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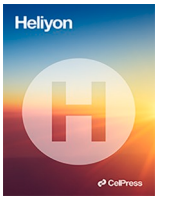

Review article

# The multifaceted potential of *TPT1* as biomarker and therapeutic target

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ABSTRACT

Tumor Protein Translationally-Controlled 1 (*TPT1*) is a highly conserved gene found across eukaryotic species. The protein encoded by *TPT1* is ubiquitously expressed both intracellularly and extracellularly across various tissues, and its levels are influenced by various external factors. TPT1 interacts with several key proteins, including p53, MCL1, and immunoglobulins, highlighting its crucial role in cellular processes. The dysregulation of TPT1 expression has been documented in a wide range of diseases, indicating its potential as a valuable biomarker. Additionally, targeting TPT1 presents a promising approach for treating and preventing various conditions. This review will assess the potential of TPT1 as a biomarker and evaluate the effectiveness of current strategies designed to inhibit TPT1 in disease contexts.

## 1. Introduction

TPT1, also known as translation-controlled tumor protein (TCTP), histamine-releasing factor (HRF), p23, p02, and fortilin. The secretion of TPT1 occurs in various cell types, including macrophages, dendritic cells, PBMCs, and different cancer cells [1]. TPT1 is essential for numerous biological processes, including cell development, proliferation, and differentiation, cytoskeletal regulation, anti-apoptosis, immune defense, and tumor suppression [2].

Biomarkers, defined as measurable indicators, provide insights into normal or pathological processes. The optimal utilisation of biomarkers is to facilitate the diagnosis of disease, the prediction of prognosis, and the assessment of therapeutic efficacy. Recent evidence underscores TPT1's involvement in diverse diseases, including various types of cancers, allergies, immune disorders, and hypertension [2–4]. The diverse manifestation of TPT1 in various pathological states highlights its potential as a diagnostic and prognostic biomarker [5–7]. Research involving TPT1 inhibitors or *TPT1* knockout/knockdown models provides insights into its therapeutic potential [8,9]. Furthermore, the identification of TPT1 as a pathogenic factor for Plasmodium and Madurai establishes it as a promising vaccine development target against malaria and mycomas [10,11]. This article will examine the role of TPT1 in the aetiology of different diseases and investigate the impacts of related drugs or inhibitors as potential treatments.

## 2. Structure and biological function of TPT1

The *TPT1* gene, located on chromosome 13, encompasses 3819 nucleotides and is constituted by 6 exons and 5 introns [12]. It is

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transcribed into two distinct mRNA molecules, the biological significance of which is yet to be elucidated [13]. The translation of *TPT1* yields the TPT1 protein, which has a molecular weight of 20–25 kDa. TPT1 is structured with 3 α-helices (H1, H2, H3) and 9 β-sheets [13]. TPT1 is present in the nucleus, cytoplasm, and extracellular spaces [14,15], where it plays a role in a number of cellular processes, including cell development, proliferation, differentiation, cytoskeleton regulation, anti-apoptosis, and immune defense [4,16].

Within cells, TPT1 interacts with Na-K ATPase, calcium ions, tubulin, and anti-apoptotic proteins. TPT1 inhibits Na-K ATPase activity in the cytoplasmic membrane in a dose-dependent manner [17]. This inhibitory effect is likely to be mediated by a homology region between the C-terminus of TPT1 and the Na,K-ATPase α subunit CD3 [18]. Such inhibition influences the enzyme's functions in signal transduction and ion transport [19], thereby contributing to the pathology of pulmonary hypertension and atherosclerosis. TPT1, as a calcium-binding protein, modulates intracellular calcium levels, affecting signal transduction and impacting cell migration, proliferation, and differentiation [20]. The potential for calcium binding has been identified in two regions of TPT1: the C-terminal part of the loop La3b8/chain b9 and the N-terminal region of chain b8 [21,22]. Additionally, TPT1 stabilizes microtubules by binding to tubulin, in a manner analogous to that observed with the microtubule-associated protein MAP-1B. However, the overexpression of TPT1 can result in impaired cell growth and morphological alterations [23]. The knockout of *TPT1* in mouse embryos significantly reduces cell number and organ size, highlighting its critical role in cell growth and development [24]. TPT1 also interacts with the anti-apoptotic protein Mcl-1, conferring anti-apoptotic effects. However, the precise chaperoning functions of these proteins remain a topic of debate [25,26]. Additionally, TPT1 regulates cell death in response to oxidative stress by promoting DNA repair or inducing autophagy [27]. Emerging research positions TPT1 as a key regulator of cell invasion, essential for development, immune responses, and cancer progression [28]. Consequently, TPT1's involvement in these biological functions supports its potential as a biomarker and therapeutic target in cancer research.

