Review Article

Do alkaline phosphatases have great potential in the diagnosis, prognosis, and treatment of tumors?

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Abstract: Alkaline phosphatase (ALP) is a group of enzymes that catalyze hydrolysis of phosphate esters at an alkaline pH, resulting in the generation of inorganic phosphate. These enzymes are widely distributed, and their activity is found in various tissues including bone, liver, intestine, and placenta. However, abnormalities in ALP expression and activity have been observed in certain types of cancer. In some cases, elevated serum levels of ALP are observed in patients with liver and bone metastasis. In other cases, increased levels of ALP have been observed in patients with pancreatic and lung cancer. On the other hand, low expression of ALP has also been associated with poor prognosis in patients with certain types of tumors, including colorectal cancer (CRC), breast cancer, and non-small cell lung cancer (NSCLC). In these cases, low ALP activity may be associated with decreased differentiation of cancer cells and increased cancer cell proliferation. Overall, the role of ALP in cancer is complex and context-dependent. This article reviews application progress of ALP in cancer, and we hypothesize that ALP might be a potential tumor biomarker, combined detection of aspartate aminotransferase (AST)/alanine aminotransferase (ALT), bone-specific alkaline phosphatase (BSAP), carbohydrate antigen 19-9 (CA 19-9), lactate dehydrogenase (LDH) and ALP isozymes levels can be used for more accurate diagnosis of a particular tumor. Further research is needed to better understand the mechanisms underlying ALP dysregulation in cancer and to identify potential therapeutic targets.

Keywords: Alkaline phosphatase (ALP); cancer; biomarker; bone metastasis

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Introduction

Alkaline phosphatase (ALP) is a crucial group of enzymes that play an essential role in the human body (1). These enzymes catalyze the hydrolysis of phosphate esters at an alkaline pH level, which results in the generation of inorganic phosphate (2). ALP is widely distributed throughout various tissues within the body, including bone, liver, intestine, and placenta. Their activity is critical for proper bone development and growth during childhood and adolescence (3). Additionally, they aid in digestion by breaking down complex molecules into simpler ones that can be absorbed by the body (3). However, abnormalities in ALP expression and activity have been observed in certain types of cancer.

ALP plays a crucial role in various physiological processes such as bone formation and liver function (4,5). However, when there are abnormal growths or

