Gremlin 2 could explain the reduced capacity of browning of visceral adipose tissue

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Obesity, which is caused by a significant imbalance between energy intake and expenditure, is considered to be one of the major health problems of the current century, promoting serious metabolic disorders that significantly increase the risk of developing cardiovascular disease, type 2 diabetes, non-alcoholic fatty liver disease and some cancers.[1] Central obesity, possibly by the harmful effects of visceral adiposity, is an important contributor to insulin resistance and obesity-associated metabolic disturbances.[2,3] Currently, bariatric surgery is the only effective therapeutic option to reduce and treat morbid obesity. Considering the risks and side effects of this intervention, other therapeutic approaches are required to treat obesity.[4] The promotion of white to brown transdifferentiation of visceral adipocytes has been recently proposed as a possible effective anti-obesity treatment in humans.[1]

In a recent issue of *EBioMedicine*, Liu et al.[5] described increased levels of circulating Gremlin 2 (Grem2) in association to central obesity and visceral adiposity in three independent cohorts. This relationship was supported in murine experiments, in which Grem2 expression was significantly increased in epididymal (visceral) white adipose tissue (eWAT), and when this fat depot was surgical removed, plasma Grem2 levels were modestly decreased. Interestingly, conditions that stimulate browning of WAT reduced Grem2 expression in eWAT, but not in inguinal WAT or brown adipose tissue. These data indicate that instances of visceral fat mass accretion resulted in increased expression and circulating levels of Grem2, whereas the reduction of visceral fat mass displayed opposite effects. Moreover, this study also demonstrated that Grem2 inhibited the expression of browning-related genes in murine eWAT-derived stromal vascular cells differentiated into beige adipocytes, but it did not display any effects when these cells were differentiated into white adipocytes.

In vivo experiments confirmed the negative effects of Grem2 on browning-related gene expression and adipocyte size in eWAT. Mechanistically, these effects could be mediated through the inhibition of the BMP4/7-BMPR2-SMAD signaling pathway in visceral preadipocytes. These findings might explain, in part, the high resistance to browning of epididymal WAT compared with subcutaneous fat.[6]

The main strengths of this study were the inclusion of *in vitro* and *in vivo* gain-loss functional experiments combined with observational data from three large human cohorts, the assessment of metabolic parameters such as glucose tolerance, and energy expenditure and food intake in metabolic cages in *in vivo* experiments, the measurement of mitochondrial respiration in differentiated beige adipocytes, and the use of various genetic experimental mice models and adipose tissue explants to demonstrate the high Grem2 production in visceral adipose tissue. Nevertheless, the modulation of Grem2 using *Grem2* transgenic or adipose *Grem2* knockout mice did not impact on glucose tolerance, energy expenditure, physical activity, and expression of adipogenic or inflammatory genes in eWAT in this study. A limitation of these experiments was that only normal chow diet was evaluated, while a high-fat diet would be more appropriate to report on the metabolic impact of Grem2 in obesogenic conditions. Additional weaknesses of this study were the absence of longer experiments in *Grem2* transgenic mice and after 10 days-cold room stress to assay the impact on metabolic parameters a few weeks after the cold stimulus, and the lack of functional *in vitro* experiments in human visceral adipocytes to explore the translational impact of Grem2 depletion.

Liu et al. suggest that the depletion of Grem2 may be a new therapeutic target to enhance browning in visceral adipose tissue and prevent weight gain and central obesity-associated metabolic disturbances. However, further experiments in mice and longitudinal studies in humans are required to confirm this suggestion. Long-term experiments in mice with fat *Grem2* gene overexpression or knockdown in obesogenic conditions could shed light on the metabolic impact of Grem2 on weight gain, fat mass accretion, ectopic fat accumulation in liver, glucose

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tolerance or insulin resistance. Otherwise, longitudinal studies in humans could help to understand the clinical relevance of circulating Gremlin 2 on insulin resistance and weight management. It is important to note that even if the positive effect of Grem2 depletion on browning of visceral adipose tissue could be confirmed in humans, recent studies have demonstrated that WAT thermogenesis might have a negligible impact on high-fat diet-induced weight gain prevention.[7,8]

Contributors

JMM-N wrote this commissioned commentary.

Declaration of interests

Author has no conflicts of interest to disclose

References

1 Giordano A, Frontini A, Cinti S. Convertible visceral fat as a therapeutic target to curb obesity. *Nat Rev Drug Discov*. 2016;15(6):405–424.
2 Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature*. 2006;444(7121):881–887.
3 Smith U. Abdominal obesity: a marker of ectopic fat accumulation. *J Clin Investig*. 2015;125(5):1790–1792.
4 Dixon JB, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. *Lancet*. 2012;379(9833):2300–2311.
5 Liu W, Li D, Yang M, et al. GREM2 is associated with human central obesity and inhibits visceral preadipocyte browning. *eBioMedicine*. 2022;78: 103969.
6 Vitali A, Murano I, Zingaretti MC, Frontini A, Ricquier D, Cinti S. The adipose organ of obesity-prone C57BL/6J mice is composed of mixed white and brown adipocytes. *J Lipid Res*. 2012;53(4):619–629.
7 Challa TD, Dapito DH, Kulenkampff E, et al. A genetic model to study the contribution of brown and brite adipocytes to metabolism. *Cell Rep*. 2020;30(10):3424–3433.
8 Mills EL, Harmon C, Jedrychowski MP, et al. Cysteine 253 of UCP1 regulates energy expenditure and sex-dependent adipose tissue inflammation. *Cell Metab*. 2022;34(1):140–157.