TPT1 is secreted via the exosome pathway under the guidance of TSAP6, allowing it to exert its extracellular effects [1]. Remarkably, TPT1 frequently functions as a dimer, with dimerization mediated by disulfide bonds between Cys 172 of two TPT1 molecules [29,30]. Additionally, hemin binding to TPT1 may induce structural changes that facilitate dimerization [31]. TPT1 also influences the release of local signaling molecules by immune cells, notably: 1) enhancing the secretion of IL-1 and IL-8 by B cells [32]; 2) stimulating basophils to release IL-4, IL-13, and histamine [33]; 3) inducing the emission of IL-8, GM-CSF, and histamine from bronchial epithelial cells [34]; 4) promoting IL-8 release from GM-CSF-sensitized eosinophils [35]; 5) suppressing the release of IL-2

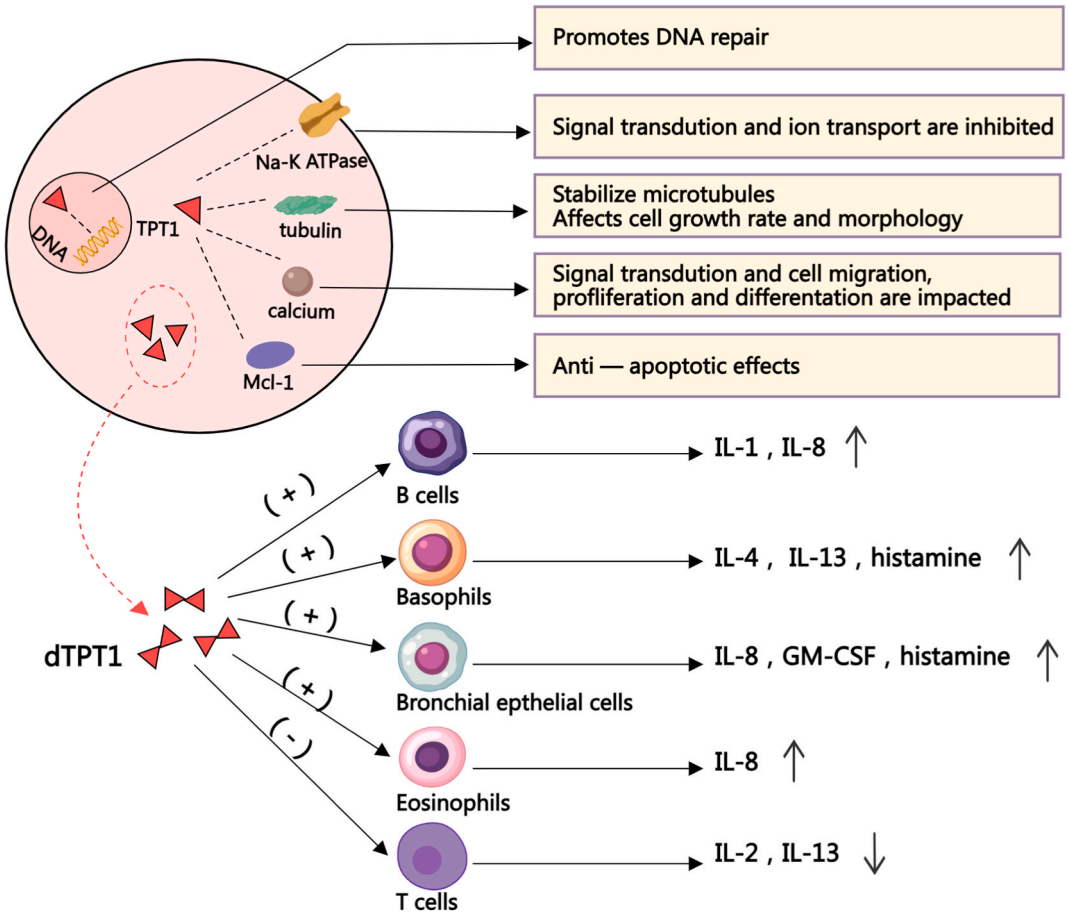


**Fig. 1.** Biological functions of TPT1 inside and outside cells.

and IL-13 by T cells [36,37]. Additionally, Hyung Sik Kang et al. discovered that TPT1 can enhanceB cell activation and function, exhibiting a potent synergistic effect with IL-2, IL-4, and IL-5 [38]. These elements are pivotal in determiningthe body's immune status. The findings underscore the potential of TPT1 as a biomarker and therapeutic target for inflammation-related diseases. And we summarize the effects of TPT1 inside and outside the cell in Fig. 1.

