

## The Roles of ANGPTL Families in Cancer Progression

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**Abstract :** Angiopoietins play important roles in angiogenesis and the maintenance of hematopoietic stem cells. Angiopoietin-like proteins (ANGPTLs) are identified as proteins structurally similar to angiopoietins, and the ANGPTL family now consists of eight members. ANGPTLs are secretory proteins, and some ANGPTLs are not only angiogenic factors but also proteins with multiple functions such as glucose metabolism, lipid metabolism, redox regulation and chronic inflammation. Chronic inflammation is one of the key factors in carcinogenesis and cancer growth, proliferation, invasion and metastasis. ANGPTL 2, 3, 4, 6 and 7 are pro-inflammatory factors and regulate cancer progression, while ANGPTL1 inhibits tumor angiogenesis and metastasis. In this review, we describe the roles of ANGPTLs in cancer progression and discuss the possibility of disturbing the progression of cancer by regulating ANGPTLs expression.

**Keywords :** angiopoietin-like protein, ANGPTL, cancer progression, inflammation.

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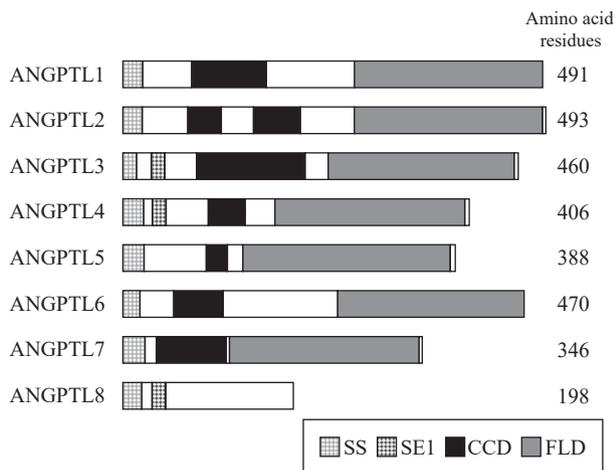
### Introduction

Cancer progression is a problem of great dimensions in the world [1]. Although various cancer treatments have been developed and survival rate has been extended over the last decade, cancer is still a major cause of death all over the world [2]. Therefore, an effective cure for cancer should be developed.

Angiopoietins bind Tie2 receptor tyrosine kinase and regulate angiogenesis and the preservation of vascular integrity and permeability. Angiopoietins have two domains: an N-terminal coiled-coil domain that mediates homo-oligomerization, and a C-terminal fibrinogen-like domain that binds Tie2. Angiopoietin-like proteins (ANGPTLs) are structurally similar to angiopoietin [3]. 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 (Fig. 1). However, ANGPTLs do not bind to either the angiopoietin receptor Tie2 or the related Tie1 receptor [4], which makes the functions of ANGPTLs different from angiopoietins. To date, several studies have shown that most ANGPTLs potentially regulate angiogenesis, yet a subset of these proteins also functions in glucose, lipid, energy metabolism and inflammation. For example, ANGPTL3, ANGPTL4 and ANGPTL8, which have a region mediating lipoprotein lipase binding (SE1), regulate lipid metabolism by inhibiting lipoprotein lipase activity [5–7]. ANGPTL6/angiopoietin-like growth factor (AGF) reportedly counteracts obesity by increasing systemic energy expenditure and thus antagonizing related metabolic diseases [8]. ANGPTLs, except

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**Fig. 1. Schematic diagram of ANGPTL proteins.** Human ANGPTL proteins are shown. SS: signal sequence, SE1: signal specific epitope 1, a region mediating lipoprotein lipase binding, CCD: coiled-coil domain, FLD: fibrinogen-like domain. Numbers on the right represent the number of amino acid residues in each protein.

ANGPTL1, 5 and 8, promote inflammation. It is well known that inflammation promotes tumorigenesis and tumor progression. Therefore, most ANGPTLs may have some functions in cancer progression.

