Seven proteins have been identified to contain a coiled-coil domain and a fibrinogen-like domain similar to those found in angiopoietins, and are therefore designated angiopoietin-like proteins (ANGPTLs; angiopoietin-related proteins) 1-7 (Figure). Although none of these proteins bind to the angiopoietin receptors, most members show angiogenic effects. More recently, ANGPTL-family members have been found to be regulators of metabolism.

CONTINUED ON NEXT PAGE
Metabolism

**ANGPTL2** is a key mediator of chronic adipose tissue inflammation and obesity-related systemic insulin resistance. It is primarily secreted by adipose tissue. Increased circulating ANGPTL2 levels are closely related to adiposity, inflammation and systemic insulin resistance [1]. ANGPTL2-treated mice show decreases in plasma glucose, insulin, triglyceride (TG) and fatty acid (FA) levels and an increase in plasma adiponectin, a therapeutic regulator of insulin resistance, leading to improvements in glucose tolerance. ANGPTL2 is therefore an anti-diabetic factor that enhances insulin sensitivity in adipocytes [2].

**ANGPTL3** (Angiopoietin-5; ANG5) for lipid metabolism was first indicated by the genetic analysis of a mutant strain of obese mice with low plasma lipid levels. Administration of recombinant ANGPTL3 to ANGPTL3-deficient as well as wild type mice increased the plasma levels of non-esterified fatty acid (NEFA), triacylglycerol (TG) and cholesterol [3]. ANGPTL3 decreases very-low-density-lipoprotein (VLDL)-TG clearance by inhibiting lipoprotein lipase (LPL) [4], but has also been shown to activate lipolysis upon direct binding to adipocytes [5]. ANGPTL3 suppresses endothelial lipase (EL) thereby regulating high-density lipoprotein (HDL) [6]. It is proteolytically cleaved by proprotein convertases to a N-terminal and C-terminal ANGPTL3 fragment [7,8]. Cleavage appears to be important for activating ANGPTL3 in vivo [7]. nANGPTL3 and full length ANGPTL3 are equally effective towards inhibiting LPL activity in vitro [7]. nANGPTL3 is a more effective EL inhibitor compared to full length ANGPTL3 [8]. The SE1 region of ANGPTL3 and ANGPTL4 functions as a domain, important for binding LPL and inhibiting its activity in vitro and in vivo [9]. ANGPTL3 levels are inversely correlated with VLDL- and IDL-cholesterol levels, and positively with HDL cholesterol. ANGPTL3 levels in hemodialysis patients are consistently associated with the major components of uremic dyslipidemia [10]. Significant correlations have been reported with systolic blood pressure, plasma LDL and plasma A-FABP [11]. Cardiac artery intima-media thickness [12] and TL3 levels were elevated in patients with more severe forms of nonalcoholic steatohepatitis (NAFLD), which could be associated with insulin resistance [13].

**ANGPTL4** (Hepatic fibrinogen/angiopoietin-related protein; HFARP [14]; Peroxisome proliferator-activated receptor γ angiopoietin-related gene (PGAR) [15]; Fasting-induced adipose factor (FIAF) [16]) is a novel peroxisome proliferator-activated receptor (PPARγ) target gene involved in the regulation of metabolism. ANGPTL4 inhibits lipoprotein lipase (LPL) and decreases plasma triglycerides [17-19], stimulates adipose tissue lipolysis [20] and improves lipid metabolism including insulin sensitivity [21]. ANGPTL4 decreases hepatic glucose production and enhances insulin-mediated inhibition of gluconeogenesis [19]. It is proteolytically cleaved by proprotein convertases to a N-terminal and C-terminal ANGPTL4 fragment [22]. ANGPTL4 undergoes oligomerization within the cells [23, 24]. Once secreted, ANGPTL4 interacts with the extracellular matrix through HSPG [25]. The SE1 region of the N-terminal coiled-coil domain of ANGPTL4 is crucial for the inhibition of LPL activity in vitro and in vivo [9].

