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Angiopoietin-like protein and Liver Diseases

Mahmoud Mohamed Amer[1], Mahmoud Tamer Ibrahim [1], Fady Maher Wadea[1], Ahmed Awad Bessar[2], Doaa Metwaly Abd Elmonem[3], Amr Talaat EL Hawary[1]

1 Internal Medicine Department, Faculty of Medicine, Zagazig University
2 Radiology Department, Faculty of Medicine, Zagazig University
3 Clinical Pathology Department, Faculty of Medicine, Zagazig University
Email:mahmoudtamernew@gmail.com

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Abstract:Background Angiopoietins have two domains: an N-terminal coiled-coil domain that mediates homo-oligomerization, and a C-terminal fibrinogen like domain that binds Tie2. Angiopoietins bind Tie2 receptor tyrosine kinase and regulate angiogenesis and the preservation of vascular integrity and permeability. Angiopoietin-like proteins (ANGPTLs) are structurally similar to angiopoietin. Seven ANGPTLs, ANGPTL1–7, exhibit an N-terminal coiled-coil domain and a C-terminal fibrinogen like domain. Only ANGPTL8, which is homologous to ANGPTL3's N-terminal domain, lacks a C-terminal fibrinogen-like domain. Angiopoietin-like proteins (ANGPTLs) are a family containing groups of proteins, which are structurally like the angiopoietins family (ANG). Only eight ANGPTLs had been discovered, from ANGPTL1 to ANGPTL8. Interestingly, some ANGPTL proteins have multibiological properties and play functional roles in lipid metabolism, inflammation, hematopoietic stem cell activity, and cancer cell invasion. Angiopoietin-like protein 3 (ANGPTL3), also known as angiopoietin-5, firstly discovered in 1999, which is closely related to the disorder of lipid metabolism. The encoded ANGPTL3 protein belongs to a kind of secreted protein factors with multiple functions such as promotion of neovascularization and hyperlipidemia. Generally, Human ANGPTL3 is a 460-amino-acid polypeptide (molecular mass of 70 kDa) with the characteristic structure of angiopoietins. ANGPTL3 gene locates on human chromosome 1 (1p31.1-p22.3) and includes seven exons and six introns. In addition, ANGPTL3 is mainly expressed in the liver. ANGPTL3 levels are significantly increased in non alcoholic steatohepatitis (NASH) patients, which may be associated with insulin resistance in NASH patients. Host lipid metabolism reprogramming is essential for hepatitis C virus (HCV) infection and progression to severe liver disease. Angiopoietin-like protein-3 (ANGPTL-3) regulates the clearance of plasma lipids by inhibiting cellular lipase activity and possesses emerging roles in tumorigenesis.

Keywords:*Angiopoietin-like protein, Liver disease*

Introduction

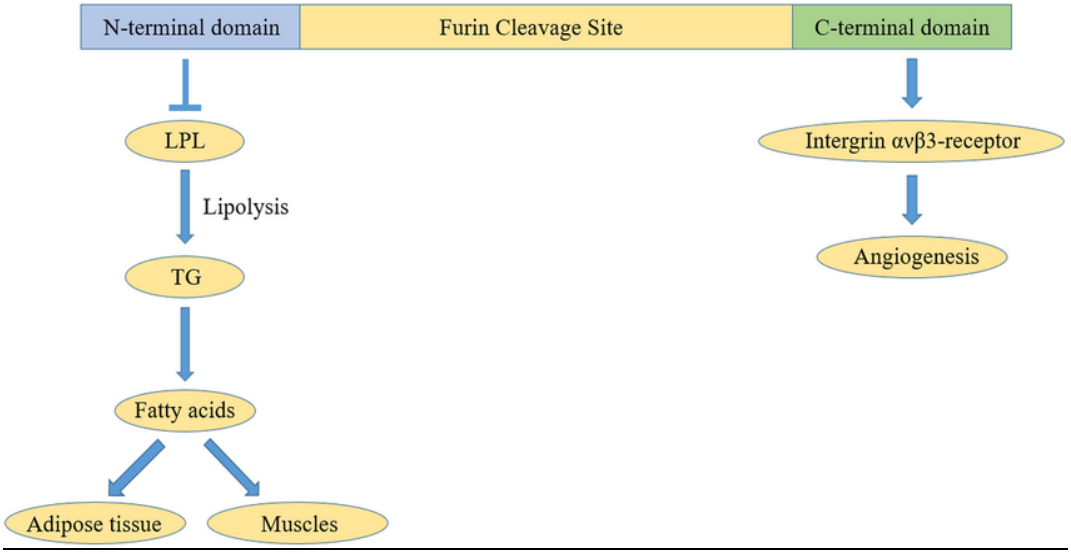
Angiopoietin-like protein 3 (ANGPTL3), also known as angiopoietin-5, firstly discovered in 1999, which is closely related to the disorder of lipid metabolism. The encoded ANGPTL3 protein belongs to a kind of secreted protein factors with multiple functions such as promotion of neovascularization and hyperlipidemia. Generally, Human ANGPTL3 is a 460-amino-acid polypeptide (molecular mass of 70 kDa) with the characteristic structure of angiopoietins. ANGPTL3gene locates on human chromosome 1 (1p31.1-p22.3) and includes seven exons and six introns. In addition, ANGPTL3 is mainly expressed in the liver. **(1)**

