2$, leading to the formation

of [4 + 2] cycloaddition product with the imidazole ring to produce an endoperoxide. Through the subsequent proton transfer, this peroxide is converted to 8-hydroperoxyguanine [102, 103], which becomes 8-hydroxyguanine [63]. The keto-enol tautomerism produces 8-oxo-G from 8-hydroxyguanine. Because single-stranded DNA is easily oxidized by ROS, 8-oxo-G formation by $^1O_2$ is increased by DNA denaturation [44]. The 8-oxo-G formation causes DNA misreplication (**Figure 12**), which can lead to mutations such as G-C:T-A transversion caused by the stable base-pair formation between 8-oxo-G and adenine [104, 105]. Since 8-oxo-G is more easily oxidized than guanine, 8-oxo-G undergoes further reaction, leading to the formation of imidazolone and oxazolone (**Figure 13**) [63, 106, 107]. Imidazolone forms more stable base pair with guanine than cytosine [106, 107]. Therefore, guanine oxidation by $^1O_2$ may cause G-C:C-G transversion [108, 109] through imidazolone formation, a further oxidized product of 8-oxo-G. Indeed, it has been reported that UVA can induce these mutations [110].

4.5. Protein oxidation by $^1O_2$

Protein oxidation is also induced by $^1O_2$. The following amino acids, tryptophan, tyrosine, cysteine, histidine, and methionine, can be oxidized by $^1O_2$ [111]. In the case of tryptophan oxidation by $^1O_2$, *N*-formylkynurenine (**Figure 14**) is a major oxidized product [112, 113]. The reported reaction rate coefficient between tryptophan and $^1O_2$ is 3.0×10^7 s^{-1} M^{-1} [114]. Oxidation of tryptophan residue in a certain protein can be examined with a fluorometer [115]. For example, human serum albumin (HSA) has one tryptophan residue, and the intrinsic fluorescence of tryptophan at around 350 nm can be diminished by the oxidative damage. Porphyrin phosphorus(V) complexes (**Figure 15**), of which the Φ_Δ is larger than 0.5, can induce oxidative damage to the tryptophan residue of HSA [116]. Photosensitized HSA damage is enhanced in D_2O, in which the lifetime of $^1O_2$ is markedly elongated compared in H_2O (**Table 1**). Furthermore, sodium azide (NaN_3), a strong physical quencher of $^1O_2$ [117], effectively suppresses this HSA damage. From the analysis of the effect of NaN_3 on the HSA damage, the contribution of $^1O_2$-mediated oxidation to the total quantum yield of protein damage

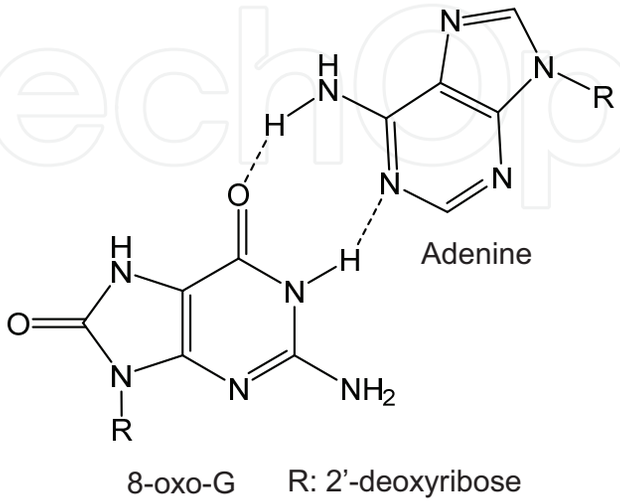

Figure 12. Hydrogen bonding between 8-oxo-G and adenine.

