ANGIOPOIKETIN-LIKE 4 (ANGPTL4) AND CANCER

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ABSTRACT

Angiopoietin-like 4 (ANGPTL4) is one of the many secreted proteins predominantly expressed adipose tissues as well as the liver, and plays a central role in both metabolic and non-metabolic processes including energy homeostasis and angiogenesis. Recently, it is demonstrated that ANGPTL4 is involved in tumorigenesis and progression of human cancers. But, the biological features, roles and mechanisms of ANGPTL4 in the tumorigenesis, development and progression of human cancers aren’t thoroughly elucidated. Therefore, identification of special biological behaviors, further understanding the roles and mechanism of ANGPTL4 in tumorigenesis and development of human cancer is of very significant. This review pays key attention to the physical, chemical and structure of ANGPTL4 and its role in different types of cancers, specially, focuses on the expression of ANGPTL4 in relation to tumorigenesis, development and progression of human cancer.

KEYWORDS: Angiopoietin-like 4; Tumorigenesis; Angiogenesis: Cancer.

INTRODUCTION

Angiopoietin-like 4 (ANGPTL4) is one of the many secreted proteins which is predominantly expressed adipose tissues as well as the liver.[1] Researchers have recognized ANGPTL4 as a significantly multi-faceted protein that plays a central role in numerous metabolic, non-metabolic conditions[2] and various aspects of energy homeostasis. The name angiopoietin-like 4 (ANGPTL4) suggests that it is structurally related to angiopoietins which are involved in angiogenesis.[3] It is recently demonstrated that ANGPTL4 is involved in tumorigenesis and progression of human cancers.[2-6] ANGPTL4 has been associated with some cancers due to its diverse roles, especially the regulation of reactive oxygen species (ROS) level, which promotes tumorigenesis.[2] This review discusses the physical, chemical and structure of ANGPTL4 and ANGPTL4’s role in causing different types of cancers, specially focusing on the expression of ANGPTL4 and its relation with the tumorigenesis, growth, development and progression of cancers, in order to further seek to establish the clinical values and prognosis significance of elevated ANGPTL4 expression in gallbladder cancer and its stroma.

I The Physical and Chemical Natures of ANGPTL4

ANGPTL4 belongs to a group of ANGPTL proteins, which form a powerful subset of secreted proteins which are also angiogenic-regulating. ANGPTL4 is produced by numerous tissues before it is secreted into the bloodstream in oligomerized, glycosylated, native and cleaved isoforms to modulate several physiological events such as cell differentiation, angiogenesis, and the cross-talk between liver, adipose, brain, and muscle tissue during the process of glucose and lipid metabolism.[5] ANGPTL4 bears high similarity to members of the ANG family. All the ANG-like family members, that is, (ANGPTL 1-8) with the exception of ANGPTL5 have been confirmed not only in mice but also in humans.[5] It is only the human orthologue that contains ANGPTL5.[2] ANGPTL4 happens to share high sequence homology with ANGPTL3 and ANGPTL8.[5,7] In human beings, the ANGPTL4 gene is located on chromosome 19p13.3.[2,5] The gene encodes a 406-amino acid glycoprotein with a molecular mass of approximately 45-65 kDa and has seven exons.[2]

