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PIK3C3/VPS34 keeps body fats healthy

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ABSTRACT

Adipose tissue, or body fat, plays a critical role in the maintenance of health and the development of metabolic diseases. The pathological expansion of adipose tissue during obesity and the pathological reduction of adipose tissue during lipodystrophy can lead to a similar array of metabolic diseases that include diabetes, but mechanisms remain to be fully defined. In our recent studies, we explored the contribution of the lipid kinase PIK3C3/VPS34 to adipose tissue health and metabolic disease. We found that adipocyte-specific PIK3C3/VPS34 deficiency causes defects in the differentiation, survival and functional properties of adipocytes, resulting in reduced adipose tissue mass, altered blood lipid levels, fatty liver disease, diabetes, and defective body temperature control. These abnormalities mirror those observed in patients with lipodystrophy. These findings identify adipocyte PIK3C3/VPS34 as a potential target for therapeutic intervention in metabolic diseases.

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Adipose tissue, also known as body fat, plays a critical role in storing and releasing energy in the form of lipids. It is predominantly composed of adipocytes and also contains adipocyte precursors, vascular endothelial cells, fibroblasts, and various immune cells. Adipose tissue is found throughout the body and its primary depots are located under the skin (subcutaneous adipose tissue) and between the internal organs (visceral adipose tissue). Adipose tissue also responds to and produces a variety of chemical mediators such as hormones (those produced by adipocytes are called adipokines) and cytokines to communicate with other organ systems and maintain health. During conditions of nutrient excess such as obesity, adipose tissue becomes overabundant, which may precipitate a constellation of disorders such as cardiovascular disease, fatty liver disease, and diabetes. Conversely, in a group of genetic or acquired disorders called lipodystrophy syndromes, the body is unable to produce or maintain fat tissue, which may result in a similar array of metabolic disorders. Thus, although obesity and lipodystrophy are characterized by opposing effects on adipose tissue mass abundance, they are associated with a similar cluster of metabolic diseases. Hence, understanding the molecular mechanisms underlying adipocyte health and dysfunction might be beneficial to the development of therapies for metabolic diseases.

The health of adipocytes is controlled by a variety of cellular processes, including macroautophagy/autophagy. In our recent study [1], we focused on the lipid kinase PIK3C3/VPS34 (phosphatidylinositol 3-kinase catalytic subunit 3), which plays critical roles in canonical autophagy as well as endocytosis and vesicle trafficking. To explore the contribution of PIK3C3/VPS34 to adipocyte health and metabolic disease, we generated and analyzed mice with a conditional knockout (cKO) of their *Pik3c3/Vps34* gene in cells expressing the *Adipoq* (adiponectin, C1Q and collagen domain containing) gene. Young cKO animals consume food and gain weight similarly to their wild-type littermates, but older animals take up more food without gaining more body weight than control animals, possibly due to their increased need for heat generation.

We then explored the distribution of the two main varieties of adipose tissue that can be distinguished by their color: white and brown adipose tissue. In normal mice, white adipose tissue is most abundant, appears in both subcutaneous and visceral locations throughout the body, and plays a primary role in energy storage. Brown adipose tissue is comparatively scarce, is mainly located in the upper back, progressively declines in abundance with age, and plays a primary role in generating heat through a process called non-shivering thermogenesis. As they age, cKO animals progressively lose their white adipose tissue in both subcutaneous and visceral depots and, as a compensatory response, accumulate lipids in the blood and develop a fatty liver. Brown adipose tissue is enlarged in young cKO mice but shows signs of brown-to-white adipose tissue transition, a phenomenon called brown adipose tissue whitening. Furthermore, aging cKO mice display a progressive loss in their brown adipose tissue abundance, similar to their white adipose tissue. Mechanistic studies further identified defects in the differentiation of adipocyte precursors to mature adipocytes (although this is less evident for white than brown adipocytes), reduced adipocyte survival, and impaired adipocyte function with regard to lipid handling, mitochondrial oxygen utilization, cytokine and adipokine production, and release of small RNAs that may participate in interorgan communication.

