Involvement of the PRDX family and its clinical functions in different types of gastrointestinal cancer (Review)

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Received April 13, 2025; Accepted May 28, 2025

DOI: 10.3892/or.2025.8923

Abstract. Peroxiredoxin (PRDX) is a large and highly conserved family of peroxidases, which can maintain the dynamic balance of intracellular oxidative stress levels based on the degradation of the hydrogen peroxide, peroxynitrite and lipid peroxides, among others. Additionally, PRDXs are expressed with varying levels in almost all tumor tissues and cells, and they can regulate the downstream signaling cascades by modulating intracellular peroxide levels in tumor cells, alongside the participation during the modulation of gene expression, cell proliferation, apoptosis, migration, differentiation and other cellular biological behaviors. It has been revealed that the PRDXs family exhibits crucial functions in the occurrence, development, diagnosis and prognosis of gastrointestinal cancer, but a systematic summary was lacking in relevant studies. Therefore, the present study aims at probing into the underlying mechanisms of the PRDXs family in the occurrence and development of gastrointestinal cancer, providing new insights into the clinical diagnosis, treatment and prognosis monitoring.

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Key words: peroxiredoxin family, gastrointestinal cancer, reactive oxygen species homeostasis, reactive oxygen species, gene expression, clinical function

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1. Introduction

In recent years, the various types of gastrointestinal cancer have accounted for ~25% of the total incidences of global cancer, and 1/3 of cancer-associated deaths (1). Gastrointestinal cancer has imposed a huge cancer burden on both sexes, especially in China (2). From the perspective of anatomical structure (from top to bottom), digestive tract tumors mainly comprise esophageal cancer (EC), gastric cancer (GC), liver cancer, gallbladder cancer, pancreatic cancer (PACA) and colorectal cancer (CRC) (3). Moreover, the continuously increasing trend in the incidence rate of gastrointestinal cancer globally is being caused by population growth, aging, lifestyle changes and other factors, and this has been accompanied by a demographic shift to younger patients (3). Therefore, it is crucial to explore novel targets for the diagnosis and treatment of gastrointestinal cancer in order to improve the current situation.

Redox signaling crucially incorporates cellular signaling pathways and performs an important role in regulating various physiological functions associated with cell proliferation, metabolism, hormone signaling and immune regulation (4-6). In addition, reactive oxygen species (ROS) exhibit a 'double-edged sword' function during cellular processes. ROS are considered to be vitally important for the regulation of normal physiological functions at low-to-moderate doses, whereas an excessive production of ROS has been shown to induce oxidative stress damage to proteins, membranes, lipids, nucleic acids, and even organelles, which thereby induces apoptosis (7,8). Among ROS, hydrogen peroxide (H_2O_2) is one

of the major signaling molecules, which has been shown to regulate both redox signaling and crucial functions in cellular signaling and metabolism (9,10).

Previous studies have shown that the peroxiredoxin (PRDX) family is a highly conserved antioxidant enzyme family, possessing specific cysteine (Cys) residues that enable the efficient scavenging of H_2O_2, alkyl hydroperoxide and peroxynitrite (11-13). Additionally, this family participates in the maintenance of ROS homeostasis in tumor cells (14), which in turn, exerts a range of diverse effects on tumor cell proliferation, genomic integrity and immunological defense, along with the promotion of tumor progression (15-17). However, imbalances in ROS homeostasis may induce the DNA damage response under conditions of cell cycle arrest and cell apoptosis, which ultimately results in the occurrence of cellular carcinogenesis (15,18-22). Therefore, the PRDX family members have been demonstrated to exhibit crucial functions during tumor progression based on the maintenance of ROS homeostasis (Fig. 1). Earlier studies showed that PRDX proteins possess the ability to regulate the proliferation, metabolism and immune regulation of tumor cells, along with their involvement in the pathological regulation or protection of various types of cancer, including gastrointestinal cancer (23-25). Furthermore, redox and antioxidants are important regulatory factors that have been shown to influence the progression of different types of gastrointestinal cancer (26-29). Therefore, the latest findings from studies that have been performed on the PRDX family in the context of gastrointestinal cancer occurrence and development are summarized in the present review, with the hope that this will assist in designing novel treatment methods to target the PRDX family members from new perspectives.

2. Origin of the PRDX family

The PRDX family was first discovered in yeast in 1987, and its members were first termed thiol-specific antioxidants (TSAs) due to their ability to remove reactive sulfur species instead of ROS (30). Additionally, alkyl hydroperoxide reductase (AhpC), which was isolated from *Salmonella typhimurium* in 1990, was found to be highly homologous with TSAs in terms of its sequence (31). According to the study by Tartaglia *et al* (31), TSAs caused a decrease the concentration of peroxides upon the application of thioredoxin (TRX) as a direct hydrogen donor, which suggested that they could also serve as peroxidases. On account of this, Chae *et al* (32) changed the name of 'TSA' to thioredoxin peroxidase (TPX) in 1994, with a subsequent further renaming to 'PRX' (an alternative abbreviation for peroxiredoxin) after it became established that certain of the PRDX members (1-Cys PRXs) did not rely on TRX as the electron donor (33). At present, 'peroxiredoxin' is the recommended name according to the International Union of Biochemistry and Molecular Biology Naming Committee, with the common abbreviation of either PRX or PRDX.

3. Structure of the PRDX family

PRDXs are a family of peroxidase enzymes with a molecular size of 22-27 kDa, which contain 160-220 amino acids (34,35) (Fig. 2). Additionally, they possess Cys residues that participate in the reduction of peroxides, and the enzymes are present in almost all living organisms (36,37). Furthermore, the PRDX family may be divided into three subgroups according to the number and position of the Cys residues involved in catalysis, namely the typical 2-Cys (PRDX1-4) subgroup of enzymes, and the atypical 2-Cys (PRDX5) and 1-Cys (PRDX6) subgroups. The PRDX1-5 group members possess two conserved Cys residues, whereas the PRDX6 group only possesses one conserved Cys residue (38-40). Moreover, the various subtypes exhibit significant differences in terms of their subcellular localization. PRDX1 is located in the nucleus and cytoplasm, and its expression is localized in the mitochondria and peroxisomes (41). Similarly, PRDX5 is widely expressed in the cytoplasm, peroxisomes and mitochondria, with a comparatively lower level of expression observed in the nucleus (42). By contrast, the localization of other PRDX members in various of the subcellular organelles has yet to be fully determined. For example, the expression of PRDX2 has only been shown in the cytoplasm and nucleus (43), that of PRDX3 is limited to the mitochondria (43), that of PRDX4 is limited to the endoplasmic reticulum (ER) and cytoplasm (37,44), and PRDX6 has been shown to be mainly expressed in the cytoplasm (37). The structures and characteristics of the PRDX family members are shown in Table I.