The ANGPTL4 like all other angiopoietin-like proteins except ANGPTL8 has a secretory signal peptide and contains a predicted N-terminal region which is believed to be intrinsically disordered, a coiled-coil oligomerization domain, and finally C-terminal fibrinogen-like domain.[2,4] The oligomerization of ANGPTL4 is important for its function as an LPL (lipoprotein lipase) inhibitor.[2,8,9] ANGPTL4 possesses three potential sites for N-glycosylation and it appears to be sialylated. Unlike many of the angiopoietins, which normally tend to retain all their domains, ANGPTL4 undergoes a process called proteolysis to release its functional fibrinogen-like domain.[10-12] The discrepancy witnessed on the ANGPTL4’s molecular mass as reported in different research studies is perhaps due to the various glycosylation, oligomerization, as well as cleavage forms which are a result of the particular cell
ANGPTL4 was initially termed as orphan ligand due to its inability to bind to the angiopoietin receptor tyrosine kinase Tie1 and Tie2. Current evidence shows that ANGPTL4 has got so many binding partners including lipoprotein lipase, integrin beta 1, integrin beta 5, integrin αvβ3, cadherin-5, cadherin-11, and syndecans. In addition, ANGPTL4 assembles into dimers and tetramers. Its two-cysteine residues (Cys-76 and Cys-80) in the N-terminal domain play a central role in ensuring the stability of the intermolecular disulfide bonds in ANDPTL4 oligomers. ANGPTL4 after it is secreted into the bloodstream by tissues it is expressed in the plasma at 60kDa in various forms. For instance, adipose tissue secretes full-length ANGPTL4 whereas the liver where the gallbladder is located secretes Nangptl4 isoforms. According to various immunoblot analyses, ARPE-19 cells are known to secrete an approximately 55kDa full-length ANGPTL4. Some studies have demonstrated that cANGPTL4 domain is a potential modulator of tumorigenesis which is associated with cancer development whereas nANGPTL4 modulates lipid metabolism.

Upon its discovery, the ANGPTL4 got classified as an adipokine simply because it was predominantly expressed adipose tissues as well as the liver. It is due to this significant expression is believed to play a critical role in lipid metabolism; in addition, to its expression in the liver makes it an easy target to be associated with causing cancer of the gallbladder, the adjoining organ embedded on the liver organ. The name angiopoietin-like 4 suggests that it is structurally related to angiopoietins which are involved in angiogenesis. Researchers have gone ahead to demonstrate that the functions of ANGPTL4 by far outstrip what was previously known and now include tumorigenesis, inflammation, angiogenesis, homoeostasis, redox regulation, cell differentiation, vascular permeability, and wound repair. Lastly, it also clear that due to its dynamism, researchers have cited ANGPTL4 as an agent involved in the occurrence of a myriad of physiological and pathological conditions including human cancers.

3 The Expression of ANGPTL4

The first thing to consider before turning on to elevated expression of ANGPTL4 is its expression. In studies done to find out the rate of expression of ANGPTL4 using mice confirmed that the angiopoietin-like 4 (ANGPTL4) protein is highly expressed in their white and brown adipose tissue. The same ANGPTL4 is less expressed in other mice tissues such as the liver, skeletal muscles, ovary, heart, and intestines. In human beings, the expression seems to be slightly different. An elevated or high ANGPTL4 expression in humans occurs in the liver, blood plasma, heart, placenta, adipose tissue, and small intestines. Despite this ubiquitously high expression on those human tissues and organs, drastic variations exist in the level of expression from one person to the next. In the blood plasma, both the truncated and full-length forms are expressed. However, the baseline levels of expression also vary from one individual to the next.

The expression of ANGPTL4 is known to be induced by different and varied stimuli. A majority of research studies done on ANGPTL4 expression indicate that under fasting conditions, but not all, strongly tend to up-regulate ANGPTL4 expression in a number of body tissues and organs. These tissues or organs include the liver, heart, adipose tissue, skeletal muscle, and plasma. Other tissues where ANGPTL4 expression is highly pronounced include brain, pituitary gland, eye, spleen, hypothalamus, and the kidney. This elevation in ANGPTL4 expression is mediated by glucocorticoid, whose levels in circulation tend to increase during fasting. In addition, high-fat, high-energy diet (HFED) and very-low-calorie diet (VLCD) have shown to elevate plasma concentrations of angiopoietin-like 4 (ANGPTL4). Apart from fasting, the elevation of ANGPTL4 is brought about by chronic carolic restriction or non-esterified fatty acids (NEFAs) or rather free fatty acids. Both the NEFA- and Fasting-induced high expression of ANGPTL4 is mediated by the nuclear hormone receptors PPARs (peroxisome proliferator-activated receptors). These hormone receptors transcriptionally stimulate the expression of angiopoietin-like 4 through a functional PPR-response element located in both mouse and human ANGPTL4 genes. Elevated expression of ANGPTL4 in adipocytes, cardiomyocytes, articular chondrocytes, endothelial cells, and the brain is sometimes associated with hypoxic conditions. Several studies confirm that certain physiological processes such as fasting, lactation, hypoxia, pregnancy, and adipocyte differentiation result inANGL4 elevation or up-regulation.

