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Focused review

The role of catalases in the prevention/promotion of oxidative stress

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ABSTRACT

Catalases, heme enzymes which catalyze decomposition of hydrogen peroxide to water and molecular oxygen, are important members of the antioxidant defense system of cells of almost all aerobic organisms. However, recent studies suggest that catalase may be involved in various other processes in the cell. The paper provides a review of reactions of catalases with their main substrate, hydrogen peroxide, and with oxidizing species such as hydroxyl radical, superoxide, nitric oxide, peroxynitrite, hypochlorous acid, and singlet oxygen. A number of these individuals are formed under oxidative eustress (good stress) as well as distress (bad stress), while others only under conditions of oxidative distress. Potential biological significance of the reactions of mammalian as well as bacterial catalases with oxidizing species is discussed. The majority of these reactions inhibit catalase. Authors emphasize that catalase inhibition, which may lead to significant increase of the local concentration of hydrogen peroxide, may be detrimental to the neighboring tissues, but in some pathological states (e.g. the defense directed against pathogenic bacteria rich in catalase, or induction of apoptosis of cancer cells which possess membrane-associated catalase) it may be beneficial for the host organism.

1. Introduction

1.1. Characteristics of catalases

Catalases are enzymes whose main function is to catalyze decomposition of hydrogen peroxide (H_2O_2) to water and molecular oxygen. According to the structural and functional similarities catalases are divided into three groups: typical or monofunctional catalases, catalase-peroxidases, and nonheme catalases [1]. This review is limited to typical catalases, simply called catalases (EC 1.16.1.6). These four subunit ferriheme enzymes are present in almost all aerobically respiring organisms (plants, animals, fungi, and bacteria). Due to the subunit size catalases can be divided into two groups: the first one contains small subunits (55 to 69 kDa), while the other one large subunits (75 to 84 kDa) [2]. The latter group includes catalases from some bacteria and fungi.

Hydrogen peroxide is generated in vivo mainly in mitochondria, but also in other eukaryotic cell compartments, e.g. peroxisomes and endoplasmic reticulum. Its concentration is tightly regulated via the action of not only catalase but also several isoforms of glutathione peroxidases (GPXs) and peroxiredoxins (PRXs). While catalase utilizes its heme group to reduce/oxidize H_2O_2 (reactions (1) and (2), below), GPXs and PRXs act through their selenocysteine or cysteine residues and need glutathione (GSH) and thioredoxin, respectively, to complete the catalytic cycle, and NADPH to reduce oxidized cofactors. Catalase in the eukaryotic cell mainly removes H_2O_2 generated by peroxisomal oxidases [3] but it can also break down H_2O_2 that diffuse to peroxisomes [4]. Catalase plays an important role in removing H_2O_2 within erythrocytes [5]. Some amount of catalase has also been detected in mitochondria of rat and mice heart [6], in the cytoplasm [7], as well as on the cytoplasmic membrane of human cancer cells [8]. GPXs and PRXs are more widely distributed throughout the cell. Due to the presence of these enzymes, the steady-state concentration of intracellular H_2O_2 under physiological conditions is kept in the range of 1–10 nM. The normal concentration of H_2O_2 in blood plasma appears to be 2–3 orders of magnitude higher than that estimated within cells ([9] and references therein). H_2O_2 can leave and enter cells through aquaporins [10].

1.2. The catalase intermediates

Catalases decompose hydrogen peroxide (catalatic activity) in the two-step process:

$$\text{Catalase} + H_2O_2 \rightarrow \text{Compound I} + H_2O \quad (1)$$

$$\text{Compound I} + H_2O_2 \rightarrow \text{Catalase} + H_2O + O_2 \quad (2)$$

where Compound I (Cpd I) is an oxoferryl porphyrin (por) π-cation radical, two-electron oxidation product of a heme group (por

