

Emerging roles of angiopoietin-like 4 in human tumors (Review)

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Received September 30, 2024; Accepted November 29, 2024

DOI: 10.3892/ijo.2024.5715

Abstract. Angiopoietin-like 4 (ANGPTL4), a member of the angiopoietin family, plays critical roles in angiogenesis, lipid metabolism and inflammation. It has been demonstrated that ANGPTL4 has significant influence on various diseases. Accumulating evidence has highlighted the impacts of ANGPTL4 on human malignancies. ANGPTL4 is commonly overexpressed in various types of cancer, such as breast, non-small cell lung, gastric and colorectal cancer. Its upregulation promotes tumor growth, invasion, metastasis and angiogenesis, as well as metabolic reprogramming and resistance to programmed cell death, radiotherapy and chemotherapy. However, ANGPTL4 has also exhibited antitumor effects under certain conditions, indicating its complex roles in tumor biology. The transcriptional regulation of ANGPTL4 is influenced by multiple factors, such as HIF-1, PPARs, TGF- β and long non-coding RNAs. In terms of signaling pathways, STATs, PI3K/AKT and COX-2/PGE2 are important in regulating cellular processes. The present review summarizes the biological functions of ANGPTL4 in tumors and its association with patient prognosis. Furthermore, the key molecular mechanisms and potential reasons for its dual roles in cancer are also discussed. In conclusion, ANGPTL4 is a valuable diagnostic biomarker and a potential therapeutic target for human cancers.

Contents

1. Introduction
2. Biological characteristics of ANGPTL4
3. Roles of ANGPTL4 in cancer

4. Regulation of ANGPTL4 expression and function in cancer
5. ANGPTL4 in the TME
6. Discussion

1. Introduction

Cancer remains a major global public health burden, with incidence and mortality rates rising rapidly. According to Global Cancer Statistics, nearly 20 million new cases of cancer and 9.7 million cancer-related deaths worldwide were reported in 2022 (1). It is estimated that ~20% of individuals will develop cancer during their lifetime. Lung cancer has the highest incidence rate (12.4%), followed by female breast cancer (BRC) (11.6%), colorectal cancer (CRC) (9.6%), prostate cancer (7.3%) and gastric cancer (GC) (4.9%) (1). Generally, the initiation and progression of tumors are caused by genetic or epigenetic alterations caused by both internal and external factors, which activate or inhibit specific signaling pathways (2,3). Therefore, investigating the mechanisms underlying tumorigenesis is essential for improving the diagnosis, prognosis and the development of targeted therapies.

The angiopoietin family consists of growth factors that regulate vascular development, maintenance and remodeling, playing a pivotal role in angiogenesis. Currently, the angiopoietin family includes angiopoietin (ANGPT) 1-4 and angiopoietin-like (ANGPTL) 1-8. ANGPTs act as ligands for the endothelial cell receptors TIE1 and TIE2 and are crucial in regulating tumor angiogenesis, inflammation, lymphatic angiogenesis and the cardiovascular system (4,5). Although ANGPTLs share structural similarities with ANGPTs, they do not bind to TIE receptors to mediate their biological functions. The homologous receptors of ANGPTLs remain unidentified, and they are classified as orphan ligands (6-9). ANGPTLs, particularly ANGPTL3, ANGPTL4 and ANGPTL8, have been extensively studied for their roles in lipid metabolism (10,11). Additionally, ANGPTLs regulate both acute and chronic inflammation (12) and atherosclerosis (13) through various mechanisms. ANGPTL4, a member of the angiopoietin family, was initially identified for its key roles in lipid metabolism (14), inflammatory response (15) and angiogenesis (6,7). As research has progressed, increasing evidence has demonstrated that ANGPTL4 is involved in various stages of tumor progression (8,9).

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Key words: angiopoietin-like 4, tumor hallmarks, cancer, malignancy, dual roles, signaling pathways, biomarker, therapeutic target

In the present review, the multifaceted roles of ANGPTL4 in tumor development and its underlying mechanisms of action are discussed. While earlier reviews (8,9) provided a foundational understanding of ANGPTL4, the current article integrates the latest research and findings, offering a comprehensive and updated perspective on its functions in cancer biology.

2. Biological characteristics of ANGPTL4

In 2000, three research teams successively identified a new member of the ANGPT family. Kim *et al* (16) isolated a new sequence from human and mouse embryonic cDNA using degeneracy PCR, which was named hepatic fibrinogen/angiopoietin-related protein (HFARP). Yoon *et al* (17) described the isolation and characterization of a novel target gene induced by peroxisome proliferator-activated receptor (PPAR) γ ligands, termed PGAR (for PPAR γ angiopoietin-related); Kersten *et al* (18) identified a novel PPAR α target gene called FIAF (fasting-induced adipose factor) through subtractive hybridization. Subsequently, the gene encoding this protein was collectively referred to as ANGPTL4 by the HUGO Gene Nomenclature Committee.

ANGPTL4 is located at 19p13.2, with an mRNA length of ~2,000 bp and an open reading frame of 1,218 bp. It encodes a secreted glycoprotein composed of 406 amino acids with a relative molecular weight of ~45-65 kDa. Structurally similar to other ANGPT family proteins, ANGPTL4 contains a highly hydrophobic signal peptide, an N-terminal helical domain with three glycosylation sites, and a larger C-terminal fibrinogen-like domain, with a small connecting peptide between these domains. The natural full-length ANGPTL4 (fANGPTL4) exists as either a dimer or tetramer. It can be cleaved by furin-like proprotein convertase to yield an N-terminal coiled-coil fragment (nANGPTL4), containing amino acids 1 to 170, and a C-terminal fibrinogen-like domain monomer fragment (cANGPTL4), consisting of amino acids 171 to 406. The cleavage of fANGPTL4 at the -RXR- site by proprotein convertase depends on the tissue in which ANGPTL4 is synthesized and the physiological or pathological conditions (19-21).

In humans, ANGPTL4 exhibits widespread expression, with notable prominence in the heart, liver, small intestine, adipose tissue, plasma and placenta, as reported in multiple studies (22-26). Its expression is regulated by PPARs (9), glucocorticoid receptors (27,28), hypoxia-inducible factor-1 α (HIF-1 α) (28), transforming growth factor- β (TGF- β) (29-31) and other regulatory factors.

3. Roles of ANGPTL4 in cancer

Previous findings suggest that ANGPTL4 is commonly dysregulated in various malignancies, and plays important dual roles, functioning as either an oncogene or a tumor suppressor (Fig. 1; Tables I and II). Altered ANGPTL4 expression impacts diverse cellular phenotypes via multiple signaling pathways, affecting tumor growth, invasion, metastasis, angiogenesis, programmed cell death, cell metabolism and treatment resistance (Fig. 2).

ANGPTL4 and tumor growth. ANGPTL4 exhibits varied regulatory effects across different types of tumors.

Ding *et al* (32) demonstrated that the recombinant ANGPTL4 protein reduces CD8⁺ T cell infiltration and activation through metabolic reprogramming, thereby diminishing immune surveillance during tumor progression and facilitating tumor growth *in vivo*. In breast tumors of obese mice, ANGPTL4 expression has been shown upregulated, and the suppression of ANGPTL4 leads to a significant reduction in obesity-induced tumor growth (33). Interleukin-1 β (IL-1 β) in primary adipocytes stimulates ANGPTL4 expression through the activation of nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways, with hypoxia further enhancing IL-1 β expression (33). This indicates that ANGPTL4 mediates the crosstalk between obesity-associated inflammation and BRC progression. Avallé *et al* (34) found that cancer-associated fibroblasts (CAFs) promote tumor growth in BRC, with signal transducer and activator of transcription 3 (STAT3) amplifying the effects of CAFs via ANGPTL4. In ovarian cancer (OVC), ANGPTL4 was significantly upregulated in clinical samples and correlated with poor prognosis (35). ANGPTL4 promotes OVC progression by activating the Janus kinase 2 (JAK2)/STAT3 pathway (35). Xu *et al* (36) further demonstrated that ANGPTL4 enhances ovarian tumor cell proliferation through the extracellular signal-related kinase (ERK) pathway, and its inhibition can suppress OVC progression via phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR2) (37). Additionally, several studies have shown that ANGPTL4 accelerates the proliferation and progression of numerous types of malignancies, including CRC (38), GC (39), hepatocellular carcinoma (HCC) (40,41), lung adenocarcinoma (42,43), osteosarcoma (OS) (44), thyroid cancer (45) and melanoma (46).

