Role of ENPP1 in cancer pathogenesis: Mechanisms and clinical implications (Review)

LUJIE ZHAO[1*], YU ZHANG[1*], YAHUI TIAN[1*], XIN DING[2], RUNLING LIN[1], LIN XIAO[1], FUJUN PENG[1,3], KAI ZHANG[4] and ZHONGFA YANG[1]

[1]School of Basic Medical Sciences, Shandong Second Medical University, Weifang, Shandong 261021, P.R. China; [2]School of Clinical Medical Sciences, Shandong Second Medical University, Weifang, Shandong 261021, P.R. China; [3]Weifang Key L2aboratory of Collaborative Innovation of Intelligent Diagnosis and Treatment and Molecular Diseases, School of Basic Medical Sciences, Shandong Second Medical University, Weifang, Shandong 261053, P.R. China; [4]Genetic Testing Centre, Qingdao University Women's and Children's Hospital, Qingdao, Shandong 266000, P.R. China

Received July 12, 2024; Accepted September 17, 2024

DOI: 10.3892/ol.2024.14722

Abstract. Cancer is a significant societal, public health and economic challenge in the 21st century, and is the primary cause of death from disease globally. Ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) serves a crucial role in several biochemical processes, including adenosine triphosphate hydrolysis, purine metabolism and regulation of signaling pathways. Specifically, ENPP1, a type II transmembrane glycoprotein and key member of the ENPP family, may be upregulated in tumor cells and implicated in the pathogenesis of multiple human cancers. The present review provides an overview of the structural, pathological and physiological roles of ENPP1 and discusses the potential mechanisms of ENPP1 in the development of cancers such as breast, colon, gallbladder, liver and lung cancers, and also summarizes the four major signaling pathways in tumors. Furthermore, the present review demonstrates that ENPP1 serves a crucial role in cell migration, proliferation and invasion, and that corresponding inhibitors have been developed and associated with clinical characterization.

Correspondence to: Professor Zhongfa Yang, School of Basic Medical Sciences, Shandong Second Medical University, 7166 Baotong West Street, Weifang, Shandong 261053, P.R. China
E-mail: zyang2005@gmail.com

Dr Kai Zhang, Genetic Testing Centre, Qingdao University Women's and Children's Hospital, 217 Liaoyang West Road, Qingdao, Shandong 266000, P.R. China
E-mail: zhangkai3725@163.com

*Contributed equally

Abbreviations: ATP, adenosine triphosphate; cGAMP, cyclic GMP-AMP; cGAS, cyclic-GMP-AMP synthase; CSC, cancer stem cell; CTCs, circulating tumor cells; EMT, epithelial-mesenchymal transition; ENPP, ectonucleotide pyrophosphatase/phosphodiesterase; ER, estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; GACI, generalized arterial calcification of infancy; GBC, gallbladder cancer; GSCs, glioblastoma stem-like cells; HER2, human epidermal growth factor receptor; HMEC, human mammary epithelial cells; Hp, haptoglobin; LIHC, liver hepatocellular carcinoma; LRF, locoregional failure; mCRPC, metastatic castration-resistant prostate cancer; NET, neutrophil extracellular trap; OSCC, oral squamous cell carcinoma; OTSCC, oral tongue squamous cell carcinoma; PD-1, programmed cell death 1; PPi, pyrophosphate; SMB1-2, somatomedin B-like domains 1-2; STING, stimulator of interferon genes; T2DM, Type 2 diabetes mellitus

Key words: ENPP1, function, human cancer

Contents

1. Introduction

According to the International Agency for Research on Cancer in 2024, there were ~20 million new cases of cancer in 2022 and 9.7 million deaths from cancer. Cancer has emerged as a significant public health issue (1). Projections based on demographics indicate that the annual number of new cancer cases may rise to 35 million by 2050, representing a 77% increase from 2022 levels. The global scope and varied cancer profiles across different regions and levels of human development underscore the importance of enhancing targeted cancer control measures worldwide (1). Despite notable advancements in cancer treatment modalities such as in surgery (2), targeted therapy (3,4), personalized cancer vaccines (5), gene editing technology (6) and chemotherapy (7), patients with advanced cancer continue to face poor survival rates and

higher mortality (8). This highlights the critical need for identifying biomarkers and potential regulatory mechanisms for early tumor detection.

The ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) family, also known as the extracellular nucleotide pyrophosphatase/phosphodiesterase family, consists of seven members, ENPP1, ENPP2, ENPP3, ENPP4, ENPP5, ENPP6 and ENPP7, which regulate extracellular pyrophosphate levels and serve a key role in influencing cell motility, migration, angiogenesis and tumor cell invasion (9-11).

The ENPP1 gene, located on chromosome 6q23.2, was originally identified as plasma cell (PC)-1, a PC differentiation antigen, in 1970. Its enzymatic activity and function as a transmembrane protein have been well studied (12). In earlier studies, researchers took advantage of the unique hydrolytic properties of ENPP1 and reported extensively on the involvement of ENPP1 in the regulation of bone mineralization and calcification, and its important role in phosphate homeostasis (13,14). Moreover, ENPP1 mutations are also associated with generalized arterial calcification of infancy (GACI) or pseudoxanthoma elasticum (15,16). However, the mechanism of action of ENPP1 in cancer has not been well studied; for example, in breast cancer, the earliest study dates back to 2010, which was a bioinformatic study that initially mentioned that ENPP1 may act as a gene with high statistical significance in relation to breast cancer (17). Furthermore, in 2013 it was identified as a potential promoter of breast cancer bone metastasis (18). In 2011, Aerts *et al* (19) reported that ENPP1 expression was associated with the grading of astrocyte tumors. Additionally, in 2012, Huhn *et al* (20) predicted that the effect of ENPP1 on metabolic syndrome risk and colorectal cancer risk may be highly dependent on other environmental factors or modifiers. Therefore, it can be seen that the early studies of ENPP1 in tumors did not involve deep mechanisms or information about its application in the clinic. The findings from the present review indicate that, in the initial stages of research, the focus was on the physiological and pathological functions of ENPP1 in non-tumor diseases. However, in recent years, there has been a shift towards investigating the regulatory mechanisms of ENPP1 in tumor diseases and the development of ENPP1 inhibitors, with a growing number of preclinical models and clinical trials (21-24). Based on these foundations, a number of studies in recent years have reported the regulatory mechanisms of ENPP1 in tumors. For example, in breast cancer, products generated by ENPP1 were reported to enhance the expression of the haptoglobin protein (Hp), an inflammatory mediator that can cause bone marrow invasion and promote neutrophil extracellular traps (NET) formation (25). Moreover, in lung cancer, ENPP1 expression was reported to be upregulated, with dysregulated ENPP1 leading to increased malignancy in human lung cancer by inducing cancer stem cell (CSC) features and epithelial-mesenchymal transition (EMT)-like phenotypes (10). Downregulated exosome-associated gene ENPP1 was also identified as a novel lipid metabolism- and immune-related biomarker in hepatocellular carcinoma (26).

Therefore, the present review summarizes early and recent studies of ENPP1 in several types of cancers, as well as the regulatory mechanisms (Table I) and clinicopathological features (Table II) that provide new insights into the mechanisms of cancer development.

2. Structure of ENPP1

ENPP1 is a membrane-bound glycoprotein that contains two consecutive somatomedin B-like domains (SMB; SMB1-2) connected together. It is classified as a type II transmembrane protein and also includes a phosphodiesterase domain, a catalytic domain (CS) and a nuclease-like domain (NUC) at its C terminus. The structure of ENPP1 is shown in Fig. 1. These domains share a structural organization with ENPP2 and ENPP3. The biological functions of ENPP1 are mediated by its different domains, with the CSs and NUCs working together in mineralization, whilst the SMB1-2 serve a role in insulin signaling (27).

3. Physiological and pathological functions of ENPP1

ENPP1 is involved in purine and adenosine metabolism. As early as 2006 it was discovered that ENPP1 is a phosphodiesterase that can hydrolyze nucleotides and can also regulate purinergic signaling pathways (28). Furthermore, a 2019 study reported that adenosine triphosphate (ATP), NAD^+ and nucleic acids are abundant purines and that ATP and NAD^+ are excitatory, adenosine has anti-inflammatory effects on immune cells, and that ENPP1 serves an important hydrolyzing role as a source of AMP (29). Another study reported that cardiac injury induced the expression of ENPP1, an enzyme that hydrolyzes extracellular ATP to form AMP. In response to AMP stimulation, cardiomyocytes release adenine and specific ribonucleosides, which either disrupt pyrimidine biosynthesis during the synthesis step of orotidine phosphate or rescue pyrimidine biosynthesis through gene targeting of the ENPP1/AMP pathway, thereby enhancing repair after cardiac injury (30). The aforementioned studies indicate the role of ENPP1 in purine metabolism and provide insights into the treatment of related diseases.

Pathological role of ENPP1 in the process of bone mineralization and calcification. Mineralization is an important part of the development of bones and teeth, during which organisms generate inorganic minerals through the regulation of biomolecules. Whilst ENPP1 is known for its role in regulating bone and soft tissue mineralization, it acts mainly through the generation of pyrophosphate, as pyrophosphate (PPi) is one of the inhibitors of hydroxyapatite. ENPP1 negatively regulates bone mineralization by hydrolyzing ATP to produce PPi (31-33). The functional role of ENPP1 in the regulation of mineralization was demonstrated in the 'tiptoe' walking mouse model (*ttw/ttw*) established in 1998, which was initially used to demonstrate an association between defective ENPP1 expression and altered bone mineralization (34). GACI is mainly caused by ENPP1 defects; therefore, inhibition of the ENPP1-PPi-Pi signaling axis could be a novel idea for the treatment of pathological calcification (35-37).

Role of ENPP1 in diabetes and obesity. ENPP1 is located on chromosome 6q23.2 and was identified as encoding a protein that inhibits insulin signaling (38). ENPP1 can interfere with insulin binding to the insulin receptor α subunit, affecting its activation and inhibiting insulin downstream signaling (39,40). It is also involved in the pathogenesis of type

Table I. Functional characterization of ectonucleotide pyrophosphatase/phosphodiesterase 1 in several cancer types.