Structure:-

Including an N-terminal signal peptide (SP), an N-terminal coiled-coil domain (CCD), a linking region, and a C-terminal fibrinogen-like domain (FLD). ANGPTL3 is mainly regulated by post-translational modifications, such as multiple cleavage and glycosylation. Cleavage of ANGPTL3 is vital for its regulatory effect on lipid metabolism while the glycosylation can block its cleavage activation. ANGPTL3 is often cleaved at two sites, Arg221 to Ala222 and Arg224 to Thr225, yielding an N-terminal fragment containing the CCD and a C-terminal fragment containing the FLD. The N-terminal fragment affects plasma TG levels via reversibly inhibiting catalytic activity of LPL; the C-terminal fragment binds to integrin αvβ3 receptor and participates in angiogenesis, which is similar to the function of Angiopoietins. **(2)**

Furin/ PCSK3 mainly mediates the intracellular cleavage of ANGPTL3 in hepatocytes, while PACE4/PCSK6 mainly involves in the extracellular cleavage. The truncated form of cleaved ANGPTL3 displays increasing inhibitory activities of lipoprotein lipase (LPL) and endothelial lipase (EL), further resulting in elevation of triglyceride (TG) and high-density lipoprotein (HDL). Therefore, furin-induced cleavage of ANGPTL3 may be more effectively in regulating lipid metabolism **(3)**

The structure of ANGPTL8 is the most homologous to ANGPTL3, but it lacks the fibrinogen-like domain. ANGPTL8 promotes the cleavage of ANGPTL3 and subsequently increases ANGPTL3 activity about inhibiting LPL by a physical interaction with ANGPTL3 that forms an ANGPTL3-ANGPTL8 complex. Most importantly, the ability of ANGPTL3 to raise plasma triglyceride levels is impaired in the absence of ANGPTL8. Therefore, the complex of ANGPTL3-ANGPTL8 has a significant ability on inhibition of LPL. **(11)**



Schematic representation of the function of angiopoietin-like protein 3 (ANGPTL3). **(4)**

Biological functions of ANGPTL3:-

1. **<u>ANGPTL3 and lipid metabolism:-</u>**

ANGPTL3 has been demonstrated to be a critical regulator of lipoprotein metabolism to inhibit lipoprotein lipase (LPL) activity. Genetic, biochemical, and clinical studies in animals and humans have shown that loss of function, inactivation, or downregulated expression of ANGPTL3 is associated with an obvious reduction in

plasma levels of triglycerides (TGs), low-density lipoprotein- cholesterol (LDL-C), and high-density lipoprotein-cholesterol (HDL-C), atherosclerotic lesions and the risk of cardiovascular events. Therefore, ANGPTL3 is considered an alternative target for lipid-lowering therapy. **(5)**