However, some studies suggest that ANGPTL4 may function as a tumor suppressor. Hsieh *et al* (47) reported the dual roles of ANGPTL4 in urothelial carcinoma (UC), showing that ANGPTL4 mRNA expression is decreased in UC cells and tumor tissues compared with adjacent normal bladder epithelial cells. Overexpression of ANGPTL4 inhibits UC cell proliferation both *in vivo* and *in vitro* (47). Hui *et al* (48) found that long non-coding RNA (lncRNA) AGAP2-AS1 down-regulates ANGPTL4 expression through its interaction with the enhancer of zeste homolog 2 (EZH2), thereby promoting the proliferation and metastasis of pancreatic cancer. A negative correlation between the expression of ANGPTL4 and OS progression has also been observed (49). Knocking out ANGPTL4 in OS cells leads to the accumulation of branched-chain amino acids (BCAAs), which activates the mechanistic target of rapamycin (mTOR) signaling pathway and enhances OS cell proliferation (49). In addition, homeobox transcription factor 1 α (LMX1A) has been shown to suppress tumor growth by activating ANGPTL4 to hinder c-Myc in GC (50). The negative regulatory effects of ANGPTL4 on tumor growth have also been reported in renal clear cell carcinoma (51) and CRC (52).

ANGPTL4 and tumor invasion and metastasis. Metastasis refers to the spread of malignant cells to distant organs, and it is often the primary cause of mortality in most cancers, as metastatic cancer cells typically exhibit high invasiveness and resistance to anticancer therapies. It has been indicated that

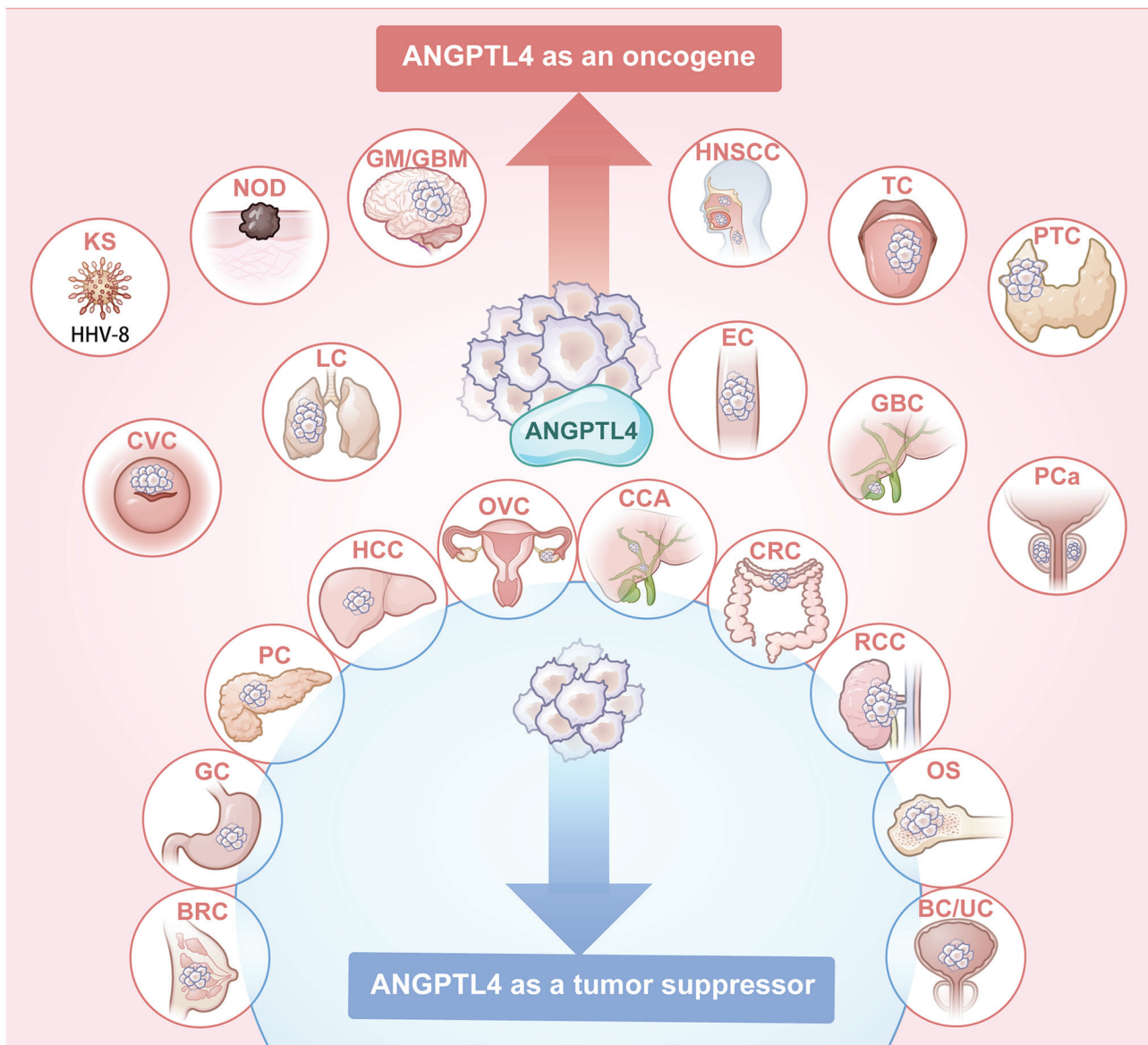


Figure 1. ANGPTL4 plays an oncogenic role in cancers in red, and plays a tumor-suppressive role in cancers in blue; ANGPTL4 has controversial roles reported in cancers with both colors. ANGPTL4, angiopoietin-like 4; KS, Kaposi's sarcoma; NOD, melanoma; GM, glioma; GBM, glioblastoma; HNSCC, head and neck squamous cell carcinoma; TC, tongue cancer; PTC, papillary thyroid cancer; CVC, cervical cancer; RCC, renal cell carcinoma; LC, lung cancer; EC, esophageal cancer; GBC, gallbladder cancer; PCa, prostate cancer; BRC, breast cancer; GC, Gastric cancer; PC, pancreatic cancer; HCC, hepatocellular carcinoma; OVC, ovarian cancer; CCA, cholangiocarcinoma; CRC, colorectal cancer; OS, osteosarcoma; BC, bladder cancer; UC, urothelial carcinoma.

ANGPTL4 plays a crucial role in cancer invasion and metastasis processes.

Hübers *et al* (53) identified cANGPTL4 and nANGPTL4 as pro- and antitumor contributors, respectively, in the bidirectional communication between primary tumors and distant metastases. It was observed that cANGPTL4 promotes tumor growth and metastasis, while nANGPTL4 inhibits metastasis and improves overall survival by suppressing Wnt signaling and reducing vascular distribution at metastasis sites. These findings suggested that cANGPTL4 could serve as a potential biomarker for tumor progression and a target for anti-metastatic therapy.

In BRC, HIF-2 induces the expression of the lncRNA RAB11B-AS1, which facilitates brain metastasis through the promotion of ANGPTL4 (54). Silencing ANGPTL4 in triple-negative BRC (TNBC) cells has been shown to reduce

the metastatic growth of brain tumors *in vivo* (31). Tumor cells secrete IL-1 β and tumor necrosis factor- α (TNF- α), which communicate with astrocytes, leading to increased expression of transforming growth factor- β 2 (TGF- β 2) and promoting the brain metastasis via the TGF- β 2/ANGPTL4 axis (31). These findings provide a theoretical basis for targeting ANGPTL4 in the treatment of BRC metastasis.

In CRC, ANGPTL4 plays a role in metastasis through various mechanisms. Shen *et al* (55) found that NADPH oxidase 4 (NOX4)/reactive oxygen species (ROS) axis is crucial for CRC metastasis induced by oleic acid (OA). Downregulation of ANGPTL4 leads to the suppression of NOX4, ROS, matrix metalloproteinase-1 (MMP-1) and MMP-9, thus inhibiting OA-induced CRC metastasis (55). Furthermore, the metastasis in KRAS/p53 mutant CRC has been shown to depend on the activation of the ANGPTL4/IL-8/NOX4 axis (56), underscoring

Table I. ANGPTL4 as an oncogene in human malignancies.