In human just like in mice, synthetic agonists for peroxisome proliferators-activated receptors (PPARs) tend to elevate ANGPTL4 levels. A critical cytokine called transforming growth factor β (TGFβ) is also credited for stimulating ANGPTL4 expression in primary tumor cells that lead to cancer, especially breast cancer to prime metastasis. The current research findings on the expression of angiopoietin-like 4 indicate
that it is possible for TGFβ and PPARβ/δ can either synergistically or antagonistically stimulate or elevate ANGPTL4 expression depending on cellular contexts or media. [28,29] PPARβ/δ and HIFI are two transcription factors that utilize synergistic transcriptional regulation through a conformational change to their common target gene ANGPTL4. [5] There is also a study that indicated the expression of human ANGPTL4 might be induced synergistically or antagonistically stimulate or elevate ANGPTL4 expression depending on cellular contexts or media. [5,29]

4 Elevated ANGPTL4 Expression and Cancers

4.1 Elevated ANGPTL4 Expression and Tumorogenesis

One of the prominent genes that play a central role in a compact in vivo hypoxia signature which points to poor outcome in multiple tumor types is ANGPTL4. [2,12,35] It has been revealed that ANGPTL4 mRNA is often elevated or up-regulated in perinecrotic areas of numerous human tumors, squamous cell carcinomas, and gastric cancers. [5,36] Besides, analysis of tissue array indicates that an elevated ANGPTL4 expression in up to around 40 well-known human epithelial tumor types. The expression tends to increase as the tumor progress from benign to metastatic states. [17] The elevated ANGPTL4 expression in a majority of cancers points to the role ANGPTL4 plays in tumor growth. There is even a study that suggested that ANGPTL4 plays a role during metastasis phase via lymphovascular invasion. [38]

Lastly, a majority of research studies suggest that the two effects of ANGPTL4 which are; proangiogenic and antiangiogenic effect are reliable and are strongly dependent on the tumor microenvironment. A good number of these studies also suggest that any tumor microenvironment seems to play a critical role in the multiple steps found in the process of tumor development and progression, including angiogenesis, drug resistance, and immune-escaping, distant metastasis. [39] Specifically, stromal cells have the capability of secreting multiple factors ANGPTL4 included which tend to increase the vasculature permeability in both brain and lung cancers. [41]

4.2 Elevated ANGPTL4 Expression and Tumor Angiogenesis

Angiogenesis is defined as the formation of new blood vessels from the already established vascular system. Angiogenesis assists a tumor to grow by virtue of feeding cancer cells with oxygen and essential nutrients. In addition, angiogenesis contributes to higher vascular permeability. It is the communication that occurs between tumor cells and the endothelium that promotes angiogenesis and vascular permeability with play a huge role in ensuring continued growth and metastasis of the tumor respectively [5]. The dissemination of cancer cells throughout the entire body, which eventually results in metastasis, is largely influenced by neovascularization. The metastasis of a tumor is positively related to increased vasculature leakiness as well as the critical steps of intravasation and extravasation. [2] Intravasation and extravasation encompass directional migration of tumor cells across the disrupted endothelium. The migration of tumor cells is what leads to the development of cancer.