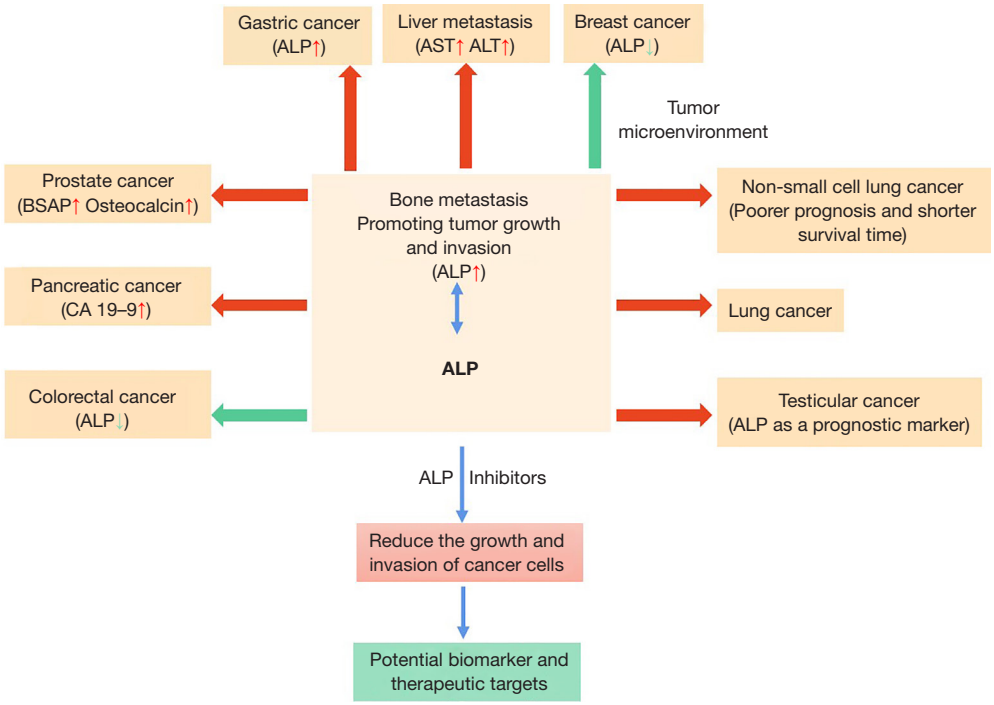

Figure 1 Abnormalities in ALP expression and activity have been observed in certain types of cancer. In some cases, including prostate cancer, liver metastasis, pancreatic cancer, lung cancer, non-small cell lung cancer, testicular cancer, elevated serum levels of ALP are observed in patients with bone metastasis. While, low ALP activity is associated with breast cancer and colorectal cancer. ALP inhibitors can reduce the growth and invasion of cancer cells. In all, ALP might be a potential tumor biomarker, and a potential therapeutic target. Red arrows indicate upregulated expression levels and green arrows indicate downregulated expression levels. ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BSAP, bone-specific alkaline phosphatase; CA 19-9, carbohydrate antigen 19-9.

tumors present in these areas of the body, it can cause an overproduction of ALP which then leak into the bloodstream. This phenomenon is especially prevalent among those suffering from prostate cancer since this type of malignancy tends to spread to bones more frequently than other types (6). Therefore, monitoring ALP levels through regular blood tests can help doctors detect any potential bone metastases early on and provide appropriate treatment options accordingly. In conclusion, while elevated serum levels of ALP may not always indicate the presence of cancerous growths or tumors within the body; they do serve as valuable indicators for physicians to monitor closely when assessing patients' overall health status (*Figure 1*).

In the realm of medical diagnosis, serum levels of ALP have been proven to be a valuable indicator for various conditions (7). One such condition is liver metastasis, where an increase in ALP levels can signify damage to the liver caused by invasive tumor cells (8). This finding has been observed in numerous studies and serves as a crucial diagnostic tool for physicians (9-11). However, it is not just liver metastasis that can cause elevated ALP levels. In fact, patients with pancreatic and lung cancer have also shown increased ALP levels, although the exact mechanism behind this phenomenon remains unclear (12,13). Nonetheless, these findings highlight the importance of monitoring ALP levels in cancer patients as they may provide early indications of disease progression or treatment efficacy. Overall, while there is still much to learn about how ALP function within the body and its relationship with various diseases, it is clear that this enzyme plays a significant role in diagnosing and treating certain conditions, particularly those related to cancer (*Table 1*). As research continues to shed light on this topic, we can hope for even more effective methods for detecting and managing illnesses moving forward.

ALP isozymes

ALP isozymes are a family of enzymes that catalyze the hydrolysis of phosphate esters at an alkaline pH. ALPs

Table 1 The level of alkaline phosphatase in human cancers

Cancer type	Levels	Functions	Combined diagnosis	References
Prostate cancer	Up	Promoting cell growth, metastasis and invasion	Osteocalcin/BSAP	(14-19)
Liver metastasis	Up	Promoting liver damage, cell invasion	AST/ALT/CT/MRI	(20-26)
Pancreatic cancer	Up	Promoting tumor growth and invasion	CA 19-9	(27-34)
Lung cancer	Up	Promoting tumor proliferation, invasion, bone metastases	N/A	(13,35-41)
Breast cancer	Down	Modulating the tumor micro-environment, cytokine expression, cell proliferation and migration	N/A	(42-47)
Colorectal cancer	Down	Promotion of cell proliferation, colony formation, and decreased tumor suppressor gene expression	N/A	(48-52)
NSCLC	Up	Promoting tumor growth and invasion	ALK/EGFR	(53-55)
NSGCT	Up	Promoting tumor growth and invasion	N/A	(56-60)
GC	Up	Increased metastasis	LDH	(19,61,62)

NSCLC, non-small cell lung cancer; NSGCT, non-seminoma germ cell tumor; GC, gastric cancer; BSAP, bone-specific alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography; MRI, magnetic resonance imaging; CA 19-9, carbohydrate antigen 19-9; N/A, not available; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; LDH, lactate dehydrogenase.