4. Expression and function of the PRDX family in different types of gastrointestinal cancer

The PRDX family members exhibit differing levels of high or low expression in the various types of gastrointestinal cancer (Table II), which has the effect of critically affecting the occurrence, development and prognosis of cancer.

PRDX1. PRDX1 possesses two conserved Cys residues, namely the conserved N-terminal Cys-52 and the C-terminal Cys-173 (35), belonging to the typical 2-Cys subgroup. Additionally, the N-terminal Cys-SH group of PRDX1 has been shown to serve as the main oxidation site. The N-terminal Cys-SH group rapidly forms an intermolecular disulfide bond with another conserved Cys-SH group at the C-terminus upon the oxidation of PRDX1 (45). Furthermore, PRDX1 exerts its effects on the biological activity of gene regulation and cell fate in the nucleus through binding to p53 c-Myc, NF-κB, androgen receptor, and other transcription factors (46). Regarding its role in the cytoplasm, PRDX1 has shown anti-apoptotic potential, based on its interaction with ROS-dependent signaling pathway factors (46). In addition, PRDX1 was demonstrated to interact with c-Abl and c-Myc as cellular oncogene products, and this interaction was found not to be dependent on antioxidant activity mediated via the inhibition of c-Abl kinase activity (47) or c-Myc-mediated transformation (48). Previous studies have also shown that PRDX1 excels in promoting the proliferation of various types of cancer cells, and this proliferation may occur via a number of different mechanisms in the different cancer types. A study by Lv *et al* (21) found that ainsliadimer A is capable of directly targeting Cys-173 of PRDX1 and Cys-172 of PRDX2, thereby leading to a corresponding inhibition of peroxidase activity, an increase in intracellular ROS levels and a marked reduction in ATP production, with the consequent inhibition of CRC cell proliferation and induction of cell apoptosis. Furthermore, knocking out PRDX1 led

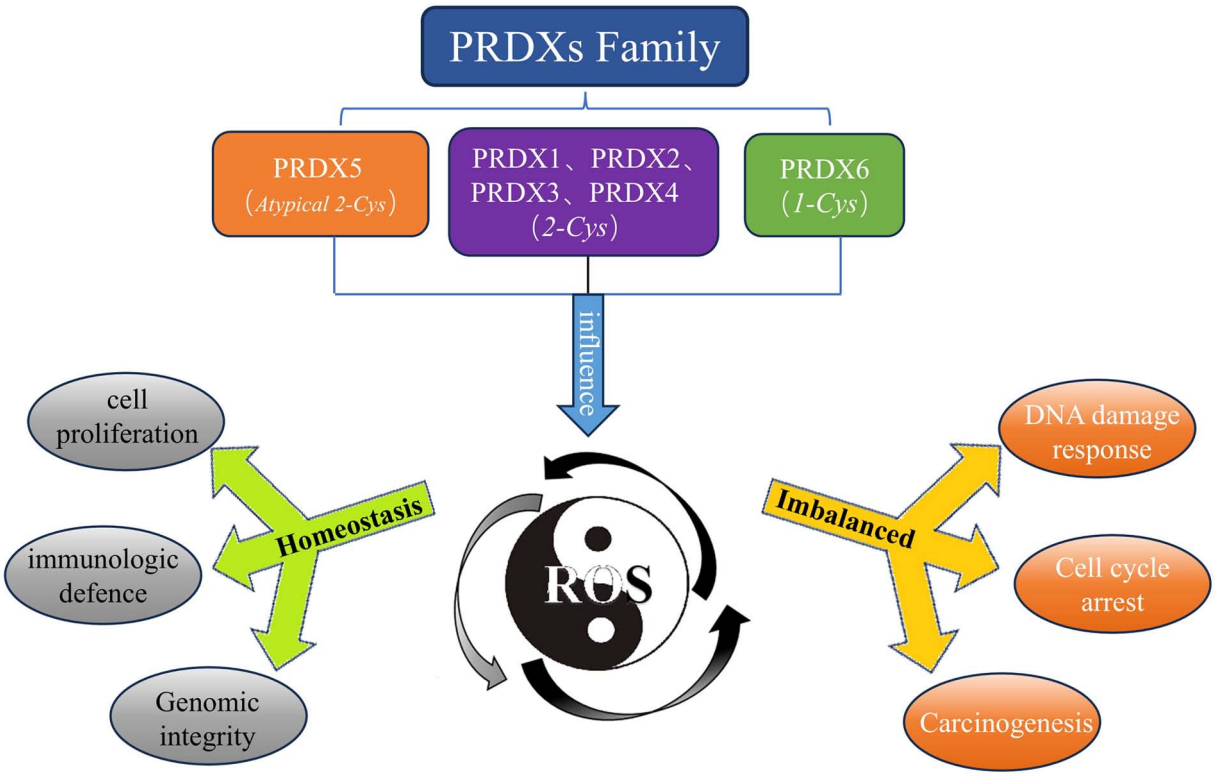

Figure 1. Role of the PRDX family in maintaining ROS homeostasis. PRDX, peroxiredoxin; ROS, reactive oxygen species.