First author/s, year	Cancer type	Upstream regulators	Downstream targets	Cellular phenotypes	(Refs.)
Kolb <i>et al</i> , 2019	Breast cancer	NLRC4/IL-1 β /NF- κ B, MAPK	-	Proliferation, angiogenesis	(33)
Avalle <i>et al</i> , 2022		STAT3	-	Proliferation, migration, invasion	(34)
Tian <i>et al</i> , 2009		PPAR γ	-	Proliferation, angiogenesis	(145)
Zhao <i>et al</i> , 2020		-	-	Prognosis	(157)
Padua <i>et al</i> , 2008		TGF- β /Smad	-	Lung metastasis	(174)
Long <i>et al</i> , 2023	Bladder cancer	-	SDC1	Prognosis, immune response	(150)
Gong <i>et al</i> , 2019	Triple-negative	TGF- β 2/Smad	-	Brain metastasis	(31)
Blücher <i>et al</i> , 2020	breast cancer	PPAR α	FAK	Lipid metabolism, motility	(133)
Adhikary <i>et al</i> , 2013		TGF- β /PPAR β , δ	-	Invasion	(144)
Simeon <i>et al</i> , 2021		-	-	Brain, liver metastases	(175)
Zhu <i>et al</i> , 2024	Colorectal cancer	TGF- β 1/Smad3	-	Glycolysis, anoikis resistance, peritoneal metastasis	(30)
Ding <i>et al</i> , 2023		-	PKC-LKB1- MAPK-mTOR	Metabolic reprogramming, proliferation, decreased CD8 ⁺ T cell activation	(32)
Wen <i>et al</i> , 2020		-	-	Proliferation, invasion, migration, apoptosis resistance, cisplatin resistance	(38)
Shen <i>et al</i> , 2020		-	c-Jun/NOX4	Metastasis	(55)
Li <i>et al</i> , 2015		-	BMP7	Invasion, migration, apoptosis resistance	(82)
Zheng <i>et al</i> , 2021		Histone H3 lysine 27	GLUT-1	Glycolysis, <i>Fusobacterium nucleatum</i> colonization	(120)
Mizuno <i>et al</i> , 2022			PI3K/AKT/ GLUTs	Glucose metabolism	(121)
Kim <i>et al</i> , 2011		PGE2/EP1	MAPK, Src/STAT1	Proliferation	(146)
Nakayama <i>et al</i> , 2011		-	-	Venous invasion, metastasis	(176)
Shen <i>et al</i> , 2023	KRAS/p53 mutant colorectal cancer	-	IL-8/NOX4	Metastasis	(56)
San <i>et al</i> , 2020	Cholangiocarcinoma	-	-	Anoikis resistance	(91)
Aung <i>et al</i> , 2022		-	-	Biomarker for vascular invasion, lymph node metastasis	(159)
Nie <i>et al</i> , 2019	Cervical cancer	-	-	Prognosis	(158)
Shibata <i>et al</i> , 2010	Esophageal cancer	-	-	Invasion, survival	(161)
Yi <i>et al</i> , 2013		-	-	Prognosis	(177)
Chen <i>et al</i> , 2018	Gastric cancer	-	-	Proliferation, invasion, apoptosis resistance, cisplatin resistance	(39)
Xiao <i>et al</i> , 2024		Leptin	LPL/ COX- 2/PGE2	Lymph node metastasis	(60)
Nakayama <i>et al</i> , 2010		-	-	Venous invasion	(178)
Baba <i>et al</i> , 2017	Scirrhus gastric cancer	HIF-1 α	c-Myc, p27; FAK /Src/ PI3K-Akt/ ERK	Proliferation, cell cycle, anoikis resistance, peritoneal metastasis	(90)
Katanasaka <i>et al</i> , 2013	Glioma	EGFRvIII/ERK/c-Myc	-	Proliferation, angiogenesis	(65)

Table I. Continued.

First author/s, year	Cancer type	Upstream regulators	Downstream targets	Cellular phenotypes	(Refs.)
Tsai <i>et al</i> , 2019	Glioblastoma	Sp4	EGFR/AKT/ 4E-BP1	Temozolomide resistance	(141)
Hefni <i>et al</i> , 2023	Head and neck squamous cell carcinoma	-	NRP1/ABL1/ PXN	Migration	(58)
Chiang <i>et al</i> , 2020		EGF/COX-2/ PGE2/ERK	-	Metastasis	(61)
Liao <i>et al</i> , 2017		EGF/integrin β 1	MMP-1	Anoikis resistance and metastasis	(87)
Shen <i>et al</i> , 2017		OA/PPARs	FN/MMP-9	Anoikis resistance and metastasis	(88)
Bai <i>et al</i> , 2024	Hepatocellular carcinoma	-	BMP7/Smad/ MAPK14	Proliferation, migration	(40)
Bai <i>et al</i> , 2024		-	-	Proliferation, invasion, migration, apoptosis resistance	(41)
Bai <i>et al</i> , 2024		-	-	Invasion, migration	(81)
Fekir <i>et al</i> , 2019		-	PDK4	Invasion, metabolic reprogramming, chemoresistance	(138)
Li <i>et al</i> , 2011		HIF-1 α	VCAM1/ integrin β 1	Metastasis	(143)
Ma <i>et al</i> , 2010	Kaposi's sarcoma	vGPCR	-	Angiogenesis	(179)
Izraely <i>et al</i> , 2018	Melanoma	TGF- β 1		Brain metastasis	(46)
Yang <i>et al</i> , 2020		MNK1	MMPs	Invasion, lung metastasis	(180)
Hu <i>et al</i> , 2016	Uveal melanoma	HIF-1	-	Angiogenesis	(67)
Hu <i>et al</i> , 2023	Non-small cell lung cancer	-	-	Proliferation, invasion, lipid metabolism	(42)
Fang <i>et al</i> , 2022		-	NLRP3/ASC/ Caspase8	Pyroptosis and apoptosis resistance, gefitinib resistance	(43)
Hao <i>et al</i> , 2022		-	-	Migration, anoikis resistance	(59)
Mo <i>et al</i> , 2020		-	-	Migration, angiogenesis	(68)
Zhang <i>et al</i> , 2022		-	GPX4, FTH1	Ferroptosis resistance, radioresistance	(101)
Zhu <i>et al</i> , 2016		-	-	Proliferation, metastasis	(181)
Lou <i>et al</i> , 2024		-	-	Migration, apoptosis resistance	(182)
Zhang <i>et al</i> , 2018	Osteosarcoma	HIF-1 α	-	Proliferation, migration	(44)
Chen <i>et al</i> , 2020		LncRNA CCAL/ miR-29b	-	Angiogenesis	(69)
Li <i>et al</i> , 2024	Ovarian cancer	-	JAK2/STAT3; ESM1	Proliferation, angiogenesis, lipid metabolism	(35)
Xu <i>et al</i> , 2024		-	ERK1/2	Proliferation, migration	(36)
Wu <i>et al</i> , 2021		-	VEGFR2	Proliferation, metastasis, Angiogenesis	(37)
Bajwa <i>et al</i> , 2023		-	-	Proliferation, cell adhesion, migration, metastasis, glycolysis	(57)
Li <i>et al</i> , 2022		TAZ	SOX2	Cisplatin resistance	(139)
Zhou <i>et al</i> , 2020		-	c-Myc/NF- κ B	Carboplatin resistance	(140)
Al-Kadash <i>et al</i> , 2024	Pancreatic cancer	-	ITGB4, APOL1	Gemcitabine resistance	(183)
Yang <i>et al</i> , 2020	Papillary thyroid cancer	-	AKT	Proliferation	(45)
Hata <i>et al</i> , 2017	Prostate cancer	-	-	Proliferation	(184)

Table I. Continued.

First author/s, year	Cancer type	Upstream regulators	Downstream targets	Cellular phenotypes	(Refs.)
Dong <i>et al</i> , 2017	Renal cell carcinoma	-	-	Prognosis	(163)
Tanaka <i>et al</i> , 2022	Tongue cancer	-	-	Prognosis	(162)
Tanaka <i>et al</i> , 2016		-	-	Lung metastasis	(185)
Hsieh <i>et al</i> , 2018	Urothelial carcinoma	-	ERK/FAK	Proliferation, migration	(47)

-, information not available; NLRC4, NOD-like receptor family, pyrin domain-containing protein 4; IL-1 β , interleukin-1 β ; NF- κ B, nuclear factor- κ B; MAPK, mitogen-activated protein kinase; STAT3, signal transducer and activator of transcription 3; PPAR γ , peroxisome proliferator-activated receptor γ ; TGF- β , transforming growth factor- β ; SDC1, Syndecan-1; FAK, focal adhesion kinase; PKC, protein kinase C; LKB1, liver kinase B1; mTOR, mechanistic target of rapamycin; BMP7, bone morphogenetic protein 7; NOX4, NADPH oxidase 4; GLUT-1, glucose transporter-1; PI3K, phosphoinositide 3-kinase; PGE2, prostaglandin E2; EP1, Prostaglandin E2 receptor 1; LPL, lipoprotein lipase; COX-2, cyclooxygenase-2; HIF-1 α , hypoxia-inducible factor-1 α ; ERK, extracellular signal-related kinase; EGFR, epidermal growth factor receptor; Sp4, specificity protein 4; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; EGF, epidermal growth factor; MMP-1, matrix metalloproteinase-1; OA, oleic acid; FN, fibronectin; VCAM1, vascular cell adhesion molecule 1; PDK4, pyruvate dehydrogenase kinase 4; vGPCR, viral G protein-coupled receptor; MNK1, MAP kinase-interacting serine/threonine-protein kinase 1; NLRP3, NOD-like receptor family, pyrin domain containing 3; ASC, apoptosis-associated Speck-like protein; GPX4, glutathione peroxidase 4; FTH1, ferritin heavy chain 1; VEGFR2, vascular endothelial growth factor receptor 2; TAZ, transcriptional coactivator with PDZ binding motif; SOX2, sex-determining region Y-box2; JAK2, Janus kinase 2; ESM1, endothelial cell-specific molecule 1; ITGB4, integrin β 4; APOL1, apolipoprotein L1.

