npj | metabolic health and disease

Review

https://doi.org/10.1038/s44324-024-00036-z

Human adipose depots' diverse functions and dysregulations during cardiometabolic disease

Andreas Kraag Ziegler[1] & Camilla Scheele[1,2] ✉

Adipose tissue depots develop specific functions in a location dependent manner. In humans, this for example includes thermogenic capacity in the brown adipose supraclavicular, deep neck and perirenal depots, healthy lipid storage primarily in the gluteofemoral subcutaneous depot, and immunogenic support in the visceral omental depot. These distinct functions are at some point programmed into adipose progenitor cells, which retain some of the phenotype from the depot they originated from upon isolation and differentiation in vitro. Cardiometabolic diseases associate with body fat distribution, with an accumulation of lipids in the visceral depot accompanied by low grade inflammation and insulin resistance as a typical phenotype. However, well-functioning subcutaneous adipose tissue and brown adipose tissue contribute to a metabolically healthy phenotype, and it is therefore worth understanding the function and regulation of these adipocytes. In this review, we will discuss the dysregulations in distinct human adipose tissue depots associated with cardiometabolic disease, some of the consequences this has on whole body metabolism, and how depot-specific dysregulations might affect other adipose depots to progress a cardiometabolic disease condition.

Obesity, with its negative impact on cardiometabolic diseases, is a major and growing global health issue. Understanding underlying mechanisms that could be targeted is therefore important. Fat storage in adipose tissue can during energy excess be expanded to extreme measures, a condition known as obesity. However, less visible is the dysregulation and loss of adipocyte function that accompanies obesity to various extent in an individualized manner. Adipose tissue is commonly divided into white, beige and brown adipose tissue. However, when discussing distinct adipose functions, these terms are incomplete. Adipocytes exist as different subtypes and have specialized functions, which are largely separated by their anatomical organization into adipose depots. Importantly, adipocytes are even found to have distinct functions within depots, displaying a wide heterogeneity at single cell resolution[1]. Analyses of human cohorts, discussed below, suggest that there is a fundamental connection between adipocyte functionality and cardiometabolic health.

Multiple studies have demonstrated that hip to waist ratio or waist circumference is a far more accurate predictor of cardiometabolic disease than body mass index (BMI)[2,3]. Accordingly, abdominal obesity is associated with a reduction in adipogenic capacity (i.e. the capacity to form new adipocytes) in the subcutaneous adipose tissue depot, in primarily the gluteofemoral region[4], and a reciprocally increased lipid storage and increased low grade inflammation in the visceral adipose depot[5,6]. At the same time, cardiometabolic disease is also associated with a loss of thermogenic activity in the supraclavicular and deep neck[7]. Thus, adipose tissue across depots is functionally compromised during cardiometabolic disease.

The explanation for what is causing adipocyte loss of specialization during cardiometabolic disease and whether it is causative or a consequence, remains elusive. Genetic predisposition[8] and genetic interaction with environmental factors including diet, stress, smoking, sleeping patterns and infrastructures discouraging physical activity and generating unhealthy eating patterns, are all contributing to a physiological challenge of excess lipids and glucose that will affect us differently dependent on genetic make-up.

In the current review, we will not discuss genetic and environmental interactions, but instead focus on the differential dysregulations occurring in each of three major adipose tissue depots that have most frequently been studied in relation to cardiometabolic disease (Fig. 1): supraclavicular/ deep neck brown adipose tissue (BAT), omental visceral adipose tissue, and gluteofemoral subcutaneous adipose tissue. We will discuss adipose depot-specific dysregulations and consequences across depots that can contribute to the progression of cardiometabolic disease.

[1]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark. [2]The Novo Nordisk Foundation Center for Genomic Mechanisms of Disease, Broad Institute of MIT and Harvard, Cambridge, MA, 02142, USA. ✉e-mail: cs@sund.ku.dk

