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Targeting catalase in cancer

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ABSTRACT

Healthy cells have developed a sophisticated network of antioxidant molecules to prevent the toxic accumulation of reactive oxygen species (ROS) generated by diverse environmental stresses. On the opposite, cancer cells often exhibit high levels of ROS and an altered levels of antioxidant molecules compared to normal cells. Among them, the antioxidant enzyme catalase plays an essential role in cell defense against oxidative stress through the dismutation of hydrogen peroxide into water and molecular oxygen, and its expression is often decreased in cancer cells. The elevation of ROS in cancer cells provides them proliferative advantages, and leads to metabolic reprogramming, immune escape and metastasis. In this context, catalase is of critical importance to control these cellular processes in cancer through various mechanisms. In this review, we will discuss the major progresses and challenges in understanding the role of catalase in cancer for this last decade. This review also aims to provide important updates regarding the regulation of catalase expression, subcellular localization and discuss about the potential role of microbial catalases in tumor environment. Finally, we will describe the different catalase-based therapies and address the advantages, disadvantages, and limitations associated with modulating catalase therapeutically in cancer treatment.

1. Introduction

The discovery of catalase (Enzyme commission number: EC 1.11.1.6) can be traced back to the early 19th century when the French chemist Louis-Jacques Thénard discovered hydrogen peroxide (H_2O_2) [1]. In 1900, Oscar Loew proposed the name 'catalase' for the substance capable to detoxify H_2O_2 and found in many organisms ranging from plants to mammals [2]. Later, the works of the Nobel prize laureates Otto Warburg, James Sumner, Christian de Duve, and studies of eminent scientists such as Britton Chance and Helmut Sies provided further insights into the mechanisms of catalase enzyme activity, its structure, subcellular localization and function [3–7]. The mammalian catalases predominantly exert a catalatic activity through the dismutation of H_2O_2 into water and molecular oxygen (Enzymatic reaction: $2H_2O_2 \rightarrow 2H_2O + O_2$). In addition, catalase can decompose peroxynitrite ($ONOO^-$) [8], oxidize nitric oxide to nitrogen dioxide [9], metabolize reactive sulfide species [10], exhibit a marginal peroxidase [11] and low oxidase activity [12]. The human catalase enzyme consists of four identical subunits of 62 kDa, each subunit containing four distinct domains, a NADPH binding site and one prosthetic heme group [13]. Catalase is a powerful and extremely efficient enzyme with the highest turnover number (k_{cat}), defined as the maximal number of molecules of substrate converted to product per active site per unit of time, of all enzymes found in living beings [14]. This antioxidant enzyme possesses the ability to metabolize tens of millions molecules of H_2O_2 per second [15], and the model of the enzyme activity predicts that catalase is never saturated with its substrate [16].

We have previously described the different aspects of rodent and human catalases encompassing the historical discovery, structure, biological functions, types of catalases, mechanisms of enzymatic action, cellular and tissue distribution, gene polymorphism, and a detailed description of the regulatory processes of catalase expression in healthy and cancerous cells [17,18]. This review will focus on the major progresses and challenges in understanding the role of catalase in cancer for this last decade. That includes the important role of catalase and reactive oxygen species (ROS) in controlling some critical cellular processes in

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cancer such as proliferation, angiogenesis, metabolism, immunity and metastasis. Finally, we will report compounds and strategies to target or enhance catalase activity in the context of cancer.

In accordance with the experimental data reported in the literature, we distinguished the role of different oxidant species and their subcellular localizations when discussing specific mechanisms and redox modulation, and used the general term "ROS" when the types of oxidant species were not determined. Of important note, since some of the oxidant species can be interconverted or metabolized to different species in the biological system, the use of "ROS" to describe the totality of oxidants in general setting is still convenient and meaningful.

2. Regulation of catalase expression and subcellular localization: an update

2.1. Regulation of catalase expression

We and others demonstrated that the expression of catalase is frequently decreased in human tumor tissues compared to normal tissues of the same origin. In contrast, an increased catalase expression has been observed in tumors from patients with gastric carcinoma, skin cancer, and chronic myeloid leukemia [18].

As shown in Table 1 and Fig. 1A, the human *catalase* gene is regulated in healthy and cancer cells by several transcription factors. Such *catalase* gene has verified DNA binding sites for specificity protein 1 (Sp1) [19], Wilms tumor 1 (WT1)/early growth response (Egr)-related factor [19], nuclear factor Y (NF-Y) [19], forkhead box protein M1 (FoxM1) [20], peroxisome proliferator-activated receptor gamma (PPARγ) [21], POU domain class 2 transcription factor 1 (POU2-F1/Oct-1) [22], and JunB [23]. It is important to note that the position of the transcription factor binding sites reported in Table 1 corresponds to the position from the ATG translation start codon and may not match with the position reported in their respective publications. The reason is that several studies can refer to different transcription initiation sites.

We demonstrated that retinoic acid receptor alpha (RARα) and JunB transcription factors respectively repress and activate the *catalase* gene transcription in human breast cancer cells. We first hypothesized that RARα might bind JunB to repress catalase expression (**Model 1**, Fig. 1B) [23]. Indeed, RARα was reported to bind and antagonize AP-1 family members [24]. We also found two possible tandem RAR/RXR binding sites in the human *catalase* promoter (**Model 2**, Fig. 1B–C). The consensus half-site for RAR-RXR is 5'-(A/G)G(G/T)TCA' (corresponding reverse sequence: TGA(C/A)C(T/C)), but there are many variations in retinoic acid response elements (RAREs) within the genome. RAREs are composed of two direct repeats (DR) of the hexanucleotide sequence separated by 0 (DR0), 1 (DR1), 2 (DR2), 5 (DR5) or 8 (DR8) nucleotides [25,26]. However, the two sequences (DR2 and DR8) identified in the *catalase* promoter are relatively different from the classical RAREs (Fig. 1C). Further experiments will be needed to determine whether RAR/RXR can bind to these potential RARE sequences or JunB to repress catalase expression.

Table 1
Transcription factors that bind and regulate the human *catalase* promoter.

Transcription factors	Binding sites	Position[#]	References
Sp1	GGGGCGGGAC	−140/-131	[19]
WT1/Egr-related factor (1)	GAGGGGGCG	−143/-135	[19]
WT1/Egr-related factor (2)	GAGGGGGTG	−130/-122	[19]
NF-Y	AGCCAATCAGA	−167/-157	[19]
FoxM1[a]	TGTTTGTT	+6108/+6115	[20]
PPARγ	TGACCTTTGCAAA	−11710/-11698	[21]
Oct-1	ATTAAATA	−656/-649	[22]
JunB	TGACCCA	−1352/-1346	[23]

Notes: # from the ATG translation start codon.
[a] The FoxM1 binding site is in the intron 1.

The affinity purification mass spectrometry (AP-MS) analyses revealed not less than thirty-nine potential transcription factors and DNA-binding proteins that could regulate human catalase expression via the −1518/-1200 promoter region (from the transcription start as described in the article) [23]. It is worth noting that only 3 out of 12 cancer cell lines (MCF-7, MDA-MB-231 and KHOS-240S) had increased catalase protein level after being treated with histone deacetylases (HDACs) and RARα inhibitors, suggesting alternative regulatory mechanisms exist in other cancer cell lines. Therefore, further studies are needed to decipher the complex transcriptional regulation of catalase in healthy and cancer cells.

In the literature, plethora of studies cite the human catalase as a target gene for forkhead box protein O (FoxO) and nuclear factor erythroid 2-related factor 2 (NRF2) transcription factors. Regarding FoxO family members, published papers often cited the works of Kops et al. [27] and Tan et al. [28] to describe the regulation of *catalase* gene transcription mediated by FoxO, which were done in *Caenorhabditis elegans* and rat models respectively. While FoxO1 and FoxO3a can bind the promoter of mouse and rat *catalase* genes [28–32], there is no experimental evidence that FoxO transcription factors can bind the human *catalase* promoter and directly drive the human *catalase* gene transcription. The reason why the catalase expression correlates with FoxO activation is most likely because both proteins are negatively regulated by the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB-Akt) signaling pathway [33–36]. Our previous study demonstrated that Akt and mechanistic target of rapamycin (mTOR) signaling pathways control catalase expression in MCF-7 breast cancer cells, while FoxO3a did not play important role in the regulation of human catalase expression [34].

NRF2 is a critical pleiotropic transcription factor that regulates the cellular antioxidant capacity in response to oxidative stress by governing the expression of genes encoding antioxidant enzymes. NRF2 plays multifaceted roles in modulating tumor metabolism, promoting immune evasion, participating in cancer metastasis and contributing to chemotherapy resistance [37,38]. Like FoxO transcription factors, the role of NRF2 in regulating human catalase expression remains controversial. The catalase expression was found significantly lower in various cell types derived from NRF2 knockout mice compared to those from wild-type control animals [39]. Our bioinformatic analyses did not identify antioxidant response element (ARE) sequences in the human catalase promoter and there was no evidence that NRF2 can bind directly to the catalase promoters. Nevertheless, a study using chromatin immunoprecipitation analysis demonstrated NRF2 can bind the rat *catalase* promoter [40]. Modulation of NRF2 expression can also indirectly alter catalase expression due to the disruption of redox homeostasis.

