Adipose tissue

https://doi.org/10.1038/s41574-026-01234-z

Making a droplet: the adipogenin–seipin complex at work

Daniel Tews & Pamela Fischer-Posovszky

Adipogenin is a microprotein expressed in adipose tissue. Previous studies have suggested its role in lipid storage, yet the underlying molecular mechanisms have been unclear. A recent study published in *Science* presents evidence that adipogenin forms complexes with seipin, a protein that is essential for lipid droplet formation in adipocytes, thereby modulating lipid storage.

Refers to Li, C. et al. Adipogenin promotes the development of lipid droplets by binding a dodecameric seipin complex. *Science* **390**, eadr9755 (2025).

Lipid droplets are defined as small organelles that store neutral lipids such as triglycerides. As such, they have a pivotal role in the storage of energy in eukaryotic cells. Lipid droplets also serve as signalling hubs, integrating lipid metabolism with cellular functions, and are involved in protein quality control, the cellular stress response and immunity. A dysregulation of lipid droplet formation has been associated with a number of pathological conditions[1]. The formation of lipid droplets is complex and involves a cascade of proteins enabling the synthesis, nucleation, cytoplasmic budding and growth of neutral lipids from the endoplasmic reticulum. The multi-pass transmembrane protein seipin has an important role in this process. However, the precise mechanism by which seipin facilitates lipid droplet formation is unclear.

Writing in *Science*, Li et al. identify adipogenin, an 80-amino-acid microprotein, as the binding partner of seipin[2]. Adipogenin serves as a molecular chaperone, facilitating seipin complex assembly, and as a regulator of seipin function. Seipin forms oligomers in the endoplasmic reticulum after translation. The authors identified both a previously known undecameric seipin complex without adipogenin (11:0 seipin–adipogenin stoichiometry)[3] and a dodecameric seipin complex with adipogenin (12:12 stoichiometry when fully saturated with adipogenin). Whereas undecameric and adipogenin-depleted dodecameric complexes seem to drive triacylglycerol nucleation and lipid droplet budding, adipogenin-saturated dodecameric complexes do not seem to be directly involved in these processes. The authors argue that the saturation of dodecameric seipin complexes with adipogenin keeps them in an inactive state, thereby limiting the number of potential lipid droplet formation sites and channelling triacylglycerols present in the cell to active seipin undecamers and adipogenin-depleted dodecamers (Fig. 1). The dynamic release of adipogenin from saturated complexes could establish further lipid droplet formation sites as needed, such as when the cell is challenged with increased amounts of lipids.

We wonder whether free adipogenin, when released from seipin complexes, is stable and present in the cytoplasm under physiological conditions and whether it might fulfil additional functions in the adipocyte. Li et al. show that adipogenin with a Flag protein tag was unstable in the absence of seipin[2], whereas eGFP–adipogenin was detected “near the periphery of the plasma membrane” when overexpressed in mouse 3T3-L1 cells, a common adipose tissue in vitro model[4]. Adipogenin might form homomers or complexes with other proteins when not bound to seipin. In 2016, adipogenin attracted attention when genome-wide association studies suggested a connection between adipogenin and leptin expression in humans[5]. Leptin is predominantly expressed in adipocytes and regulates satiety and energy homeostasis in the hypothalamus. Plasma levels of leptin correlate with adipocyte size, adipose tissue mass and BMI, yet the precise triggers of leptin expression and secretion remain to be elucidated. Adipose explants from adipogenin knockout mice as well as 3T3-L1 cells with a small interfering RNA (siRNA)-mediated knockdown of adipogenin exhibited reduced secretion of leptin compared with control tissue from wild-type mice or with control cells[6]. We wonder whether adipogenin is the missing link between the formation of lipid droplets and leptin production. We propose that in case of ongoing lipid droplet formation, adipogenin is not in complex with seipin and might therefore be available for unknown signalling events that maintain leptin production (Fig. 1). Leptin signals energy sufficiency to the hypothalamus and a substantial decrease in its circulating level can stimulate food intake and curb energy expenditure. When adipogenin is bound to seipin or when adipogenin levels are low for other reasons, leptin levels decrease, leading to orexigenic signalling in the brain. In that scenario, adipogenin would serve as a cellular sensor of lipid storage and communicate the sensed information to the central nervous system via leptin. At this point, this concept is highly speculative and needs to be tested experimentally.

In both mice and humans, the absence or dysfunction of seipin causes a severe form of lipodystrophy characterized by the absence of adipose tissue, which results in hypertriglyceridaemia, liver steatosis and severe insulin resistance[7,8]. This clinical phenotype is referred to as congenital generalized lipodystrophy type 2 (CGL2)[8]. As seipin and adipogenin act in a complex, *ADIG* (the gene encoding adipogenin) might also be considered a candidate gene for lipodystrophy. In mice, adipogenin is expressed in white and brown adipose tissue and upregulated during adipogenesis[2,4]. A siRNA-mediated knockdown of *Adig* resulted in the inhibition of triglyceride accumulation[6]. Of note, the expression of *Pparγ* and other marker genes of mature adipocytes was also reduced, suggesting that adipogenin regulates the process of adipogenesis[6]. In contrast to seipin deficiency, however, mice with a systemic knockout of adipogenin had a similar adipose tissue mass to wild-type mice when on a chow diet[6].