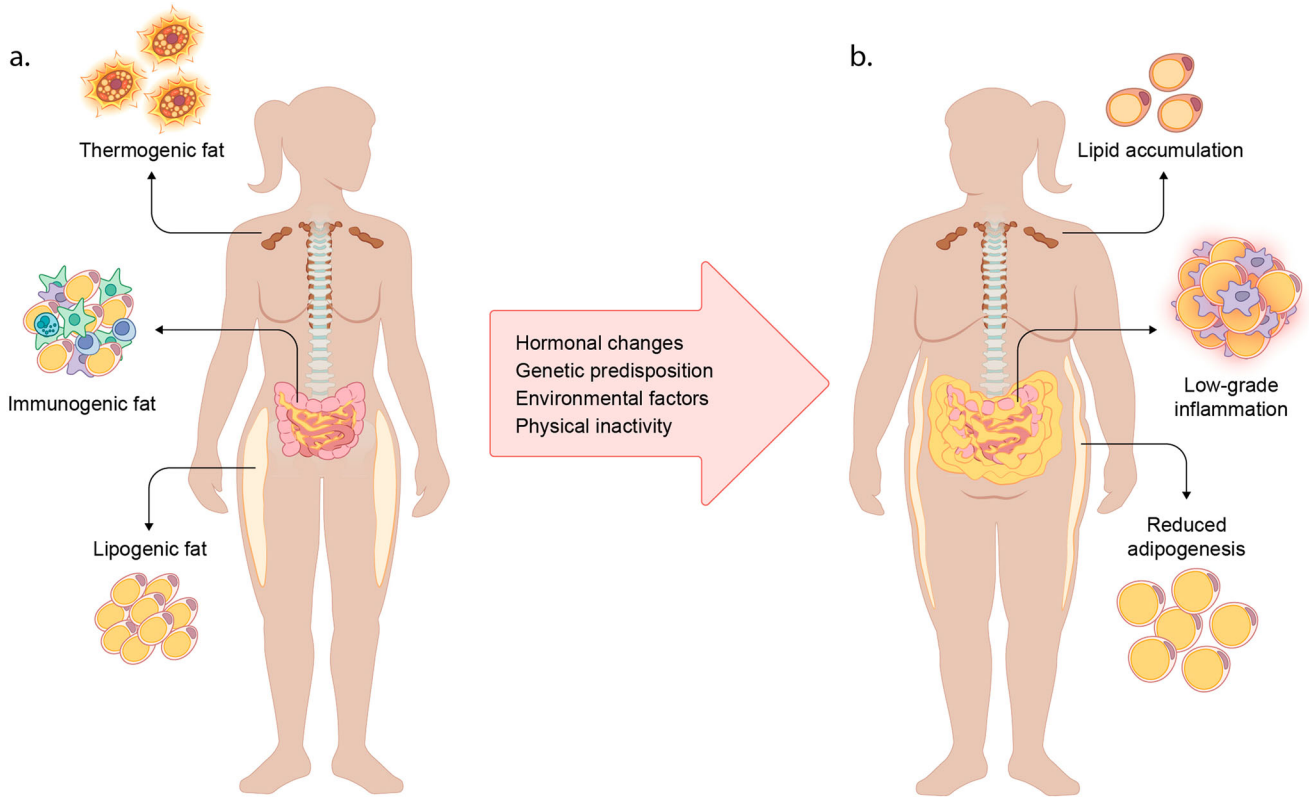

Fig. 1 | Loss of functions of adipose tissues in relation to metabolic dysfunction. In a healthy state (**a**), thermogenic fat (brown adipose tissue) is sympathetically activated in response to cold, producing heat and taking up glucose and fatty acids from the circulation. In the visceral depot, immunogenic fat interacts with the immune system to battle inflammation and infections. Subcutaneous adipose tissue is highly lipogenic and provides safe energy storage. Several factors including hormonal changes, genetic predisposition, environmental factors and physical inactivity, contributes to metabolic dysfunction (**b**). Thermogenic depots lose their capacity of substrate uptake and thermogenesis. Ectopic fat is accumulating in the visceral adipose depot, accompanied by a chronically inflammatory state. Subcutaneous adipocytes reach their maximal capacity of fat storage and adipogenesis is downregulated, diminishing the potential of safe lipid storage and accelerating ectopic fat accumulation.

