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Mini Review

Proof of Evidence: PPAR-induced ANGPTL4 in Lipid and Glucose Metabolism

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Angiopoietin-like protein 4 (ANGPTL4) was identified as a peroxisome proliferator-activated receptor (PPAR)-induced gene. The genetic finding that mutation in ANGPTL3 causes hypolipidemia in mice moved us to test whether ANGPTL4 could also regulate lipid metabolism *in vivo*. We successfully proved that the introduction of ANGPTL4 as well as ANGPTL3 protein into mice rapidly induced hyperlipidemia. This suggests that the identification of novel PPAR-induced secreted proteins would contribute greatly to the elucidation of the molecular mechanisms of metabolic syndrome, including cardiovascular disease. In addition to lipid metabolism, ANGPTL4 is now regarded as a regulator of glucose metabolism. Emerging biochemical and genetic studies are expected to establish proof-of-evidence of ANGPTL4 as a promising drug development target.

Key words: Angiopoietin-like protein 4, peroxisome proliferator-activated receptor, lipid metabolism, drug target

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INTRODUCTION

ANGPTL4 (angiopoietin-like protein 4) was first identified a protein whose expression is induced by peroxisome proliferator-activated receptor (PPAR) gamma ligands (Yoon et al., 2000). The expression of ANGPTL4 is also elevated in genetic models of obesity. Almost simultaneously, ANGPTL4 was also reported as a FIAF (fasting-induced adipose factor) using subtractive hybridization comparing liver mRNA from wild-type and PPAR alpha null mice (Kersten et al., 2000). ANGPTL4/FIFA mRNA is predominantly detected in adipose tissue and is strongly up-regulated in white adipose tissue and the liver during fasting. These evidences suggest that ANGPTL4 is a circulating protein predominantly secreted from adipose tissue and liver. Overexpression of ANGPTL4 reduced hyperglycemia to a normal level and markedly alleviated glucose intolerance and hyperinsulinemia in db/db diabetic mice (Xu et al., 2005). It has been reported that ANGPTL3 is a target gene of liver X receptor (LXR), while ANGPTL4 expression is not (Ge et al., 2005; Kaplan et al., 2003). ANGPTL4 could exert distinct effects on lipid and glucose metabolism mainly through PPAR signaling but not through LXR, because ANGPTL4 mRNA was up-regulated by PPARalpha, PPARgamma, and PPARbeta/delta agonists (Mandard et al., 2004). PPARalpha plays an important role during fasting via the ligand-dependent transcriptional activation of target genes, while PPARgamma regulates systemic insulin signaling. It is also known that ANGPTL4 decreases hepatic glucose production and enhances insulin-media-ted inhibition of gluconeogenesis in primary rat hepatocytes

(Xu et al., 2005). Therefore, these findings suggest a possi-ble role for ANGPTL4 in the regulation of glucose homeo-stasis as well as lipid metabolism. In this opinion, we intro-duce the nature of ANGPTL4 and established proof-of-evi-dence about ANGPTL4.

Biochemistry of ANGPTL4 protein

ANGPTL4 is a member of the angiopoietin family of secreted proteins. Among this family, ANGPTL4 is most closely related to ANGPTL3 protein. Surprisingly, the positional cloning of KK/Snk, an obese and diabetic mouse model with a unique hypotriglyceridemia phenol-type, revealed that ANGPTL3 regulates lipid metabolism in mice (Koishi et al., 2002). Apolipoprotein E knockout-KK/Snk mice developed three-fold smaller atherogenic le-sions in the aortic sinus compared with apolipoprotein E knockout mice, indicating that ANGPTL3 could affect arteriosclerosis (Ando et al., 2003). We, for the first time, demonstrated that the intravenous injection of ANGPTL4 protein in KK/Snk mice rapidly increased the circulating plasma lipid levels (Yoshida et al., 2002). Moreover, ANGPTL4 as well as ANGPTL3 increased the plasma lipid levels by inhibiting the lipoprotein lipase (LPL) acti-vity (Shimizugawa et al., 2002; Yoshida et al., 2002). LPL has a central role in lipoprotein metabolism to maintain normal lipoprotein levels in blood and also in certain tis-sue (Otarod and Goldberg, 2004).