### ANGPTL1

Angiopoietin-like protein 1 (ANGPTL1) is known as angiostatin, which is identified as an anti-angiogenic factor [9]. ANGPTL1 inhibits vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (b-FGF) [10]. Therefore, ANGPTL1 acts as a tumor suppressor by inhibiting angiogenesis. In fact, *Angptl1* knockout mice show a significant tumor metastasis in a tumor xenograft model compared to control mice [11]. In hepatocellular carcinoma (HCC), ANGPTL1 decreases angiogenesis [12], promotes apoptosis via inhibition of STAT3 pathway, and decreases HCC cell migration and invasion via down-regulation of SLUG and SNAIL [12, 13]. In colorectal cancer (CRC), ANGPTL1 up-regulates microRNA-138 and attenuates CRC cells metastasis [14]. In lung cancer, ANGPTL1 expression plays an important role in the inhibition of oncogenesis [15]. ANGPTL1 expression is inversely correlated with invasion, lymph node metastasis, and poor clinical outcomes [13]. In breast cancer, ANGPTL1 expression suppresses the migra-

tion and invasive capabilities [13]. Integrin  $\alpha 1\beta 1$  is reported to be an ANGPTL1 receptor [12]. ANGPTL1 binds to it and suppresses phosphorylated FAK and Src to inhibit the JAK-STAT3 pathway. It has also been reported recently that 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 HGF [16]. Therefore, inducing ANGPTL1 expression might be a good method for inhibiting metastasis in HCC, CRC, lung cancer and breast cancer.

### ANGPTL2

Angiopoietin-like protein 2 (ANGPTL2) is known to be a chronic inflammatory mediator that activates NF- $\kappa$ B inflammatory signaling through integrin  $\alpha 5\beta 1$  [17]. For example, in the pathology of obesity, enlargement of fat cells accelerates the secretion of ANGPTL2, which promotes the inflammation and the onset of obesity associated with insulin resistance [17]. ANGPTL2 also causes the inflammation of blood vessels and promotes the infiltration of macrophages to cause arteriosclerosis [18]. Therefore, ANGPTL2 plays an important role in the pathogenesis of various non-infectious inflammatory diseases.

Chronic inflammation functions at different stages of cancer development, including carcinogenesis, tumor invasion, and metastasis [19]. Oncogenic mutations in normal cells are important factors in carcinogenesis. DNA repair mechanisms often prevent carcinogenesis when an oncogenic mutation occurs within a normal cell, but sustained ANGPTL2 expression in normal tissues causes chronic inflammation and accumulates reactive oxygen species (ROS) that inactivate DNA repair enzymes [20]. The production of ROS is significantly reduced in *Angptl2* knockout mice, and carcinogenesis is more suppressed in *Angptl2* knockout mice compared to control mice [20]. The inflammation associated with ANGPTL2 in normal tissues, therefore, increases the risk of carcinogenesis by enhancing susceptibility to "pre-neoplastic changes" and "malignant conversion" [21].

High expression of ANGPTL2 in cancer cells also promotes metastasis [22, 23]. In lung and breast cancer, tumor cell-derived ANGPTL2 accelerates tumor cell motility and promotes invasive capacity through

integrin  $\alpha 5\beta 1$  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 cell resistance to anti neoplastic therapies [24, 25].

ANGPTL2 is a secretory protein, and the serum level of ANGPTL2 can be measured. Serum ANGPTL2 levels reflect the clinical features of breast, lung, colon, and gastric cancer patients [26–30], while the inhibition of ANGPTL2 by siRNA in cancer cells represses cancer progression and metastasis [22]. Therefore, inhibiting ANGPTL2 activity or secretion from cancer cells might be a good therapy in cancer progression and metastasis.

Integrin  $\alpha 5\beta 1$  has been reported as an ANGPTL2 receptor [17]. It has been reported recently that the human leukocyte immunoglobulin-like receptor B2 (LILRB2) and its mouse orthologue paired immunoglobulin-like receptor B2 (PIRB2) are receptors for ANGPTL2 and ANGPTL5, and that the binding of these ANGPTLs to receptors supports *ex vivo* expansion of hematopoietic stem cells (HSCs) [31]. As LILRB2 might be an ANGPTL2 receptor for cancer progression in some cancers, the precious signaling pathway of ANGPTL2-LILRB2 is not well understood and should be examined more.

Tumor microenvironment is also an important factor in cancer progression [32, 33]. It is reported that cancer-associated fibroblasts (CAFs) in cancer tissues refractory to anti-VEGF therapy express high ANGPTL2. This report suggests that ANGPTL2 might function in tumor refractoriness to anti-VEGF therapy. As with the previously mentioned mechanisms, it is not clear why ANGPTL2 expression in CAFs causes the refractory to anti-VEGF therapy. The inhibition of ANGPTL2 in CAFs might be a new therapy in resistance to anti-VEGF therapy.

### ANGPTL3

Angiopoietin-like protein 3 (ANGPTL3) plays an important role in lipid metabolism by inhibiting the activity of lipoprotein lipase (LPL) [5]. It has been reported that the plasma level of ANGPTL3 is positively associated with low-density lipoprotein cholesterol [34]. Therefore, ANGPTL3 is garnering attention as a targeting drug for metabolic disorders [35].