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**FIGURE:** Schematic diagram showing potential roles of ANGPTL2 and ANGPTL6 in obesity and related metabolic diseases. The expression of ANGPTL2 and ANGPTL6 is induced in obese conditions. ANGPTL2 induces chronic adipose tissue inflammation and systemic insulin resistance through the induction of vascular inflammation and monocyte migration. ANGPTL6 antagonizes obesity and insulin resistance through the enhancement of systemic energy expenditure. Adapted from T. Kadomatsu, et al.; FEBS J. 559 (2011).

**FIGURE:** Role of ANGPTL3 and ANGPTL4 in regulating metabolic homeostasis. ANGPTL3 derived from liver directly targets adipose cells, inhibits LPL activity and activates lipolysis. ANGPTL4 affects lipid metabolism by inhibiting LPL activity and stimulating lipolysis and glucose metabolism by suppressing basal glucose output and gluconeogenesis and by enhancing the sensitivity of insulin in liver. Adapted from T. Oke, et al.; TMM 11, 473 (2005).
ANGPTL4 is a novel regulator of food intake and body weight. Hypothalamic ANGPTL4 is regulated by physiologic appetite regulators and mediates their anorexigenic effects via inhibition of hypothalamic AMPK activity. It plays an important role in central regulation of energy metabolism [26]. Recently, ANGPTL4 serum levels were shown to correlate with renal function, glucose and lipid metabolism, as well as inflammation [27].

ANGPTL5 plays a role in triglyceride (TG) metabolism in humans [28].

ANGPTL6 (Angiopoietin-related growth factor; AGF) has anti-obesity and insulin-sensitizing effects [29]. ANGPTL6 overexpression counteracts obesity and insulin resistance by increasing systemic energy expenditure. It was shown to be involved in the development of obesity and its related insulin resistance in mouse models [30]. ANGPTL6 suppresses gluconeogenesis through an Akt/FocO1-dependent pathway [31]. Circulating levels of human ANGPTL6 are elevated in obese or diabetic conditions and positively correlate with fasting serum glucose levels [32]. Chronic hemodialysis patients have lower ANGPTL6 concentrations than controls [32], whereas patients with type 2 diabetes or preeclampsia have higher ANGPTL6 concentrations than nondiabetic patients [33].

LITERATURE REFERENCES:

Inflammation

ANGPTL2 is an important factor in chronic inflammatory diseases. It is primarily secreted by adipose tissues and its expression is increased in obesity and obesity-related pathological conditions, including hypoxia and endoplasmic reticulum (ER) stress. In endothelial cells, ANGPTL2 activates an inflammatory cascade through αvβ3 integrin receptors and induces chemotaxis of monocytes and macrophages through α4 and β2 integrin receptors. It plays a key role in inflammation of adipose tissue via inflammatory vascular remodelling and recruitment of macrophages into adipose tissue [1]. ANGPTL2 acts as an important rheumatoid synovium-derived inflammatory mediator in rheumatoid arthritis (RA) pathogenesis [2].

LITERATURE REFERENCES:

SELECTED REVIEW ARTICLES

• Impacts of angiopoietin-like proteins on lipid metabolism and cardiovascular events: T. Mida & S. Hirayama; Curr. Opin. Lipidol. 21, 70 (2010)
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**GENERAL:** CCD: Coiled-coil Domain; ED: Ectodomain; FLD: Fibrinogen-like Domain; GD: Globular Domain; HDLTH: Homeodomain-like Helix-Turn-Helix

**SPECIES:** Hu = Human; Ms = Mouse; Rt = Rat; Dg = Dog
## Polyclonal Antibodies

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**GENERAL:** CCD: Coiled-coil Domain; ED: Ectodomain; FLD: Fibrinogen-like Domain; GD: Globular Domain; PF: Preservative Free  
**APPLICATIONS:** EM: Electron Microscopy; FACS: Flow Cytometry;  
**FUNC:** Functional Application; ICC: Immunocytochemistry; IHC: Immunohistochemistry (FS = Frozen Sections, PS = Paraffin Sections); IP: Immunoprecipitation; WB: Western blot  
**SPECIES:** Hu = Human; Ms = Mouse; Rt = Rat; Dg = Dog; Ds = Drosophila; Gp = Guinea Pig; HCV = Hepatitis C virus; Lst. = Listeria; Mnk = Monkey; Pg = Pig; Rb = Rabbit

