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Review

The role of transketolase in human cancer progression and therapy

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ABSTRACT

Transketolase (TKT) is an enzyme that is ubiquitously expressed in all living organisms and has been identified as an important regulator of cancer. Recent studies have shown that the TKT family includes the TKT gene and two TKT-like (TKTL) genes; TKTL1 and TKTL2. TKT and TKTL1 have been reported to be involved in the regulation of multiple cancer-related events, such as cancer cell proliferation, metastasis, invasion, epithelial-mesenchymal transition, chemoradiotherapy resistance, and patient survival and prognosis. Therefore, TKT may be an ideal target for cancer treatment. More importantly, the levels of TKTL1 were detected using EDIM technology for the early detection of some malignancies, and TKTL1 was more sensitive and specific than traditional tumor markers. Detecting TKTL1 levels before and after surgery could be used to evaluate the surgery's effect. While targeted TKT suppresses cancer in multiple ways, in some cases, it has detrimental effects on the organism. In this review, we discuss the role of TKT in different tumors and the detailed mechanisms while evaluating its value and limitations in clinical applications. Therefore, this review provides a basis for the clinical application of targeted therapy for TKT in the future, and a strategy for subsequent cancer-related research.

1. Introduction

Metabolic reprogramming is considered a hallmark of cancer [1]. Tumor cells consume far more glucose than normal cells. More importantly, even under aerobic conditions, glucose in tumor cells preferentially utilizes glycolysis instead of oxidative phosphorylation for energy production. This metabolic shift is known as the Warburg effect. In addition to providing cells with energy, metabolic intermediates of glycolysis play pivotal roles in macromolecular biosynthesis to provide a favorable environment for tumor growth [2]. The pentose phosphate pathway (PPP), which branches from glycolysis in the first step of glucose metabolism, provides raw materials for nucleotide biosynthesis and is the main source of NADPH. NADPH is essential for fatty acid synthesis and the elimination of reactive oxygen species (ROS). Thus, PPP plays a key role in meeting the anabolic demands of cancer cells and in combating oxidative stress [3]. The PPP is divided into oxidative and non-oxidative branches, which control NADPH and ribose production, respectively. TKT, a key enzyme in non-oxidative PPP, plays an indispensable role in both cell metabolism and tumor growth. An increasing number of studies have shown that TKT is overexpressed in a variety of tumors and is closely related to their malignant characteristics and clinical indicators. Most importantly, TKT is associated with

Abbreviations: ALDOC, Aldolase, fructose-bisphosphate C; BOT, Benfooxythiamine; CDK4, Cyclin Dependent Kinase 4; CML, Chronic myeloid leukemia; c-MYC, Cellular-myelocytomatosis viral oncogene; CRC, Colorectal cancer; CTS, Cryptotanshinone; E4P, Erythrose 4-phosphate; ESCC, Esophageal squamous cell carcinoma; F6P, Fructose 6-phosphate; FH, Fumarate hydratase; FXR, Farnesoid receptor; G3P, Glycoraldehyde 3-phosphate; GRP78, glucose regulated protein 78; HBx, Hepatitis B virus X protein; HCC, Hepatocellular carcinoma; HDAC3, Histone deacetylase 3; HIF-1α, Hypoxia-inducible factor-1Alpha; HK2, Hexokinase 2; HNSCC, Head and neck squamous cell carcinoma; LC, Lung cancer; LDHA, Lactate dehydrogenase; LSIL, Low-grade squamous intraepithelial lesions; NEK9, NIMA Related Kinase 9; Nrf2, Nuclear factor erythroid 2-related factor 2; NSCLC, Non-small cell lung cancer; OT, Oxythiamine; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGK1, Phosphoglycerate Kinase 1; PHD2, Prolyl hydroxylase 2; PPP, Pentose posphate pathway; PRLR, Prolactin receptor; R5P, Ribose 5-phosphate; RA, Retinoic acid; ROS, Reactive oxygen species; S7P, Sedoheptulose 7-phosphate; SDH, Succinate dehydrogenase; SH2D5, SH2 domain - containing 5; SRC-3, Steroid receptor coactivator-3; STAT1, Signal transducer and activator of transcription 1; STAT3, Signal transducer and activator of transcription 3; TAL, Transaldolase; TKT, Transketolase; TKTL1, Transketolase -like 1; TKTL2, Transketolase -like 2; TNBC, Triple-negative breast cancer; TPP, Thiamine diphosphate; Xu5P, Xylulose 5-phosphate; YAP, Yes-associated protein; αKG, Alpha-ketoglutarate.

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chemoradiotherapy resistance. Targeted TKT inhibits tumor proliferation and increases sensitivity to multiple chemotherapeutic agents. In general, TKT may be a novel biomarker, and targeted inhibition of TKT holds promise as a new approach for the treatment of tumors.

2. TKT: a ubiquitous enzyme with a complex structure

The human genome contains three TKT genes: TKT, TKT-like 1 (TKTL1), and TKTL2. TKT is a key enzyme in the PPP and is present in all known organisms [4]. TKT is a homodimer, meaning that the active site is located at the interface formed by two identical subunits. Thiamine diphosphate (ThDP), a derivative of vitamin B1, binds to this active site as a cofactor to regulate TKT enzyme activity. The activation requires two conditions: ThDP and divalent metal ions for catalytic activity (such as Mg^{2+}, Ca^{2+}, Mn^{2+}, and CO^{2+}), which are the same as those of other ThDP-dependent enzymes [5]. TKT is located on chromosome 3 at position 3p21.1, while TKTs such as TKTL1 and TKTL2 are located at position Xq28 of chromosome X and 4q32.2 of chromosome 4, respectively. Among them, TKT is the most widely studied and has been reported to be related to the occurrence of a variety of diseases. TKTL1 has been widely studied, but there have been few reports on TKTL2 [6]. As early as 1996, when the concept of TKTL1 was proposed, researchers believed that it might change TKT enzyme activity [7]. Other scholars believe that TKTL1 is a pseudogene [8], and Coy et al. showed that there are differences in the structures of human TKT and TKTL1 in that their amino acid composition and primary structure are different [7]. Therefore, whether TKTL1 is a TKT needs to be further explored [9,10]. In 2019, researchers found that TKTL1 and TKTL2 have the same folding structure as TKT, suggesting that both TKTL1 and TKTL2 are functional TKTs that may play similar roles in many diseases [6].

3. TKT: a key regulator of metabolism

3.1. TKT as a key enzyme and junction in glucose metabolism

The PPP is a branch of glycolysis and an important component of cell metabolism. TKT is a key enzyme in the PPP and is the bridge between it and glycolysis. TKT plays a significant role in the non-oxidative phase of the PPP [11]. TKT, together with transaldolase (TAL), catalyzes the non-oxidative phase of the PPP, in which TKT seems to control the non-oxidative phase. TKT is responsible for a relatively complex (multi-substrate) mutual conversion reaction at the core of the non-oxidative PPP and catalyzes two different reactions [12]. Reactions catalyzed by TKT transfer two carbon atoms from xylulose 5-phosphate (Xu5P) to ribose 5-phosphate (R5P) or erythrose 4-phosphate (E4P), and then R5P and E4P become sedoheptulose 7-phosphate (S7P) or fructose 6-phosphate (F6P), respectively. Simultaneously, the Xu5P that provided the carbon atom becomes glyceraldehyde 3-phosphate (G3P). Reactions catalyzed by TAL involve the transfer of three carbon atoms from S7P to G3P, and G3P becomes F6P, while S7P, which provides carbon atoms, becomes E4P (Fig. 1).

