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Invited Review Article

Catalase: A critical node in the regulation of cell fate

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ABSTRACT

Catalase (CAT) is an extensively studied if somewhat enigmatic enzyme that is at the heart of eukaryotic antioxidant systems with a canonical role in peroxisomal function. The CAT family of proteins exert control over a wide range of plant growth and defence processes. CAT proteins are subject to many types of post-translational modification (PTM), which modify activity, ligand binding, stability, compartmentation and function. The CAT interactome involves many cytosolic and nuclear proteins that appear to be essential for protein functions. Hence, the CAT network of roles extends far beyond those associated with peroxisomal metabolism. Some pathogen effector proteins are able to redirect CAT to the nucleus and recent evidence indicates CAT can traffic to the nucleus in the absence of exogenous proteins. While the mechanisms that target CAT to the nucleus are not understood, CAT activity in the cytosol and nucleus is promoted by interactions with nucleoredoxin. Here we discuss recent findings that have been pivotal in generating a step change in our understanding of CAT functions in plant cells.

1. Introduction

Catalase (CAT) is a core antioxidant enzyme in most organisms that catalyses the decomposition of hydrogen peroxide (H_2O_2), thereby controlling the abundance of this essential cellular signalling molecule. The enzyme is targeted to the peroxisomes, where it catalyses the two-step dismutation (disproportion) of H_2O_2 producing water and molecular oxygen (Fig. 1) [3]. In addition, under some circumstances, CAT can perform peroxidative reactions in the peroxisomes. CAT functions alongside other major cellular H_2O_2-processing systems such as thioredoxins (TRX), peroxiredoxins (PRX), glutaredoxins (GRX), superoxide dismutase (SOD) and the enzymes of the ascorbate/glutathione cycle, which is comprised of APX, monodehydroascorbate reductase (MDHAR), dehydroascorbate reductase (DHAR) and glutathione reductase (GR), to regulate oxidant accumulation and signalling in a compartment-specific manner. Together, these reduction-oxidation (redox) systems form a H_2O_2-processing network that is critical not only for maintaining the cellular redox balance but also cellular and intercellular signalling. For example, in plants antioxidative enzymes such as CAT and APX play a key role in regulating the successive waves of ROS accumulation that are important for cell to cell communication [4–6]. The activation of the respiratory burst homolog (RBOH) proteins on the plasma membrane generates superoxide radicals in the apoplast. Superoxide is converted to H_2O_2 through the action of SOD. Thereafter, H_2O_2 enters the cells through aquaporins and/or activates cytosolic calcium signalling through the plasma membrane-localized H_2O_2-receptor called HPCA1 [7]. Once H_2O_2 enters the cytoplasm, it can alter the redox state of the cell to trigger acclimation and defence responses, or it can be eliminated by the antioxidant network. Rapid systemic cell-to cell ROS signalling plays a pivotal role in local and systemic responses, leading to stress acclimation and survival [8]. However, as discussed below CAT fulfils functions that extend far beyond its antioxidant roles in the peroxisomes.

CAT proteins are classified according to sequence homology into monofunctional haem-containing proteins, bifunctional haem-containing CAT-peroxidases, and manganese-containing (non-haem) CAT proteins [reviewed in Ref. [9]]. Of these, the monofunctional or 'typical' CAT proteins are the largest and best characterised group that are abundant in plants. The following discussion will therefore largely focus on the functions of these proteins, which are tetrameric enzymes

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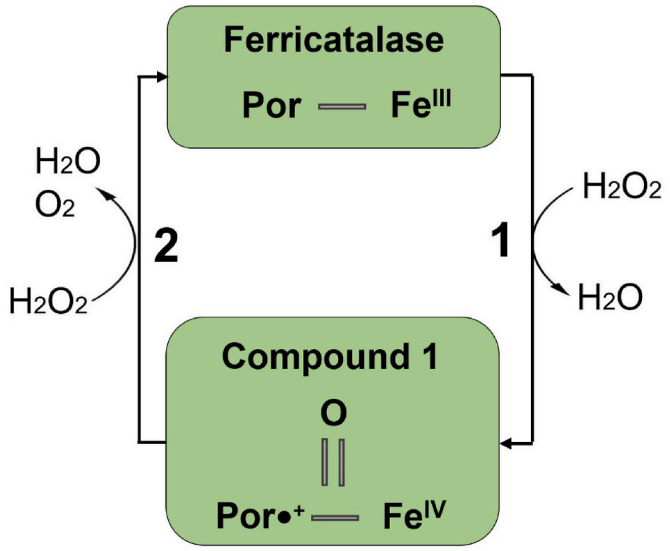


Fig. 1. Dismutation reaction by catalase
One molecule of H_2O_2 oxidizes the Fe atom in ferricatalase, producing an oxoferryl-porphyrin cation radical (compound 1) and releasing one molecule of H_2O (1). A second H_2O_2 molecule reduces compound 1 back to its initial state, producing one molecule of oxygen and another molecule of water as by-products (2). Roman numerals show oxidative state of the haem iron; Por represents the porphyrin ring and its valence(based on diagrams and descriptions by Refs. [1,2].

comprised of 50–70 kDa polypeptides, each monomer containing a haem prosthetic group [2]. The reaction begins with the oxidation of the central Fe atom in the haem group by one H_2O_2 molecule to form an oxoferryl porphyrin cation radical (compound I) [1] with the release of one molecule of water (Fig. 1, Stage 1) [10] In the second step a second H_2O_2 molecule is required to reduce compound I, leading to the production of water and oxygen (Fig. 1, Stage 2). Multiple high-resolution molecular structures are available for the CAT proteins from different sources including human, bovine and yeast [11–13], but not plants. Each monomer shows a highly conserved "CAT fold" consisting of an N-terminal arm, a beta barrel domain, a wrapping domain and an alpha helical domain [14]. The tetrameric enzyme is composed of a dimer of dimers, with each of the two subunits linked by inter wrapping of the N terminal arms. The active site resides at the bottom of a long channel below the surface. The residues involved in haem and substrate binding are well conserved in sequences of typical CAT proteins [14]. In contrast to plants, mammalian CAT proteins contain bound NADPH.

CAT is the most abundant protein in plant peroxisomes and has one of the highest catalytic rates known to biology. CAT proteins in plant peroxisomes are often seen as crystalline 'cores' in electron micrograph images, suggesting self-association and also association with other peroxisomal enzymes (see section **Protein-protein interactions**). However, while CAT has a high capacity for H_2O_2 removal, the K_m is in the mM range because of the requirement of two H_2O_2 to impinge simultaneously on the active site (Fig. 1). The values for the K_m in different systems range from high μM to low mM [15].