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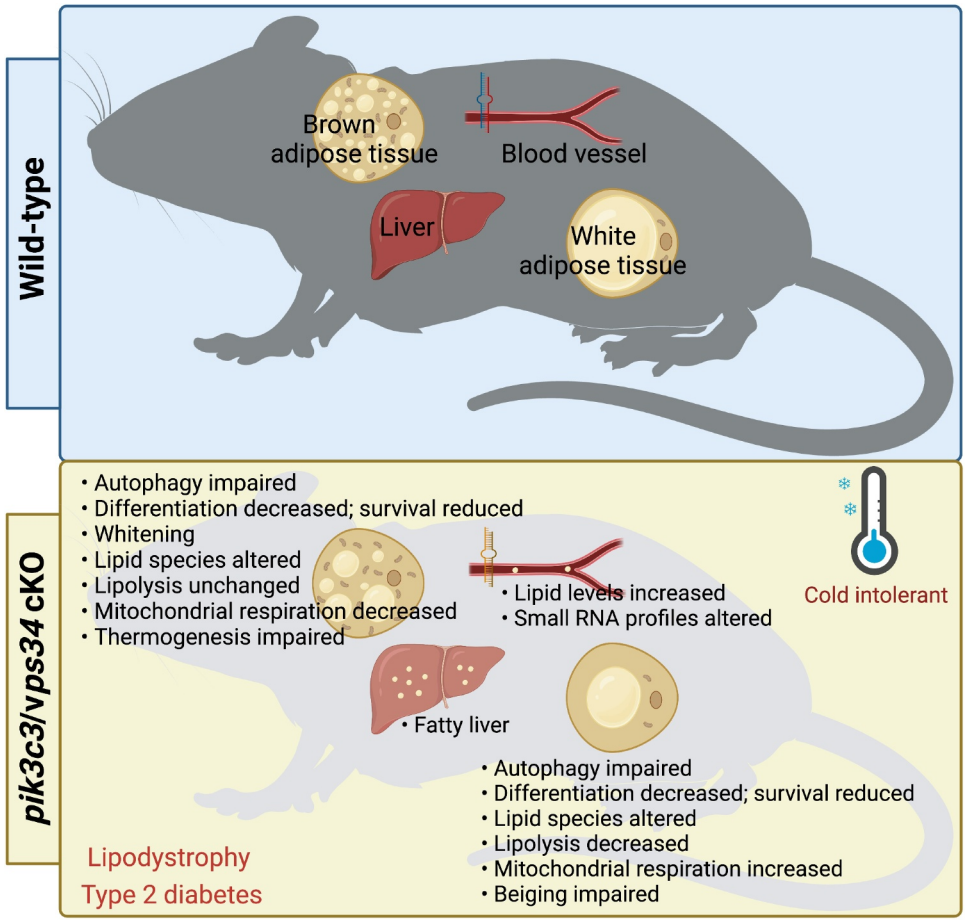

Figure 1. Lipid kinase PIK3C3/VPS34 promotes the health of adipose tissues to protect against metabolic diseases. Wild-type mice are compared with mice containing a conditional knockout (cKO) of their *Pik3c3/Vps34* gene selectively in adipocytes. Alterations observed in white and brown adipose tissues of cKO mice and their systemic consequences on overall health and disease are depicted. This figure was made with Biorender.com.

We next determined the systemic metabolic consequences of impaired adipose tissue health in cKO mice, which revealed impaired responses of tissues to insulin stimulation, called insulin resistance, a hallmark of type 2 diabetes. Surprisingly, however, these animals retain their capacity to respond well to a glucose bolus, indicating glucose responsiveness in the face of insulin resistance. To determine whether this is also the case under conditions of nutrient excess, we fed cKO animals a high-fat diet, of which they consume more than their wild-type littermates while gaining less weight. These animals develop severe fatty liver disease and frank diabetes, while their glucose responsiveness remains substantially spared as compared with their obese wild-type littermates. Although underlying reasons for these divergent effects of PIK3C3/VPS34 deficiency on insulin versus glucose sensitivity remain unclear, we speculate that dysregulated production of secretory factors (such as adipokines, cytokines or small RNAs) might be at play.

When animals are exposed to cold temperatures or adrenergic stimuli, their white adipose tissue generates adipocytes with brown characteristics, called beige adipocytes, which can burn energy and produce heat. This beiging of white adipose tissue in response to adrenergic drugs is impaired in cKO mice. In concert with the observed defects in the generation of brown adipose tissue, these findings prompted us to explore the capacity of cKO mice to maintain their body temperature in response to cold exposure, which revealed a normal thermogenic response. However, when we superimpose food deprivation, a potent autophagy inducer, to these cold conditions, cKO animals fail to maintain their body temperature.

Because the *Pik3c3/Vps34* gene in cKO mice is ablated in adipocytes as soon as they express ADIPOQ, its role in maintaining the health and metabolic functions of mature adipocytes remained unclear. We therefore generated a model where *Pik3c3/Vps34* is inducibly deleted in adipocytes of adult animals, which results in phenotypes similar to those observed for cKO animals.

The abnormalities observed in *pik3c3/vps34* cKO mice are similar to those described for mice with an adipocyte-specific deficiency in other autophagy-related (ATG) factors such as ATG16L1 and BECN1/Beclin 1, but opposite to those observed for mice with an adipocyte-specific deficiency in ATG5 or ATG7. To further explore this apparent discrepancy we analyzed mice with a combined, adipocyte-specific ablation of the *Pik3c3/Vps34* and *Atg7* genes, which largely recapitulated our findings with the cKO animals, indicating dominance of the PIK3C3/VPS34-deficient phenotype. These findings also raised the question as to the relevance of autophagy to the phenotype of cKO animals. We found that PIK3C3/VPS34-deficient adipocytes display defective autophagy, whereas endocytosis is only modestly affected. While

these findings suggest defective autophagy as the primary culprit to explain the phenotype of cKO animals, other PIK3C3/VPS34 functions such as vesicle trafficking may contribute as well.

In conclusion, we found that PIK3C3/VPS34 plays a critical role in maintaining the health of adipose tissues and that adipocyte-specific ablation of its gene in mice causes a complex phenotype mimicking patients with lipodystrophy (Figure 1). These findings also highlight the potential of intervening in metabolic diseases by promoting PIK3C3/VPS34 kinase activity in adipose tissues containing shades of white, brown or beige.

Disclosure statement

L. Van Kaer is a member of the scientific advisory board of Isu Abxis Co., Ltd. (South Korea). The other authors have declared that no conflict of interest exists.

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Reference

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