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Mechanistic studies on versatile metal-assisted hydrogen peroxide activation processes for biomedical and environmental incentives

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Abbreviations: ROS, reactive oxygen species; SOD, superoxide dismutase; Por, porphyrin; TAML, tetraamido macrocyclic ligand; DFT, density functional theory; AOPs, advanced oxidation processes; CYPs, cytochromes P450; NAD(P)H, nicotinamide adenine dinucleotide phosphate/nicotinamide adenine dinucleotide; PhIO, iodosylbenzene; TPFPP, *meso*-tetrakis(pentafluorophenyl)porphyrin; TF_4TMAP, *meso*-tetrakis(2,3,5,6-tetrafluoro-N,N,N-trimethyl-4-aniliniumyl)porphyrin; TPPS, *meso*-tetrakis(4-sulphonatophenyl)porphyrin; TOF, turnover frequency; ORII, orange II; NOX, NADPH oxidase; IBD, inflammatory bowel diseases; LMCT, ligand to metal charge transfer; AMD, age-related macular degeneration; PS, photosensitizer; DLI, drug-to-light interval; IL, interleukins; TNF, tumor necrosis factor; IFR, interferon; PET, positron emission tomography; F_2PMet, *meso*-tetrakis(2,6-difluoro-5-*N*-methylsulfamylophenyl)porphyrin; WST9 (padaporfin), palladium derivatives of bacteriochlorophyll; PDT, photodynamic therapy; V-PDT, vascular target PDT; C-PDT, cellular target PDT; S^*, excited sensitizer; CAT-skl, analog of catalase that enters peroxisomes; CT29, colon carcinoma cell line; A549, human lung cancer cell line; 3AT, 3-amino-1,2,4-triazole; 2ME, 2-methoxyestradiol; BSO, buthionine sulfoximine; CT26, colon carcinoma cell line; AH_2, ascorbic acid; DHS, dehydroascorbate; LED, light-emitting diode; TNSs, titanate nanosheets; GO, graphene oxide; RGO, reduced form of graphene; Pd-BPh, palladium bacteriopheophorbide; Pd-[Bchl], palladium bacteriochlorin; Pd-2Ac-Ph, 2-desvynil-2-acetyl-Pd-pheophorbide.

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ABSTRACT

This article focuses on the versatile ways in which hydrogen peroxide can be activated by metal ions and metal compounds, in terms of possible biomedical and environmental applications and future incentives in these areas. Mechanistic studies performed in our group are discussed in reference to related studies reported in the literature. It covers various thermal activation pathways, including Fenton and Fenton-like reactions, the application of iron, manganese and other metals complexes, as well as metalloenzymes. Furthermore, light-induced generation, activation and utilization of hydrogen peroxide are presented for the photo-Fenton reactions, the application of macrocyclic photosensitizers and the use of semiconductors such as TiO_2 as heterogeneous photosensitizers. Mechanistic aspects of several thermal and photochemical pathways in metal-assisted hydrogen peroxide applications for biomedical or environmental purposes are discussed, and some obstacles to be overcome are highlighted.

1. Introduction

The activation of small redox-active inorganic molecules has a significant impact in biology, medicine, environmental protection and industrial processes [1–5]. Metal ions and their compounds play a very important role not only in thermal, but also in photochemical processes of small molecule activation. They can mediate the actual active form of small molecules, as well as control their spatial concentration dynamics. In homogenous systems, metal species can operate as a coordination and/or energy, electron, hydrogen atom transfer center. In heterogeneous systems, small molecules can undergo adsorption followed by electron or energy transfer processes involving solid surface participation. Coordination compounds or solid surface participating in the activation process point to an appropriate reaction site where the geometry plays a key role. The metal ion and its ligands control the redox properties and therefore the nature of coordinated or chemisorbed small molecules.

This review focuses on the versatility of transition metal-assisted activation processes of hydrogen peroxide (H_2O_2), a neutral reactive oxygen species (ROS) with significant biomedical and environmental impact.