Recent advances in genetically-encoded sensors for H_2O_2 has led to an improved understanding of the dynamic compartment-specific changes in H_2O_2 accumulation [16,17] but have not yet allowed precise information on concentrations of H_2O_2 *in vivo*. Calculations suggest that the peroxisomal H_2O_2 concentration is about 10 μM [18], which is below average concentrations inferred from in vitro measurements of H_2O_2 extracted from plant tissues (typically above 100 μM). This difference might reflect relatively high H_2O_2 concentrations in compartments that lack catalase and other powerful antioxidant systems, such as the apoplast/cell wall.

2. CAT transcription

Plant CAT proteins are generally encoded by small gene families. In Arabidopsis, for example, there are three CAT family members that display varied but partially overlapping expression patterns in different tissues [2]. CAT1 is predominantly expressed in pollen and seeds, CAT2 is the main photorespiratory CAT form that is found largely in green tissue, while CAT3 is primarily expressed in vascular tissue and in senescencing organs. Much of our current understanding of the relative importance of the different enzyme forms has come from the analysis of the phenotypes of the many *cat* mutants that are available. CAT3 accounts for the residual leaf CAT activity in *cat2* mutants, however, the *cat2cat3* double mutants showed only a minor decrease in rosette size compared to that observed in the *cat2* mutants, together with a delay in the transition to flowering [19]. The *cat1* mutants have a similar seed yield to the wild type plants, but the *cat1cat2* double mutants showed an increase level of seed abortion [19]. The triple *cat1cat2cat3* mutant are viable, but they have enhanced growth and developmental defects with modified oxidative signalling [20]. Promoter swop experiments revealed that complementation of the *cat2* mutant phenotype with CAT3 was dependent upon the CAT2 promoter, indicating that differences in the expression patterns are responsible for the differences in the functional roles of these proteins [21]. Interestingly the 3' untranslated region of the CAT2 sequence was important in the regulation of CAT2 protein levels under photorespiratory conditions [21]. The *CAT2* and *CAT3* genes show tissue-specific differences in expression, as well as marked circadian rhythms. The levels of *CAT2* transcripts peak at the end of the dark phase and rapidly decline during the light phase, whilst the levels of *CAT3* transcripts are almost the mirror image of the changes *in CAT2* transcripts [2].

CAT gene expression is regulated by a number of transcription factors (Fig. 2). For example, CAT1 is regulated by the bZIP transcription factor ABCISIC ACID INSENSITIVE 5 (ABI5) during seed germination [22]. ABI5 binds to a double G-box motif (ACGT) in the *CAT1* sequence within 500bp of the start codon. The expression of ABI5 activates the expression of proCAT1Luciferase in tobacco cells. ABI5 over-expression lines are more resistant to H_2O_2-mediated inhibition of seed germination and also to the addition of the CAT inhibitor 3-AT [23]. The G-BOX BINDING FACTOR 1/Z-BOX BINDING FACTOR 2 (GBF1/ZBF2) -mediated regulation of *CAT2* expression also plays an important role in plant immunity. The *gbf1* mutants are more sensitive to attack by *Pseudomonas. Syringae*, while conversely a higher resistance to pathogen infection was seen in *GBF1* overexpression lines. GBF1 negatively regulates *CAT2* expression, promoting the hypersensitive response. Interestingly GBF1 positively regulates PHYTOALEXIN DEFICIENT 4 (PAD4), which is required for salicylic acid (SA) and phytoalexin biosynthesis [24] (and section on **plant immunity**). The diurnal regulation of *CAT2* transcript levels is also dependent on G-box motifs. The second G-box motif is also important for expression in vegetative cells. Interestingly, the diurnal changes in transcript levels are strongly correlated with the histone modification H3K9Ac within the promoter and coding regions, and RNA pol binding. The *CAT2* promoter is nucleosome deficient, which is also a hallmark of active genes [25].

3. Post transcriptional regulation

Alternative splicing is an additional mechanism control that can produce multiple isoforms of a protein from a single gene. Recent studies indicate that alternative splicing is extensive in plants, and includes both intron retention and exon skips [26]. It is interesting that *CAT2* in Arabidopsis has an alternative splice variant that retains an intron at the C-terminus of the protein resulting in a premature stop codon and deletion of the C-terminal most 18 amino acids [27]. Curiously Arabidopsis *CAT3* has the same gene structure but *CAT1* which is adjacent on the chromosome does not. Interestingly the *CAT1* 3′UTR could not substitute for the *CAT2* 3′UTR in *cat2* mutant complementation

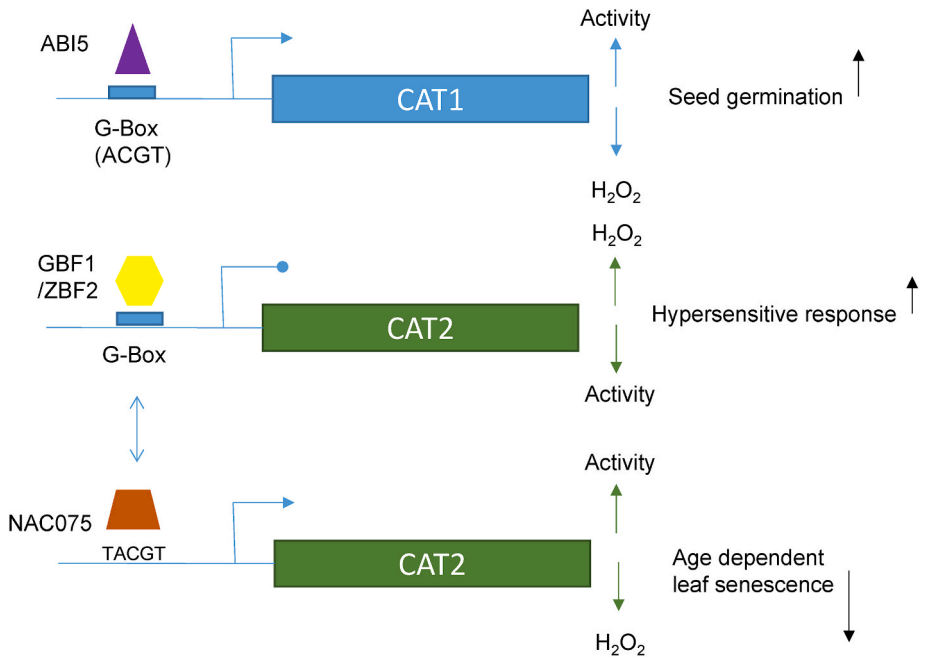


Fig. 2. Regulation of catalase transcription
The G-box sequence in the CAT promoter is a binding site for multiple transcription factors that can increase or decrease transcription with concomitant changes in activity and H_2O_2 level.

experiments, and replacing the *CAT2* 3′ UTR with the *CAT1* 3′UTR led to reduced levels of CAT2 protein and activity [21]. However, expression of the CAT2 protein variant lacking the C-terminal 18 amino acids could complement all tested phenotypes of the *cat2-1* mutant [27]. The biological significance of these observations requires further investigation but hints at additional levels of complexity in CAT regulation.

