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Invited Mini Review

Potential role of ANGPTL4 in cancer progression, metastasis, and metabolism: a brief review

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Angiopoietin-like 4 (ANGPTL4) has been identified as an adipokine involved in several non-metabolic and metabolic diseases, including angiogenesis, glucose homeostasis, and lipid metabolism. To date, the role of ANGPTL4 in cancer growth and progression, and metastasis, has been variable. Accumulating evidence suggests that proteolytic processing and post-translational modifications of ANGPTL4 can significantly alter its function, and may contribute to the multiple and conflicting roles of ANGPTL4 in a tissue-dependent manner. With the growing interest in ANGPTL4 in cancer diagnosis and therapy, we aim to provide an up-to-date review of the implications of ANGPTL4 as a biomarker/oncogene in cancer metabolism, metastasis, and the tumor microenvironment (TME). In cancer cells, ANGPTL4 plays an important role in regulating metabolism by altering intracellular glucose, lipid, and amino acid metabolism. We also highlight the knowledge gaps and future prospect of ANGPTL4 in lymphatic metastasis and perineural invasion through various signaling pathways, underscoring its importance in cancer progression and prognosis. Through this review, a better understanding of the role of ANGPTL4 in cancer progression within the TME will provide new insights into other aspects of tumorigenesis and the potential therapeutic value of ANGPTL4. [BMB Reports 2024; 57(8): 343-351]

INTRODUCTION

ANGPTL4, a circulating fusion protein, is cleaved by furin-like proprotein convertases into two major domains: an N–terminal coiled-coil domain (nANGPTL4), and a C–terminal fibrinogen-like domain (cANGPTL4) (1). nANGPTL4 is an adipokine that inhibits lipoprotein lipase (LPL), an enzyme crucial for hydrolyzing circulating triglycerides (TGs) (2, 3). This inhibition impacts metabolic functions, including nutrient distribution and insulin sensitivity. In contrast, cANGPTL4 is involved in angiogenesis, vascular hyperpermeability, tumor growth, and metastasis (4-7).

The role of ANGPTL4 as a diagnostic and/or prognostic marker of cancer progression in several cancers has been proposed (8-10). ANGPTL4 upregulation has been reported to correlate with poor prognosis and reduced cancer-free survival, although this is not entirely clear, as ANGPTL4 expression appears to have different effects in various cancers, depending on the organ and context.

The tumor microenvironment (TME) is a complex ecosystem surrounding a tumor, and is composed of cancer cells and stromal tissues that include blood vessels, immune cells, fibroblasts, and the extracellular matrix (ECM) (11). Therefore, reciprocal cell–cell and cell–matrix communications in TME dictate nearly every aspect of tumor development, which encourages the cancer cells to sustain proliferative signals, induce angiogenesis, activate invasion and metastasis, reprogram their energy metabolism, and evade immune destruction (12), with a negative impact on the efficacy of antitumor therapies. In recent years, cancer research has focused on understanding how cancer cells interact with their microenvironment (13, 14), and ANGPTL4 has also been implicated in this research.

This review first discusses whether ANGPTL4 can provide a diagnostic tool for early cancer detection and metastasis/recurrence prediction, based on the evidence that the use of oncogenes/biomarkers may provide a novel approach to the molecular epidemiological assessment of carcinogenesis. The review also summarizes the role of ANGPTL4 in cancer metabolism, and metastasis by interactions with other cells within the TME, and further, its role requiring further elucidation.

ROLE OF ANGPTL4 AS AN ONCOGENE AND BIOMARKER

ANGPTL4 as an oncogene

Cancer is a complex disease that is characterized by abnormal cell proliferation and tumor formation. There is growing interest in the critical role of ANGPTL4 in the development and progression of cancer. ANGPTL4 has been reported to promote cancer invasion and metastasis, induce cell proliferation, and

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increase the malignant properties of tumors by regulating angiogenesis and promoting nutrient supply (15-17). However, how ANGPTL4 acts on specific types of tumors and the mechanisms of tumor suppression are variable.