Besides its transcriptional regulation, catalase expression can be controlled through epigenetic modifications [18]. Our previous reports indicated that the chromatin remodeling was the main regulator of catalase expression in breast cancer cells after chronic exposure to an oxidative stress due to changes in histone acetylation and DNA methylation [23,41]. In line with these findings, recent studies showed the CpG methylation can negatively control catalase expression in chronic lymphocytic leukemia [42,43]. Moreover, epigenetic silencing of catalase was found in cells with an abnormal karyotype, and this mechanism is associated with an increase of H_2O_2 levels and spontaneous transformation of human pluripotent stem cells towards malignant cells [44].

Modulation of H_2O_2 levels and catalase activity can also be interconnected with microRNA (miR) and long non-coding RNA (LncRNA), two types of non-coding RNAs that play crucial roles in the regulation of gene expression. A recent study revealed a significant difference in LncRNA expression between pancreatic cancer and non-cancerous cells in their response to H_2O_2 stress [45], suggesting that catalase could play an important role in regulating LncRNAs expression due to its dysregulation in cancer cells. On the other hand, LncRNAs can also affect

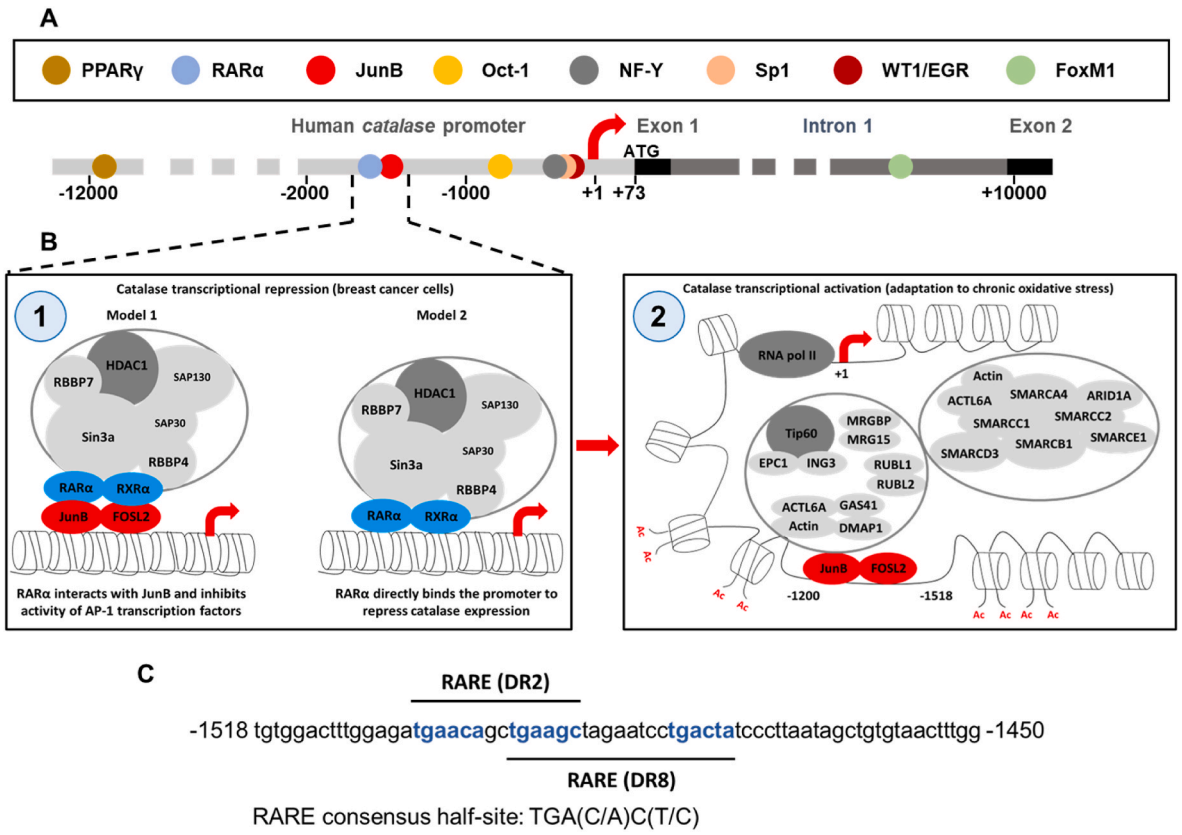

Fig. 1. Transcriptional regulation of catalase expression in human breast cancer cells. (**A**) Position of the transcription factor binding sites in the human *catalase* promoter that control *catalase* gene transcription (see also Table 1). (**B**) Proposed models of *catalase* gene transcription repression and activation, mediated by retinoic acid receptor alpha (RARα) and JunB respectively, in human breast cancer cells exposed to chronic oxidative stress through chromatin remodeling. (1) RARα can recruit co-repressor complexes and histone deacetylases (HDACs) to repress *catalase* gene transcription. RARα might interact with JunB [Model 1] or directly bind the *catalase* promoter [Model 2]. (2) AP-1 family members can recruit co-activator complexes leading to histone acetylation, an open chromatin, and the binding of RNA polymerase II to drive *catalase* gene transcription during adaptation to chronic oxidative stress. (**C**) Predicted RAR/RXR binding sites in the human *catalase* promoter. This figure was adapted from Fig. 8 in Glorieux et al., *Free Rad Biol Med*, 99:436–450, Copyright Elsevier (2016) [23].

catalase expression. Indeed, the expressions of metastasis associated lung adenocarcinoma transcript 1 (MALAT1) [46], metastasis-associated in colon cancer 1-antisense RNA 1 (MACC1-AS1) [47] and brain-derived neurotrophic factor-antisense (BDNF-AS) [48] LncRNAs correlated with a decreased catalase activity in different pathological models. Regarding microRNAs, miR-21 [49], miR-30b [50], miR-146a [51], miR-511b [52] have shown ability to decrease catalase expression.

2.2. Catalase subcellular localization

Originally, the functional homotetramer catalase protein was exclusively found in peroxisomes. Catalase monomers are imported into peroxisomes through interaction with its "KANL" peroxisome-targeting signal sequence (PTS) and peroxins (PEXs). In peroxisomes, catalase undergoes tetramerization and binds to the catalytic heme group [4]. In this context, nitric oxide (NO), S-nitrosylated glyceraldehyde 3-phosphate dehydrogenase (GAPDH), thioredoxin-1 and serum/glucocorticoid regulated kinase family member 3 (SGK3) are involved in the catalase heme maturation, oligomerization and function [53,54]. Until recently, other catalase localizations than peroxisomes were considered as experimental artifacts. As shown in Fig. 2, we will describe the different subcellular localizations of catalase in cytosol, mitochondria, membrane, extracellular compartment and membraneless organelles.

Several lines of evidence proved the existence of a cytosolic active tetrameric catalase, which might have different function compared to peroxisomal catalase [55]. New findings showed a dynamic and highly regulated catalase subcellular localization between the peroxisomes and the cytosol [56]. Previous reports showed that the regulation of catalase import is controlled by PEX5 [57], PEX13 [58], PEX14 [59] and PEX19 [60]. Demers et al. recently demonstrated that depletion of PEX1, PEX5, PEX13 and PEX14, enhanced catalase cytosolic localization [61]. In addition, patient-derived cell lines with PEX16 mutations have a reduced catalase activity and altered response to oxidative stress [62]. The PEX16 liver-specific knockout mice lack intact peroxisome and have higher catalase cytosolic expression. Nevertheless, intact peroxisomes seem to be an important factor for catalase to metabolize ethanol in liver [63]. Interestingly, the mitochondrial BCL2 antagonist/killer (BAK) protein has shown the ability to generate pores to permeabilize peroxisomes leading to the release of catalase in cytosol in normal cells [64]. Of note, such regulatory mechanisms have not yet been investigated in cancer cells.

Catalase has also been localized in the mitochondria of rat and mouse cardiomyocytes [65,66], and mouse hepatocytes [67], however, a mitochondrial catalase has never been detected in mammalian cells.