Homozygous loss-of-function mutations in ANGPTL3 lead to familial hypobetalipoproteinaemia-2 (FHBL2), a disorder characterized by the reduction of glucose, insulin, and all major plasma lipoprotein classes, including very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), HDL and low circulating non-esterified fatty acids (NEFAs) level. **(6).**

LPL hydrolyzes VLDL and TGs, which are encapsulated in chylomicrons (CM). By acting as a lipoprotein receptor ligand, LPL promotes lipoprotein uptake.Accumulating evidence has documented that the deficiency of ANGPTL3 results in enhancement of LPL, and subsequently decreasing levels of VLDL-C, LDL-C and HDL-C. ANGPTL3 inhibits LPL by enhancing their cleavage mostly on endogenous furin. **(7)**

2. **ANGPTL3 and angiogenesis:-**

ANGPTL3 binds to integrin αvβ3 and induces endothelial cell adhesion and migration in integrin αvβ3-dependent manner, further stimulates downstream signaling cascades phosphorylation of protein kinase B (PKB), mitogen-activated protein kinase (MAPK), as well as focal adhesion kinase (FAK). FAK, a cytoplasmic non-receptor protein–tyrosine kinase, is closely related to the tumorigenesis. **(8)**

3. **ANGPTL3 and hematopoietic function:-**

The transcription factor Ikaros, as key regulator of hematopoietic cell differentiation, can inhibit the repopulation activity of hematopoietic stem cells (HSCs). However, ANGPTL3 suppresses the expression of Ikaros, subsequently promotes the expansion of HSCs. **(9)**

ANGPTL3 and diseases:-

1. **ANGPTL3 and Atherosclerosis:-**

Dyslipidemia is one of risks for atherosclerotic cardiovascular diseases.ANGPTL3 deficiency seems to be a protective factor against hyperlipidemia and atherosclerosis.

There are two types: complete (compound heterozygote) and partial (heterozygote) loss of ANGPTL3 function resulted in different serum lipid levels. **(10)**

Complete ANGPTL3 deficiency is associated with a recessive hypolipidemia, which is characterized by a reduction of apoB and apoA-I-containing lipoproteins, abnormal changes in subclasses of HDL, as well as a disorder of cholesterol efflux. However, partial ANGPTL3 deficiency is just relevant to a moderate reduction of LDL. **(10)**

ANGPTL3 deficiency decreased blood lipid levels and significantly reduced the risk of coronary artery disease (CAD) and atherosclerosis in patients with ANGPTL3 loss-of-function mutation, which indicated that ANGPTL3 acts as a protective role in cardiovascular diseases. **(11)**

2. **ANGPTL3 and metabolic diseases:-**

Loss-of-function mutation of ANGPTL3 exhibits a reduction of insulin levels. Furthermore, hyperinsulinemia significantly reduces plasma ANGPTL3 and suppresses ANGPTL3 gene expression and secretion into growth medium in immortalized human hepatocytes (IHH). **(12)**

The illnesses of lipid metabolism and glucose metabolism are serious risk factors for metabolic diseases such as diabetes. Plasma TG and fatty acids often exhibit a higher level in diabetic patients than in normal subjects. Increased circulating TG and fatty acid concentrations can trigger hyperlipidemia and aggravate insulin resistance in liver and peripheral tissues. It has been reported that plasma level of ANGPTL3 is obviously increased in subjects with type 2 diabetic patients, partly because ANGPTL3 can inhibit the activity of LPL and reduce the hydrolysis of TG and induce high level of TG. Additionally, high expression of ANGPTL3 can inhibit the decomposition of fat cells, leading to intracellular TG accumulation. **(13)**

ANGPTL3 plays a major role in promoting uptake of circulating VLDL-TGs into white adipose tissue (WAT) in the fed state. It is likely that the increased uptake of glucose into WAT can explain the increased insulin sensitivity associated with inactivation of ANGPTL3. **(14)**

Studies showed that insulin down-regulated the secretion of ANGPTL3 in a dose-dependent manner. ANGPTL3 silence increases glucose uptake in human hepatocytes in vitro and downregulates the gluconeogenic genes, suggesting that silencing of ANGPTL3 improves insulin sensitivity. **(6).**

The positive effect of ANGPTL3 deficiency on glucose and lipoprotein metabolism is a very promising strategy for the treatment of diabetes in the future.