Table 2 Classification and function of alkaline phosphatase isozymes in human

Classes	Locations/stages	Protein/gene	Functions	References
Germ cell	Male germ cells	GCAP/*ALPG*	Up-regulation in primary seminoma of the prostate	(64,65)
Placental	Cervix, uterine, pregnancy	PLALP/*ALPP*	Biomarker for placental health, biomarker for pancreatic cancer	(66,67)
Intestinal	Brush border of intestinal cells	IAP/*ALPI*	Absorption of dietary phosphates	(68,69)
Liver/bone/kidney (tissue-nonspecific)	Liver, bone, kidney	TNAP/*ALPL*	Bone metabolism and mineralization	(70-72)

are found in different tissues and organs in the body, and different tissues express different ALP isozymes. There are four major ALP isozymes: placental, intestinal, liver/bone/kidney (tissue-nonspecific), and germ cell (63). Placental and intestinal isozymes are present in fetal and adult tissues, respectively, while the liver/bone/kidney isozyme is found in the liver, bone, and kidney (*Table 2*). The different ALP isozymes differ in their enzymatic properties, tissue distribution, and regulation. For example, germ cell ALP is only found in some stages of germ cell development in males (64,65). Placental ALP isozyme is produced exclusively during pregnancy, and its levels in maternal serum serve as a marker for placental health (66,67). Intestinal ALP is expressed in the brush border of intestinal cells and is involved in the absorption of dietary phosphates (68,69). Intestinal and placental ALP isoenzymes are not usually associated with tumor metastasis diagnosis, but their measurement can help exclude non-tumor-related causes of elevated ALP levels (70-72). Liver/bone/kidney ALP is the most widely expressed isozyme and is involved in bone metabolism and mineralization. By assessing the levels and ratios of ALP isoenzymes, along with total ALP, healthcare professionals can obtain valuable information regarding the potential presence and source of tumor metastasis. The combination of ALP isoenzyme analysis with other clinical and imaging investigations can aid in the diagnosis, staging, and monitoring of tumor metastasis, particularly in cases where bone or liver involvement is suspected (73-75). The measurement of ALP isozymes in blood serum or tissue has diagnostic and prognostic value in different

diseases. In some diseases, specific ALP isozymes can be used as biomarkers to differentiate between normal and pathological conditions (73-75).

Overall, the study of ALP isozymes is important in understanding their different roles in the body, their regulation, and their potential use as diagnostic and prognostic markers in cancers. By studying the function of each ALP isozyme in specific tissues and organs, the non-specific ALP can be used as a molecular marker for specific tumor diseases.

ALPs in advanced prostate cancer

In advanced prostate cancer, the level of tissue-nonspecific alkaline phosphatase (TNAP), an enzyme involved in bone formation, is often elevated (14). This is because prostate cancer cells can grow in the bones, leading to an increase in ALP activity, indicating the presence of bone metastases (15). Bone metastases in prostate cancer patients cause bone pain and increase the risk of fracture, leading to a decreased quality of life (16). The increased ALP levels, therefore, serve as an important biomarker to monitor prostate cancer progression and assess the effectiveness of treatment. ALP has also been studied as a potential target for treatment in advanced prostate cancer (17). Studies have shown that targeting ALP with ALP inhibitors can reduce the growth and invasion of prostate cancer cells *in vitro* and *in vivo* (15-18). In bone metastatic castration-resistant prostate cancer, ALP-bouncing and lactate dehydrogenase (LDH)-normalization may be a good prognostic marker (19). However, more clinical trials are needed to evaluate the safety and efficacy of ALP inhibitors in prostate cancer patients. In addition to ALP, other bone-related markers such as osteocalcin and bone-specific alkaline phosphatase (BSAP) have also been found to be useful in monitoring the progression of bone metastases in prostate cancer patients (20).

The combination of ALP with other bone markers may provide a more comprehensive understanding of bone metastasis in advanced prostate cancer and assist in personalized treatment decision-making. We believe that we can explore the specific targets of ALP in prostate tissue, and further determine the association between ALP and prostate cancer through the targets of ALP.

ALPs in liver metastasis

In liver metastasis, ALP levels can be elevated in serum and signify liver damage due to the invasion of tumor cells (21). The liver is a common site for the metastasis of tumors originating from other organs including the colon, stomach, pancreas, and breast (22). The presence of liver metastasis may be associated with a worse prognosis, as it often indicates advanced disease. In cases of liver metastasis, ALP can serve as a useful biomarker to monitor the progression of the disease and assess the effectiveness of treatment (23). In addition to ALP, other liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may also be elevated with liver metastasis (24). These liver enzymes are released into the bloodstream when liver cells are damaged. In addition to monitoring the levels of ALP and other liver enzymes, diagnostic imaging modalities like computed tomography (CT) scans and magnetic resonance imaging (MRI) can also detect the presence and location of liver metastasis. Treatment options for liver metastasis depend on the type and stage of cancer, and may include surgery, radiation therapy, chemotherapy, and targeted therapy (25,26).