## 3. The potential of TPT1 as a biomarker

*TPT1* is a gene with differential expression across a range of diseases, making it a potential diagnostic and prognostic biomarker. As a biomarker, TPT1 may assist clinicians in predicting disease progression and evaluating the efficacy of therapeutic interventions.The cDNA sequence of human *TPT1* was initially identified in breast cancer [39], and subsequent research has demonstrated significant increases in *TPT1* mRNA in early stages of rat liver cancer [40]. Tim Hon Man Chan and colleagues identified TPT1 as an independent prognostic marker in hepatocellular carcinoma (HCC). They verified that CHD1L, an HCC-specific oncogene, initiates *TPT1* transcription by binding to its promoter region. This activation accelerates mitosis, leading to aneuploid cell formation and promoting HCC development [41,42]. Additional bioinformatics analysis suggests that TPT1 could predict the prognosis of liver cancer patients and the occurrence of portal vein tumor thrombus [43]. Ongoing research has revealed that *TPT1* overexpression is present in a number of different tumors, including glioma, lung cancer, colorectal cancer, and ovarian cancer [2,4,44]. However, *TPT1* upregulation has not been noted in gastric cancer, cervical cancer, or esophageal cancer [45,46]. Despite its limited specificity in tumor diagnosis, TPT1 remains a valuable prognostic marker for cancer.

Elevated serum TPT1-reactive IgE has been observed in immune-related diseases such as asthma [47], food allergy [48], atopic dermatitis [49] and chronic idiopathic urticaria [50]. Research by Kazumi Kasakura et al. found that human bronchial epithelial cells stimulated with house dust mites significantly increased TPT1 secretion. Furthermore, administration of recombinant TPT1 to house dust mite-sensitized mice resulted in pronounced airway inflammation, suggesting TPT1's role as a novel alarm protein in allergic airway inflammation [51]. Recent studies also reveal that rhinovirus (RV) induces TPT1 secretion from bronchial epithelial cells both