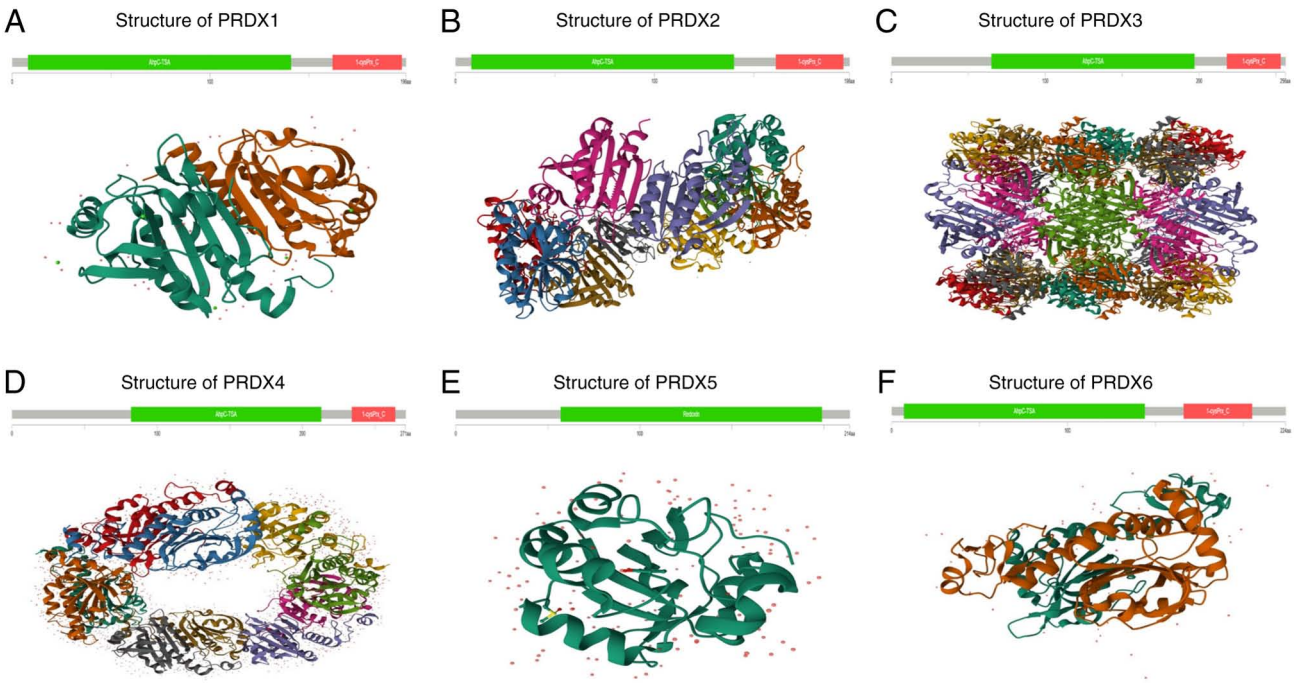

Figure 2. (A-F) The structural domain and crystal structure of PRDX1-PRDX6. PRDX, peroxiredoxin.

to an activation of cleaved caspase-3, cleaved caspase-9 and poly(ADP-ribose) polymerase 1, resulting in the apoptosis of liver cancer cells (49). Similarly, overexpression of PRDX1 led to an increase in the gene expression of proliferating cell nuclear antigen (PCNA) and Bcl-2, and a downregulation of BAX expression, in cervical cancer cells, causing both a marked acceleration of cell proliferation and the inhibition of cell apoptosis (50). The DNA damage response process was shown to be accompanied by the translocation of PRDX1 to the nucleus, thereby decreasing the levels of nuclear ROS induced by DNA damage and consequently benefitting DNA damage repair (51). Owing to PRDX1 knockout, cells were

Table I. Structure and characteristics of the PRDX family members.

Name	Location	AA number	Classification	Disulfide bond	Reductant	(Refs.)
PRDX1	Cytosol/nucleus/ mitochondria/peroxisome	199	2-Cys	Homodimer	Trx	(41,46)
PRDX2	Cytosol/nucleus	198	2-Cys	Homodimer	Trx	(43,91)
PRDX3	Mitochondria	256	2-Cys	Homodimer	Trx	(11,43)
PRDX4	Cytosol/endoplasmic reticulum	271	2-Cys	Homodimer	Trx	(37,44,146)
PRDX5	Cytosol/mitochondria/ peroxisomes	214	Atypical 2-Cys	Monomer	Trx	(42,154)
PRDX6	Cytosol	224	1-Cys	Heterodimer	Glutathione	(37,162)

PRDX, peroxiredoxin.

shown to be capable of accumulating DNA damage and replication stress, which accordingly led to a deficiency in their ability to proliferate (51). Finally, in experiments performed on mouse embryonic fibroblasts and PRDX1-deficient human breast cancer cells, RAD51 foci formation was found to be disrupted and homologous recombination was decreased, leading to consequent DNA damage, which led to the cells being more sensitized to irradiation (52).

Overexpression of PRDX1 has also been reported in EC cells compared with the adjacent normal tissues in several studies (53-56). Furthermore, an enhanced expression of PRDX1 was found to strongly correlate with EC onset and development; by contrast, a reduced expression of PRDX1 tended to inhibit tumorigenesis (57). Based on the aforementioned findings, it was possible to infer putative oncogenic functions of PRDX1 in EC. Gong *et al* (53) found that a high expression of PRDX1 promoted the tumorigenesis of EC cells through regulating the mTOR/p70S6K pathway. Furthermore, according to the study by Chen *et al* (57), PRDX1 both strengthened tumor formation and increased EC cell invasion rates through regulating the HEF1-Aurora A-histone deacetylase 6 signaling axis. In addition, a high expression level of PRDX1 in EC was demonstrated by Song *et al* (58), suggesting that PRDX1 silencing may inhibit EC proliferation, as well as enhancing cell apoptosis. The underlying mechanism possibly involves blocking the PI3K/AKT signaling pathway. Notably, PRDX1 expression in EC was reported in another study, and this was markedly and negatively correlated with lymph node metastasis and TNM staging (59). Additionally, the PRDX1 low-expression group in that study presented with shorter overall survival (OS) times compared with the high-expression group of PRDX1(59). Considered altogether, potential tumor-suppressive functions of PRDX1 were suggested by the aforementioned findings. Additionally, the downregulation of PRDX1 has been shown to contribute to the progression of EC, and PRDX1 may be an important marker for disease prognosis (59). However, to the best of the authors' knowledge, there are no published studies at present that have clearly delineated the precise functions of PRDX1 in EC, and this aspect needs to be investigated further in future studies.