ANGPTL4 is involved in the initiation and progression of pancreatic cancer. Its overexpression activates multiple signaling pathways and alters cellular processes, promoting chemoresistance and the survival of tumor cells (18). It also promotes carcinogenesis by accelerating the acinar to ductal transition induced by $KRAS^{G12D}$ gene mutation (19). Furthermore, ANGPTL4 regulates the migration and invasion ability of pancreatic cancer cells, promoting tumor vascularization and enhancing growth and metastasis (20). In lung cancer, ANGPTL4 promotes angiogenesis, tumor growth, and metastasis (21). It regulates ferroptosis and apoptosis through the NLRP3 (NLR family pyrin domain containing 3)/ASC (apoptosis-associated speck-like protein containing a CARD)/Caspase−8 signaling pathway to promote resistance to anticancer drugs, such as gefitinib, allowing tumor cells to acquire resistance and continue to grow (22). ANGPTL4 is also involved in regulating mechanisms that promote tumor survival and growth by counteracting oxidative stress and inhibiting ferroptosis (23).

In breast cancer, ANGPTL4 promotes tumor initiation and progression (24). ANGPTL4 secretion induced by STAT3 activation alters the extracellular matrix to promote tumor cell growth and metastasis (25). In ovarian cancer, it contributes to tumor growth and metastasis by enhancing proliferation and migration through the ERK1/2 signaling pathway (26). In colorectal cancer, knockdown of ANGPTL4 suppresses tumor growth by inhibiting cell proliferation and survival (27). Furthermore, in glioblastoma, ANGPTL4 activation by the EGFR/AKT/4E-BP1 pathway induces stem cell properties and chemoresistance

Table 1. ANGPTL4 as a biomarker/oncogene in various human cancers

Type of cancer	Sample type	Association of ANGPTL4 with cancer	Diagnostic and/ or prognostic value	Ref.
Pancreatic cancer (PDAC)	Patient tissue (n = 51)	High ANGPTL4 expression in short-term survivors and gemcitabine-resistant pancreatic cancer cells	Diagnostic biomarker for metastasis of PDAC (late-stage)	(29)
	PACA-CA project cohort (n = 143)	Important regulators of PDAC invasiveness	Prognostic biomarker (lymph node metastasis)	(30)
	Patient tissue (n = 140)	ANGPTL4 induced $KRAS^{G12D}$-induced acinar to ductal metaplasia and pancreatic carcinogenesis	Diagnostic marker for early PDAC	(19)
Lung cancer (LUAD)	TCGA-LUAD patient (n = 522)	Increased ANGPTL4 expression accelerates lipid metabolism, proliferation, and invasion	Prognostic biomarker for BRCA	(31) (32)
Breast cancer (BRCA)	Patient tissue (n = 205)	High ANGPTL4 expression was positively associated with pathological stage, tumor size, histological grade, lymph node metastasis, distant metastasis, and local recurrence	Prognostic biomarker for BRCA	(33)
	Patient tissue (n = 75)	Higher expression in tumors with high grades	Prognostic biomarker for young women with invasive BRCA	(36)
Gallbladder cancer (GBC)	Patient tissue (n = 85)	Elevated ANGPTL4 expression in gallbladder cancer-associated fibroblasts	Prognostic biomarker for GBC	(41)
Cervical cancer (CC)	Patient tissue (n = 160)	Upregulation od ANGPTL4 in cancer and advanced tumor stage, deep stromal invasion, lymph node metastasis, lymphovascular space invasion	Prognostic biomarker for CC	(40)
Colorectal cancer (CRC)	Patient tissue	High expression of ANGPTLs led to a relatively poor oncological outcome and positively correlated with the stage	Prognostic biomarker of CRC	(39)
Renal-cell carcinoma (RCC)	Patient tissue (n = 253)	High ANGPTL4 expression in clear cell renal-cell carcinoma (ccRCC)	Diagnostic biomarker for primary ccRCC (metastasis)	(37)
	Patient serum (n = 110)	High ANGPTL4 level in serum of patients, and Its low serum level had longer progression	Diagnostic and prognostic biomarker for RCC	(38)
Uterine carcinosarcoma (UCS)	Patienttissue (n = 57)	Prognostic ability of ANGPTL4 was molecular subtype-specific	Prognostic biomarker for UCS	(43)
Tongue cancer (TC)	Patient tissue (n = 48) Patient plasma (n = 40)	Lung metastasis exhibited a high rate of ANGPTL4 and high plasma ANGPTL4 concentrations	Diagnostic biomarker for lung metastasis of TC	(34)
Prostate cancer (PC)	Patient tissue (n = 70)	Hypoxia-induced ANGPTL4 expression promoted cancer progression	Prognostic biomarker for PC	(42)
Cholangiocarcinoma (CCA)	Patient tissue (n = 40) Patient serum (n = 90)	ANGPTL4 as a secreted protein expressed the highest signal intensity in CCA	Prognostic biomarker for CCA with lymph node metastasis	(35)