Even though H_2O_2 is a strong two-electron oxidant (standard reduction potential $E^{pH=7}$ is 1.32 V at pH 7.0) (Fig. 1), it exhibits poor or no reactivity at all toward most pollutants or biological molecules. This behavior is a consequence of a high activation energy barrier indicating that the oxidation reaction is a kinetically-controlled process. One-electron reduction makes H_2O_2 a rather weak oxidant ($E^{pH=7}$ is 0.38 V); however, the resulting product, the hydroxyl radical ($HO^{\bullet}$), is one of the strongest oxidants known ($E^{pH=7}$ is 2.31 V). The reactions of $HO^{\bullet}$ have a very low activation energy barrier and proceed very fast at rates close to diffusion-controlled. Therefore, the activation of H_2O_2 by facilitating one-electron reduction plays a crucial role in the application of this molecule as an efficient oxidant. One of the most explored ways to enable H_2O_2 utilization is its transition metal-assisted activation.

Hydrogen peroxide is an important biological reactive oxygen species; it is generated as a by-product of mitochondrial electron transport of aerobic respiration, or as an end product of various metabolic reactions, and is suggested to be the transmitter of cellular signaling [6]. Overproduction of H_2O_2 is well known to lead to oxidative damage of macromolecules and to be the cause of various diseases and aging, whereby the role of H_2O_2 as a messenger molecule in redox signaling is emerging. Although H_2O_2 is less reactive

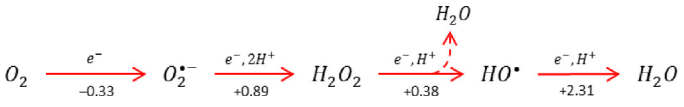

Fig. 1. ROS standard reduction potentials adapted from Reference 6.

than superoxide, $O_2^{\bullet-}$, control of H_2O_2 levels is critical, given that H_2O_2 can readily diffuse across cellular membranes, and thus have an extended sphere of influence. Active transport is also possible through membranes of the aquaporin family [7]. Since one-electron reduction of O_2 is thermodynamically unfavorable in contrast to one-electron reduction of $O_2^{\bullet-}$, disproportionation of $O_2^{\bullet-}$ leading to O_2 and H_2O_2 proceeds spontaneously or is significantly accelerated by superoxide dismutases (SODs). In mitochondria, SOD is a manganese (Mn(III)/Mn(II)) enzyme and in cytoplasm a Cu(II)/Cu(I) Zn(II) enzyme.

On the assumption that all diseases have the perturbation of the cellular redox environment in common, the development of SOD mimics seems to be an appropriate strategy for the design of potent redox active therapeutics.

There are three major groups of enzymes, viz. catalases, glutathione peroxidases and peroxiredoxins, that are involved in cell defense systems against H_2O_2. Among them, only catalase possesses the metal cofactor, either non-heme manganese or heme (Fig. 2A and B).

Heme catalases possess four heme groups with phenolate from tyrosine as an axial ligand (Fig. 2B) that enable the enzyme to react with hydrogen peroxide. There is a continuing debate in the literature on the mechanism of catalase activity [8]; among others, it is postulated that the oxoferryl porphyrin π-cation radical ($(Por^{+\bullet})Fe^{IV}=O$, compound I), formed by heterolytic O-O bond cleavage, is a major reactive intermediate as outlined in the following reactions:

$$(Por)Fe^{III} + H_2O_2 \rightarrow H_2O + (Por^{+\bullet})Fe^{IV}=O \quad (1)$$

$$(Por^{+\bullet})Fe^{IV}=O + H_2O_2 \rightarrow (Por)Fe^{III} + H_2O + O_2 \quad (2)$$

In some revised mechanisms, the formation of the oxoferryl porphyrin ($(Por)Fe^{IV}=O$ or $(Por)Fe^{IV}OH$, compound II) is also proposed to be involved in the catalytic cycle of catalase. Manganese catalases contain a binuclear manganese complex (Fig. 2A) as their catalytic active site and perform a two-electron catalytic cycle in two distinguished steps [9,10] as outlined in the following reactions:

$$\{Mn_2(III,III)\} + H_2O_2 \rightarrow \{Mn_2(II,II) + 2H^+\} + O_2 \quad (3)$$

$$\{Mn_2(II,II) + 2H^+\} + H_2O_2 \rightarrow 2H_2O + \{Mn_2(III,III)\} \quad (4)$$

The H_2O_2 molecule coordinates to Mn1 in the $\{Mn_2(III,III)\}$ cluster by displacing the terminally bound solvent molecule [9,10]. Proton-coupled, two-electron oxidation of the terminally bound hydroperoxide results in formation of the enzyme in the reduced $\{Mn_2(II,II)\}$ state, with two protons bound to solvent bridges and dioxygen. The release of dioxygen is accompanied by the coordination of solvent in the axial position of Mn1. Subsequently, a second

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