Angiogenesis that is tumor-induced is mainly sustained by the production and secretion of angiogenic factors such as vascular endothelial growth factor and ANGs which origins from tumor and stromal cells. [2,42] This realization confirms that the elevation of ANGPTL4 in the stromal cells of any organ predicts a wrong prognosis for cancer because these cells’ secretions just aid the progression of tumor growth though tumor-induced angiogenesis. Owing to the close similarity between ANGs and ANGPTL groups of proteins, the subject of ANGPTL4 taking part in angiogenesis is one that has created a lot of interest among many researchers. [2] Up to date, a lot of controversies exist concerning the role of
ANGPTL4 in angiogenesis and vascular leaking all of which contribute to the growth and spread of tumor cells. Some people are of the opinion that ANGPTL4 acts as a gate-keeper that takes part in regulating vascular integrity in a context-dependent manner.[23] Amid all the controversies surrounding the role of ANGPTL4 in angiogenesis hence cancer development, a growing number of reports suggest that it is both pro-angiogenic and pro-metastatic.[43] There is a finding that supported the claim that ANGPTL4 significantly promotes the in vitro sprouting vascular endothelial cells and this result has been supported by a study that found that ANGPTL4 is a pro-angiogenic factor during ischemia. Furthermore, ANGPTL4 has been confirmed as one of the genes identified that can predict breast cancer to even lung metastasis with the greatest or highest frequency. On further investigations, researchers pointed out that TGFβ primes breast tumors for seeding of lung metastasis through ANGPTL4.[39] The TGFβ-induced ANGPTL4 is said to promote the retention of cancer cells in the lungs, enhances the permeability of the lung capillaries, disrupts vascular endothelial cell-cell junctions, and facilitates the trans-endothelial passage of tumor cells thereby promoting the most crucial steps in metastasis development.[34] Until recently, the real effect of ANGPTL4 in promoting vascular leakiness remained unknown. However, it is now clear that elevated expression of tumor-derived cANGPTL4 initiates the disruption of endothelial continuity by way of directly interacting with three novel binding partners which are VE-cadherin, claudin-5, and integrin α5β1, in a partially sequential manner, thus leading to metastasis.[36] Indeed, finding of another study demonstrated that tumor cells and mice that did not have elevated ANGPTL4 expression recorded reduced vascular permeability with such mice further indicating attenuated lung metastasis.[44] The evidence so far shows that elevated ANGPTL4 is one way or the other involved in cancer growth or cancer progression.

4.3 Elevated ANGPTL4 Expression and Cancer Development

A majority of published works underscore that ANGPTL4 expression plays an important role in cancer onset, its progression, metastasis, and anoikis resistance.[9] However, elevated levels of ANGPTL4 is usually associated with poor prognoses in solid tumors, such as melanoma, hepatocellular carcinoma, prostate cancer, giant cell tumor, oral tongue cancer, scirrhus gastric cancer, and tongue squamous cell carcinoma.[14] This happens because T266 cANGPTL4 binds to integrin α5β1 thus leading to weaker activation of downstream signaling molecules, resulting into reduced proliferation, anoikis resistance, migratory capability and impaired adenylate energy charge.[45] Surprisingly, it was found that ANGPTL4 exerts both tumor-suppressive and oncogenic roles and the circulating level of ANGPTL4 level was a biomarker of tumor progression. The case is different from that of breast cancer. In breast cancer, a knockdown of ANGPTL4 was found to have absolutely no effect on tumor metastasis in local lymph nodes and bones, but it could inhibit metastasis in the lung.[5]

An elevated ANGPTL4 expression could be used to indicate proper prognosis in hepatocellular carcinoma patients because it is known to promote trans-endothelial migration of hepatocellular carcinoma by stimulating vascular cell adhesion molecule-1 (VCAM-1). Still, in hepatocellular carcinoma, the angiopoietin-like 4 activates VCAM-1/ integrin β1 axis.[6] In such a case, hypoxia induces the expression of prostaglandin E2 (PGE2) receptor EP1. Thereafter, PGE2 binds to EP1 resulting in the activation of the EP1 signaling pathway. The activation of the EP1 signaling pathway is known to promote tumor expression of ANGPTL4 and cANGPTL4 through activation on transcriptional activator 1 (STAT1).[5] In colorectal cancer, the EP1 signaling pathway in turn tends to accelerate tumor growth and proliferation. Further, it was shown that cANGPTL4 majorly regulates tumor cell proliferation as well as inducing STAT1 production based on the Src/MAPK signaling pathway activation.[5]