(28). Taken together, ANGPTL4 plays a potential role as an oncogene that enhances the malignant properties of tumors, promoting tumor initiation, progression, invasion, and metastasis (Table 1).

ANGPTL4 as a diagnostic biomarker for cancer patients

ANGPTL4 has been suggested as a diagnostic biomarker for various cancers. RNA sequencing has reported that ANGPTL4 expression is associated with long-term survival, and plays a significant role in pancreatic cancer. Its higher expression has been identified in patients with lymph node-positive pancreatic cancer rather than negative, suggesting that it may serve as a useful biomarker for prognosis prediction in pancreatic cancer (29). Furthermore, ANGPTL4 accelerates $KRAS^{G12D}$-induced acinar to ductal metaplasia (ADM) and pancreatic carcinogenesis, implicating it as a crucial biomarker in the onset and progression of pancreatic cancer (30). Additionally, high expression of ANGPTL4 in lung adenocarcinoma promotes tumor progression and metastasis, indicating a more aggressive cancer phenotype (31). Moreover, its expression in lung cancer cells is associated with specific pathological conditions, suggesting its potential role as a biomarker (32). Changes in the expression level of ANGPTL4 in response to certain environmental factors can be monitored, making it a valuable indicator to predict disease diagnosis and progression.

Similarly, overexpression of ANGPTL4 in breast cancer, tongue cancer, and cholangiocarcinoma is associated with lung metastasis and poor prognosis, where its high cellular expression promotes tumor cell migration, with high plasma levels (33-35). The ANGPTL4 protein is predominantly detected in invasive breast carcinoma, serving as a significant prognostic indicator, particularly in young women (36). In renal cell carcinoma, ANGPTL4 mRNA expression has also gained attention as a diagnostic biomarker that reflects the biological characteristics of the tumor, and predicts its development and metastatic potential (37, 38). The potential prognostic value of ANGPTLs has also been found in colorectal cancer, cervical cancer, and gallbladder cancer- ssociated fibroblasts, where high levels of ANGPTL4 expression were associated with an increased likelihood of malignancy and metastasis, closely related to patient survival (39-41). It has been identified as significantly upregulated in prostate cancer tissues, particularly under hypoxic conditions, where its role as a clinical biomarker and potential therapeutic target has been investigated (42). The high levels of ANGPTL4 expression have been identified as an important prognostic indicator associated with poorer outcomes in uterine carcinosarcoma (43). Taken together, these findings highlight the potential role of ANGPTL4 as a biomarker to help predict tumor progression and patient prognosis.

ROLE OF ANGPTL4 IN CANCER METASTASIS

Malignant cancer cells metastasize from the primary tumor to surrounding tissues and distant organs (12). Metastasis is recognized as one of the leading causes of death in cancer patients, because it is highly aggressive, and occurs late in the course of cancer progression (6). Metastases travel rapidly through blood vessels and lymphatic vessels, and during this process, metastasized cancer cells stimulate new blood vessel formation, regulate tumor microenvironments (TMEs), resist anoikis, and invade distant organs (44). As such, metastasis is a complex process, requiring fuller understanding of the molecular mechanisms by which cancers metastasize (Fig. 1).