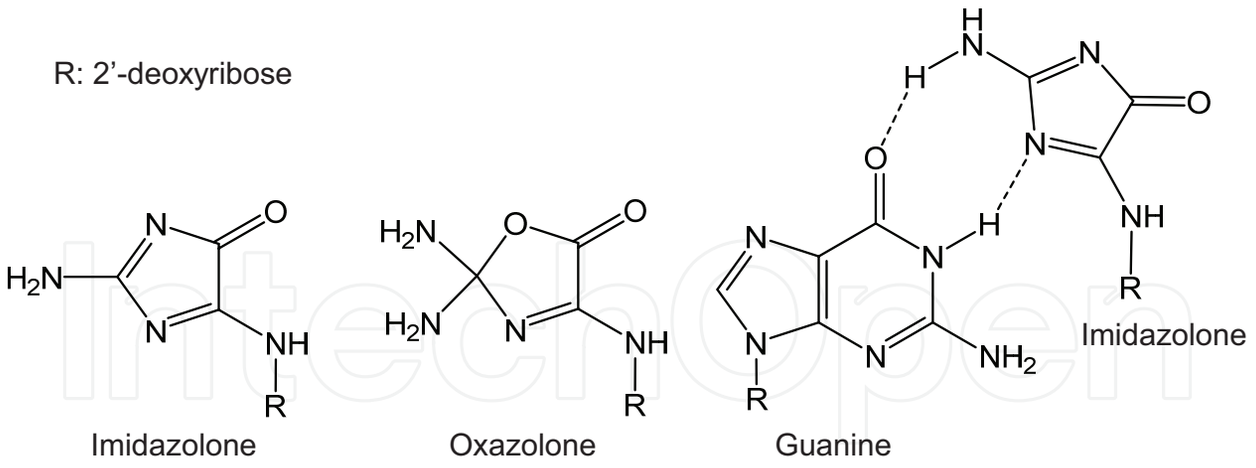

Figure 13. Structures of imidazolone and oxazolone and the hydrogen bonding between guanine and imidazolone.

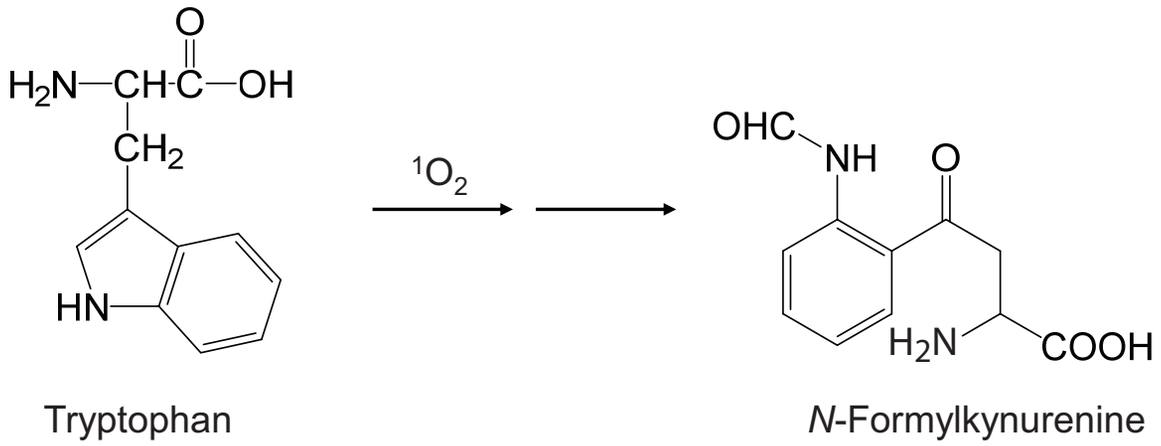

Figure 14. Structures of tryptophan and *N*-formylkynurenine, an oxidized product of tryptophan by $^1O_2$.

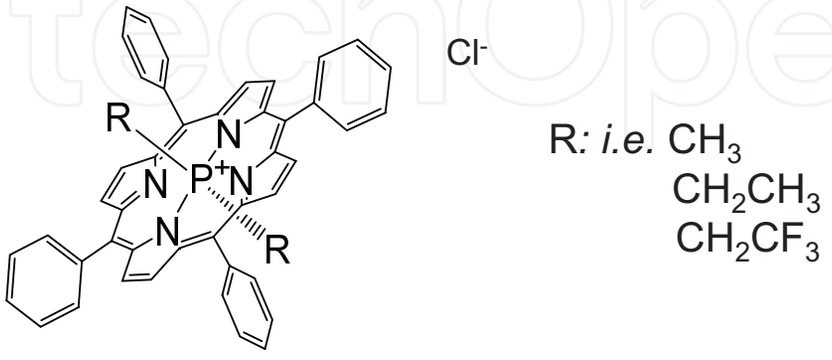

Figure 15. Example of P(V)porphyrin photosensitizer.