Dysregulation of thermogenic and immunogenic functions in visceral adipose tissue

Visceral adipose tissue (VAT) is a collection of adipose depots surrounding the inner organs. These include the intraperitoneal depots (omental and mesenteric), which drain into the hepatic portal vein. It also includes the retroperitoneal, which is located behind the abdominal space, in the peritoneal cavity where the perirenal adipose depot is found. Whereas perirenal fat is classified as a brown adipose depot[9] and has been frequently observed as activated along with supraclavicular and deep neck regions[10], omental and mesenteric fat are not thermogenic under normal conditions. Nevertheless, thermogenic adipocytes have been detected at least in the omental fat among other adipocyte subtypes when the tissue has been studied at single cell resolution[11,12]. This aligns well with the observation that the whole visceral compartment can differentiate into highly thermogenic fat during pathological conditions such as pheochromocytoma (tumor leading to overproduction of norepinephrine from the adrenal gland)[13]. As discussed in further detail below, thermogenic adipocytes become dysfunctional during cardiometabolic disease[7].

The omental adipose tissue has immunogenic capacity and interacts with the immune system during abdominal inflammation. Interestingly, adipose progenitors isolated from omental adipose tissue display a more immunogenic transcription profile and commit less to adipogenic differentiation compared to subcutaneous adipocytes[14]. The limited adipogenesis in cells from the omental depot is further emphasized by differentiating adipose progenitors from the visceral depot having a lower proportion of adipogenic cells compared to cells isolated from subcutaneous, supraclavicular and perirenal depots, when analyzed at a single cell level[15]. In vivo, the omental depot is highly vascularized and appears to play an important part in mobilizing the immune defense against pathogens as well as during non-infectious inflammation[16,17]. During these conditions, the omental fat relocates to the affected area and encapsulates it. A dramatic increase in immune cell number has been observed in the omentum attaching to the inflamed and/or infected site[18]. During obesity- induced cardiometabolic disease, an expansion of ectopic fat storage in the visceral depots typically occur[19]. This fat accumulation is associated with a chronic low-grade inflammation[20], hallmarked by increased infiltration and residency of pro-inflammatory immune cells into the adipose tissue. Importantly, inflammatory cytokines including TNF have inhibitory effects on adipogenesis[14], and an inflamed adipose tissue can thus impair healthy adipogenesis and further accelerate ectopic fat storage. Whether this increased ectopic fat storage in turn hampers the capacity of omental adipose tissue to react properly to infection and regulate inflammation remains largely unexplored. In conclusion, human visceral adipose tissue during healthy conditions, encompasses thermogenic and immunogenic capacities, which are both dysregulated during cardiometabolic diseases in favor of lipid storage, inactivate thermogenic capacity, and onset of low-grade inflammation. The reason behind ectopic fat storage in the visceral depots might be related to a dysfunctional subcutaneous adipogenesis, expansion and signaling in response to excess energy intake, which is further discussed below.

Exhaustion of subcutaneous adipose tissue and loss of adipogenic capacity

In humans, subcutaneous fat has no contact with inner organs and has evolved to exhibit an extraordinary capacity of safe energy storing. Fat

accumulation in the gluteofemoral subcutaneous adipose tissue has been identified as particularly healthy and associated with insulin sensitivity[4]. Insulin stimulates lipogenesis and plays an important role in adipogenesis[21]. In accordance, insulin resistance and type 2 diabetes are associated with premature adipose cell senescence along with reduced adipogenesis[22–24]. The reduced adipogenic capacity is in turn associated with increased adipocyte hypertrophy[24], which correlate with elevated plasma insulin levels and reduced insulin sensitivity[25].

Another important regulator of adipogenesis is estrogen which appears crucial for maintenance of the gluteofemoral subcutaneous adipose tissue[26]. In women, estrogen promotes adipogenesis specifically in the gluteofemoral depot due to higher expression of the estrogen receptor in the gluteofemoral adipose progenitor cells[27], while inhibiting fat accumulation in visceral regions[28]. This relationship is emphasized by the body fat redistribution occurring during menopause when estrogen levels decrease[29]. In accordance, women's cardiometabolic health falls drastically following menopause[30].

Additional observations emphasize subcutaneous adipose tissue as a gate keeper of cardiometabolic health. For example, a compensatory increase in visceral fat mass has been observed 6 months after liposuction of subcutaneous adipose tissue[31]. Moreover, patients suffering from lipodystrophy, failing to store fat in subcutaneous depots, exhibit both visceral fat mass expansion and increased cardiometabolic burden[32].

Whereas safe lipid storage is a key function of the subcutaneous adipose tissue, a loss of functional adipocytes is likely also affecting the adipokine signature, which represent a crucial feedback mechanism for regulating food intake, reviewed in detailed elsewhere[33].