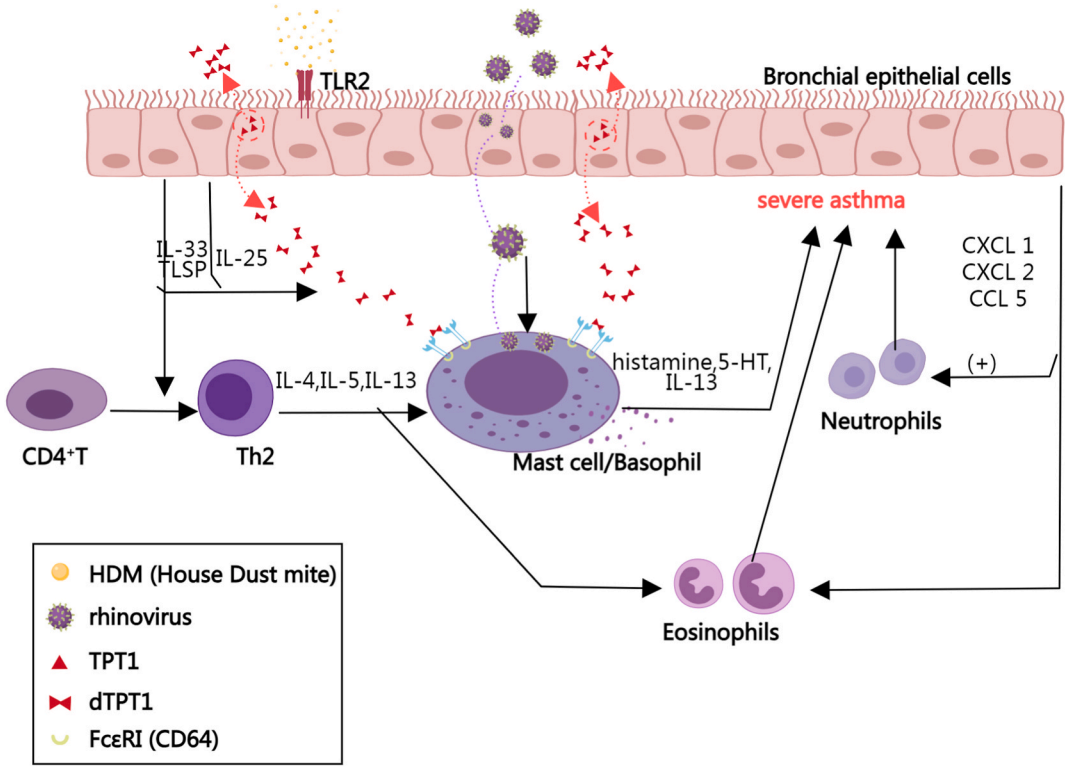


**Fig. 2.** TPT1-mediated severe asthma and rhinovirus (RV)-related asthma exacerbation model. House dust mites (HDM) are recognized by Toll-like receptor 2 (TLR2), triggering the secretion of TPT1. Bronchial epithelium-derived cytokines including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), can promote HDM-induced TPT1 secretion [53]. IL-33 and TSLP further drive the differentiation of $CD4^+$ cells into Th2. Th2-related cytokines like IL-5 contribute to increased bone marrow-derived eosinophils, while IL-4 and IL-13 facilitate eosinophil migration into tissues and promote IgE class switching [54]. RV infection recruits mast cells to the bronchial epithelium, where RV can replicate and activate these mast cells [55]. dTPT1 mediates mast cell activation, releasing histamine, 5-HT, and IL-13 through the high-affinity IgE receptor (FcεRI) [56,57]. Additionally, HDM and RV together increase chemokine secretion (CXCL1, CXCL2, and CCL5) from bronchial epithelial cells [58]. CCL5 contributes to both neutrophilic inflammation and sputum eosinophilia [59]. The interplay of these factors leads to the development of severe asthma and acute asthma exacerbations.

in vivo and in vitro, exacerbating asthma. RV achieves this effect by recruiting and activating mast cells. The combined action of house dust mites (HDM) and RV leads to chemokine secretion, resulting in neutrophilic inflammation and severe asthma exacerbation [52] (Fig. 2).

There is evidence to suggest that TPT1 plays a role in the progression of infection-related diseases. In visceral leishmaniasis caused by Leishmania donovani, TPT1 represents a promising diagnostic marker in serological tests [5]. Moreover, studies indicate that *TPT1* is upregulated in sepsis-induced cardiomyopathy (SIC) as the disease progresses, indicating its potential involvement in this condition's advancement [60]. Additionally, TPT1 is involved in the development of pulmonary arterial hypertension by promoting the proliferation and anti-apoptosis of pulmonary artery smooth muscle cells [6]. These findings underscore the potential role of TPT1 in the advancement and complications of infection-related diseases. We summarize the relevant results of detecting TPT1 in Table 1.

## 4. Potential of TPT1 as a therapeutic target in disease

### 4.1. *TPT1* in cancers

TPT1 is crucial in tumor progression via multiple pathways, including anti-apoptotic activity [61,62], stimulation of mitosis [63], modulation of tumor signal transduction [64], fostering of cell growth and proliferation [65], enhancement of tumor invasion and metastasis [66,67], and contribution to the development of resistance to anti-tumor drugs [65]. For example, *TPT1* overexpression may suppress the tumor suppressor gene p53, thereby facilitating tumorigenesis [68]. TPT1 promotes the degradation of p53 via the ubiquitination pathway mediated by the E3 ubiquitin ligase MDM2, disrupting p53's role in cell cycle regulation and apoptosis [69]. The inhibition of p53 by TPT1 reduces apoptosis, promoting tumor cell survival and proliferation [70]. Furthermore, TPT1 has been demonstrated to inhibit the function of the pro-apoptotic protein Bax, thereby enhancing the survival ability of cancer cells [71]. TPT1 upregulates the RhoA signaling pathway, reorganizing the cytoskeleton and enhancing tumor cell migration and invasion [46]. Moreover, TPT1 has been demonstrated to interact with the anti-apoptotic protein MCL1, thereby preventing its ubiquitination-mediated degradation and consequently enhancing anti-apoptotic signals [26]. In cancer cells, the TPT1-MCL1 interaction increases resistance to chemotherapeutic drugs that induce apoptosis [72].Additionally, studies have demonstrated that TPT1 serves as an immune resistance factor in anti-PD-L1 therapy, activating the EGFR-AKT-MCL-1/CXCL10 pathway through phosphorylation-dependent interaction with Na-K ATPase, leading to immune-refractory tumors [73]. These insights underscore the complex role of TPT1 in cancer development and underscore its importance for therapeutic strategies.

Several knockout experiments have explored TPT1 as an anti-cancer target. In colorectal cancer cells, *TPT1* knockout has demonstrated reduced cell proliferation, migration, and invasion [45,74]. Baylot et al. found that *TPT1* is expressed at elevated levels in castration-resistant prostate cancer (CRPC) and identified it as a client protein of heat shock protein 27 (HSP27). Their study showed that TPT1-ASO treatment can inhibit tumor growth in CRPC, enhance the effect of docetaxel chemotherapy, and delay cancer progression [9]. In leukemia, a peptide aptamer targeting TPT1 has shown potential for selectively killing tumor cells, though the anticancer efficacy of this anti-TPT1 peptide requires further investigation [75]. However, because *TPT1* is crucial for the growth and development of animals and cells, it remains uncertain whether gene knockout or mRNA inhibition is a reliable method for studying its function.