A high expression of PRDX1 in liver cancer was found to be inversely correlated with the prognosis of patients with liver cancer. Therefore, PRDX1 may be a potential biomarker for liver cancer diagnosis and prognosis, and its inhibitors are currently being employed as candidate drugs in treating liver cancer (60-64). The study by Sun *et al* (49) revealed that PRDX1 knockout could induce cell apoptosis and promote mitochondrial fission; thereby preventing the liver cancer cells from undergoing cell proliferation. Additionally, according to the study by Luo *et al* (65), PRDX1 silencing led to both an accumulation of ferrous ions and enhanced rates of lipid peroxidation in HepG2 cells, which in turn, induced iron-induced apoptosis; similar observations were made in the study by Aguilar-Melero *et al* (66). In terms of the underlying mechanism, Zhang *et al* (67) found that PRDX1 is able to bind to UHRF2, a E3 ubiquitin ligase, and its protein expression was upregulated to facilitate the biological functions of UHRF2 in liver cancer. In a previous study (68), the expression of PRDX1 was shown to have clinical value in gastrointestinal cancer: PRDX1 was highly expressed in liver cancer, and this expression of PRDX1 was associated with high diagnostic values and poor prognosis. Therefore, inhibitors of PRDX1 may be employed as candidate drugs for treating liver cancer in the future, as the significant clinical value of PRDX1 has been demonstrated for liver cancer cell therapy (49).

According to numerous studies, GC tissues present with higher mRNA and protein expression levels of PRDX1 compared with surrounding normal tissues (69-71). Furthermore, in the study by Yu *et al* (72), PRDX1 could regulate the invasion and metastasis of a GC cell line, based on the inhibition of E-cadherin expression. Additionally, Zhang *et al* (73) discovered that the levels of the microRNA (miR)-596 exhibited a decreasing trend with an overexpression of PRDX1 in GC. miR-596 was clearly shown to directly target PRDX1 mRNA, leading to the subsequent downregulation of PRDX1 expression, which exerted an inhibitory effect on GC cells. Taken together, these findings suggested that a trend of increasing PRDX1 expression in GC results in a poor prognosis.

According to two previous studies (74,75), PRDX1 expression was also found to be positively correlated with vascular density, lymph node metastasis and tumor grade in

Table II. Expression and effects of PRDXs family in gastrointestinal cancer.

Name	Cancer type	Expression	Effects	(Refs.)
PRDX1	Esophageal cancer	Up	Controversial	(53-59)
	Liver cancer	Up	Promotion	(49,60-68)
	Gastric cancer	Up	Promotion	(69-73)
	Colorectal cancer	Up	Controversial	(74-80)
	Pancreatic cancer	Up	Promotion	(81,82)
	Cholangiocarcinoma	Up	Promotion	(83,84)
PRDX2	Esophageal cancer	Controversial	Controversial	(96-98)
	Liver cancer	Controversial	Controversial	(99-102)
	Gastric cancer	Up	Promotion	(103-105)
	Colorectal cancer	Up	Controversial	(92,106-110)
	Pancreatic cancer	Down	N/A	(111)
	Cholangiocarcinoma	Up	Promotion	(112-114)
PRDX3	Esophageal cancer	N/A	N/A	N/A
	Liver cancer	Up	Promotion	(121,123-125)
	Gastric cancer	Up	Promotion	(126,127)
	Colorectal cancer	Up	Promotion	(128)
	Pancreatic cancer	Up	N/A	(129)
	Cholangiocarcinoma	N/A	N/A	N/A
PRDX4	Esophageal cancer	Up	N/A	(142)
	Liver cancer	N/A	Controversial	(140,143)
	Gastric cancer	Up	Promotion	(71,144,145)
	Colorectal cancer	Up	Controversial	(146-148)
	Pancreatic cancer	N/A	Promotion	(149)
	Cholangiocarcinoma	N/A	N/A	N/A
PRDX5	Esophageal cancer	N/A	N/A	N/A
	Liver cancer	Up	Promotion	(157,158)
	Gastric cancer	Up	Promotion	(71,159,160)
	Colorectal cancer	Up	Promotion	(161)
	Pancreatic cancer	N/A	N/A	N/A
	Cholangiocarcinoma	N/A	N/A	N/A
PRDX6	Esophageal cancer	Controversial	Controversial	(173,174)
	Liver cancer	Controversial	Controversial	(175,176)
	Gastric cancer	Controversial	Controversial	(172,177,178)
	Colorectal cancer	Up	Controversial	(170,179-181)
	Pancreatic cancer	Up	N/A	(182)
	Cholangiocarcinoma	Up	Promotion	(183)

PRDX, peroxiredoxin.

CRC. According to Kaplan-Meier survival plot analysis, the PRDX1-positive group possessed a shorter OS rate compared with the PRDX1-negative group. Therefore, a high expression of PRDX1 led to poor prognosis in CRC (74). In terms of the underlying mechanism, Song *et al* (76) showed that PRDX1 could enhance the stability of the antioxidant response regulator nuclear factor erythroid 2-related factor 2 (NRF2) by binding to Cullin 3, thereby inhibiting iron deposition and promoting the progression of CRC. PRDX1 has been revealed to have different cell migratory and invasive capabilities across a range of different CRC cell lines, and these findings were indicative of its tumor prognosis predictive effects, preparing the way for further exploration of the underlying regulatory mechanisms acting against CRC metastasis and angiogenesis. Additionally, PRDX1 may be a biomarker for the detection of cancer progression in its early stages and for identifying potential pathogenesis (77,78). At present, studies exploring treatment of the PRDX family in gastrointestinal cancer have been mainly focused on PRDX1. Li *et al* (79) developed several celastrol urea derivatives that were displayed as co-crystal structures with PRDX1, with the aim of developing a PRDX1-specific inhibitor. Among the derivatives mentioned in their study, derivative 15 exhibited excellent anti-PRDX1 activity (with an IC_{50} value of 0.35 μM) and antiproliferative

capability against CRC cells (79). Their analysis revealed that derivative 15 may represent a promising PRDX1-specific inhibitor in the quest to develop anti-CRC agents. In the study by Tai *et al* (80), *Gynostemma pentaphyllum* saponins were found to restrict the development of CRC based on an upregulation of PRDX1 and PRDX2 expression, along with inhibition of the Ras, RAF/MEK/ERK/STAT and PI3K/AKT/mTOR signaling pathways, as well as the regulation of the JNK/p38 MAPK signaling pathway. Their findings may help to address any potential controversies regarding the functions of PRDX1 in CRC.

The expression levels of PRDX1 have also been found to exhibit a significantly increasing trend in PACA, and an upregulation of PRDX1 expression was shown to be strongly correlated with tumor angiogenesis; therefore, PRDX1 may be a promising tumor marker for PACA diagnosis and prognosis (81). Additionally, according to the study by Taniuchi *et al* (82), PRDX1 exhibited a high expression level in PACA cells, where it was shown to interact with p38 MAPK to inhibit both membrane folding and membranous processes, thereby promoting the invasion of pancreatic ductal adenocarcinoma (PDAC) cells.