can be determined [115]. Photosensitized $^1O_2$ production by porphyrin phosphorus(V) complexes induces the damage of tyrosinase, which is an enzyme to catalyze the hydroxylation of tyrosine, resulting in the deactivation of tyrosinase [118]. Oxidation of the amino acid residue by $^1O_2$ can cause the deactivation of protein function. The protein oxidation photosensitized by porphyrins through ROS production is an important mechanism of PDT.

Photocatalyzed $^1O_2$ production by TiO_2 may not play an important role in the oxidation reaction [31, 94]. Formed $^1O_2$ on the TiO_2 surface is quenched by TiO_2 itself with relatively large quenching rate coefficient (e.g., $2.4 \times 10^9\ M^{-1}\ s^{-1}$ [95]). In the presence of bovine serum albumin, $^1O_2$ produced by TiO_2 photocatalysis is effectively quenched, suggesting the protein oxidation [94]. However, in the case of TiO_2 photocatalyst, other ROS are more important for protein oxidation than $^1O_2$-mediated reaction [29–32].

5. Detection of ROS

ROS detection is an important theme to investigate a biological effect of ROS or evaluation of the activity of PDT photosensitizers [119–122]. Fluorometry is one of the most important and effective methods of ROS detection. For example, 5-carboxyfluorescein-based probe has been developed (**Figure 16**) [123]. This probe can detect H_2O_2 in the living cell. As an inexpensive method, the fluorometry using folic acid (**Figure 17**) was reported [23, 119, 124]. Folic acid can be decomposed by H_2O_2 in the presence of Cu^{2+}, resulting in the fluorescence enhancement. The limit of detection (LOD, at signal/noise = 3) for this method was 0.5 μM H_2O_2. This method is based on the oxidative decomposition of folic acid by Cu(I)-OOH. In the presence of Fe^{2+}, $^{\bullet}OH$ slightly induces the folic acid decomposition; however, the effect of $^{\bullet}OH$ on this folic acid decomposition is negligibly small because of the very short lifetime [125, 126]. In addition, $O_2^{\bullet-}$ does not

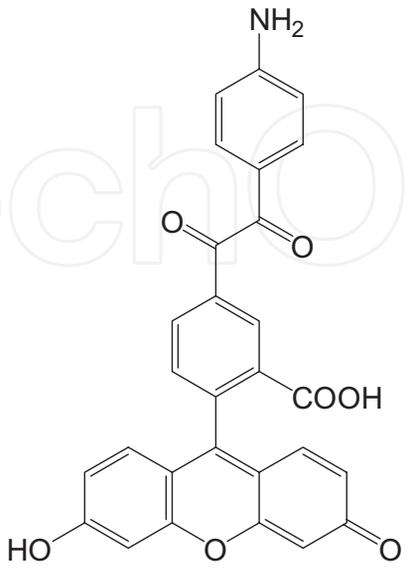

Figure 16. Structure of 5-carboxyfluorescein-based fluorescence probe for H_2O_2 [123].