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$\cdot^{+}Fe^{IV}$ = O) [2]. As regards mammalian catalases, the rate constants of both reactions are of the order of $10^7\,M^{-1}\,s^{-1}$ [11]. The catalase active center is deeply buried within the enzyme structure and the heme can be accessed via a narrow channel only by small molecules [2]. Under conditions where H_2O_2 concentration is low, catalase Cpd I can return to the native enzyme oxidizing secondary two-electron donors, e.g. low molecular alcohols (peroxidatic activity). Alternatively, under above conditions, Cpd I may react with internal or external one-electron/hydrogen donors. In the case of an internal donor, porphyrin radical site is moved to the protein site (prot) ($porFe^{IV}=O$ prot$\cdot$), possibly in several steps [12,13]. One-electron reduction of Cpd I by an external one-electron or hydrogen atom donor results in the formation of Compound II (Cpd II), an oxoferryl derivative without radical site ($porFe^{IV}=O$) ([14] and references therein). Contrary to Cpd II of heme peroxidases, Cpd II of catalase is not effectively reduced to the native enzyme and therefore its accumulation leads to the catalase inactivation. Only a few compounds can reduce Cpd II to native catalase [15]. Mammalian (and also a number of other) catalases contain NADPH in some fractions of their subunits [16–18]. Its role is to reduce Cpd I to the active ferric form under conditions when the rate of H_2O_2 production is too low to maintain the normal catalase turnover, i.e. to prevent the formation of inactive Cpd II [2,19,20]. Catalases may also form another intermediate product, known as Compound III (Cpd III), which structurally resembles oxy forms of mioglobin and hemoglobin (Fe^{II}-$O_2 \rightleftarrows Fe^{III}$-$O_2\cdot^{-}$). It can be generated in the reactions of Cpd II with H_2O_2, or ferric catalases with superoxide ($O_2\cdot^{-}$). Compound III takes no part in the normal catalytic cycle of catalase, is generally inactive towards most electron donors [21] and has never been detected under physiological conditions. Relations between catalase and its Compounds are shown in Scheme 1.

1.3. Catalytic reactions of catalase in the absence of hydrogen peroxide

Catalases are also catalytically active in the absence of H_2O_2. They demonstrate low oxidase activity, which means they can catalyze oxidation of some highly reductive substrates, such as benzidine, using molecular oxygen [22]. Olson et al. have recently showed that bovine and *Aspergillus niger* catalases are able to oxidize hydrogen sulfide (H_2S) in the presence of oxygen. Moreover, mammalian, but not fungal, catalase can act as the sulfur reductase generating H_2S from, for example, dithiothreitol, thioredoxin or sulfur dioxide but not from sulfite, cysteine or glutathione [23]. Mammalian catalase is also able to catalytically decompose peroxynitrite [24]. This reaction is described in more detail in chapter 2.5. Considering the catalase reactions described in this and the previous chapter, it is not surprising that catalase is currently regarded as a multifunctional enzyme.

1.4. The concept of oxidative stress

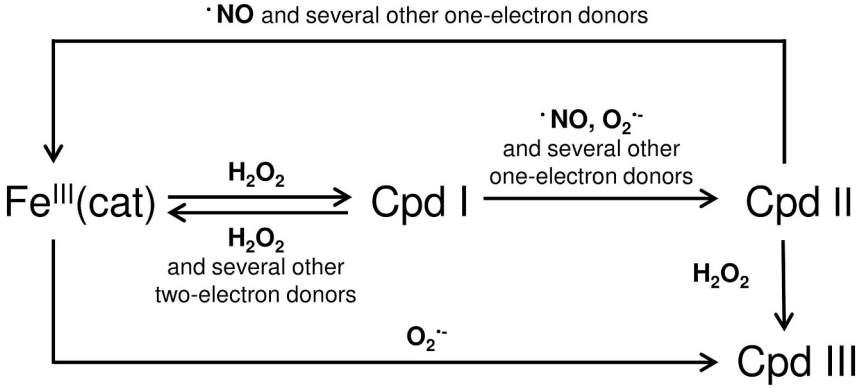
The concept of oxidative stress has evolved over the years. The original definition, offered by Helmut Sies and published in 1985, described this term as “a disturbance in the prooxidant-antioxidant balance in favour of the former” [25]. However, later studies have shown that low exposure of cells, tissues and organisms to oxidants produced by endogeneous or exogeneous sources is necessary to maintain homeostasis and adopt to stress. This physiological oxidative stress (good stress) is termed *oxidative eustress* [26]. However, supraphysiological oxidants level in the body leads to pathologies (bad stress). Therefore, the current definition of oxidative stress (*oxidative distress*) states that it is “an imbalance between oxidants and antioxidants in favor of the oxidants, leading to the disruption of redox signalling and control and/or molecular damage” [27]. Hydrogen peroxide at the physiological concentration plays a significant role in the cell signalling, by controlling such processes as differentiation and proliferation, as well as recruitment of immune cells [28]. Under pathological conditions additional activation of enzymes producing $O_2\cdot^{-}$ (and as a consequence H_2O_2) and nitric oxide ($\cdot$NO) occurs. This results in an increase of H_2O_2 level above the optimal range, and generation of other oxidative species (see below). All this leads to the aberrant cell signalling and oxidative damage. Abnormal increase of oxidants level in the body may also be caused by external factors.