The release of an extracellular catalase from human leukemic cells has also been reported [68,69]. Amino acid sequencing revealed the extracellular enzyme was a 60 kDa protein that contained the region 350–370 of the human catalase [69]. This soluble catalase was protective against extracellular H_2O_2 and prevented cell death. Bauer et al. demonstrated that catalase can be located at the membrane, especially in cancer cells [70,71]. The assumption of the existence of a membrane-bound catalase was based on the use of neutralizing cell-impermeable antibodies, and measurement of intracellular and

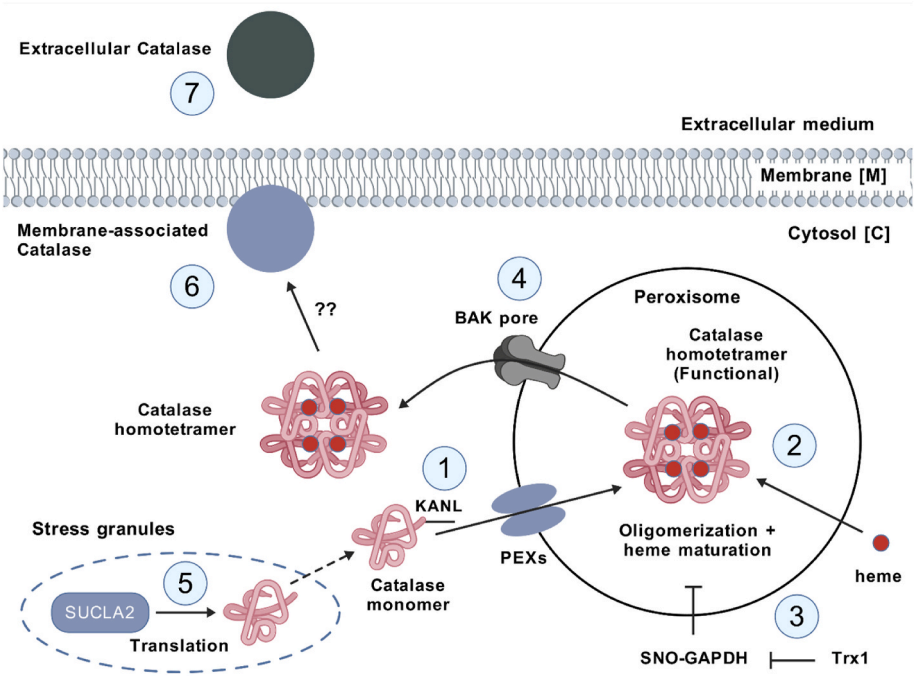

Fig. 2. Subcellular localization of catalase in mammalian cells. (1) Catalase monomers are imported into peroxisomes through interaction with its "KANL" peroxisome-targeting signal sequence (PTS) and peroxins (PEXs). (2) In peroxisomes, catalase undergoes homotetramerization and binds to the catalytic heme group. (3) The S-nitrosylated glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and thioredoxin-1 (Trx 1) can interfere with catalase heme maturation and function. (4) The BCL2 antagonist/killer (BAK) can generate pores to permeabilize peroxisomes leading to the release of a functional catalase in the cytosol. (5) The succinyl-CoA ligase ADP-forming subunit beta (SUCLA2) can promote the formation of the membraneless stress granules to facilitate wherein the translation of catalase protein. (6) The existence of a membrane-associated catalase and (7) extracellular catalase has been reported, but the exact nature of these proteins remains to be elucidated. This figure was generated with Generic Diagramming Platform (GDP) software (https://gdp.rjmart.cn).

extracellular H_2O_2/$ONOO^-$ levels. Nevertheless, such catalase localizations are still subject of debate in the field. One of the main reasons is that catalase was often used as a peroxisome marker in immunofluorescence studies and catalase has never been reported on membranes. Thus, there are still not enough experimental findings to demonstrate the existence of a membrane-associated or extracellular catalase. In early 1980's, Aviram and Shaklai showed the association of catalase with the membranes of human erythrocytes [72], suggesting that this catalase localization could not be a specific mechanism of cancer cells. They also demonstrated that the binding of catalase to the cytoplasmic membrane is inhibited by aldolase, GAPDH and hemoglobin. Moreover, insect cells transfected with tagged GFP-catalase showed that catalase can be delocalized to membranes after ultraviolet treatment [73]. Such experimental tools represent an interesting approach to investigate the role and phase separation of a membrane-associated catalase in healthy and cancerous cells under different conditions and stresses. Many questions remain to be answered about the mechanisms of the transfer of catalase to or across the membranes, and the exact nature of these membrane and extracellular catalases. Some findings also indicated that peroxisomes can interact indirectly with plasma membrane [74], suggesting the so-called membrane-bound catalase could be indeed a peroxisomal catalase. However, a direct interaction between peroxisomes and plasma membrane in human or animal cells have not yet been described.

Membraneless organelles can undergo phase separation, a process wherein biomolecules can segregate into dense and dilute phases, and contribute to various specific biological functions [75]. For example, catalase has ability to induce metastasis through phase separation. The succinyl-CoA ligase ADP-forming subunit beta (SUCLA2) can promote the formation of stress granules to facilitate wherein the translation of catalase and other antioxidant enzymes in order to alleviate oxidative stress and promote lung and breast cancer metastasis [76]. The study does not notify whether the catalase is functional within the stress granules or need to be transported to peroxisomes. It is important to note that these findings contrast with those reported in section 3.4. (Role of catalase in cancer stem cells and metastasis).

Despite supporting evidence tend to demonstrate that catalase is not exclusively found in peroxisomes, the mechanisms of the subcellular catalase localization and its function in these different cellular compartments are largely underappreciated especially in the context of cancer and deserve further investigation. We hope this review will relaunch the debate on this important issue.

3. Involvement of catalase in cellular processes during cancer progression

ROS are involved in various processes during carcinogenesis including tumor cell proliferation, metabolic reprogramming, immune escape and metastasis [77]. The role of ROS and catalase in controlling these hallmarks of cancer is illustrated in Fig. 3. The specific mechanisms and redox-sensitive proteins regulating these cellular processes during cancer progression are explained in the following sections.

3.1. Catalase inhibits tumor proliferation and angiogenesis

Elevation of ROS in cancer cells can provide them proliferative advantages [78]. The overexpression of catalase leads to a less aggressive phenotype and induces resistance to pro-oxidant compounds in breast cancer cells [79]. In line with our findings, decreased catalase expression in metastatic castration-resistant prostate cancer cells triggered high sensitivity to H_2O_2, had low proliferative and migration capacity [80]. The tumors harboring low catalase activity are significantly smaller compared to the wild-type tumors and the rescue of catalase activity restore the tumor growth rate [80]. These data demonstrated that targeting catalase can be a promising approach to kill cancer cells. Oncogenic signaling can also impair antioxidant system in cancer cells.

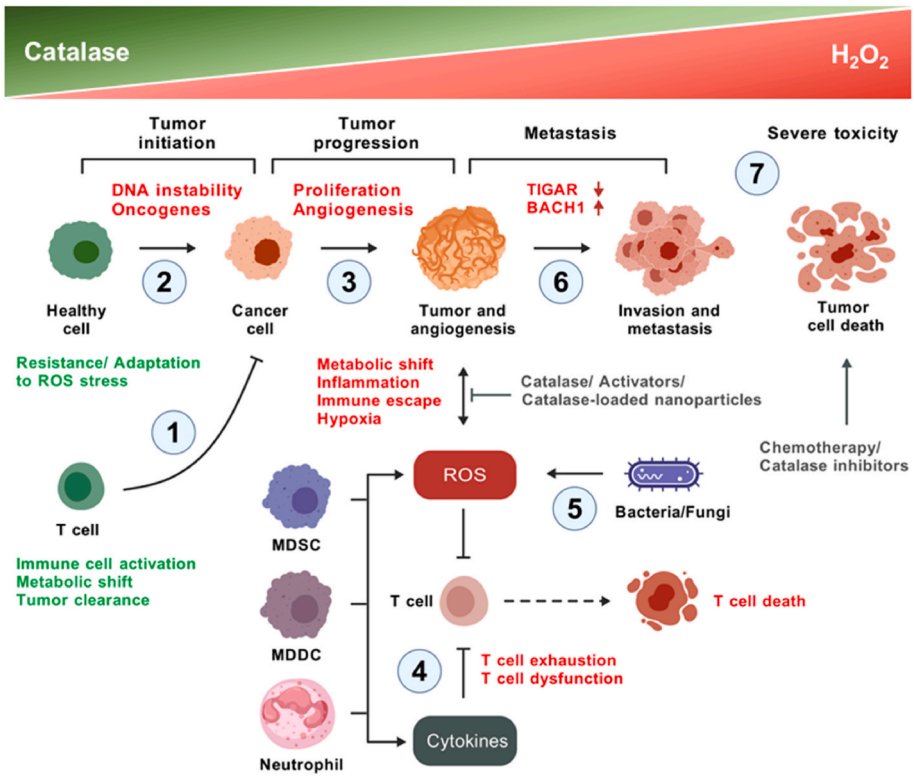

Fig. 3. Effects of a decreased catalase expression during tumor progression. (1) Among various antioxidant molecules, catalase protects healthy cells against toxic accumulation of H_2O_2 caused by diverse environmental stresses. During stimulation processes, a moderate increase in ROS (such as $O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$) plays important role in activating immune cells and modulating their metabolism. (2) At the initial stage of cancer, oncogenic signaling, such as mutant KRAS, can lead to a decreased catalase expression and an increase in ROS levels. (3) The expression of catalase is often found decreased in cancer cells compared to healthy cells, and is associated with tumor angiogenesis and higher proliferation rate. (4) The elevation of ROS in the tumor microenvironment can lead to selection of immunosuppressive cells, which can release ROS and immunosuppressive cytokines, leading to T cell dysfunction and cell death. The delivery of catalase, catalase activators and catalase-loaded nanoparticles can attenuate hypoxia, decrease tumor inflammation and block the immunosuppressive effects caused by high levels of H_2O_2. (5) The intratumoral microbiota can contribute to enhance oxidative stress, inflammation and immune escape. (6) Later in the cancer development, invasive tumor cells exhibit lower catalase activity and an increased ROS levels that contribute to DNA instability. (7) Targeted by chemotherapy (i.e., ascorbate and arsenic trioxide), pro-oxidants and catalase inhibitors, an excess of ROS in cancer cells will cause irreversible DNA damage and cell death. This figure was generated with GDP software (https://gdp.rjmart.cn).