Table II. ANGPTL4 as a tumor suppressor in human malignancies.

First author/s, year	Cancer type	Upstream regulators	Downstream targets	Cellular phenotypes	(Refs.)
Xu <i>et al</i> , 2023	Colorectal cancer	STAT2/ linc0223/ hnRNPA1	-	Angiogenesis	(52)
Zhang <i>et al</i> , 2021		-	ERK	Proliferation, invasion, migration, metastasis	(63)
Yu <i>et al</i> , 2018	Cholangiocarcinoma	lncRNA PVT1	-	Proliferation, migration	(186)
Qian <i>et al</i> , 2019	Gastric cancer	LMX1A	c-Myc	Tumorigenesis	(50)
Kubo <i>et al</i> , 2016		-	-	Prognosis	(164)
Ng <i>et al</i> , 2014	Hepatocellular carcinoma	-	-	Apoptosis, angiogenesis	(72)
Lin <i>et al</i> , 2022	Osteosarcoma	-	BCAAs/mTOR	Amino acid metabolism, proliferation	(49)
Yang <i>et al</i> , 2020	Ovarian cancer	TAZ	NOX2	Ferroptosis, chemoresistance	(102)
Hui <i>et al</i> , 2019	Pancreatic cancer	lncRNA AGAP2- AS1/EZH2	-	Proliferation, migration	(48)
Jin <i>et al</i> , 2024	Renal cell carcinoma		LAL	Proliferation	(51)
Cai <i>et al</i> , 2020	Triple-negative breast cancer	-	-	Adhesion, invasion, migration	(62)
Hsieh <i>et al</i> , 2018	Urothelial carcinoma	-	-	Proliferation, invasion, migration	(47)

-, information not available; STAT2, signal transducer and activator of transcription 2; ERK, extracellular signal-related kinase; LMX1A, homeobox transcription factor 1 α ; BCAAs, branched-chain amino acids; mTOR, mechanistic target of rapamycin; TAZ, transcriptional coactivator with PDZ binding motif; NOX2, NADPH oxidase 2; EZH2, zeste homolog 2; LAL, lysosomal acid lipase.

the importance of the ANGPTL4/NOX4 signaling axis in dyslipidemia-related and KRAS/p53 mutant CRC metastasis.

Zhu *et al* (30) focused on the peritoneal metastasis of CRC. They reported that adipose-derived stem cells (ADSCs) secrete

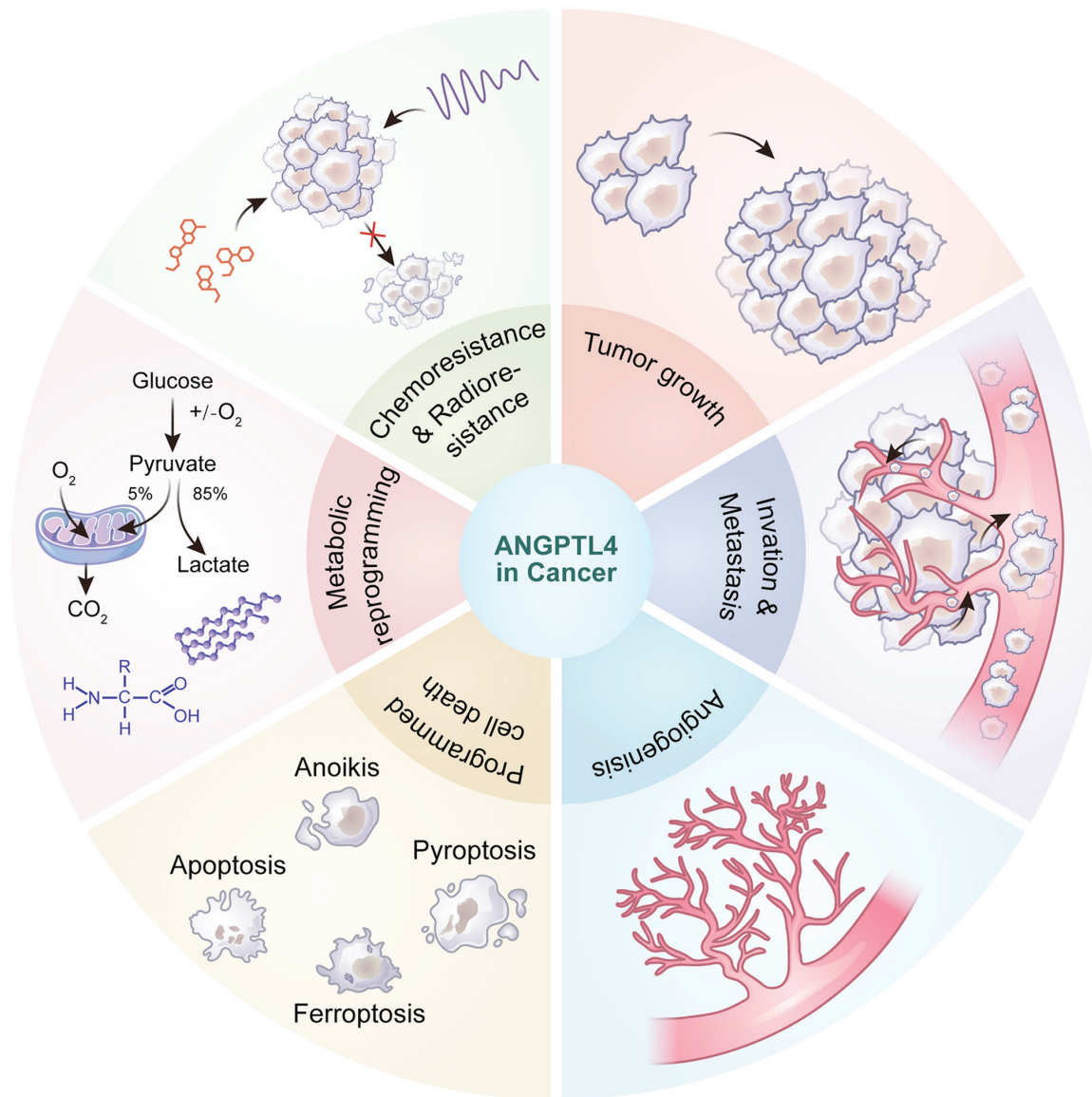


Figure 2. ANGPTL4 and the hallmarks of cancer. ANGPTL4 has shown a remarkable ability to regulate several fundamental biological processes involved in tumor growth, invasion and metastasis, angiogenesis, programmed cell death, metabolic reprogramming, and chemoresistance and radioresistance. ANGPTL4, angiopoietin-like 4.

TGF- β 1 to activate Smad3 in CRC cells, which enhances ANGPTL4 transcription. The upregulation of ANGPTL4 increases the anoikis resistance, facilitating CRC cell survival in the peritoneum and promoting metastatic foci formation (30).

Bajwa *et al* (57) reported that ANGPTL4, derived from cancer-associated mesothelial cells, promotes the early-stage OVC metastasis through the interactions between mesothelial cells and the tumor microenvironment (TME). Additionally, Hefni *et al* (58) found that ANGPTL4 induces the migration of head and neck squamous cell carcinoma (HNSCC) cells via the neuropilin1/ABL1/paxillin pathway. Similarly, ANGPTL4 has been implicated in the invasion and metastasis of lung cancer (42,59), with studies showing that modified Bu Fei decoction inhibits the metastasis of non-small cell lung cancer (NSCLC) by suppressing ANGPTL4 expression in endothelial cells (59).

Previous studies have highlighted the pivotal role of the cyclooxygenase-2 (COX-2)/prostaglandin E2 (PGE2) pathway

in promoting metastasis through ANGPTL4. In GC, leptin induces the phosphorylation of ANGPTL4 at the serine 30 residue, reducing its binding affinity to lipoprotein lipase (LPL), thus enhancing lipid uptake and intracellular arachidonic acid levels. This accumulation subsequently activates the COX-2/PGE2 pathway, promoting lymph node metastasis (60). Moreover, Chiang *et al* (61) demonstrated that the COX-2/PGE2/ANGPTL4 axis, activated by epidermal growth factor (EGF), enhances metastasis in HNSCC, with PGE2 promoting ANGPTL4 expression through the ERK pathway.

Despite the general role of ANGPTL4 in promoting metastasis, some studies have identified its inhibitory effects. Overexpression of ANGPTL4 has been found to inhibit the adhesion, migration and invasion of TNBC cells *in vitro*, with positive correlations to favorable outcomes in patients with TNBC (62). Moreover, lncRNA AGAP2-AS1 epigenetically inhibits ANKRD1 and ANGPTL4 expression by recruiting EZH2, promoting pancreatic cancer metastasis (48). In CRC,

DNA methylation-mediated downregulation of ANGPTL4 activates CAFs in the TME, promoting epithelial-mesenchymal transition (EMT) through the ERK signaling pathway, which leads to metastasis (63). *In vivo* experiments also revealed that overexpression of ANGPTL4 inhibits lung metastasis in CRC models (63). Additionally, inhibitory effects of ANGPTL4 on tumor metastasis have been also observed in OS (64).