The use of in vivo DNA electrotransfer overexpressing ANGPTL4 confirms that 3LL cells express less lung metastasis. The finding suggests that ANGPTL4 plays a role sometimes in preventing metastasis. Still, ANGPTL4 binds to syndecans to form a ternary complex with Wnt co-receptor lipoprotein receptor-related protein 6 (LRP6) which serves as a Wnt signaling antagonist.[16] Bone-morphogenetic protein is also highly up-regulated by ANGPTL4 thus inhibiting apoptosis of colorectal cancer cells and the promotion of metastasis. Besides, it has been found out that in Kaposi’s sarcoma, the viral G protein-coupled receptor can enhance angiogenesis and vascular permeability by ANGPTL4 up-regulation.[5] To this end, the expression and mechanism of ANGPTL4 may be related to tumor type.

5 Elevated ANGPTL4 Expression and the Growth and Development of Specific Cancer

5.1 Hepatocellular Cancer

The commonest type of liver cancer is the hepatocellular carcinoma (HCC). HCC is a typical malignant tumor with high incidence and poor survival rate.[6] Previous studies have already confirmed that angiopoietin-like 4 by TGFβ, through the Smad signaling pathway is very crucial in the trans-endothelial passage of tumor cells thus resulting in tumor metastasis.[14] Further investigations also revealed that ANGPTL4 plays a role in regulating endothelial cell junction organization[48] and pericyte coverage thereby leading to a disruption in endothelial cell-cell junctions. However, a study that entailed rational measurement of ANGPTL4 in paracancerous and cancerous liver tissues showed that there was no significant correlation between ANGPTL4 with either lymphatic or vessel invasion.[47] This outcome what contrary to prior findings that had revealed that expression of ANGPTL4 was indeed statistically correlated with lymphatic invasion, venous invasion, and
the degree of invasion.\cite{38,46} It was also confirmed that ANGPTL4 had a significant correlation with the T classification of tumors.\cite{47} Therefore, the elevation of ANGPTL4 expression in the liver plays a central role in the development and progression of hepatocellular cancer.

5.2 Breast Cancer

The presence of ANGPTL4 has already been confirmed in various solid tumors and one of them is breast cancer.\cite{41} This confirmation makes the suggestion that this protein plays a significant role in cancer growth and progression.\cite{2,36} A potential link between tumorigenesis and ANGPTL4 is available by hypoxia conditions, which happen to capture a prominent feature of the tumor microenvironment. In such an environment, hypoxia induces the overexpression of cyclooxygenase-2 abbreviated as COX-2 by hypoxia-inducible factor-1 (HIF-1) resulting into the synthesis of prostanooids more so prostaglandins PGE2.\cite{51} High levels of PGE2 stimulate an intracellular signaling cascade which leads to the induction ofANGPTL4 expression then cANGPTL4 secretion.\cite{49} The exact role played by ANGPTL4 in cancer progression is not fully defined up to now. However, the role of cANGPTL4 seems to be well-known, especially its involvement in anoikis resistance which is a special feature that enables metastatic cells to acquire the ability to escape what is known as programmed cell death. The cANGPTL4 maintains an elevated ROS rate via its interaction with beta-integrins thus inducing a redox-based survival mechanism that greatly involved in the activation of the SRC kinase and mitogen-activated protein kinase (MAPK) signaling pathways that favor cancer cells growth and survival, especially in breast cancer.\cite{57}