Although AST and ALT are classic indicators of abnormal liver function, the abnormality of ALP is also closely related to liver metastasis. Therefore, exploring the regulatory relationship between ALP and AST will greatly improve the accuracy of ALP as a marker of liver cancer. In short, monitoring ALP levels along with other liver enzymes and diagnostic imaging is an important part of managing liver metastasis in cancer patients.

ALPs in pancreatic cancer

ALPs have been found to be elevated in some cases of pancreatic cancer, though the exact mechanism is not well understood (27). In one study, elevated levels of ALP were observed in approximately 30% of patients with pancreatic cancer (28). However, in combination with other tumor markers like carbohydrate antigen 19-9 (CA 19-9), elevated ALP levels may be used to aid in diagnosing pancreatic cancer (29,30). While the exact role of ALPs in pancreatic cancer is still unknown, some studies have suggested that ALP may be involved in promoting tumor growth and invasion (31-33). In animal studies, inhibiting ALP has been found to reduce the progression and metastasis of pancreatic cancer (34).

ALP is not specific to pancreatic cancer and can also be elevated in other conditions such as liver and bone disease, making it an unspecific marker of pancreatic cancer. While placental isozymes, PLALP, is localized in the pancreas, so we can study the specific mechanism of PLALP in the

pancreas, and this isozyme can be further used as a marker of pancreatic cancer. Overall, while elevated ALP levels may be a potential marker for pancreatic cancer, more research is needed to fully understand the role of ALPs in pancreatic cancer progression and to identify the potential therapeutic benefit of targeting ALP in the treatment of pancreatic cancer.

ALPs in lung cancer

ALP has been found to be elevated in some cases of lung cancer, though the exact mechanism is not well understood (35). In one study, elevated levels of ALP were observed in approximately 10% of patients with lung cancer (36). In some cases, high levels of ALP in patients with lung cancer may indicate the presence of bone metastases (37). Bone metastases are a common complication of lung cancer and result in the release of ALP into the bloodstream due to the breakdown of bone tissue (38). In addition to being a potential marker of bone metastases, ALP may also be involved in promoting tumor growth and invasion in lung cancer (39). In animal studies, inhibiting ALP has been found to reduce lung cancer cell proliferation and migration (13,40,41).

In sum, while elevated ALP levels may be a potential marker of bone metastases in lung cancer patients, the clinical significance of ALP as a biomarker and its role in lung cancer progression is still unclear, and more research is needed to better understand the mechanisms underlying ALP. We know ALP dysregulation in lung cancer and accompanied by bone metastases. While tissue-nonspecific isozymes are involved in bone metabolism and mineralization, so we could detect the level of TNAP in lung cancer, to investigate the mechanism of TNAP in the proliferation and migration of lung cancer cells.

ALPs in breast cancer

ALPs have been studied in breast cancer as potential biomarkers for diagnosis, prognosis, and treatment (42). ALP has been found to be low in breast cancer, and researchers have reported a correlation between low ALP levels and a more aggressive cancer subtype, higher tumor stage, and poorer outcomes (43). Low ALP activity is associated with a higher probability of recurrence and metastasis, as well as a reduced overall survival rate in breast cancer patients (44). However, the exact mechanisms underlying the association between ALP and breast cancer progression remain unclear. In breast cancer cell lines, studies have shown that ALP may be involved in modulating the tumor microenvironment by regulating extracellular matrix (ECM) and cytokine expression, as well as cell proliferation and migration (33,40,41). Additionally, ALP may play a role in bone homeostasis and remodeling, which are important processes in the metastasis of breast cancer to the bone (45). ALP has also been studied as a potential target for breast cancer treatment (46). *In vitro*, high ALP-expressing breast cancer cell lines were shown to be more sensitive to treatment with some chemotherapeutic agents (47).

However, more studies are needed to explore the therapeutic potential of targeting ALP in breast cancer treatment. ALP levels in breast cancer and other cancers are diametrically opposite, suggesting that ALP functions differently in different tissues. Breast tissue is mainly tissue-nonspecific isoenzymes, future studies can explore the expression level of TNAP in different tumors and study how TNAP regulates the occurrence and development of breast cancer. In summary, low ALP activity may serve as a potential biomarker for breast cancer diagnosis and prognosis. Further research is needed to fully understand the underlying mechanisms linking ALP with breast cancer progression and to determine its therapeutic potential.