The aim of this review is to gather available literature data concerning reactions of catalases with species formed under both oxidative eustress and distress, in order to consider the role of these enzymes in preventing/promoting oxidative stress. Most of the data refers to mammalian catalases, but we also draw attention to the catalases contained in pathogenic bacteria.

2. Reactions of catalases with species formed during oxidative eustress and distress

2.1. Reactions with hydrogen peroxide

The rate of H_2O_2 decomposition catalyzed by catalases via reactions (1) and (2) obeys first order kinetics and therefore the enzyme is never saturated with this substrate. Thus, V_{max}, K_M and k_{cat} parameters do not have the meaning they possess for standard Michaelis-Menten (M-M) kinetics, despite the fact that for low substrate concentration the data may be fitted with M-M equation. As regards small-subunit catalases, hydrogen peroxide at the concentrations higher than 100–200 mM causes enzyme inactivation [29]. It has been shown, that catalase from the bovine liver (BLC) is both reversibly inhibited and irreversibly inactivated at high H_2O_2 concentration. Kinetic modeling has highlighted the role of Cpd III in both types of the activity loss [30]. It has been suggested, that under such conditions Cpd III is formed in the reaction of Cpd II with H_2O_2 with the rate constant of $(6.1 \pm 0.2) \times 10^4\,M^{-1}\,s^{-1}$ [31]. On the other hand, large subunit catalases are relatively insensitive to the substrate-induced inactivation [29,30,32].



Scheme 1. Relations between catalase and its Compounds. The list of one-electron as well two-electron donors can be found in the reference [2].

2.2. Reactions with hydroxyl radical

Hydroxyl radical (·OH) can be formed in vivo in the Fenton reaction, during spontaneous peroxynitrite isomerization (see below) or in the reaction of superoxide with hypochlorous acid [33]. As one of the strongest one-electron oxidant ($E^{o'}$(·OH, H^+/H_2O) = 2.31 V [34]), this radical is extremely unspecific and reacts with most biologically important molecules at the diffusion-controlled rates. Proteins, due to their abundance in vivo, are considered to be the main targets of ·OH. The kinetics of the BLC reaction with ·OH was studied by pulse irradiation of N_2O-saturated aqueous solution of the enzyme. The rate constant of this reaction was determined to be within the range of 8–11 × 10^{10} M^{-1} s^{-1} [35,36]. Moreover, pulse radiolysis experiments have also revealed that ·OH radical does not react directly with heme (no absorption changes in the Soret band which is characteristic for the heme group), but only with amino acid residues on the surface of catalase molecule [37]. However, steady-state radiolysis experiments have shown the dose-dependent, i.e. cumulative ·OH concentration-dependent, decrease of the Soret band of catalase, which has been correlated with the loss of activity of this enzyme. [38]. These may be due to the radical transfer from the primary amino acid targets to the heme center and/or may be a consequence of ·OH-induced conformational changes of the protein molecule, as a result of which the heme group may become available to radicals generated continuously during the steady-state radiolysis. Thus ·OH-induced catalase damage depends not only on the concentration of this radical but also on the rate of its generation.

2.3. Reactions with superoxide

The main sources of $O_2\cdot^-$ are mitochondrial respiratory chain and NADPH oxidases localized mainly on the plasma membrane but also on the endoplasmic reticulum and mitochondrial membranes. Under physiological conditions, $O_2\cdot^-$ is rapidly converted to H_2O_2 by several superoxide dismutase (SOD) enzymes and H_2O_2 is then metabolized by GPX, PRX and catalase. Under pathological conditions, additional enzymatic sources of superoxide are activated, which in turn leads to the generation of elevated amount of H_2O_2. Under such conditions, other oxidative species, such as hydroxyl radicals, hypochlorous acid or peroxynitrite may be formed.