First author/s, year	Cancer type	Expression	Function roles	Related genes	Role	(Refs.)
Lau *et al*, 2013	Breast cancer	Upregulated	Metastasis	-	Oncogenic	(18)
Takahashi *et al*, 2015	Breast cancer	Upregulated	Proliferation	miR-27b, ABCG2	Oncogenic	(61)
Kawaguchi *et al*, 2019	Breast cancer	Upregulated	-	-	Oncogenic	(62)
Ruiz-Fernandez de Cordoba *et al*, 2022	Breast cancer	Upregulated	Proliferation	Hp	Oncogenic	(25)
Goswami *et al*, 2022	Breast cancer	Upregulated	EMT, proliferation, metastasis	2'3'-CGAMP, Vimentin, N-cadherin, E-cadherin, TWIST1, IFN-β	Oncogenic	(63)
Zhang *et al*, 2023	Gallbladder cancer	Upregulated	-	-	Oncogenic	(83)
Yano *et al*, 2004	Gallbladder cancer	Upregulated	Differentiation, migration	-	Oncogenic	(81)
Bageritz and Goidts, 2014	Glioblastoma	Upregulated	Proliferation, cell cycle	E2F1	Oncogenic	(11)
Aerts *et al*, 2011	Glioblastoma	Upregulated	-	-	Oncogenic	(19)
Bageritz *et al*, 2014	Glioblastoma	Upregulated	Differentiation, proliferation, apoptosis, cell cycle	E2F1	Oncogenic	(76)
Li *et al*, 2022	Liver cancer	Downregulated	-	-	Non-oncogenic	(26)
Hu *et al*, 2019	Lung cancer	Upregulated	Tumor progression, proliferation, apoptosis, migration, EMT	ABCG2, SOX2, NANOG, CD44, TGF-β, E-cadherin, Vimentin	Oncogenic	(10)
Ma *et al*, 2024	Oral squamous cell carcinoma	Upregulated	Proliferation, apoptosis, autophagy	PCNA, cyclin D1, BAX, Cl-caspase3, caspase3, Bcl-2, LC3B I, LC3B II, SQSTM1, ATG5, p-PRKAA1, PRKAA1, p-ULK1, ULK1	Oncogenic	(93)
Wang *et al*, 2021	Ovarian carcinoma	Upregulated	Proliferation, apoptosis, migration, invasion, EMT	Caspase3, E-cadherin, N-cadherin, Vimentin, PCNA, MMP9	Oncogenic	(73)

ABCG2, ATP binding cassette subfamily G member 2; ATG5, autophagy related 5; Bcl-2, B-cell lymphoma 2; BAX, Bcl-2-associated X protein; EMT, epithelial-mesenchymal transition; E2F1, E2F transcription factor 1; Hp, haptoglobin; IFN-β, type β interferon; LC3B, microtubule associated protein 1 light chain 3 β; miR-27b, microRNA 27b; MMP9, matrix metalloproteinase 9; NANOG, Nanog Homeobox; PCNA, proliferating cell nuclear antigen; PRKAA1, protein kinase AMP-activated catalytic subunit α1; SOX2, SRY-Box transcription factor 2; TGF-β, transforming growth factor β; ULK1, unc-51 like autophagy activating kinase 1.

Table II. Clinical significance of ectonucleotide pyrophosphatase/phosphodiesterase 1 in several cancer types.

First author/s, year	Cancer type	Clinicopathologic features	(Refs.)
Takahashi *et al*, 2015	Breast cancer	Recurrence-free survival	(61)
Kawaguchi *et al*, 2019	Breast cancer	Recurrence-free survival	(62)
Ruiz-Fernandez de Cordoba *et al*, 2022	Breast cancer	Poor survival	(25)
Goswami *et al*, 2022	Breast cancer	Tumor volume	(63)
Aerts *et al*, 2011	Glioblastoma	WHO grade	(19)
Li *et al*, 2022	Liver cancer	Poor prognosis	(26)
Hu *et al*, 2019	Lung cancer	Tumor burden and tumor size	(10)
Ma *et al*, 2024	Oral squamous cell carcinoma	Tumor volume and tumor size	(93)
Wang *et al*, 2021	Ovarian carcinoma	Preoperative serum, volume of ascites, tumor maximum size, FIGO stage, differentiation grade and chemotherapy sensitivity	(73)

FIGO, International Federation of Gynecology and Obstetrics; WHO, World Health Organization.

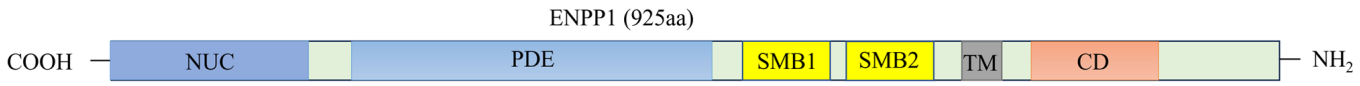

Figure 1. Structure of ectonucleotide pyrophosphatase/phosphodiesterase 1. NUC, nuclease-like domain; PDE, phosphodiesterase domain; SMB, somatomedin B-like domain; TM, transmembrane domain; CD, cytoplasmic domain.

2 diabetes mellitus (T2DM) (41). Moreover, several mutants of ENPP1 have been reported to be associated with childhood and adult obesity and to increase the risk of T2DM (42). These findings could provide a molecular basis for the physiological link between insulin resistance and obesity and offer a fresh perspective on the prevention of such diseases. However, to date, there are few studies on the relationship between ENPP1 and diabetes and obesity, and further work is required to elucidate its physiological role.

Mutations in ENPP1 are associated with Cole disease. Cole disease is a rare autosomal dominant disorder in which patients present with areas of hypopigmentation of the skin and thickening of the skin of the palms and feet. Notably, Cole disease has both an autosomal dominant and an autosomal recessive mode of inheritance, depending on the specific ENPP1 variant (43,44). A 2013 study using a genome-wide approach reported that mutations in ENPP1 were associated with Cole disease (44) and that the mutations occur in the structural domain of SMB2 (45). In conclusion, this mutational characterization of ENPP1 may provide genetic evidence for the treatment of similar skin diseases.

Pathological roles of ENPP1 in anti-aging. Klotho is a well-known anti-aging factor that regulates phosphate metabolism, and mice with mutations or defects in klotho exhibit a phenotype similar to human aging. Moreover, it has been reported that ENPP1 acts as an anti-aging factor under phosphate overload by regulating klotho expression, provided that ENPP1 is mutated. This result suggests that the ENPP1-klotho axis is required to prevent the aging phenotype under phosphate overload conditions (46-48).

4. ENPP1 in human cancers

A review of the literature revealed that ENPP1 has been the subject of relevant studies in a number of common human cancers. Accordingly, the present review summarizes the associations between ENPP1 and several human cancers in order of incidence, with reference to the latest global cancer statistics, released in 2024. The association of ENPP1 with cancer is presented in Fig. 2.

Regulatory mechanisms of ENPP1 in several cancers and current research status

ENPP1 and lung cancer. Lung cancer continues to be the primary cause of cancer-related deaths globally. The most recent global cancer statistics project ~2.5 million new cases and 1.8 million deaths in 2022, with lung cancer ranking first among men and second among women in terms of both incidence and mortality (1). Among the several subtypes of lung cancer, lung adenocarcinoma is the most prevalent subtype of non-small cell lung cancer, representing >40% of all cases (49). Whilst surgical resection is currently the preferred treatment for patients with early-stage lung cancer, they still face a significant risk of tumor recurrence even after complete resection (50). Therefore, the search for a novel and effective treatment strategy is crucial to enhance the prognosis and survival rates of these patients.

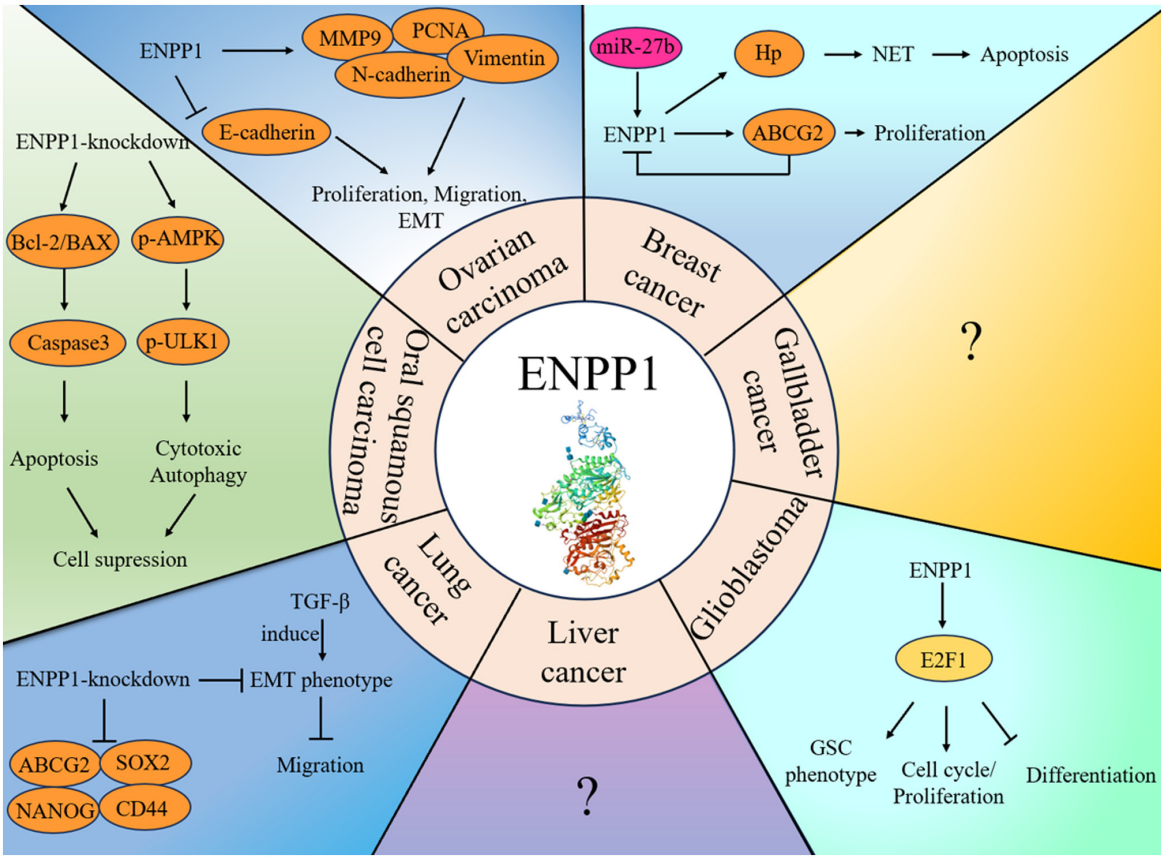

Figure 2. Molecular mechanisms of ENPP1 in different human cancers. ABCG2, ATP binding cassette subfamily G member 2; AMPK, adenosine 5'-monophosphate-activated protein kinase; BAX, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; EMT, epithelial-mesenchymal transition; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; E2F1, E2F transcription factor 1; GSC, glioma stem cell; Hp, haptoglobin; miR-27b, microRNA 27b; MMP9, matrix metalloproteinase 9; NANOG, Nanog Homeobox; NET, neutrophil extracellular traps; PCNA, proliferating cell nuclear antigen; TGF-β, transforming growth factor-β; ULK1, unc-51 like autophagy activating kinase 1.

