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Spontaneous hypertension occurs with adipose tissue dysfunction in perilipin-1 null mice☆

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ABSTRACT

Perilipin-1 (Plin1) coats lipid droplets exclusively in adipocytes and regulates two principle functions of adipose tissue, triglyceride storage and hydrolysis, which are disrupted upon Plin1 deficiency. In the present study, we investigated the alterations in systemic metabolites and hormones, vascular function and adipose function in spontaneous hypertensive mice lacking perilipin-1 (Plin1 −/−).

Plin1 −/− mice developed spontaneous hypertension without obvious alterations in systemic metabolites and hormones. Plin1 expressed only in adipose cells but not in vascular cells, so its ablation would have no direct effect in situ on blood vessels. Instead, Plin1 −/− mice showed dysfunctions of perivascular adipose tissue (PVAT), a fat depot that anatomically surrounds systemic arteries and has an anticontractile effect. In Plin1 −/− mice, aortic and mesenteric PVAT were reduced in mass and adipocyte derived relaxing factor secretion, but increased in basal lipolysis, angiotensin II secretion, macrophage infiltration and oxidative stress. Such multiple culprits impaired the anticontractile effect of PVAT to promote vasoconstriction of aortic and mesenteric arteries of Plin1 −/− mice. Furthermore, arterial vessels of Plin1 −/− mice showed increasing angiotensin II receptor type 1, monocyte chemotactic protein-1 and interlukin-6 expression, structural damage of endothelial and smooth muscle cells, along with impaired endothelium-dependent relaxation.

Hypertension in Plin1 −/− mice might occur as a deleterious consequence of PVAT dysfunction. This finding provides the direct evidence that links dysfunctional PVAT to vascular dysfunction and hypertension, particularly in pathophysiological states. This hypertensive mouse model might mimic and explain the hypertension occurring in patients with adipose tissue dysfunction, particularly with Plin1 mutations.

1. Introduction

Perilipin 1 (Plin1) is the founding member of the perilipin family of five lipid-droplet proteins loosely grouped by similarity in the first ~100 amino-terminal residues [1]. The other four members, Plin2 to Plin5, distribute in various types of cells and locate on lipid droplets or in cytosolic compartments, but their functions remain largely unclear. Plin1 is just located at the surface of lipid droplets only in adipose and steroidogenic cells [1–4]. It functions to dually control fat storage and hydrolysis in adipocytes. Native Plin1 may prevent droplet triglycerides from lipase hydrolysis, thereby inhibiting basal lipolysis and enhancing lipid droplet formation. On stimulation of catecholamines, Plin1 is phosphorylated to mediate translocation of hormone-sensitive lipase from the cytosol to lipid droplets, and also indirectly activates adipose triglyceride lipase [1,5], thereby conferring a full lipolysis response. In mice, Plin1 ablation (Plin1 −/−) leads to reduced body fat but increased basal lipolysis close to the maximal lipolysis response to catecholamines in adipocytes [6,7].

Most systemic arteries have significant amounts of perivascular adipose tissue (PVAT) in adventitia. Like other fat depots, PVAT fat primarily functions to store and release glycerol and free fatty acids (FFAs) as fuel and secrete bioactive hormones and adipokines. The close proximity and lack of anatomic barrier allow for crosstalk between PVAT and blood vessels. PVAT releases one or multiple adipocyte-derived relaxing factors (ADRFs) that physiologically induce endothelium-independent vasorelaxation by opening smooth muscle potassium channels [8,9]. Therefore, PVAT has an anticontractile effect; indeed, the presence of intact PVAT in arterial-ring preparations markedly inhibited the contraction response to various vasoconstrictors [8–10]. Substances such as superoxide anion, nitric oxide, methyl palmitate, adiponectin and leptin may mediate the PVAT

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vasorelaxant effect in part [10]. We and others previously suggested that PVAT-released hydrogen sulfide induces vasorelaxation via potassium channels, which might represent a potential candidate or modulator of ADRFs [10–12]. Nevertheless, the chemical nature of ADRFs is still unclear, because ADRF is likely not a singular entity.

Although the anticontractile effect of PVAT is well discussed in states of health, we lack direct evidence that links dysfunctional PVAT to vascular dysfunction and hypertension, particularly in pathophysiological states. We investigated Plin1 −/− mice, which showed vascular dysfunction and hypertension as a deleterious consequence of perivascular adipose dysfunction. This novel hypertensive mouse model may mimic the hypertension occurring in lipodystrophic patients with loss-of-function Plin1 mutation [13].