ANGPTL4 and angiogenesis in cancer metastasis

Angiogenesis is a critical process that supplies cancer with essential nutrients and oxygen, allowing tumors to thrive. It also creates new blood vessels, providing a means for cancer cells to spread to distant organs via the bloodstream (45). ANGPTL4 is well known for its role in directly affecting vascular endothelial cells, and indirectly controlling factors such as VEGF and FGF that promote angiogenesis (46). Several studies have also revealed the angiogenic function of ANGPTL4 in cancer metastasis. It induces the development of ovarian serous cystic carcinoma, and promotes angiogenesis by activating the JAK2/STAT3 pathway and interacting with ESM1 (Endothelial cell-specific molecule 1) within the TME (47). It is involved in angiogenesis by affecting vascular junction integrity and interfering with intercellular VE–cadherin and Claudin–5 clusters, which may promote lung tumor metastasis (48). Similarly, under hypoxic conditions, ANGPTL4 triggered by prostaglandin E2 enhances the invasiveness of colon cancer cells by stimulating angiogenesis, the formation of new blood vessels that provide a pathway for cancer cells to metastasize to distant sites (49).

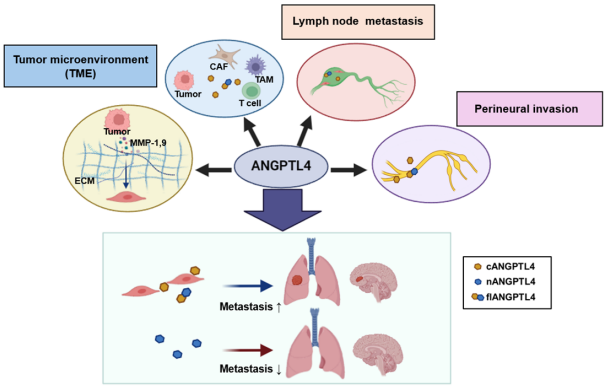

Fig. 1. Role of ANGPTL4 in cancer metastasis. ANGPTL4 plays a crucial role in various aspects of cancer metastasis. It promotes the growth of new blood vessels, which is pivotal to tumor nutrition and spread. It also influences cancer metastasis by impacting EMT and signaling pathways. Within the tumor microenvironment (TME), ANGPTL4 interacts with CAF, TAM, T-cell, and secretes MMP- and -9, influencing ECM remodeling, metastatic process, lymph node metastasis, and perineural invasion. flANGPTL4 and cANGPTL4 typically promote tumor growth and lung metastasis, whereas nANGPTL4 inhibits metastasis by reducing vascularity at metastatic sites.

ANGPTL4 and signaling pathway in cancer metastasis

ANGPTL4 is a highly hydrophobic protein that is secreted by cells, and is characterized by its ability to act as a signaling peptide. Upregulated by the release of TGF−β2 from astrocytes, it plays a key role in promoting brain metastasis of triple-negative breast cancer cells through the TGF−β2/Smad/ANGPTL4 axis (50). In non-small cell lung cancer, it promotes metastasis by increasing the mesenchymal marker vimentin through the ERK signaling pathway (51). Oleic acid-induced ANGPTL4 activates the fibronectin/Rac1 (Ras-related C3 botulinum toxin substrate 1)/Cdc42 signaling pathway to increase anoikis resistance and metastasis in head and neck squamous cell carcinoma (52).

Full-length ANGPTL4 (flANGPTL4) naturally forms dimers or tetramers, and can be cleaved by proteolytic process to generate nANGPTL4 and cANGPTL4 (53). Both flANGPTL4 and cANGPTL4 typically promote tumor growth and metastasis. cANGPTL4 stimulates PI3K/PKBa (Protein Kinase Bα) and ERK survival pathways through increased oxygen production and Src activation, which in turn promote tumor growth and metastasis (16). On the other hand, nANGPTL4 is primarily known to be involved in lipid metabolism and inflammation, whose role in cancer is limited (6). By inhibiting WNT signaling and reducing vascularity at metastatic sites, nANGPTL4 inhibits metastasis and improves overall survival, implying the potential of nANGPTL4 as an anti-metastatic molecule (54).

ANGPTL4 and TME in cancer metastasis

The tumor microenvironment includes a variety of cell types, immune cells, cancer-associated fibroblasts, and structural elements, such as collagen and fibronectin, that make up the ECM. Previous studies have shown that cytokines secreted by various cells in the TME promote tumor progression and induce metastasis (55). Similarly, ANGPTL4 is directly secreted from cells in the TME, and influences tumor metastasis (24). Cancer-associated fibroblasts (CAFs) activated in the TME are induced by the transcription factor STAT3 and its inducer IL-6 to produce ANGPTL4, which promotes breast cancer growth and metastasis (24). In addition, ANGPTL4 secretion by cancer-ssociated mesothelial cells plays an important role in promoting the tumor microenvironment, crosstalk with cancer cell adhesion, migration, and proliferation, and inducing EMT to promote the early stages of ovarian cancer metastasis (56).