ANGPTL4 and tumor angiogenesis. Angiogenesis and increased vascular permeability are ubiquitous characteristics of all solid tumors. Therefore, research on the role of ANGPTL4 in cancer angiogenesis holds significant potential to profoundly enhance our comprehension of cancer pathogenesis and inform the development of therapeutic strategies.

Wu *et al* (37) found that the pro-angiogenic effects of ANGPTL4 in OVC are mediated via its association with VEGF2. Similarly, Li *et al* (35) discovered that ANGPTL4 enhances angiogenesis in ovarian serous cystadenocarcinoma by activating the JAK2/STAT3 signaling pathway. The mechanism is potentially due to the interaction among ANGPTL4, endothelial cell specific molecule 1 and the TME (35). ANGPTL4 has also been reported to exert pro-angiogenic effects in malignant glioma cells (65). Knockdown of ANGPTL4 significantly reduces microvascular density in xenograft tumors and inhibits tumor growth (65). Additionally, EGF receptor (EGFR) variant III induces ANGPTL4 expression through the ERK/c-Myc pathway to regulate angiogenesis (65). In Kaposi's sarcoma, the upregulation of ANGPTL4 by viral G protein-coupled receptors has been shown to enhance tumor angiogenesis and vascular permeability through the Rho/Rho-associated kinase pathway (66). The complementary effect on VEGF, a potent angiogenic factor, has also been confirmed (66). Furthermore, ANGPTL4 has exhibited a stimulatory effect on tumor angiogenesis in various cancer types, including BRC (33), uveal melanoma (67), NSCLC (68) and OS (69).

The inhibitory effects of ANGPTL4 on angiogenesis are partially attributed to its suppression of the ERK signaling pathway and post-translational modifications. Tumor-derived ANGPTL4 has been found to inhibit the angiogenesis and proliferation of umbilical endothelial cells by suppressing ERK signaling (70). The inactivation of ANGPTL4 through genetic and epigenetic mechanisms, such as hypermethylation of CpG islands in the promoter region, causes an increase in tumor growth and angiogenesis in GC (70). Yang *et al* (71) reported that N-glycosylated cANGPTL4 exerts an inhibitory effect on the Raf/MEK/ERK signaling cascade in endothelial cells, which suppresses the angiogenesis induced by alkaline fibroblast growth factor and VEGF. Furthermore, The inhibitory effects of ANGPTL4 on angiogenesis have also been observed in CRC (52) and HCC (72), reinforcing its potential as a modulator of angiogenesis across various cancer types.

ANGPTL4 and programmed cell death (PCD). PCD is a widespread mechanism in living organisms, essential for maintaining cellular homeostasis, development, immunity and stress response (73). PCD is regulated by numerous evolutionarily conserved pathways and well-characterized mechanisms of action (74). Based on specific morphological, immunological and genetic characteristics, PCD can be classified into several

forms, including apoptosis, ferroptosis, necroptosis, pyroptosis and autophagy-dependent cell death (75,76). PCD is crucial in tumor suppression through its involvement in anticancer therapies. In the present review, the interactions between various forms of PCD and ANGPTL4 in cancer are discussed.

ANGPTL4 and apoptosis. Apoptosis, the most extensively studied form of PCD, was first described by Kerr *et al* in 1972 (77). Apoptosis relies on a cascade of caspase proteases and can be initiated via extrinsic or intrinsic pathways (78). As early as the 1970s, studies demonstrated that apoptosis is crucial for eliminating potentially malignant cells, controlling hyperplasia, and inhibiting tumor progression (79). The induction of apoptosis is fundamental in cancer therapy. The dual role of ANGPTL4 in regulating tumor cell apoptosis has been reported.

Lim *et al* (80) reported the anti-apoptotic effect of ANGPTL4 and observed that inhibiting ANGPTL4 leads to the accumulation of chemotherapy drugs in cells, thereby inducing apoptosis. The mechanism involves reduced energy production and accumulation in cancer cells and the weakened drug efflux during EMT. In HCC (81), ANGPTL4 knockout cell lines exhibited significantly higher levels of apoptosis. Bai *et al* (41) further investigated the role of different ANGPTL4 transcripts and found a notable increase in ANGPTL4-Transcript 3 expression in HCC tissues. The overexpression of ANGPTL4-Transcript 3 significantly confers apoptosis resistance to HCC cells, whereas Transcript 1 has no such effects (41). Fang *et al* (43) conducted a study on the role of ANGPTL4 in regulating gefitinib resistance in NSCLC cells. The aforementioned study demonstrated that ANGPTL4 is crucial in inhibiting cell apoptosis by suppressing the NOD-like receptor family, pyrin domain containing 3 (NLRP3)/apoptosis-associated Speck-like protein (ASC)/caspase-8 pathway, thereby enhancing resistance to gefitinib (43). ANGPTL4 also enhances the apoptosis resistance in CRC (38,82). Knocking down bone morphogenetic protein 7 (BMP7) reverses the anti-apoptotic effect of ANGPTL4 overexpression, suggesting that ANGPTL4 may inhibit apoptosis in CRC cells by upregulating BMP7 (82).

Most studies to date have highlighted the anti-apoptotic effect of ANGPTL4 in tumors. However, Hsieh *et al* (83) reported the pro-apoptotic effect of ANGPTL4 in UC. Cyproheptadine was found to upregulate ANGPTL4 expression and activate apoptosis-related proteins such as caspase-3 and poly (ADP-ribose) polymerase (PARP), thereby promoting apoptosis and inhibiting the growth of UC cells. This process might involve the regulation of glycogen synthase kinase 3 β (GSK3 β)/tuberous sclerosis complex subunit 2 (TSC2)/mTOR and GSK3 β / β -catenin signaling pathways.

ANGPTL4 and anoikis. Anoikis is a specialized form of apoptosis that occurs when cells detach from the surrounding cellular or extracellular matrix (ECM) (84,85). However, tumor cells can develop resistance to anoikis, enabling them to evade cell death and continue proliferating after detachment. Anoikis resistance facilitates immune evasion, alters the TME, and ultimately contributes to the invasion and metastasis (85,86).

In HNSCC, EGF induces ANGPTL4 expression, significantly enhancing anoikis resistance, and promoting

migration and invasion (87). This effect is mediated through the expression of MMPs, particularly MMP-1, as regulated by ANGPTL4 (87). Shen *et al* (88) discovered that OA induces ANGPTL4 expression in HNSCC, which significantly enhances the anoikis resistance by upregulating Ras-related C3 botulinum toxin substrate 1 (Rac1)/cell division control protein 42 (Cdc42) and MMP-9 pathways, thus promoting tumor metastasis.

Zhu *et al* (89) found that ANGPTL4 secreted by tumors specifically binds to integrins $\beta 1$ and $\beta 5$, leading to the activation of focal adhesion kinase (FAK) and Rac1. This activation increases the O₂:-H₂O₂ ratio, subsequently activating the Src, which triggers the phosphatidylinositol 3-kinase (PI3K)/AKT and extracellular signal-regulated kinase (ERK) pathways, resulting in the resistance to anoikis (89). Similarly, in GC, ANGPTL4 inhibits the occurrence of anoikis by regulating the focal FAK/Src/PI3K-AKT/ERK pathway and suppressing caspases-3, -8, and -9 (90).

During the peritoneal metastasis of CRC, ADSCs enhance the anoikis resistance of CRC cells through the TGF- $\beta 1$ /Smad3/ANGPTL4 axis (30). Additionally, Hao *et al* (59) demonstrated that the downregulation of ANGPTL4 weakens the endothelial barrier disruption and promotes anoikis in lung cancer. Furthermore, the overexpression of ANGPTL4 is closely associated with anoikis resistance in cholangiocarcinoma (91), HCC (92) and uveal melanoma (93).

These findings provide new insights into the mechanisms of metastasis, suggesting that ANGPTL4 may serve as a promising therapeutic target for intervening in anoikis and tumor metastasis. The FAK/Src/PI3K-AKT/ERK pathway, along with MMPs, is the key mediator of anoikis regulated by ANGPTL4.

ANGPTL4 and ferroptosis. Ferroptosis, an iron-dependent form of cell death, is characterized by excessive iron accumulation, lipid peroxidation and cell membrane rupture (94,95). It can be triggered via the inhibition of intracellular antioxidant enzymes such as glutathione peroxidase 4 (GPX4) (96,97). Ferroptosis has been identified as a key mechanism in tumor development and radiation response (98-100).