4. Protein folding and maturation

After synthesis, the CAT apoprotein must fold and acquire haem, a process that is coordinated by the proximal ligand. Somewhat surprisingly, there is a lack of definitive information about the maturation pathway of plant CAT enzymes. However, the NO CATALASE ACTIVITY 1 (NCA1) protein is required for this process. The *nca1* mutants have a severely reduced CAT activity and exhibit defects in the hypersensitive response and pathogen-induced autophagy [28]. Subsequent work showed that NCA1 acts as a cytosolic chaperone that promotes CAT folding and activity. NCA1 is required for resistance to abiotic stresses such as cold and salinity. Interestingly, NCA1 was only able to rescue CAT activity when it was targeted to peroxisomes, and not to mitochondria [29]. This finding suggests that NCA1 can act as a CAT chaperone, either before or after import into the peroxisomes. The Arabidopsis peroxisome-localised heatshock protein called Hsp17.6CII was shown to be a binding partner of CAT2 by immunoprecipitation and mass spectrometry. This interaction was independent of NCA1 and moreover, Hsp17.6CII does not interact with NCA1. Hsp17.6CII is able

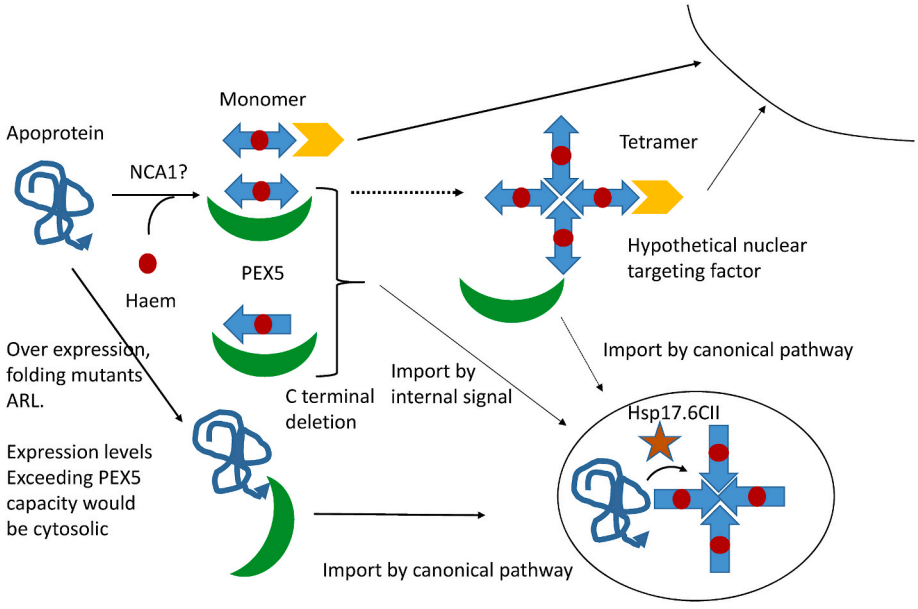


Fig. 3. Hypothetical model of catalase import into peroxisome and nucleus
Catalase is synthesised in the cytosol as an apoprotein (blue squiggle) where it folds with the assistance of NCA1. At some point the monomer will acquire haem (red dot) and tetramerise. Catalase also interacts with PEX5 (green crescent) in the cytosol and it is hypothesised that it can do so in two different ways via an internal signal (which may only be available in the folded monomer) or via the C-terminus if the protein has been mutated to contain a consensus PTS1 signal such as ARL. Similarly catalase proteins that are improperly folded, either due to mutation, or over expression where the level of protein exceeds the capacity of NCA1 to fold it, could be imported by this pathway and potentially fold in the peroxisome with assistance from hsp17.6CII. Catalase can also be trafficked to the nucleus by certain pathogen effectors or by a hypothetical endogenous nuclear targeting factor (yellow shape). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

to supress CAT2 aggregation in vitro but not as efficiently as NCA1. While overexpression of Hsp17.6CII increased CAT activity and resistance to high pH and salt stresses in a CAT2-dependent manner, these effects were dependent on NCA1. These findings suggest that these two proteins work additively in the cytosol and peroxisomes respectively to promote the formation of a functional CAT protein [30] (Fig. 3).

Outstanding questions concerning the processes of CAT maturation remain to be addressed. A key issue concerns where the CAT protein acquires haem. Although it was proposed 50 years ago that haem may be inserted into the CAT protein in the peroxisomes [31], there are no known transporters of haem in the peroxisomal membrane. The haem moiety is too large to enter via the non-specific anion pore, which accommodates molecules of 300–400 Da [32]. It is also clear that haem acquisition is not obligatorily linked to the presence of CAT in the peroxisomes, because an active cytosolic CAT form is found in cell lines that lack peroxisomes. Moreover, a functional CAT protein can be produced in recombinant form in *Escherichia coli*. While it is certainly possible that novel transporters remain to be discovered, it seems likely that haem is acquired during the folding process in the cytosol, and the haem-containing protein is imported into the peroxisomes (Fig. 3).

Other outstanding questions concern the mechanism of haem insertion. Nitric oxide (NO) blocks the insertion of haem into a variety of haemoproteins, including CAT, in mammalian cells [33]. The inhibition of haem synthesis resulted in a reduction in the formation of tetrameric CAT [34]. Furthermore, the nitrosylated form of glyceraldehyde 3-phosphate dehydrogenase (SNO-GAPDH) is involved in the NO-mediated inhibition of haem insertion. The mutation of Cys152 in GAPDH prevented haem insertion. TRX 1, which acts as a denitrosylase of SNO-GAPDH, counteracted the effects of NO on haem insertion into the CAT protein [34]. Precisely how NO prevents haem insertion is not known, but NO binds to the iron atom and weakens the axial bonding between the haem iron and the amino acid ligand (tyrosine) in the CAT protein. NO-induced inhibition can cause conformational changes in the protein that reduce additional stabilising interactions between the protein and the haem group [33]. *In vitro* assembly of *Enterococcus faecalis* CAT protein has been reported. This process is slow at low temperatures but *in vivo* assembly is rapid at 37 °C, implying that chaperone machinery is required for the assembly process [35]. It is uncertain whether similar mechanisms occur in plant cells or whether the requirement for NCA1 is for haem insertion. The plant GAPC protein is known to undergo multiple redox-related modifications including *S*-nitrosylation [36]. Whether CAT assembly is affected by NO in plants has not (to our knowledge) been reported although the CAT protein undergoes multiple types of post translational modification, and plays an important role in NO based signalling as described later.