Regarding cholangiocarcinoma, according to a multivariate analysis (83), PRDX1 is overexpressed and the expression of PRDX1 was found to be strongly correlated with the invasion, nodal metastasis and advanced disease stages of cholangiocarcinoma, and PRDX1 could potentially serve as an independent predictor for the prognosis of patients with hilar cholangiocarcinoma. Furthermore, in the mechanistic study performed by Liao *et al* (84), competitive interaction between the circular RNA cZNF215 and PRDX1 restricted the interaction between PRDX1 and PTEN, resulting in oxidation-induced inactivation of the PTEN/AKT pathway and subsequent cholangiocarcinoma progression and metastasis.

PRDX2. PRDX2 is one of the typical 2-Cys subgroup members of the PRDX family, which exhibits a similar structure to that of PRDX1 and is mainly expressed in the cytoplasm (85). Additionally, the PRDX2 gene was found to be located on chromosome 8 in mice (86). The PRDX1 and PRDX2 proteins in mice share a sequence similarity of 89% and a sequence identity of 74%, and they also possess both common and different biological functions (86). In terms of the immune response, PRDX2 was found to possess some ability in clearing ROS and in inhibiting the immune cell response (87). Furthermore, a deficiency in PRDX2 was shown to result in an increased exposure to ROS, which was shown to activate T lymphocyte proliferation and dendritic cell differentiation (88). Moreover, this deficiency of PRDX2 aggravated the accumulation of immune cells in atherosclerotic lesions, which in turn, exacerbated atherosclerosis in mice wherein apolipoprotein E had been silenced (89). It was found that PRDX2 silencing led to the inhibition of tumor angiogenesis (90). PRDX2 has also been shown to be a useful scavenger of ROS from tumor cells, and this activity was confirmed to contribute towards the regulation of cell apoptosis and proliferation, as well as the activities of various signaling pathways (91). PRDX2 is able to bind to ribosomal protein L4 (RPL4), thereby weakening the interaction between RPL4 and mouse double minute 2 homolog and causing p53 ubiquitination degradation and promoting CRC cell proliferation (92). Decreased levels of PRDX2 expression have been shown to markedly enhance the apoptosis of non-small cell lung cancer (NSCLC) cells through the downregulation of Bcl-2 expression and an upregulation of the expression levels of Bax, cleaved-caspase 3 and cleaved-caspase 9 (93). PRDX2 was also found to activate the PI3K/AKT signaling pathway, which, in turn, enhanced the binding of the transcription factor SP1 to the fibronectin 1 (FN1) gene promoter, ultimately triggering the proliferation of triple-negative breast cancer cells (94). In another study, PRDX2 knockdown impeded activation of the JNK/c-Jun signaling pathway, which consequently damaged the DNA repair process (95).

A high expression level of PRDX2 in EC was identified by Feng *et al* (96), and in their study, knocking down PRDX2 was found to result in inactivation of the Wnt/β-catenin and AKT signaling pathways, thereby restricting the proliferation, migration, invasion and cell-cycle arrest of EC cells. Additionally, in the study by Zhan *et al* (97), miR-92A-5p was found to suppress the proliferation and migration of EC cells, in addition to the growth of subcutaneous tumors, via targeting PRDX2. Furthermore, it was surmised that the mediation of these effects could be attributed to suppression of the AKT/mTOR and Wnt3a/β-catenin signaling pathways upon performing miR-92A-5p stimulated transfection experiments, which revealed that the findings of these two studies (97) were broadly in agreement with each other. However, a study based on proteomics technology found that PRDX2 is downregulated in EC (98). Therefore, the expression and role of PRDX2 in EC are still controversial.

In the study by Yang *et al* (99), PRDX2 was found to be highly expressed in liver cancer, and this, in turn, could activate the Wnt/β-catenin pathway through inducing the nuclear translocation of β-catenin, which subsequently enhanced liver cancer cell proliferation. Additionally, PRDX2 overexpression was found to alleviate the exosome-induced suppression of liver cancer cell proliferation and angiogenesis by increasing the expression of vascular endothelial growth factor (100). Furthermore, in their study, Zhou *et al* (101) showed that PRDX2 exhibited pro-tumorigenic functions in liver cancer, at least via partially restricting ROS-mediated apoptosis under conditions of oxidative stress. However, in the study by Bai *et al* (102), PRDX2 protein expression was found to be clearly decreased in liver cancer tissues; this research group also found that the PRDX2 high-expression group experienced longer OS and disease-free survival times compared with the PRDX2 low-expression group. Overall, it must be noted that the expression and function of PRDX2 in liver cancer appears to be a controversial topic so far.

PRDX2 was also found to exhibit high expression levels in GC tissues and cell lines, and overexpression of PRDX2 was found to be strongly associated with GC progression (103). Notably, the silencing of PRDX2 led to an inhibition of GC cell proliferation and the promotion of apoptosis. In addition, in the same study, the knockdown of PRDX2 contributed towards an attenuation of the growth of GC in BALB/c nude mice (103). Chen *et al* (104) also found that inhibiting PRDX2 by treatment with celastrol led to an increase in the levels of cellular ROS in GC cells, which in turn, triggered the ROS-dependent ER stress response, mitochondrial dysfunction and apoptosis.

Zhou *et al* (105) demonstrated that PRDX2 could interact with pyruvate kinase M2 (PKM2), thereby preventing the enzyme from undergoing ubiquitination and degradation, consequently enhancing glycolysis in the GC cells. Moreover, the interaction of PRDX2 with PKM2 also strengthened the binding affinity of PKM2 with the protein importin α5, which induced PKM2 to undergo nuclear translocation, as well as activating the STAT3 signaling pathway. Therefore, PRDX2 has been shown to be highly expressed in GC, and a positive correlation has been identified with GC progression.

In the study of Lu *et al* (106), CRC tissues and cells were found to exhibit upregulated PRDX2 expression, and this increase in PRDX2 expression was found to be positively correlated with CRC tumor metastasis and the TNM stage. However, other studies have found that the association between PRDX2 expression and CRC prognosis is controversial (92,107,108). In addition, the silencing of PRDX2 was shown to induce apoptosis in CRC cells (106). Furthermore, in another study (109), PRDX2 was shown to exert a regulatory influence on Wnt/β-catenin signaling. Xu *et al* (110) showed that PRDX2 silencing resulted in a decrease in phosphorylated (p)-AKT expression, with the consequent suppression of the PI3K/AKT pathway, in CRC cell lines, which in turn, promoted cell apoptosis.