ALPs in colorectal cancer (CRC)

CRC is one of the most common malignancies worldwide, and several studies have reported that ALP levels are decreased in patients with newly diagnosed, untreated CRC (48-50). Low ALP activity has been associated with a poor prognosis in patients with advanced or metastatic CRC, indicating a correlation between low ALP expression and more aggressive tumor behaviour (49). However, the specific mechanism for this relationship is not yet well understood. In colon cancer cell lines, inhibiting ALP activity has been found to result in the promotion of cell proliferation, colony formation, and decreased tumor suppressor gene expression (50). These findings suggest that ALP modulates the growth and progression of colon cancer cells, though more research is needed to investigate the role of ALP in human CRC. Additionally, ALP has been used as a marker to monitor the effectiveness of chemotherapy in CRC patients (51). Studies have shown that elevated serum ALP levels can be reduced after chemotherapy regimens and that this reduction is associated with a better clinical outcome (51,52).

In a word, the role of ALP in the development and progression of CRC is complex and context-dependent. While low ALP activity may indicate a poor prognosis in advanced or metastatic CRC, is similar to that in breast cancer, but opposite to that in other cancers, indicating that the mechanism of ALP action in cancer is a double-edged sword. Further investigations are required to fully elucidate the underlying mechanisms and determine if it could serve as a therapeutic target.

ALPs in non-small cell lung cancer (NSCLC)

ALPs have been found to be elevated in NSCLC patients, though the exact mechanism is not well understood (53). In some cases, elevated levels of ALP in NSCLC patients may indicate the presence of bone metastases. Bone metastases are a common complication of NSCLC and result in the release of ALP into the bloodstream due to the breakdown of bone tissue (54). ALP has also been studied as a potential biomarker in NSCLC patients, though the results of studies have been inconsistent (38). Some studies have reported that high levels of ALP are associated with a poorer prognosis and shorter survival time in NSCLC patients, while others have found no significant correlation between ALP levels and prognosis in NSCLC (38,54,55). In addition to being a potential marker of bone metastases, ALP may also be involved in promoting tumor growth and invasion in NSCLC. In animal studies, inhibiting ALP has been found to reduce lung cancer cell proliferation and migration (40,41).

All in all, elevated ALP levels may be a potential marker of bone metastases in NSCLC patients, the role of ALP as a prognostic or therapeutic biomarker in NSCLC is still unclear and requires further research. ALP is not strongly correlated with the diagnosis of NSCLC, so it is necessary to identify the regulatory targets of ALP in NSCLC. While *ALK* fusion oncogene, *EGFR* mutations are served as predictive biomarkers in NSCLC, to explore the effect of ALP on ALK fusion oncogene and *EGFR* mutations and to use *ALK* and *EGFR* together as a diagnostic marker for NSCLC.

ALPs in testicular cancer

ALPs have been studied in testicular cancer, specifically in non-seminoma germ cell tumors (NSGCTs), and have shown potential as a diagnostic and prognostic marker (56). In NSGCT, elevations in serum ALP levels are commonly seen when there is a presence of metastases in the body, primarily bone metastases (57). Elevated ALP levels can aid in the diagnosis of NSGCT and in monitoring the treatment response of the tumor. Studies have suggested that high ALP levels in NSGCT patients are associated with an increased risk of disease recurrence and a decreased overall survival rate, indicating a potential role for ALP as a prognostic marker (57-59). ALP can also help identify chemotherapy-resistant or metastatic NSGCT, which can guide personalized treatment decisions (59). ALP has also been studied as a potential therapeutic target in NSGCT (59). In preclinical studies, inhibiting ALP activity has been found to reduce the growth and invasion of testicular cancer cells (60).

In a nutshell, the study of ALP in testicular cancer has potential in the detection, prognosis, and treatment of NSGCT. Further research is necessary to confirm the clinical significance of ALP in testicular cancer treatment. It is known that germ cell ALP isoenzyme is found in the testes, so GCAP protein is enriched in the testis tissue. Next, we can study the specific mechanism of GCAP in NSGCT, and this ALP isozyme can be further used as a marker of pancreatic cancer.

ALPs in gastric cancer (GC)

Elevated levels of ALP can be observed in the blood of some GC patients, particularly in cases with liver metastasis. High levels of ALP have been associated with poorer prognosis and shorter survival rates in GC patients (61). Elevated levels of ALP and LDH have been associated with poorer prognosis in various types of cancers, including GC (62). Studies have shown that high levels of ALP and LDH are associated with advanced tumor stage, increased metastasis, and worse overall survival in patients with unresectable advanced GC. Higher levels of ALP and LDH are indicative of greater tumor volume and aggressiveness. They are associated with larger tumor size, lymph node involvement, and the presence of distant metastases, all of which contribute to a poor prognosis (62).