5. Import into peroxisomes

The mechanism of import of CAT into peroxisomes has been unclear. The so called 'canonical' PTS1 import pathway involves the binding of the peroxisome protein import receptor PEX5 to a conserved tripeptide signal (PTS1). The PTS1 has a consensus of [small amino acid-basic amino acid-hydrophobic amino acid] and must be at the C-terminus of the protein as the C-terminal carboxylate of the protein makes important bonding interactions within the ligand binding pocket of the receptor [37]. Plant CATs do not match this consensus, and although Arabidopsis CATs contain the PTS1 matching tripeptide QKL close to the C-terminus it is not possible for this sequence to act as a PTS1 in this context, despite mutagenesis suggesting some of these residues are important for targeting [38]. Instead evidence from studies on mammalian [39] yeast [40] and plant CATs [41] all point to requirement for the N-terminal part of the PEX5 receptor which is not involved in canonical PTS1 binding. Furthermore, several studies demonstrate that the C-termini of plant CATs are not required for peroxisomal targeting when stable expression systems are used [27,42] but are when proteins are expressed transiently [42,43]. Additionally, mutations in internal regions of the protein (including those residues important for haem binding which would be expected to interfere with protein folding) prevent import [43]. How can these discrepancies be resolved? We propose that the capacity of the cellular machinery to fold CAT is of prime importance (Fig. 3). Under conditions of transient expression or heterologous expression, production of apoCAT may exceed the ability of the cell to produce the haem inserted monomer, which we propose is recognised by PEX5 via contacts outside of the PTS1 recognition domain as previously reported [39–41]. Interestingly human PEX5 blocks the tetramerisation of CAT suggesting the monomer may be the form imported, and this is consistent with other work which shows that although peroxisomes can import oligomeric proteins monomers appear to be the favoured clients of the import machinery [44,45]. It is noteworthy that an internal region of *S. cerevisiae* CatA was identified as important for peroxisomal targeting many years ago [46]. Part of this sequence is quite well conserved in human and plant CATs and is located at the interface of subunits in the CAT tetramer (Fig. 4) [12]. If this is part of the sequence that binds PEX5 it could explain the reported blocking of tetramerisation [39]. While the exact nature of the CAT peroxisome targeting signal remains elusive, if this hypothesis is correct it could be a signal patch analogous to that reported for *S.cerevisiae* Acyl CoA Oxidase [47] and *Hansenula polymorpha* Alcohol Oxidase [48] import. Like CAT, Acyl CoA oxidase and alcohol oxidase also bind a cofactor (FAD), and so this could be a mechanism for essentially 'proofreading' the folded state of certain enzymes prior to import. If the CAT C-terminus is converted to a PTS1 consensus sequence its import becomes dependent on a free C-terminus as expected [27] and it has reduced activity [27,49]. It was suggested that CAT may require slower import to allow proper maturation and this could be a reason for the non-canonical import pathway [49] (Fig. 3). By extension of this argument, conditions that could interfere with proper folding could potentially result in reduced peroxisomal targeting. In this context it may be significant that NO, which is a well-known signal molecule including in plants, can inhibit haem insertion into CAT [34] (see also section **Protein folding and maturation**).

In mammalian cells import of CAT has been linked to cell redox state via modification to the PEX5 receptor. During the peroxisomal import cycle PEX5 becomes ubiquitinated on an N-terminal cysteine (Cys) residue; this modification is essential for the receptor to be recycled from the peroxisome membrane back to the cytosol where it is deubiquitinated by glutathione to allow further rounds of import. Therefore the glutathione pool is important in the regulation of import of proteins into peroxisomes [50] and import of CAT shows greater sensitivity to oxidising conditions than do other peroxisomal proteins, though the basis for this differential effect is unclear as changing redox state did not affect cargo binding to PEX5 [51]. In plant PEX5 this redox sensitive Cys is conserved but an important difference is that mammalian CAT import is enhanced by addition of a consensus PTS1 sequence [52] while plant [27] and yeast [49] CAT is not.

6. Physiological functions

H_2O_2 is produced by enzymes in different cellular compartments [53]. Peroxisomes contain H_2O_2-producing flavin oxidases including glucose oxidase, xanthine oxidase, sulfite oxidase, sarcosine oxidase, diamine oxidase, polyamine oxidase and glycolate oxidase [38]. Peroxisomes serve as an intracellular hub of H_2O_2 production, metabolism and signalling [54].

6.1. Photorespiration

Glycolate oxidase is a key step in the photorespiratory pathway, which is the major source of H_2O_2 in the leaves of C3 plants [55]. Calculations of the rates of photorespiratory H_2O_2-production based on the relative fluxes through the photosynthetic and photorespiratory pathways suggest that photorespiration can account for 70% of the metabolic H_2O_2 production in leaves [55]. Increases in the photorespiratory flux

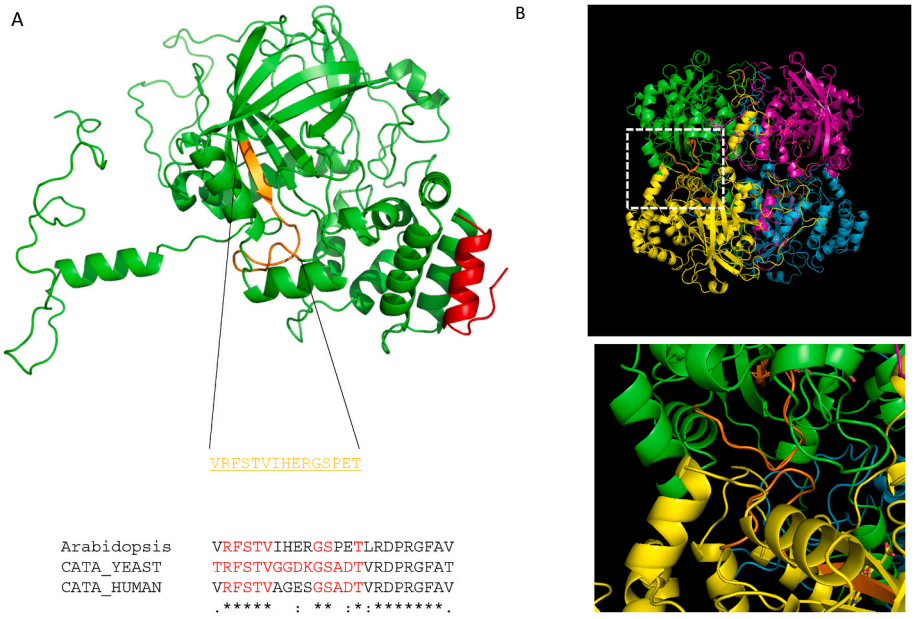


Fig. 4. Structural model of Arabidopsis catalase 2
A: The predicted *Arabidopsis thaliana* CAT2 monomeric structure was taken from the AlphaFold Protein Structure Database. The last 18 residues of CAT2 is highlighted in red and the region that shows homology to the internal peroxisomal targeting signal of *S. cerevisiae* CATA is shown in orange
Inset: Sequence alignment of the conserved targeting signal region
B: The tetrameric structure of yeast catalase (PDB: 1A4E). The zoom-in image of the region indicated by the dotted lines shows that the conserved targeting signal regions (orange) from each monomeric molecule were located in the interface. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

can impact on the extent of leaf H_2O_2 accumulation, leading to oxidation of the glutathione but not the ascorbate pool [55].