However, only a limited number of studies have been performed on PRDX2 in PACA. According to the study by Chen *et al* (111), patients with PACA presented with a relatively lower level of PRDX2 expression compared with normal subjects.

Moreover, it was demonstrated by Zhang *et al* (112) that PRDX2 downregulation could trigger a G1/S blockade in the cell cycle, which, in turn, impaired cell invasion in intrahepatic cholangiocarcinoma, together with an inhibition of the PI3K/AKT/c-Myc signaling pathway. An upregulation of PRDX2 in cholangiocarcinoma was also identified by Cavalloni *et al* (113) based on mass spectrometry analysis. Similarly, the aforementioned phenomenon was discovered by Tang *et al* (114) through their use of the isobaric tags for relative and absolute quantitation proteomics technique.

PRDX3. PRDX3 has been identified to be mainly located in the mitochondria, where it serves as an essential gene during the process of mitochondrial balance, tumor transformation and antioxidant activity (115-117). Moreover, PRDX3 has been shown to regulate the physiological level of H_2O_2, to maintain the cell growth rate, and to protect the cells from apoptosis induced by high concentrations of H_2O_2 (118-120). In addition, under the regulatory influence of c-Myc, PRDX3 was found to preserve normal mitochondrial function, and exhibited an important role in the regulation of mitochondrial redox (115). Furthermore, PRDX3 has also been shown to have important effects in inflammatory disease responses (12,116). Additionally, defects in endogenous PRDX3 were found to alter the mitochondrial redox status and mitochondrial functions, as well as the expression of adipokines in adipocytes, which resulted in the observed metabolic changes (116). PRDX3 knockdown triggers the downregulation of ATP synthases, thereby lowering the cellular ATP level, which impedes cell proliferation. In a study by Liu *et al* (121), silencing PRDX3 was revealed to downregulate tissue inhibitor of metalloproteinases 1 and to strengthen degradation of the extracellular matrix (ECM), thereby improving the invasive properties of HepG2 cells. Similarly, PRDX3 silencing was demonstrated to induce the inhibition of breast cancer cell proliferation and cell-cycle arrest (122). In another study (123), silencing PRDX3 enhanced the apoptosis, and intensified the caspase-3 activity, of liver cancer cells, suggesting that PRDX3 is an indispensable ROS scavenger that prevents the oxidative damage caused to, and apoptosis of, liver cancer cells.

PRDX3 was also found to be highly expressed in both liver cancer cells and tissues, and its high expression was associated with poor tissue differentiation (124). As aforementioned, it was shown by Wang *et al* (123) that PRDX3 could serve as an indispensable ROS scavenger, blocking oxidative damage and apoptosis of the tumor cells, which provided evidence to support PRDX3 being utilized as a chemotherapeutic agent specific for liver cancer. Moreover, Liu *et al* (121) showed that PRDX3 could facilitate the growth of liver cancer, and mediate cell migration and invasiveness. Notably, knocking down PRDX3 led to the downregulation of ATP synthases and a decrease in the cellular ATP level, which subsequently retarded cell proliferation. Additionally, Shi *et al* (125), through measuring the serum samples from 297 Chinese patients, found that the high-serum PRDX3 expression group exhibits a shorter median survival time compared with the low-expression PRDX3 group. Furthermore, the serum expression of PRDX3 could independently predict the OS rate, and it could therefore be employed as a non-invasive biomarker for liver cancer diagnosis and/or prognosis.

With regard to GC, Yan *et al* (126) found PRDX3 to be overexpressed in GC tissues compared with the adjacent non-cancer tissue, and this rendered GC cells more resistant to cisplatin through reducing the level of apoptosis; PRDX3 overexpression may therefore serve as a target to overcome the cisplatin resistance. In addition, according to Zhao *et al* (127), the Forkhead box M1 (FOXM1)-anti-silencing function 1B histone chaperone-PRDX3 signaling axis was found to be a potential therapeutic target for the treatment of GC.

Similarly, Song *et al* (128) showed that PRDX3 was overexpressed in CRC, and FOXM1-induced PRDX3 could maintain the mitochondrial functions, and the FOXM1/PRDX3-associated mitochondrial pathway could maintain survival of the CRC cells. Additionally, it was found that PRDX3 is a potential therapeutic target for the treatment of CRC (128).

A recent study showed that the level of PRDX3 in the plasma of patients with PACA increased, indicating that PRDX3 may affect the occurrence and development of PACA (129). However, relevant studies on the role of PRDX3 in EC and cholangiocarcinoma are currently lacking, and further research in this area is warranted.

PRDX4. The chromosome position of PRDX4 is 10p22.13, and PRDX4 contains 271 amino acids (40). Unlike other typical members of the 2-Cys PRDX family, PRDX4 contains a hydrophobic signal sequence in the N-terminal region, which is associated with crucial functions with respect to the localization of PRDX4 (130,131). Moreover, PRDX4 may be organized into pentamers with five homodimeric units, and the subunits of PRDX4 are capable of being assembled

in a disulfide end-to-end manner (132-134). Additionally, PRDX4 has been shown to be mainly expressed in the ER, together with its being identified in cytoplasmic lysosomes, the nucleus, cell matrix and ECM (135-137). Furthermore, the location of PRDX4 in the ER may ensure the appropriate folding process for newly formed proteins, along with the prevention of selective oxidation. At the same time, the study by Zito (138) showed that H_2O_2 catabolism is coupled with oxidative protein folding by PRDX4, which may serve to maintain the ER redox balance and circumvent the misfolding of proteins. In addition, PRDX4 was found to regulate signal transduction via 'fine-tuning' the H_2O_2 concentration, and this was shown to be crucial for cell proliferation (139). PRDX4 was also demonstrated to reduce anoikis and to promote the proliferation of hepatocellular carcinoma cells through stabilizing β-catenin protein and upregulating ID2 (140). In a subsequent study (141), lowering the expression of PRDX4 contributed to a clear slowing of glioblastoma cell proliferation and a weakening of radiation resistance *in vitro*, with an observed concomitant rise in the ROS level and enhancement of DNA damage and apoptosis.