3. ANGPTL3 and Cancers:-

ANGPTL3 is abnormally expressed in several types of human cancers. ANGPTL3 stimulates cancer growth by promoting angiogenesis, cell proliferation and migration.

a) In HCC:-

ANGPTL3 may be functionally involved in hepatocellular carcinoma cell proliferation and invasion and is a potential target for hepatocellular carcinoma therapy. **(15)**

The positive rates of ANGPTL3 and VEGF expression in HCC were significantly higher than that in tumor-adjacent tissue. Active angiogenesis was detected in HCC compared to tumor-adjacent tissue. Tumor angiogenesis was related with ANGPTL3 expression in HCC. The expression of ANGPTL3 and VEGF protein was significantly up regulated in HCC compared with matched tumor-adjacent noncancerous tissue. So high expression of ANGPTL3 is associated with tumor angiogenesis in HCC. **(15)**

Interestingly, there is a significant association between serum ANGPTL 3 and its expression and the tumor stage, so a correlation between ANGPTL3 and HCC invasion and metastasis was established**. (16)**

It was reported that the levels of ANGPTL3 in serum can be a promising and non-invasive biomarkers in diagnosis and differential diagnosis such as discriminate of chronic hepatitis and HCC. Also recommended ANGPTL3 to be used as prognostic markers of HCC. **(17)**

b) In cervical cancer (CC):-

ANGPTL3 expression was significantly higher in CC cells relative to that in normal cervical cells. Silencing of ANGPTL3 suppressed cell proliferation, migration and invasion. Besides, downregulation of ANGPTL3 inhibites human umbilical vein endothelial cell (HUVEC) angiogenesis and represses protein level of integrin alpha v beta 3 (αvβ3). Upregulation of αvβ3 offsets the inhibitory effect of ANGPTL3 on proliferation, migration and invasion in CC cells. Upregulated expression of αvβ3 promoted blood vessel formation and secretions of VEGF and VEGFR2. ANGPTL3 silencing may serve as a tumor suppressor in CC through integrin αvβ3, which provides a potentially novel therapeutic target for patients with CC. **(18)**

c) In oral squamous cell carcinoma (OSCC):-

ANGPTL3 is significantly induced in oral squamous cell carcinoma (OSCC), whereby it activates the extracellular-regulated kinase (ERK) pathway and promotes cell proliferation. ANGPTL3 expression level was correlated closely with tumoral size. In patients with T3/T4 tumors, the overall survival rate with an ANGPTL3- positive tumor was significantly lower than that of ANGPTL3-negative cases. In vitro, cellular growth in ANGPTL3 knockdown cells significantly decreased with inactivated extracellular regulated kinase (ERK) and cell-cycle arrest at the G1 phase. The current data indicates that ANGPTL3 may play a role in OSCCs via mitogen-activated protein kinase (MAPK) signaling cascades, making it a potentially useful diagnostic/therapeutic target for use in patients with OSCC. **(19)**

d) Cancer Associated Fibroblasts (CAFs):-

ANGPTL3 released from oral cancer cells can induce CAF-like phenotypes in stromal fibroblasts, as an increase in tumor-promoting cytokines and CAF markers. **(20)**

Transforming growth factor-beta (TGF-β), Interleukin(IL)-6 and IL-8, secreted from CAFs, which are typically secreted by CAFs, form the tumor-promoting microenvironment in oral squamous cell carcinoma (OSCC) progression, including proliferation, angiogenesis, and invasion. The interaction between CAFs and OSCC cells is essential for cancer progression. **(21)**

e) In esophageal cancer:-

The expression levels of ANGPTL3 in esophageal cancer tissues were significantly higher than those in adjacent noncancerous tissues. **(22)**