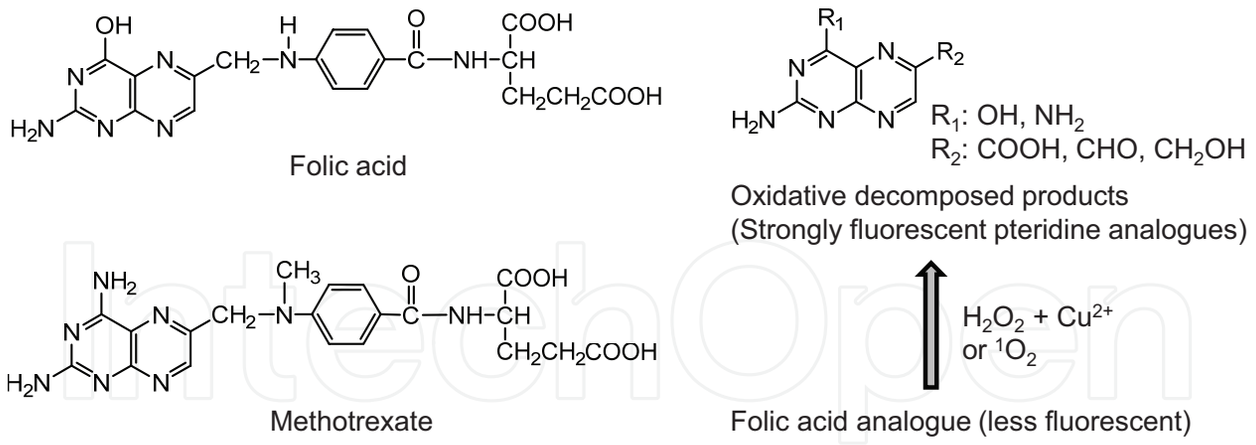

Figure 17. Structures of folic acid and methotrexate and the fluorometry of ROS [119, 124].

have the activity of folic acid decomposition. Using folic acid or its analogue, $^1O_2$ can be also detected [124]. Specifically, in D_2O, folic acid or methotrexate (**Figure 17**), an analogue of folic acid, is effectively decomposed by $^1O_2$, resulting in the fluorescence enhancement [124]. Using this method, the values of Φ_Δ of various water-soluble photosensitizers can be determined.

6. Control of singlet oxygen production

Control of photosensitized $^1O_2$ is an important theme for biology or medicine, for example, to realize target-selective PDT [127] or "theranostics" (therapy and diagnosis) [128]. The pH-dependent control [129] and target-selective control [127, 128, 130–132] methods have been reported. It has been reported that free base porphyrins were synthesized to control their photosensitized $^1O_2$ generating activity by pH (**Figure 18**) [129]. The S_1 state of this porphyrin

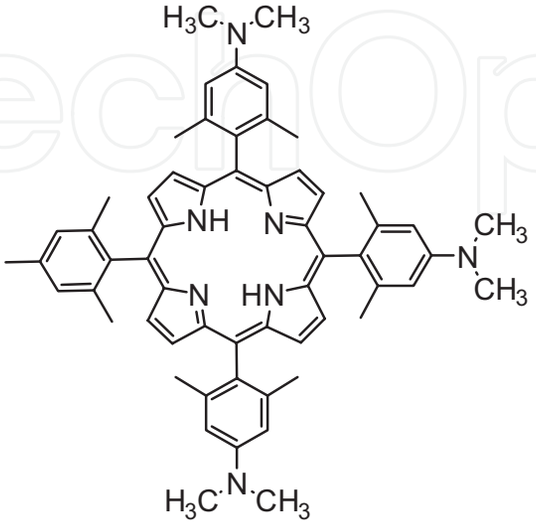

Figure 18. Example of the reported pH-responsive porphyrin [129].