The catalase protein levels were decreased after oncogenic activation in a 293T doxycycline-inducible $KRAS^{G12V}$ expression cell system, and correlated with an increased generation of ROS. In addition, the removal of doxycycline in the culture medium led to complete disappearance of KRAS expression and a time-dependent recovery of catalase expression [81]. These findings suggest KRAS signaling generates oxidative stress partly due to a decrease in antioxidant enzyme expression. Interestingly, 30–40 % of male and female acatalasemic mice spontaneously develop mammary tumors, which can be prevented by vitamin E [82]. These results demonstrate the important role of H_2O_2 in promoting breast tumors. It is worth noting that acatalasemia, characterized by a low catalase rate, is rare and often benign in humans [17], and these observations contrast with those found in mouse models. In opposite to breast and prostate cancer models, catalase is often upregulated in glioblastoma and drives an aggressive phenotype [83]. Therefore, the role of H_2O_2 and catalase function can be different in diverse tumor environments, and the understanding of such conflicting results deserves further investigation.

Catalase can also play important role for cell proliferation and homeostasis of angiogenesis which provides nutrients and oxygen to cancer cells. Hydrogen peroxide can stabilize hypoxia-inducible factor-1 alpha (HIF-1α), a transcription factor crucial for angiogenesis, under normoxic conditions [84]. HIF-1α induces in turn the expression of pro-angiogenic genes, including vascular endothelial growth factor (VEGF). At low and moderate levels, H_2O_2 enhances VEGF production and signaling, primarily by inhibiting protein tyrosine phosphatases (PTPs) that negatively regulate VEGF receptor activation, leading to stimulation of endothelial cell proliferation and migration, and promoting new blood vessel formation [85]. In this context, catalase overexpression can inhibit the proliferation of human vascular smooth muscle cells [86]. Catalase and H_2O_2 regulate the expression of angiogenic factors, such as tissue inhibitor of metalloprotease 3 (TIMP-3) and thrombospondin 1 (THBS1), in tumor cells to generate a neighboring vessel network [87]. In contrast, high concentrations of H_2O_2 can inhibit angiogenesis by inducing oxidative damage in endothelial cells, leading to apoptosis and the disruption of vascular structures [88].

Together, catalase has the ability to promote or inhibit tumor proliferation and angiogenesis due to its catalatic activity and degradation of H_2O_2. This latter molecule can promote cancer or be cytotoxic for cancer cells, and cell fates will be mainly concentration-dependent and compartment-dependent. As such, these observations must prompt clinicians to carefully consider cancer treatment aiming to modulate ROS levels in tumor environment.

3.2. *Catalase modulates glucose and lipid metabolisms*

H_2O_2 and superoxide anion radicals ($O_2^{\bullet-}$) can directly influence metabolism by oxidizing key amino acids in metabolic enzymes (such as PKM2, ACO2, GAPDH) [89–92], or indirectly through activation of redox-sensitive signaling pathways (such as NRF2, mTOR, HIF-1α) [93]. In this context, catalase can particularly influence the metabolism of glucose and lipids.

For example, mouse thymic lymphoma cells overexpressing catalase exhibit a delayed apoptosis, have higher hexokinase enzyme activity, enhanced lactate production and energy metabolism, compared to the parental cell line. This altered metabolism mediated by catalase overexpression conferred resistance to glucocorticoids [94]. Glucose deprivation can induce generation of H_2O_2 and cytotoxicity in human prostate adenocarcinoma DU-145 cells, which can be overcome by catalase overexpression. Mechanistically, catalase overexpression inhibited the activation of apoptosis signal-regulating kinase 1 (ASK1) and c-Jun N-terminal kinase 1 (JNK1) during glucose deprivation [95]. Of note, metabolites and glycation of catalase and superoxide dismutase (SOD) may lead to their inactivation [96].

Catalase can also influence lipid metabolism in healthy and cancerous tissues. A decreased catalase activity reduced glucose uptake, lipolysis and inhibit AMP-activated protein kinase (AMPK) in adipocytes [97]. In addition, mutant KRAS decreased catalase expression in pancreatic adenocarcinoma, resulting in higher levels of H_2O_2 and changes in metabolic profiles that promote cancer cell survival. Panc-1 cells with $KRAS^{G12D}$ mutation treated with catalase showed significant alteration in lipid profile (nordeoxycholic acid and palmitoylcarnitine levels) [98].

Altogether, catalase and H_2O_2 can influence cellular metabolism, and changes in metabolism can alter catalase activity in healthy and cancerous cells.

3.3. Role of ROS and catalase in tumor immunology

3.3.1. Role of ROS and catalase in immune cells

ROS and catalase activity can have various impacts on immune cell differentiation and function through different mechanisms.

On the one hand, excessive amount of H_2O_2 can impair T cell function through oxidative damage. Mitochondrial oxidative stress and persistent antigenic stimulation promote the exhaustion of cytotoxic T cells, which is a state of dysfunction that is often observed in the tumor microenvironment [99,100]. Hydrogen peroxide can induce cytotoxicity against T cells, while catalase provides protection against oxidative stress in immune cells. Catalase treatment induced a decrease in mitochondrial and intracellular ROS levels, prevented T cell exhaustion, enhanced secretion of interferon gamma (IFNγ) and tumor necrosis alpha (TNFα), activated mouse memory T cells and increased their bioenergetic capacity under *in vitro* chronic activation conditions. However, exogenous catalase treatment can prevent the differentiation of active memory T cells under acute activation conditions [101]. Moreover, the ageing thymus atrophy is likely due to a decreased catalase activity in stromal cells and oxidative damage [102]. Interestingly, administration of *E. coli* strain harboring *catalase* gene attenuates symptoms of colitis in mice through a decrease in inflammatory molecules and augmentation of regulatory T (Treg) cell populations [103]. It is worth noting that the important role of catalase in decreasing expression of inflammatory molecules could also have beneficial effects in reducing angiogenesis, a key process involved in inflammation [104] and cancer occurrence [105]. These findings demonstrated that H_2O_2 is involved in many pathological conditions, and modulating ROS levels can be an interesting approach to alleviate these diseases.

On the other hand, several lines of evidence showed the crucial role of ROS such as $O_2^{\bullet-}$, H_2O_2 and hydroxyl radical ($HO^{\bullet}$) in stimulating T cell function. The mitochondrial oxidative phosphorylation (OXPHOS) and enhanced NADPH oxidase (NOX) activities rapidly lead to generation of $O_2^{\bullet-}$ and H_2O_2 associated with metabolic changes in T cells upon T cell receptor (TCR) stimulation to promote proliferation and production of interleukins (IL) [106,107]. Low levels of mitochondrial ROS induce nuclear factor of activated T cells (NFAT), a master regulator of T cell activation, and promote IL-2 secretion [108]. ROS also activate HIF-1α, MYC and enhance glycolysis to stimulate T cell proliferation, clonal expansion, and clearance of tumors [109,110]. At physiological concentrations, H_2O_2 fine-tunes T cell activation, differentiation, and effector functions likely by modulating redox-sensitive signaling pathways. Indeed, H_2O_2 inhibits PTPs such as SHP-1 (Src homology region 2 domain-containing phosphatase-1) and CD45, which are crucial for negatively regulating TCR signaling [111]. In addition, H_2O_2 influences T cell differentiation, skewing toward either pro-inflammatory or anti-inflammatory phenotypes. It has been observed to promote T helper 1 differentiation through the oxidation of transcription factors such as signal transducer and activator of transcription 1 (STAT1) and nuclear factor kappa B (NF-κB) [112]. In this context, supplementation with exogenous catalase could have a potentially dramatic effect on T cell function, and its therapeutic efficacy could be context-dependent.

Immunosuppressive cells, including neutrophils and myeloid-derived suppressor cells (MDSCs), utilize redox-dependent mechanisms to functionally inhibit T cell responses. For example, the neutrophils stimulated with the ROS-inducer PMA (phorbol-12-myristate-13-acetate) can inhibit migration of activated T cells and catalase abrogated this inhibition, suggesting that H_2O_2 play important role in inhibiting immune cells and controlling T cell infiltration [113]. In addition, MDSCs secrete H_2O_2 to block T cell responses, and exogenous catalase can partly restore T cell function [114]. Although ROS are known inducers of immunosuppressive cells, a study unexpectedly showed that the addition of exogenous catalase or catalase overexpression in stromal cells can drive the induction of MDSCs from $CD14^+$ monocytes [115]. Addition of exogenous catalase in culture medium of monocyte-derived dendritic cells (MDDCs) exerted ability to suppress T cell function through several mechanisms. Of note, treatment with extracellular catalase augmented intracellular H_2O_2 levels in MDDCs through activation of NOXs [116], suggesting that intracellular H_2O_2 promote immunosuppressive effects in MDDCs and extracellular catalase can lead to activation of compensatory mechanisms and pro-oxidant molecules. Therefore, it is of crucial importance to measure intracellular ROS levels as a control experiment when studying the role of antioxidant molecules.