In 2019, Hu *et al* (10) first proposed that ENPP1 serves a role in the invasion and metastasis of lung cancer. Moreover, elevated levels of ENPP1 expression were reported in most human lung tumor tissues compared with adjacent normal lung tissue. The dysregulation of ENPP1 contributes to increased malignancy in human lung cancer by promoting CSC characteristics and EMT-like phenotypes. Additionally, Hu *et al* reported that downregulation of ENPP1 gene expression led to decreased levels of CSC markers and reversed the TGF-β-induced EMT phenotype, resulting in diminished cell migration, restoration of E-cadherin expression and suppression of vimentin-induced inhibition (10). A total of 3 years after the publication of this result, Han *et al* (51) analyzed data from the Gene Expression Omnibus database using weighted correlation network analysis, the Least Absolute Shrinkage and Selection Operator method and Cox proportional hazards regression, and reported that ENPP1 may serve as a potential predictor for the recurrence of early lung adenocarcinoma. However, whilst the therapeutic potential of ENPP1 in lung cancer has been established, the specific molecular mechanisms underlying its effects remain to be elucidated.

ENPP1 and breast cancer. Breast cancer is a prevalent form of cancer among women, as highlighted in the 2020 global cancer statistics. Surpassing lung cancer, breast cancer accounted for an ~2.3 million new cases (11.7%) in 2020, making it the most common cancer worldwide (52). In the latest 2022 global cancer statistics, breast cancer ranked second with 11.6% of new cancer cases, following lung cancer at 12.4% (1). Recent advancements in therapeutic methods and chemotherapy drugs have markedly improved the survival rates of patients with breast cancer. Despite these developments, distant metastasis (53) and acquired drug resistance (54) continue to be major factors contributing to the poor prognosis of patients with breast cancer.

Lau *et al* (18) reported an increase in ENPP1 expression in human breast cancer cells, MDA-MB-231 and MDA-MB-468, as well as that heightened ENPP1 expression enhanced the tumor-forming ability of MDA-MB-231 cells in bone. Later, Awolaran *et al* (55) identified ENPP1 as a factor expressed in breast cancer cells that mediates bone metastasis in breast cancer and also serves a role in cell proliferation and differentiation. Moreover, through RNA sequencing of the triple-negative/mesenchymal cell lines, MDA-MB-231 and MDA-MB-157, it was reported that ENPP1 is influenced by a circular RNA originating from the dedicator of cytokinesis 1 gene, leading to its upregulation (56). These findings are specific to circular RNA and offer novel perspectives on the involvement of RNA in breast cancer development and progression.

Compared with human mammary epithelial cells (HMEC), the breast cancer cell MDA-MB-231 exhibits overexpression of ENPP1 and CD73. The enzyme converts extracellular ATP

released by cells into adenosine, which in turn stimulates the A3 receptor, promoting cell migration with frequent changes in direction. MDA-MB-231 cells, HMECs and neutrophils demonstrate distinct purinergic signaling mechanisms that regulate their motility patterns. The subcellular distribution of A3 adenosine receptors in MDA-MB-231 breast cancer cells serves a role in cell motility dysfunction (57). These findings suggest that targeting the purinergic signaling mechanism associated with ENPP1 could be a potential therapeutic strategy to interfere with breast cancer cell motility, thereby reducing the risk of cancer cell spread and metastasis (57). Additionally, it is hypothesized that the enzymatic function of ENPP1 serves a pivotal role in the promotion of breast tumor growth and metastasis by limiting the infiltration of adaptive immune cells, which ultimately leads to the enhancement of antitumor immunity. Furthermore, ENPP1 is postulated to serve a pivotal role in the tumor microenvironment. It functions as an innate immune checkpoint, inhibiting the activation of the cyclic GMP-AMP (cGAMP)-stimulator of interferon genes (STING) pathway and simultaneously enhancing the extracellular adenosine pathway (22). Therefore, the present review underscores the potential of ENPP1 as a target for cancer immunotherapy, offering new possibilities for enhancing immune checkpoint blockade therapeutic strategies (22).

The 'immune hot' microenvironment is defined by a significant presence of antitumor T cells that express markers of immune activation and exhaustion, including programmed cell death 1 (PD-1). By contrast, immune cold tumors do not have many antitumor immune cells and do not respond well to anti-PD-1 therapy (58). Through *in vitro*, *in vivo* and bioinformatics studies, Attalla *et al* (21) reported that human epidermal growth factor receptor (HER)2Δ16-dependent activation of ENPP1, an oncogenic splicing variant of the HER2, is associated with aggressive $HER2^+$ breast cancer. This activation influences the immune microenvironment in HER2Δ16 tumors by modulating cytokine expression, reducing those that stimulate immune cells and increasing those with immunosuppressive effects. The presence of ENPP1 on the surface of HER2Δ16 tumor cells contributes to an immune-cold environment, suggesting a potential target for transforming immune-cold tumors into immune-hot tumors.

Schettini *et al* (59) reported that ENPP1 is a potentially safe and feasible new target for molecular and pathological subtypes of breast cancer antibody-drug conjugates and chimeric antigen receptor T-cell immunotherapy, and used the Human Protein Atlas to perform a comprehensive analysis of protein expression. Moreover, in a study characterizing gene expression profiles in estrogen receptor (ER)-positive breast cancer, differential expression of ENPP1 was reported between $ER\alpha^+$ and ERα-primary breast tumors. This finding was confirmed using reverse transcription-quantitative PCR and immunohistochemistry, indicating that ENPP1 may be a potential target for breast cancer treatment (17). A subsequent study also reported upregulation of ENPP1 in patients with $ER\alpha^+$ (60).

Furthermore, a study reported elevated levels of ENPP1 in patients with breast cancer, with ENPP1 being targeted by microRNA (miR)-27b to control its efflux activity by influencing the expression and surface localization of ATP binding cassette subfamily G member 2 (61). Additionally, in breast cancer, the 'SP fraction' is defined as $CD44^{-high}/CD24^{-low}$ cells, aldehyde dehydrogenase-positive cells and side population cells. ENPP1 has been found to play a role in regulating SP in breast cancer, leading to partial drug resistance (61).

Kawaguchi *et al* (62) developed a new fluorescent probe, TG-mAMP, to assess the prognosis of malignant breast cancer by detecting ENPP1 activity with high sensitivity. This probe can also be used to screen ENPP1 inhibitors in chemical libraries, potentially leading to the discovery of effective and selective inhibitors. Therefore, the study of TG-mAMP as a fluorescent probe could provide a rapid and cost-effective method for predicting the prognosis of patients with malignant breast cancer. To date, efficient ENPP1 inhibitors have also been developed. A team of researchers has already reported that a selective and potent ENPP1 inhibitor, AVA-NP-695, regulates tumor metastasis by negatively modulating EMT in addition to its immunomodulatory effects. AVA-NP-695, as an immunomodulatory and anti-metastatic drug, provides a strong theoretical basis for the treatment of triple-negative breast cancer (TNBC) (63). Another study reported that an ENPP1 inhibitor could retard tumor growth in a mouse model of breast cancer (64).

ENPP1 and colon cancer. Colon cancer is a prevalent type of cancer in developed countries and a major contributor to cancer-related mortality. According to Cancer Outcomes 2022, there were ~1.93 million new cases of colon cancer, accounting for 9.6% of all cancer cases. Additionally, colon cancer causes ~900,000 deaths, representing 9.3% of cancer-related deaths (1). There is already evidence of a potential association between ENPP1 and an increased risk of colorectal cancer. An experimental study reported that specific alleles of polymorphisms in ENPP1 may be associated with an increased susceptibility to colorectal cancer among the Czech population. Furthermore, the impact of ENPP1 on the risk of both metabolic syndrome and colorectal cancer could be influenced by several environmental factors or modifiers (20). However, the molecular regulatory mechanism of ENPP1 in colon cancer has not been studied yet, to the best of our knowledge, so this may be a promising research direction.

ENPP1 and prostate cancer. Prostate cancer accounts for ~7% of male cancers worldwide, with >1.2 million new cases and >350,000 deaths annually, positioning it as a prominent cause of cancer-related mortality in men (65). Metastatic castration-resistant prostate cancer (mCRPC) is the most lethal form of prostate cancer (66). A recent study used RNA sequencing on a cohort of 60 patients and identified 14 gene clusters strongly associated with mCRPC bone metastasis, among which ENPP1 was highlighted. Subsequent Kyoto Encyclopedia of Genes and Genomes enrichment analysis revealed a connection between ENPP1 and the synthesis and secretion of parathyroid hormone. Despite these findings, experimental validation of the role of ENPP1 in prostate cancer remains pending, underscoring the need for further investigation (67).

ENPP1 and liver cancer. Liver hepatocellular carcinoma (LIHC) is a prevalent form of primary liver cancer, ranking sixth among the most common cancers globally (1). LIHC is characterized by a poor prognosis and high mortality rates, often being diagnosed in advanced stages. As a result, there is a critical need to identify biomarkers and therapeutic targets for

improving LIHC prognosis (68). ENPP1, an exosome-related gene, was reported to be markedly downregulated in LIHC tissues based on comprehensive bioinformatics analysis from multiple databases, and patients with downregulated ENPP1 displayed a poor prognosis (26). Li *et al* (26) further assessed the co-expression network of ENPP1 to elucidate its role in potential signaling pathways such as fatty acid degradation and PPAR signaling pathways. Moreover, an immunological analysis revealed that ENPP1 may serve a role in several immune-related characteristics, and can function as an immunosuppressant, immunostimulant and chemokine. These findings contribute to a deeper understanding of ENPP1 in the pathogenesis and immune response of LIHC, offering new insights for ENPP1-related immunotherapy in clinical treatment. However, this is only a 'dry' experiment, and further research is required to verify this conclusion with 'wet' experiments.