The presence of regulatory T (Treg)-cells and M2 macrophages (TAM) in colon cancer tissues is positively correlated with ANGPTL4 expression. ANGPTL4 promotes the induction of Treg cells and TAM, suggesting a potential mechanism of ANGPTL4-mediated tumor promotion and metastasis (57). In colorectal cancer, it has been shown to suppress immune surveillance by inhibiting the activation of CD8+ T-cells (58). Thus, in cancer metastasis, ANGPTL4 appears to closely affect the immune response.

The extracellular matrix (ECM) provides structural support to cells, with collagen being a key component. Matrix metalloproteinases (MMPs) are enzymes that break down ECM components like collagen (59, 60). During cancer progression, increased MMP activity degrades collagen, altering the ECM and enhancing cancer cell movement and invasiveness, which promotes tumor growth and metastasis (61, 62).

ANGPTL4 is essential for metastasis via the EGF-activated PGE2 (Prostaglandin E2)/ANGPTL4 axis by promoting anoikis resistance and upregulating MMP-1 expression in head and neck squamous cell carcinoma (63). It also plays an important role in hyperlipidemia-associated colorectal cancer metastasis, promoting metastasis through the activation of MMP-1 and MMP-9 (64). This suggests that MMP activity-mediated ECM remodeling by ANGPTL4 significantly contributes to cancer metastasis by enhancing cell mobility, invasiveness, and resistance to anoikis.

Role of ANGPTL4 in lymphatic metastasis and perineural invasion (PNI)

Lymphatic metastasis occurs when cancer cells spread through the lymphatic system to other parts of the body. Lymph node metastasis of cancer is well recognized to have a significant impact on patient survival and cancer treatment (65). Although the molecular mechanisms of lymphatic metastasis through the regulation of ANGPTL4 are still unclear, clinical data have shown a positive correlation between ANGPTL4 expression and lymphatic metastasis in cancer patients. ANGPTL4 expression is significantly associated with lymph node metastasis in cholangiocarcinoma, and may be used as a novel prognostic biomarker to predict vascular invasion and lymph node metastasis in cholangiocarcinoma patients (35). Further, in tongue squamous cell carcinoma, ANGPTL4 expression is associated with lymph node metastasis and poor overall survival, suggesting that it may be a novel biomarker and therapeutic target for TSCC (66). In cancer patients, co-occurrence of lymphatic invasion, metastasis, and perineural involvement has been shown to be associated with a worse prognosis for patients (67).

Perineural invasion of cancer is important, because it represents a more aggressive form of cancer, and is associated with a worse prognosis and lower survival rate. It increases the risk of recurrence, and can cause severe pain and neurologic symptoms (68). ANGPTL4 expression is high in colorectal cancer patients, and is associated with a significantly increased rate of perineural invasion of the tumor (69). These clinical data suggest that ANGPTL4 is an important factor driving perineural invasion of cancer; however, specific mechanistic studies of how ANGPTL4 is involved in the process of perineal invasion are still needed.

ROLE OF ANGPTL4 IN CANCER METABOLISM

Cancer metabolism

The metabolic processes of cancer are different from those of normal cells (70), and alterations in metabolic processes are essential for cancer progression in the face of rapid growth and

insufficient energy resources (71, 72). In particular, protein, lipid, and glucose metabolic pathways are critical for the survival, growth, and metastasis of cancer cells (12), and metabolic reprogramming in response to genetic and environmental alterations in cancer is essential (73). Furthermore, metabolic alterations in cancer play an essential and central role in the occurrence and development of cancer; and glucose, lipid, and amino acid metabolism have been found to be important in determining cancer characteristics (74).