ANGPTL3 is significantly induced in oral squamous cell carcinoma (OSCC) [36], whereby it activates the ERK pathway and promotes cell proliferation. In HCC *in vitro* cells, ANGPTL3 antisense oligodeoxynucleotides inhibit cell proliferation and invasion [37]. ANGPTL3 mRNA level in high-grade serous ovarian carcinoma is associated with shorter survival [38]. In glioblastoma and breast cancer, ANGPTL3 expression in cancer cells provides a predictive factor [39, 40], while high ANGPTL3 expression in renal cell carcinoma (RCC) upregulates in sorafenib-responsive RCC. ANGPTL3 expression in RCC promotes apoptosis of RCC cells treated with sorafenib [41]. Therefore, the role of ANGPTL3 in cancer progression is controversial.

### ANGPTL4

Along with cancer progression, hypoxia and undernutrition occur in cancer tissues due to rapid cancer proliferation [42]. Angiopoietin-like protein 4 (ANGPTL4) is known to be induced by hypoxia and undernutrition [43], and is induced by IL-1 $\beta$  in a manner dependent on NF- $\kappa$ B- and MAPK- activation to promote angiogenesis and progression in breast cancer [44]. In oral cancer, ANGPTL4 enhances the tumorigenesis and poor prognosis based on the clinical tumor tissues [45]. ANGPTL4 expression is correlated with venous and lymphatic invasion in human gastric cancer and CRC [46, 47], and down-regulation of ANGPTL4 in prostate cancer cells suppresses tumor growth [48]. An increased level of ANGPTL4 has been found to inhibit tumor angiogenesis, vascular permeability and invasiveness of cancer cells [49–51].

The full length of ANGPTL4 is known to be proteolytically cleaved to the N-terminal coiled-coil fragment (nANGPTL4) and the C-terminal fibrinogen-like domain (cANGPTL4) [6]. The nANGPTL4 is responsible for the oligomeric assembly of ANGPTL4 and binds to LPL to inhibit their activity. On the other hand, cANGPTL4 is highly expressed in major epithelial tumors such as SCC [52]. cANGPTL4 induces vascular leakiness and facilitates tumor metastasis by binding to integrin  $\alpha 5\beta 1$ , VE-cadherin and claudin5 [53]. cANGPTL4 activates the Rac1/PAK pathway to weaken cell-cell contact through integrin  $\alpha 5\beta 1$ . cANGPTL4 is also associated with VE-cadherin and claudin5 to lead endothelial disruption. In clinical

samples, cANGPTL4 expression is observed in breast cancer and melanoma [53]. Therefore, cANGPTL4 seems to promote cancer progression. Cleavage of ANGPTL4 appears to be tissue-dependent in humans; liver secretes cleaved ANGPTL4, whereas adipose tissue secretes the full-length form [54]. Therefore, the functions of ANGPTL4 might be different in each tissue. The roles of ANGPTL4 in cancer should be examined more closely.

#### *ANGPTL5*

There is no report to date that Angiopoietin-like protein 5 (ANGPTL5) plays a role in angiogenesis. ANGPTL5 supports efficient expansion of HSCs [55], and in human primary non-small cell lung cancer, co-expression of immunoglobulin-like transcript 4- (ILT4) and ANGPTL5- positive expression present poor overall survival rates [56]. However, there are few reports about ANGPTL5 in cancer. As the role of ANGPTL5 in cancer progression has not been completely explained yet, further study is needed.

#### *ANGPTL6*

Angiopoietin-like protein 6 (ANGPTL6) is known as an angiopoietin-related growth factor (AGF) and has been identified as angiogenic factor [8]. ANGPTL6 plays a role in epidermal proliferation, wound healing and adhesion by activating ERK1/2 [8]. It also regulates lipid, glucose, and energy metabolism in a mouse model [8, 57]. ANGPTL6 expression in keratinocyte promotes inflammation to enhance susceptibility to psoriasis [57], and is highly expressed in liver and interacts with integrin  $\alpha 6$  and E-cadherin [58]. It is reported that CRC cells, which express high integrin  $\alpha 6$  and E-cadherin, represent a poor prognostic factor for patients [58], but there are few reports about ANGPTL6 in cancer progression.