Higher baseline levels of ALP and LDH have been associated with poorer response to chemotherapy and targeted therapies in GC (19). Monitoring ALP and LDH during treatment can help assess treatment efficacy and identify patients who may benefit from alternative therapies. it is important to note that the prognostic value of ALP and

LDH, along with host-related factors, may vary depending on other tumor characteristics, patient demographics, and the specific treatment regimen. Assessing these factors in combination with ALP and LDH can provide a more comprehensive prognostic evaluation for patients with unresectable advanced GC (19).

ALPs in chemotherapy and radiation therapy

ALPs have been investigated as potential biomarkers for assessing the effectiveness of chemotherapy and radiation therapy in cancer treatment (25,26,51,52,59). In some types of cancer, such as testicular cancer, elevation of ALP levels in the blood can indicate the presence of chemotherapy-resistant or metastatic disease (59). In these cases, monitoring of ALP levels can be an important tool in the management of cancer treatment. ALP levels have also been studied as potential prognostic biomarkers in chemotherapy-treated cancer patients (57,58). In some studies, a reduction in ALP levels after chemotherapy has been associated with improved outcomes in certain types of cancer, including CRC and pancreatic cancer (28,29,52). This suggests that changes in ALP levels can serve as a marker for treatment response and guide personalized treatment decisions. In radiation therapy, ALP activity has been found to be increased in normal tissue after radiation-induced injury (76). This elevation in ALP levels is thought to reflect the changes in the cellular environment of the injured tissue. Studies have shown that measuring ALP levels before and after radiation therapy can provide insights into the effectiveness of the treatment and the level of tissue toxicity (76,77). To sum up, the role of ALP in assessing the effectiveness of chemotherapy and radiation therapy in cancer treatment is promising. Further research is needed to fully understand the use of ALP as a prognostic biomarker and to explore the therapeutic potential of targeting ALP in combination with chemotherapy and radiation therapy.

Challenges of ALPs in tumor diagnosis

There are several methods available for analyzing ALP activity in clinical samples. Such as enzyme assays, which measure the enzymatic activity of ALP by monitoring the conversion of substrate to product. Different substrates can be used, such as p-nitrophenyl phosphate (p-NPP) or 5-bromo-4-chloro-3-indolyl phosphate (BCIP) (78,79). If we want to improve the sensitivity and specificity of detecting and quantifying ALP activity, enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay (CLIA) can be used (80,81). While ALP isoenzymes can be separated and analyzed using methods like electrophoresis or high-performance liquid chromatography (HPLC). This helps to identify different forms of ALP and distinguish them from other isoenzymes (82).

Although there are so many methods to analyze ALP activity. The biggest problem often faced in ALP analysis is the interference from other enzymes or compounds present in clinical samples. Some compounds can lead to false-positive or false-negative results, affecting the accuracy of ALP activity measurements. To overcome this problem, various measures can be taken: (I) selective inhibitors: addition of specific inhibitors can help suppress interfering enzymes while measuring ALP activity. For example, levamisole is commonly used to inhibit interference from intestinal ALP (83). (II) Sample preparation: proper sample preparation techniques, such as sample dilution or filtration, can help remove interfering substances and improve the accuracy of ALP activity measurements. (III) Validation and quality control: regular validation and quality control should be performed to monitor the accuracy and precision of the analytical methods used for ALP analysis. This ensures reliable and consistent results.

Regulation pathways of ALP in cancer

The expression of ALPs in cancer is complex and context-dependent. Its abnormal expression is associated with multiple molecular pathways (*Figure 2*). Activation of the Wnt/β-catenin pathway is associated with increased ALP expression in multiple cancer types, including colon, liver, and bone cancers. β-catenin translocates to the nucleus and promotes the transcription of *ALP* gene, leading to increased ALP production (84). Activation of bone morphogenetic protein (BMP) pathway leads to increased ALP expression in cancer cells, particularly in bone metastases of solid tumors, where tumor cells acquire osteoblastic features (85). In the tumor microenvironment, changes in ECM composition and stiffness can modulate ALP expression in cancer cells (86). Activation of integrin-mediated signaling pathways, such as focal adhesion kinase (FAK) or Rho GTPases, can upregulate ALP expression and promote cancer cell invasion and metastasis (87). MiR-122 targets ALP in hepatocellular carcinoma (liver cancer) and