Many mutants in photorespiratory pathway enzymes including CAT have now been characterised. These mutants grow well in high CO_2 (or low O_2) and are often indistinguishable from the wild type in these conditions because photorespiration is suppressed. However, when the photorespiratory mutants are transferred to ambient CO_2 conditions (low CO_2) they show stress-induced symptoms, such as chlorosis [56]. Studies on the Arabidopsis *cat1*, *cat2* and *cat3* mutants has revealed that although CAT1 and CAT3 have some overlapping functions, CAT2 makes the major contribution to activity in roots and leaves. The *cat2* mutants, which have about 80% lower extractable leaf CAT activities and about 50% lower root CAT activities, show an inhibition of shoot and root growth relative to the wild type under ambient CO_2 conditions [19]. Furthermore, day length-dependent responses to CAT2 deficiency were observed that are independent of the duration of oxidative stress. For example, when plants were grown short days or long days, a much stronger induction of H_2O_2 marker genes was observed under short day conditions. The *cat2* mutants also developed lesions associated with programmed cell death (PCD) on the leaves, particularly when plants are grown in long days but not in short day conditions. In Arabidopsis it was shown that the photoperiod-conditional PCD phenotype is dependent on the accumulation of salicylic acid (SA) [57,58] and results in an increased resistance to pathogens compared to the wild type plants, as is also seen in tobacco *cat* antisense plants [59–61]. The pathogenesis responses were abolished by the *sid2* mutation and in *cat2atrbohF* double mutants [62]. Such findings suggest that the enhanced intracellular oxidative signalling in the *cat2* mutants activates PCD and hypersensitive response-specific markers, and that the *atrbohF* mutation modulates these. In rice CAT and Glycolate oxidase interact physically and this interaction is regulated by SA [15]. It was proposed that the physical interaction could support metabolite channelling of Glycolate oxidase produced H_2O_2 to CAT, helping to overcome the high *K*m of CAT for its substrate and that SA induced dissociation of CAT and GOX would allow H_2O_2 levels to rise.

The above findings suggest that CAT2 is a key player in photorespiration [57]. Transgenic tobacco plants overexpressing the cottonseed CAT1 showed lower photorespiratory losses of CO_2 at high temperatures, suggesting that the stoichiometry of photorespiratory CO_2 formation per glycolate oxidized increases at higher temperatures because of enhanced peroxidation [63]. Conversely, analysis of plants expressing antisense constructs revealed a significant linear increase in the leaf CO_2 compensation point (Γ) with decreasing CAT activities, such that a at 50% decrease in CAT activity increased Γ by 39%.

6.2. Senescence and ageing

In addition to metabolic functions, CAT plays important roles in plant development, particularly seed ageing and viability, and organ senescence.

CAT may be considered to be a longevity determinant in plants, animals and yeast [64–66]. Senescence is characterised by the degradation of cellular structures and redistribution of nutrients and metabolites within the plant [67,68] and involves the differential expression of several thousand senescence-associated genes (SAGs) [68,69]. The senescence process requires the accumulation of ROS and/or Reactive Nitrogen Species (RNS). Increases in cytoplasmic ROS levels are considered to be critical for the induction and maintenance of cell senescence process. The fine balance between oxidant-antioxidant processes leads to continuous modulation of ROS accumulation in different intracellular and extracellular locations. Within this context, enhanced ROS accumulation can occur as a result of enhanced ROS production or withdrawal of antioxidants, such as CAT or other antioxidant enzymes, together with ascorbate, glutathione or thioredoxins that are indispensable factors in the ROS detoxifying system. The increases in ROS levels that occur during senescence are caused by decreased antioxidant capacity [70]. A number of NAC transcription factors including JUB1 (ANAC042) [71], ATAF1 (ANAC002) [72], ORS1 (ANAC059) [73] NTL4 (NAC53) [74], ANAC017 [75], and ANAC032 [76] regulate leaf senescence by modulating ROS levels. However, the expression of at least some of these transcription factors such as JUB1 and ORS1 is also induced by H_2O_2 [71,73]. The NAC transcription factor NAC075 is a negative regulator of leaf senescence [77] that functions by directly increasing CAT2 expression and suppressing ROS accumulation [77] (Fig. 2). Moreover, overexpression of CAT2 suppresses the early senescence phenotype of *nac075* mutants [77]. The findings suggest that NAC075 acts as an upstream negative regulator of ROS accumulation although it is not induced by ROS.

Metabolic ROS accumulation for a relatively long period is an important senescence-related signal [78]. A long-term increase in intracellular hydrogen peroxide levels that has been observed at the onset of senescence in monocarpic species such as Arabidopsis and

oilseed rape results from decreased activities of the hydrogen peroxide-scavenging enzymes such as CAT and APX, together with lower levels of ascorbate. These changes are intrinsically related to the bolting and flowering stages of plant development, because the exogenous application of hydrogen peroxide is only effective during this period [79].

A prominent feature of senescence is the regulated degradation of cellular contents by autophagy to facilitate recovery and recycling of nutrients [80]. As well as generalised autophagy, this process can also be specific to specific organelles e.g mitophagy, chlorophagy [81] pexophagy [82] and can also occur under stress conditions. Mutants in the autophagy pathway accumulate clustered defective peroxisomes with aggregated CAT, and *cat2* mutants or plants treated with H_2O_2 contained aggregated peroxisomes [83]. Basal and starvation induced autophagy does not require CAT. Rather CAT acts upstream of immunity trigged autophagy [28].

It is also likely that CAT has functions in other age-related phenomena such as "age-related resistance" (ARR). In contrast to humans, where the aging process causes a gradual decrease in stress resistance and susceptibility to disease, there is a positive correlation between host age and disease resistance in plants. ARR describes the gain or reinforcement of disease resistance during the process of plant maturation. Age-related biotic and abiotic stress resilience manifests by differential responses with respect to (i) morphological plasticity to allow stress escape or endurance; (ii) an altered tolerance toward ROS build-up that prevents oxidative damage; and (iii) a changing sensitivity toward induced senescence to facilitate resource allocation and stress survival. A growing number of literature studies have implicated CAT in plant immune responses as discussed below.