Finally, H_2O_2 and catalase play a crucial role in modulating macrophage function. Chronic exposure of murine RAW264.7 macrophages to H_2O_2 triggered catalase upregulation and provided them protection against sustained oxidative stress [117]. This could be particularly important in inflammatory chronic diseases such as cancer. Catalase also protects macrophages by upregulating B-cell lymphoma 2 (BCL2) and preventing apoptosis [118].

3.3.2. Role of ROS and catalase in tumor environment

Tumor cells can evade immune system through various mechanisms, and ROS play important role in stimulating and inhibiting immune responses. In general, all lymphocyte subpopulations are relatively sensitive to H_2O_2 *in vitro* [119]. In this context, the increase in the antioxidant capacity in patient-derived tumor-infiltrating lymphocytes and chimeric antigen receptor (CAR)-T cells show promising therapeutic effects. In order to render these cells resistant to the high H_2O_2 levels in tumor environment and avoid cytotoxicity, T cells were pre-incubated with a NRF2 activator or catalase was overexpressing. The ROS-resistant T cells promote antitumor effects, exert bystander protection to non-transfected immune cells (i.e., NK), and importantly does not alter immune cell functions [120,121]. In line with these findings, overexpression of catalase in human T cells protect them against oxidative stress and enhanced secretion of cytokines [122]. To counteract the sensitivity of T cells to oxidative stress and their inhibition by MDSCs that produced high levels of ROS in head and neck cancer, Horinaka et al. proposed to design cancer immunotherapy to enhance antitumor activity of invariant natural killer T (NKT) populations. Unlike T cells, NKT are more resistant to the H_2O_2 released by MDSCs, and NKT can still exert antitumor effects even in presence of MDSCs [123]. However, efficacy of such treatments still needs to be evaluated *in vivo* and clinical trials.

ROS/RNS can also help cancer cells to evade immune system through the upregulation of immune checkpoints and redox modifications of molecules involved in immune response. A recent study demonstrated

activation of oncogenic KRAS pathway led to an increased ROS generation and exogenous H_2O_2 induced programmed death-ligand 1 (PD-L1) expression in pancreatic cancer cells. Mechanistically, the KRAS-mediated oxidative stress stimulated the fibroblast growth factor receptor 1 (FGFR1) pathway which control PD-L1 expression through transcriptional and translational processes. Moreover, extracellular catalase treatment and knockout of FGFR1 decreased tumor PD-L1 expression [124]. Generation of peroxynitrite can also lead to immune escape through nitration of the TCR-CD8 complex [125], chemokines such as CCL2 [126] and tumor antigens [127], causing T cell dysfunction and resistance to immunotherapy.

Owing to their high intrinsic oxidative stress, cancer cells are more vulnerable to ROS-mediated damage and ROS-based therapeutic strategies have shown promising anticancer activity [128,129]. In addition to their direct cytotoxic effect against tumor cells, pro-oxidant molecules can activate the antitumoral N1 neutrophils and potentiate cancer immunotherapy to target cancer cells and catalase abrogates the neutrophil-mediated killing of cancer cells [130]. Several catalase-based nanoparticles have been designed to modulate immune cell functions in the tumor environment and will be further discussed in detailed in section 4.5. (Nanotechnology-based delivery of catalase enzyme).

Owing to the context-dependent effect of ROS on immunity, using ROS-based strategies by antioxidants including catalase or by targeting redox regulation should be considered cautiously in cancer treatment. On the one hand, a low or moderate increase of intracellular ROS can stimulate immune cell functions [107,108,131–134], and targeting intracellular antioxidants, reactive species in specific subcellular or extracellular compartments showed promising potential to activate immune responses [127,135–138]. On the other hand, an excess of ROS can create an inhospitable environment for intratumoral T cell populations through infiltration of immunosuppressive cells and upregulation of immune checkpoints. Based on the specific context, modulating ROS levels can lead to either stimulation or inhibition of immune cell functions. It is worth noting that some studies investigated the role of ROS and catalase in immune cells grown in monocultures and *in vitro* systems. Nevertheless, some of these studies described above revealed a complex redox interplay between immune and stromal cells, and in the context of cancer, tumor cells will profoundly alter immune cell functions. Therefore, a better understanding of the connections between ROS and diverse cells present in the tumor environment is crucial to find new anticancer strategies and improve cancer immunotherapy.

3.4. Role of catalase in cancer stem cells and metastasis

Certain subpopulations of cancer cells can survive after chemotherapy or radiotherapy, and acquire several characteristics of cancer stem cells (CSCs). Compared to cancer cells, CSCs have robust antioxidant defenses, high FoxO and NRF2 activity, and lower ROS levels, which confer an increased survival potential under conditions of oxidative stress [139,140]. In this context, the thioredoxin reductase inhibitor auronafin reduced the proportion of breast CSCs. The introduction of exogenous catalase did not rescue the observed phenotype, suggesting that H_2O_2 did not play role in cytotoxicity against breast CSCs when the thioredoxin pathway was inhibited [141]. In contrast, high doses of vitamin C or ascorbate generates H_2O_2 [142], inducing mitochondria dysfunction and cell death in breast CSCs without affecting SOD and catalase enzyme activities [143]. Interestingly, arsenic trioxide can sensitize CSCs in hepatocellular carcinoma to cisplatin and 5-fluorouracil in part due to its ability to decrease glutathione (GSH), SOD and catalase enzyme activities [144]. While there are findings supporting the role of NRF2 and BTB and CNC homology 1 (BACH1) in protecting cancer stem cells against oxidative stress and chemotherapy [139,145], only scarce information regarding the role of specific ROS and expression of the antioxidant enzymes in CSCs is currently available.

In a recent study, Cheung et al. reported the pivotal role of temporal and dynamic regulation of ROS levels during the progression of pancreatic cancer [146]. In invasive tumor cells, p53-induced glycolysis regulatory phosphatase (TIGAR) and NRF2 expression diminish, resulting in increased ROS levels that contribute to DNA instability. The treatment with the antioxidant N-acetyl cysteine (NAC) can suppress metastases in TIGAR knockout tumors [146]. Conversely, long-term supplementation with NAC and Trolox promotes metastasis in a KRAS-driven lung cancer model due to the stabilization of BACH1 and a metabolic shift in invasive cancer cells [147]. These findings showed a complex interplay between ROS and metastatic processes. In line with these findings, the presence of SOD can promote pancreatic cancer cell invasion through enhanced expression of epithelial-mesenchymal transition (EMT)-related markers. Treatment with catalase can abolish the SOD-mediated invasive ability of cancer cells, suggesting a crucial role of H_2O_2 in tumor metastasis [148]. Miar et al. also demonstrated that SOD2 levels were augmented and catalase levels decreased in metastases, and proposed to quantify the ratios SOD2/catalase and SOD2/GPX1 (glutathione peroxidase 1) as potential markers during tumor progression to metastasis [149]. Importantly, overexpression of mitochondrial catalase in MMTV-PyMT mice reduced lung metastasis, suggesting that an increase in mitochondrial antioxidant capacity can be a promising therapeutic approach for invasive breast carcinoma [150]. Catalase was overexpressed in highly metastatic melanoma, and different clones with distinct phenotype were analyzed. All clones exhibited a decreased ability to metabolize H_2O_2, but the clones had different levels of cellular ROS and mitochondrial $O_2^{\bullet-}$. The clone with the highest levels of cellular ROS and $O_2^{\bullet-}$ had a decreased tumorigenicity but had higher potential for metastasis, while tumor growth in the clone with low ROS levels was completely inhibited [151]. These findings showed that H_2O_2 levels do not always correlate with tumor progression and metastasis, and ROS such as $O_2^{\bullet-}$ can be the key driver of metastasis. Superoxide radicals also generate other types of ROS/RNS and peroxynitrite in cancer cells, which has been associated with higher proliferation of metastatic cells [152], and bypass the generation of H_2O_2 and catalase overexpression. This study also demonstrated that manipulating antioxidant enzyme activity can lead to the opposite desired effect with compensatory modulation of anti-/pro-oxidant systems and an enhanced intracellular ROS level, which promotes a more aggressive phenotype.