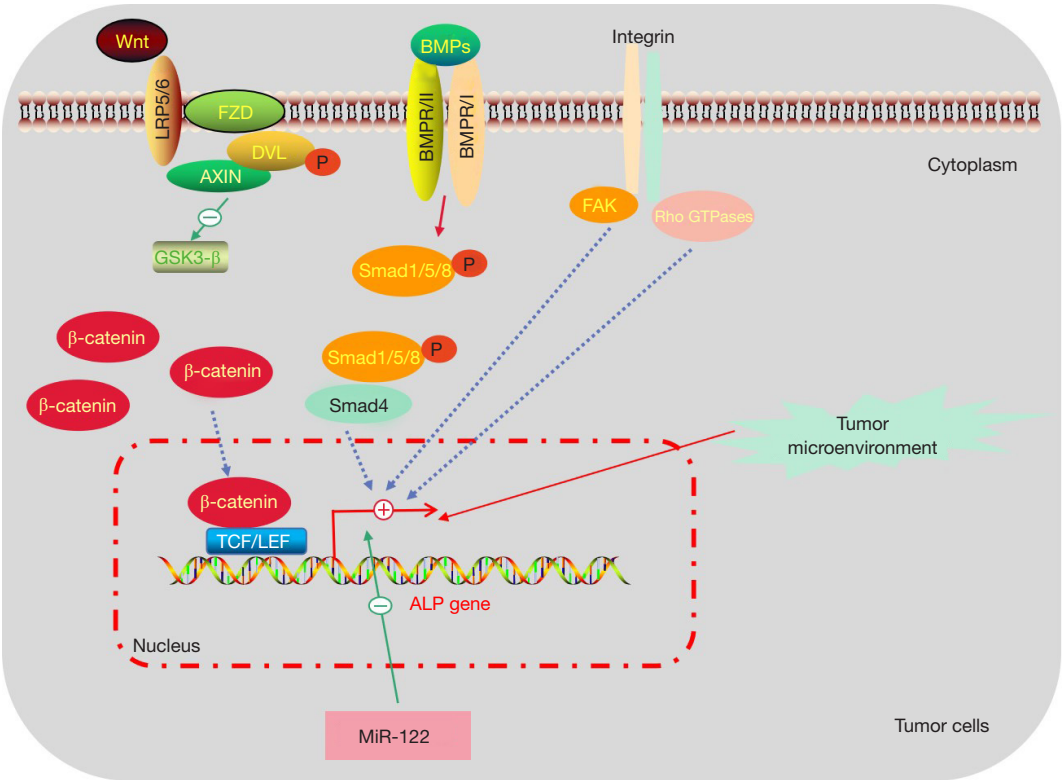

Figure 2 The mechanisms underlying ALP dysregulation in tumor cells. Wnt/β-catenin pathway, BMP pathway, integrin-mediated signaling pathways, and tumor microenvironment lead to increased ALP expression in tumor cells. While MiR-122 is associated with reduced ALP activity. Wnt, Wingless-Type MMTV Integration Site Family; LRP5/6, lipoprotein receptor-associated protein 5/6; FZD, frizzled; DVL, dishevelled; GSK3-β, glycogen synthase kinase 3 beta; BMP, bone morphogenetic protein; BMPR-I/II, BMP receptor I/II; FAK, focal adhesin kinase; TCF, T-cell factor; LEF, lymphoid enhance factor; ALP, alkaline phosphatase.

is associated with reduced ALP activity (88).

More and more studies are exploring how ALP affects the occurrence and development of tumors. Therefore, we can detect the abnormal expression of upstream regulatory molecules in specific tumors, and then design targets in the upstream molecular pathways to control ALP expression.

Conclusions

ALPs have been studied extensively in various types of tumors and have shown potential as diagnostic, prognostic, and therapeutic markers. One of the key applications of ALPs in tumor diagnosis is as a marker for bone metastases (15,19,37,54,57). Elevated levels of ALPs in the blood have been shown to be associated with bone metastases in prostate cancer, breast cancer, and other types of cancer (34,36). ALP levels can be measured to determine the presence of bone metastases, which can help guide treatment decisions.