The main metabolites of the PPP are NADPH and R5P. The former is produced by the oxidized PPP catalyzed by glucose 6-phosphate dehydrogenase, and the latter is produced by the non-oxidized PPP catalyzed by TKT (Fig. 1). NADPH provides the reducing potential for most antioxidants, such as the glutathione/glutaredoxin and thioredoxin systems [13], and R5P is the precursor for the synthesis of nucleic and amino acids [11]. NADPH is also required for fatty acid and cholesterol synthesis. Although NADPH is produced by the oxidative PPP, TKT indirectly replenishes NADPH to prevent ROS-induced damage when exposed to oxidative stress [14]. The mechanism by which TKT indirectly regulates NADPH production is addressed later. The non-oxidative PPP exists in almost all organisms, whereas the oxidative PPP is not found in some archaea or thermophilic bacteria [15,16]. Therefore, TKT may be ubiquitous in all organisms and associated with growth and development.

Interestingly, the reversibility of the non-oxidative PPP and the allosteric regulation of the enzymes in this pathway enable it to adapt to the metabolic needs of the cell, operating in different ways. For example, maintaining the redox homeostasis of a cell is more important than nucleic acid synthesis when the cell is under oxidative stress. TKT is activated at this time and the non-oxidative PPP is accelerated, which promotes the resynthesis of F6P from pentose phosphate and subsequent conversion back to G6P to promote NADPH production (Fig. 1). In general, TKT, as a key enzyme in the PPP, is essential for biosynthesis and metabolic regulation.

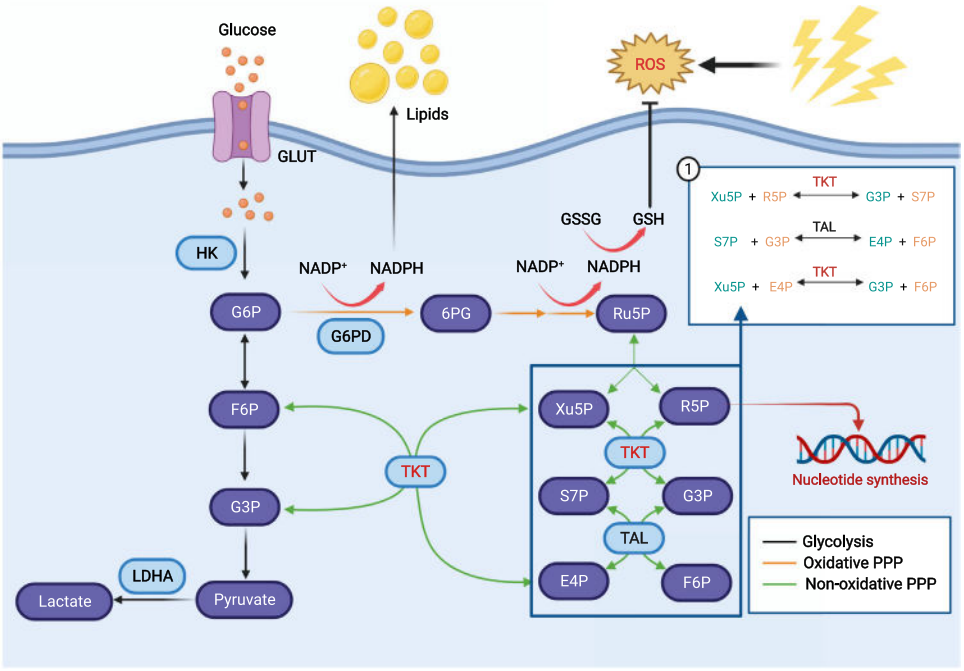

Fig. 1. Schematic of glycolytic and PPP metabolism and group transfer reactions in the non-oxidative PPP. TKT is a key enzyme of the non-oxidative PPP responsible for the generation of R5P. The TKT-mediated reactions are all reversible, which allows the non-oxidative PPP to dynamically meet the cellular metabolic balance. TKT is activated under oxidative stress and promotes the resynthesis of F6P, which is subsequently converted to G6P to promote NADPH production, thus, resistance to oxidative stress.

3.2. TKT indirectly modulates lipid metabolism

Surprisingly, although TKT is a key enzyme in glycolysis, it also indirectly affects lipid metabolism (Fig. 2). One experiment showed that knockout of one TKT allele resulted in an ~77% reduction in adipose tissue weight [17]. In addition, TKT deficiency protected mice from diet-induced obesity by accelerating lipolysis. Specifically, adipocyte-specific knockout of TKT inhibits glycolysis and reduces pyruvate production, resulting in an insufficient energy supply. Providing sufficient energy for cells leads to a compensatory increase in lipolysis. Mechanistically, knockout of TKT increases the gene expression of the mitochondrial electron transport chain, thus, promoting fatty acid oxidation [18]. In conclusion, TKT is one of the key enzymes of glucose metabolism, and it also indirectly regulates other metabolic modes, which reveals a surprising and novel role of TKT.

4. TKT in tumors: an essential regulator of tumorigenesis

Tumor growth requires a large amount of energy. Aerobic glycolysis not only meets the energy needs of tumor cells but also provides biological macromolecules for biosynthesis [19,20]. Several studies have shown that TKT and TKTL1 promote tumor cell proliferation and reduce damage resulting from oxidative stress, whereas TKTL2 does not appear to exert these effects [21,22]. As mentioned earlier, the TKT-mediated non-oxidative PPP not only generates R5P but also indirectly regulates NADPH production [14]. These two substances are crucial for tumor survival. NADPH is the prime antioxidant in cells, which reduces the level of ROS and avoids oxidative stress injury in cancer cells by maintaining glutathione in a reduced state [23]. R5P is a substrate for the synthesis of DNA and RNA that plays a vital role in regulating the proliferation of cancer cells and the DNA damage response [24]. In addition, studies have confirmed that more than 85% of the ribose generated by the PPP is directly or indirectly produced by the non-oxidative branch of the PPP via isotope labeling [25].

Table 1
Transcriptional regulation of the TKT family in cancer.

Tumor type	Gene	Regulation
Pancreatic cancer [53,90]	TKT	TKT is transcriptionally activated by MUC1/HIF-1α TKT is transcriptionally activated by TEAD1
Cholangiocarcinoma [91]	TKT	TKT is transcriptionally activated by Nrf2
Breast cancer [92]	TKT	TKT is transcriptionally activated by PFKFB4/SRC-3
Cervical cancer [93]	TKT	TKT is transcriptionally activated by miR-497–5p
Lung cancer [94,95]	TKT	TKT is transcriptionally activated by Nrf2
Leukemia [96]	TKT	TKT is transcriptionally activated by HIF-1α
Liver cancer [97]	TKT	TKT is transcriptionally activated by Nrf2 TKT is transcriptionally repressed by BACH1
Esophageal cancer [81]	TKTL1	TKT is transcriptionally activated by miR-497–5p