It has been demonstrated that bovine liver catalase is inhibited by superoxide and this inhibition is due to the reactions of $O_2\cdot^-$ with both ferric catalase and Cpd I to give Cpd III and Cpd II, respectively (reactions (3) and (4), Scheme 1) [39]:

$$\text{Catalase} + O_2^{\cdot-} \rightarrow \text{Compound III} \quad (3)$$

$$\text{Compound I} + O_2^{\cdot-} \rightarrow \text{Compound II} \quad (4)$$

The occurrence of these reactions for BLC has been proved by the pulse radiolysis experiments, where superoxide has been generated upon irradiation of oxygenated aqueous solution of catalase [40,41] and, in stationary experiments under exposure of this enzyme to H_2O_2 and $O_2\cdot^-$ fluxes generated by glucose/glucose oxidase and xanthine/xanthine oxidase system [31]. In both cases it is possible to detect all three catalase intermediates. In the pulse radiolysis experiments, where H_2O_2 and $O_2\cdot^-$ are generated in (sub)microsecond time scale, by appropriate selection of measurement conditions, the rate constants of the reactions (3) and (4) have been estimated to be 2 × 10^5 M^{-1} s^{-1} (pH 7.4) [40], and 5.0 × 10^6 M^{-1} s^{-1} (pH 7.5) [41], respectively. It should be noted that $O_2\cdot^-$ neither reduces ferric catalase to its ferrous form nor Cpd II to ferric catalase [31,40,41].

2.4. Reactions with nitric oxide

Nitric oxide (·NO) is synthetized in vivo from L-arginine by various nitric oxide synthases (NOS) and at nanomolar concentrations it is one of the most significant signalling molecules in the organism. Under pathological conditions, ·NO is additionally produced with the help of inducible NOS, as a part of immune response (precursor of peroxynitrite).

In vitro studies have shown that nitric oxide slows down the rate of H_2O_2 decomposition catalyzed by bovine liver catalase, but on the other hand, catalase in the presence of H_2O_2 oxidizes ·NO (Scheme 1) [42–44]. This is the result of the reversible binding of ·NO to the heme iron and/or of the reaction of ·NO with Cpd I and Cpd II [45]. The rate constant of the reaction of catalase with ·NO, to form Cat^{III}(NO) complex, equal to 3.0 × 10^7 M^{-1} s^{-1} (pH 6.5), was determined using nanosecond laser photolysis technique [46]. In the same study the value of K_d of this complex, equal to 1.8 × 10^5 M^{-1}, was reported. As can be seen, the values of the rate constants of the reactions of catalase with H_2O_2 and with ·NO are comparable, which means that ·NO is capable competing with H_2O_2 for catalase [44]. As it was mentioned above, catalase, in the presence of H_2O_2, can oxidize nitric oxide, probably in two, one-electron steps, to form nitrite [44,45,47]. However, to our knowledge the kinetics of these reactions have not been studied.

2.5. Reactions with peroxynitrite and radicals formed during its reaction with carbon dioxide

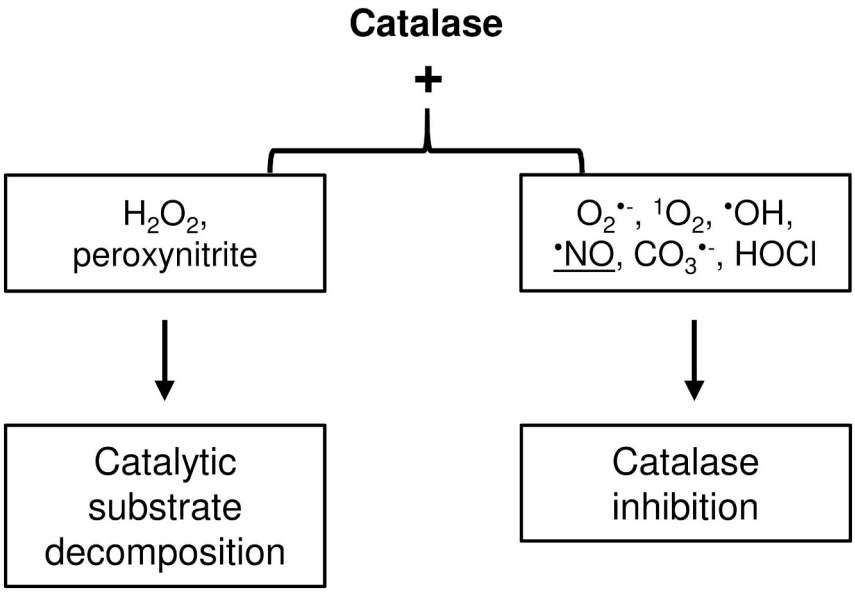
Peroxynitrite ($ONOOH/ONOO^-$, pK_a = 6.8) is formed in vivo under oxidative distress in a diffusion-controlled reaction between nitric oxide and superoxide radicals. Peroxynitrite is a strong oxidizing and nitrating agent. It can damage molecules both directly and indirectly. In the latter case the damage proceeds via hydroxyl and nitrogen dioxide ($\cdot NO_2$) radicals formed with ~30% yield as intermediates during rapid spontaneous isomerization of peroxynitrite to nitrate, or via carbonate ($CO_3\cdot^-$) and $\cdot NO_2$ radicals formed with ~35% yield as intermediates in the reaction of peroxynitrite with CO_2 [48]. Catalase from bovine liver catalytically scavenges peroxynitrite. The rate constant of peroxynitrite decay, catalyzed by this enzyme, has been reported as (2.7 ± 0.2) × 10^6 and (1.7 ± 0.1) × 10^6 M^{-1} s^{-1} at pH 6.1 and 7.1, respectively, at 25 °C [24]. In the above stopped-flow measurements catalase Cpd I was not detected during the catalytic cycle, and the formation of catalase-peroxynitrito complex, which may decay directly to catalase or via Cpd II, has been suggested. However, under stationary experiments, the formation of catalase Cpd I, as an intermediate in the catalytic scavenging of peroxynitrite, has been demonstrated [49].