In conclusion, preserving functionality and sustained safe storage capacity of free fatty acids in the subcutaneous adipose depot is fundamental for avoiding ectopic fat accumulation in the visceral regions. Individual capacity for expanding subcutaneous adipose tissue before reaching adipose tissue exhaustion and dysregulation is a possible explanation to why obesity is not always leading to cardiometabolic disease.

Loss of thermogenic function in brown adipose tissue during cardiometabolic disease

Humans are among the mammals that still possess the capacity of activating thermogenesis through mitochondrial uncoupling protein 1[34,35]. This occurs via sympathetic activation in response to cold, mainly in adipose tissue in the supraclavicular and deep neck region, along the spinal cord and in the perirenal adipose tissue surrounding the kidneys[10]. When adipose progenitors are isolated from surgical biopsies from these regions, they differentiate into thermogenic brown adipocytes in vitro, regardless of the thermogenic in vivo phenotype[9,36]. However, in vivo this function is gradually declining with age and even more severely and rapidly with cardiometabolic diseases[7]. Thermogenic activity was found to be reduced with obesity, while fat accumulation in brown adipose tissue (BAT) was higher compared to BAT of normal weight subjects[10]. Importantly, in larger cohorts, BAT activity correlates with insulin sensitivity and cardiometabolic health independently of BMI[7]. Whether this correlation represents a functional role of BAT in the maintenance of a healthy metabolism in humans, is currently unclear.

In mice, diet-induced obesity increase BAT inflammation, promotes white adipocyte infiltration, distorts BAT function, and inhibits tissue glucose uptake[37], while BAT transplantation from healthy wild type mice into ob/ob mice improves insulin sensitivity and counteracts hepatic steatosis[38]. In fact, increasing BAT activity in mice directly counteracts obesity. Nevertheless, considering the differences between mice and humans in lipid storage capacity, thermogenic capacity and metabolism, it is difficult to directly translate these observations to humans. Given the smaller proportions of BAT present in humans in comparison to mice, there is likely an alternative explanation to its correlation with cardiometabolic health.

First, the gold standard for measuring BAT activity in humans is through FDG-PET/CT-scanning, measuring the glucose uptake in BAT during cold exposure as an estimate of BAT activation[39]. With an increased lipid accumulation in BAT, it is possible that the glucose uptake is severely reduced. Another potential explanation is altered batokine secretion pattern. Brown and white adipose tissue secrete metabolic regulators[33,40]. Thus, regardless of whether adult humans have enough BAT to significantly affect energy expenditure through cold exposure, BAT might still play a role in regulating metabolic homeostasis in human through organ crosstalk[41,42]. In conclusion, the correlation between reduced BAT activity during cardiometabolic disease, how this relates to the overall dysfunction of other adipose depots, and how it impacts whole body metabolism remains to be explored.

Concluding remarks and perspectives

We here discuss the loss of adipocyte specialization in three major adipose depots in humans and how this relates to the development of cardiometabolic disease. Expansion of the visceral adipose tissue, accelerating low-grade inflammation, is a key driver of insulin resistance. At the same time, losing adipogenic and storage capacity in subcutaneous depots and thermogenic capacity in BAT, will accelerate lipid deposition in the visceral depot. Indeed, emerging reports about futile cycling, reviewed elsewhere[43] demonstrate capacity for energy dissipation in adipose depots other than BAT as well. In addition, loss of adipocyte specialization should be expected to also affect adipocyte subtype secretomes, potentially causing disturbances in whole body energy homeostasis. Future studies should investigate depot-specific regulation of adipocytes in relation to metabolic phenotypes for discovering new pathways and candidates with the ultimate goal of reversing cardiometabolic disease and reinstall adipose tissue as a functional regulator of metabolic homeostasis.

Data availability

No datasets were generated or analysed during the current study.