#### *ANGPTL7*

Angiopoietin-like protein 7 (ANGPTL7) is known as cornea-derived transcript 6 (CDT6), and is expressed in neural tissues, keratoconus cornea and trabecular meshwork [59]. In human hematopoietic progenitors, ANGPTL7 regulates the expansion and regeneration of HSCs by activating the expression of CXCR4, HOXB4 and Wnt downstream targets [60]

and is an inflammatory factor to activate p38 MAPK [61]. It is reported that ANGPTL7 is over-expressed in colon cancer and in breast and ovary cancer cells [62]. ANGPTL7 promotes angiogenesis, cell proliferation, motility and invasiveness [62], and is marginally expressed under standard growth conditions, while it is specifically up-regulated by hypoxia [62]. On the other hand, ANGPTL7 expression in colon and lung cancer cells inhibits angiogenesis and metastasis [63]. Therefore, the role of ANGPTL7 in cancer progression is still unclear.

#### *ANGPTL8*

Angiopoietin-like protein 8 (ANGPTL8) is known as betatrophin and is highly expressed in liver [64]. ANGPTL8 interacts with ANGPTL3 and increases plasma levels of triglycerides and non-esterified fatty acids [7]. It is reported that ANGPTL8 is expressed in hepatocellular carcinoma [65]. The biological functions of ANGPTL8 are not fully clarified, and the role of ANGPTL8 in cancer progression should be examined in more detail.

#### *The regulation of ANGPTL genes*

Some ANGPTL genes are known to be induced by specific stimulations. ANGPTL2 is induced by endoplasmic reticulum (ER) stresses such as hypoxia and under-nutrition [17]. The regulation of ANGPTL4 is well examined. ANGPTL4 is also induced by hypoxia and under-nutrition, similar to ANGPTL2 [43], and is induced by peroxisome proliferator-activated receptor (PPAR) alpha and gamma ligands [66]. ANGPTL7 is induced by hypoxia [62]. The regulations of ANGPTL1, 3, 5, 6 and 8 by specific stimulation have not been clarified. It has been reported that the epigenetic change (hypomethylation) of enhancer regions is important for the expression of ANGPTL1, 2, 3, 4 and 8 [67]. Epigenetic change is influenced by various environmental factors such as nutrition, growth factors, and interaction with other cells; therefore, more complex mechanisms must be involved in the regulation of ANGPTL 1, 2, 3, 4 and 8. Further studies are needed to regulate ANGPTL genes.

## Conclusion

A summary of the functions and roles of the ANGPTLs is listed in Table 1. Chronic inflammation increases the risk of carcinogenesis in non-tumor tissues and promotes tumor growth and metastasis in tumor tissues [19, 68]. Therefore, the development of inhibition of the function of ANGPTLs, which promote inflammation (ANGPTL2, 3, 4, 6, 7), might be a good candidate for cancer therapy.

Therapeutic strategy targeting ANGPTL3 has been developed for reducing plasma triglycerides and low-density lipoprotein in mice [69]. Oligonucleotides targeting human ANGPTL3 reduce levels of atherogenic lipoproteins in humans [69]. Monoclonal antibody inhibition of ANGPTL4 has also been developed, and the inhibition of ANGPTL4 in mice and monkeys reduces triglyceride levels to decrease coronary artery diseases [70]. As ANGPTLs have not been applied as a therapeutic strategy target for cancer progression, strategies similar to those above might be effective therapies for cancers which express high ANGPTL3, such as oral squamous cell carcinomas, hepatocellular and ovarian cancers, or which express high ANGPTL4, such as

gastric, colorectal and prostate cancers. On the other hand, ANGPTL1 inhibits tumor angiogenesis and the migratory and invasive ability of cancer cells. It also suppresses EMT, which is a crucial process in tumor progression. The development of induction of ANGPTL1 might be a strategy for preventing cancer metastasis.

As ANGPTLs are secretory proteins which affect in an autocrine/paracrine manner, strategies targeting ANGPTLs in cancer progression might be more effective with both cancer itself and cells in a tumor microenvironment if conditions are fine. However, the signal pathways of ANGPTLs have not been fully clarified, and should be examined in future studies.

## Conflict of Interest

The author declares no conflict of interest associated with this manuscript.