Reaction of BLC with carbonate radical anion, one of the intermediates of the peroxynitrite reaction with CO_2 has also been studied. This strong oxidant ($E^{o'}$($CO_3\cdot^-$, H^+/HCO_3^-) = 1.78 V [50]) is more selective versus proteins, than ·OH. It reacts preferentially with cysteine (Cys), tryptophan (Trp), tyrosine (Tyr), and methionine (Met) residues with the rate constants of the order of 10^7–10^8 M^{-1} s^{-1} [51]. The results obtained from pulse radiolysis experiments demonstrate that, similarly to hydroxyl radical, $CO_3\cdot^-$ does not react directly with catalase heme iron. The rate constant of the reaction of bovine liver catalase with $CO_3\cdot^-$ is of the order of 10^9 M^{-1} s^{-1} [38]. Thus, catalase is, so far, the best known protein target for $CO_3\cdot^-$.

$\cdot NO_2$ is a considerably weaker oxidant than ·OH or $CO_3\cdot^-$ ($E^{o'}$ · NO_2/NO_2^- = 0.99 V [52]). It oxidizes, at moderate rates, Tyr, Trp, and Cys residues in proteins and reacts with protein-tyrosyl radicals to form nitrated proteins. The latter have been detected in various pathological states [52]. There is no literature data on the kinetics of the reaction of catalases with $\cdot NO_2$, and the influence of $\cdot NO_2$ on catalase activity. The measurement difficulties result from the necessity of using nitrite as · NO_2 precursor. Unfortunately, nitrite inhibits mammalian catalase forming a complex with catalase heme iron [53,54] and/or via peroxidatic reaction in the presence of H_2O_2 [54,55].

2.6. Reactions with hypochlorous acid

Hypochlorous acid ($HOCl/OCl^-$) is formed in the immune response to invading pathogens by the reaction of hydrogen peroxide with



Scheme 2. Reactions of catalase with species formed under oxidative stress. Underlining ·NO means that this species inhibits catalase or can be consumed by this enzyme (details in chapter 2.4).

chloride catalyzed by heme enzyme myeloperoxidase (MPO). In the first reaction of the catalytic cycle, MPO reacts with H_2O_2 with the rate constant of the order of $10^7\ M^{-1}\ s^{-1}$ to form Cpd I, analogous to that formed in the catalase reaction with H_2O_2 (reaction (1)). Thus, these two enzymes, although being located in different cell compartments, may compete for H_2O_2. Hypochlorous acid is an efficient oxidizing and chlorinating agent. Its pK_a is 7.5 (25 °C) [56] and therefore both forms - HOCl and OCl^- - are present at physiological pH. Interactions of HOCl/OCl^- with proteins include oxidation of amino acid residues, amine groups, and the heme group, as well as chlorination of tyrosine residues [57–59]. In vitro studies have shown that HOCl/OCl^- being in molar excess towards the enzyme at physiological pH inhibits mammalian catalase activity, oxidizes its amino acid residues, initiates protein aggregation, and causes reversible and/or irreversible changes in the heme group [60–64].