A previous study showed that the level of PRDX4 in the serum of patients with EC increased, indicating that PRDX4 may affect the occurrence and development of EC (142). In terms of liver cancer, according to the study by Guo *et al* (143), human liver cancer specimens with low PRDX4 expression presented a higher ROS level, together with a highly malignant phenotype, which may lead to a consequent decrease in the OS rate. However, in terms of cells (143), knocking down PRDX4 in human liver cancer cell lines resulted in a rapidly increasing trend in intracellular ROS level, and the inhibition of cell proliferation, along with the induction of cell death. Collectively, the aforementioned findings may suggest that PRDX4 has an inhibitory effect in the initiation of HCC, but a dual (inhibitory or promoting) role in the progression of HCC. As aforementioned, it was shown by Wang *et al* (140) that PRDX4 could reduce anoikis and promote the tumorigenesis and metastasis of liver cancer cells via stabilizing the β-catenin protein and upregulating ID2. Taken together, targeting PRDX4 might hold promise in terms of restricting the growth and metastasis of liver cancer cells.

In the study by Zhang *et al* (144), GC tissues presented markedly higher PRDX4 mRNA expression levels compared with normal tissues, which may be attributed to the fact that PRDX4 participates in tumor immunity, along with promotion of the development of GC through regulating the neutrophil degranulation signaling pathway (144). Additionally, in the study by Park *et al* (145), PRDX4 served as a biomarker for poor prognosis in GC, and PRDX4 was found to be associated with cancer cell migration and invasion via epithelial-mesenchymal transition (EMT). Moreover, PRDX4 exhibited a strong correlation with the aggravation of OS among patients with GC (71). It was also shown by Jia *et al* (146) that the gene and protein expression levels of PRDX4 were higher in CRC tissues compared with the adjacent normal tissues, and these data conformed with those of Yi *et al* (147). Moreover, it was found that the expression intensity of the PRDX4 protein was positively correlated with the invasion depth, lymph node metastasis and Dukes' classification in CRC, and a high expression of PRDX4 indicated short survival times, according to Kaplan-Meier survival curve analysis (147). However, Zhou *et al* (148) suggested that low PRDX4 expression indicated poor prognosis in CRC. Therefore, the relevance of PRDX4 expression to the prognosis of CRC remains controversial.

A recent study found that the low expression of PRDX4 predicts longer survival and an imprved clinical condition in patients with PDAC (149). PRDX4 plays a main role in prognosis and has the potential to become a clinical prognostic indicator of PDAC. However, relevant studies on PRDX4 in cholangiocarcinoma are comparatively lacking, and further studies are required to fill this knowledge gap.

PRDX5. PRDX5 is the only member of the atypical 2-Cys subgroup of the PRDX family (150). Similarly to the other members, however, PRDX5 exhibits a wide range of different expression levels in tissues. By contrast, differently from the others, it is distributed in plentiful subcellular structures. In human cells, PRDX5 was shown to be widely expressed in mitochondria, peroxisomes, cytoplasm and in the nucleus (151). In other studies, PRDX5 was primarily considered to be a cell-protective antioxidant enzyme that is able to counteract endogenous or exogenous peroxide attacks (152,153). Therefore, the overexpression of this enzyme may protect cells from cell death that is caused by nitro-oxidative stress, whereas the silencing of this enzyme renders the cells more susceptible to oxidative damage (154). Overexpression of PRDX5 in NSCLC was shown to promote its binding to NRF2, to enhance the expression of NAD(P)H quinone oxidoreductase 1, and to accelerate the proliferation of NSCLC cells (155). In a study by Bai *et al* (156), the long non-coding RNA prostate cancer-associated transcript 6 was shown to sponge miR-143-3p, thereby leading to PRDX5 upregulation, with the resultant acceleration of the proliferation and stemness of gastrointestinal stromal tumor cells. Moreover, PRDX5 overexpression in HepG2 cells was revealed to markedly suppress beta-carboline-3-carboxylic acid ethyl ester-induced cell apoptosis and cellular ROS levels, as well as weakening mitochondrial dysfunction (157).

PRDX5 mRNA expression was observed to be incrementally upregulated with normal and liver cancer tissues analyzed in the TNMplot database (157). In a previous study, Qi *et al* (158) reported that downregulation of the PRDX5 gene could attenuate the antioxidant capacity of liver cancer cells, thereby significantly suppressing the cell survival rate.

By contrast, Kim *et al* (159) found that PRDX5 was highly expressed in GC, and the overexpression of PRDX5 exhibited clear correlation with tumor size, tumor depth and lymphatic invasion among patients with GC. Furthermore, via upregulating the expression of Snail, PRDX5 overexpression was found to enhance the proliferation and invasiveness of the GC cells, thereby increasing their carcinogenicity (159). It was suggested that PRDX5 might contribute to the poor prognosis of GC through intensifying the mesenchymal phenotype. Additionally, PRDX5 may serve as a strong molecular target for GC chemotherapy, and functions of PRDX5 in oxidative stress-induced cell apoptosis have been further elucidated (160).

In addition, it was demonstrated that PRDX5 is overexpressed in CRC, and PRDX5 overexpression led to a marked augmentation of CRC cell proliferation, migration and invasion (161). Furthermore, in the same study (161), PRDX5 was found to modulate the expression of the two hallmark EMT proteins, E-cadherin and vimentin, together with the EMT-inducing transcription factors, Snail and Slug. Collectively, based on the current research, our knowledge on the role on PRDX5 in gastrointestinal cancer is relatively limited.