## References

1. Ebos JM & Kerbel RS (2011): Antiangiogenic therapy: Impact on invasion, disease progression, and metastasis. *Nat Rev Clin Oncol* 8: 210–221
2. Ventura SJ (2018): The U.S. National Vital Statistics System: Transitioning into the 21st century, 1990–2017. *Vital Health Stat* 1 (62): 1–84
3. Yancopoulos GD, Davis S, Gale NW, Rudge JS, Wiegand SJ & Holash J (2000): Vascular-specific growth factors and blood vessel formation. *Nature* 407: 242–248
4. Kadomatsu T, Tabata M & Oike Y (2011): Angiotensin-like proteins: Emerging targets for treatment of obesity and related metabolic diseases. *FEBS J* 278: 559–564
5. Arca M, Minicocci I & Maranghi M (2013): The angiotensin-like protein 3: A hepatokine with expanding role in metabolism. *Curr Opin Lipidol* 24: 313–320
6. Lei X, Shi F, Basu D, Huq A, Routhier S, Day R & Jin W (2011): Proteolytic processing of angiotensin-like protein 4 by proprotein convertases modulates its inhibitory effects on lipoprotein lipase activity. *J Biol Chem* 286: 15747–15756
7. Abu-Farha M, Sriraman D, Cherian P, AlKhairi I, Elkum N, Behbehani K & Abubaker J (2016): Circulating ANGPTL8/Betatrophin is increased in obesity and reduced

**Table 1. ANGPTL proteins functions and roles in cancer**

Protein	Function	Inflammation	Role in cancer
ANGPTL1	Anti-angiogenesis Anti-apoptosis Angiogenesis	No report	Suppressing
ANGPTL2	Cancer development Glucose metabolism	Pro-inflammatory	Promoting
ANGPTL3	Angiogenesis Lipid metabolism Lipid metabolism	Pro-inflammatory	Promoting or Suppressing
ANGPTL4	Glucose metabolism Cancer development	Pro-inflammatory	Promoting or Suppressing
ANGPTL5	Expansion of HSCs Angiogenesis	No report	Promoting ?
ANGPTL6	Lipid metabolism Energy metabolism	Pro-inflammatory	Promoting
ANGPTL7	Expansion of HSCs	Pro-inflammatory	Promoting or Suppressing
ANGPTL8	Lipid metabolism	Anti-inflammatory ?	No report

