

Angiopoietin-like 4: An endogenous break of intestinal lipid digestion^{*}



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Obesity is characterized by excessive adipose tissue mass and cause for a variety of pathologic conditions like cardiovascular disease, type 2 diabetes and cancer [1]. One important factor in the development of obesity is the overconsumption of high calorie, fat-rich diets. Prior to their uptake, dietary fats mostly composed of mixed triacylglycerols (TAGs) are processed in the digestive tract by extracellular lipases. While small portions of ingested lipids are hydrolyzed by lingual lipase and gastric lipase in the stomach, the vast majority of ingested TAGs are metabolized in the small intestine. There they are emulsified by bile acids and hydrolyzed by the action of pancreatic lipase (PL), co-lipase, PL-related protein 2, and carboxyl ester lipase [1,2]. The resulting free fatty acids (FFA) and monoacylglycerols are subsequently taken up by enterocytes, re-esterified to TAGs, packed into chylomicrons and released into the lymphatic system where they enter the circulation via the thoracic duct. Within the blood stream chylomicrons are transported to peripheral organs like adipose tissue (AT), skeletal muscle and heart, where the lipoprotein-associated TAGs are hydrolyzed again by lipoprotein lipase (LPL) and FFA are absorbed by the underlying tissues. Accordingly, LPL serves as a “gate-keeper” for the uptake of FFA in peripheral tissues. Altered LPL activities or enzyme defects are associated with various forms of hypertriglyceridemias and associated diseases such as cardiovascular disease [1,3].

Various members of the angiopoietin-like (Angptl) protein family inhibit LPL enzyme activity by a post-translational mechanism [4]. The Angptl-protein family consists of eight identified members (Angptl1–8) of which at least Angptl3, Angptl4, and Angptl8 affect LPL activity and plasma TAG concentrations [5,6]. Gene knockout of each of these Angptl-proteins decreases plasma TAG levels whereas the transgenic overexpression of Angptl4 raises plasma TAG concentrations. Angptl3 is predominantly expressed in liver, whereas Angptl4 is expressed in a variety of tissues and cell types, including adipose tissue, liver, heart and macrophages [4,5].

Interestingly, Kersten et al. recently reported that Angptl4 is also expressed and secreted from human entero-endocrine cells into the intestinal tract [7]. This suggested that Angptl4 expression and release might have a dual function in the intestine: It could act as endocrine

hormone to regulate vascular lipoprotein metabolism or it could affect lipid absorption and turnover directly in the gut [7]. In this issue of *Molecular Metabolism* the same group provides strong evidence for a role of Angptl4 in intestinal lipid digestion. Angptl4^{-/-} mice exhibited increased intestinal lipid uptake and decreased fat excretion resulting in increased weight gain and an obese phenotype [8]. These results pointed towards a specific inhibitory role of Angptl4 on lipid hydrolysis by digestive lipases. Indeed, enzymatic assays of fecal water of Angptl4^{-/-} mice demonstrated that PL activity was significantly increased compared to wild-type (WT) controls. Mattijssen et al. [8] also showed that recombinant Angptl4 inhibits PL activity *in vitro* in a dose dependent manner. These findings were also translatable to humans as recombinant Angptl4 inhibited PL activity in human feces samples. Taken together, these results assign a novel role to Angptl4 affecting intestinal lipid catabolism via inhibition of PL [8]. This is exciting but also raises a number of new questions.

For example, it remains unclear how increased intestinal lipid uptake translates into weight gain and obesity observed in Angptl4^{-/-} mice [8]. Despite increased lipid tracer abundance in the intestine of Angptl4^{-/-} mice in lipid tolerance tests, the synthesis and secretion rates of chylomicrons are not different between Angptl4^{-/-} animals and controls. This suggests that obesity results from changes in FFA partitioning rather than increased fat delivery to adipose tissue. It is conceivable that the increased activity of adipose-specific LPL in global Angptl4 knockout mice leads to a more efficient uptake of chylomicron-associated TAG in adipose tissue. Unfortunately, it is currently not known whether adipose-specific overexpression or deletion of Angptl4 affects adipose tissue mass. Alternatively, Angptl4 may affect intracellular lipolysis of fat stores in adipose tissue. Gray et al. showed that Angptl4^{-/-} mice had decreased glycerol release of fat pad explants and decreased plasma FFA levels when fasted [9]. Accordingly, decreased lipolysis in adipocytes lacking Angptl4 may result in enhanced lipid accumulation. Finally, it is conceivable that the obese phenotype in Angptl4^{-/-} mice results from changes in total body energy expenditure by a currently unknown mechanism similarly as previously reported for acyl CoA:monoacylglycerol acyltransferase-2 deficient mice. In this mouse model, increased energy expenditure and

DOI of original article: <http://dx.doi.org/10.1016/j.molmet.2013.11.004>

This commentary refers to “Angptl4 serves as endogenous inhibitor of intestinal lipid digestion, Frits Mattijssen et al.” (10.1016/j.molmet.2013.11.004).

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Received January 13, 2014 • Accepted January 15, 2014 • Available online 21 January 2014

<http://dx.doi.org/10.1016/j.molmet.2014.01.009>

body temperature leads to resistance to diet induced obesity despite the fact that fat resorption in the gut and mucosal chylomicron synthesis are unaltered compared to WT mice [10]. Clarifying which of the mechanisms mentioned above affects the body composition in Angptl4 deficiency will require a detailed characterization of mice overexpressing or lacking Angptl4 in specific tissues.

The present study emphasizes the idea that Angptl4-mediated inhibition of PL may serve as protective mechanism against nutritional lipid overload [8]. The concept is based on the observation that intestinal Angptl4 expression significantly increases when mice were fed a high fat diet. Increasing Angptl4 levels may result in decreased PL activity and via a protective feedback loop prevent lipid overload. A similar role for Angptl4 in the protection from lipotoxicity has been reported for macrophages [11].

Another important aspect relates to the finding that Angptl4 expression in the intestine is regulated by gut microbiota [12–14]. Although the species of microorganisms and the involved mechanisms that regulate Angptl4 levels in the gut are unknown, changes in the gut microbiome during the course of obesity may affect intestinal lipid uptake via Angptl4 expression and PL inhibition.

Future studies should focus on the biochemical mechanisms by which Angptl4 inhibits PL. What is the role of co-lipase? Does Angptl4 also affect the activity of PL-related protein 2? Once these questions are answered, intestinal Angptl4 could serve as a potential pharmacological target to selectively decrease lipid uptake and thereby affect energy balance.

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