f) In ovarian cancer:-

ANGPTL3 overexpression in vitro may restrain the metastatic potential and NK cell-mediated killing of ovarian cancer cells by blocking the JAK/STAT3 pathway. Thus, these findings reveal the important roles of ANGPTL3 in the malignant progression of ovarian cancer and its immune evasion from NK cells. These findings reveal that angiopoietin-like protein 3 may act as an anti-oncogenic regulator to inhibit the metastatic potential and enhance the susceptibility of ovarian cancer cells to natural killer cell-mediated killing, indicating a promising therapeutic agent for this malignancy.ANGPTL3 mRNA level in high-grade serous ovarian carcinoma is associated with shorter survival. **(23)**

g) In renalcell carcinoma (RCC):-

Overexpression of ANGPTL3 was associated with a good prognosis of RCC patients because ANGPTL3 up regulation inhibited the tumor proliferation and metastasis via the Wnt/β-catenin pathway. ANGPTL3 may be a novel therapeutic target and a prognostic biomarker for RCC patients. **(24)**

h) In glioblastoma:-

The expression of ANGPTL3 proteins in glioblastoma was proved as an independent marker of prognosis in patients' overall survival. It was suggested that integrin αVβ3 might mediate ANGPTL3 for promoting angiogenesis and promote the invasiveness and growth of glioblastoma. **(25)**

4. ANGPTL3 and nephrotic syndrome:-

Podocyte is an essential member of the filtration barrier in kidney glomerulus. Moreover, podocyte detachment and apoptosis are two risk factors for podocyte loss, eventually lead to glomerular disease and proteinuria. **(25)**

ANGPTL3 expression is upregulated in glomerular podocytes of patients with nephrotic syndrome. Overexpression of ANGPTL3 expression increased the motility of podocytes by inducing actin filament (F-actin) rearrangement, mainly in lamellipodia formation. Definitely, F-actin rearrangement is involved in the podocyte detachment and apoptosis. In addition, ANGPTL3 interacts with podocyte-expressed integrin β3, and raise the expression of α-actinin-4, which may result in the cytoskeletal rearrangement of podocytes. ANGPTL3 significantly disturbs the normal expression of α-actinin-4 at both mRNA and protein level, which induces podocyte actin realignment. **(7)**

Overexpression of ANGPTL3 causes podocyte injury through increasing podocyte movement and permeability. ANGPTL3 expression knockdown or interfering with the ANGPTL3-integrin β3 interaction may be of benefit in podocyte protection and proteinuria prevention. **(11)**

5. ANGPTL3 and liver diseases:-

ANGPTL3 levels are significantly increased in non alcoholic steatohepatitis (NASH) patients, which may be associated with insulin resistance in NASH patients. Host lipid metabolism reprogramming is essential for hepatitis C virus (HCV) infection and progression to severe liver disease. Angiopoietin-like protein-3 (ANGPTL-3) regulates the clearance of plasma lipids by inhibiting cellular lipase activity and possesses emerging roles in tumorigenesis. **(26)**

6. ANGPTL3 and rheumatic diseases:-

In rheumatic diseases, including rheumatoid arthritis (RA), systemic lupus erythematous (SLE), systemic sclerosis (SSc), polymyositis/dermatomyositis (PM/DM), vascular abnormalities is one of the common characteristics caused by endothelial damage. In SSc, serum ANGPTL3 levels are increased intensely. More importantly, the prevalence of cutaneous ulcers is significantly greater in patients with elevated ANGPTL3 level than those with normal ANPGTL3 level in SSc patients. Therefore, ANGPTL3 may contribute to the development of progressive skin sclerosis and proliferative obliterative vasculopathy in SSc. **(27)**

ANGPTL3 as an underlying theraputictarget :-

1. ANGPTL3 Monoclonal Antibody as a Lipid-Lowering Therapy:-

Evinacumab, a fully human monoclonal antibody that specifically binds to ANGPTL3, has been developed and proven to reverse ANGPTL3-mediated inhibition of LPL activity in vitro and in vivo. The United States Food and Drug Administration (FDA) recently approved Evinacumabas a complementary agent to other LDL-C

lowering regimens for patients aged 12 or older with homozygous familial hypercholesterolemia (HoFH). **(28)**

2. ANGPTL3 antisense oligonucleotides (ASOs) as a Lipid-Lowering Therapy:-

ASOs targeting ANGPTL3 mRNA have been developed as inhibitors. ANGPTL3 ASOs effectively decreased the levels of hepatic ANGPTL3 mRNA and plasma ANGPTL3 protein, resulting in marked reduction of plasma TGs, LDL-C and, to a lesser extent, HDL-C levels.