## Monoclonal Antibodies

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ANGPTL2, ANGPTL3, ANGPTL5 and ANGPTL7 were shown to be potent stimulators of ex vivo expansion of hematopoietic stem cells (HSCs) [1]. ANGPTL-2 and ANGPTL3 enhance survival and replating capacity of human cordal blood hematopoietic progenitor cells (HPCs) subjected to delayed addition of cytokines [2]. ANGPTL3 supports the stemness of HSCs in the bone marrow niche [3] and the expansion of HSCs ex vivo [4]. ANGPTL5 can stimulate ex vivo expansion of human cord blood HSCs [5] and supports efficient expansion of human hematopoietic stem cells [6, 7]. ANGPTL6 was identified as an important factor in the KRAS-G12V secretome that mediated enhanced proliferation of human CB CD34(+) cells, while only ANGPTL6 induced a rather modest increase in expansion, suggesting that most likely a multitude of the KRASG12V-secreted factors act in collaboration [8].

LITERATURE REFERENCES:

Figure: Overview on hematopoietic stem cell development.

**MFAP4**

MFAP4 (Microfibril-associated glycoprotein 4) [1] is a collagen-binding protein playing a potential role in extracellular matrix (ECM) turnover during fibrogenesis. It contains a C-terminal fibrinogen-like domain and a N-terminal located integrin-binding motif. MFAP4 exhibits sequence similarity to ANGPTLs and also stimulates the ex vivo expansion of hematopoietic stem cells [2]. In a proteomics approach specifically MFAP4 has been identified as a potential new serum biomarker of hepatic fibrosis [3]. A novel role for MFAP4 in teleost immune responses was described [4].

**Related Product**

**MFAP4 (human) (rec.)**

- **AG-40A-0072-C010**
  - 10 µg
- **AG-40A-0072-C050**
  - 50 µg

Produced in HEK 293 cells. Human MFAP4 (aa 1-255) is fused at the C-terminus to a FLAG®-tag. **PURITY:** ≥90% (SDS-PAGE), **ENDOTOXIN CONTENT:** <0.1 EU/µg protein (LAL-test).

**anti-MFAP4 (human), pAb**

- **AG-25A-0061-C100**
  - 100 µg

From rabbit. **IMMUNOGEN:** Recombinant human MFAP4. **SPECIFICITY:** Recognizes human MFAP4. **APPLICATION:** WB.

**LITERATURE REFERENCES:**
ANGPTL1 (Angiopoietin-3; ANG3; Angioarrestin) exhibits weak endothelial cell-sprouting activities in vitro [1, 2] and inhibits VEGF-induced angiogenesis [3]. ANGPTL1 transcript is down-regulated in many types of tumors, including lung, prostate, kidney, thyroid and urinary bladder cancers, compared to levels in unaffected parts of the same organ [3]. ANGPTL1 inhibits VEGF and bFGF-induced bromodeoxyuridine incorporation, cell migration, and tube formation of cultured human umbilical vein endothelial cells (HUVECs) [4]. It exhibits anti-apoptotic activity [5]. ANGPTL1 is related to development of the connective tissue and cartilage and may have a beneficial role in the preservation of vascular integrity following focal cerebral ischemia [6, 7].

ANGPTL2 exhibits weak endothelial cell-sprouting activities in vitro [1, 2] and anti-apoptotic activity [5]. Loss of ANGPTL2 function is a factor in the carcinogenesis of ovarian cancer [8].