There have been several studies that tried to correlate elevated ANGPTL4 levels with breast cancer. One of the studies noted that the overexpression of ANGPTL4 strongly predicted inferior disease-free survival (DFS) in basal as opposed to HER2-enriched tumors in young women.\cite{50} Any altered expression of secreted factors by the action of tumor cells or other cells found within a tumor microenvironment is a central event in cancer development and progression. The autocrine and the paracrine activity of ANGPTL protein family members going by the existing evidence they play a huge role in breast cancer development and progression. Recent studies show that elevated ANGPTL4 expression is a very significant player in redox-mediated cancer progression.\cite{57} Studies have shown that the overexpression of ANGPTL4 can further aggravate tumorigenesis and also metastasis based on different contexts of different cancers.\cite{19,36} One of those contexts where the elevation of ANGPTL4 aids cancer development and progression is the breast. Here, the elevation of ANGPTL4 promotes migration of cancer cells and invasion. Despite the conclusion that ANGPTL4 elevation does not correlate with the overall survival; high ANGPTL4 expression level is positively correlated with the depth of tumor invasion as well as venous invasion.\cite{46} In many aggressive cancers, aberrant expression of ANGPTL4 is a common phenomenon. However in breast cancer patients’ blood it has been demonstrated that ANGPTL4 enjoys high expression levels.\cite{51} Another study confirmed that elevation ANGPTL4 expression had a correlation with a minor disease-free survival (DFS) of breast cancer in young patients.\cite{50} A whole genome expression on circulating tumor cell in breast cancer patient consists of a signature of genes including ANGPTL4 has been identified to enhance tumor-aggressiveness of the breast cancer. In spite of the sufficient evidence that implicates a role of elevated ANGPTL4 in cancer metastasis, the role of ANGPTL4 in vascular integrity remains a blurred subject.\cite{5}

In hypoxic peri-necrotic regions where solid tumors are found, ANGPTL is also overexpressed. In these regions, the elevated ANGPTL4 plays central roles associated with cancer growth, angiogenesis, and metastasis.\cite{49} ANGPTL4 has only been described in relation to breast cancer metastasis. However, its pro-metastatic role is largely related to distant lung or brain metastases. It is critical to note that ANGPTL4 is just a single part of a gene signature linked with distant metastasis and tumor aggressiveness in breast cancer.\cite{52} The elevation of ANGPTL4 expression has also been associated with increased breast cancer lung metastasis by MDA-MB-231 cells.\cite{47}

5.3 Gallbladder Cancer

There is hardly any study that explores the role of ANGPTL4 expression in gallbladder cancer and tumor stroma. Adenocarcinoma is one of the commonest type of gallbladder cancers (GBCs). No study quotes elevation of ANGPTL4 expression as a cause behind the development of gallbladder cancers including adenocarcinoma. However, the expression or overexpression of several genes such as TP53, P16, FHIT, and ERBB2 has been identified as a potential biomarker for GBC progression.\cite{53} A study gap exists because there is no particular study that tries to link elevated ANGPTL4 expression with gallbladder cancers like adenocarcinoma.

5.4 Melanoma

ANGPTL4 expression maybe related to cutaneous melanoma metastasis. Recently, a research by Sivan izraely study have determined the significance and function of ANGPTL4 and established expression of ANGPTL4 in notably higher in cells that metastasized to the brain than in cells from the original tumor at the same melanoma in a nude mouse xenograft model, and also in combined clinical samples of melanoma metastases than in main melanomas from the same patients. Cutaneous cell ANGPTL4 cells migrated more efficiently than the corresponding CONpQC cells, In contrast, ANGPTL4hi MBM cells migrated less efficiently than the corresponding CONpQC cells, Melanoma cells can
secrete high amounts of TGFβ1 up-regulated ANGPTL4 expression by melanoma cells. Enforced, including its own expression through a positive response.\(^{[54]}\)