- after exercise training. *PLoS One* 11: e0147367
8. Oike Y, Yasunaga K & Suda T (2004): Angiotensin-related/angiotensin-like proteins regulate angiogenesis. *Int J Hematol* 80: 21–28
  9. Chatterjee TK, Aronow BJ, Tong WS *et al* (2013): Human coronary artery perivascular adipocytes overexpress genes responsible for regulating vascular morphology, inflammation, and hemostasis. *Physiol Genomics* 45: 697–709
  10. Dhanabal M, Jeffers M, LaRochelle WJ & Lichenstein HS (2005): Angioarrestin: A unique angiotensin-related protein with anti-angiogenic properties. *Biochem Biophys Res Commun* 333: 308–315
  11. Michael IP, Orebrand M, Lima M, Pereira B, Volpert O, Quaggin SE & Jeansson M (2017): Angiotensin-1 deficiency increases tumor metastasis in mice. *BMC Cancer* 17: 539
  12. Yan Q, Jiang L, Liu M *et al* (2017): ANGPTL1 interacts with integrin  $\alpha 1\beta 1$  to suppress HCC angiogenesis and metastasis by inhibiting JAK2/STAT3 signaling. *Cancer Res* 77: 5831–5845
  13. Kuo TC, Tan CT, Chang YW *et al* (2013): Angiotensin-like protein 1 suppresses SLUG to inhibit cancer cell motility. *J Clin Invest* 123: 1082–1095
  14. Chen H, Xiao Q, Hu Y *et al* (2017): ANGPTL1 attenuates colorectal cancer metastasis by up-regulating microRNA-138. *J Exp Clin Cancer Res* 36: 78
  15. Sasaki H, Moriyama S, Sekimura A *et al* (2003): Angioarrestin mRNA expression in early-stage lung cancers. *Eur J Surg Oncol* 29: 649–653
  16. Chen HA, Kuo TC, Tseng CF, Ma JT, Yang ST, Yen CJ, Yang CY, Sung SY & Su JL (2016): Angiotensin-like protein 1 antagonizes MET receptor activity to repress sorafenib resistance and cancer stemness in hepatocellular carcinoma. *Hepatology* 64: 1637–1651
  17. Tabata M, Kadomatsu T, Fukuhara S *et al* (2009): Angiotensin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance. *Cell Metab* 10: 178–188
  18. Horio E, Kadomatsu T, Miyata K *et al* (2014): Role of endothelial cell-derived angptl2 in vascular inflammation leading to endothelial dysfunction and atherosclerosis progression. *Arterioscler Thromb Vasc Biol* 34: 790–800
  19. Grivennikov SI, Greten FR & Karin M (2010): Immunity, inflammation, and cancer. *Cell* 140: 883–899
  20. Aoi J, Endo M, Kadomatsu T *et al* (2014): Angiotensin-like protein 2 accelerates carcinogenesis by activating chronic inflammation and oxidative stress. *Mol Cancer Res* 12: 239–249
  21. Aoi J, Endo M, Kadomatsu T *et al* (2011): Angiotensin-like protein 2 is an important facilitator of inflammatory carcinogenesis and metastasis. *Cancer Res* 71: 7502–7512
  22. Endo M, Nakano M, Kadomatsu T *et al* (2012): Tumor cell-derived angiotensin-like protein ANGPTL2 is a critical driver of metastasis. *Cancer Res* 72: 1784–1794
  23. Masuda T, Endo M, Yamamoto Y *et al* (2015): ANGPTL2 increases bone metastasis of breast cancer cells through enhancing CXCR4 signaling. *Sci Rep* 5: 9170
  24. Horiguchi H, Endo M, Miyamoto Y *et al* (2014): Angiotensin-like protein 2 renders colorectal cancer cells resistant to chemotherapy by activating spleen tyrosine kinase-phosphoinositide 3-kinase-dependent anti-apoptotic signaling. *Cancer Sci* 105: 1550–1559
  25. Gao L, Ge C, Fang T, Zhao F, Chen T, Yao M, Li J & Li H (2015): ANGPTL2 promotes tumor metastasis in hepatocellular carcinoma. *J Gastroenterol Hepatol* 30: 396–404
  26. Chen Y, Jiang H, Zhu L, Wang P, Liu S, Xiao X, Yu H & Dong W (2017): Diagnostic and prognostic value of serum angiotensin-like protein 2 in patients with non-small cell lung cancer. *Clin Lab* 63: 59–65
  27. Yoshinaga T, Shigemitsu T, Nishimata H, Kitazono M, Hori E, Tomiyoshi A, Takei T & Yoshida M (2015): Angiotensin-like protein 2 as a potential biomarker for colorectal cancer. *Mol Clin Oncol* 3: 1080–1084
  28. Toiyama Y, Tanaka K, Kitajima T *et al* (2015): Serum angiotensin-like protein 2 as a potential biomarker for diagnosis, early recurrence and prognosis in gastric cancer patients. *Carcinogenesis* 36: 1474–1483
  29. Toiyama Y, Tanaka K, Kitajima T *et al* (2014): Elevated serum angiotensin-like protein 2 correlates with the metastatic properties of colorectal cancer: A serum biomarker for early diagnosis and recurrence. *Clin Cancer Res* 20: 6175–6186
  30. Endo M, Yamamoto Y, Nakano M *et al* (2014): Serum ANGPTL2 levels reflect clinical features of breast cancer patients: Implications for the pathogenesis of breast cancer metastasis. *Int J Biol Markers* 29: e239–e245
  31. Zheng J, Umikawa M, Cui C *et al* (2012): Inhibitory