3. CRISPR-Cas9 genome editing technology:-

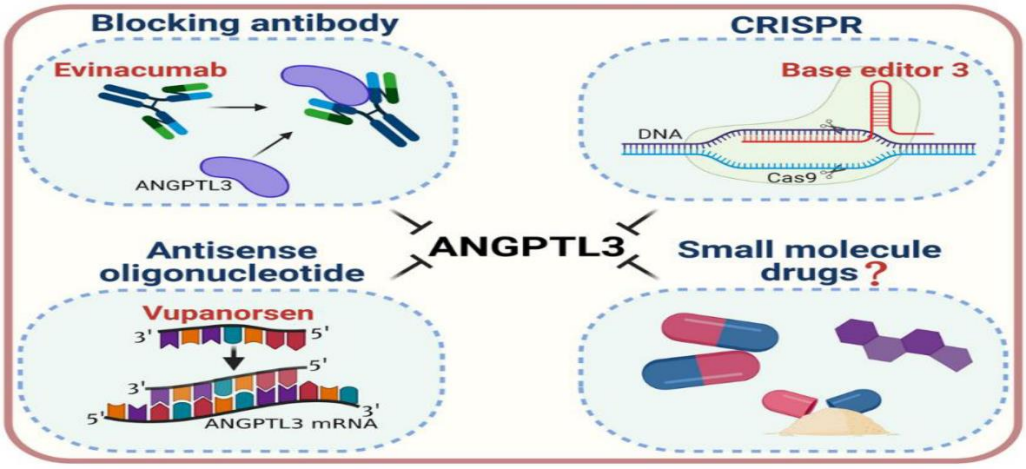
In vivo genome editing by the Clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 approach is based on an innovative mechanism to introduce mutations in ANGPTL3 and has been demonstrated to reduce lipid levels in mice. The efficacy and safety of this therapeutic strategy remain unclear and need to be investigated in further studies. **(29)**

4. Small molecule drug:-

Understanding the structure of the binding region of the monoclonal antibody by molecular modeling analysis may help to develop small-molecule inhibitors of ANGPTL3. The rational design of oral, small molecules as ANGPTL3 inhibitors may serve as a novel pharmacological approach for the treatment of dyslipidemia. **(5)**

5. Other drugs:-

Atorvastatin suppresses ANGPTL3 transcription and resultes in decreased plasma VLDL-TG levels. Fenofibrate, another widely used lipid-lowering agent, significantly preventes high glucose induced apoptosis and inflammation by inhibiting ANGPLT3 activity in diabetic retinopathy. **(25)**



Strategies for pharmacological inactivation of ANGPTL3. Various strategies have been developed to pharmacologically inactivate ANGPTL3, which include blocking monoclonal antibodies (such as Evinacumab), antisense oligonucleotides (such as Vupanorsen), and a CRISPR genome editing system (such as base editor 3, BE3) for treatment of dyslipidemia. The development of oral, small-molecule inhibitors may serve as a novel pharmacological approach for ANGPTL3 inactivation (created with BioRender.com, accessed on 2 July 2021) **(5)**

Other ANGPTLs functions:-

1. ANGPTL1:-

Angiopoietin-like protein 1 (ANGPTL1) is known as angioarrestin, which is identified as an anti-angiogenic factor**.** By binding to integrin α1β1 of HCC cells, ANGPTL1 suppresses the integrin α1β1/focal adhesion kinase (FAK)-Src/JAK/STAT3 signaling axis to prevent angiogenesis and metastasis in HCC. In colorectal cancer (CRC), ANGPTL1 up-regulates microRNA-138 and attenuates CRC cells metastasis. **(5)**

In addition, ANGPTL1-integrin α1β1 mediated signaling suppresses lung cance by inhibiting the expression of the zinc-finger protein SLUG. In breast cancer, ANGPTL1 expression suppresses the migration and invasive capabilities. **(30)**

ANGPTL1 inhibits sorafenib resistance and cancer stemness in HCC cells by repressing epithelial-mesenchymal transition (EMT) through the inhibition of the MET receptor competing with hepatocyte growth factor (HGF). **(5)**

2. ANGPTL2:-

ANGPTL2 is the most intensively studied ANGPTL in inflammation.