### 5.5 Colorectal Cancer

The tumor microenvironment plays an important role in the molecular mechanisms of metastasis.\(^{[56]}\) Primary cancers and metastases consist of tumor cells and stromal cells, including fibroblasts, endothelial cells, and inflammatory cells. The cytokine TGF-β is responsive to hypoxia or inflammation or fibrotic cystic carcinoma\(^{[57]}\) in a tumor environment produced by mucosal stromal cells. Newly published article by Padova et al showed that TGF-β2 stimulates the expression of adiposin in ANGPTL4 by activating the transcription factor SMAD.\(^{[58]}\) ANPCPL4 derived from tumor cells prevents the formation of vascular endothelial cells, increases the length of capillaries, and promotes the transendothelialization of tumor cells. Secretion of ANGPTL4 allows extravasation of tumor cells in other tissues and tissues. In this study, the expression of ANGPTL4 protein was stronger in all three tissues of human colorectal cancer invasive carcinoma than in normal tissue. Therefore, ANGPTL4 may help eliminate vascular invasion and metastasis of human colorectal cancer.\(^{[36]}\)

### 5.6 Renal Cell Carcinoma

The ability of renal cell carcinoma (RCC) cells to isolate ANGPTL4 protein in the blood was confirmed by detecting the expression of ANGPTL4 in the culture supernatant of RCC cell lines such as 786-O, A498, Caki-1 and Os-RC-2 did. Measurement was performed using ELISA. Serum ANGPTL4 levels were higher in patients with bigger tumor size, but the difference was not statistically significant. Thus, a large cohort should be used to verify the diagnostic efficiency of serum ANGPTL4 for patients with RCC. The lipid metabolism levels of patients with RCC and healthy controls should be taken into consideration in future research, because ANGPTL4 plays an important role in the metabolism of lipids. In conclusion, the present study suggested that serum ANGPTL4 might be a diagnostic and prognostic biomarker for RCC.\(^{[30]}\)

### CONCLUSIONS

From review done in this paper, angiopoietin-like 4 (ANGPTL4) has been described as a secreted, multifaceted protein that plays a central role in numerous metabolic and non-metabolic conditions. Some of the functions associated with ANGPTL4 include tumorigenesis, inflammation, angiogenesis, homeostasis, redox regulation, cell differentiation, vascular permeability, and wound repair. Numerous tissues produce ANGPTL4 before it is secreted into the bloodstream in oligomerized, glycosylated, native and cleaved isoforms. An elevated or high ANGPTL4 expression of in humans occurs in the liver, blood plasma, heart, placenta, adipose tissue, and small intestines. The elevation of ANGPTL4 expression is brought by fasting, chronic carolic restriction or non-esterified fatty acids (NEFAs) or rather free fatty acids, high-fat, high-energy diet (HFED) and very-low-calorie diet (VLCD).

This review has confirmed that elevated ANGPTL4 greatly contributes to the growth and progression of cancers, especially hepatocellular and breast cancers. However, there are no studies that link ANGPTL4 expression with development of gallbladder cancers. Numerous research studies suggest that ANGPTL4 has both proangiogenic and antiangiogenic effects which are reliable and are strongly dependent on the tumor microenvironment, which plays role in the multiple steps found in the process of tumor development and progression. Due to this factor, elevation of ANGPTL4 expression in some case leads to cancer growth and development while in others the case is different and as such elevated ANGPTL4 leads to wrong cancer prognosis. Elevated levels of ANGPTL4 are usually associated with poor prognosis in solid tumors, such as gallbladder cancer stroma. This happens because T266 cANGPTL4 binds to integrin α5β1 thus leading to weaker activation of downstream signaling molecules, resulting in reduced proliferation, anoikis resistance, migratory capability, and impaired adenylate energy charge. The stromal cells have the capability of secreting multiple factors ANGPTL4 included which tend to increase the vasculature permeability in tumor stroma. Therefore, from this review, one can accept the claim that elevated ANGPTL4 in gallbladder cancer and its stroma maybe predicts poor prognosis.

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