- receptors bind ANGPTLs and support blood stem cells and leukaemia development. *Nature* 485: 656–660
32. Rofstad EK (2000): Microenvironment-induced cancer metastasis. *Int J Radiat Biol* 76: 589–605
  33. Postovit LM, Seftor EA, Seftor RE & Hendrix MJ (2006): Influence of the microenvironment on melanoma cell fate determination and phenotype. *Cancer Res* 66: 7833–7836
  34. Mehta N, Qamar A, Qu L, Qasim AN, Mehta NN, Reilly MP & Rader DJ (2014): Differential association of plasma angiopoietin-like proteins 3 and 4 with lipid and metabolic traits. *Arterioscler Thromb Vasc Biol* 34: 1057–1063
  35. Graham MJ, Lee RG, Brandt TA *et al* (2017): Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med* 377: 222–232
  36. Koyama T, Ogawara K, Kasamatsu A *et al* (2015): ANGPTL3 is a novel biomarker as it activates ERK/MAPK pathway in oral cancer. *Cancer Med* 4: 759–769
  37. Yu H, Zhang H, Li D, Xue H, Pan C, Zhao S & Wang L (2011): Effects of ANGPTL3 antisense oligodeoxynucleotides transfection on the cell growths and invasion of human hepatocellular carcinoma cells. *Hepatogastroenterology* 58: 1742–1746
  38. Siamakpour-Reihani S, Owzar K, Jiang C *et al* (2015): Prognostic significance of differential expression of angiogenic genes in women with high-grade serous ovarian carcinoma. *Gynecol Oncol* 139: 23–29
  39. Wang PF, Li HL, Qi X, Yao K, Han S, Liu N, Yang YK, Li SW & Yan CX (2016): Clinical significance of angiopoietin-like protein 3 expression in patients with glioblastoma. *Neoplasma* 63: 93–98
  40. Zhu L, Jiang L, Wang W, Jia W, Liu F, Jiao X, Zhu X, Bao J & Yu H (2015): Angiopoietin-like protein 3 is an indicator of prognosis in esophageal cancer patients. *Int J Clin Exp Med* 8: 16101–16106
  41. Bao Y, Yang F, Liu B, Zhao T, Xu Z, Xiong Y, Sun S, Qu L & Wang L (2018): Angiopoietin-like protein 3 blocks nuclear import of FAK and contributes to sorafenib response. *Br J Cancer* 119: 450–461
  42. Pezzuto A & Carico E (2018): Role of HIF-1 in cancer progression: Novel insights. A review. *Curr Mol Med* 18: 343–351
  43. Tan MJ, Teo Z, Sng MK, Zhu P & Tan NS (2012): Emerging roles of angiopoietin-like 4 in human cancer. *Mol Cancer Res* 10: 677–688
  44. Kolb R, Kluz P, Tan ZW *et al* (2019): Obesity-associated inflammation promotes angiogenesis and breast cancer via angiopoietin-like 4. *Oncogene* 38: 2351–2363. doi: 10.1038/s41388-018-0592-6
  45. Hu J, Jham BC, Ma T, Friedman ER, Ferreira L, Wright JM, Accurso B, Allen CM, Basile JR & Montaner S (2011): Angiopoietin-like 4: A novel molecular hallmark in oral Kaposi's sarcoma. *Oral Oncol* 47: 371–375
  46. Nakayama T, Hirakawa H, Shibata K, Nazneen A, Abe K, Nagayasu T & Taguchi T (2011): Expression of angiopoietin-like 4 (ANGPTL4) in human colorectal cancer: ANGPTL4 promotes venous invasion and distant metastasis. *Oncol Rep* 25: 929–935
  47. Nakayama T, Hirakawa H, Shibata K, Abe K, Nagayasu T & Taguchi T (2010): Expression of angiopoietin-like 4 in human gastric cancer: ANGPTL4 promotes venous invasion. *Oncol Rep* 24: 599–606
  48. Ifon ET, Pang AL, Johnson W, Cashman K, Zimmerman S, Muralidhar S, Chan WY, Casey J & Rosenthal LJ (2005): U94 alters FN1 and ANGPTL4 gene expression and inhibits tumorigenesis of prostate cancer cell line PC3. *Cancer Cell Int* 5: 19
  49. Galaup A, Cazes A, Le Jan S *et al* (2006): Angiopoietin-like 4 prevents metastasis through inhibition of vascular permeability and tumor cell motility and invasiveness. *Proc Natl Acad Sci USA* 103: 18721–18726
  50. Cazes A, Galaup A, Chomel C *et al* (2006): Extracellular matrix-bound angiopoietin-like 4 inhibits endothelial cell adhesion, migration, and sprouting and alters actin cytoskeleton. *Circ Res* 99: 1207–1215
  51. Ito Y, Oike Y, Yasunaga K, Hamada K, Miyata K, Matsumoto S, Sugano S, Tanihara H, Masuho Y & Suda T (2003): Inhibition of angiogenesis and vascular leakiness by angiopoietin-related protein 4. *Cancer Res* 63: 6651–6657
  52. Zhu P, Tan MJ, Huang RL *et al* (2011): Angiopoietin-like 4 protein elevates the pro-survival intracellular O<sub>2</sub>(-): H<sub>2</sub>O<sub>2</sub> ratio and confers anoikis resistance to tumors. *Cancer Cell* 19: 401–415
  53. Huang RL, Teo Z, Chong HC *et al* (2011): ANGPTL4 modulates vascular junction integrity by integrin signaling and disruption of intercellular VE-cadherin and claudin-5 clusters. *Blood* 118: 3990–4002
  54. Mandard S, Zandbergen F, Tan NS *et al* (2004): The direct peroxisome proliferator-activated receptor target fasting-induced adipose factor (FIAF/PGAR/ANG-