PRDX6. PRDX6 has been shown to be widely expressed in almost all mammalian cells, especially in solid organs such as the eyes, lungs and liver (162-166). PRDX6 is the only 1-Cys member to have been identified in the PRDX family, and it possesses several unique characteristics that distinguish it from the other PRDX members (43). First, the underlying catalytic mechanism for its peroxidase activity is not based on thioredoxin; instead, glutathione is employed as the physiological reducing agent to reduce the phospholipid hydroperoxides, and this PRDX member exhibits acidic Ca^{2+}-independent phospholipase A_2 (PLA2) activity (167). Secondly, PRDX6 may have a role in the reduction of short-chain hydroperoxides and phospholipid hydroperoxides. Thirdly, PRDX6 was revealed to possess PLA2 activity that is distinct from its peroxidative functions. Overall, these characteristics provide the basis for our current understanding of the physiological functions of PRDX6, as a key enzyme in antioxidant defense and phospholipid homeostasis (168,169). The inactivation of PRDX6 may lead to decreases in the levels of N-cadherin, β-catenin, vimentin, Slug, Snail and Twist-1 levels via activating the PI3K/AKT/p38/p50 pathway, thereby further inhibiting CRC cell proliferation (170). PRDX6 was shown to trigger lung tumor growth via simultaneously increasing the activities of glutathione peroxidase and iPLA2 (171). Silencing of PRDX6 resulted in an increase in Bax protein expression, whereas the expression levels of PCNA, Bcl-2, PI3K, p-Akt and p-mTOR were decreased, thereby suppressing GC cell proliferation and facilitating cell apoptosis (172).

In the study by Guo *et al* (173), the protein expression of PRDX6 was high in tumor-adjacent normal esophageal epithelial tissues, and the protein expression of PRDX6 was found to decrease with the progression of esophageal lesions. Additionally, well-differentiated EC tissues exhibited markedly higher expression levels of PRDX6 protein compared with poorly differentiated EC tissues (173). However, He *et al* (174) found that EC tissues had a markedly higher expression level of PRDX6 compared with normal esophageal tissues or tumor-adjacent tissues, and the PRDX6 expression level was positively correlated with the proliferation-associated markers. Furthermore, PRDX6 overexpression based on an adenovirus was found to significantly increase the rates of EC cell proliferation, migration and invasion (174). Therefore, the expression and functions of PRDX6 in EC remain controversial.

Mu *et al* (175) identified that the mRNA level of PRDX6 was significantly increased in HCC tissues and the expression of PRDX6 may critically affect liver cancer prognosis. Additionally, the knockdown of lentivirus-mediated PRDX6 was shown to impede the proliferation, migration and invasion of liver cancer cells through regulating the PI3K/Akt/mTOR and Notch1 signaling pathways (175). Moreover, in the study by Xu *et al* (176), PRDX6 exhibited high mRNA and protein expression levels in peri-tumoral tissues, whereas a decreased PRDX6 expression level in liver cancer tissues could independently indicate a poor prognosis. Therefore, the expression and functions of PRDX6 in hepatocellular carcinoma remain controversial to a certain extent.

The expression of PRDX6 was found to be significantly associated with an increasing trend in GC progression, as revealed by Mu *et al* (172), in which knocking down the gene expression of PRDX6 in BGC-823 cells led to a suppression of GC cell proliferation, migration and invasion, together with the promotion of apoptosis. Moreover, in a different study (177), PRDX6 was highly upregulated in metastatic GC cells, which exhibited a relative resistance to TNF-related apoptosis-inducing ligand compared with the primary GC cells. However, a previous study showed that the level of PRDX6 protein is lower in GC tissues than that in normal para-cancer ones, and it is significantly correlated with the differentiation degree of GC (178). Therefore, the expression and functions of PRDX6 in GC remain controversial.

According to Huang *et al* (170), PRDX6 is overexpressed in CRC, and the expression of PRDX6 exhibited characteristic growth-promoting functions in CRC metastasis, and PRDX6 might lead to poor prognosis in CRC, given its ability to significantly regulate the cancer cell tumorigenicity in CRC (170). Furthermore, Wang *et al* (179) found that nucleophosmin could promote cell proliferation by targeting PRDX6 in CRC. In a different study (180), silencing PRDX6 in HCT116 cells contributed to an increasing trend of ROS and lipid peroxidation, along with a decrease in the level of NRF2, mitochondrial dysfunction, as well as an enhanced sensitivity to ferroptosis. All these modifications would result in an attenuation of the proliferation, migration and invasiveness of the HCT116 cells (180). However, Huang *et al* (181) considered that the expression of PRDX6 could be upregulated by baicalein, which thereby reduced ROS production and inhibited the proliferation of CRC cells. Taken together, according to the aforementioned studies, the effects of PRDX6 in CRC remain controversial.

The proteinogram showed that the expression of PRDX6 in pancreatic juice of PACA patients was higher than that of normal people, and it was verified with PACA tissue (182). However, its mechanism in PACA needs further study.

The expression of PRDX6 was demonstrated to exhibit a significantly increasing trend in intrahepatic cholangiocarcinoma tissues compared with the peritumoral tissues, and PRDX6 expression was positively correlated with the malignant phenotype among patients with intrahepatic cholangiocarcinoma (183). Additionally, PRDX6 may also promote intrahepatic cholangiocarcinoma through regulation of the Wnt7a/b pathway, and it may therefore be recruited as a novel therapeutic target for intrahepatic cholangiocarcinoma (183).

5. Conclusions and future perspectives

The PRDX family is considered to be one of the most important antioxidant enzyme systems, which exhibits a dual effect during the carcinogenic process of different types of gastrointestinal cancer. Furthermore, the members of the PRDX family

demonstrate an ability to eliminate the peroxides, superoxide and ROS that are produced by metabolism in the body, thereby preventing the occurrence of tumors. Simultaneously, they have crucial functions in the protection of tumor cells from damage, and the promotion of tumor progression based on the clearance of ROS inside cancer cells. At present, compared with other members of the PRDX family, a larger number of studies have been performed on PRDX1, PRDX2 and PRDX6. Consequently, knowledge on their roles in gastrointestinal cancer is also more extensive.

The complexity and importance of the PRDX family in the progression of gastrointestinal cancer has been gradually clarified with the advancement of research, together with their value in the diagnosis and treatment of gastrointestinal cancer and evaluations of patient prognosis.

At present, it has been determined that the PRDX family is highly expressed in the majority of digestive tract tumors, and that it may extensively promote the proliferation and migration of tumor cells, thereby assisting in our ability to understand the treatment of digestive tract tumors from novel perspectives. However, a lack of relevant studies focused on small-molecule drugs that target the PRDX family (with the exception of PRDX1) means that more coordinated research efforts are required in the future.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

ZZ and CQ conceived the study. ZZ, YW and YL performed literature searches and collected information. ZZ, YW and HW were responsible for analysis of the literature and the drawing of tables. ZZ, YL, XX and KW were responsible for drawing the figures. ZZ, YW, YL, CH and CQ wrote the original draft of the review. ZZ, CH and CQ participated in the final manuscript review and editing. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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