

ANGPTLs

[Angiopoietin-like/related Proteins]

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.

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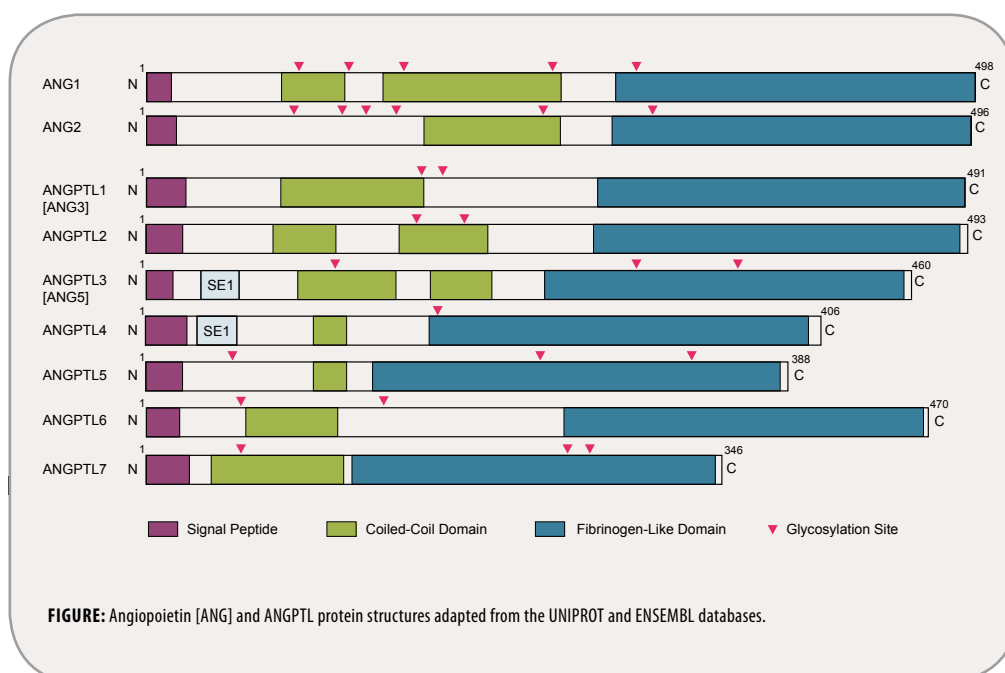


FIGURE: Angiopoietin [ANG] and ANGPTL protein structures adapted from the UNIPROT and ENSEMBL databases.

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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 decrease 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].

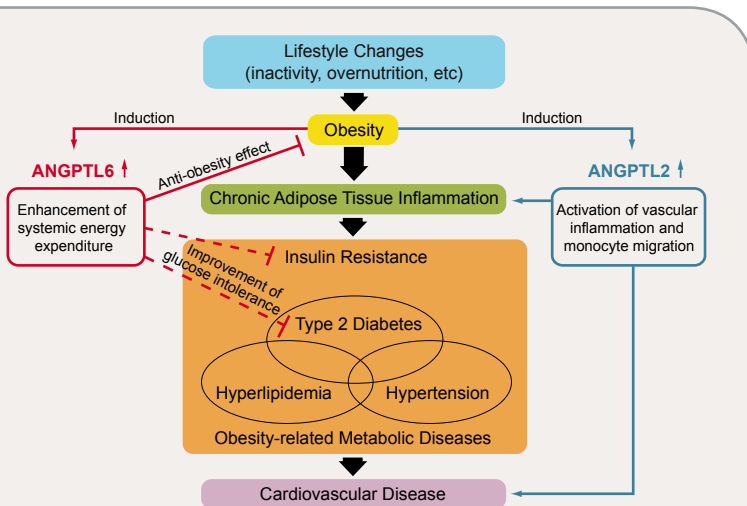


FIGURE: Schematic diagram showing potential roles of ANGPTL2 and ANGPTL6 in obesity and related metabolic diseases. The expression of ANGPTL2 and ANGPTL6 is induced in obese conditions. ANGPTL2 induces chronic adipose tissue inflammation and systemic insulin resistance through the induction of vascular inflammation and monocyte migration. ANGPTL6 antagonizes obesity and insulin resistance through the enhancement of systemic energy expenditure. Adapted from T. Kadamatsu, et al.; FEBS J. 278, 559 (2011).