- PTL4) is present in blood plasma as a truncated protein that is increased by fenofibrate treatment. *J Biol Chem* 279: 34411–34420
55. Khoury M, Drake A, Chen Q *et al* (2011): Mesenchymal stem cells secreting angiopoietin-like-5 support efficient expansion of human hematopoietic stem cells without compromising their repopulating potential. *Stem Cells Dev* 20: 1371–1381
  56. Wang L, Geng T, Guo X, Liu J, Zhang P, Yang D, Li J, Yu S & Sun Y (2015): Co-expression of immunoglobulin-like transcript 4 and angiopoietin-like proteins in human non-small cell lung cancer. *Mol Med Rep* 11: 2789–2796
  57. Tanigawa H, Miyata K, Tian Z *et al* (2016): Upregulation of ANGPTL6 in mouse keratinocytes enhances susceptibility to psoriasis. *Sci Rep* 6: 34690
  58. Marchio S, Soster M, Cardaci S *et al* (2012): A complex of  $\alpha 6$  integrin and E-cadherin drives liver metastasis of colorectal cancer cells through hepatic angiopoietin-like 6. *EMBO Mol Med* 4: 1156–1175
  59. Katoh Y & Katoh M (2006): Comparative integromics on Angiopoietin family members. *Int J Mol Med* 17: 1145–1149
  60. Xiao Y, Jiang Z, Li Y *et al* (2015): ANGPTL7 regulates the expansion and repopulation of human hematopoietic stem and progenitor cells. *Haematologica* 100: 585–594
  61. Qian T, Wang K, Cui J, He Y & Yang Z (2016): Angiopoietin-like protein 7 promotes an inflammatory phenotype in RAW264.7 macrophages through the P38 MAPK signaling pathway. *Inflammation* 39: 974–985
  62. Parri M, Pietrovito L, Grandi A *et al* (2014): Angiopoietin-like 7, a novel pro-angiogenic factor overexpressed in cancer. *Angiogenesis* 17: 881–896
  63. Lim SY, Gordon-Weeks A, Allen D, Kersemans V, Beech J, Smart S & Muschel RJ (2015): Cd11b(+) myeloid cells support hepatic metastasis through down-regulation of angiopoietin-like 7 in cancer cells. *Hepatology* 62: 521–533
  64. Tseng YH, Yeh YH, Chen WJ & Lin KH (2014): Emerging regulation and function of betatrophin. *Int J Mol Sci* 15: 23640–23657
  65. Dong XY, Pang XW, Yu ST, Su YR, Wang HC, Yin YH, Wang YD & Chen WF (2004): Identification of genes differentially expressed in human hepatocellular carcinoma by a modified suppression subtractive hybridization method. *Int J Cancer* 112: 239–248
  66. Yoon JC, Chickering TW, Rosen ED, Dussault B, Qin Y, Soukas A, Friedman JM, Holmes WE & Spiegelman BM (2000): Peroxisome proliferator-activated receptor gamma target gene encoding a novel angiopoietin-related protein associated with adipose differentiation. *Mol Cell Biol* 20: 5343–5349
  67. Ehrlich KC, Lacey M & Ehrlich M (2019): Tissue-specific epigenetics of atherosclerosis-related ANGPT and ANGPTL genes. *Epigenomics* 11: 169–186
  68. de Martel C & Franceschi S (2009): Infections and cancer: Established associations and new hypotheses. *Crit Rev Oncol Hematol* 70: 183–194
  69. Dewey FE, Gusarova V, Dunbar RL *et al* (2017): Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med* 377: 211–221
  70. Dewey FE, Gusarova V, O'Dushlaine C *et al* (2016): Inactivating variants in ANGPTL4 and risk of coronary artery disease. *N Engl J Med* 374: 1123–1133
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## がん進展におけるアンジオポエチン様因子の機能

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**要 旨：**アンジオポエチン(angiotensin)は血管新生, 造血系幹細胞の恒常性維持に重要な役割を担っている。アンジオポエチン様因子(angiotensin-like proteins : ANGPTLs)は, アンジオポエチンに構造上類似するタンパクとして同定され, 現在までに8種類報告されている。ANGPTLsは分泌タンパクであり, 血管新生以外に糖代謝, 脂質代謝, レドックス制御, 慢性炎症などにも関与する。近年, 慢性炎症が発がん, がん浸潤・転移の重要な因子の一つであることが報告され注目されている。ANGPTL2, 3, 4, 6, 7は炎症を促進させ, がん進展に関与する。一方, ANGPTL1は腫瘍血管新生を抑制することで, がん進展を抑制する。本総説では, がん進展におけるANGPTLsの機能を概説し, ANGPTLsを標的としたがん浸潤・転移抑制法開発の可能性についても紹介したい。

**キーワード：**アンジオポエチン様因子, がん進展, 炎症。

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