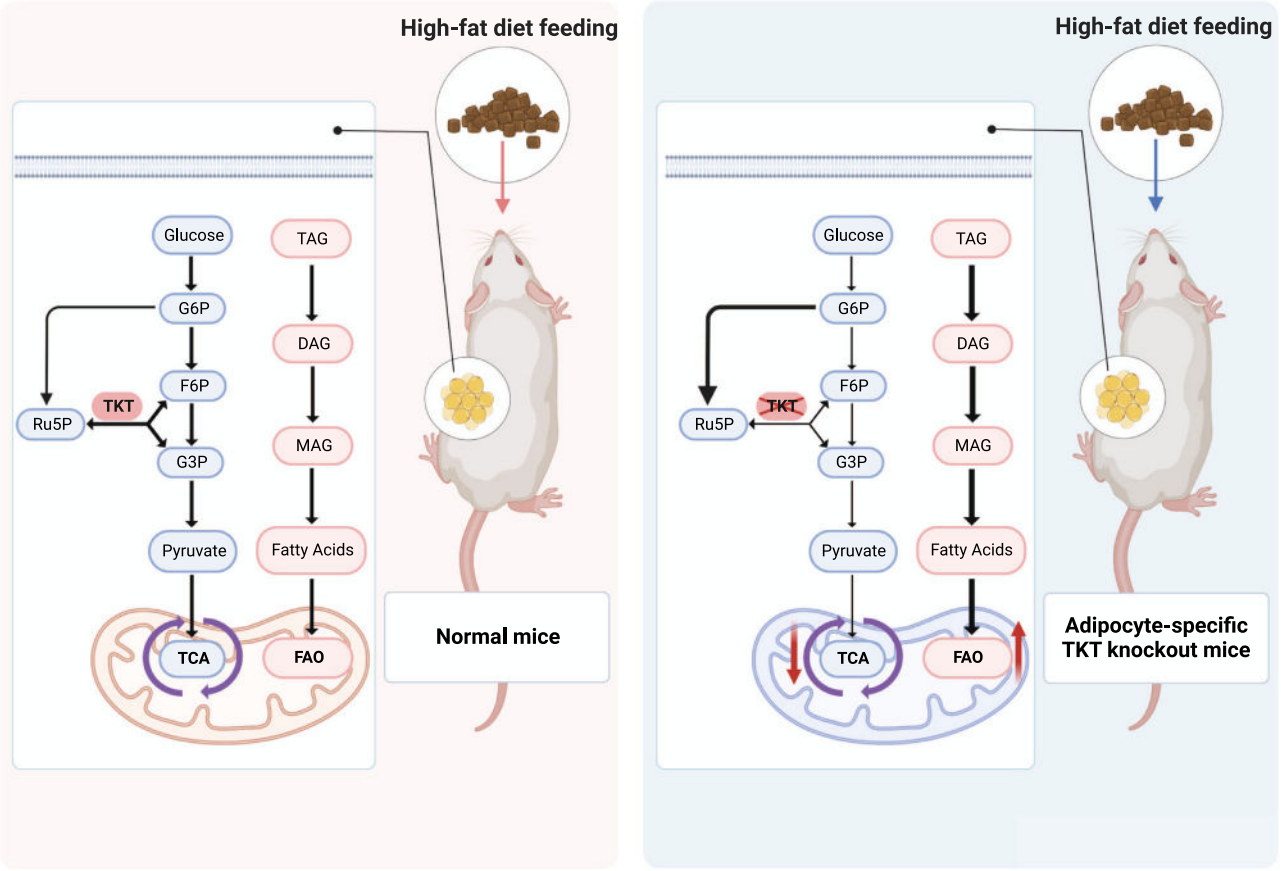

Fig. 2. As an enzyme of glucose metabolism, TKT also indirectly affects other metabolic pathways. The adipocyte-specific metabolism pattern is shown on the right. Specific knockout of TKT in adipocytes suppressed the non-oxidative PPP, leading to the accumulation of metabolites, such as Ru5P, and reduced glycolytic flux, which resulted in insufficient energy provided by glucose. To meet the energy demand, there is a compensatory increase in lipolysis, which produces large amounts of fatty acids. These fatty acids enter mitochondria and are oxidized. G6P, Glucose 6-phosphate; F6P, Fructose 6-phosphate; G3P, Glyceraldehyde 3-phosphate; Ru5P, Ribulose 5-phosphate; TKT, Transketolase; TCA, Tricarboxylic acid cycle; TAG, Triacylglycerol; DAG, Diacylglycerol; MAG, Monoacylglycerol; FAO, Fatty acid oxidation.

Indeed, an increasing number of studies have shown that TKT family members are highly expressed in a variety of tumors (Table 2), and this was confirmed in data from databases (Fig. 3). Interestingly, data from The Cancer Genome Atlas (TCGA) indicate that aberrant TKT expression correlates with the overall survival of patients (Fig. 4). In conclusion, TKT, a key enzyme in the PPP, is an important regulatory factor in tumorigenesis and development. Next, we introduce the role and mechanism of TKT in different human cancers (Fig. 5).

4.1. TKT and digestive system tumors

4.1.1. Liver cancer

Liver cancer is the fifth most common cancer and second leading cause of cancer-related death worldwide. Xu et al. indicated that TKT was significantly upregulated in hepatocellular carcinoma (HCC), and the other two family members, TKTL1 and TKTL2, were hardly detected. Thus, TKT may play a crucial role in HCC development and metabolism. How does TKT affect HCC development? Liver injury due to drug abuse is one of the most common causes of liver cancer [26]. An independent study showed that TKT knockout cells accumulate R5P, which promotes nucleotide synthesis. Moreover, high nucleotide levels can protect the liver from drug-induced liver injury [27].

The utilization of lipids occurs mainly through the action of bile acids, which are essential for the discharge of waste (such as carcinogens and drugs) and endogenous compounds (such as cholesterol) [28,29]. However, cholestasis also promotes liver fibrosis and sclerosis, eventually leading to liver cancer. Several studies have shown that farnesoid receptor (FXR) is a nuclear receptor [30] that plays a crucial role in regulating liver fibrosis, cholestasis, and inflammation [31]. In addition, FXR deficiency promotes spontaneous liver cancer in mice [32–34]. Li et al. found that TKT promoted the malignant proliferation of liver cancer cells by regulating FXR expression. Specifically, TKT interacts with signal transducer and activator of transcription 1 (STAT1) to form a complex and translocates into the nucleus of HCC cells. They further clarified that after TKT enters the nucleus, it strengthens the binding between histone deacetylase 3 and the FXR promoter, thereby inhibiting FXR expression [35]. In summary, the occurrence and development of liver cancer, mediated by FXR, are closely related to TKT.

Hepatitis B virus (HBV) is one of the most common causes of liver cancer and more than half of patients with liver cancer worldwide are infected with HBV [36]. Zheng et al. confirmed that HBV X protein promotes the combination of SH2 domain-containing 5 (SH2D5) and TKT and that the SH2D5-TKT compound enhances the recruitment of SAT3 and thereby activates STAT3, which, in turn, promotes liver cancer development. Further studies have shown that SH2D5-TKT promotes IL-6-induced STAT3 activation, which affects the proliferation of hepatoma cells [37]. Interestingly, a recent study concluded that TKT is ectopic in the nucleus and promotes the proliferation of hepatoma cells in a non-metabolic manner through the EGFR pathway [38]. In conclusion, TKT is overexpressed in HCC and is involved in the development of liver cancer (Fig. 5).

Table 2
Expression and effects of TKT and TKTL1 in different cancers.

Tumor type	Expression level		Effect of expression level
	TKT	TKTL1	
Colorectal cancer [21,42,110–113]	High	High	Poor prognosis, Advanced stage, Poor survival
Pancreatic cancer [78,90]	High	High	EDIM blood test, Poor survival
Gastric cancer [114–116]		High	Poor prognosis, Advanced stage, Metastasis, Poor survival
Cholangiocarcinoma [117]		High	EDIM blood test
Breast cancer [118–120]	High	High	Poor survival, Poor prognosis, EDIM blood test
Cervical cancer [60,61,93,121]	High	High	Poor prognosis, Proliferation, Migration, Invasion
Ovarian cancer [122–124]	High	High	Poor prognosis, Proliferation, Chemoresistance
Lung cancer [65,125,126]	High	High	Poor survival, Poor prognosis, High grade
Head and neck squamous cell carcinoma [74]		High	Proliferation
Esophageal squamous cell cancer [77,78]	High	High	Poor survival, Proliferation, Advanced stage, High grade
Oral squamous cell cancer [127–131]		High	Poor survival, Metastasis, EDIM blood test
Thyroid cancer [132]		High	Metastasis
Laryngeal squamous cell carcinoma [133]		High	Poor survival, Proliferation
Nasopharyngeal carcinoma [134]		High	Chemoresistance, Proliferation, Poor survival
Prostate cancer [135–138]		High	EDIM blood test
Melanoma [139]		High	Invasion
Liver cancer [97]	High		Metastasis, Migration, Invasion

The TKT family is highly expressed in a variety of cancers, which is associated with malignant features of tumors and clinical indicators.