ANGPTL3 (Angiopoietin-5; ANG5) stimulates adhesion and migration of endothelial cells as well induces blood vessel formation through the integrin αvβ3 receptor [9].

ANGPTL4 (Hepatic fibrinogen/angiopoietin-related protein; HFARP) is linked to angiogenesis, tumor cell motility and invasiveness [10, 11], cell migration [12], endothelial cell function, vascular leakage, neoangiogenesis [13] and cell adhesion [14-16]. CANGPTL4 is responsible for these functions independently of nANGPTL4. CANGPTL4 binds and activates integrin 5β1α-mediated Rac/PKA signaling to weaken cell-cell contacts [17]. Elevated expression of ANGPTL4 is widespread in tumors [18-20]. Recently, ANGPTL4 was suggested to be an important player in redox-mediated cancer progression [21]. It was also shown to be a potential angiogenic mediator in arthritis [22] and to interact with matrix proteins to modulate wound healing [23].

ANGPTL6 (Angiopoietin-related growth factor; AGF) is an angiogenic factor involved in epidermal proliferation, wound healing [24-26] and mediates adhesion by interacting with integrin receptors [24].

ANGPTL7 (Cornea-derived transcript 6; CDT6) reduces tumor growth and aberrant blood vessel formation by inducing massive fibrosis [27, 28]. Characterized as potent target gene of the Wnt/β-catenin signaling pathway, it is a pharmacogenomics target in the fields of oncology and regenerative medicine [29]. Overexpression of ANGPTL7 increases collagen expression and might exert a pathogenic role in glaucoma [30, 31].

LITERATURE REFERENCES:
[26] Angiopoietin-related growth factor (AGF) supports adhesion, spreading, and migration of keratinocytes, fibroblasts, and endothelial cells through interaction with RGD-binding integrins: Y. Zhang, et al., BBRC 347, 100 (2006)
ANGPTL ELISA Kits

ANGPTL3 (human) ELISA Kit
AG-45A-0014EK-KI01 96 wells
AG-45A-0014TP-KI01 2 x 96 wells
AG-45A-0014PP-KI01 5 x 96 wells

SPECIES REACTIVITY: Human
SENSITIVITY: 150 pg/ml
RANGE: 0.156 to 10 ng/ml
DETECTION TYPE: Colorimetric
ASSAY TYPE: Sandwich
SAMPLE TYPE: Plasma, Serum, Cell Culture Supernatant

ANGPTL3 (mouse/rat) Dual ELISA Kit
AG-45A-0015EK-KI01 96 wells
AG-45A-0015TP-KI01 2 x 96 wells
AG-45A-0015PP-KI01 5 x 96 wells

SPECIES REACTIVITY: Mouse, rat
SENSITIVITY: 15 pg/ml
RANGE: 0.016 to 1 ng/ml
DETECTION TYPE: Colorimetric
ASSAY TYPE: Sandwich
SAMPLE TYPE: Plasma, Serum, Cell Culture Supernatant

ANGPTL6 (human) ELISA Kit
AG-45A-0016EK-KI01 96 wells
AG-45A-0016TP-KI01 2 x 96 wells
AG-45A-0016PP-KI01 5 x 96 wells

SPECIES REACTIVITY: Human
SENSITIVITY: 1.2 ng/ml
RANGE: 1.56 to 100 ng/ml
DETECTION TYPE: Colorimetric
ASSAY TYPE: Sandwich
SAMPLE TYPE: Plasma, Serum, Cell Culture Supernatant

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ANGPTL2 & 3 increase Hematopoietic Stem Cell Expansion

Several angiopoietin-like (ANGPTL) molecules have been implicated in enhancement of ex vivo expansion of murine and human hematopoietic stem cells. H. E. Broxmeyer, et al. have recently shown, using the biological active ANGPTL proteins from AdipoGen™, that ANGPTL2 and -3 had enhancing activities on human cordal blood hematopoietic progenitor cells (HPC) survival and replating activity. These effects require the CC domain of the ANGPTL molecules, which might be of relevance to human HPC regulation.


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