ENPP1 and ovarian carcinoma. In 2022, it was estimated that >200,000 women would die from ovarian cancer (1). This type of cancer represents 2.5% of all malignant tumors in women but contributes to ~5% of all cancer-related deaths due to its high mortality rate. The primary emphasis in treating ovarian cancer lies in early detection and prevention (69).

Extracellular nucleotides and nucleosides serve a crucial role in regulating tissue homeostasis. ENPP1 is known to hydrolyze ATP and cleave several substrates and chemical bonds (70). It has been reported that ovarian cancer cells, specifically SKOV-3 cells, express ENPP1. Notably, the conversion of ADP to AMP serves as a control point for the SKOV-3 cell phenotype, indicating a potential mechanism for regulating cell behavior. This highlights the significance of extracellular purine ratio in the migration phenotype of ovarian cancer cells. ENPP1, as a key hydrolase, serves a vital role in this process (71).

In 2020, Zhang *et al* (72) used bioinformatics techniques to forecast genes related to tumor metabolism. The study also revealed a potential association between ENPP1 and the prognosis of patients with ovarian cancer. Additionally, they developed a network of metabolism-related genes, which included ENPP1. By performing further gene analysis, high-risk groups can be differentiated from low-risk groups and additional clinical insights could be elucidated. Based on these currently known theoretical foundations, a previous study reported that the expression of ENPP1 mRNA and protein in high-grade serous ovarian carcinoma was notably higher compared with normal ovarian tissue. Moreover, the study revealed that the stronger the expression of ENPP1, the more advanced the International Federation of Gynecology and Obstetrics stage, and the poorer the differentiation of tumor cells. However, the research did not establish an association between EMPP1 expression and chemosensitivity. By interfering with the expression of ENPP1, the study reported a marked reduction in the proliferation, metastasis and invasion of ovarian cancer cells. This suggests that ENPP1 could potentially serve as a target for molecular treatment of ovarian cancer (73).

ENPP1 and glioblastoma. Glioblastoma, the most common primary brain tumor and one of the deadliest human cancers, can develop anywhere in the central nervous system (74). With a 5-year survival rate of only ~10%, there is an urgent need for effective treatments (75).

Glioblastoma encompasses astrocytomas derived from astrocytes. In 2011, it was first proposed that glioblastoma could be graded based on ENPP1 expression levels (19). Subsequent studies have identified ENPP1 as a potential therapeutic target for glioblastoma (11,76). ENPP1 is frequently regarded as a proto-oncogene in this aggressive brain tumor and is highly expressed, underscoring its significant role (11,19). The knockdown of ENPP1 impairs cell proliferation and results in the accumulation of cells in the G1 phase of the cell cycle. Furthermore, ENPP1 functions upstream of E2F transcription factor 1 (E2F1), which may lead to a reduction in the transcriptional activity of E2F1 (11).

A subset of glioblastoma stem-like cells (GSCs) with characteristics similar to neural precursor cells has been identified as resistant to treatment, potentially contributing to the high recurrence rate of glioblastoma (77). Bageritz *et al* (76) reported that GSCs express high levels of ENPP1. By knocking out ENPP1 in cultured GSCs, they reported a decrease in stem cell-related genes, differentiation into astrocyte lineage, impairment of sphere formation and cell death. This led to an accumulation of cells in the G1/G0 cell cycle phase, increased sensitivity to chemotherapy and phenotypic changes attributed to reduced E2F1 transcriptional function. The expression of ENPP1 is crucial for maintaining undifferentiated proliferation state of GSCs *in vitro*. The present review did not find any clinically relevant experiments using the high expression of ENPP1 in GSCs, and no study has explored the molecular mechanism of ENPP1 in glioblastoma since 2014, to the best of our knowledge, which could be an entry point for the treatment of glioblastoma in the future.

ENPP1 and gallbladder cancer (GBC). GBC is the most prevalent malignant tumor of the biliary tract, characterized by poor prognosis and a high likelihood of metastasis (78,79). It is estimated that in 2022, there would be ~130,000 new cases of GBC resulting in ~90,000 deaths (1). Currently, complete surgical resection remains a viable treatment option (80). However, the lack of distinct symptoms often leads to late-stage diagnosis, resulting in missed opportunities for optimal treatment (78). A comprehensive understanding of the molecular mechanisms underlying gallbladder cancer progression is crucial for improving treatment outcomes. Furthermore, early identification of effective prognostic biomarkers holds promise for enhancing the management of GBC.

Yano *et al* (81) first reported that ENPP1 is predominantly located on the apical cytoplasmic side of bile duct tumor cells in 2004, a finding that was corroborated through immunohistochemistry and western blot analysis. This finding indicates that ENPP1 may serve a role in the invasion of neoplastic bile duct carcinoma and holds promise as a potential tumor marker. In a previous study performed in 2021, researchers used transcriptome bioinformatics analysis to identify and validate early candidate diagnostic and prognostic RNA methylation-related genes for GBC. The study highlighted ENPP1 as a potential hub gene in the methylation pathway and bile metabolism-related pathways, with high expression levels of ENPP1 being markedly associated with poor prognosis in patients with GBC. This suggests that ENPP1 could serve as a novel biomarker for both early diagnosis and prognosis assessment in GBC (82).

A prospective study performed in 2023 demonstrated the potential development implications of the ENPP1 gene. Zhang *et al* (83) used ultrasensitive electrochemical cell sensors to accurately identify and detect circulating tumor cells (CTCs) and their resistance to chemotherapy in GBC. The researchers developed a three-layer silica-QDs/PEI@ SiO2 electrochemical probe by encapsulating CdSe/ZnS quantum dots within silica nanoparticles. By incorporating anti-ENPP1 antibodies, the electrochemical probes were able to specifically label CTCs extracted from GBC, offering a novel approach for the creation of innovative chemotherapy regimens. However, no research team has performed a clinical trial to prove whether this treatment is feasible, to the best of our knowledge, so subsequent work could be focused on clinical validation and translation.

ENPP1 and oral squamous cell carcinoma (OSCC). OSCC primarily affects the oral mucosal epithelium, representing ~90% of oral malignant tumors. Symptoms may include impaired taste and difficulty swallowing (84,85). In 2020, there were 377,713 reported cases of OSCC globally, with the majority occurring in Asian countries (86). Certain studies suggest that targeted oncogene sequencing could be a promising approach for the diagnosis, prevention and treatment of OSCC in the future (87-89). Notably, tumor progression often involves the accumulation of genetic mutations in tumor cells, leading to drug resistance (90,91). A study performed RNA-sequencing analysis on five SCC9-derived oral cancer cell lines and predicted that ENPP1 may serve as a potential biomarker and therapeutic target that interferes with the occurrence and progression of oral tongue squamous cell carcinoma (OTSCC). Analysis of 248 clinical data points during the trial revealed a marked association between the up- and down-regulation of ENPP1 and patient survival. Furthermore, the upregulation of the ENPP1 gene was associated with increased lethality, indicating that ENPP1 could be a promising molecular target for future OTSCC treatment studies. However, to date, there is no relevant data to substantiate the applicability of these findings in clinical studies, to the best of our knowledge (92). Based on this theoretical basis, Ma *et al* (93) later reported an association between ENPP1 and cytotoxic autophagy, leading to a novel treatment approach for OSCC. The study reported that reducing ENPP1 expression effectively suppressed OSCC cell growth and triggered apoptosis. Moreover, ENPP1 depletion activated the AMPK signaling pathway, resulting in increased Unc-51-like kinase 1 (ULK1) levels and AMPK phosphorylation in OSCC cells. This activation induced autophagy in OSCC cells, highlighting ENPP1 as a promising therapeutic target.

In conclusion, the expression and function of ENPP1 varies in different cancer types, and ENPP1 is upregulated in most tumors, such as lung cancer, breast cancer and glioblastoma. ENPP1 acts as an oncogene but is downregulated as an oncogene in hepatocellular carcinoma, and we consider that this may be related to the localization of the ENPP1 gene (6q23.2). However, according to bioinformatics predictions, ENPP1 is notably downregulated in liver cancer, which may be related to the pathogenesis of liver cancer. Therefore, further studies are needed to confirm these findings in order to elucidate more detailed regulatory mechanisms.

Signaling pathways associated with ENPP1 ENPP1 and cGAMP-STING pathway. In recent years, ENPP1 has been reported to serve an important role in the immune response to several stimuli through the cyclic-GMP-AMP synthase (cGAS)-STING pathway (94). In this pathway, cGAS senses and responds to self and pathogenic double-stranded DNA in the cytoplasm, catalyzing the conversion of GTP and ATP to cGAMP (95). cGAMP then binds to its endoplasmic reticulum membrane-localized STING and activates downstream transcription of interferon and other cytokines, triggering powerful antiviral (96) and anticancer defense mechanisms (97-99). ENPP1 is the main hydrolyzing enzyme of extracellular cGAMP, and the hydrolysis of cGAMP by ENPP1 can attenuate the cGAS-STING signaling pathway (100,101). Therefore, an ENPP1 inhibitor can be safely administered systemically to enhance the extracellular level of cGAMP and activate STING to achieve the anticancer effect (102,103). The signaling pathway diagram is presented in Fig. 3A.

ENPP1-Hp signaling pathway. Locoregional failure (LRF) following surgery and post-irradiation in patients with breast cancer is associated with a poor prognosis (104). A recent study reported a strong association between ENPP1 and LRF, suggesting that ENPP1-overexpressing CTCs serve a role in promoting recurrence through self-seeding mechanisms. Whilst first ENPP1-generated adenosinergic metabolites enhance the expression of Hp, an inflammatory mediator that can cause bone marrow invasion and promote NET formation, researchers have identified an unexpected mechanism of the ENPP1-Hp signaling axis, namely, that ENPP1-highly-expressing CTCs have an increased fitness for homing and colonization of recurrent tumor beds with the recruitment of polymorphonuclear myeloid derived suppressor cells capacity. This infiltration of an immunosuppressed myeloid subpopulation is triggered by Hp tumor secretion via the ENPP1-water metabolite through an autocrine/paracrine loop (25). At present, no role has been identified for the ENPP1-Hp signaling pathway to serve in other tumor types, to the best of our knowledge, which needs to be further explored. The signaling pathway diagram is presented in Fig. 3B.

ENPP1-E2F1 signaling pathway. Knockdown of ENPP1 affects the homeostasis of the intracellular nucleotide pool, and this dysregulation may be attributed to the enzymatic activity of ENPP1 in the extracellular gap, leading to a reduction in the transcriptional function of the cell cycle regulator, E2F1. Notably, ENPP1 knockdown has been reported to impair cell proliferation and affect cell cycle progression (11). The signaling pathway diagram is presented in Fig. 3C.