Received: 23 May 2024; Accepted: 6 October 2024;
Published online: 29 November 2024

References

1. Maniyadath, B., Zhang, Q., Gupta, R. K. & Mandrup, S. Adipose tissue at single-cell resolution. *Cell Metab.* **35**, 386–413 (2023).
2. Czernichow, S., Kengne, A.-P., Stamatakis, E., Hamer, M. & Batty, G. D. Body mass index, waist circumference and waist-hip ratio: which is the better discriminator of cardiovascular disease mortality risk? evidence from an individual-participant meta-analysis of 82 864 participants from nine cohort studies. *Obesity Rev.* **12**, 680–687 (2011).
3. De Koning, L., Merchant, A. T., Pogue, J. & Anand, S. S. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur. Heart J.* **28**, 850–856 (2007).
4. Karpe, F. & Pinnick, K. E. Biology of upper-body and lower-body adipose tissue-link to whole-body phenotypes. *Nat. Rev. Endocrinol.* **11**, 90–100 (2014).
5. Weisberg, S. P. et al. Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* **112**, 1796–1808 (2003).
6. Xu, H. et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* **112**, 1821–1830 (2003).
7. Becher, T. et al. Brown adipose tissue is associated with cardiometabolic health. *Nat. Med.* **27**, 58–65 (2021).
8. Loos, R. J. F. & Yeo, G. S. H. The genetics of obesity: from discovery to biology. *Nat. Rev. Genet.* **23**, 120–133 (2022).