4.1.2. Colorectal cancer (CRC)

CRC is a common digestive malignancy with hundreds of thousands of deaths reported annually, making it the fourth leading cause of cancer-related deaths worldwide [39]. Approximately 30% of patients with CRC have distant metastasis after diagnosis [40], and nearly 90% of patients with advanced CRC die within 5 years of diagnosis [41]. TKTL1 is overexpressed in invasive CRC [42]. Hypoxia-inducible factor-1alpha (HIF-1α) induces TKTL1 expression under hypoxic conditions, affecting tumor development [43]. In addition, TKT expression changes significantly during transition from normal colorectal epithelium to invasive tumor cells [44]. During this process, TKT interacts with glucose-regulated protein 78 to enhance AKT phosphorylation, which promotes CRC metastasis [4]. In addition, TKT affects the malignant progression of CRC by regulating the cell cycle [21].

Clinical data suggest that patients with colitis are more likely to develop CRC [44,45]. Tian et al. provided evidence that TKT deletion induces enteritis development. Mechanistically, TKT deficiency promotes excessive apoptosis, affects normal intestinal barrier function by inhibiting ATP production, and finally induces colitis [46]. Although colitis is a risk factor for CRC, it is not contradictory that TKT inhibits the development of colitis but promotes the progression of CRC. TKT deletion leads to excessive apoptosis of normal intestinal epithelial cells, leading to colitis. Under these conditions, they are harmful to the body. In contrast, TKT deletion leads to limited DNA synthesis, which inhibits the proliferation and metastasis of tumor cells. Under these conditions, the deletion is beneficial to the body. TKT is related to the development and metastasis of CRC and is a promising biomarker.

4.1.3. Pancreatic cancer

Pancreatic cancer is a highly malignant tumor. This type of tumor is difficult to detect and has no symptoms in the early stages. It usually develops into an advanced stage after diagnosis and spreads easily to surrounding organs. Therefore, it is one of the deadliest cancers [47,48]. Several studies have shown that pancreatic cancer has an extremely poor prognosis, with less than 20% 1-year survival after diagnosis and less than 5% 5-year survival [49–51].

Nie et al. found significantly higher TKT levels in KPC mouse and human pancreatic cancer tissues than in adjacent normal tissues by immunohistochemistry. Prolactin receptor (PRLR), a member of the

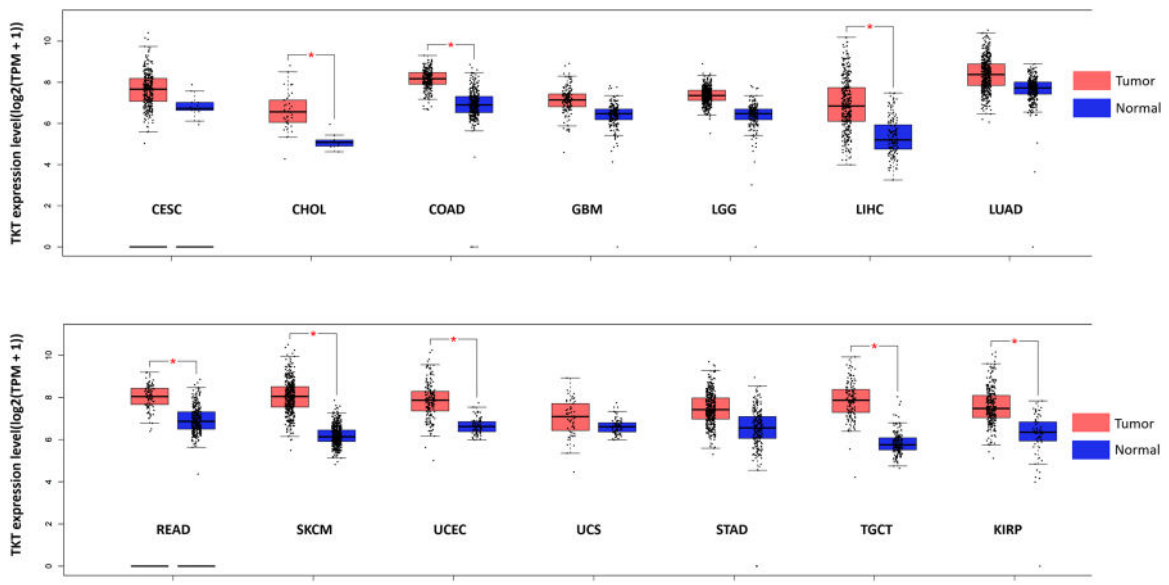

Fig. 3. TKT is highly expressed in a variety of tumor tissues compared with normal tissues. Data were derived from The Cancer Genome Atlas and GEPIA (gepia.cancer-pku.cn). Log_2FC, 1; P value, 0.01. CESC, Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, Cholangiocarcinoma; COAD, Colon adenocarcinoma; GBM, Glioblastoma multiforme; LGG, Brain Lower Grade Glioma; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; READ, Rectum adenocarcinoma; SKCM, Skin Cutaneous Melanoma; UCEC, Uterine Corpus Endometrial Carcinoma; UCS, Uterine Carcinosarcoma; STAD, Stomach adenocarcinoma; TGCT, Testicular Germ Cell Tumors; KIRP, Kidney renal papillary cell carcinoma.