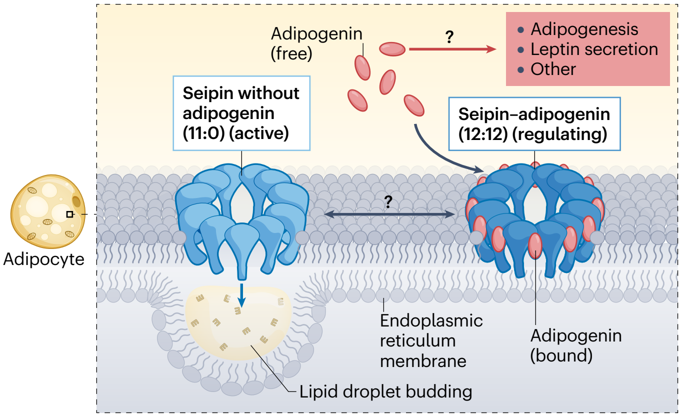

Fig. 1 | Proposed model of adipogenin function. Seipin and adipogenin are assembled to form a stable dodecamer in 12:12 stoichiometry, serving as a progenitor pool of pre-assembled seipin complexes. When needed, adipogenin is released, leading to an 'active', undecameric complex of seipin (11:0 stoichiometry), which initiates lipid droplet formation. Adipogenin-rich complexes might also have a regulatory function, restricting the transport of triacylglycerol to a limited number of active seipin complexes.

Interestingly, the expression of adipogenin was not only enriched in white and brown adipose tissue but also in the testis[2]. This finding raises the question of whether adipogenin has a role in spermatogenesis and, if so, whether this role involves lipid droplets. Spermatozoa have a specific lipid composition, typically containing 70% phospholipids, 25% neutral lipids and 5% glycolipids (for a review see ref. 9). Around a quarter of the sperm proteome is related to lipid metabolism, underlining the central role of lipids in sperm function[9]. An increase in lipid droplet formation was observed in different cell types during spermatogenesis, including in Leydig and Sertoli cells[9]. Whereas Leydig cells provide the cholesterol required for steroidogenesis, Sertoli cells have a role in transferring cholesterol and phospholipids to spermatocytes[9]. The role of adipogenin in spermatogenesis has not been studied so far; however, seipin has been shown to have an important role in male fertility, at least in rodents. Deletion of *Bscl2* (the gene encoding seipin) in germ cells in mice resulted in complete male infertility and teratozoospermia[10]. Notably, ectopic lipid spheres were detected in the sperm of those mice[10]. Male infertility is not a common feature of CGL2, yet reduced sperm count and quality have been reported in a few patients, for example, in a 2014 study[10]. This finding suggests a role for seipin, and therefore potentially also adipogenin, in spermatogenesis.

The most important unanswered question at this moment is whether the findings from Li et al. are relevant to human biology. A sequence comparison of the mouse and human *ADIG* genes revealed a high degree of homology[2], suggesting that adipogenin could fulfil analogous functions in humans. It will now be interesting to study the expression and regulation of *ADIG* in human adipose tissue and testis to evaluate its potential as a therapeutic target in obesity, lipodystrophy or reproductive medicine.

Daniel Tews [1,2,3] **& Pamela Fischer-Posovszky** [2,3] ✉

[1]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, Ulm University Medical Center, Ulm, Germany. [2]Department of Pediatrics and Adolescent Medicine, Ulm University Medical Center, Ulm, Germany. [3]German Center for Child and Adolescent Health (DZKJ), partner site Ulm, Ulm, Germany.
✉e-mail: pamela.fischer@uniklinik-ulm.de

References

1. Zadoorian, A., Du, X. & Yang, H. Lipid droplet biogenesis and functions in health and disease. *Nat. Rev. Endocrinol.* **19**, 443–459 (2023).
2. Li, C. et al. Adipogenin promotes the development of lipid droplets by binding a dodecameric seipin complex. *Science* **390**, eadr9755 (2025).
3. Yan, R. et al. Human SEIPIN binds anionic phospholipids. *Dev. Cell* **47**, 248–256.e4 (2018).
4. Hong, Y.-H. et al. Up-regulation of adipogenin, an adipocyte plasma transmembrane protein, during adipogenesis. *Mol. Cell Biochem.* **276**, 133–141 (2005).
5. Kilpeläinen, T. O. et al. Genome-wide meta-analysis uncovers novel loci influencing circulating leptin levels. *Nat. Commun.* **7**, 10494 (2016).
6. Alvarez-Guaita, A. et al. Phenotypic characterization of *Adig* null mice suggests roles for adipogenin in the regulation of fat mass accrual and leptin secretion. *Cell Rep.* **34**, 108810 (2021).
7. Cui, X. et al. Seipin ablation in mice results in severe generalized lipodystrophy. *Hum. Mol. Genet.* **20**, 3022–3030 (2011).
8. Lightbourne, M. & Brown, R. J. Genetics of lipodystrophy. *Endocrinol. Metab. Clin. North Am.* **46**, 539–554 (2017).
9. Serafini, S. & O'Flaherty, C. Novel insights into the lipid signalling in human spermatozoa. *Hum. Reprod.* **40**, 1440–1451 (2025).
10. Jiang, M. et al. Lack of testicular seipin causes teratozoospermia syndrome in men. *Proc. Natl Acad. Sci. USA* **111**, 7054–7059 (2014).

Acknowledgements

We acknowledge the use of ChatGPT, v.5.1, for wording suggestions during the writing process.

Competing interests

The authors declare no competing interests.