Zhang *et al* (101) uncovered the molecular function of ANGPTL4 in hypoxic TME and proposed that hypoxia-induced ANGPTL4 contributes to radiotherapy resistance in NSCLC by regulating ferroptosis. Under hypoxic conditions, the expression of ANGPTL4 is significantly upregulated in NSCLC cells and can be enriched in extracellular vesicles, which can be transferred to adjacent normoxic cells (101). Both *in vivo* and *in vitro* experiments have confirmed that ANGPTL4 inhibits ferroptosis by regulating radiation-induced lipid peroxidation and the expression of hallmark ferroptosis proteins, such as GPX4 and ferritin heavy chain 1 (101).

By contrast, Yang *et al* (102) reported the opposite effect in OVC. The study identified ANGPTL4 as a direct target gene of transcriptional coactivator with PDZ binding motif (TAZ) through the integrated genomic analysis (102). The upregulation of ANGPTL4 activated NADPH oxidase 2 (NOX2) *in vitro*, thereby increasing the sensitivity to ferroptosis (102).

ANGPTL4 and pyroptosis. Pyroptosis is a previously identified form of PCD characterized by immune responses and

inflammation (103,104). As a critical innate immune response, pyroptosis induces immune phagocytosis to counter infections and endogenous threats (105-107). Pyroptosis is triggered by caspase-1, -4, -5 and -11, and activated by inflammasomes such as NLRP3 (108-110).

The role of ANGPTL4 in pyroptosis has been reported in sepsis-induced acute lung injury, where its knockdown was shown to inhibit macrophage M1 polarization and pyroptosis, thereby providing a protective effect (111). In a study by Fang *et al* (43), ANGPTL4 was found to be highly expressed in lung adenocarcinoma cells, and its knockdown leads to increased pyroptosis via the NLRP3/apoptosis-associated speck-like protein containing a CARD (ASC)/Caspase-8 signaling pathway (43). Currently, the research on the regulation of tumor pyroptosis by ANGPTL4 is limited, and further studies are needed to clarify its precise role in the pyroptosis of tumor cells.

ANGPTL4 and tumor metabolism. Metabolism is a fundamental biological activity intrinsic to all organisms, reflecting the processes of matter and energy transformation. The rapid proliferation and high energy demand of tumor cells lead to the significant metabolic alterations, which provide a biochemical basis and directly promote tumorigenicity and malignancy (112-116). The metabolic reprogramming of glucose, lipids and amino acids, three major functional biomolecules, enables tumor cells to acquire energy through various pathways, supporting their uncontrolled proliferation and survival. Targeting these metabolic pathways has become a promising anticancer strategy.

ANGPTL4 and glucose metabolic reprogramming. Glucose is the most critical energy source for living organisms, and its metabolic pathways include glycolysis, the pentose phosphate pathway and oxidative phosphorylation. Even in the presence of oxygen, tumor cells predominantly produce ATP through glycolysis, a phenomenon known as aerobic glycolysis or the Warburg effect (117,118). Aerobic glycolysis is crucial for the proliferation, growth, invasion and treatment of cancer (119).

In recent years, an increasing number of studies have shown that ANGPTL4 plays a significant role in tumor aerobic glycolysis. Zheng *et al* (120) found that in *Fusobacterium nucleatum*-infected CRC cells, increased acetylation of histone H3 lysine 27 upregulates the expression of ANGPTL4. ANGPTL4 promotes glucose uptake and aerobic glycolysis in CRC cells both *in vitro* and *in vivo*, which in turn enhances *Fusobacterium nucleatum* colonization. This effect is mediated by ANGPTL4's regulation of glucose transporter-1 (GLUT-1), thereby promoting the development, metastasis and chemoresistance of CRC. Similarly, in a study by Mizuno *et al* (121), it has been shown that ANGPTL4 affects the expression of GLUT-1 and GLUT-3 in CRC, and is associated with glucose metabolism activity and cancer progression. These studies indicate that GLUTs, particularly GLUT-1, is a key molecule in ANGPTL4-mediated regulation of aerobic glycolysis. Additionally, ADSCs derived from fat tissues have been shown to promote glycolysis in CRC cells through the TGF- $\beta 1$ /Smad3/ANGPTL4 axis, ultimately facilitating peritoneal metastasis (30). Overall, ANGPTL4 serves as a key

target for regulating aerobic glycolysis and tumor progression in CRC.

At present, most research on the regulation of glucose metabolic reprogramming by ANGPTL4 has focused on CRC, and its regulatory roles and associated molecular mechanisms in other tumors require further investigations.

ANGPTL4 and lipid metabolic reprogramming. Reprogramming of lipid metabolism is a newly recognized hallmark of malignancy (122,123). Increased lipid uptake, storage and lipogenesis are observed in various cancers and contribute to accelerated tumor growth (124-127). ANGPTL4, as a lipid regulatory factor, has been widely reported for its role in lipid metabolism, particularly its effects on LPL (7,14,128-131).

Numerous studies have demonstrated the close association between ANGPTL4 and lipid metabolism in tumors. In GC, Xiao *et al* (60) discovered that leptin induces the phosphorylation of the serine 30 residue of ANGPTL4, thereby reducing its binding affinity with LPL. This reduction promotes LPL-mediated lipid uptake and increases intracellular arachidonic acid levels, disrupting cellular lipid homeostasis, and triggering the COX-2/PGE2 pathway. Consequently, this process promotes tumor lymphangiogenesis and lymph node metastasis in GC. Xiao *et al* (132) reported that ANGPTL4 significantly affects fatty acid oxidation and promotes energy generation in NSCLC cells, which may be achieved through carnitine palmitoyl-transferase 1 (CPT1). Hu *et al* (42) identified ANGPTL4 as a direct target of miR-133a-3p, with its expression significantly accelerating lipid metabolism in lung adenocarcinoma.

ANGPTL4 also mediates the metabolic crosstalk between tumor cells and adipocytes. Blücher *et al* (133) demonstrated that adipose tissue secretory factors reprogram tumor lipid metabolism and induce motility by regulating PPAR α /ANGPTL4 and FAK in TNBC cells, with ANGPTL4 identified as the key factor in lipid metabolism regulation. In pancreatic cancer, adipocytes activate the hypoxia signaling pathway, leading to increased expression of ANGPTL4 (134). This upregulation enhances β -oxidation in cancer cells and activates the STAT3 signaling pathway, promoting lipid metabolic reprogramming and metastasis of pancreatic cancer (134).

ANGPTL4 and amino acid metabolic reprogramming. Amino acids, the building blocks of proteins, generate metabolites that fuel biosynthetic pathways, produce energy, and support cancer cell survival. Due to their heightened proliferative needs, cancer cells often cannot synthesize sufficient quantities of amino acids. The reprogramming of amino acid metabolism fulfills this increased demand (135).

Currently, limited research exists on the relationship between ANGPTL4 and the reprogramming of amino acid metabolism in cancer. Xiao *et al* (132) utilized tracer technology and Seahorse XF technology to explore the metabolic effects of ANGPTL4 in NSCLC. Their findings revealed that ANGPTL4 promotes glutamine consumption and fatty acid oxidation in NSCLC, both *in vitro* and *in vivo*, while having no significant effect on glycolysis. ANGPTL4 regulates glutaminase and CPT1, thereby facilitating glutamine metabolism

and fatty acid oxidation, which in turn supports NSCLC cell proliferation (132). Lin *et al* (49) identified a negative correlation between ANGPTL4 and BCAA metabolism in OS samples and cell lines. The downregulation of ANGPTL4 in OS cells leads to the accumulation of BCAAs and the activation of mTOR signaling, which promotes OS cell proliferation (49).

ANGPTL4, chemoresistance and radioresistance. Chemotherapy and radiotherapy are essential treatments for unresectable tumors and serve as neoadjuvant therapies. However, their clinical efficacy is often hindered by the development of resistance. Chemoresistance and radioresistance also contribute to tumor recurrence and metastasis, posing major challenges to patient prognosis (136,137). Research has increasingly focused on how ANGPTL4, a multifunctional molecule in tumor cell survival, proliferation and apoptosis, influences the resistance to chemotherapy and radiotherapy (Table III).

Chemoresistance promoted by ANGPTL4 is closely tied to its metabolic reprogramming functions. It has been shown that ANGPTL4 enhances cellular ATP through the c-Myc and NF- κ B signaling pathways during EMT (80). The increased ATP provides fuel for multiple ATP-binding cassette (ABC) transporters to upregulate their expression, ensuring sufficient cellular energy for drug efflux, thereby conferring chemoresistance in tumors (80). In HCC, ANGPTL4 induces the upregulation of pyruvate dehydrogenase kinase 4, an inhibitor of mitochondrial pyruvate dehydrogenase, enhancing the resistance to sorafenib and cisplatin in stem cells (138). These findings suggest that targeting the metabolic function of ANGPTL4 and combining the restoration of mitochondrial metabolic activity with chemotherapy present attractive therapeutic options in cancer treatment.