ENPP1-AMPK-ULK1-cell autophagy signaling pathway. In this pathway, downregulation of ENPP1 leads to activation of AMPK, which in turn increases the expression and phosphorylation of ULK1, leading to cytotoxic autophagy and tumor growth inhibition. In recent years, only one study has reported a role for this pathway in oral squamous carcinoma, to the best of our knowledge, and there have been no studies related to this pathway in other common human cancers (93). The signaling pathway is presented in Fig. 3D.

Prospects of ENPP1 in clinical diagnosis and treatment of tumors. The present review identified almost no trials investigating ENPP1-related tumor therapeutic drugs, and there are no

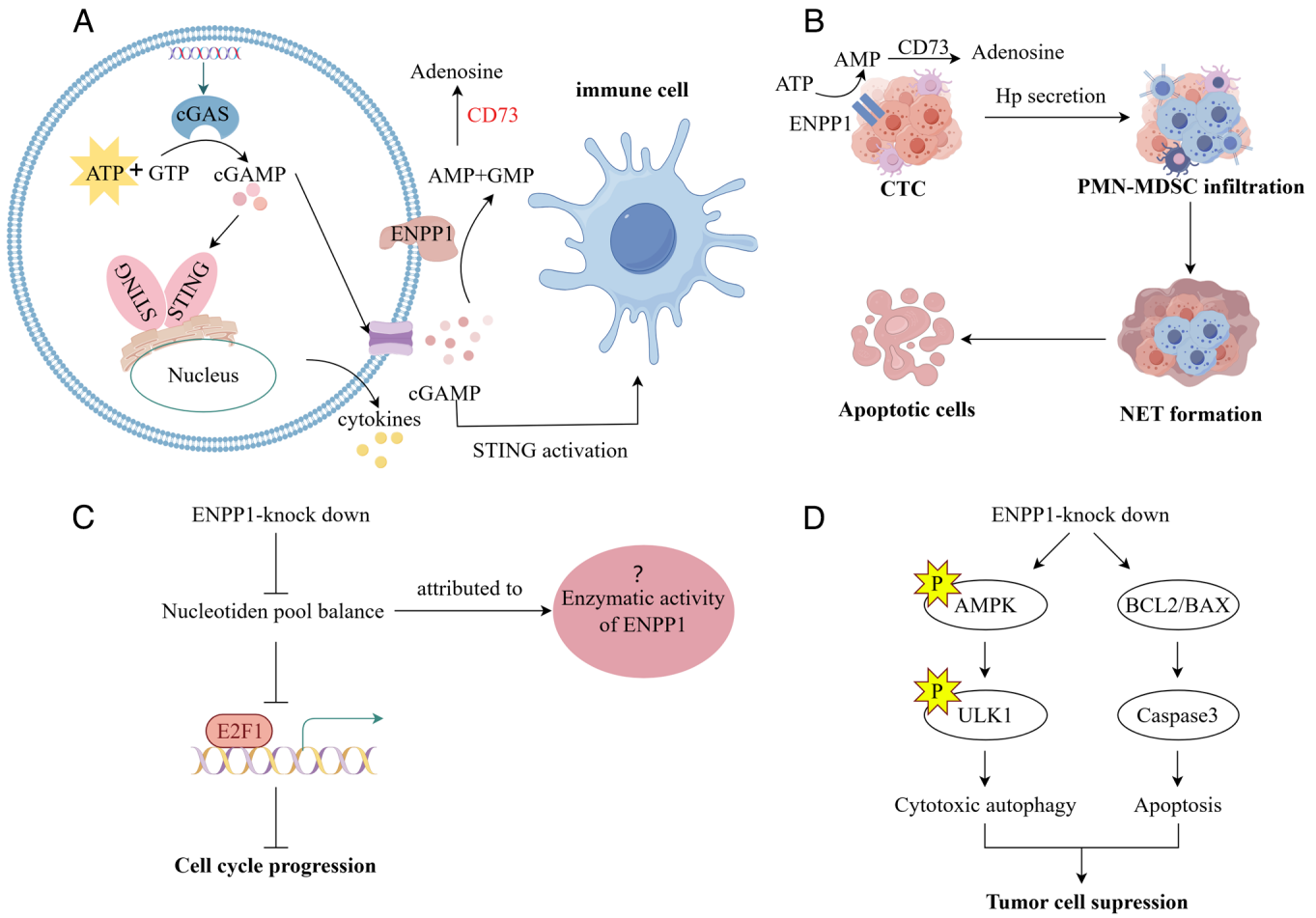

Figure 3. Major signaling pathways associated with ENPP1. (A) ENPP1 and cGAMP-STING pathway. (B) ENPP1-Hp signaling pathway. (C) ENPP1-E2F1 signaling pathway. (D) ENPP1-AMPK-ULK1-cell autophagy signaling pathway. AMP, adenosine monophosphate; AMPK, adenosine 5'-monophosphate-activated protein kinase; ATP, adenosine triphosphate; BAX, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; CD73, 5'-nucleotidase ecto; cGAMP, cyclic GMP-AMP; cGAS, cyclic-GMP-AMP synthase; CTC, circulating tumor cell; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; E2F1, E2F transcription factor 1; GTP, guanosine triphosphate; Hp, haptoglobin; NET, neutrophil extracellular traps; PMN-MDSC, polymorphonuclear myeloid derived suppressor cells; STING, stimulator of interferon genes; ULK1, unc-51 like autophagy activating kinase 1. This figure was created using Figdraw 2.0 (www.figdraw.com).

examples of using ENPP1 features to diagnose or treat cancer, to the best of our knowledge. However, the present review found that between 2019 and 2024, several novel inhibitors of ENPP1 have been in development for cancer immunotherapy, such as 3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one, 3,4-dihydropyrido[2,3-d]pyrimidin-2(1H)-one, pyrrolopyrimidine and pyrrolopyridine derivatives and phthalazinone analogues (23,24,105-109). However, these inhibitors are currently only being tested in preclinical models and are rarely, if ever, actually used in clinical trials (106,107,110). Of these, there is only one ongoing clinical trial of an oral, potent, selective small molecule inhibitor of ENPP1 called RBS2418 (Riboscience), which has the potential to activate an antitumor innate immune response leading to an antitumor response in adult patients with advanced or metastatic tumors, and the clinical results have not demonstrated toxicity with increasing doses (111). Although only one clinical trial is currently underway, clinical trials with several ENPP1 inhibitors in combination with other therapies may be performed (111). In 2024, Sun *et al* (24) reported the use of an ENPP1 inhibitor in a 4T1 mouse model of TNBC and demonstrated *in vivo* efficacy. These experimental data provide a promising lead compound for cancer immunotherapy. The development of a large number of inhibitors indicates the potential of ENPP1 as a cancer therapeutic marker. The mechanism of ENPP1 in tumors has not yet been fully explored, therefore the elucidation of the inhibitors may begin as a starting point to gain a deeper understanding of the antitumor mechanism of ENPP1 inhibitors to perform more clinically meaningful trials and provide more theoretical basis for earlier treatment of cancer.

5. Discussion and conclusions

The majority of initial studies have concentrated on the distinctive hydrolytic characteristics of ENPP1. These properties were utilized not only to regulate purinergic signaling (28), but also to facilitate cardiac injury repair by regulating the ENPP1/AMP axis (30). Many studies have also reported the pathological role of ENPP1 in bone mineralization and calcification, which can be demonstrated by the classic model of 'tiptoe' walking mouse (*ttw/ttw*) (34), and the inhibition of the ENPP1-PPi-Pi signaling axis may be a new idea for the treatment of pathological calcification (35-37). The association between ENPP1 and diabetes and obesity is also strong, as

ENPP1 has been identified as a protein that inhibits signaling downstream of insulin (38), and is also involved in the pathogenesis of T2DM (41). Several of its mutants have been implicated in obesity and Cole disease, but further study of the mechanisms involved is needed to better pinpoint the treatment of such diseases (42,44). A notable function of ENPP1 is that it regulates the expression of the anti-aging factor klotho and prevents aging by acting on the ENPP1-klotho axis (48). These several physiological and pathological functions could provide new ideas for the treatment of early non-tumor diseases.

In recent years, the emerging ENPP family has been identified as a potential proto-oncogene or tumor suppressor gene. These ENPPs serve a crucial role in the occurrence and development of several diseases and tumors, as highlighted in several studies (61,112-116). ENPP1, the most comprehensively studied member of the ENPP family, is widely expressed in several cancers including breast cancer, gallbladder cancer, glioblastoma and lung cancer (Table I). Conversely, Li *et al* (26) reported the downregulation of ENPP1 expression in liver cancer tissues, although this finding requires further validation through additional experiments.

Upregulation and downregulation of ENPP1 have been associated with several clinicopathological characteristics and prognosis, including recurrence-free survival, tumor volume, tumor size and World Health Organization grade (61-63,73,93). Additionally, ENPP1 severs a role in processes such as cell proliferation, migration, apoptosis, EMT and metastasis (10,18,63,73). Mechanistically, ENPP1 can act as a direct target gene of specific miRs, such as miR-27b, influencing downstream signaling pathways (61). It also impacts the function of transcription factor like E2F1, which in turn affects cell cycle, proliferation, GSC phenotype, and regulates tumor cell development (11,117). Knocking down ENPP1 has been reported to affect processes such as proliferation and EMT-related phenotypes (10,73). Based on these identified regulatory mechanisms, the present review summarized four major ENPP1-related signaling pathways in tumors, namely ENPP1 and cGAMP-STING pathway, the ENPP1-Hp signaling pathway, the ENPP1-E2F1 signaling pathway and the ENPP1-AMPK-ULK1-cell autophagy signaling pathway. Among them, the ENPP1 and cGAMP-STING pathway has been the most widely studied and applied, and researchers have elucidated inhibitors for cancer immunotherapy based on this pathway (118). The other three have only been found to be studied in breast cancer, glioblastoma and OSCC, and the research is highly limited (11,25,93). Therefore, these identified regulatory mechanisms could be used as a basis to fully explore the role of these signaling pathways in other cancers.

Several ENPP1 inhibitors have been developed, including the ENPP1 inhibitor AVA-NP-695 (63) which is specifically targeted at breast cancer, as well as other types of inhibitors such as nucleotide-based and non-nucleotide-based inhibitors (23,24,105,107,118,119). Despite progress in the discovery of these inhibitors, the diversity of their chemical structures and the efficacy of the drugs are not yet ideal, and their application in clinical trials has not been verified.