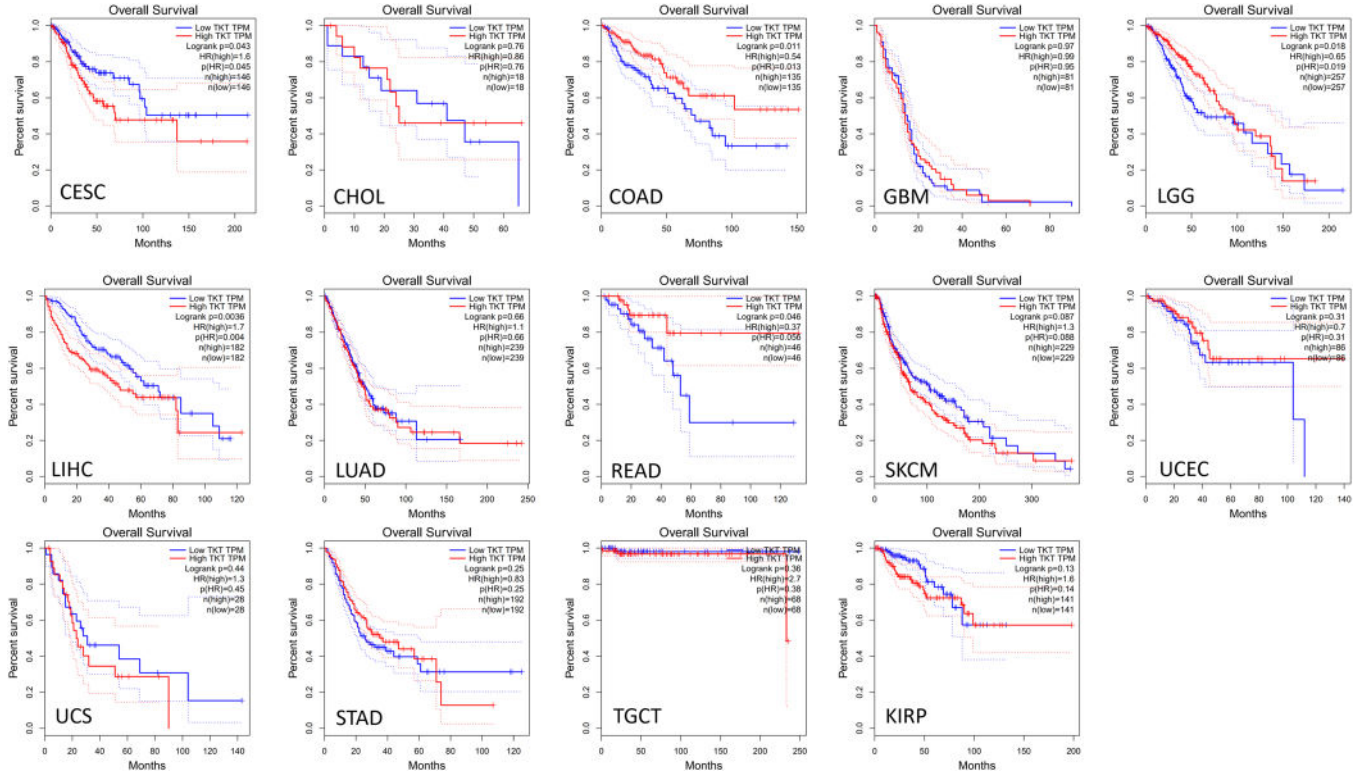

Fig. 4. Correlation between TKT levels and overall survival (OS) in different tumor tissues. Data were obtained from the Gene Expression Profiling Interactive Analysis (GEPIA) public database (gepia.cancer-pku.cn). CESC, Cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, Cholangiocarcinoma; COAD, Colon adenocarcinoma; GBM, Glioblastoma multiforme; LGG, Brain Lower Grade Glioma; LIHC, Liver hepatocellular carcinoma; LUAD, Lung adenocarcinoma; READ, Rectum adenocarcinoma; SKCM, Skin Cutaneous Melanoma; UCEC, Uterine Corpus Endometrial Carcinoma; UCS, Uterine Carcinosarcoma; STAD, Stomach adenocarcinoma; TGCT, Testicular Germ Cell Tumors; KIRP, Kidney renal papillary cell carcinoma.

cytokine receptor superfamily, is closely associated with cancer development [52]. Further studies have found that PRLR inhibits pancreatic cancer proliferation by downregulating TKT expression. Specifically, PRLR activates the Hippo pathway by binding to NIMA-related kinase 9. Yes-associated protein, a transcriptional regulator of the Hippo pathway, is a member of the Transcriptional enhanced associate domain

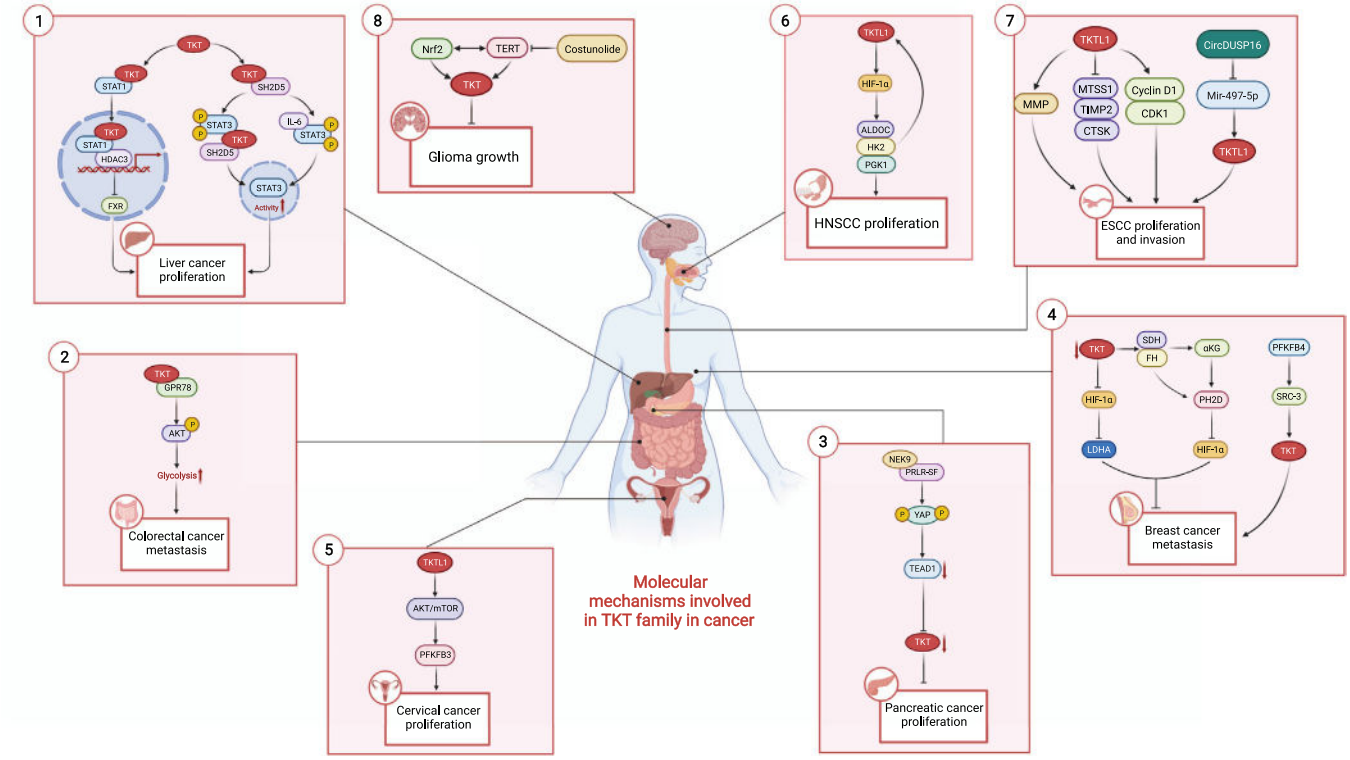

Fig. 5. TKT promotes tumor malignant progression through multiple signaling pathways in HCC, breast cancer, and colorectal cancer. TKT in glioma, breast cancer, and pancreatic cancer is regulated by multiple transcription factors or signaling pathways to promote tumor malignant progression. TKTL1 promotes tumor malignant progression through downstream signaling pathways or molecules in HNSCC, ESCC, and cervical cancer. In ESCC, TKTL1 is regulated by transcription factors to promote tumor malignant progression.

(TEAD) family of transcriptional co-activators. Their study further showed that TEAD1 directly regulates TKT transcription to affect pancreatic cancer proliferation [53] (Fig. 5).

4.2. TKT and reproductive system tumors

4.2.1. Breast cancer

Breast cancer is one of the most common cancers and the second leading cause of cancer-related deaths in women [52]. The 5-year survival rate of patients with primary breast cancer is high. Due to the lack of effective treatment, the 5-year survival rate of patients with metastatic breast cancer is less than 30% [54]. Triple-negative breast cancer (TNBC), which is prone to recurrence and metastasis and responds poorly to radiotherapy and chemotherapy, is a major cause of decreased patient survival [55].

The expression of TKT in TNBC tumor tissues was upregulated in the TNBC PDX model, and silencing TKT inhibited the invasion and proliferation of TNBC cells [56]. How does TKT play a role in breast cancer? Mechanistically, TKT suppresses breast cancer metastasis by regulating tumor suppressor succinate dehydrogenase and fumarate hydratase, and promotes HIF-1α stability and LDHA expression by regulating prolyl hydroxylase 2 (PHD2) expression via the alpha-ketoglutarate (αKG) signaling pathway, which, in turn, leads to breast cancer metastasis [57]. In contrast, TP53 mutations result in enhanced glycolysis in cancer cells, and TKT is significantly upregulated in TP53 mutant breast cancer tissues [58]. Taken together, TKT may be involved in breast cancer development in several ways (Fig. 5).

4.2.2. Cervical cancer

Cervical cancer is a common malignancy that seriously endangers female health [59]. TKT plays an important role in the development of cervical cancer, and serum TKT levels have been reported to be significantly increased in patients with cervical cancer, suggesting that it may be a biomarker for cervical cancer [60].

Other members of the TKT family are involved in the malignant progression of cervical cancer. TKTL1 regulates 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 expression and subsequently controls glycolysis through Akt signaling, which ultimately affects cervical cancer progression [61]. This suggests that TKTL1, a member of the TKT family, is an important regulator of cervical cancer development (Fig. 5).