ANGPTL4 and metabolism

ANGPTL4 has been reported to play an important role in metabolic processes, most notably in lipid metabolism, by degrading triglycerides (TGs) (75, 76). TGs are converted to fatty acids (FAs) via lipoprotein lipase (LPL). Fats are broken down and distributed to different organs to be used as energy sources. ANGPTL4 inhibits LPL activity, allowing TG to accumulate and regulate its metabolism, so that it can be utilized in cancer metabolism (77). In addition to lipid metabolism, ANGPTL4 can also affect glucose metabolism and protein metabolism. Promoting angiogenesis to accelerate wound healing in diabetic patients, it can modulate STAT3–iNOS expression to regulate signaling related to glucose metabolism (78). ANGPTL4 expression induced by butyrate and rosiglitazone utilizes an independent pathway that may influence cellular TG-rich lipoprotein production. These findings suggest that ANGPTL4 may play an important role in regulating glucose metabolism and altering intracellular lipid metabolism (79).

ANGPTL4 and cancer metabolism

Glucose metabolism: ANGPTL4 plays an important role in promoting glucose metabolism by increasing the expression of glucose transporters, such as glucose transporter 1 (GLUT1) and GLUT4 in colorectal cancer (Fig. 2). This increases glucose uptake by cancer cells, which in turn promotes processes such as glycolysis and the pentose phosphate pathway. Ultimately, ANGPTL4-induced metabolic changes support tumor growth and survival by meeting the increased energy demands of rapidly dividing cancer cells (80). The increased glycolytic activity mediated by ANGPTL4 facilitates colonization of *Fusobacterium nucleatum* within the tumor, inducing colorectal cancer progression. Understanding the mechanisms underlying ANGPTL4-mediated glycolysis that promotes *Fusobacterium nucleatum* colonization may provide insight into the complex interplay between host metabolism and the tumor microbiome (81).

ANGPTL4 regulates adipose-derived stem cell (ADSC) homing and promotes cancer progression by the TGF–β1/SMAD3/ANGPTL4 axis. Indeed, ADSCs promote the glycolysis of cancer cells to enhance glucose metabolism. This effect is mediated by the TGF–β1/SMAD3 signaling pathway, upregulating ANGPTL4 expression. The increased glycolytic activity promoted by ANGPTL4 promotes peritoneal metastasis in colorectal cancer. Understanding the role of the TGF–β1/SMAD3/ANGPTL4 axis in regulating cancer metabolism may reveal potential therapeutic targets to inhibit cancer metastasis (82).

Lipid metabolism: ANGPTL4 affects lipid metabolism in cancer by regulating fatty acid oxidation. In non-small cell lung cancer, it promotes fatty acid oxidation to fuel energy metabolism and proliferation. In addition, ANGPTL4 affects the expression of key enzymes in lipid metabolism, such as carnitine palmitoyltransferase 1 (CPT1) (83). Similarly, in pancreatic cancer, ANGPTL4 is involved in metabolic crosstalk between cancer cells and adipocytes.