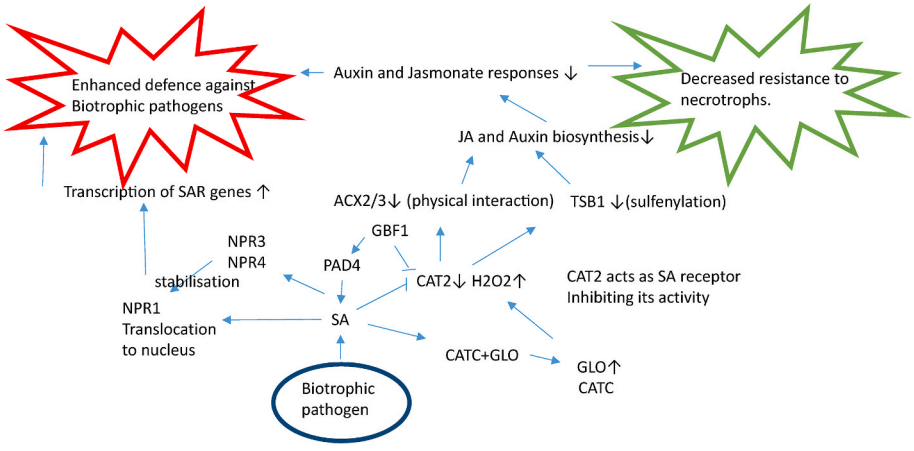
6.3. Immunity and programmed cell death

Multiple reports have demonstrated that changes in CAT activity/expression are linked to plant immunity. CAT plays important roles in plant defences against biotic and abiotic stresses. All of the CAT isoforms contribute to CAT-dependent PCD responses [28]. CAT3 and other CAT isoforms interact with LESION SIMULATING DISEASE1 (LSD1), which is an important negative PCD regulator in Arabidopsis [29]. This interaction regulates SA accumulation, light-dependent runaway PCD and hypersensitive-type cell death. CAT binds to SA in a manner that leads to inhibition of enzyme activity [84]. Although the physiological significance of this process remains to be demonstrated, the inhibition of CAT2 activity that is observed following infection by *Pseudomonas syringae* pv. Tomato DC3000 has been implicated in the SA-mediated repression of auxin and jasmonic acid synthesis [22]. CAT2 binds to acyl CoA oxidase (ACX) 2 and 3 and stimulates their activity. ACX is required for stimulation of JA production on infection and the interaction with CAT is disrupted by SA. SA inhibition of CAT2 activity also results in increased sulfenylation of Tryptophan Synthase Beta subunit (TSB1) C308 resulting in decreased activity, decreased Tryptophan synthesis and IAA accumulation. So CAT2 is a central player in co-ordinating antagonistic responses of IAA and JA with consequences for defence responses [22] (Fig. 5).

Plant immunity is comprised of three modules; an initial layer of defence called microbe associated molecular pattern (MAMP)-triggered immunity (MTI), effector-triggered immunity (ETI) and systemic acquired resistance (SAR) [86]. MTI provides broad-spectrum defence against a diverse range of pathogens. It also potentiates ETI responses. Early MTI responses include apoplastic ROS production and increases in cytosolic Ca^{2+}, leading to the activation of MAPK signalling cascades and PCD. Microbes that are successful in colonisation secrete effectors into both inter- or intracellular locations, which can dampen MTI signalling. An increasing number of studies have demonstrated that CAT is a target for effector proteins [87,88]. Interestingly, the fungal effectors PsCRN115 and PsCRN63 traffic CAT to the nucleus but they have opposite actions with regard to PCD. PsCRN115 stabilizes CAT and decreases PCD, whereas PsCRN63 destabilizes CAT and increases PCD [89]. Similarly, the *Blumeria graminis* effector protein called CSEP0027 also re-directs the barley CAT to the nucleus to regulate host immunity [90]. In contrast, the rice AvrPiz-*t*-ROD1-CATs-APIP6/RIP1 regulatory immunity module operates by regulating CAT degradation [91]. Such studies not only demonstrate that CAT is a key target for pathogen effectors, thereby regulating metabolic H_2O_2 degradation, a process that must be physiologically relevant in pathogen responses, but also that re-direction of CAT to the nucleus has physiological significance, although the processes involved remain largely unidentified. Recently it was shown that Arabidopsis CAT2 could be targeted to the nucleus without the assistance of pathogen effectors, raising the possibility that pathogens have hijacked an endogenous pathway [27]. CAT proteins interact with a bewildering array of other proteins from many different subcellular compartments (Table 1) which also hints that the location of CAT is not fixed in space and time (see section **Protein-protein interactions**).

7. Post translational regulation

CAT undergoes several types of PTM including; acylation, glycation, nitration, oxidation/carbonylation, and phosphorylation, which have been reported as fine-tuning mechanisms that regulate the activities of haem-proteins [106] including CAT [107,108]. The functional



NPR1, 3 &4 are nuclear receptors for SA

Fig. 5. CAT2 is a central player in co-ordinating antagonistic responses of IAA and JA in plant defence Biotrophic pathogens induce production of salicylic acid (SA). SA induces SAR genes via stabilisation and translocation of NPR1 to the nucleus. SA disrupts physical interaction of CAT with Acyl CoA Oxidase (ACX) 2 and 3 which is required for stimulation of JA production on infection, whilst SA inhibition of CAT2 activity results in increased sulfenylation of Tryptophan synthase beta(TSB) 1C308 resulting in decreased activity so decreased Tryptophan synthesis and hence reduced IAA accumulation. Transcription factor GBF1 TF inhibits CAT2 transcription, increasing H_2O_2 and the hypersensitive response when infected w PstAvr GBF1 also stimulates SA production via Phytoalexin deficient (PAD)4 which further reduces CAT activity. Glycolate oxidase (GLO) is also a binding partner of CATC in rice and SA induced CAT2-GLO dissociation and increased H_2O_2 *in vivo*. Model based on data from Refs. [15,22,24,85].

Table 1
Catalase interacting proteins.

Species and isoform	Interacting protein (s)	Impact on CAT activity	Reference
Plant proteins			
Pumpkin CAT1	Arabidopsis PEX5		[41,42]
Arabidopsis CAT3 (only)	CaM (calmodulin)	Stimulates CAT3 activity	[92]
Arabidopsis CAT1, 2 & 3	LSD1	reduced in the *lsd1* mutant	[93]
Arabidopsis CAT2	NCA1	CAT protein level and activity reduced in *nca1* mutant; NCA1-CAT2 direct interactions increases CAT activity	[151]
Rice CATC	NCA1a and NCA1b	CAT activity reduced in *nca1a/nca1b* double mutant.	[29]
Arabidopsis CAT2 & 3	SOS2 (CIPK24)		[94]
Arabidopsis CAT3 (only)	CDPK8	phosphorylates CAT3 on S261 and promotes its activity.	[95]
Rice CATC	Glycolate oxidase		[15,96]
Arabidopsis CAT2	Hsp17.6CII (At5g12020)	Increase in CAT3 activity	[30,97]
Rice CATA,B & C	STRK1 receptor like kinase	STRK1 phosphorylates Cat C at Y210 and enhances activity	[98]
Rice CATB	ROD1	Enhances Cat activity in Ca^{2+} dependent manner	[91]
Arabidopsis CAT2, 1 & 3	NDK1	could not detect enhanced CAT activity in plants expressing NDK1	[99]
Arabidopsis CAT1, 2 & 3	NRX1	Mutant *nrx1* plants have reduced CAT activity. NRX1 maintains catalase in reduced form, promoting CAT activity.	[100]
Pathogen proteins			
Arabidopsis CAT3	CMV 2b protein		[101]
Nicotiana benthamiana CAT1 and AtCAT1, 2 & 3	BAR11 (*Saccharothrix yangliensis* Hhs.015)		[102]
Tomato CAT1	Pepino mosaic virus TGBp1 (p26)	p26 increases Cat activity	[87]
Nicotiana benthamiana CAT2	tomato leaf curl Palampur virus (ToLCPalV) AV2	ToLCPalV-infected plants have 2-fold decrease in total Catalase activity	[103]
Maize CAT1 and 3, possibly CAT2	maize chlorotic mottle virus (MCMV) P31	Coexpression of P31 with ZmCAT1 or ZmCAT3 led to a lowered catalase activity	[104]
Tobacco CAT1 & 3	Chilli veinal mottle virus (ChiVMV) HCPro helper component proteinase	Inhibition of CAT1 and 3 activity in vitro, and total CAT activity reduced in plants expressing HCPro	[105]
Barley catalase HvCAT1	barley mildew fungus *Blumeria graminis f. Sp. Hordei* CSEP0027		[90]
N. benthamiana CAT1	*Phytophthora sojae* PsCRN63/115		[89]