4.3. TKT and respiratory tumors

4.3.1. Lung cancer (LC)

LC is the leading cause of cancer death, accounting for approximately 200,000 new affected patients each year [62,63]. LC has less than 20% 5-year survival rate and is one of the cancers with the lowest survival rate owing to a lack of effective treatment [64].

Immunohistochemical staining of 119 tissues from patients with non-small cell LC (NSCLC) showed that the levels of TKT and TKTL1 were significantly higher than those in non-tumor tissues [65]. Another study found similar results; TKT was significantly highly expressed in tumor tissues from patients with lung adenocarcinoma [66]. Overall, aberrant expression of the TKT family members may contribute to LC development.

p53 is the most common tumor suppressor gene, with more than half of tumors harboring p53 mutations [67]. Eprenetapopt (Apr-246) is a clinical phase I compound that can restore mutant p53 to its normal wild-type conformation and exert anticancer effects [68]. In H1299 cells (a p53 mutated NSCLC cell line), TKT reduces the sensitivity of the cells to Apr-246 [69]. In general, TKT is involved in the chemoresistance of LC, which means that targeting TKT is expected to provide a new strategy for the treatment of LC.

4.4. TKT and head and neck tumors

4.4.1. Head and neck squamous cell carcinoma (HNSCC)

HNSCC, a high-grade tumor, has a poor 5-year survival rate and prognosis. Common HNSCCs include cancers of the thyroid, oral cavity, larynx, and pharynx [70–72]. Despite the high cure rate of HNSCC, its recurrence and metastasis greatly reduce the survival rate of patients. Studies have shown that nuclear factor erythroid 2-related factor 2 (Nrf2) promotes the development of HNSCC by regulating TKT, and the expression of Nrf2 is regulated by the upstream factor cellular-myelocytomatosis viral oncogene (c-myc) [73]. However, whether c-myc can regulate Nrf2 via TKT to promote cancer development requires further exploration.

Interestingly, another study showed that TKTL1 also promotes malignant proliferation of HNSCC cells by promoting glycolysis and the expression of HIF-1α, which, in turn, upregulates the expression of the glycolytic enzymes hexokinase 2, aldolase, fructose-bisphosphate C, and phosphoglycerate kinase 1 to further promote TKTL1-mediated proliferation of HNSCC cells [74]. This shows that TKT and TKTL1 mediate the development of HNSCC in different ways (Fig. 5).

4.4.2. Esophageal cancer

There are two subtypes of esophageal cancer; esophageal squamous cell carcinoma (ESCC) and adenocarcinoma, with nearly half a million newly diagnosed patients worldwide in 2012 and 400,200 deaths as a result [75]. The 5-year survival rate of esophageal cancer is less than 20%, which is caused by the inability to diagnose at an early stage, the high invasiveness of the tumor, and the lack of effective treatments [76].

TKT and its family member TKTL1 have been reported to be highly expressed in ESCC [77,78]. Multiple clinical studies suggest that high levels of TKT are positively correlated with poor patient survival, and TKT promotes the proliferation of cancer cells by mediating the EMT process [77]. In addition, TKTL1 expression has been strongly correlated with the grade, stage, and lymph node metastasis of ESCC but not with factors such as age and sex [78].

In addition to clinical evidence, different molecular mechanisms have been described for the TKTL1-mediated oncogenic effects in ESCC. Specifically, TKTL1 alters the cell cycle by regulating cyclin D1 and cyclin-dependent kinase 4 expression, thereby promoting ESCC cell invasion [78]. In addition, TKTL1 promotes the transfer of metastatic proteins (MMP2, MMP9, MMP10, and MMP13) and inhibits the expression of anti-metastatic proteins (MTSS1, TIMP2, and CTSK), thereby promoting ESCC invasion [79].

Accumulating evidence suggests that circRNAs play crucial roles in cancer [80]. Specifically, circDUSP16 is significantly upregulated in ESCC, and silencing circDUSP16 inhibits hypoxia-induced ESCC cell proliferation, invasion, and glycolysis by regulating TKTL1 expression via miR-497–5p [81]. Collectively, TKTL1 plays a crucial role in the regulation of ESCC malignant progression (Fig. 5).

4.4.3. Thyroid cancer

Thyroid cancer is the most common endocrine tumor and is a malignant tumor of the head and neck. Retinoic acid (RA) is used to treat thyroid cancer, acute promyelocytic leukemia, other head and neck cancers, LC, and skin tumors [82]. A study confirmed that RA inhibits the development of thyroid cancer by inhibiting the expression of TKT; however, the authors did not specifically describe the mechanism of TKT in thyroid cancer, which requires further exploration.

4.5. TKT and nervous system tumors

4.5.1. Glioma

Gliomas are the most common malignant intracranial tumor [83]. The poor prognosis of patients results from their extremely invasive ability and inability to undergo complete resection by surgery [84]. The current treatment of glioma mainly involves a combination of surgery and chemoradiotherapy [85]. The apoptosis regulator (tigar) protects glioma cells from ROS-induced cell death in a TKTL1-dependent manner [86].

Telomerase is a ribonucleoprotein that maintains telomere length. The maintenance of telomere length is required for the long-term survival of cells; therefore, telomerase levels are high in most malignancies [87]. Costunolide, a telomerase inhibitor in glioma cells, was reported to suppress glioma cell progression by suppressing TKT expression via regulation of the Nrf2-TERT loop [88]. In conclusion, TKTL1 and TKT are important regulatory factors for radiotherapy resistance and malignant progression of gliomas (Fig. 5).

4.6. TKT and urologic tumors

4.6.1. Prostate cancer

Sugiol, a diterpenoid, has anticancer effects in addition to its antioxidant and anti-inflammatory properties [89]. Jung et al. reported that in UD145 prostate cancer cells, the interaction of sugiol with TKT induces ROS production, thus, ERK activation, which results in decreased STAT3 activity and, consequently, tumor growth inhibition [14]. In conclusion, TKT plays an important role in the treatment of prostate cancer and has great potential for clinical applications.

5. Regulation of TKT by upstream signaling pathways

Here, we summarized the functions and mechanisms of TKT in different tumors. However, TKT is also regulated by multiple factors during the development of tumors, and these factors alter tumor chemoresistance by regulating the transcriptional activity of TKT. Next, we address the role of transcriptional regulation of TKT by different signaling molecules in the malignant features of tumors (Table 1).

5.1. HIF-1α

HIF-1α is an oxygen-sensitive transcriptional activator. An increasing number of studies have shown that high levels of HIF-1α are strongly correlated with tumor metastasis, poor patient prognosis, and chemoresistance [98–101]. Gemcitabine is a first-line drug for the clinical treatment of pancreatic cancer that inhibits DNA replication, thereby inhibiting tumor growth [102]. However, gemcitabine causes resistance in many patients. Thus, clarifying the reason why gemcitabine develops resistance might help improve the survival of patients with pancreatic cancer. It has been reported that increased pyrimidine synthesis resulting from the enhanced non-oxidative PPP is a major cause of gemcitabine resistance in pancreatic cancer. Specifically, in GEM-R cells (gemcitabine-resistant pancreatic cancer cell lines), HIF-1α controls pyrimidine synthesis by promoting transcription, leading to gemcitabine resistance in pancreatic cancer [90]. Similarly, HIF-1α regulates TKT transcription in imatinib-resistant cells and maintains the survival and proliferation of resistant cells [96].