ANGPTL2 acts as a pro-inflammatory factor inducible by tissue stress and plays important role in maintaining tissue homeostasis by enhancing adaptive inflammation and the following tissue reconstruction. However, overactivation of ANGPTL2 is a driving factor in various diseases such as metabolic syndrome, acute or chronic organ/tissue injuries, partly due to over-activation of the immune system. **(31)**.

In metabolic syndromes, ANGPTL2 secreted by adipose tissue is positively correlated with adiposity, systemic insulin resistance, and inflammation. In contrast, deletion of Angptl2 attenuates adipose tissue inflammation and systemic insulin resistance. These effects are partly explained by ANGPTL2-trigged integrin signaling via activating Rac1 and NF-κB via integrin α5β1 to potentiate the inflammation and also by binding to integrin α4 or β2. In chronic organ/tissue injuries and repair as in chronic kidney disease (CKD), ANGPTL2 is highly expressed in renal tubule cells in CKD patients triggering chronic kidney injuries by enhancing transforming growth factor-β (TGFβ) induced signaling through a positive feedback mechanism that exacerbates renal fibrosis. In addition, ANGPTL2 is highly expressed in synovial cells of Rheumatoid arthritis (RA) patients, and excessive activation of ANGPTL2 exacerbates RA progression through recruitment of macrophages into joints and promotion of inflammatory vascular remodeling **(32)**.

The inflammation is associated with ANGPTL2 in normal tissues, therefore, increases the risk of carcinogenesis by enhancing susceptibility to (pre-neoplastic changes) and (malignant conversion)**.** In breast cancer, tumor cell-derived ANGPTL2 accelerates tumor cell motility and promotes invasive capacity through integrin α5β1 to activate Rac in an autocrine/paracrine manner. ANGPTL2 also promotes tumor angiogenesis resulting in acquisition of aggressive, metastatic tumor phenotypes. In CRC, ANGPTL2 expression activates the Syk-NFAT pathway to increase tumor cells' resistance to anti neoplastic therapies**. (33)**

3. ANGPTL4:-

ANGPTL4 has roles in angiogenesis, vascular permeability, cell differentiation, glucose homoeostasis, energy homeostasis, and inflammation.

In metabolic syndromes, ANGPTL4 may regulate atherosclerosis in a tissue specific manner depending on different physiological or pathological conditions.In chronic organ/tissue injuries and repair, mesenchymal stem cells (MSCs) -derived ANGPTL4 has been shown to act as an anti-inflammatory molecule by inhibiting NF-κB activation and blocking integrin β1/αVβ3 signaling to blunt inflammatory macrophage polarization. Furthermore, rhANGPTL4 treatment significantly improves cardiac function and pathology after myocardial infarction, suggesting that ANGPTL4 facilitated tissue repair is a promising stem cell free regeneration therapy. **(34)**

ANGPTL4 seems to have a protective effect in diseases such as obesity related fibrinopurulent peritonitis, myocardial infarction, and colonic inflammation. In oral cancer, ANGPTL4 enhances the tumorigenesis and poor prognosis based on the clinical tumor tissues, while in human gastric cancer and CRC,ANGPTL4 expression is correlated with venous and lymphatic invasion**.** As well asin breast cancer and melanoma, C-terminal fibrinogen-like domain (cANGPTL4) induces vascular leakiness and facilitates tumor metastasis by binding to integrin α5β1, VE-cadherin and claudin5.In prostate cancer, down-regulation of ANGPTL4 cells suppresses tumor growth. **(35)**

4. ANGPTL5:-

ANGPTL5 may be associated with inflammation based on the elevated level of circulating ANGPTL5 found in obese individuals and patients with type 2 diabetes mellitus (T2DM). **(36)**

There is no significant role played by ANGPTL5 in angiogenesis.