Research has revealed that certain drugs can suppress tumor growth by either reducing the expression of *TPT1* or by binding to TPT1, thereby disrupting its interaction with other chaperone proteins [76]. TPT1, also known as histamine-releasing factor, can be targeted byantihistamines like buclizine and levomepromazine, which inhibit cancer cell growth through binding to TPT1 and inducing cell differentiation [77]. Antidepressants have also demonstrated efficacy in tumor treatment. Robert Amson et al. confirmed a mutually inhibitory feedback pathway between TPT1 and p53 [69]. The binding of drugs such as sertraline and thioridazine to TPT1 results in a reduction in its effect on p53 ubiquitination, which in turn leads to the interference of the mTOR pathway. This interaction has the effect of suppressing suppresses the positive feedback regulation of *TPT1* translation and inhibiting *TPT1* transcription, thereby

**Table 1**
Expression of *TPT1* in different diseases.

| Disease | Detection Type | Findings | References |
|---|---|---|---|
| Breast cancer, Glioma, lung cancer, colorectal cancer, ovarian cancer | mRNA expression, protein | ↑*TPT1* mRNA,TPT1 | [2,4,39,44] |
| Liver cancer | mRNA expression | Prognosis biomarker, ↑ portal vein tumor thrombus | [40,43] |
| Hepatocellular carcinoma (HCC) | mRNA expression, protein | Poor prognosis indicator | [41,42] |
| Gastric cancer, cervical cancer, esophageal cancer | mRNA expression, protein | No ↑ TPT1 | [45,46] |
| Asthma, food allergy, atopic dermatitis, chronic idiopathic urticaria | Serum TPT1-reactive IgE | ↑ TPT1-reactive IgE | [47–50] |
| House dust mite-induced asthma | Serum TPT1, tissue TPT1 | ↑ TPT1, airway inflammation | [51] |
| Rhinovirus-induced asthma exacerbation | Serum TPT1, tissue TPT1 | ↑ TPT1 secretion | [52] |
| Visceral leishmaniasis | Serology | Diagnostic marker | [5] |
| Sepsis-induced cardiomyopathy | Tissue mRNA expression | ↑*TPT1* mRNA | [60] |
| Pulmonary arterial hypertension | Tissue mRNA expression, protein | ↑ Proliferation, anti-apoptosis | [6] |

↑, increased.

hindering tumor development [78,79]. Arsenic trioxide (ATO) has been demonstrated to inhibit *TPT1* expression by inducing oxidative stress and apoptosis, thereby playing a role in the treatment of acute promyelocytic leukemia (APL) [80,81]. Recently, artemisinin has received increased attention in the treatment of tumors, particularly in combination therapy for drug-resistant cancers. In trastuzumab-resistant breast tumors, artemisinin targets phosphorylated TPT1, reducing cell proliferation and inducing apoptosis [82]. Furthermore, artemisinin is promising in obstructing TPT1 phosphorylation and bolstering T cell-mediated immunotherapy in immune-refractory tumors [73]. These insights underscore the potential of targeting *TPT1*/TPT1 and leveraging drugs such as antihistamines, antidepressants, and artemisinin as viable strategies for combating tumor progression, including drug-resistant and immune-refractory tumors. However, we should also note that treatment targeting *TPT1*/TPT1 may bring some potential side effects. For example, sertraline may also cause cognitive impairment, gastrointestinal disorders, nutritional and metabolic diseases [83]. When artemisinin is used for TPT1-targeted therapy, it may cause QT interval prolongation, thereby increasing cardiovascular risk and may disrupt the function of normal cells such as platelets [84]. We summarize the role of TPT1 and related inhibitors in different cancers in Table 2.

### 4.2. *TPT1 in allergic diseases*

TPT1 possesses histamine-releasing activity, playing a crucial role in various allergic diseases, including asthma, food allergy, atopic dermatitis, and chronic idiopathic urticaria. Elevated levels of TPT1 have been identified in skin blisters and bronchoalveolar lavage fluid (BALF) [86]. TPT1 facilitates the activation of basophils and mast cells via the high-affinity IgE receptor (FcεRI), triggering the release of inflammatory mediators such as histamine, 5-HT, IL-4, IL-13, and IL-8 [56,57]. These factors ultimately promote type 2 inflammation, which in turn gives rise to the typical symptoms of an allergic reaction, including pruritus, erythema, and wheezing [87]. Individuals exhibiting this allergy type possess a specific IgE variant, known as IgE+. The responsiveness of basophils to TPT1 is contingent upon the presence of IgE + [88]. Nevertheless, the factors contributing to the heterogeneity of IgE remain to be fully elucidated, potentially due to variations in IgE structure, IgE glycosylation, or antigen-antibody interactions [89,90]. Further research is imperative to decipher the mechanisms underlying IgE heterogeneity in the context of allergic diseases.