2.7. Reactions with singlet oxygen

Singlet oxygen ($^1O_2$) is formed from illuminating either natural or synthetic photosensitising molecules with visible light in the presence of oxygen. This phenomenon is used in photodynamic therapy (PDT) for selective destruction of tumor cells. In this method certain photosensitizer (PS), accumulated in cancer cells, is exposed to light of the appropriate wavelength, which leads to PS excitation. The excitation energy can then be transferred to oxygen ($^3O_2$), converting it to the singlet state. Singlet oxygen has a short lifetime (a few microseconds in an organic environment) and therefore can only act close to the site of generation. Another $^1O_2$-generating reactions which may occur in vivo, under pathological conditions are the reactions of hypochlorite or peroxynitrite with hydrogen peroxide [65,66]. Singlet oxygen reacts rapidly with the most biologically important molecules which leads to their damage. Among the amino acid residues, histidine (His), Met, Trp, Tyr, and alanine (Ala) are most sensitive to $^1O_2$ [67]. There are contradictory results concerning the effect of singlet oxygen on the catalase activity. Whereas some reports show that catalase from different sources is oxidized by $^1O_2$ to active, more acidic enzyme conformers, and such modified catalase may be used as a marker to detect intracellular singlet oxygen [68], in several other studies $^1O_2$-induced catalase inactivation has been reported [69–71].

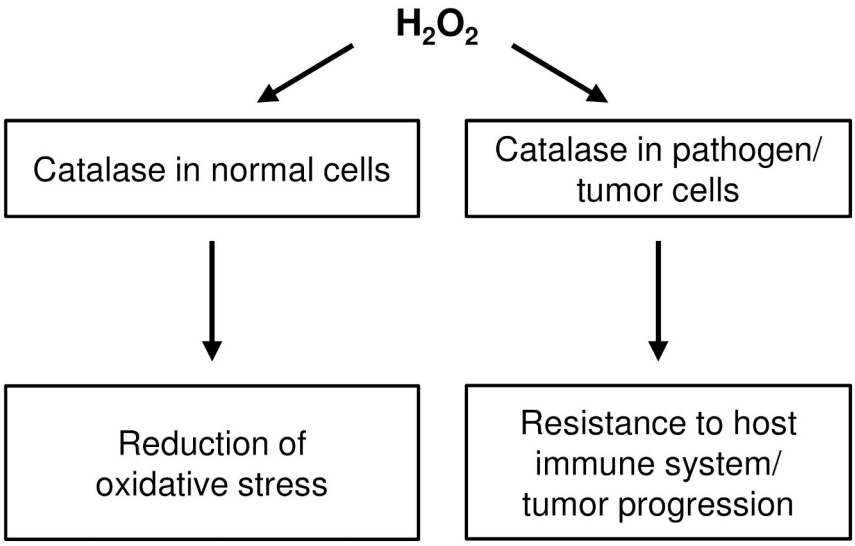
2.8. A summary of the effects of catalase reactions with oxidative species

Most catalase reactions with species formed under oxidative stress are very fast. Catalase catalytically removes H_2O_2 and peroxynitrite without losing enzymatic activity (except for high concentrations of these substrates). The interaction of catalase with ·NO in the presence of H_2O_2 is more complex and depends on the ratio of concentrations between ·NO and H_2O_2. This ratio controls a balance between reversible inhibition of catalase by ·NO and oxidation of this radical by Cpd I and Cpd II. Other species discussed in this work inhibit catalase (Scheme 2).

3. Potential biological significance of the catalase reactions with oxidizing species

Catalase along with GPXs and PRXs play a key role in keeping low steady-state H_2O_2 concentration, which allows to maintain mammalian cell homeostasis and adapts it to stress. Unlike two other enzymes involved in H_2O_2 elimination, catalase does not need cofactors to carry out catalytic cycle. It is generally accepted that GPXs and PRXs are mainly responsible for the elimination of H_2O_2 at low concentration, whereas catalase is more efficient at higher H_2O_2 concentrations. The main limiting factor for GPXs and PRXs in scavenging higher amounts of H_2O_2 seems to be the rate of recycling of GSH/thioredoxin, which is necessary to maintain the catalytic cycle. Due to the effective elimination of H_2O_2, generated under pathological conditions (above 0.1 μM in the intracellular space [72]), active catalase prevents the formation of HOCl/OCl^-, ·OH in the Fenton reaction or singlet oxygen. Scavenging of nitric oxide, generated under pathological conditions, by catalase, although leading to partial enzyme inhibition, may reduce peroxynitrite formation. This enzyme may also play a role in peroxynitrite detoxification in the tissues with high catalase expression (blood, liver), especially, when the local pH is lowered.