2. Methods

2.1. Antibodies

Polyclonal antibodies against Plin1 or Plin2 [14] were generous gifts from C. Londos (US National Institutes of Health). Other antibodies were from Abcam or Santa Cruz Biotechnology.

2.2. Animals and blood pressure

The animal study was performed in accordance with the NIH guidelines for the care and use of laboratory animals and approved by the animal care and utilization committee of Peking University Health

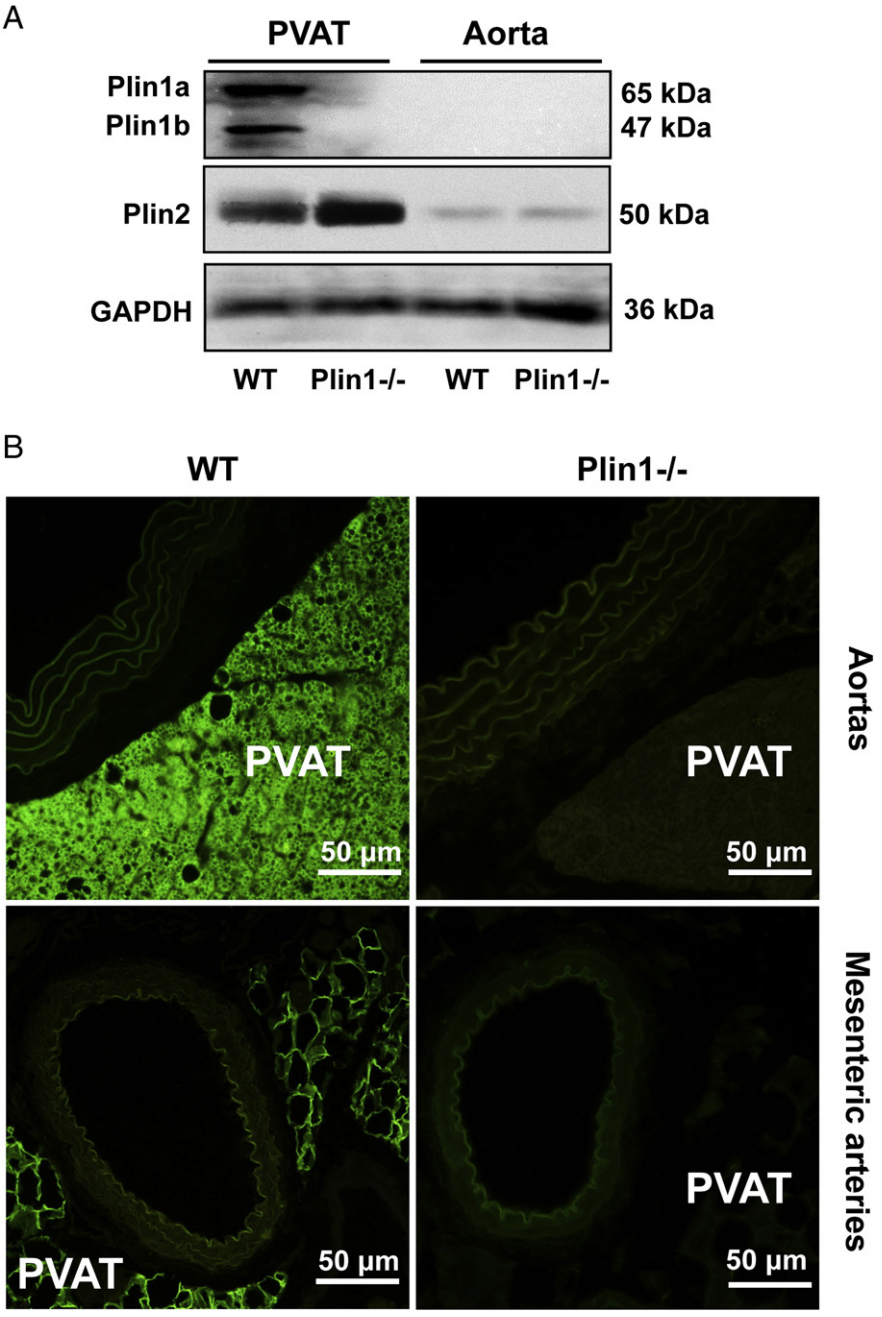

Fig. 1. Perilipin 1 (Plin1) expression in perivascular adipose tissue (PVAT) Aortic and mesenteric PVAT and adjacent arteries were from Plin1 −/− mice and wild-type (WT) littermates at 20 weeks old. Immunoblotting (A) and immunostaining (B) showed Plin1 expression in PVAT but not vascular vessels in wild-type mice.