The importance of **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 bind-

ing 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]. Carotic 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 (PPAR) γ 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].

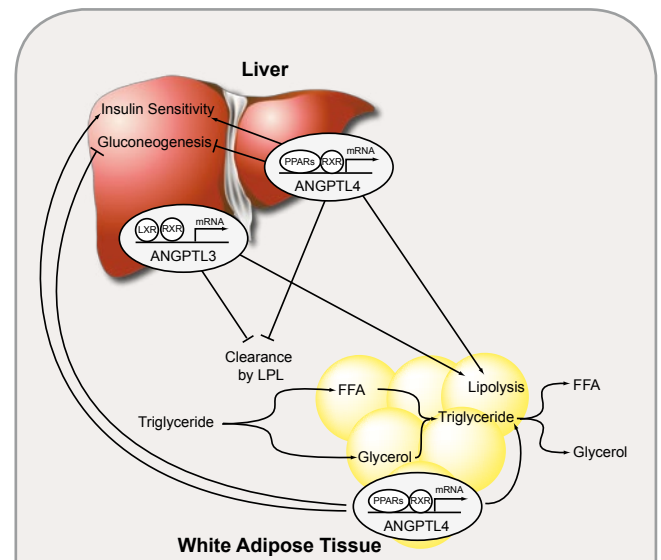


FIGURE: Role of ANGPTL3 and ANGPTL4 in regulating metabolic homeostasis. ANGPTL3 derived from liver directly targets adipose cells, inhibits LPL activity and activates lipolysis. ANGPTL4 affects lipid metabolism by inhibiting LPL activity and stimulating lipolysis and glucose metabolism by suppressing basal glucose output and gluconeogenesis and by enhancing the sensitivity of insulin in liver. Adapted from Y. Oike, et al.; TIMM 11, 473 (2005).

ANGPTL4 is a novel regulator of food intake and body weight. Hypothalamic ANGPTL4 is regulated by physiological 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/FoxO1-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].