The molecular mechanism of ENPP1 in several cancers, including gallbladder and liver cancer, remains poorly understood. Clarifying the precise molecular pathway of ENPP1 would enhance the understanding of its involvement in cancer advancement, offering valuable clinical perspectives for tumor diagnosis and treatment.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Youth Natural Science Foundation of Shandong Province (grant nos. ZR2021QH367 and ZR2022QH146) and the Shandong Students' Platform for innovation and entrepreneurship training program (grant no. X2024265).

Availability of data and materials

Not applicable.

Authors' contributions

ZY, FP and LX conceptualized the study. LZ, YZ, XD, RL and KZ wrote the manuscript. XD, RL and YT designed the figures and tables. LZ, YT and FP revised and submitted the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

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.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Sana H and Pigeolet M: The role of surgery in global cancer services. Lancet 403: 1237-1238, 2024.
3. Paul S, Konig MF, Pardoll DM, Bettegowda C, Papadopoulos N, Wright KM, Gabelli SB, Ho M, van Elsas A and Zhou S: Cancer therapy with antibodies. Nat Rev Cancer 24: 399-426, 2024.
4. Jin H, Wang L and Bernards R: Rational combinations of targeted cancer therapies: Background, advances and challenges. Nat Rev Drug Discov 22: 213-234, 2023.
5. Terai M and Sato T: Individualised neoantigen cancer vaccine therapy. Lancet 403: 590-591, 2024.
6. Awwad SW, Serrano-Benitez A, Thomas JC, Gupta V and Jackson SP: Revolutionizing DNA repair research and cancer therapy with CRISPR-Cas screens. Nat Rev Mol Cell Biol 24: 477-494, 2023.
7. Wu X, Liu J, Wang J, Wang L, Lin Z, Wang X, Zhu J, Kong B, Fei J, Tang Y, *et al*: Senaparib as First-line maintenance therapy in advanced ovarian cancer: A randomized phase 3 trial. Nat Med 30: 1612-1621, 2024.

8. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J and Siegel RL: Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin 72: 409-436, 2022.
9. Li Y, Zhang L, Xu T, Zhao X, Jiang X, Xiao F, Sun H and Wang L: Aberrant ENPP2 expression promotes tumor progression in multiple myeloma. Leuk Lymphoma 63: 963-974, 2022.
10. Hu M, Guo W, Liao Y, Xu D, Sun B, Song H, Wang T, Kuang Y, Jing B, Li K, *et al*: Dysregulated ENPP1 increases the malignancy of human lung cancer by inducing epithelial-mesenchymal transition phenotypes and stem cell features. Am J Cancer Res 9: 134-144, 2019.
11. Bageritz J and Goidts V: Functional characterization of ENPP1 reveals a link between cell cycle progression and stem-like phenotype in glioblastoma. Mol Cell Oncol 1: e964028, 2014.
12. Takahashi T, Old LJ and Boyse EA: Surface alloantigens of plasma cells. J Exp Med 131: 1325-1341, 1970.
13. Goding JW, Grobben B and Slegers H: Physiological and pathophysiological functions of the Ecto-nucleotide pyrophosphatase/phosphodiesterase family. Biochim Biophys Acta 1638: 1-19, 2003.
14. Stefan C, Jansen S and Bollen M: NPP-type ectophosphodiesterases: Unity in diversity. Trends Biochem Sci 30: 542-550, 2005.
15. Ruf N, Uhlenberg B, Terkeltaub R, Nurnberg P and Rutsch F: The mutational spectrum of ENPP1 as arising after the analysis of 23 unrelated patients with generalized arterial calcification of infancy (GACI). Hum Mutat 25: 98, 2005.
16. Rutsch F, Vaingankar S, Johnson K, Goldfine I, Maddux B, Schauerte P, Kalhoff H, Sano K, Boisvert WA, Superti-Furga A and Terkeltaub R: PC-1 nucleoside triphosphate pyrophosphohydrolase deficiency in idiopathic infantile arterial calcification. Am J Pathol 158: 543-554, 2001.
17. Thakkar AD, Raj H, Chakrabarti D, Ravishankar, Saravanan N, Muthuvelan B, Balakrishnan A and Padigaru M: Identification of gene expression signature in estrogen receptor positive breast carcinoma. Biomark Cancer 2: 1-15, 2010.
18. Lau WM, Doucet M, Stadel R, Huang D, Weber KL and Kominsky SL: Enpp1: A potential facilitator of breast cancer bone metastasis. PLoS One 8: e66752, 2013.
19. Aerts I, Martin JJ, De Deyn PP, Van Ginniken C, Van Ostade X, Kockx M, Dua G and Slegers H: The expression of ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (E-NPP1) is correlated with astrocytic tumor grade. Clin Neurol Neurosurg 113: 224-229, 2011.
20. Huhn S, Bevier M, Rudolph A, Pardini B, Naccarati A, Hein R, Hoffmeister M, Vodickova L, Novotny J, Brenner H, *et al*: Shared ancestral susceptibility to colorectal cancer and other nutrition related diseases. BMC Med Genet 13: 94, 2012.
21. Attalla SS, Boucher J, Proud H, Taifour T, Zuo D, Sanguin-Gendreau V, Ling C, Johnson G, Li V, Luo RB, *et al*: HER2Delta16 engages ENPP1 to promote an Immune-Cold microenvironment in breast cancer. Cancer Immunol Res 11: 1184-1202, 2023.
22. Wang S, Bohnert V, Joseph AJ, Sudaryo V, Skariah G, Swinderman JT, Yu FB, Subramanyam V, Wolf DM, Lyu X, *et al*: ENPP1 is an innate immune checkpoint of the anticancer cGAMP-STING pathway in breast cancer. Proc Natl Acad Sci USA 120: e2313693120, 2023.
23. Duangiad P, Nutho B, Chaijarasphong T, Morales NP, Pongtharangkul T, Hamachi I, Ojida A and Wongkongkatep J: Naturally occurring quercetin and myricetin as potent inhibitors for human ectonucleotide pyrophosphatase/phosphodiesterase 1. Sci Rep 14: 125, 2024.
24. Sun Y, Chen M, Han Y, Li W, Ma X, Shi Z, Zhou Y, Xu L, Yu L, Wang Y, *et al*: Discovery of Pyrido[2,3-d]pyrimidin-7-one derivatives as highly potent and efficacious ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) inhibitors for cancer treatment. J Med Chem 67: 3986-4006, 2024.
25. Ruiz-Fernandez de Cordoba B, Moreno H, Valencia K, Perurena N, Ruedas P, Walle T, Pezonaga-Torres A, Hinojosa J, Guruceaga E, Pineda-Lucena A, *et al*: Tumor ENPP1 (CD203a)/Haptoglobin axis exploits Myeloid-derived suppressor cells to promote Post-radiotherapy local recurrence in breast cancer. Cancer Discov 12: 1356-1377, 2022.
26. Li Z, He Q, Peng J, Yan Y and Fu C: Identification of down-regulated Exosome-associated gene ENPP1 as a novel lipid metabolism and Immune-Associated biomarker for hepatocellular carcinoma. J Oncol 2022: 4834791, 2022.
27. Kato K, Nishimasu H, Okudaira S, Mihara E, Ishitani R, Takagi J, Aoki J and Nureki O: Crystal structure of Enpp1, an extracellular glycoprotein involved in bone mineralization and insulin signaling. Proc Natl Acad Sci USA 109: 16876-16881, 2012.
28. Stefan C, Jansen S and Bollen M: Modulation of purinergic signaling by NPP-type ectophosphodiesterases. Purinergic Signal 2: 361-370, 2006.
29. Linden J, Koch-Nolte F and Dahl G: Purine release, metabolism, and signaling in the inflammatory response. Annu Rev Immunol 37: 325-347, 2019.
30. Li S, Yokota T, Wang P, Ten Hoeve J, Ma F, Le TM, Abt ER, Zhou Y, Wu R, Nanthavongdouangsy M, *et al*: Cardiomyocytes disrupt pyrimidine biosynthesis in nonmyocytes to regulate heart repair. J Clin Invest 132: e149711, 2022.
31. Cimpean A, Stefan C, Gijsbers R, Stalmans W and Bollen M: Substrate-specifying determinants of the nucleotide pyrophosphatases/phosphodiesterases NPP1 and NPP2. Biochem J 381: 71-77, 2004.
32. Ferreira CR, Carpenter TO and Braddock DT: ENPP1 in blood and bone: Skeletal and soft tissue diseases induced by ENPP1 deficiency. Annu Rev Pathol 19: 507-540, 2024.
33. Novais EJ, Narayanan R, Canseco JA, van de Wetering K, Kepler CK, Hilibrand AS, Vaccaro AR and Risbud MV: A new perspective on intervertebral disc Calcification-from bench to bedside. Bone Res 12: 3, 2024.
34. Okawa A, Nakamura I, Goto S, Moriya H, Nakamura Y and Ikegawa S: Mutation in Npps in a mouse model of ossification of the posterior longitudinal ligament of the spine. Nat Genet 19: 271-273, 1998.
35. Brampton C, Pomozi V, Le Corre Y, Zoll J, Kauffenstein G, Ma C, Hoffmann PR, Martin L and Le Saux O: Bone marrow-derived ABCC6 is an essential regulator of ectopic calcification in pseudoxanthoma elasticum. J Invest Dermatol 144: 1772-1783. e3, 2024.
36. Harmey D, Hessle L, Narisawa S, Johnson KA, Terkeltaub R and Millan JL: Concerted regulation of inorganic pyrophosphate and osteopontin by akp2, enpp1, and ank: An integrated model of the pathogenesis of mineralization disorders. Am J Pathol 164: 1199-1209, 2004.
37. Pillai ICL, Li S, Romay M, Lam L, Lu Y, Huang J, Dillard N, Zemanova M, Rubbi L, Wang Y, *et al*: Cardiac fibroblasts adopt osteogenic fates and can be targeted to attenuate pathological heart calcification. Cell Stem Cell 20: 218-232.e5, 2017.
38. Abate N, Carulli L, Cabo-Chan A Jr, Chandalia M, Snell PG and Grundy SM: Genetic polymorphism PC-1 K121Q and ethnic susceptibility to insulin resistance. J Clin Endocrinol Metab 88: 5927-5934, 2003.
39. Maddux BA and Goldfine ID: Membrane glycoprotein PC-1 inhibition of insulin receptor function occurs via direct interaction with the receptor alpha-subunit. Diabetes 49: 13-19, 2000.
40. Maddux BA, Sbraccia P, Kumakura S, Sasson S, Youngren J, Fisher A, Spencer S, Grupe A, Henzel W and Stewart TA: Membrane glycoprotein PC-1 and insulin resistance in non-insulin-dependent diabetes mellitus. Nature 373: 448-451, 1995.
41. Besic V, Stubbs RS and Hayes MT: Liver ENPP1 protein increases with remission of type 2 diabetes after gastric bypass surgery. BMC Gastroenterol 14: 222, 2014.
42. Meyre D, Bouatia-Naji N, Tounian A, Samson C, Lecoeur C, Vatin V, Ghoussaini M, Wachter C, Hercberg S, Charpentier G, *et al*: Variants of ENPP1 are associated with childhood and adult obesity and increase the risk of glucose intolerance and type 2 diabetes. Nat Genet 37: 863-867, 2005.
43. Chourabi M, Liew MS, Lim S, H'mida-Ben Brahim D, Boussofara L, Dai L, Wong PM, Foo JN, Sriha B, Robinson KS, *et al*: ENPP1 mutation causes recessive cole disease by altering melanogenesis. J Invest Dermatol 138: 291-300, 2018.
44. Eytan O, Morice-Picard F, Sarig O, Ezzedine K, Isakov O, Li Q, Ishida-Yamamoto A, Shomron N, Goldsmith T, Fuchs-Telem D, *et al*: Cole disease results from mutations in ENPP1. Am J Hum Genet 93: 752-757, 2013.
45. Nanda A, Xiong X, AlLafi A, Cesarato N and Betz RC: Cole disease due to a novel pathogenic variant in the ENPP1 gene. J Eur Acad Dermatol Venereol 36: e559-e561, 2022.
46. Arima T, Sugimoto K, Taniwaki T, Maeda K, Shibata Y, Tateyama M, Karasugi T, Tokunaga T, Sueyoshi T, Hisanaga S, *et al*: Cartilage tissues regulate systemic aging via ectonucleotide pyrophosphatase/phosphodiesterase 1 in mice. J Biol Chem 300: 105512, 2024.
47. Wang H, Gonzalez-Garcia I, Traba J, Jain S, Conteh S, Shin DM, Qi C, Gao Y, Sun J, Kang S, *et al*: ATP-degrading ENPP1 is required for survival (or persistence) of Long-lived plasma cells. Sci Rep 7: 17867, 2017.