In OVC, TAZ has been shown to promote the resistance to cisplatin via the ANGPTL4/sex-determining region Y-box2 (SOX2) axis (139). Similarly, Zhou *et al* (140) reported that adipocyte-derived ANGPTL4 induces carboplatin resistance in OVC. ANGPTL4 activates the c-Myc/NF- κ B pathway, which subsequently stimulates the expression of the anti-apoptotic proteins and ABC transporter family members. However, Xu *et al* (102) came to the opposite conclusion. They found that TAZ activates the ANGPTL4/NOX2 axis, making OVC cells sensitive to ferroptosis and chemotherapy. TAZ levels were lower in chemotherapy-resistant recurrent OVC cells.

In GBM, where temozolomide (TMZ) combined with radiotherapy is the standard therapy, glioma stem-like cells (GSCs) are considered to be the primary cause of drug resistance. In the study of Tsai *et al* (141), ANGPTL4 expression was significantly increased in GSCs. The overexpression of ANGPTL4 activates the PI3K/AKT, EGFR and ERK signaling pathways, enriching GSCs and resulting in TMZ resistance (141). Additionally, Gordon *et al* (142) showed that ANGPTL4 contributes to gemcitabine resistance in pancreatic cancer and shortens patient survival by regulating the expression of apolipoprotein L1 and integrin β 4. In cholangiocarcinoma, Curcumin has been shown to enhance chemotherapy efficacy via the inhibition of ANGPTL4 (91). Furthermore, ANGPTL4 inhibits pyroptosis and apoptosis of lung adenocarcinoma cells through the NLRP3/ASC/Caspase-8 signaling pathway, contributing to the resistance against gefitinib (43).

Table III. Roles of ANGPTL4 in drug- or radio-resistance in human malignancies.

First authors/s, year	Cancer type	ANGPTL4 expression	Upstream regulators	Downstream targets	Therapy	(Refs.)
Wen <i>et al</i> , 2020	Colorectal cancer	High	-	-	Cisplatin resistance	(38)
Chen <i>et al</i> , 2018	Gastric cancer	High	-	-	Cisplatin resistance	(39)
Tsai <i>et al</i> , 2019	Glioblastoma	High	Sp4	EGFR/AKT/4E-BP1	Temozolomide resistance	(141)
Fekir <i>et al</i> , 2019	Hepatocellular carcinoma	High	-	PKD4	Sorafenib/cisplatin resistance	(138)
Fang <i>et al</i> , 2022	Non-small cell lung cancer	High	-	NLRP3/ASC/ Caspase-8	Gefitinib resistance	(43)
Zhang <i>et al</i> , 2022	Ovarian cancer	High	-	GPX4, FTH1	Radioresistance	(101)
Li <i>et al</i> , 2022			TAZ	SOX2	Cisplatin resistance	(139)
Zhou <i>et al</i> , 2020			-	c-Myc/NF-κ B	Carboplatin resistance	(140)
Yang <i>et al</i> , 2020	Pancreatic cancer	High	TAZ	NOX2	Carboplatin sensitivity	(102)
Cazes <i>et al</i> , 2006		-	-	ITGB4, APOL1	Gemcitabine resistance	(172)

-, information not available; Sp4, specificity protein 4; EGFR, epidermal growth factor receptor; 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; PKD4, pyruvate dehydrogenase kinase 4; NLRP3, NOD-like receptor family, pyrin domain containing 3; ASC, apoptosis-associated Speck-like protein; GPX4, glutathione peroxidase 4; FTH1, ferritin heavy chain 1; TAZ, transcriptional coactivator with PDZ binding motif; SOX2, sex-determining region Y-box2; NF-κ B, nuclear factor-κ B; NOX2, NADPH oxidase 2; APOL1, apolipoprotein L1.

The role of ANGPTL4 in radioresistance has also been recently explored. Hypoxia-induced ANGPTL4 expression has been positively correlated with radiotherapy resistance in NSCLC cells and xenograft tumors (101). ANGPTL4 promotes resistance through two mechanisms: intracellular ANGPTL4 and exosomal ANGPTL4. One pathway involves the upregulation of GPX4, which inhibits ferroptosis and lipid peroxidation (101).

The aforementioned studies suggest that ANGPTL4 could serve as a potential therapeutic target to enhance the efficacy of radiotherapy and chemotherapy. However, research on the relationship between ANGPTL4 and radioresistance remains limited, and further investigations are required to improve understanding of its effects, and underlying mechanisms in chemoresistance and radioresistance.

4. Regulation of ANGPTL4 expression and function in cancer

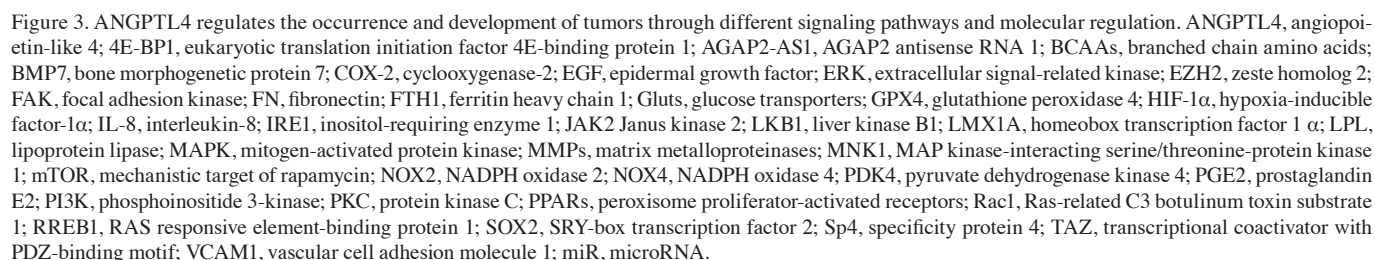
The expression of ANGPTL4 is quite common in cancer cells, but the molecular mechanisms of ANGPTL4 in cancer are quite complex. HIF-1, TGF-β and PPARs are critical upstream regulators of ANGPTL4 (Table I; Fig. 3). HIF-1, a heterodimeric protein composed of HIF-1α and HIF-1β subunits, activates the transcription of numerous genes involved in numerous aspects of cancer biology. Studies in scirrhous GC (90), HCC (143), uveal melanoma (67), and OS (44) have shown that the expression of ANGPTL4 is directly regulated by HIF-1α, subsequently promoting malignant processes, including tumor growth and metastasis.

TGF-β is a multifunctional cytokine that plays important roles in cell proliferation, differentiation, immune regulation,

apoptosis, and tissue repair. The Smad pathway and PPARs are essential for the expression of ANGPTL4 induced by TGF-β. In BRC, TGF-β promotes ANGPTL4 expression via the Smad pathway, mediating the lung metastasis and brain metastasis (31,127). Similarly, TGF-β1 activates Smad3, which binds to the ANGPTL4 promoter and promotes the transcription in CRC (30). Adhikary *et al* (144) found that TGF-β can also induce ANGPTL4 expression in a PPAR β/δ-dependent manner.

PPARs are a class of ligand-dependent transcription factors in the nuclear receptor superfamily. PPARs regulate the expression of ANGPTL4 in several cancers, including BRC and HNSCC. In BRC, PPAR α, PPAR β, and PPAR γ target ANGPTL4 to promote lipid metabolism, angiogenesis, tumor growth and invasion (133,144,145). In HNSCC, PPARs are induced by OA and target ANGPTL4, promoting anoikis resistance and metastasis (88).

Multiple signaling pathways are associated with the regulation of tumor development by ANGPTL4, with the STATs, PI3K/AKT, and COX-2/PGE2 pathways being particularly prominent (Table I; Fig. 3). The STAT family is the transcription factors, which have been implicated in cancer development, metastasis and resistance to treatments. To date, seven STAT genes have been identified: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. Specifically, the functions of ANGPTL4 are closely linked to the STAT1, STAT2 and STAT3 pathways. ANGPTL4 activates the JAK2/STAT3 pathway, which promotes the malignant progression of OVC (35). In pancreatic cancer, STAT3 activated by ANGPTL4 also drives metabolic reprogramming, invasion and metastasis (134). Additionally, ANGPTL4 enhances CRC cell proliferation through the activation of STAT1 (146).



The COX-2/PGE2 pathway, which plays a significant role in inflammation, is also implicated in tumor progression.

The TME consists of various components, including tumor cells, stromal cells, blood vessels, immune cells and ECM. These elements affect the biological characteristics of tumors

through complex interactions and are crucial in tumor initiation and progression (148). The critical involvement of ANGPTL4 in the TME has been increasingly highlighted. For example, ANGPTL4 has been shown to activate the JAK2/STAT3 pathway, enhancing tumorigenesis and angiogenesis in the TME (35). Zhu *et al* (30) emphasized that ADSCs in the TME promote tumor glycolysis and metastasis via ANGPTL4 in CRC. Immune cells are an important component of TME, and new evidence links ANGPTL4 with immune cell dynamics in the TME. In patients with CRC, ANGPTL4 suppresses the activation of CD8⁺ T cells through metabolic reprogramming, leading to diminished immune surveillance (32). Recombinant ANGPTL4 has also been reported to induce regulatory T (Treg) cells and M2 macrophages in mice, which may contribute to the tumor progression (149). Furthermore, spatial transcriptomics analyses have revealed that bladder cancer cells in the stressed or hypoxic state interact with plasma cells via the ANGPTL4/Syndecan-1 (SDC1) axis, which is associated with ineffective responses to immunotherapy and poor survival (150).