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[1] Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance: M. Tabata, et al.; *Cell Metab.* **10**, 178 (2009) • [2] Angiopoietin-like 2, a circadian gene, improves type 2 diabetes through potentiation of insulin sensitivity in mice adipocytes: M. Kitazawa, et al.; *Endocrinology* **152**, 2558 (2011) • [3] Angptl3 regulates lipid metabolism in mice: R. Koishi, et al.; *Nat. Genet.* **30**, 151 (2002) • [4] ANGPTL3 decreases very low density lipoprotein triglyceride clearance by inhibition of lipoprotein lipase: T. Shimizugawa, et al.; *J. Biol. Chem.* **277**, 33742 (2002) • [5] Angiopoietin-like protein 3, a hepatic secretory factor, activates lipolysis in adipocytes: M. Shimamura, et al.; *BBRC* **301**, 604 (2003) • [6] Angiopoietin-like protein3 regulates plasma HDL cholesterol through suppression of endothelial lipase: M. Shimamura, et al.; *Arterioscler. Thromb. Vasc. Biol.* **27**, 366 (2007) • [7] Protein region important for regulation of lipid metabolism in angiopoietin-like 3 (ANGPTL3): ANGPTL3 is cleaved and activated in vivo: M. Ono, et al.; *J. Biol. Chem.* **278**, 41804 (2003) • [8] Hepatic proprotein convertases modulate HDL metabolism: W. Jin, et al.; *Cell Metab.* **6**, 129 (2007) • [9] Identification of a new functional domain in angiopoietin-like 3 (ANGPTL3) and angiopoietin-like 4 (ANGPTL4) involved in binding and inhibition of lipoprotein lipase (LPL): E.C. Lee, et al.; *J. Biol. Chem.* **284**, 13735 (2009) • [10] Plasma angiopoietin-like protein 3 (ANGPTL3) concentration is associated with uremic dyslipidemia: T. Shoji, et al.; *Atheroscler.* **207**, 579 (2009) • [11] Angiopoietin-like protein 3: development, analytical characterization, and clinical testing of a new ELISA: D. Stejskal, et al.; *Gen. Physiol. Biophys.* **26**, 230 (2007) • [12] Association between plasma angiopoietin-like protein 3 and arterial wall thickness in healthy subjects: S. Hatsuda, et al.; *J. Vasc. Res.* **44**, 61 (2007) • [13] Serum concentrations of human angiopoietin-like protein 3 in patients with nonalcoholic fatty liver disease: association with insulin resistance: Y. Yilmaz, et al.; *Eur. J. Gastroenterol. Hepatol.* **21**, 1247 (2009) • [14] Hepatic expression, synthesis and secretion of a novel fibrinogen/angiopoietin-related protein that prevents endothelial-cell apoptosis: I. Kim, et al.; *Biochem. J.* **346**, 603 (2000) • [15] Peroxisome proliferator-activated receptor gamma target gene encoding a novel angiopoietin-related protein associated with adipose differentiation: J. C. Yoon, et al.; *Mol. Cell. Biol.* **20**, 5343 (2000) • [16] Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene: S. Kersten, et al.; *J. Biol. Chem.* **275**, 28488 (2000) • [17] Angiopoietin-like protein 4 is a potent hyperlipidemia-inducing factor in mice and inhibitor of lipoprotein lipase: K. Yoshida, et al.; *J. Lipid Res.* **43**, 1770 (2002) • [18] Transgenic angiopoietin-like (angptl)4 overexpression and targeted disruption of angptl4 and angptl3: regulation of triglyceride metabolism: A. Koster, et al.; *Endocrinology* **146**, 4943 (2005) • [19] Angiopoietin-like protein 4 decreases blood glucose and improves glucose tolerance but induces hyperlipidemia and hepatic steatosis in mice: A. Xu, et al.; *PNAS* **102**, 6086 (2005) • [20] The fasting-induced adipose factor/angiopoietin-like protein 4 is physically associated with lipoproteins and governs plasma lipid levels and adiposity: S. Mandard, et al.; *J. Biol. Chem.* **281**, 934 (2006) • [21] Angptl 4 deficiency improves lipid metabolism, suppresses foam cell formation and protects against atherosclerosis: H. Adachi, et al.; *BBRC* **379**, 806 (2009) • [22] Proteo-

lytic processing of angiopoietin-like protein 4 by proprotein convertases modulates its inhibitory effects on lipoprotein lipase activity: X. Lei, et al.; *J. Biol. Chem.* **286**, 15747 (2011) • [23] Oligomerization and regulated proteolytic processing of angiopoietin-like protein 4: H. Ge, et al.; *J. Biol. Chem.* **279**, 2038 (2004) • [24] The angiopoietin-like proteins ANGPTL3 and ANGPTL4 inhibit lipoprotein lipase activity through distinct mechanisms: L. Shan, et al.; *J. Biol. Chem.* **284**, 1419 (2009) • [25] Extracellular matrix-bound angiopoietin-like 4 inhibits endothelial cell adhesion, migration, and sprouting and alters actin cytoskeleton: A. Cazes, et al.; *Circ. Res.* **99**, 1207 (2006) • [26] Hypothalamic Angptl4/Fiaf is a novel regulator of food intake and body weight: H. K. Kim, et al.; *Diabetes* **59**, 2772 (2010) • [27] Serum levels of the adipokine fasting-induced adipose factor/angiopoietin-like protein 4 depend on renal function: T. Baranowski, et al.; *Horm. Metab. Res.* **43**, 117 (2011) • [28] Rare loss-of-function mutations in ANGPTL family members contribute to plasma triglyceride levels in humans: S. Romeo, et al.; *J. Clin. Invest.* **119**, 70 (2009) • [29] The role of angiopoietin-like proteins in angiogenesis and metabolism: T. Hato, et al.; *Trends Cardiovasc. Med.* **18**, 6 (2008) (Review) • [30] Angiopoietin-related growth factor antagonizes obesity and insulin resistance: Y. Oike, et al.; *Nat. Med.* **11**, 400 (2005) • [31] Angiopoietin-related growth factor suppresses gluconeogenesis through the Akt/forkhead box class O1-dependent pathway in hepatocytes: M. Kitazawa, et al.; *J. Pharmacol. Exp. Ther.* **323**, 787 (2007) • [32] Serum levels of angiopoietin-related growth factor in diabetes mellitus and chronic hemodialysis: T. Ebert, et al.; *Metabolism* **58**, 547 (2009) • [33] Serum levels of angiopoietin-related growth factor are increased in preeclampsia: H. Stepan, et al.; *Am. J. Hypertens.* **22**, 314 (2009)

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 $\alpha 5\beta 1$ integrin receptors and induces chemotaxis of monocytes and macrophages through $\alpha 4$ and $\beta 2$ 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].