In airway inflammation, oxidative stress induces bronchial epithelial cells to release TPT1. Human recombinant TPT1 (hrTPT1) stimulates these cells to secrete IL-8 and granulocyte/macrophage colony-stimulating factor (GM-CSF), indicating TPT1's role in regulating a complex cytokine network involved in airway inflammation [47]. Further research on related mechanisms and inhibitors has identified the activation of the NF-κB pathway, ERK, JNK, and p38 MAPK in BEAS-2B cells stimulated by dTPT1. Activation of the NF-κB pathway leads to the upregulation of IL-8 transcription, thereby promoting inflammation [91]. Other studies have demonstrated that lipopolysaccharide (LPS) induces the production of dTPT1 in mast cells, which acts on airway epithelial cells in a paracrine manner, stimulating them to secrete pro-inflammatory factors and contributing to the development of severe asthma [1]. Inhibitors such as Dehydrocostus lactone (DCL) and cardamonin have been identified as potential antagonists of TPT1. In vitro, they inhibit the secretion of IL-8 by BEAS-2B cells induced by dTPT1 and reduce the production of inflammatory factors in bronchoalveolar lavage fluid (BALF) in an ovalbumin (OVA)-sensitized mouse model. Additionally, they have shown a reduction in OVA-specific IgE secretion and inhibition of NF-κB activation [92,93]. DTPT1-binding peptide 2 (dTBP2) has also been found to block the inflammatory network mediated by dTPT1, resulting in reduced immune cell infiltration. The administration of dBP2 has been demonstrated to result in a reduction in IκB degradation, a decrease in the secretion of IL-8, and a notable reduction in the severity of cutaneous allergic reactions [1,49]. Pegylated dTPT1-binding peptide 2 exhibits a stronger inhibitory effect than dTBP2 [94]. The deposition of dTPT1 has been observed in the lesional skin of patients with atopic dermatitis (AD), and its cytokine-like effects promote the development of AD. In a clinical trial involving paediatric patients with severe atopic dermatitis, short-term treatment with thymopentin was associated with reduced TPT1 production and improved clinical efficacy [95]. TPT1 also increases eosinophil activation, exacerbating chronic idiopathic urticaria (CIU) [96]. In the context of food allergy, TPT1 dimers and antigens amplify the intestinal inflammatory response by activating mast cells through cross-linking of IgE. The binding sites of dTPT1 and IgE are located at N19 and H378 [97]. GST-tagged N-terminal 19 amino acids (GST-N19) and GST-H3 inhibit intestinal inflammation by binding to IgE instead of dTPT1 [48,98].

TPT1 is expressed in parasites and triggers histamine release from basophils and mast cells during allergic inflammation caused by schistosomiasis and scabies, resulting in Th2 immune responses [99,100]. This indicates that TPT1 from diverse biological sources may induce analogous effects in humans. However, further investigation is required to elucidate the precise mechanisms involved.

**Table 2**
TPT1 in different cancers.

| cancers | The role of TPT1 | inhibitors | references |
|---|---|---|---|
| breast cancer | Inhibits oncogene p53 and increases cancer cell proliferation | artemisinin | [69,82] |
| colorectal cancer | Increased proliferation, migration and invasive activity of cancer cells | rapamycin | [45,74,78] |
| leukemia | Increased resistance of leukemia cells to chemotherapeutic drugs | Peptide aptamers targeting TPT1、Arsenic Trioxide | [8,75,76,85] |
| pancreatic cancer | Promote the growth and migration of cancer cells | miR-216 a-5 p | [79] |
| prostate cancer | Increased tumor growth, resistance to chemotherapy drugs | TPT1 antisense oligonucleotide (ASO) | [9] |
| cervical cancer | PI 3-K/Akt/mTORC 1 signaling pathway upregulates *TPT1* | mTOR kinase inhibitor | [78] |
| immune-refractory tumors | Activation of the EGFR-AKT-MCL-1/CXCL 10 pathway | artemisinin | [73] |

### 4.3. TPT1 in circulatory diseases

TPT1 has been demonstrated to disrupt the $Na+/Ca^{2+}$ exchange process by inhibiting $Na^{+}$-$K^{+}$ ATPase, which subsequently affects the circulatory system. This inhibition affects the contraction of vascular smooth muscle and the maintenance of cellular ion homeostasis [101,102]. Maeng et al. found that transgenic mice overexpressing TPT1 had an exaggerated contractile response in the aorta. Further cell experiments revealed that TPT1 upregulates the RhoA pathway, involved in cardiovascular diseases, particularly hypertension [103]. Activation of the RhoA-ROK pathway leads to increased phosphorylation of myosin phosphatase target protein (MYPT-1) and myosin light chain (MLC), disrupting the vasoconstriction signaling pathway and contributing to hypertension. Additionally, these transgenic mice showed increased sensitivity to vasoconstrictors due to elevated Ca2+ levels in vascular smooth muscle cells at rest [104]. TPT1 contributes to pulmonary hypertension by being secreted through TSAP 6-mediated exosomes and transferring to pulmonary artery smooth muscle cells. In this context, it inhibits the pro-apoptotic protein Bax and stabilizes the anti-apoptotic protein Mcl-1 in mitochondria, thereby promoting smooth muscle cell proliferation and resistance to apoptosis. This ultimately leads to pulmonary vascular remodeling and pulmonary hypertension [6]. Therefore, TPT1 represents a potential therapeutic target for hypertension and vasoconstrictor dysfunction.