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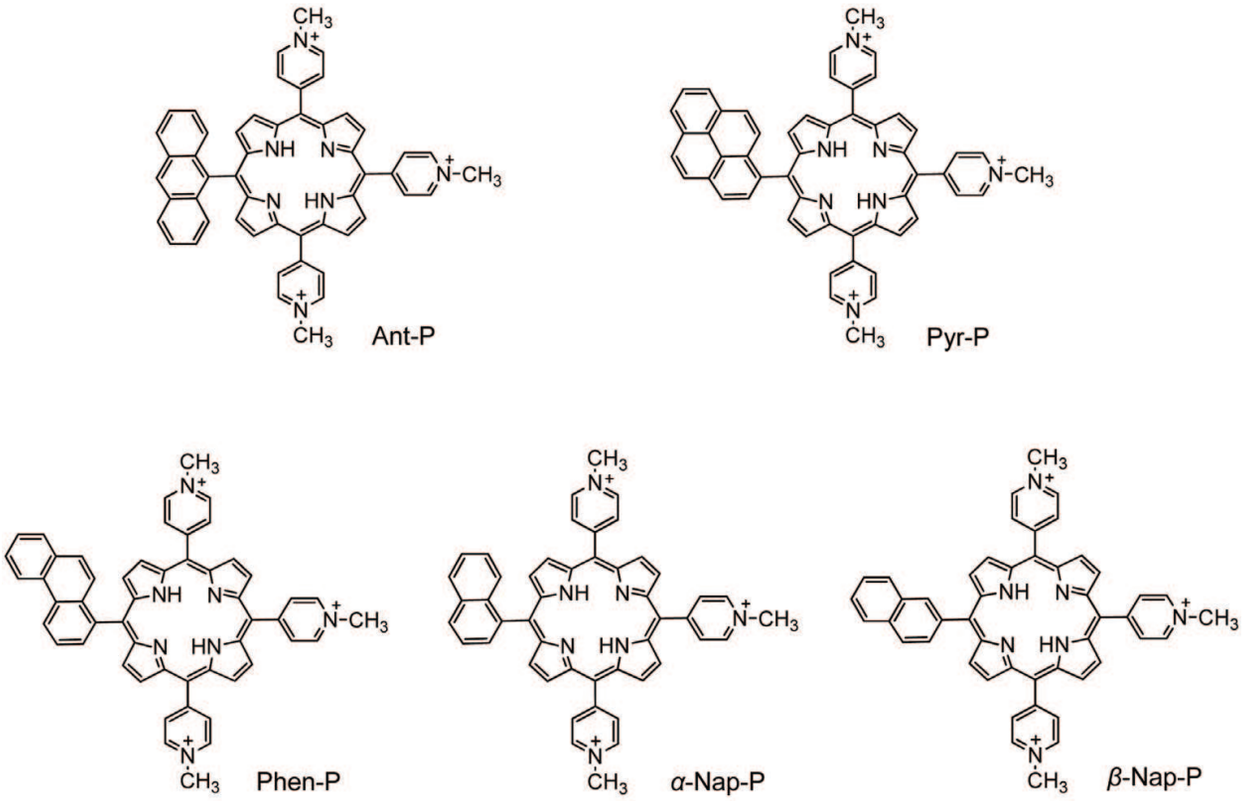

Figure 19. The examples of DNA-targeting porphyrins: Ant-P [81], Pyr-P [130], Phen-P [131], and Nap-Ps [132].

is quenched by the electron-donating moiety in neutral or alkali solution. However, protonation of this electron-donating moiety under acidic condition suppresses the electron transfer, leading to the recovery of the $^1O_2$ production activity of porphyrin ring. Because cancer cell is slightly a more acidic condition compared with normal cells [133–135], this pH-based control of photosensitized $^1O_2$ production can be applied to cancer-selective PDT. DNA-targeting control of photosensitized $^1O_2$ generation has been also reported [127, 128]. For example, electron donor-connecting porphyrins have been studied (**Figure 19**) [81, 130–132]. These compounds can be photoexcited by visible light irradiation, and their S_1 states are effectively quenched through intramolecular electron transfer. The charge-transfer state energy can be raised through the binding interaction with DNA, an anionic polymer, resulting in the inhibition of the intramolecular electron transfer and enhancement of $^1O_2$ generation.

7. Conclusions

Hydrogen peroxide is easily produced from the oxidation processes of chemical compounds by oxygen molecules. In addition, UVA-irradiated NADH and semiconductor photocatalytic materials can also produce H_2O_2. Formed H_2O_2 in cells can be incorporated into cell nucleus and activated by endogenous metal ions. Copper ion induces Cu(I)-OOH formation from H_2O_2,

whereas $^{\bullet}OH$ is produced from H_2O_2 and iron ion. These ROS cause base oxidation, and $^{\bullet}OH$ can induce strand break of DNA. Base modifications lead to carcinogenesis or lethal effect. Photoirradiation to various sensitizing materials induces $^1O_2$ production. Visible light has sufficient energy to produce $^1O_2$. Therefore, $^1O_2$ is easily produced by various dyes under photoirradiation. Photocatalytic $^1O_2$ formation through reoxidation of $O_2^{\bullet-}$ is also possible. Formed $^1O_2$ can oxidize guanine residues of DNA without sequence specificity and several amino acid residues of protein within its lifetime, which depends on the surroundings. Various detection methods of these ROS have been developed. In addition, the target-selective or condition-selective productions of ROS become important strategies for PDT and cancer "theranostics."

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