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[1] Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation and obesity-related systemic insulin resistance: M. Tabata, et al.; *Cell Metab.* **10**, 178 (2009) • [2] Synovial cell-derived angiopoietin-like protein 2 contributes to synovial chronic inflammation in rheumatoid arthritis: T. Okada, et al.; *Am. J. Pathol.* **176**, 2309 (2010)

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- Angiopoietin-like proteins: potential new targets for metabolic syndrome therapy: Y. Oike, et al.; *TIMM* **11**, 473 (2005)
- The role of angiopoietin-like proteins in angiogenesis and metabolism: T. Hato, et al.; *Trends Cardiovasc. Med.* **18**, 6 (2008)
- Angiopoietin-like proteins - potential therapeutic targets for metabolic syndrome and cardiovascular disease: Y. Oike & M. Tabata; *Circ. J.* **73**, 2192 (2009)
- Modulation of plasma TG lipolysis by Angiopoietin-like proteins and GPIIb/IIIa: L. Lichtenstein & S. Kersten; *Biochim. Biophys. Acta* **1801**, 415 (2010)
- Impacts of angiopoietin-like proteins on lipoprotein metabolism and cardiovascular events: T. Miida & S. Hirayama; *Curr. Opin. Lipidol.* **21**, 70 (2010)
- Angiopoietin-like proteins: emerging targets for treatment of obesity and related metabolic diseases: T. Kadomatsu, et al.; *FEBS J.* **278**, 559 (2011)

Proteins

PRODUCT NAME	PID	SIZE	TAG	MW BY SDS-PAGE	SOURCE	SPECIES	LIT REF.
ANGPTL1 (FLD) (human) (rec.)	AG-40A-0078	10 µg 50 µg	FLAG	~35kDa	HEK 293 cells	Hu	
ANGPTL2 (CCD) (human) (rec.)	AG-40A-0087	10 µg 50 µg	FLAG	~32kDa	HEK 293 cells	Hu	✓
ANGPTL2 (FLD) (human) (rec.)	AG-40A-0083	10 µg 50 µg	FLAG	~35kDa	HEK 293 cells	Hu	
ANGPTL3 (human) (rec.)	AG-40A-0051	10 µg 50 µg	FLAG	~60kDa	HEK 293 cells	Hu	✓
ANGPTL3 (mouse) (rec.)	AG-40A-0082	10 µg 50 µg	FLAG	~70kDa	HEK 293 cells	Ms	
ANGPTL3 (CCD) (human) (rec.)	AG-40A-0069	10 µg 50 µg	FLAG	~25kDa	HEK 293 cells	Hu	✓
ANGPTL3 (CCD) (mouse) (rec.)	AG-40A-0103	10 µg 50 µg	His	~20kDa	HEK 293 cells	Ms	
ANGPTL3 (FLD) (human) (rec.)	AG-40A-0071	10 µg 50 µg	FLAG	~35kDa	HEK 293 cells	Hu	✓
ANGPTL3 (FLD) (mouse) (rec.)	AG-40A-0096	10 µg 50 µg	FLAG	~30kDa	HEK 293 cells	Ms	
ANGPTL4 (human) (rec.)	AG-40A-0033	10 µg 50 µg	FLAG	~40kDa	HEK 293 cells	Hu	✓
ANGPTL4 (mouse) (rec.)	AG-40A-0075	10 µg 50 µg	FLAG	~50kDa	COS-7 cells	Ms	
ANGPTL4 (CCD) (human) (rec.)	AG-40A-0065	10 µg 50 µg	FLAG	~18kDa	HEK 293 cells	Hu	✓
ANGPTL4 (CCD) (mouse) (rec.)	AG-40A-0104	10 µg 50 µg	His	~18kDa	HEK 293 cells	Ms	
ANGPTL4 (FLD) (human) (rec.)	AG-40A-0070	10 µg 50 µg	FLAG	~35kDa	HEK 293 cells	Hu	
ANGPTL4 (FLD) (mouse) (rec.)	AG-40A-0115	10 µg 50 µg	FLAG	~40kDa	HEK 293 cells	Ms	
ANGPTL4 (FLD) (rat) (rec.)	AG-40A-0175	10 µg 50 µg	FLAG	~30kDa	HEK 293 cells	Rt	
ANGPTL4 (intact form) (rat) (rec.)	AG-40A-0123	10 µg	His	~75kDa	<i>E. coli</i>	Rt	
ANGPTL5 (CCD) (human) (rec.)	AG-40A-0076	10 µg 50 µg	FLAG	~20kDa	HEK 293 cells	Hu	✓
ANGPTL5 (FLD) (human) (rec.)	AG-40A-0084	10 µg 50 µg	FLAG	~32kDa	HEK 293 cells	Hu	
ANGPTL6 (human) (rec.)	AG-40A-0032	10 µg 50 µg	FLAG	~65kDa	HEK 293 cells	Hu	✓
ANGPTL6 (FLD) (human) (rec.)	AG-40A-0085	10 µg 50 µg	FLAG	~32kDa	HEK 293 cells	Hu	
ANGPTL7 (human) (rec.)	AG-40A-0060	10 µg 50 µg	FLAG	~45kDa	HEK 293 cells	Hu	✓
ANGPTL7 (FLD) (human) (rec.)	AG-40A-0086	10 µg 50 µg	FLAG	~32kDa	HEK 293 cells	Hu	