Apolipoprotein E (apoE) is a ligand involved in scavenging chylomicron residue receptors and very low-density lipoprotein. Spontaneous atherosclerosis (AS) mouse models were established by APO-E knockout, and subsequent studies revealed that TPT1 overexpression exacerbates atherosclerotic lesions in apoE knockout mice [105,106]. These results indicate that TPT1 accelerates the development of atherosclerotic lesions induced by high-fat diets. Interestingly, these mice exhibited normal lipid metabolism and did not develop atherosclerosis, indicating that TPT1 does not influence atherosclerosis through lipid metabolism [105]. Further studies have shown that TPT1 overexpression promotes atherosclerotic plaque formation by inducing hypertension or reducing macrophage apoptosis [107]. Macrophages play a critical role in atherosclerosis: M1 macrophages contribute to cholesterol accumulation and unstable plaque formation through pro-inflammatory effects, while M2 macrophages aid in tissue repair, remodeling, and plaque stabilization [108,109].

### 4.4. TPT1 in other diseases

TPT1 has also been found to play a significant role in the pathogenesis of diabetes and psoriasis. In type 1 diabetes, the expression of *TPT1* is increased and may be related to the development of nephropathy [110]. Studies indicate that TPT1 has both beneficial and detrimental effects in diabetes. On one hand, TPT1 is overexpressed in diabetic wounds, promoting cell growth and facilitating wound healing. On the other hand, it may be a risk factor for diabetes-related complications such as dementia, kidney disease, and autoimmune diabetes [111]. However, it remains unclear whether inhibiting TPT1 would be beneficial for individuals with diabetes.

Psoriasis is a chronic skin inflammation caused by immune system dysfunction, resulting in systemic inflammation affecting

**Table 3**
TPT1 in different diseases (Non-tumor).

| Diseases | The role of TPT1 | Inhibitors | references |
|---|---|---|---|
| Asthma | TPT1→NF-κB,ERK, JNK and p38 MAPK pathways↑→IL-33,TLSP,IL-4 and IL-13 etc.↑; dTPT1 binds to IgEs→CD64-mediated release of histamine from macrophages/mast cells | Meclizine; Dehydrocostus lactone; Cardamonin; N19 peptide; H3 peptide | [56,91–93,97,113,114] |
| Food allergy | dTPT1 activates mast cells→Inflammation of the intestines↑ | GST-N19; GST-H3 | [48,97] |
| Atopic dermatitis (AD) | dTPT1 deposites on the diseased skin; Exerts cytokine-like activity | dTBP2; Thymus pentapeptide | [95,115] |
| Chronic idiopathic urticaria (CIU) | TPT1→Basophil activation and mast cell degranulation↑ | N/A | [96] |
| Allergic inflammation associated with schistosomiasis/Scale mites | Parasite TPT1→Basophil/mast cells release histamine↑, Th2 response↑ | N/A | [99,100] |
| Pulmonary arterial hypertension (PAH) | BOECs secretes TPT1→Pulmonary artery smooth muscle cell proliferation and anti-apoptosis↑ | N/A | [6] |
| Atherosclerosis (AS) | TPT1→Development of AS caused by a high-fat diet↑ | N/A | [105] |
| Systemic hypertension | TPT1→RhoA pathway↑→Vasoconstriction↑ | N/A | [116] |
| Diabetes (DM) | Expression of TPT1 in DM wounds→Cell division or growth↑; TPT1→Development of DM-related dementia, nephropathy, and autoimmune DM↑ | N/A | [110,111] |
| Psoriasis | dTPT1→Treg↓and M1 macrophages↑→Disruption of immune balance | dTBP2 | [49] |
| Sepsis-induced cardiomyopathy (SIC) | TPT1 promotes SIC progression | N/A | [117] |
| Visceral leishmaniasis | TPT1 binds to Mcl-1→Protection of protozoa within macrophages→Parasite burden↑ | N/A | [118] |

→induced; ↓, decreased; ↑, increased. N/A, not applicable.

various organs and tissues [112]. In mouse models of psoriasis, TPT1 has been found to be significantly increased in inflamed skin as well as immune cells like T cells, B cells, and macrophages. Once secreted into the serum and dimerized, TPT1 selectively inhibits regulatory T (Treg) cells and increases M1 macrophages, disrupting immune homeostasis. However, intervention with dTBP2 has shown an increase in Treg cells and restoration of immune homeostasis [49]. Overall, these findings highlight the involvement of TPT1 in the pathogenesis of diabetes and psoriasis, providing insights into potential therapeutic strategies for managing these conditions. We summarize the role of TPT1 and related inhibitors in different diseases in Table 3.