consequences of these PTMs is largely unknown, and has been investigated only in some cases. However, PTMs have the potential to regulate CAT activity directly or via interaction with binding partners.

The phosphorylation of mammalian CAT has been intensively studied but little is known about how phosphorylation regulates CAT in plants. The rice calcium-dependent protein kinase OsCPK10 phosphorylates CAT enhancing abiotic stress resistance and immunity to blast disease [109]. In addition, the salt tolerance receptor-like cytoplasmic kinase 1 (STRK1) interacts with CATC phosphorylating the CAT protein at Tyr-210, enhancing CAT activity and salt tolerance [98]. The phosphorylation of Arabidopsis proteins is modified by nitrogen supply [110]. The calcium-dependent protein kinase CPK8 phosphorylates CAT3 at Ser-261 regulating its activity, but it does not interact with CAT1 and CAT2 [95]. In contrast, the brassinosteroid-insensitive 1 (BRI1) associated receptor kinase 1 (BAK1) phosphorylates all three CAT isoforms [111]. The BAK1-dependent phosphorylation of all three CAT forms is triggered by high light and is important for the regulation of plant growth and development. Additional serine and threonine phosphorylation sites [112] (Thr 85 [110], Thr 408 [113], Thr 439 [114], Ser 484 [113] and Ser 491 [115]) have been identified in the Arabidopsis CAT2 protein but the functional significance of these protein phosphorylation sites remain to be demonstrated.

Cys residues are highly susceptible to non-enzymatic oxidation by ROS and RNS. The reversibility of Cys thiol PTMs allows Cys residues to act as regulatory switches that can alter the interactome, enzyme activity, conformational integrity, signaling functions and protein stability in response to cellular redox state changes [116]. Little is known about whether the oxidation of the Cys residues influences CAT activity. However, a *Neurospora crassa* CAT protein was oxidized in the presence of singlet oxygen in a sequential reaction that resulted in the formation of active CAT conformers [117].

S-Nitrosylation is mediated by the binding of NO groups to Cys residues. One of the most biologically relevant *S*-nitrosothiols involves the interaction between NO and reduced glutathione (GSH) to form *S*-nitrosoglutathione (GSNO). Thereafter, NO is transferred to targeted proteins such as CAT via nitrosylation. GSNO negatively regulates the CAT activity of Arabidopsis [108]. Cys-377 in commercially available bovine liver CAT undergoes *S*-nitrosylation following incubation with *S*-nitroso-L-Cys [118]. The Cys-370 residue and surrounding amino acids in Arabidopsis share a high sequence similarity with the bovine CAT. Hence, Cys 370 is a potential *S*-nitration site in Arabidopsis. This predicted PTM site was confirmed using a site-specific proteomics approach (biotin-switch method) [119]. While this study also identified additional Cys residues (86, 230 and 413) as *S*-nitrosylation sites, the functional consequences of this regulation for the Arabidopsis CAT2 remain to be elucidated.

Tyrosine nitration, is formed by interaction with either peroxynitrite (ONOO–) or nitrogen dioxide ($\bullet NO_2$) in the presence of oxidants, was found to decrease CAT activity in ripening pepper fruit [120].

Protein persulfidation has not received much attention in plant systems, although a proteomics study revealed that at least 5% of the Arabidopsis proteome is persulfidated [121]. Persulfidation is mediated by the gaso-transmitter molecule H_2S, which is an important signalling molecule that regulates plant growth and to adaptation to abiotic stress [121–124]. H_2S mediates the persulfidation of Cys residues (RSH) to persulfides (RSSH) [123]. H_2S inhibits CAT activity in Arabidopsis peroxisomes [125].

Glycation involves the covalent binding of reducing sugars to lysine and arginine residues. The glycation of bovine liver CAT decreases activity [126]. However, the physiological relevance of protein glycation in plants remains poorly characterised. The glycation of the CAT2 and CAT3 proteins has been demonstrated in Arabidopsis in response to stresses such as high light, heat and drought [127]. The glycation of carbohydrate metabolism enzymes inhibits activity, suggesting that protein glycation can have a strong impact on function [127]. However, the impact of glycation on CAT activity is unknown.

N-terminal acetylation (NTA) is one of the most common protein modifications in eukaryotes. However, the biological function of NTA of CAT catalysed by N-terminal acetyltransferases remains to be demonstrated [128].

Lysine acetylation is a major PTM in Arabidopsis [129,130] that controls the activities of a number of metabolic enzymes [129]. It also regulates transcription, gene expression and nucleotide metabolism [130]. While the role of acetylation of the Arabidopsis CAT proteins is unknown, acetylation of beef liver CAT resulted in a significant inhibition of CAT activity [131] CAT acetylation also increased the reactivities of several other amino acid residues including tyrosine and tryptophan [131], suggesting that acetylation may have an impact on other CAT PTMs. The CAT protein was also acetylated in animal liver peroxisomes and mitochondria [132,133] and in rice [134].

Lysine succinylation has been reported in some plant species [135]. CAT proteins have been reported to be succinylated in wheat (K481 [136], Aspergillus flavus [137] and Turnip (K396/K481, [138]. Succinylation was found to inhibit the activity of a recombinant rice CAT ([98]) but conversely to enhance turnip CAT activity [138].

Protein carbonylation is an irreversible PTM that inhibits protein functions [139]. Carbonylated proteins including CAT2 were identified in salt-stressed Arabidopsis leaves [140] but the effects of carbonylation on CAT activity are unknown.

8. Protein-protein interactions

CAT has a large interactome and participates in a wide range of protein-protein interactions that regulate CAT activity, localisation and oligomeric state. The critical protein interactions that influence folding and import have already been discussed (See **Import into peroxisomes**). Various high-throughput approaches have revealed potential interacting CAT partners (see also section **Immunity and programmed cell death**). These approaches have varying levels of follow-up and validation, from screening hits with no confirmation (Supporting Table S1 to proteins where the interaction has been confirmed by multiple methods and where these is functional information on the consequences (Table 1).