GENERAL: CCD: Coiled-coil Domain; ED: Ectodomain; FLD: Fibrinogen-like Domain; GD: Globular Domain; HDLH: Homeodomain-like Helix-Turn-Helix
SPECIES: Hu = Human; Ms = Mouse; Rt = Rat; Dg = Dog

Polyclonal Antibodies

PRODUCT NAME	PID	SIZE	CLONE	SOURCE/ ISOTYPE	APPLICATION	SPE- CIES	LIT. REF.
ANGPTL2 (human), pAb	AG-25A-0068	100 µg		Rb	ELISA, WB	Hu	
ANGPTL3 (human), pAb	AG-25A-0046	100 µg		Rb	ELISA, WB	Hu	✓
ANGPTL3 (human), pAb	AG-25A-0052	100 µg		Rb	ELISA, WB	Hu	
ANGPTL3 (CCD) (human), pAb	AG-25A-0060	100 µg		Rb	ELISA, WB	Hu	
ANGPTL3 (FLD) (human), pAb	AG-25A-0064	100 µg		Rb	ELISA, WB	Hu	
ANGPTL3 (mouse), pAb	AG-25A-0070	100 µg		Rb	ELISA, WB	Ms	
ANGPTL4 (human), pAb	AG-25A-0038	100 µg		Rb	ELISA, WB	Hu	✓
ANGPTL4 (human), pAb	AG-25A-0055	100 µg		Rb	ELISA, WB	Hu	
ANGPTL4 (CCD) (human), pAb	AG-25A-0066	100 µg		Rb	ELISA, WB	Hu	
ANGPTL4 (FLD) (human), pAb	AG-25A-0065	100 µg		Rb	ELISA, WB	Hu	
ANGPTL4 (mouse), pAb	AG-25A-0071	100 µg		Rb	ELISA, WB	Ms	✓
ANGPTL5 (CCD) (human), pAb	AG-25A-0069	100 µg		Rb	ELISA, WB	Hu	
ANGPTL6 (human), pAb	AG-25A-0030	100 µg		Rb	ELISA, WB	Hu	
ANGPTL6 (human), pAb	AG-25A-0037	100 µg		Rb	ELISA, WB	Hu	
ANGPTL7 (human), pAb	AG-25A-0050	100 µg		Rb	ELISA, WB	Hu	✓
ANGPTL7 (CCD) (human), pAb	AG-25A-0095	100 µg		Rb	ELISA, WB	Hu	