3.5. Role of bacterial catalases in human pathologies and the emerging role of intratumoral microbiota

Based on their structure and functions, catalases are classified into four groups: (1) typical or true catalases that includes the human catalase, (2) catalase-peroxidases, (3) non-heme manganese catalases, and (4) minor catalases which comprise heme-containing proteins that exhibit a low catalatic activity. The catalases in the groups 2, 3 and 4 are mostly found in bacteria, fungi and plants [17]. In contrast to mammalian cells, bacteria often express several types of catalases, which play crucial role in cell proliferation, production of metabolites and protection against oxidative stress [153]. Bacterial catalases might affect human protein functions, and on the opposite, certain bacterial components might induce oxidative stress and alter the host catalase enzyme activity in human cells. In this context, the microorganisms that colonize the human body can be involved in the multi-step cancer processes [154]. For example, the catalase KatA of the bacteria *Helicobacter pylori*, which can cause gastric cancer, has ability to bind cholesterol [155] and vitronectin to escape immune system [156]. Interestingly, catalase epitopes from *H. pylori* can be used as suitable vaccination tool and promote immune responses [157]. Treatment with secreted exopolysaccharides from *Lactobacillus paracasei* induced oxidative stress and apoptosis in part due to a decreased catalase activity in HT-29 human colon cancer cells [158]. *Mycobacterium tuberculosis* catalase can also lead to immune escape through inhibition of mast cells [159]. Altogether, these findings demonstrated that microorganisms can modulate the redox environment, notably through their catalases, to

escape immune system.

Recently, growing evidence show a complex intratumoral microbiota which controls cancer cell metabolism and immune responses [160]. Several studies reported specific microbiota, including bacteria and fungi, in multiple tumors [161,162]. The origin of these intratumoral microbes is diverse: they can come from intestines, mucosal barriers, adjacent normal tissues, and hematogenous spread [160]. Interestingly, the vast majority of intratumoral bacteria and fungi is mostly localized in cancer and immune cells [163]. These microbes can alter cellular metabolism, damage DNA in cells, causing mutations and DNA instability, immunosuppression, that can lead eventually to carcinogenesis [164,165]. They may also produce ROS into the tumor microenvironment through a variety of pro-oxidant enzymes such as the spermine oxidase [166]. Geller et al. demonstrated that tumor microbiota also induces resistance to gemcitabine in pancreatic cancer [167]. However, the redox-mediated mechanisms of interaction between intratumoral microbiota, cancer cells, and immune cells are still largely unknown. Currently, there is no experimental data demonstrating a possible role of bacterial catalases or other antioxidant enzymes in cancer development, and it would merit further investigation.

4. Catalase in cancer therapy

On the one hand, tumor cells often generate high levels of ROS, which play important role in cancer development, due to mitochondrial dysfunction, alteration of the antioxidant system and activation of pro-oxidants (such as NOXs). Thus, the use of antioxidants including catalase have been proposed as anticancer strategy. On the other hand, cancer cells show vulnerability to ROS-based compounds owing to their high intrinsic oxidative stress and decreased ability to metabolize H_2O_2. Both strategies will be discussed in the following section and summarized in Table 2. It is worth noting that some of these studies are preliminary and show the effects of these compounds in a single cell line and must be repeated in multiple cell lines and animal models of cancer.

4.1. Chemotherapies

The effects of H_2O_2 and standard chemotherapies on catalase activity have been investigated in several studies. Catalase levels increased after short and repeated treatments to H_2O_2 [188–190], and in cancer cell lines rendered resistant to chronic exposures to H_2O_2 [19,191] or the pro-oxidant combination of ascorbate and menadione (Asc/Men) [23]. In contrast, catalase expression decreased in different cancer cells resistant to doxorubicin [192,193]. An increased antioxidant capacity in cancer cells is a major factor that affects sensitivity to chemotherapeutic agents. This defense mechanism is particularly efficient against platinum-derived compounds and doxorubicin, and contributes to worsening cancer outcome [194,195].

Certain chemotherapies can decrease catalase expression by inhibiting its transcriptional and translational regulations. In this context, ascorbate decreased catalase expression in human pancreatic cancer cell lines, but not in non-tumorigenic cells. In addition, high catalase expression correlated with poor prognosis for pancreatic cancer patients treated with gemcitabine, ascorbate and radiation, indicating that catalase induced resistance to vitamin C [168]. In line with these findings, catalase overexpression also induced strong resistance to Asc/Men in breast cancer cells [79], as well as the SOD mimetic and pro-oxidant Avasopasem manganese in lung and breast cancer models [196]. Finally, arsenic trioxide can decrease catalase activity and potentiate cytotoxicity of Asc/Men in breast cancer cells [169], and sensitize liver CSCs to chemotherapy [144].

4.2. Catalase inhibitors

The structure and the mechanism of human catalase reaction have been previously reviewed [17]. Few catalase inhibitors have been

Table 2
Catalase in cancer therapy. Multiple catalase-based therapies (including chemotherapies, catalase inhibitors, catalase activators, the delivery of catalase and catalase-loaded nanoparticles) have shown promising antitumor effects in preclinical studies through inhibition of cancer cell proliferation, activation of immune system, and potentiation of chemotherapy.

Compounds	Biological effects	Models	References
1. Chemotherapies			
Ascorbate	Decreased catalase expression in cancer cells	Human pancreatic cancer cells	[168]
Arsenic trioxide	Decreased catalase mRNA/protein/activity, potentiation of cytotoxicity of pro-oxidants	MCF-7 breast cancer cells	[169]
2. Catalase inhibitors			
Aminotriazole	Antitumor and carcinogenic effects	Rat, acatalasemic and normal catalase mice Models of lymphoma, breast and ovarian cancer	[170,171]
Pyocyanin	Decreased catalase mRNA, binds NADPH, induced cancer cell death *in vitro*	A549 lung cancer cells	[172]
BT-Br	Binds the NADPH-binding site, decreased catalase mRNA and protein, increased ROS and cell death, decreased *in vivo* tumor growth	DU145 prostate cancer cells	[173]
ATN-224	Dual inhibitor SOD1/catalase, increased ROS and DNA damage	DU145, RWPE-1 and A549 cancer cells	[174]
BT-1	Dual inhibitor SOD1/catalase, increased ROS and apoptosis, decreased *in vivo* tumor growth	DU145 and RWPE-1 cancer cells	[174]
3. Catalase activators			
Curcumin	Augmented catalase activity, decreased cancer cell proliferation	MCF-7 breast cancer cells	[175]
Metformin (+Resveratrol)	Augmented catalase activity and NADPH, decreased cancer cell proliferation	MDA-MB-231 breast cancer cells	[176]
4. Delivery of catalase in mice			
PEG-catalase	Prevention of lung metastasis	Mice with subcutaneous tumor of B16-BL6/Luc melanoma	[177,178]
Gal-catalase	Inhibitory effect on hepatic metastasis, increased MMP activity	Hepatic metastasis model of colon carcinoma cells	[179]
5. Nanotechnology-based delivery of catalase enzyme			
Au@CAT (+RT)	Augmented $CD8^+$ T cell infiltration, diminished hypoxia and *in vivo* tumor growth	CT26 colon cancer cells	[180]
M + C + siPD-L1	Decreased *in vivo* tumor growth, increased antitumor immunity	Hepa1-6 and 4T1 tumor-bearing mouse models	[181]
DOX/CAT@PLGA-M1	Decreased *in vivo* tumor growth and lung metastasis	4T1 breast cancer cells	[182]
R + C + DOX	Decreased *in vivo* tumor growth, increased antitumor immunity	Hepa1-6 and CT26 cancer cells	[183]
CAT@aPDL1-SSLs	Augmented $CD8^+$ T cell infiltration, diminished hypoxia and *in vivo* tumor growth	B16F10 melanoma	[184]

(*continued on next page*)

Table 2 (*continued*)

CAT-Ce6@OMV-aPDL1 (+PDT)	Increased antitumor immunity, decreased hypoxia and *in vivo* tumor growth	4T1 breast cancer cells	[185]
PDA-ICG@CAT-DTA-1 (+PDT)	Decreased *in vivo* tumor growth, increased antitumor immunity	4T1 breast cancer cells	[186]
FA-L@MD@CAT (+PDT)	Increased tumor oxygenation and antitumor immunity, decreased *in vivo* tumor growth	MCF-7 and 4T1 breast cancer cells	[187]

reported, and mainly interact with key amino acid residues in the catalytic site or the cofactor NADPH.

Aminotriazole (3-Amino-1,2,4-triazole) is the most famous catalase inhibitor. This compound interacts with the distal histidine in the catalytic site leading to an adduct formation and inhibition of catalase activity [197]. Early studies demonstrated that aminotriazole exerted antitumor effects, but can also be carcinogenic in rodents [170,171]. Sodium azide and cyanides also possess ability to inhibit catalase activity, but obviously cannot be used for treatment due to their high toxicity.

Interestingly, pyocyanin, secreted by the bacteria *Pseudomonas aeruginosa*, can induce cytotoxicity in human A549 lung cancer cells by decreasing catalase mRNA and protein expression and a direct inhibition of the catalase enzyme activity through its interaction with NADPH [172].