48. Watanabe R, Fujita N, Sato Y, Kobayashi T, Morita M, Oike T, Miyamoto K, Kuro-O M, Michigami T, Fukumoto S, *et al*: Enpp1 is an Anti-aging factor that regulates Klotho under phosphate overload conditions. Sci Rep 7: 7786, 2017.
49. Shi J, Hua X, Zhu B, Ravichandran S, Wang M, Nguyen C, Brodie SA, Palleschi A, Alloisio M, Pariscenti G, *et al*: Somatic genomics and clinical features of lung adenocarcinoma: A retrospective study. PLoS Med 13: e1002162, 2016.
50. Crabtree TD, Puri V, Chen SB, Gierada DS, Bell JM, Broderick S, Krupnick AS, Kreisel D, Patterson GA, Meyers BF, *et al*: Does the method of radiologic surveillance affect survival after resection of stage I non-small cell lung cancer? J Thorac Cardiovasc Surg 149: 45-52, 53.e1-3, 2015.
51. Han Y, Wong FC, Wang D and Kahlert C: An in silico analysis reveals an EMT-associated gene signature for predicting recurrence of Early-Stage lung adenocarcinoma. Cancer Inform 21: 11769351221100727, 2022.
52. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
53. Cancer Genome Atlas N: Comprehensive molecular portraits of human breast tumours. Nature 490: 61-70, 2012.
54. Nolan E, Lindeman GJ and Visvader JE: Deciphering breast cancer: From biology to the clinic. Cell 186: 1708-1728, 2023.
55. Awolaran O, Brooks SA and Lavender V: Breast cancer osteomimicry and its role in bone specific metastasis; an integrative, systematic review of preclinical evidence. Breast 30: 156-171, 2016.
56. Kurosaki M, Terao M, Liu D, Zanetti A, Guarrera L, Bolis M, Gianni' M, Paroni G, Goodall GJ and Garattini E: A DOCK1 Gene-derived circular RNA is highly expressed in luminal mammary tumours and is involved in the epithelial differentiation, growth, and motility of breast cancer cells. Cancers (Basel) 13: 5325, 2021.
57. Ledderose C, Hefti MM, Chen Y, Bao Y, Seier T, Li L, Woehrle T, Zhang J and Junger WG: Adenosine arrests breast cancer cell motility by A3 receptor stimulation. Purinergic Signal 12: 673-685, 2016.
58. Attalla S, Taifour T and Muller W: Tailoring therapies to counter the divergent immune landscapes of breast cancer. Front Cell Dev Biol 11: 1111796, 2023.
59. Schettini F, Barbao P, Braso-Maristany F, Galván P, Martínez D, Paré L, De Placido S, Prat A and Guedan S: Identification of cell surface targets for CAR-T cell therapies and antibody-drug conjugates in breast cancer. ESMO Open 6: 100102, 2021.
60. Manzano RG, Martinez-Navarro EM, Forteza J and Brugarolas A: Microarray phosphatome profiling of breast cancer patients unveils a complex phosphatase regulatory role of the MAPK and PI3K pathways in estrogen Receptor-negative breast cancers. Int J Oncol 45: 2250-2266, 2014.
61. Takahashi RU, Miyazaki H, Takeshita F, Yamamoto Y, Minoura K, Ono M, Kodaira M, Tamura K, Mori M and Ochiya T: Loss of microRNA-27b contributes to breast cancer stem cell generation by activating ENPP1. Nat Commun 6: 7318, 2015.
62. Kawaguchi M, Han X, Hisada T, Nishikawa S, Kano K, Ieda N, Aoki J, Toyama T and Nakagawa H: Development of an ENPP1 fluorescence probe for inhibitor screening, cellular imaging, and prognostic assessment of malignant breast cancer. J Med Chem 62: 9254-9269, 2019.
63. Goswami A, Deb B, Goyal S, Gosavi A, Mali M, Martis AM, Khurana P, Gangar M, Raykar D, Mohanty A and Kulkarni A: AVA-NP-695 selectively inhibits ENPP1 to activate STING pathway and abrogate tumor metastasis in 4T1 breast cancer syngeneic mouse model. Molecules 27: 6721, 2022.
64. Carozza JA, Brown JA, Bohnert V, Fernandez D, AlSaif Y, Mardjuki RE, Smith M and Li L: Structure-aided development of Small-molecule inhibitors of ENPP1, the extracellular phosphodiesterase of the immunotransmitter cGAMP. Cell Chem Biol 27: 1347-1358.e5, 2020.
65. Prostate cancer. Nat Rev Dis Primers 7: 8, 2021.
66. Cai M, Song XL, Li XA, Chen M, Guo J, Yang DH, Chen Z and Zhao SC: Current therapy and drug resistance in metastatic Castration-resistant prostate cancer. Drug Resist Updat 68: 100962, 2023.
67. McKinney LP, Singh R, Jordan IK, Varambally S, Dammer EB and Lillard JW Jr: Transcriptome analysis identifies tumor immune microenvironment signaling networks supporting metastatic Castration-Resistant prostate cancer. Onco (Basel) 3: 81-95, 2023.
68. Wang QJ, Bin C, Xue Q, Gao Q, Huang A, Wang K and Tang N: GSTZ1 sensitizes hepatocellular carcinoma cells to sorafenib-induced ferroptosis via inhibition of NRF2/GPX4 axis. Cell Death Dis 12: 426, 2021.
69. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A and Siegel RL: Ovarian cancer statistics, 2018. CA Cancer J Clin 68: 284-296, 2018.
70. Stella J, Buers I, van de Wetering K, Hohne W, Rutsch F and Nitschke Y: Effects of different variants in the ENPP1 gene on the functional properties of ectonucleotide pyrophosphatase/phosphodiesterase family member 1. Hum Mutat 37: 1190-1201, 2016.
71. Martinez-Ramirez AS, Diaz-Munoz M, Battastini AM, Campos-Contreras A, Olvera A, Bergamin L, Glaser T, Jacintho Moritz CE, Ulrich H and Vázquez-Cuevas FG: Cellular migration ability is modulated by extracellular purines in ovarian carcinoma SKOV-3 Cells. J Cell Biochem 118: 4468-4478, 2017.
72. Zhang QF, Li YK, Chen CY, Zhang XD, Cao L, Quan FF, Zeng X, Wang J and Liu J: Identification and validation of a prognostic index based on a metabolic-genomic landscape analysis of ovarian cancer. Biosci Rep 40: BSR20201937, 2020.
73. Wang H, Ye F, Zhou C, Cheng Q and Chen H: High expression of ENPP1 in high-grade serous ovarian carcinoma predicts poor prognosis and as a molecular therapy target. PLoS One 16: e0245733, 2021.
74. Larjavaara S, Mantyla R, Salminen T, Haapasalo H, Raitanen J, Jääskeläinen J and Auvinen A: Incidence of gliomas by anatomic location. Neuro Oncol 9: 319-325, 2007.
75. Tykocki T and Eltayeb M: Ten-year survival in glioblastoma. A systematic review. J Clin Neurosci 54: 7-13, 2018.
76. Bageritz J, Puccio L, Piro RM, Hovestadt V, Phillips E, Pankert T, Lohr J, Herold-Mende C, Lichter P and Goidts V: Stem cell characteristics in glioblastoma are maintained by the Ecto-nucleotidase E-NPP1. Cell Death Differ 21: 929-940, 2014.
77. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, Dewhirst MW, Bigner DD and Rich JN: Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 444: 756-760, 2006.
78. Roa JC, Garcia P, Kapoor VK, Maithel SK, Javle M and Koshiol J: Gallbladder cancer. Nat Rev Dis Primers 8: 69, 2022.
79. Montalvo-Jave EE, Rahnemai-Azar AA, Papaconstantinou D, Deloiza ME, Tsilimigras DI, Moris D, Mendoza-Barrera GE, Weber SM and Pawlik TM: Molecular pathways and potential biomarkers in gallbladder cancer: A comprehensive review. Surg Oncol 31: 83-89, 2019.
80. Turgeon MK and Maithel SK: Cholangiocarcinoma: A Site-specific update on the current state of surgical management and multi-modality therapy. Chin Clin Oncol 9: 4, 2020.
81. Yano Y, Hayashi Y, Sano K, Nagano H, Nakaji M, Seo Y, Ninomiya T, Yoon S, Yokozaki H and Kasuga M: Expression and localization of ecto-nucleotide pyrophosphatase/phosphodiesterase I-1 (E-NPP1/PC-1) and -3 (E-NPP3/CD203c/PD-Ibeta/B10/gp130(RB13-6)) in inflammatory and neoplastic bile duct diseases. Cancer Lett 207: 139-147, 2004.
82. Yang C, Chen J, Yu Z, Luo J, Li X, Zhou B and Jiang N: Mining of RNA Methylation-related genes and elucidation of their molecular biology in gallbladder carcinoma. Front Oncol 11: 621806, 2021.
83. Zhang X, Li L, Zhang M, Zhang L, Liu S, Guo J, Jiang N, Peng Q, Wang J and Ding S: Intelligent recognition of CTCs from gallbladder cancer by ultrasensitive electrochemical cytosensor and diagnosis of chemotherapeutic resistance. Biosens Bioelectron 228: 115183, 2023.
84. Ng JH, Iyer NG, Tan MH and Edgren G: Changing epidemiology of oral squamous cell carcinoma of the tongue: A global study. Head Neck 39: 297-304, 2017.
85. Tan Y, Wang Z, Xu M, Li B, Huang Z, Qin S, Nice EC, Tang J and Huang C: Oral squamous cell carcinomas: State of the field and emerging directions. Int J Oral Sci 15: 44, 2023.
86. Romano A, Di Stasio D, Petruzzi M, Fiori F, Lajolo C, Santarelli A, Lucchese A, Serpico R and Contaldo M: Noninvasive imaging methods to improve the diagnosis of oral carcinoma and its precursors: State of the art and proposal of a Three-step diagnostic process. Cancers (Basel) 13: 2864, 2021.
87. Li J, Qiao Z, Li Y, Lu X, Shao T and Lv X: Bioinformatic analysis indicated that STARD4-AS1 might be a novel Ferroptosis-related biomarker of oral squamous cell carcinoma. Heliyon 10: e33193, 2024.
88. Radaic A, Kamarajan P, Cho A, Wang S, Hung GC, Najarzadegan F, Wong DT, Ton-That H, Wang CY and Kapila YL: Biological biomarkers of oral cancer. Periodontol 2000: Dec 10, 2023 doi: 10.1111/prd.12542 (Epub ahead of print).