5. ANGPTL6:-

It is known as an angiopoietin-related growth factor (AGF) and has been identified as angiogenic factor. It has anti-inflammatory roles in chronic inflammation of metabolic syndromes**.** ANGPTL6 is elevated in patients with psoriasis **(37)**, so existing evidence suggests its potential as a biomarker or a drug target in chronic or autoimmune skin inflammation in the future.

6. ANGPTL7:-

ANGPTL7 has roles in angiogenesis and inflammation and is highly expressed in some tumors promoting proliferation, motility and invasiveness of endothelial cells. The level of ANGPTL7 in the eyes is significantly elevated in a TNF-α induced mouse model, and overexpression of ANGPTL7 activates P38 MAPK and NF-κB in LPS-stimulated RAW264.7 cells, a monocyte/macrophage cell line. These effects were blocked by an ANGPTL7 antibody, suggesting that extracellular ANGPTL7 exerts a pro-inflammatory effect. **(38)**

In patients with hypertension, there is elevated ANGPTL7 levels that is positively correlated with chronic low-grade inflammation and vascular inflammation. Additionally, Angiotensin II induces the expression of ANGPTL7 in vascular smooth muscle cells, which in turn potentiates Angiotensin II induced cell proliferation and inflammatory cell responses **(14)**

7. ANGPTL8:-

The most well known function of ANGPTL8 is inhibition of LPL activity by binding to the N-terminal domain of ANGPTL3 making it another important drug target for treating hyperlipidemia. ANGPTL8 is also expressed in hepatocellular carcinoma HCC. **(39,40)**

Name	Role in Cancer	Inflammation	Cancer Disease Association	Function
ANGPTL1	Tumor suppressor	not reported	low expression in kidney, lung, prostate, bladder, thyroid, breast and lung cancers, melanoma and hepatocarcinoma	Reduces migratory and invasive abilities of different cancer cell lines in vitro and to suppress the epithelial to mesenchymal transition (EMT).
ANGPTL2	Tumor promoting	proinflammatory	high expression in esophageal, colorectal, prostate, pancreatic lung, breast and skin cancers, hepatocarinoma	Pro-angiogenic and antiapoptotic abilities. Increase migratory and invasive ability. Driver of metastases was demonstrated in lung, breast and liver cancer and in osteosarcoma cell lines.
ANGPTL3	Tumor promoting	proinflammatory	high expression in oral squamous cell carcinoma, hepatocarcinoma and ovarian cancer	Cancer growth, motility and invasion.
ANGPTL4	Tumor-type dependent	proinflammatory	high expression in lung, colorectal, oral, breast cancers, hepatocarcinoma, oral squamous cell carcinoma,	A pro- and an anti-angiogenic protein, regulating vascular integrity and angiogenesis in a context-dependent manner suggesting that it might be tumor-type dependent.
ANGPTL5	Tumor promoting	proinflammatory	high expression in non-small cell lung cancer	Among its related pathways are Hematopoietic Stem Cell Differentiation Pathways and Lineage-specific Markers. An important paralog of this gene is ANGPTL3.
ANGPTL6	Tumor promoting	proinflammatory	high expression in glioma, glioblastoma multiforme and colorectal cancer	Tumor growth, and metastases driver.
ANGPTL7	Tumor promoting	proinflammatory	high expression in colorectal, lung, breast and ovarian cancers	A pro-angiogenic factor. Stimulates proliferation, motility, invasiveness and capability to form capillary-like networks in human differentiated endothelial cells.
ANGPTL8	not reported	not reported	Breast Angiosarcoma and Breast Sarcoma	Promote proliferation of pancreatic beta cells and increase insulin release in an insulin-deficient mouse model of insulin resistance. Among its related pathways are Metabolism and Lipoprotein metabolism.

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