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; List. = Listeria; Mk = Monkey; Pg = Pig; Rb = Rabbit

Monoclonal Antibodies

PRODUCT NAME	PID	SIZE	CLONE	SOURCE/ ISOTYPE	APPLICATION	SPE- CIES	LIT. REF.
ANGPTL3 (human), mAb (Kairos-37)	AG-20A-0039	50 µg 100 µg	Kairos-37	Ms IgG1κ	ELISA, WB	Hu	
ANGPTL3 (mouse), mAb (Kairos3-1541)	AG-20A-0089	50 µg 100 µg	Kairos 3-1541	Rt IgG2aκ	ELISA, WB	Ms	
ANGPTL3 (mouse), mAb (Kairos3-3741)	AG-20A-0090	50 µg 100 µg	Kairos 3-3741	Rt IgG2aκ	ELISA, WB	Ms	
ANGPTL4 (human), mAb (Kairos-1)	AG-20A-0038	50 µg 100 µg	Kairos-1	Ms IgG1κ	ELISA, IHC (PS), WB	Hu	
ANGPTL4 (CCD) (human), mAb (Kairos4-153AD)	AG-20A-0046	50 µg 100 µg	Kairos 4-153AD	Ms IgG1κ	ELISA, WB	Hu	
ANGPTL4 (CCD) (human), mAb (Kairos4-397G)	AG-20A-0047	50 µg 100 µg	Kairos 4-397G	Ms IgG1κ	ELISA, WB	Hu	
ANGPTL4 (mouse), mAb (Kairos 142-2)	AG-20A-0054	100 µg	Kairos 142-2	Rt IgG2aκ	ELISA, WB	Ms	
ANGPTL6 (human), mAb (Kairos-60)	AG-20A-0040	50 µg 100 µg	Kairos-60	Ms IgMκ	ELISA, WB	Hu	
ANGPTL7 (human), mAb (Kairos 108-4)	AG-20A-0053	100 µg	Kairos 108-4	Ms IgG1κ	ELISA, IHC, WB	Hu	
ANGPTL7 (human), mAb (Kairos 397-7)	AG-20A-0055	100 µg	Kairos 397-7	Ms IgG1κ	ELISA, WB	Hu	

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; List. = Listeria; Mk = Monkey; Pg = Pig; Rb = Rabbit

Stem Cell Biology

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 cordal 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].

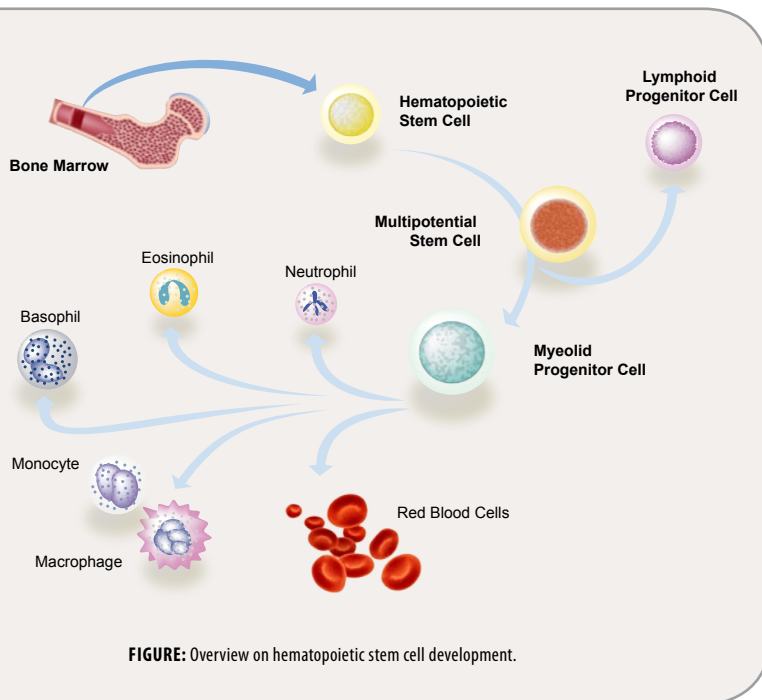


FIGURE: Overview on hematopoietic stem cell development.