89. Wu T, Jiao Z, Li Y, Su X, Yao F, Peng J, Chen W and Yang A: HPRT1 promotes chemoresistance in oral squamous cell carcinoma via activating MMP1/PI3K/Akt signaling pathway. Cancers (Basel) 14: 855, 2022.
90. Liu Y, Wang Y, Li X, Jia Y, Wang J and Ao X: FOXO3a in cancer drug resistance. Cancer Lett 540: 215724, 2022.
91. Narayanan S, Cai CY, Assaraf YG, Guo HQ, Cui Q, Wei L, Huang JJ, Ashby CR Jr and Chen ZS: Targeting the ubiquitin-proteasome pathway to overcome Anti-cancer drug resistance. Drug Resist Updat 48: 100663, 2020.
92. Perez-Valencia JA, Prosdocimi F, Cesari IM, da Costa IR, Furtado C, Agostini M and Rumjanek FD: Angiogenesis and evading immune destruction are the main related transcriptomic characteristics to the invasive process of oral tongue cancer. Sci Rep 8: 2007, 2018.
93. Ma C, Zhao J, Zhou L, Jia C, Shi Y, Li X, Jihu K and Zhang T: Targeting ENPP1 depletion may be a promising therapeutic strategy for treating oral squamous cell carcinoma via cytotoxic autophagy-related apoptosis. FASEB J 38: e23420, 2024.
94. Carozza JA, Cordova AF, Brown JA, AlSaif Y, Böhnert V, Cao X, Mardjuki RE, Skariah G, Fernandez D and Li L: ENPP1's regulation of extracellular cGAMP is a ubiquitous mechanism of attenuating STING signaling. Proc Natl Acad Sci USA 119: e2119189119, 2022.
95. Sun L, Wu J, Du F, Chen X and Chen ZJ: Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the type I interferon pathway. Science 339: 786-791, 2013.
96. Wu J, Sun L, Chen X, Du F, Shi H, Chen C and Chen ZJ: Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science 339: 826-830, 2013.
97. Harding SM, Benci JL, Irianto J, Discher DE, Minn AJ and Greenberg RA: Mitotic progression following DNA damage enables pattern recognition within micronuclei. Nature 548: 466-470, 2017.
98. Li L: Stimulating STING for cancer therapy: Taking the extracellular route. Cell Chem Biol 31: 851-861, 2024.
99. Mackenzie KJ, Carroll P, Martin CA, Murina O, Fluteau A, Simpson DJ, Olova N, Sutcliffe H, Rainger JK and Leitch A: cGAS surveillance of micronuclei links genome instability to innate immunity. Nature 548: 461-465, 2017.
100. Haag SM, Gulen MF, Reymond L, Gibelin A, Abrami L, Decout A, Heymann M, van der Goot FG, Turcatti G, Behrendt R and Ablasser A: Targeting STING with covalent small-molecule inhibitors. Nature 559: 269-273, 2018.
101. Kato K, Nishimasu H, Oikawa D, Hirano S, Hirano H, Kasuya G, Ishitani R, Tokunaga F and Nureki O: Structural insights into cGAMP degradation by Ecto-nucleotide pyrophosphatase phosphodiesterase 1. Nat Commun 9: 4424, 2018.
102. Wang X, Lu X, Yan D, Zhou Y and Tan X: Development of Novel Ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1) inhibitors for tumor immunotherapy. Int J Mol Sci 23: 7104, 2022.
103. Wu J, Dobbs N, Yang K and Yan N: Interferon-Independent activities of mammalian STING mediate antiviral response and tumor immune evasion. Immunity 53: 115-126.e5, 2020.
104. Liu FF, Shi W, Done SJ, Miller N, Pintilie M, Voduc D, Nielsen TO, Nofech-Mozes S, Chang MC, Whelan TJ, *et al*: Identification of a Low-Risk luminal a breast cancer cohort that may not benefit from breast radiotherapy. J Clin Oncol 33: 2035-2040, 2015.
105. Cho Y, Kang M, Ji SH, Jeong HJ, Jung JE, Oh DH, Park S, Park YY, Choi J, Kim S, *et al*: Discovery of orally bioavailable phthalazinone analogues as an ENPP1 inhibitor for STING-mediated cancer immunotherapy. J Med Chem 66: 15141-15170, 2023.
106. Jeong HJ, Lee HL, Kim SJ, Jeong JH, Ji SH, Kim HB, Kang M, Chung HW, Park CS, Choo H, *et al*: Identification of novel pyrrolopyrimidine and pyrrolopyridine derivatives as potent ENPP1 inhibitors. J Enzyme Inhib Med Chem 37: 2434-2451, 2022.
107. Jung JE, Jang Y, Jeong HJ, Kim SJ, Park K, Oh DH, Yu A, Park CS and Han SJ: Discovery of 3,4-dihydropyrimido[4,5-d] pyrimidin-2(1H)-one and 3,4-dihydropyrido[2,3-d] pyrimidin-2(1H)-one derivatives as novel ENPP1 inhibitors. Bioorg Med Chem Lett 75: 128947, 2022.
108. Khan Jadoon MS, Pelletier J, Sevigny J and Iqbal J: Synthesis of new class of indole acetic acid sulfonate derivatives as ecto-nucleotidases inhibitors. RSC Adv 13: 29496-29511, 2023.
109. Rohilla A, Singh AK, Koleske B, Srikrishna G and Bishai WR: Structure-based virtual screening and in vitro validation of inhibitors of cyclic dinucleotide phosphodiesterases ENPP1 and CdnP. Microbiol Spectr 12: e0201223, 2024.
110. Guan D, Fang L, Feng M, Guo S, Xie L, Chen C, Sun X, Wu Q, Yuan X, Xie Z, *et al*: Ecto-nucleotide pyrophosphatase/phosphodiesterase 1 inhibitors: Research progress and prospects. Eur J Med Chem 267: 116211, 2024.
111. Ruiz-Fernandez de Cordoba B, Martinez-Monge R and Lecanda F: ENPP1 immunobiology as a therapeutic target. Clin Cancer Res 29: 2184-2193, 2023.
112. Dillon S, Suchacki K, Hsu SN, Stephen LA, Wang R, Cawthorn WP, Stewart AJ, Nudelman F, Morton NM and Farquharson C: Ablation of Enpp6 results in transient bone hypomineralization. JBMR Plus 5: e10439, 2021.
113. Yan J, Duan W, Gao Q, Mao T, Wang M, Duan J and Li J: ENPP2 inhibitor improves proliferation in AOM/DSS-induced colorectal cancer mice via remodeling the gut barrier function and gut microbiota composition. Pharmacol Res 195: 106877, 2023.
114. Masse K, Bhamra S, Paroissin C, Maneta-Peyret L, Boue-Grabot E and Jones EA: The enpp4 ectonucleotidase regulates kidney patterning signalling networks in Xenopus embryos. Commun Biol 4: 1158, 2021.
115. Thompson JA, Motzer RJ, Molina AM, Choueiri TK, Heath EI, Redman BG, Sangha RS, Ernst DS, Pili R, Kim SK, *et al*: Phase I trials of Anti-ENPP3 Antibody-drug conjugates in advanced refractory renal cell carcinomas. Clin Cancer Res 24: 4399-4406, 2018.
116. Takaya K and Kishi K: Regulation of ENPP5, a senescence-associated secretory phenotype factor, prevents skin aging. Biogerontology 25: 529-542, 2024.
117. Boccon-Gibod L: Etiopathogenesis of benign prostatic hypertrophy. Recent acquisitions. Ann Urol (Paris) 22: 3-8, 1988 (In French).
118. Onyedibe KI, Wang M and Sintim HO: ENPP1, an old enzyme with new functions, and small molecule Inhibitors-A STING in the tale of ENPP1. Molecules 24: 4192, 2019.
119. Ullah S, Pelletier J, Sevigny J and Iqbal J: Synthesis and biological evaluation of arylamide sulphonate derivatives as ectonucleotide Pyrophosphatase/phosphodiesterase-1 and -3 inhibitors. ACS Omega 7: 26905-26918, 2022.