In addition to diagnosis, ALPs have also shown potential as prognostic markers in tumors (56,58,73-75). In some cancers, such as CRC, breast cancer, and NSCLC, low levels of ALP have been associated with a worse prognosis (43,44,49). This suggests that ALP activity may play a role in tumor growth and proliferation.

ALPs have also been investigated as therapeutic targets in tumors. In preclinical studies, ALP inhibitors were shown to reduce the growth and invasion of tumor cells, indicating that ALPs may play a role in tumor progression (18,76). Other studies have shown that ALP can modulate the tumor microenvironment, and that targeting ALP may be an effective strategy to treat certain tumors (33,40,41,77,86).

Furthermore, ALP levels have been used to monitor the effectiveness of cancer treatments, including chemotherapy

and radiation therapy. Decreased ALP levels after treatment have been associated with improved clinical outcomes in some types of cancer, suggesting that ALP monitoring may be a useful tool in assessing treatment response (61,62).

Low ALP activity was found in CRC, and breast cancer, but opposite to that in prostate cancer, liver metastasis, pancreatic cancer, lung cancer, NSCLC and NSGCT, indicating that the mechanism of ALP action in cancer is a double-edged sword. We should analyze the regulatory mechanism of ALP in different tumors, explore the functions of different ALP isoenzymes in various tumors, and combine variety of molecular markers on cancer diagnosis.

The *ALP* gene overexpression and gene amplification by polyploidy of chromosomes 1 and 2 may be related in certain lesions, although it is important to note that the specific relationship can vary depending on the context and specific biological system (89). In certain lesions or diseases, such as certain types of cancer, genetic alterations can occur, leading to the overexpression of specific genes and the amplification of certain chromosomal regions. In this context, it is possible that *ALP* gene overexpression and gene amplification by polyploidy of chromosomes 1 and 2 are associated in these lesions. The increased number of chromosomes 1 and 2 due to polyploidy could contribute to the amplified copy number of the *ALP* gene, leading to its overexpression (89,90). Therefore, we need to further distinguish between these two conditions in clinical research, such as DNA copy number analysis, DNA sequencing and other methods.

In the context of ALP, there are genetic polymorphisms that can affect its expression, activity, or other characteristics. These polymorphisms can have implications for various biological processes and disease conditions (91). ALP isozyme polymorphisms, the *ALPL* gene encodes TNAP (*Table 2*), mutations or single nucleotide polymorphisms in the *ALPL* gene can lead to different forms of TNAP with varying enzymatic activity and stability (92). Vitamin D plays a role in the regulation of ALP expression. Polymorphisms in the vitamin D receptor (*VDR*) gene can affect ALP levels (92). For example, the FokI and BsmI polymorphisms in the *VDR* gene have been associated with ALP activity variations in different populations (93).

On the other hand, it is worth noting that a deficiency in ALP can also have negative implications for cancer patients. Studies have shown that low levels of ALPs are linked to poorer outcomes in individuals with specific types of tumors, such as CRC, breast cancer, and NSCLC (44,47-52,54,55). This is because reduced ALP activity may be indicative of decreased differentiation among cancer cells, meaning they are less specialized and more likely to grow uncontrollably. Additionally, low ALP levels could contribute to increased proliferation of malignant cells within the body (43,44,49). Therefore, it is crucial for healthcare professionals to monitor ALP levels in cancer patients and take appropriate action if deficiencies are detected. By doing so, we can help improve prognosis and ultimately save lives.

The intricate relationship between ALPs and cancer is a multifaceted one, with various factors influencing their role in the disease. To fully comprehend the mechanisms underlying ALP dysregulation in cancer, further research is imperative. Only then can we identify potential therapeutic targets that could revolutionize cancer treatment. It is important to note that the context of each individual case plays a significant role in determining how ALPs function within it. This means that there are no universal rules when it comes to understanding ALPs' impact on cancer development and progression. Despite this complexity, researchers remain optimistic about uncovering new insights into this critical area of study. With continued investigation and collaboration across disciplines, we may be able to unlock novel approaches for treating even the most challenging forms of cancer. In conclusion, while much remains unknown about the precise nature of ALP involvement in cancer, ongoing research offers hope for future breakthroughs. By working together towards a better understanding of these complex interactions, we can pave the way for more effective treatments and ultimately improve outcomes for patients worldwide.

Overall, ALPs have shown great potential in the diagnosis, prognosis, and treatment of tumors. Further research and clinical trials are necessary to fully understand the clinical significance of ALPs in tumor management and develop effective therapeutic strategies targeting these enzymes.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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