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[1] Angiotensin-like proteins stimulate *ex vivo* expansion of hematopoietic stem cells: C.C. Zhang, et al.; Nat. Med. **12**, 240 (2006) [2] Angiotensin-like-2 and -3 act through their coiled-coil domains to enhance survival and replating capacity of human cord blood hematopoietic progenitors: H.E. Broxmeyer, et al.; Blood Cells Mol. Dis. (Epub ahead of print) (2011) • [3] Angiotensin-like protein 3 supports the activity of hematopoietic stem cells in the bone marrow niche: J. Zheng, et al.; Blood **117**, 470 (2011) • [4] Fetal liver hepatic progenitors are supportive stromal cells for hematopoietic stem cells: S. Chou & H. F. Lodish; PNAS **107**, 7799 (2010) • [5] Angiotensin-like 5 and IGFBP2 stimulate *ex vivo* expansion of human cord blood hematopoietic stem cells as assayed by NOD/SCID transplantation: C.C. Zhang, et al.; Blood **111**, 3415 (2008) • [6] Mesenchymal stem cells secreting angiotensin-like-5 support efficient expansion of human hematopoietic stem cells without compromising their repopulating potential: M. Khoury, et al.; Stem Cells Dev. **20**, 1371 (2011) • [7] Human CD34+ CD133+ hematopoietic stem cells cultured with growth factors including Angptl5 efficiently engraft adult NOD-SCID Il2γ^{-/-} (NSG) mice: A.C. Drake, et al.; PLoS One **6**, e18382 (2011) • [8] KRAS(G12V) enhances proliferation and initiates myelomonocytic differentiation in human stem/progenitor cells via intrinsic and extrinsic pathways: S. Fatrai, et al.; J. Biol. Chem. **286**, 6061 (2011)

Related Product

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].

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[1] The gene for a human microfibril-associated glycoprotein is commonly deleted in Smith-Magenis syndrome patients: Z. Zhao, et al.; Hum. Mol. Genet. **4**, 589 (1995) • [2] Angiotensin-like proteins stimulate *ex vivo* ex-

pansion of hematopoietic stem cells: C.C. Zhang, et al.; Nat. Med. **12**, 240 (2006) • [3] Detection of novel biomarkers of liver cirrhosis by proteomic analysis: C. Molleken, et al.; Hepatology **49**, 1257 (2009) • [4] Microfibrillar-associated protein 4 (MFAP4) genes in catfish play a novel role in innate immune responses: D. Niu, et al.; Dev. Comp. Immunol. **35**, 568 (2011)

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: <0.1EU/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.

Angiogenesis – Cancer

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 $\alpha v \beta 3$ 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 $5\beta 1\alpha$ -mediated Rac1/PAK 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].

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ANGPTL ELISA Kits

ANGPTL3 (human) ELISA Kit

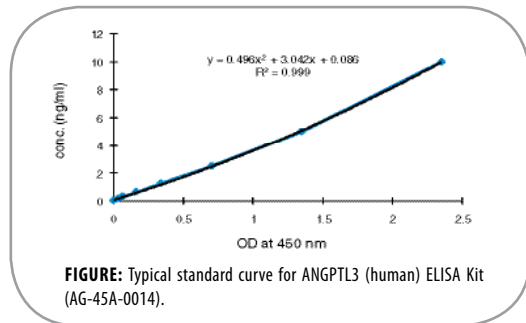
AG-45A-0014EK-KI01 96 wells
 AG-45A-0014TP-KI01 2 x 96 wells
 AG-45A-0014PP-KI01 5 x 96 wells

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

Latest Insight

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.

LIT: Angiopoietin-like-2 and -3 act through their coiled-coil domains to enhance survival and replating capacity of human cord blood hematopoietic progenitors: H.E. Broxmeyer, et al.; Blood Cells Mol. Dis. (Epub ahead of print) (2011)

In ITALY and SLOVENIA: Vinci-Biochem / Vinci (Firenze) / Tel +39 0571 568 147 / vb@vincibiochem.it / www.vincibiochem.it