Sialylation, a common glycosylation modification of attaching sialic acid to the ends of sugar chains, is widely present in cell membranes, secreted proteins and serum proteins (151,152). This process significantly influences the function, stability, immune recognition and intercellular communication of cells and proteins in the TME (151). Recent studies have identified the distinct roles of ANGPTL4 in podocytopathies due to varying degrees of sialylation. Hyposialylated ANGPTL4 with a high isoelectric point (high-pI) is upregulated in patients with minimal change disease and correlates with increased proteinuria. By contrast, normal sialylated ANGPTL4 with a neutral isoelectric point (neutral-pI) reduces proteinuria by binding to β 5 integrin (153,154).

In tumors, high-pI ANGPTL4, with fewer negative charges, may enhance tumor cell adhesion and migration by binding more effectively to collagen and fibronectin in the ECM. Its high affinity for vascular endothelial cells may also enable it to play a more direct role in angiogenesis. Conversely, neutral-pI ANGPTL4 demonstrates greater stability in body fluids and may support the sustained regulation of angiogenesis. Moreover, neutral-pI ANGPTL4 can directly bind to sialic acid-binding immunoglobulin-like lectin (Siglec) receptors, which may inhibit the activity of natural killer (NK) cells and macrophages, thereby facilitating tumor immune evasion (155,156). Jin *et al* (51) found that nANGPTL4 exerts antitumor effects in clear cell renal cell carcinoma (ccRCC) by regulating the lysosomal acid lipase activity. However, no studies have explored whether high-pI and neutral-pI ANGPTL4 exhibit different impacts in renal and other tumors, as they do in podocytopathies. Future research could focus on the sialylation of ANGPTL4 in the TME to clarify its roles and associated mechanisms.

6. Discussion

A substantial body of research has demonstrated that ANGPTL4 plays critical biological roles, including the regulation of tumor growth, metastasis and angiogenesis (Fig. 2). It is also involved in the regulatory processes of programmed cell death, metabolic reprogramming and drug resistance (Fig. 2).

Taken together, all the evidence cited in the present review indicates that ANGPTL4 is an important molecule implicated in various aspects of cancer progression.

ANGPTL4 is overexpressed in various cancers and its expression is closely linked to clinicopathological features, such as BRC, cholangiocarcinoma, cervical, esophageal and gallbladder cancer (157-161). In the majority of cancers, such as TNBC, GBM and NSCLC, the overexpression of ANGPTL4 significantly enhances tumor progression (31,42,141). Additionally, ANGPTL4 has been found to promote the resistance to treatments (Table III).

However, the role of ANGPTL4 in tumors remains complex and controversial due to its dual effects. ANGPTL4 can both promote and inhibit tumorigenesis (31,34,62) (Fig. 1). It not only serves as a biomarker for poor prognosis (157,158,162,163), but also indicates favorable prognosis (164), and even exhibits the opposing roles within the same type of cancers (47). It is hypothesized that these contradictory effects are related to the structural and functional characteristics of ANGPTL4. Firstly, ANGPTL4 undergoes proteolytic cleavage, producing different functional fragments. The hydrolysis-generated nANGPTL4 and cANGPTL4 fragments may exert distinct biological effects compared with fANGPTL4. The nANGPTL4 inhibits LPL activity in both blood and adipocytes, leading to reduced circulating triglyceride levels (165-170). The nANGPTL4 also inhibits metastasis and improves overall survival by inhibiting WNT signaling and reducing vascularity at the metastatic site (53). Meanwhile, the cANGPTL4 fragment plays a role in angiogenesis, increases vascular permeability, causes endothelial damage, and promotes tumor growth and metastasis in multiple tumor models (47,53,171,172). Furthermore, fANGPTL4 exists in tumor tissues, whereas nANGPTL4 is more prevalent in systemic circulation (53). Secondly, as a protein capable of entering the nucleus, ANGPTL4 can directly or indirectly influence the expression of various genes, thereby performing multiple functions. It may also be secreted into the extracellular space or transported through exosomes and extracellular vesicles, potentially contributing to the intercellular and the inter-organ communication (68,101). This diversity in function may help explain its complex roles. Finally, differences in the TME and tissue-specific conditions may contribute to the diverse functions of ANGPTL4. For instance, while ANGPTL4 expression is low in UC cell lines and tissue samples, the elevated circulating levels are observed in patient samples (47).

The strong association between ANGPTL4 and the tumor progression highlights its potential as a promising biomarker and therapeutic target. Its expression is closely associated with prognosis in various cancers, supporting the rationale for developing ANGPTL4 as a biomarker (157,158,162-164). Additionally, the differential expression and functions of ANGPTL4 across cancer types suggest that targeting ANGPTL4 enables offering personalized treatment strategies tailored to specific tumor characteristics (31,34,62) (Fig. 1). Jin *et al* (51) identified a subset of patients with no ANGPTL4 increase in ccRCC, who had a poorer prognosis than those with high ANGPTL4 expression. This finding highlights the potential of stratifying patients based on ANGPTL4 expression levels, which may not only provide the more

accurate predictions of survival outcomes but also optimize therapeutic interventions. Furthermore, as ANGPTL4 is closely connected with chemoresistance and radioresistance (Table III), the development of ANGPTL4-targeted drugs or antibodies for combination therapy holds significant promise to enhance treatment efficacy and patient outcomes. ANGPTL4 also acts as a potent pro-angiogenic factor in certain cancers (35,37,65,66). Targeting ANGPTL4 may therefore provide a novel anti-angiogenic approach. In addition, as aforementioned, ANGPTL4 regulates various immune cells in the TME, including CD8⁺T cells, NK cells, macrophages and plasma cells (32,164,165,173). Antibodies against ANGPTL4 may help restore immune surveillance and enhance antitumor immunity. Combining ANGPTL4-targeted antibodies with existing immunotherapies, such as programmed cell death protein 1 and programmed death-ligand 1 inhibitors, offers new perspectives for the combination immunotherapy.

Despite current advancements in research, numerous key gaps remain in fully understanding ANGPTL4. Firstly, ANGPTL4 exhibits both tumor-promoting and tumor-inhibiting effects in the progression of different cancers, yet its underlying molecular mechanisms have not been insufficiently elucidated. Secondly, although ANGPTL4 can be expressed in the nucleus or secreted, the specific form in which it exists across various organs and diseases is unclear. Whether the ANGPTL4 protein is modified post-secretion during this process remains unknown. Thirdly, ANGPTL4 can undergo glycosylation modifications structurally, but it is unclear how different modifications such as sialylation affect the role and mechanism of ANGPTL4 in tumors. Finally, although some inhibitors targeting the ANGPT family have been explored, including MEDI-3617 and nesvacumab (targeting ANGPT2), and trebananib and AMG780 (targeting both ANGPT1 and ANGPT2), no inhibitors or drugs targeting ANGPTL4 have been developed to date (173). The clinical application of ANGPTL4 as a biomarker for cancer and the development of novel antitumor drugs targeting ANGPTL4 still require extensive experimental research and exploration.

The present review updates the understanding of ANGPTL4 in tumors by systematically analyzing its roles in the six hallmarks of cancer and its interactions with the TME. It also addresses the dual effects of ANGPTL4 across different cancer types and highlights its potential in precision medicine. These contributions provide a comprehensive, in-depth and innovative perspective on ANGPTL4 in malignancies.

In conclusion, ANGPTL4 predominantly exerts pro-tumor effects, yet its antitumor functions should not be overlooked. Further research is necessary to fully understand its roles, including the functions of different ANGPTL4 fragments, and the effects and interactions of ANGPTL4 in the TME. Exploring the diverse mechanisms of ANGPTL4 in human cancers and assessing its clinical value will be crucial for future studies. With a deeper understanding of its structure, function and drug response, supported by comprehensive preclinical analyses, ANGPTL4 holds significant potential for future application in clinical prediction and therapy.

Acknowledgements

Not applicable.

Funding

The present study was supported by the National Natural Science Foundation of China (grant no. 82172664) and the Natural Science Foundation of Shandong (grant no. ZR2022MH074).

Availability of data and materials

Not applicable.

Authors' contributions

ZW and YC conceived the study. RL, MF and PC wrote the original draft of the manuscript. RL, YL, XS and PZ wrote, reviewed and edited the manuscript. RL, MF and WH illustrated the figures. ZW and YC supervised the study. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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.

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