Incubation with adipocytes activates the hypoxia signaling

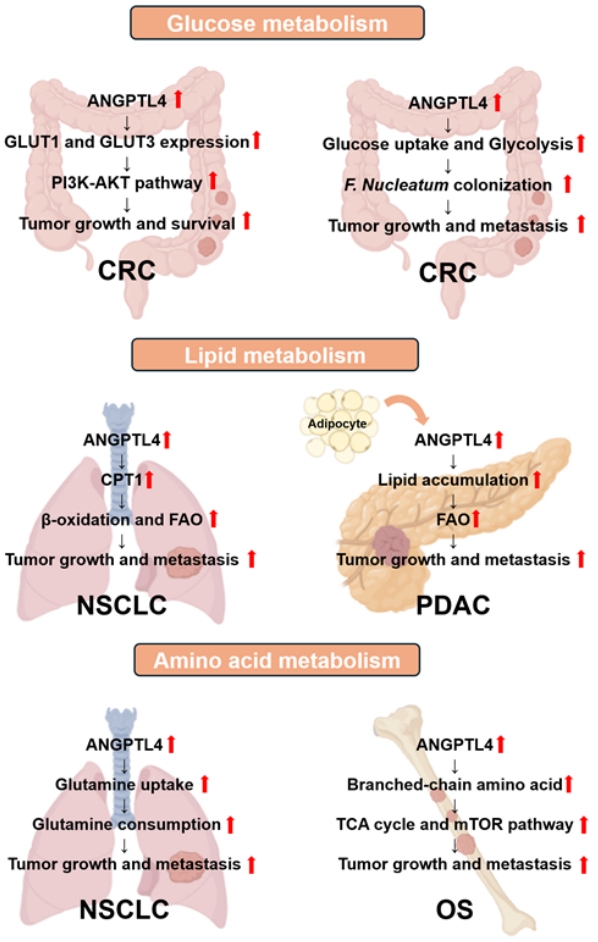

Fig. 2. Role and mechanism pathway of ANGPTL4 in cancer metabolism. In colorectal cancer (CRC), ANGPTL4 promotes tumor growth and survival by upregulating glucose uptake through GLUT1/3 and PI3K/AKT signaling. It also regulates lipid metabolism in non-small cell lung cancer (NSCLC) and pancreatic cancer (PDAC), promoting tumor growth and metastasis through upregulation of the β–oxidation and FAO pathways. In addition, ANGPTL4 affects amino acid metabolism, increasing glutamine and branched-chain amino acid uptake, which promotes cancer metastasis in NSCLC and osteosarcoma (OS).

pathway, resulting in increased ANGPTL4 expression in pancreatic cancer cells. And it increases β-oxidation in cancer cells and activates the STAT3 signaling pathway, which promotes cancer metastasis and dissemination (84). Taken together, these findings suggest that ANGPTL4 plays an important role in regulating lipid metabolism within the TME, and alters energy metabolism and lipid processing to promote cancer progression and metastasis.

Targeting ANGPTL4-mediated lipid metabolism may provide a therapeutic opportunity to combat cancer metastasis. ANGPTL4, secreted from adipose tissue, affected tumor lipid metabolism reprogramming and motility induction in breast cancer. Specifically, the PPARα/ANGPTL4 and FAK signaling pathways were involved in mediating these effects. This study sheds light on the role of ANGPTL4 as a key regulator of lipid metabolism that affects the lipid metabolism of breast cancer cells (85).

Amino acid metabolism: ANGPTL4 regulates amino acid metabolism in cancer cells. Glutamine is an essential nutrient for cancer cells, supporting energy production and biosynthesis. ANGPTL4 regulates glutamine metabolism by affecting the uptake, conversion, and utilization of glutamine in non-small cell lung cancer cells. Specifically, it enhances glutamine uptake by upregulating transporter expression, and affects the activity of key enzymes involved in the glutamine metabolic pathway. This regulation of glutamine metabolism by ANGPTL4 contributes to the growth and survival of the cancer, highlighting its importance as a potential therapeutic target (84).

ANGPTL4 also affects amino acid metabolism in osteosarcoma, with particular focus on the remodeling of branched-chain amino acid (BCAA) metabolism by ANGPTL4 and its impact on tumor progression. It negatively regulates BCAA metabolism in osteosarcoma cells, altering the levels and utilization of BCAAs within the tumor microenvironment. This remodeling of amino acid metabolism by ANGPTL4 disrupts the metabolic balance essential for tumor growth and survival, thereby hindering the progression of osteosarcoma. These findings highlight the potential of targeting ANGPTL4-mediated amino acid metabolism in the treatment of osteosarcoma (86).

SUMMARY

Recent findings have identified ANGPTL4 as a promising oncogene/biomarker in various types of cancer. It plays increasingly important roles in cancer development, progression, and metastasis. In addition to the pro-angiogenic effect of ANGPTL4 in tumors (87), the recent collective data have shown that ANGPTL4 regulates cancer metastasis by interaction with other cells, such as nerve, CAF, TAM, T-cells, and ECM within the TME. Also, ANGPTL4 in cancer metabolic alteration plays an essential and central role in the occurrence and development of cancer by the regulation of glucose, lipid, and amino acid metabolism. These findings suggest the potential of ANGPTL4 as a therapeutic target in cancer treatment that focuses on oncogene, metastasis, and metabolism. However, future studies should address the function of flANGPTL4 and its truncated fragments, cANGPTL4 and nANGPTL4 in cancer, to clarify the context-dependent roles of ANGPTL4 fragments in different cancers. Nevertheless, this study provides new insights into the role of ANGPTL4 and the network of cancer molecular mechanisms as a key factor in cancer development, metastasis, and metabolism, to better understand its utility and effectiveness in future clinical applications.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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