Studies then shifted to the biochemical characterization of ANGPTL4 proteins. Similar to other angiopoietin-like proteins, ANGPTL4 consists of an N-terminal coiled-coil domain and a C-terminal fibrinogen-like domain. The N-terminal coiled-coil domain of ANGPTL4 is sufficient to mediate its oligomerization. Oligomerized ANGPTL4 un-dergoes proteolytic processing to release its carboxyl fibrinogen-like domain (Ge et al., 2004a). Treatment with fenofibrate, a potent PPARalpha agonist, markedly inc-reased the plasma levels of truncated ANGPTL4, but not of full-length ANGPTL4, in humans. Together, these data suggested that the oligomerization and proteolytic pro-cessing of ANGPTL4 may regulate its biological activi-ties *in vivo* (Mandard et al., 2004). Indeed, a loss of oligo-merization decreased the stability of the N-terminal coiled-coil domain of ANGPTL4 and also reduced its abili-ty to increase plasma triglyceride levels (Ge et al., 2004b). The N-terminal coiled-coil domain of ANGPTL4 binds transiently to LPL, and this interaction results in the conversion of the enzyme from catalytically active dimers to inactive monomers (Sukonina et al., 2006).

ANGPTL4 mice model

Using genetically engineered mice, we were able to elucidate the importance of ANGPTL4 in lipid and glucose metabolism *in vivo*. Transgenic mice that overexpress ANGPTL4 exclusively in the heart exhibited a restricted inhibition of cardiac LPL activity and developed left ventric-ular dysfunction (Yu et al., 2005). This outcome was ex-plained by the inhibition of lipoprotein-derived fatty acid delivery as a result of the induction of ANGPTL4 in the heart. In addition, transgenic mice overexpressing ANGPTL4 in the liver displayed elevated plasma trigly-ceride levels. In contrast to the transgenic mice, ANGPTL4- as well as ANGPTL3-deficient mice displayed hypotriglyceridemia; however, we now know that ANGPTL4 and ANGPTL3 function to regulate circulating triglyceride levels during different nutritional states caused by feeding/fasting through the differential inhibit-tion of LPL (Koster et al., 2005; Li, 2006).

Concluding remarks

We have learned much about the nature of ANGPTL4 and have established proof-of-evidence that ANGPTL4 is involved in the regulation of fat, lipid and glucose meta-bolic homeostasis. However, the exact roles of ANGPTL4 in regard to physiology and pathology in humans remain uncertain. Recently, ANGPTL3 has been shown to be associated closely with arterial wall thickness in human subjects (Hatsuda et al., 2007). Genetic association studies, such as assigning single nucleotide polymer-phisms (SNP) in the ANGPTL4 gene and ELISA to moni-tor plasma concentrations of ANGPTL4 protein during changes in nutritional status or the pathogenesis of meta-bolic syndrome, are needed to predict cardiovascular and other disease risk. In patients with type 2 diabetes, serum levels of ANGPTL4 protein were significantly lower than those in healthy subjects (Xu et al. 2005). Recently, sequencing of a large population (n = 3,551) to examine the role of the ANGPTL4 in lipid metabolism revealed that nonsynonymous variants in ANGPTL4 are prevalent in individuals with triglyceride levels (Romea et al., 2007). We suggest that ANGPTL4 is a fasting-induced regulator of LPL especially in adipose tissue. Moreover, ANGPTL4 sits on a unique situation where ANGPTL4 regulates glu-cose metabolism as well as lipid metabolism. From these evidences, ANGPTL4 is now regarded as a promising drug development target.

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