On the other hand, some pathogenic bacteria (e.g. *Helicobacter pylori, Campylobacter jejuni, Haemophilis influenzale, Neisseria meningitidis*), rich in catalase, are relatively resistant to the attack of neutrophils and other defense cells [73], ([74] and references therein). *H. pylori* catalase, among others, plays an important role in the protection of this gastric pathogen against HOCl produced by neutrophils [75,76]. This enzyme contains several Met-residues exposed on the protein surface,



Scheme 3. The role of catalase under physiological and some pathological conditions.

which are preferentially oxidized by HOCl to form methionine sulfoxide. Oxidized methionine is reduced back to Met by methionine sulfoxide reductase, with concomitant return of most of catalase activity (in the latter process chaperonin GroEL is also involved [75]). Moreover, the *H.pylori* mutant strain containing catalase without enzyme activity but retaining all Met-residues is much more resistant to HOCl than a catalase null strain [76].

Unexpectedly it has been found that catalase in human and mouse keratinocytes is responsible for the generation of reactive oxygen species (ROS) (most probably hydroperoxides) upon exposure to UVB light [77]. It has been suggested that NADPH bound to the enzyme may play a significant role in this process [18,78]. This catalase property may have both positive and negative consequences, depending on the redox status of keratinocyte cells. Under normal antioxidant status of these cells, catalase, due to the UVB light absorption, protects DNA against it, and ROS which are formed during this catalase activity are detoxified by antioxidant enzymes present in these cells. However, when antioxidant status of the cells is reduced, accumulation of UVB-induced catalase-mediated ROS, may lead to the DNA damage and to the development of skin cancer [77].

Down-regulation of the catalase activity, correlated with higher steady-state concentration of H_2O_2, has been observed in some carcinoma tissues. On the other hand, increased catalase expression in various cancer lines has also been reported (reviewed by Glorieux et al. [79,80]). Apart from catalase residing in peroxisome, many types of human cancer cells possess membrane-associated catalase on the outside surface of the cells, which protects these cells from intercellular apoptosis signalling through ·NO/peroxynitrite and HOCl/OCl^- pathways [8,49]. Thus, several strategies to decrease membrane-associated catalase expression and activity of this enzyme in tumor cells, such as the use of specific antibodies or inhibitors, have been proposed [8,79–81]. Inhibition of membrane-associated catalase should result in a significant increase of local H_2O_2 concentration, which, in turn may increase the rate of HOCl/OCl^- generation, and local steady-state peroxynitrite concentration (catalase catalytically decomposes peroxynitrite). Under such conditions, the formation of singlet oxygen (in the reaction of OCl^- or peroxynitrite with H_2O_2), hydroxyl, nitrogen dioxide and carbonate radicals (formed in the reaction of spontaneous peroxynitrite isomerization, as well as in peroxynitrite reaction with CO_2) are possible. As many of these reactive individuals are also inhibitors of catalase, their generation should enhance the primary inhibition of the enzyme and/or activate mitochondrial pathway of tumor cells apoptosis [8,71,82].

4. Conclusion

As an effective H_2O_2 scavenger, catalase is an important member of the enzymatic antioxidant defense system of the mammalian cells. On the other hand, for the same reason, pathogenic bacteria with high catalase expression may inhibit host antibacterial defense. In turn, catalase occurring on the outside surface of the cancer cells, thanks to its multifunctionality, protects these cells from intercellular apoptosis. This dual role of catalase is depicted in Scheme 3. Thus, catalase inhibition by various species formed during oxidative stress may be detrimental or beneficial, depending on the circumstances.

Abbreviations

BLC	catalase from bovine liver
Cpd I	catalase Compound I
Cpd II	catalase Compound II
Cpd III	catalase Compound III
GPX	glutathione peroxidase
GSH	glutathione
MPO	myeloperoxidase
NOS	nitric oxide synthase
PRX	peroxiredoxin
ROS	reactive oxygen species

Declaration of conflict of interest

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