5.2. Nrf2

As a transcription factor, Nrf2 is a primary regulator of cellular antioxidative stress and is associated with tumor progression, metastasis, and chemoresistance [103]. Currently, breakthrough progress has been made globally in the treatment of LC, and targeted therapy has achieved very good efficacy. For example, gefitinib has shown promising results in patients with NSCLC with EGFR mutations [104]. However, most patients develop resistance after approximately 1 year, which complicates the treatment of NSCLC [105]. A recent study showed that the combination of cryptotanshinone (CTS) and gefitinib enhances LC sensitivity to gefitinib. Mechanistically, CTS enhances the inhibitory effect of gefitinib on LC cells by inhibiting the transcription of TKT via Nrf2 [94]. Another study showed that in LC cell lines, such as A549, Nrf2 activates TKT transcription and promotes TKT expression [95]. In

addition, Nrf2 enhances the sensitivity of cholangiocarcinoma cells to chemotherapeutic agents, and this effect is mediated by TKT [91]. Interestingly, Nrf2 activates the transcription of TKT and promotes its expression, while BACH1 exhibits the opposite effect compared to Nrf2 in liver cancer [97]. Taken together, Nrf2, as a transcription factor, alters chemoresistance by regulating transcription in different cancers.

5.3. MicroRNA (miRNA)

miRNAs are involved in the post-transcriptional regulation of gene expression. Recent studies have shown that dysregulation of miRNAs contributes to the development of multiple cancers, which makes miRNAs novel therapeutic targets [106]. The biggest challenge in current cervical cancer treatment is resistance to chemotherapeutic agents. Yang et al. demonstrated that miR-497–5p promotes GSH production and reduces ROS levels by suppressing TKT expression, which, in turn, promotes the sensitivity of cervical cancer cells to cisplatin [93].

5.4. Steroid receptor coactivator 3 (SRC-3)

SRC-3, also known as amplified in breast cancer 1, is a member of the SRC family. In addition to regulating the transcriptional activity of nuclear receptors, SRC-3 regulates many other transcription factors. As an oncogene, SRC-3 plays an important role in cancer development [107]. A study showed that PFKFB4 could promote TKT transcription by activating SRC-3, which promotes breast cancer growth and metastasis [92].

5.5. TEAD

TEAD1 is a member of the TEAD transcription factor family, and several studies have demonstrated the important role of the TEAD family in development, cell proliferation, tumor malignant characteristics, and chemoresistance [108]. Chip-PCR and luciferase reporter assays have indicated that TEAD1 directly regulates TKT transcription in pancreatic cancer [53].

6. Clinical significance of TKT: a potential target and biomarker for cancer therapy

6.1. TKT as a potential prognostic biomarker

The expression levels of TKT and TKTL1 in tumors are closely related to many clinical indicators. According to clinical classification criteria, low-grade squamous intraepithelial lesions (LSILs) belong to the precancerous category of cervical cancer. Recent clinical data suggest that high levels of TKTL1 are found in the tissues of patients with LSIL compared with tissues of healthy individuals [109], and the sensitivity and specificity are similar to those of biomarkers used to diagnose LSIL clinically [109]. This finding implies that TKTL1 may be a new biomarker for the prediction and diagnosis of LSIL. In addition, the expression levels of the TKT family are associated with several indicators (Table 2), such as patient prognosis and survival.

6.2. TKT as a potential diagnostic biomarker

The lack of effective methods for the early diagnosis of cancer leads to the poor prognosis and short survival of most patients with malignant tumors. In addition, early-stage cancer is easier to treat and has a better prognosis; therefore, the diagnosis of early-stage cancer is the key to cancer treatment. Accumulating evidence suggests that EDIM is a new method for the early detection of malignancies [140,141].

EDIM technology determines whether carcinogenesis occurs by detecting two biomarkers; Apo10 and TKTL1, in blood macrophages. As part of the immune system, activated monocytes (macrophages) reach every region of the body to engulf harmful cells (cancer cells) and store tumor proteins inside cells. After macrophages return to the blood, the use of specific antibodies that can detect macrophages with tumor proteins aids in the early diagnosis of tumors [141,142]. EDIM-TKTL1 positivity is reported to be nearly 100% in patients with cholangiocellular carcinoma, pancreatic cancer, and CRC, compared with 33.7% and 63.6% on average for the traditional tumor markers CEA and CA19–9, and the positive rate of EDIM-TKTL1 in healthy and inflammatory patients is only 7.7% [117]. EDIM-TKTL1 positivity was 93% in 92 patients with SOCCs before surgery, and this value decreased significantly in patients after surgery. Therefore, the surgical clearance effect was evaluated according to this indicator [127]. In addition, EDIM-TKTL1 has been used for breast and prostate cancer detection [140]. This blood test technique improves the detection rate of early stage tumors with high specificity and sensitivity and helps to evaluate the effect of surgery and patient prognosis [142].

6.3. TKT inhibitor: Effective cancer treatment drugs

ThDP is the active form of thiamine and, as a cofactor of TKT, is required for TKT activation [143]. Oxythiamine (OT) inhibits the transition of thiamine to its active form and is one of the most commonly used TKT inhibitors [143]. Accumulating evidence shows that a reduction in oxidative stress protects cancer cells from the damage caused by radiotherapy and chemotherapy. In addition to inhibiting tumor proliferation [25,144,145], OT promotes the sensitivity of tumor cells to chemotherapeutic agents. As mentioned earlier, TKT is responsible for nucleic acid synthesis. However, when cells experience high oxidative stress, metabolites from the non-oxidative PPP re-enter glycolysis to replenish the oxidative PPP for the synthesis of NAPDH. NADPH counteracts ROS, making cancer cells more prone to oxidative stress. Therefore, combination treatment with OT and chemotherapeutic agents may further increase the sensitivity of tumors to antitumor therapies based on oxidative stress or apoptosis (Fig. 6). Many studies have suggested that OT, as a TKT inhibitor, increases the effects of chemotherapeutic agents through these two modalities.

Sorafenib, which increases intracellular ROS levels to inhibit tumor growth, is a first-line drug for the treatment of HCC and is currently used clinically. The combination of sorafenib and OT can promote the level of ROS induced by sorafenib to further inhibit cell proliferation and restore cell sensitivity to sorafenib [97]. Imatinib (Gleevec, STI571) is effective for treating chronic myeloid leukemia (CML). The imatinib and OT combination restores CML sensitivity to imatinib and further inhibits tumor growth [96]. In addition, cisplatin, a chemotherapeutic agent that inhibits cell proliferation by damaging DNA, has a killing effect on a variety of tumors and is currently used clinically. Recent evidence suggests that TKTL1 inhibition further promotes cisplatin-induced DNA damage by regulating R5P levels, which, in turn, further inhibits cell proliferation and restores cell sensitivity to cisplatin [134]. Gemcitabine, which inhibits DNA replication and thereby tumor growth, is a widely used chemotherapeutic agent for pancreatic cancer. Shukla et al. demonstrated that gemcitabine resistance is associated with increased pyrimidine synthesis regulated by TKT; thus, TKT levels are strongly correlated with gemcitabine sensitivity [90]. Docetaxel and doxorubicin are commonly used clinically to treat TNBC; however, most patients develop resistance after a period of use. Recent emerging evidence confirms that the combination of OT with docetaxel and/or doxorubicin increases the sensitivity of breast cancer cells to these two chemotherapeutic agents, leading to further inhibition of proliferation [58]. In addition, an in vitro study showed that inhibition of TKTL1 promoted the response of ovarian cancer cells to the chemotherapeutic drug paclitaxel [122]. Because chemotherapy drugs have difficulty passing through the blood-brain barrier, nervous system tumors are mostly treated with radiotherapy. Clinically, however, some patients develop radiotherapy resistance after several courses of treatment. To solve this problem, Heller et al. found that inhibition of TKTL1 promoted glioma sensitivity to radiotherapy [146].