Consistent with the role of CAT as a cellular redox guardian [38], many interactors have roles in stress signalling and responses, including LSD1, CA1, Salt overly sensitive 2 (SOS2), Calcium-dependent kinase 8 (CDPK8), Calmodulin (CaM) and Nucleoredoxin 1 (NRX1) (*vida infra*). Although CAT is predominantly found in the peroxisomes, many interactions have been shown to occur in the cytosol or nucleus, including those with the plant proteins NCA1 [29], CDPK8 [95], NDK1 [99] and NRX1 [100], and the pathogen effectors CMV2b [101], BAR11 [102], TGBp1 [87], CSEP0027 [90] and CRN63/115 [89]. This suggests that CAT fulfils roles in compartments other than the peroxisome, particularly under conditions of biotic and abiotic stress. ROD1 and STRK1 appear to localise CAT to the plasma membrane [91,98]. How does CAT end up in these multiple locations? Does a kinetically slow import allow opportunities to interact with other binding partners that could retain CAT in the cytosol or relocate it to other compartments [116]? Or can peroxisomal CAT be released from this organelle and be relocated? [141].

LSD1, NCA1, CDPK8, STRK1 and NRX1 indirectly or directly increase CAT activity as shown *in planta* or in vitro. Mechanisms for this enhancement often remain obscure but evidence so far suggests that they could be diverse, with some interactions that promote CAT stability and others that alter PTM state (Cys oxidation or phosphorylation). For example, NCA1 has holdase chaperone activity and is involved in formation of active CAT in the cytosol, presumably following protein synthesis and before import to the peroxisome [29]. CAT is a substrate of the thioredoxin NRX1, which maintains the CAT protein in a reduced and active state, presumably in the cytosol and/or nucleus [100]. CAT phosphorylation by STRK1 and CDPK8 also promotes activity [95,98]. How these PTMs activate CAT at the structural and molecular level is unknown.

9. Is CAT a moonlighting protein?

The observations of nuclear localisation of CAT described in previous sections raises the question of what the function of nuclear localisation is. Is it a case of withdrawing CAT activity from other compartments or increasing it within the nucleus? Or does the ability of CAT to undergo a bewildering variety of PTMs and interact with a large and diverse complement of endogenous and pathogen effector proteins point to CAT being an organiser of protein complexes, or could CAT have an unrelated activity?

While most proteins have only a single function, some proteins have evolved to carry out different and unrelated functions ('moonlighting') [142,143]. Importantly, proteins whose different functions are due to fusion or splice variants are not moonlighting proteins [144]; instead to be classified in this way a single variant must have multiple functions. Moonlighting proteins are involved in a large range of biological functions; and more than 300 moonlighting proteins have been identified in plants, animals, yeast, and prokaryotes [143,145].

Interestingly, many moonlighting proteins are cytoplasmic metabolic enzymes and mitochondrial enzymes, but they can also have a wide range of non-catalytic activity functions [146,147]. One interesting example is of the antioxidant enzyme SUPEROXIDE DISMUTASE1 (SOD1) in *S. cerevisae* which undergoes translocation to the nucleus in the presence of H_2O_2 where it acts as a transcription factor to regulate expression of oxidative resistance and repair genes [148]. This movement is associated with phosphorylation of SOD1 on specific Ser residues [148]. SOD1 also translocates to the nucleus in mammalian cells in response to H_2O_2 where it also binds DNA (reviewed in Ref. [149]). Interestingly, neither yeast nor mammalian SOD1 has a canonical nuclear localisation signal. Nuclear localised SOD1 is increased in many cancers and other diseases showing that it can influence cell growth and proliferation [149].

Arabidopsis CAT3 was shown to have a transnitrosylase activity that regulates NO-based redox signalling in the nucleus [150]. The *rog1* mutant was isolated as a suppressor of *gsnor1* a key component of NO based signalling in plants. GSNOR1 catalyses the degradation of GSNO and *gsnor1* mutants cause elevated levels of NO. GSNOR1 is itself regulated by *S*-nitrosylation; modification of Cys10 leads to GSNOR1 degradation and therefore elevated levels of NO. ROG1 is identical with CAT3, and CAT3 expression could supress the *rog1* phenotype. *Cat2* mutants could not suppress the *gsnor1* phenotype showing this is specific for *cat3/rog1*. CAT activity is actually higher in *gsnor1* suggesting it is not loss of activity that causes the phenotype and H_2O_2 and the CAT inhibitor 3AT cannot supress the *gsnor1* phenotype. CAT3/ROG1 binds GSNOR1 and CAT3, which is S nitrosylated on Cys 343, can transnitrosylate GSNOR1 on Cys10. The C343T mutant lacks transnitrosylase activity. The equivalent residue in CAT2 is T and CAT 2 T343C has increased transnitrosylase and reduced CAT activity. Thus, a single amino acid change can lead to a novel function.

10. Future perspectives

The above information supports the concept that CAT proteins have roles far beyond the removal of metabolically produced hydrogen peroxide in peroxisomes. An accumulating body of genetic evidence has demonstrated the important roles of CAT in immune and developmental responses, linked to oxidative signalling (Fig. 5). Moreover, the catalogue of PTMs and CAT interacting proteins continues to grow. In some cases, the biological significance is known. However, in many studies, interactions have simply been described and the physiological significance of the diverse CAT interactome remains to be elucidated (Table 1 Supplementary Table S1).

The ROS burst is a fundamental and intrinsic response to abiotic and biotic stresses. Plant stress responses are integrated through signalling modules that recognize a common set of second messengers (calcium, ROS and NO) often through kinase-associated signal transduction

cascades. Several pathogens target CAT activity to alter ROS metabolism and so fine-tune or suppress host immunity. For example, as discussed above ROD1 promotes H_2O_2 degradation by activating CatB thus exploiting host protein-mediated immune regulation.

CAT is a frequent target of pathogen effector proteins, leading to degradation or relocation to the nucleus. Recently it was shown that CAT is localized in the nucleus, regardless of the absence or presence of pathogen effectors. While CAT functions in the nucleus are unknown, the oxidoreductase nucleoredoxin 1 (NRX1) protects antioxidant enzymes such as CAT from oxidation [100] The nrx1 mutants show low CAT activities and are hypersensitive to oxidative stress, suggesting that NRX1 and CAT2 act together in the same hydrogen peroxide-detoxification pathway.

CAT3 has been demonstrated to have a moonlighting function as a transnitrosylase that regulates NO signalling via GSNOR1. Another antioxidant enzyme SOD1 offers a different paradigm in mammalian and yeast cells where nuclear localisation leads to a moonlighting function as a transcription factor. Despite CAT having been studied for over a century many questions remain to be answered.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.freeradbiomed.2023.02.009.

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