9. Jespersen, N. Z. et al. Heterogeneity in the perirenal region of humans suggests presence of dormant brown adipose tissue that contains brown fat precursor cells. *Mol. Metab.* **24**, 30–43 (2019).
10. Leitner, B. P. et al. Mapping of human brown adipose tissue in lean and obese young men. *Proc. Natl. Acad. Sci. USA* **114**, 6–11 (2017).
11. Scheele, C. & Nielsen, S. Can we target obesity using a single-cell atlas of adipose tissue? *Med (N Y)* **3**, 276–278 (2022).
12. Emont, M. P. et al. A single-cell atlas of human and mouse white adipose tissue. *Nature* **603**, 926–933 (2022).
13. Søndergaard, E. et al. Chronic adrenergic stimulation induces brown adipose tissue differentiation in visceral adipose tissue. *Diabet. Med.* **32**, e4–e8 (2015).
14. Mathur, N. et al. Human visceral and subcutaneous adipose stem and progenitor cells retain depot-specific adipogenic properties during obesity. *Front. Cell Dev. Biol.* **10**, 983899 (2022).
15. Palani, N. P. et al. Adipogenic and SWAT cells separate from a common progenitor in human brown and white adipose depots. *Nat. Metab.* **5**, 996–1013 (2023).
16. Collins, D., Hogan, A. M., O'Shea, D. & Winter, D. C. The omentum: anatomical, metabolic, and surgical aspects. *J. Gastrointest Surg.* **13**, 1138–1146 (2009).
17. Català, C. et al. Innate immune response to peritoneal bacterial infection. *Int. Rev. Cell Mol. Biol.* **371**, 43–61 (2022).
18. Jackson-Jones, L. H. et al. Stromal cells covering omental fat-associated lymphoid clusters trigger formation of neutrophil aggregates to capture peritoneal contaminants. *Immunity* **52**, 700–715.e6 (2020).
19. Lee, M.-J. & Kim, J. The pathophysiology of visceral adipose tissues in cardiometabolic diseases. *Biochem. Pharmacol.* **222**, 116116 (2024).
20. Rohm, T. V., Meier, D. T., Olefsky, J. M. & Donath, M. Y. Inflammation in obesity, diabetes, and related disorders. *Immunity* **55**, 31–55 (2022).
21. Klemm, D. J. et al. Insulin-induced adipocyte differentiation. Activation of CREB rescues adipogenesis from the arrest caused by inhibition of prenylation. *J. Biol. Chem.* **276**, 28430–28435 (2001).
22. Dubois, S. G. et al. Decreased expression of adipogenic genes in obese subjects with type 2 diabetes. *Obesity (Silver Spring)* **14**, 1543–1552 (2006).
23. Li, Q. et al. Obesity and hyperinsulinemia drive adipocytes to activate a cell cycle program and senesce. *Nat. Med.* **27**, 1941–1953 (2021).
24. Gustafson, B., Nerstedt, A. & Smith, U. Reduced subcutaneous adipogenesis in human hypertrophic obesity is linked to senescent precursor cells. *Nat. Commun.* **10**, 2757 (2019).
25. Arner, E. et al. Adipocyte turnover: relevance to human adipose tissue morphology. *Diabetes* **59**, 105–109 (2010).
26. Cox-York, K. A., Erickson, C. B., Pereira, R. I., Bessesen, D. H. & Van Pelt, R. E. Region-specific effects of oestradiol on adipose-derived stem cell differentiation in post-menopausal women. *J. Cell Mol. Med.* **21**, 677–684 (2017).
27. D'Eon, T. M. et al. Estrogen regulation of adiposity and fuel partitioning. Evidence of genomic and non-genomic regulation of lipogenic and oxidative pathways. *J. Biol. Chem.* **280**, 35983–35991 (2005).
28. Lindberg, U. B., Crona, N., Silfverstolpe, G., Björntorp, P. & Rebuffé-Scrive, M. Regional adipose tissue metabolism in postmenopausal women after treatment with exogenous sex steroids. *Horm. Metab. Res.* **22**, 345–351 (1990).
29. Abildgaard, J. et al. Changes in abdominal subcutaneous adipose tissue phenotype following menopause is associated with increased visceral fat mass. *Sci. Rep.* **11**, 14750 (2021).
30. Abildgaard, J. et al. Ectopic lipid deposition is associated with insulin resistance in postmenopausal women. *J. Clin. Endocrinol. Metab.* **103**, 3394–3404 (2018).
31. Benatti, F. et al. Liposuction induces a compensatory increase of visceral fat which is effectively counteracted by physical activity: a randomized trial. *J. Clin. Endocrinol. Metab.* **97**, 2388–2395 (2012).
32. Al-Attar, S. A. et al. Quantitative and qualitative differences in subcutaneous adipose tissue stores across lipodystrophy types shown by magnetic resonance imaging. *BMC Med. Imag.* **7**, 3 (2007).
33. Stern, J. H., Rutkowski, J. M. & Scherer, P. E. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. *Cell Metab.* **23**, 770–784 (2016).
34. Cannon, B. & Nedergaard, J. Brown adipose tissue: function and physiological significance. *Physiol. Rev.* **84**, 277–359 (2004).
35. Gaudry, M. J., Campbell, K. L. & Jastroch, M. Evolution of UCP1. *Handb. Exp. Pharmacol.* **251**, 127–141 (2019).
36. Jespersen, N. Z. et al. A classical brown adipose tissue mrna signature partly overlaps with brite in the supraclavicular region of adult humans. *Cell Metab.* **17**, 798–805 (2013).
37. Roberts-Toler, C., O'Neill, B. T. & Cypess, A. M. Diet-induced obesity causes insulin resistance in mouse brown adipose tissue. *Obesity (Silver Spring)* **23**, 1765–1770 (2015).
38. Liu, X. et al. Brown adipose tissue transplantation reverses obesity in Ob/Ob mice. *Endocrinology* **156**, 2461–2469 (2015).
39. Chen, K. Y. Y. et al. Brown adipose reporting criteria in imaging studies (BARCIST 1.0): recommendations for standardized FDG-PET/CT experiments in humans. *Cell Metab.* **24**, 210–222 (2016).
40. Deshmukh, A. S. et al. Proteomics-based comparative mapping of the secretomes of human brown and white adipocytes reveals EPDR1 as a novel batokine. *Cell Metab.* **30**, 963–975.e7 (2019).
41. Scheele, C. & Wolfrum, C. Brown adipose cross talk in tissue plasticity and human metabolism. *Endocr. Rev.* **41**, 53–65 (2019).
42. Henningsen, J. B. & Scheele, C. Brown adipose tissue: a metabolic regulator in a hypothalamic cross talk? *Annu. Rev. Physiol.* **83**, 279–301 (2021).
43. Sharma, A. K., Khandelwal, R. & Wolfrum, C. Futile cycles: emerging utility from apparent futility. *Cell Metab.* **36**, 1184–1203 (2024).

Acknowledgements

The Novo Nordisk Foundation Center for Basic Metabolic Research is an independent research center at the University of Copenhagen, partially funded by an unrestricted donation from the Novo Nordisk Foundation (Grant Agreement ID: NNF18CC0034900). The Novo Nordisk Foundation Center for Genomic Mechanisms of Disease is supported by a grant from the Novo Nordisk Foundation (NNF21SA0072102) This project has received funding from the European Research Council under the European Union's Horizon 2020 research and innovation program (grant agreement no. 101002725, to C.S.).

Author contributions

A.K.Z. and C.S. wrote the manuscript. Both authors read and approved the manuscript.

Competing interests

The authors declare no competing interests

Additional information

Correspondence and requests for materials should be addressed to Camilla Scheele.