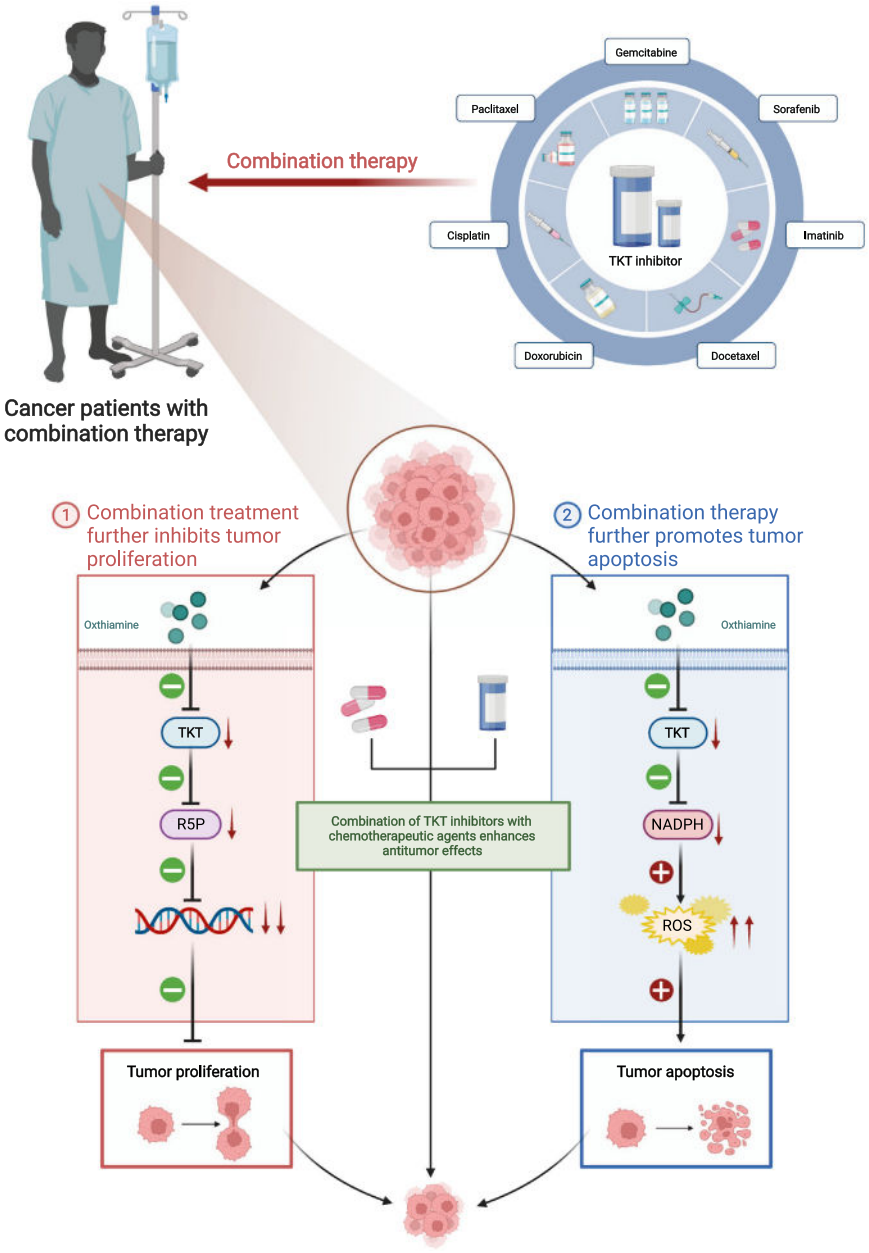

Fig. 6. Combination of TKT inhibitors with chemotherapeutic agents enhances chemotherapeutic efficacy. Mechanistically, TKT inhibitors inhibit the generation of R5P, resulting in attenuated DNA synthesis, which potentiates the effects of DNA-damaging drugs. TKT inhibitors reduce the level of GSH by inhibiting the production of NADPH, and GSH reduction increases the intracellular ROS level, which enhances the effect of some chemotherapeutic agents.

Taken together, OT restored the sensitivity of cancer cells to chemotherapy by inhibiting DNA synthesis and increasing ROS levels. This provides a solution for clinical chemoresistance in the future, and OT could be used as an adjuvant drug for chemotherapy, thereby increasing the effectiveness of chemotherapy strategies.

6.4. The double-edged sword behavior of TKT

Given that TKT and TKTL1 are highly expressed in a variety of tumors and promote malignant progression, it is possible to target TKT in cancer treatment. It is important to note the dual nature of TKT, while it's hyperactivation is a major contributor to the malignant progression of tumors, it is undeniable that TKT is also indispensable during the normal growth and development of the body.

Studies have confirmed that a lack of TKT destroys normal intestinal barrier function and induces enteritis. Moreover, TKT is an important factor in the prevention of hyperglycemia-induced vascular cell dysfunction. The reduction of TKT activity promotes the occurrence of diabetic complications [147], and the prevention of diabetic retinopathy and cardiomyopathy by activating TKT could also accelerate the healing of diabetic limbs and alleviate the symptoms of diabetic nephropathy [24]. More importantly, TKT inhibitors combined with chemotherapeutic drugs can produce side effects. For example, TKT inhibitors combined with lovastatin offset the antitumor effects of each other [148]. This means that more exhaustive characterization is required before clinical application.

7. Conclusions and future perspectives

TKT is responsible for ribose production and the regulation of NADPH production, which is essential for cell and organismal growth and development. However, TKT is hyperactivated during the

progression of most tumors. Sustained activation of TKT provides cancer cells with a favorable environment for survival and proliferation in multiple ways, and with the inherent ability to resist traditional cancer therapies.

In addition to its close association with tumor development, TKT plays an important role in other diseases. For example, it was recently reported that TKT overexpression exacerbates cardiac dysfunction after myocardial infarction [149]. SARS-CoV-2-infected cells showed significantly increased TKT levels, and replication of SARS-CoV-2 could be inhibited by the TKT inhibitor benfooxythiamine (BOT); thus, BOT could exert an antiviral effect to improve COVID-19 treatment efficacy [150]. Targeting TKT is a promising therapeutic approach for both tumors and other diseases.

Depending on the role of TKT in tumors and other diseases, targeting TKT inhibits the malignant progression of tumors and enhances the antitumor effect of certain chemotherapeutic drugs; however, in some cases, it is harmful to the body. Therefore, when targeting TKT, which cancers and specific tumor stages TKT tends to show persistent activation for should first be determined. When treating patients with targeted TKT, clinicians should identify those who are more likely to benefit from TKT-targeted therapies, and those who are likely to have poor outcomes with targeted TKT therapies. In particular, diabetic patients with cancer should be treated with great caution when it comes to TKT-targeted therapy. Additionally, inhibition of TKT improves chemotherapeutic efficacy, and TKT levels must be maintained in normal cells during treatment. Therefore, establishing personalized treatment regimens is necessary when targeting TKT for cancer treatment, which is a major challenge for future clinical applications. EDIM blood tests currently allow early diagnosis of some cancers; however, whether EDIM technology can be applied to pan-cancer detection remains to be confirmed.

Moreover, we summarized the functions and mechanisms of TKT in different tumors to provide strategies for future studies on cancer treatment and resistance to chemotherapy. Overall, TKT has the potential to be a new biomarker for predicting tumorigenesis and outcomes. There is still a long way to go before targeted TKT can be applied clinically, but hopefully, with the continuous deepening of research, TKT will have more promising developments in the future treatment of cancer and other diseases.

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This article does not contain any studies with animals.

CRediT authorship contribution statement

Shiming Hao: Writing – original draft. **Qingfei Meng:** Writing – review & editing. **Huihui Sun:** Writing – review & editing. **Yunkuo Li:** Writing – review & editing. **Honglan Zhou:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. **Zhixiang Xu:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing. **Yishu Wang:** Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Conflict of interest statement

All authors have declared that they have not received any funds or other support from any organization that may be interested in the submitted works, and that there are no other relationships or activities that may affect the submitted works.

Data Availability

Data will be made available on request.

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