## 5. TPT1-related vaccines

*TPT1* is widely expressed in eukaryotes, not only in the human body but also in parasites and fungi, where it plays a role in their invasion. Vaccines targeting parasitic/fungal TPT1 have been proposed as a potential approach. Malaria, caused by Plasmodium, poses a significant mortality risk, particularly in cases of Plasmodium falciparum infection [119]. In 2001, Plasmodium falciparum TPT1 (PfTPT1) was discovered in the plasma of malaria patients. Pf TPT1 promotes the release of histamine from human basophils and the secretion of IL-8 from eosinophils, potentially affecting the host immune response [120]. Mouse studies using PfTPT1 as a malaria vaccine showed delayed and reduced peak parasitemia, indicating a potential protective effect [121]. Similarly, other vaccines against blood-stage malaria are primarily subunit vaccines, but live-attenuated vaccines may offer broader and longer-lasting protection [122].Demarta-Gatsi et al. reported a live attenuated vaccine lacking TPT1-related secreted factors, termed Plasmodium genetically attenuated parasite (GAP). This GAP increases IL-6 secretion, thereby enhancing T cell and B cell responses to combat Plasmodium infection, and even leaving cross-stage, cross-species and long-lasting immunity [11]. Similarly, a live attenuated vaccine against Plasmodium berghei (PbNK65) that lacked TPT1 was discovered showing long-lasting immune protection in mice pretreated with PbNK65, even when repeatedly dosed with antimalarial drugs [123]. Infection with Medureella can induce mycomas, and patients with advanced mycomas often face severe consequences of amputation [124]. TPT1 is the first fully characterized immunogenic antigen of Medureella and the first single-molecule vaccine candidate antigen [10]. TPT1 antigenicity has also been identified in other parasites such as Filaria malayi, Uuchella bancrofti, and Schistosoma mansoni [125,126]. Nonetheless, the effectiveness and safety of relevant vaccines still need further testing.

## 6. Conclusion

In summary, TPT1 exhibits a wide range of biological functions in a variety of diseases, especially in tumors, infection-related diseases, and immune-related diseases. Although existing studies have revealed the key role of TPT1 in the occurrence and progression of diseases, its specific mechanisms in different diseases still need to be further explored. However, there are certain challenges in basic medical research on *TPT1*, because it is an important gene for animal and cell growth and development, and it becomes complicated to study its function by gene knockout or inhibition of *TPT1* mRNA levels. Therefore, future research should be committed to a deeper understanding of the mechanism of action of TPT1 in different diseases, especially in diseases that have not been fully studied, through more sophisticated gene editing technology and functional analysis.

It is worth emphasizing that TPT1, as an important biomarker, has great potential in early disease diagnosis, prognosis evaluation, and monitoring of treatment effects. With the advancement of high-throughput sequencing technology and bioinformatics analysis methods, we are expected to discover more biomarkers related to TPT1 and provide new tools for personalized medicine. Unfortunately, how TPT1 specifically affects the occurrence and development of the disease still needs further study. Meanwhile, there is no relevant literature evaluating the prognostic and diagnostic efficacy of TPT1. But we believe there will be research in this area in the future. In addition, the widespread expression of *TPT1* in a variety of diseases makes it an attractive therapeutic target. By deeply studying the regulatory network and mechanism of action of TPT1, new targets and ideas can be provided for drug development. Although the current research on *TPT1*/TPT1 inhibitors has not yet made a breakthrough in the clinic, with the development of biotechnology, new drug development strategies may provide more effective treatment options. This also means that future research needs to explore more innovative treatment methods and gain a deeper understanding of the mechanism of action of TPT1 in order to bring more personalized treatment strategies to the field of precision medicine. It is worth noting that in the process of exploring *TPT1*/TPT1 targeted therapy, attention should also be paid to its potential side effects and unexpected consequences.

In conclusion, despite the challenges faced by TPT1 research, its prospects as a biomarker and therapeutic target are still promising. Future research should continue to deepen the exploration of the mechanism of action and clinical application of TPT1 in diseases, thereby opening up new avenues for the diagnosis and treatment of diseases.

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## Data availability statement

This study is a review and the raw data are available in references studies.

## Ethics statement

Review and approval by an ethics committee was not needed for this study because this was a literature review and no new data were collected and analysed. For the same reason, informed consent was not required.

## CRediT authorship contribution statement

**Gelan Miao:** Writing – original draft. **Yulian Yang:** Writing – review & editing. **Xuelian Yang:** Writing – review & editing. **Dexiu Chen:** Writing – review & editing. **Li Liu:** Writing – review & editing. **Xianying Lei:** Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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