Recently, two catalase inhibitors have been designed by Dr. Yang's group. The inhibitor BT-Br, a benzaldehyde thiosemicarbazone (BT) derivative, binds the NADPH-binding site to inhibit catalase enzyme activity and elicit antitumor effects against DU145 prostate xenografts [173]. Finally, the SOD1 inhibitor ATN-224 and BT-1 exert dual inhibition on both SOD1 and catalase, induce generation of ROS and suppress tumor growth *in vivo* [174]. Although these compounds show interesting inhibition of tumor growth *in vitro* and *in vivo*, they did not undergo carcinogenicity studies as it was done with aminotriazole. For this latter, it remains unclear whether the aminotriazole-induced carcinogenesis is caused by the specificity of the compound itself or by the prolonged increase in H_2O_2 levels and accumulation of the compound in some organs (such as the thyroid) particularly sensitive to oxidative stress.

In addition, other compounds can physically interact with catalase and inhibit its enzyme activity. The formation of disulfide bonds between flavonoids and catalase can inhibit the enzyme activity. Among flavonoids, the most potent catalase inhibitors are myricetin (approximately 300 times more potent than azide sodium), epicatechin gallate and epigallocatechin gallate but other compounds such as catechol, quercetin, luteolin can decrease catalase activity to some extent [198]. The synthetic food dye Sunset Yellow FCF (disodium 6-hydroxy-5-[(4--sulfophenyl)azo]-2-naphthalenesulfonate) can bind and inhibit catalase activity in erythrocytes [199]. However, the effects of flavonoids and Sunset Yellow FCF on catalase activity have been studied *in vitro* and still need to be confirmed in cancer cell lines and animal models.

Phenolic compounds such as salicylic acid, benzoic acid, acetylsalicylic acid and o-coumaric acid caused inhibition of maize catalases [200]. Salicylic acid, up to 100 μM concentrations, can inhibit plant and mammalian catalases [201]. However, the impact of most of these phenolic compounds on human catalase activity and their mechanism of enzyme inhibition have not yet been investigated.

Finally, catalase activity can be inactivated by 400–420 nm blue light, and photoinactivation of catalase and H_2O_2 can eliminate a wide range of catalase-positive bacteria [202]. However, such treatments have never been tested in models of cancer.

4.3. Catalase activators

Few compounds exert ability to augment catalase activity. For instance, the polyphenol curcumin, which possesses antioxidant potential, induces a decreased proliferation rate in human breast MCF-7 cells associated with an augmented catalase activity [175]. The bisphenol S compound can physically interact with catalase and lead to an increased catalase activity in mouse derived hepatocytes and renal cells [203]. In addition, forskolin and okadaic acid, which are protein kinases PKA and PKCzeta activators, increased catalase activity in mouse NIH/3T3 fibroblasts and suppressed the cell growth, but the mechanisms by which these compounds increased the enzyme activity remain unknown [204].

Resveratrol, belonging to polyphenols, was first thought to be a catalase activator due to its impact on sirtuins (SIRTs) and FoxO activation but showed conflicting findings in several studies. Indeed, resveratrol (10–100 μM) can induce catalase activity and decreased cell proliferation in human cancer cell lines [205]. At higher doses, resveratrol decreased proliferation of other human cancer cells without altering catalase activity [206]. In contrast, this compound decreased catalase activity in lenses of diabetic rats [207].

Interestingly, a molecular docking analysis showed that metformin can form hydrogen bonds and interact with catalase. This interaction leads to an increased catalase activity in mouse liver and protects mice against CCl_4-induced liver injury [208]. Metformin, combined with resveratrol, exerts synergistic effects, and prevents triple-negative breast cancer progression in part due to an enhanced catalase activity [176].

It is worth noting that all these compounds have multiple and various effects in cancer cells and are not specific catalase activators. Although few of them physically interact with the enzyme, the mechanisms of drug-induced catalase enzyme activation are still obscure. Their impact on catalase enzyme activity will most likely depend on their concentration and the cellular context.

4.4. Delivery of catalase in mice

Because they observed that surgical removal of tumor produced ROS and aggravated metastatic tumor growth, Dr. Hashida's team thought to deliver catalase in mice to alleviate metastasis [209]. They designed different catalase derivatives in order to have diverse tissue distributions and to increase the circulation time. The animal experiments showed that administration of PEGylated-catalase (PEG-CAT) and galactosylated-catalase (Gal-CAT) were the best molecules to suppress liver and lung metastasis [177–179,209].

As previously described in section 3.3., microbial-targeted therapy is an interesting approach to deliver catalase, attenuate inflammation and block immunosuppressive effects [103]. However, inoculation of bacteria overexpressing *catalase* gene has never been tested in mouse models of cancer, and safety of such treatments remains to be evaluated.

Some catalase mimics compounds, including low molecular weight metal complexes that reproduce the activity of catalase, have been synthesized in order to regulate H_2O_2 levels for clinical applications. Nevertheless, most of these molecules exert poor solubility in aqueous solution and the k_{cat} is lower than the enzyme itself. Recently, several peptidyl copper complexes derivatives mimicking catalase activity have been designed, and exhibited better thermodynamic stability and resistance to H_2O_2 degradation [210]. These studies using catalase mimics have been done *in vitro*, and the k_{cat} of these compounds delivered into tumor environment is unknown as well as their ability to cross the cell membrane and potential side-effects.

4.5. Nanotechnology-based delivery of catalase enzyme

Diverse nanoparticles containing catalase have been designed in an attempt to enhance cytotoxic effects of cancer treatments, attenuate hypoxia, or modulate tumor and immune environment.

First, catalase in nanoparticles can be used to suppress the H_2O_2-

mediated immunosuppressive effects on $CD8^+$ T cells. Administration of a pH-sensitive catalase-gold cross-linked nanocomposite (Au@CAT), in combination with radiotherapy (RT), led to an increased infiltration of $CD8^+$ T cells and decrease in proportion of immunosuppressive cells, attenuation of hypoxia and inhibition of tumor growth in CT26 tumor-bearing mice [180]. Nanoparticles (M + C + siPD-L1), containing Toll-like receptor (TLR) agonist (M), catalase (C) and siRNA against PD-L1, exert antitumor effects through activation of antitumor immunity [181].

Second, catalase within the nanoparticles can also act as an oxygen generator to decompose H_2O_2 within tumor environment and produce O_2 in order to improve hypoxia and sensitize cancer cells to chemotherapy. DOX/CAT@PLGA-M1 nanoparticles, which are loaded with doxorubicin and catalase by poly-(lactic-co-glycolic acid) (PLGA) and coated with M1 macrophage membrane, reduced migration of mouse 4T1 breast cancer cells *in vitro*, and decreased tumor growth *in vivo* and lung metastasis [182]. Nanoparticles (R + C + DOX) containing the resiquimod TLR agonist (R), catalase (C) and doxorubicin (DOX) can also activate antitumor immunity through enhancement of immunogenic cell death and activation of dendritic cells [183]. Liposomes CAT@aPDL1-SSLs containing catalase and *anti*-PD-L1 antibody ameliorated tumor hypoxia, infiltration of intratumoral $CD8^+$ T cells and inhibition of tumor growth [184]. Other nanocomposites containing catalase to alleviate tumor hypoxia and reactivate innate immune system have also been discussed and reviewed [211].

Third, catalase can also be used to generate sufficient O_2 to generate strong immune response followed by photodynamic therapy (PDT). The nanocomplex CAT-Ce6@OMV-aPDL1, comprising of catalase, photosensitizer chlorin e6 (Ce6), and coated with PD-L1 antibody modified-attenuated salmonella outer membrane vesicles (OMV-aPDL1) has been designed to decrease hypoxia and induce antitumor immunity [185]. Catalase (CAT) and *anti*-GITR antibody (DTA-1) were also loaded to photothermal agent and photosensitizer PDA-ICG nanoparticles. The PDA-ICG@CAT-DTA-1 nanoparticles enhanced ROS generation within the tumor environment and stimulated tumor immune responses [186]. Moreover, FA-L@MD@CAT liposomes that encapsulate catalase, a photosensitizer and doxorubicin, increased tumor oxygenation and potentiate the combination of chemotherapy and PDT through generation of singlet oxygen and abrogation of tumor immune suppression [187].

Altogether, catalase is used to suppress H_2O_2 to abrogate T cell immunosuppression and increase tumor oxygenation to potentiate radiotherapy, chemotherapy, immunotherapy and PDT. In our opinion, the impact of such nanoparticles in augmenting substantial intratumoral O_2 levels to attenuate hypoxia is questionable. Their effects most likely would rely on the ability of catalase to remove extracellular H_2O_2 to block the immunosuppressive effects and reduce tumor inflammation, and ROS are well known inducers of HIF activity. The choice of drug combination might also have a great impact on the antitumor effect and immune cell functions. We do not know if the choice of using doxorubicin in these studies was trivial, because it is a common drug loaded with nanoparticles or due to its pro-oxidant activity. But indeed doxorubicin can be an interesting choice for combination due to its ability to induce DNA damage and intracellular ROS generation in cancer cells, and furthermore it can exhibit immunostimulatory effects [212].

Box 1
Major progresses and challenges in understanding the role of catalase in cancer.

In the last decade, several progresses to decipher the role and function of catalase in cancer have been achieved. The most important discoveries include:

Regulation of catalase expression: Several transcription factors are known to control *catalase* gene transcription [18]. JunB and RARα can activate or repress respectively catalase expression in breast cancer cells through chromatin remodeling [23]. However, the mechanisms of regulation of catalase expression in cancer cells are still not well understood.

Catalase subcellular localization: Several findings provide a further insight into the transport of catalase between peroxisomes and cytosol [61,63,64]. Catalase is also found at the membrane or in the extracellular compartment of cancer cells [70,71], and membraneless organelles [76]. Such catalase localizations and the function of cytosolic catalase are still subject of debate in the field, and the nature of the membrane-associated catalase is unknown.

Tumor aggressiveness: Overexpression of catalase in breast and prostate cancer cells inhibits proliferative and migration capacity [79,80]. In contrast, catalase is often upregulated in glioblastoma and drives an aggressive phenotype [83]. Therefore, the role of H_2O_2 and catalase function can be different in diverse tumor environments, and the understanding of such conflicting results deserves further investigation.

Tumor metabolism: Catalase can influence glucose and lipid metabolism in cancer cells through distinct mechanisms [95,98]. Although the role of ROS in tumor metabolism is better characterized, information regarding the specific role of catalase in inducing metabolic reprogramming in cancer cells is still scarce.

Tumor immunology: Important progresses regarding the protective role of catalase in tumor immunology have been recently achieved. In this context, the increase in the antioxidant capacity in patient-derived tumor-infiltrating lymphocytes and CAR-T cells, while preserving T cell function, promotes promising *in vivo* therapeutic effects [120,121]. H_2O_2 can also induce immune escape through the upregulation of immune checkpoints in cancer cells, and extracellular catalase treatment can decrease tumor PD-L1 expression [124].

Metastasis: Several findings show that ROS play crucial role to induce metastatic processes and catalase can be a potential target to prevent metastasis. TIGAR and NRF2 expression diminish in invasive tumor cells, resulting in increased ROS levels that contribute to DNA instability [146]. SOD2 levels are often augmented whereas catalase levels are decreased in metastases [149]. Moreover, overexpression of mitochondrial catalase in MMTV-PyMT mice reduces lung metastasis, suggesting that an increase in mitochondrial antioxidant capacity is a promising therapeutic approach for invasive breast carcinoma [150].

Microbial catalases: Recently, growing evidence suggest a complex intratumoral microbiota that control cancer cell metabolism and immune responses [161,162]. Some findings show that bacterial catalases can modulate the redox environment to escape immune system [156,159]. However, there is currently no experimental data demonstrating a possible role of bacterial catalases in cancer development.

Catalase in cancer therapy: Multiple catalase-based therapies including chemotherapies, catalase inhibitors, catalase activators, and catalase-loaded nanoparticles have shown promising antitumor effects in preclinical studies through induction of cell death, inhibition of cancer cell proliferation and activation of immune system [168–187].

5. Conclusions and future perspectives

As described in this review, major progresses in understanding the role of catalase in tumor environment have been made this last decade (Box 1). Among them, supporting data tend to demonstrate that catalase localization is not limited to peroxisomes and could have different functions in other cell compartments. New findings also show that catalase play important role in tumor proliferation, metabolism reprogramming, immune escape and metastasis. Several strategies that aim to modulate catalase and ROS in tumor environment have been developed and have shown some promising therapeutic effects. However, the use of ROS-based and catalase-based therapies should be considered cautiously in cancer treatment because it could suppress immune system and have several adverse effects. In this context, several publications showed that treatment with extracellular catalase can lead to an increase in intracellular ROS levels in cancer cells associated with activation of compensatory mechanisms and pro-oxidant molecules such as NADPH oxidases. In theory, one of the best strategies could be the removal of extracellular H_2O_2 to reverse immunosuppression while augmenting intracellular H_2O_2 levels in cancer cells, which are not well adapted to detoxify high flux of H_2O_2 compared to healthy cells. In line with this theory, the combination of catalase-loaded nanoparticles and ROS-generating chemotherapies showed promising antitumor effects in preclinical studies.

Although some progresses in elucidating the role of catalase in cancer have been achieved, some important questions remain to be unanswered. Among them: (1) Catalase expression is regulated in breast cancer cells by JunB/RARα transcription factors but the mechanisms of RARα-mediated catalase transcriptional repression remain unclear; (2) Catalase was found in membrane and extracellular compartment but the exact nature and function of these catalases are unknown; (3) Catalase expression is often decreased in cancer cells, participating to an increased oxidative stress and tumor progression. However, the reasons for which catalase overexpression can lead to an aggressive phenotype in certain types of tumors are unrevealed; (4) It is unclear why catalase activity can either stimulate or inhibit secretion of cytokines in immune cells; (5) CSCs have robust antioxidant defense and are more resistant to chemotherapy but the specific roles of antioxidant enzymes in protecting CSCs against oxidative stress and promoting metastasis are not specified; (6) Microbial catalases can lead to immune escape but their impact in the tumor environment is unknown; (7) Catalase-based therapies showed promising antitumor effects in pre-clinical models. Nevertheless, their potential benefits in clinical trials and the mechanisms of resistance of such compounds remain to be elucidated. Answering those questions would bring new insights into the role of catalase in cancer and lead to development of new anticancer strategies.

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List of abbreviations:

αKGDH, alpha ketoglutarate dehydrogenase; ACO2, aconitase 2; AMPK, AMP-activated protein kinase; AP-MS, affinity purification mass spectrometry; ARE, antioxidant response element; Asc/Men, ascorbate and menadione; ASK1, apoptosis signal-regulating kinase 1; BACH1, BTB and CNC homology 1; BAK, BCL2 antagonist/killer; BCL2, B-cell lymphoma 2; BDNF-AS, brain-derived neurotrophic factor-antisense; BT, benzaldehyde thiosemicarbazone; CAR, chimeric antigen receptor; CAT, catalase; CCL2, C-C motif chemokine ligand 2; Ce6, chlorin e6; CSC, cancer stem cell; DOX, doxorubicin; DTA-1, *anti*-GITR antibody; Egr, early growth response; EMT, epithelial-mesenchymal transition; FGFR1, fibroblast growth factor receptor 1; FoxO, forkhead box protein O; FoxM1, forkhead box protein M1; Gal-CAT, galactosylated-catalase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GFP, green fluorescent protein; GPX1, glutathione peroxidase 1; GSH, glutathione; HDAC, histone deacetylase; HIF-1α, hypoxia-inducible factor-1 alpha; IFNγ, interferon gamma; IL, interleukin; JNK1, c-Jun N-terminal kinase 1; LncRNA, long non-coding RNA; MACC1-AS1, metastasis-associated in colon cancer 1-antisense RNA 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MDDC, monocyte-derived dendritic cell; MDSC, myeloid-derived suppressor cell; miR, micro-RNA; mTOR, mechanistic target of rapamycin; NAC, N-acetyl cysteine; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa B; NF-Y, nuclear factor Y; NK(T), natural killer (T); NOX, NADPH oxidase; NRF2, nuclear factor erythroid 2-related factor 2; OMV-aPDL1, PD-L1 antibody modified-attenuated salmonella outer membrane vesicles; OXPHOS, oxidative phosphorylation; PD-L1, programmed death-ligand 1; PDT, photodynamic therapy; PKB (Akt), protein kinase B; PEG-CAT, PEGylated-catalase; PEX, peroxins; PI3K, phosphoinositide 3-kinase; PKM2, pyruvate kinase M2; PLGA, poly-(lactic-co-glycolic acid); POU2F1 (Oct-1), PMA, phorbol-12-myristate-13-acetate; POU domain class 2 transcription factor 1; PPARγ, peroxisome proliferator-activated receptor gamma; PTP, protein tyrosine phosphatase; PTS, peroxisome-targeting signal sequence; RARα, retinoic acid receptor alpha; RARE, retinoic acid response element; SIRT, sirtuins; RNS, reactive nitrogen species; ROS, reactive oxygen species; RSS, reactive sulfide species; RT, radiotherapy; SGK3, serum/glucocorticoid regulated kinase family member 3; SHP-1, Src homology region 2 domain-containing phosphatase-1; SOD, superoxide dismutase; Sp1, specificity protein 1; STAT1, signal transducer and activator of transcription 1; SUCLA2, succinyl-CoA ligase ADP-forming subunit beta; TCR, T cell receptor; THBS1, thrombospondin 1; TIGAR, p53-induced glycolysis regulatory phosphatase; TIMP-3, tissue inhibitor of metalloprotease 3; TLR, Toll-like receptor; TNFα, tumor necrosis alpha; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; WT1, Wilms tumor 1.

CRediT authorship contribution statement

Christophe Glorieux: Writing – review & editing, Writing – original draft, Conceptualization. **Pedro Buc Calderon:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

All authors declare that there are no conflicts of interest to be disclosed.

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Data availability

No data was used for the research described in the article.

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