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Vimentin is required for normal accumulation of body fat

https://doi.org/10.1515/hsz-2019-0170
Received February 25, 2019; accepted April 11, 2019; previously published online April 17, 2019

Abstract: Intermediate filaments (nanofilaments) have many functions, especially in response to cellular stress. Mice lacking vimentin (*Vim*$^{-/-}$) display phenotypes reflecting reduced levels of cell activation and ability to counteract stress, for example, decreased reactivity of astrocytes after neurotrauma, decreased migration of astrocytes and fibroblasts, attenuated inflammation and fibrosis in lung injury, delayed wound healing, impaired vascular adaptation to nephrectomy, impaired transendothelial migration of lymphocytes and attenuated atherosclerosis. To address the role of vimentin in fat accumulation, we assessed the body weight and fat by dual-energy X-ray absorptiometry (DEXA) in *Vim*$^{-/-}$ and matched wildtype (WT) mice. While the weight of 1.5-month-old *Vim*$^{-/-}$ and WT mice was comparable, *Vim*$^{-/-}$ mice showed decreased body weight at 3.5, 5.5 and 8.5 months (males by 19–22%, females by 18–29%). At 8.5 months, *Vim*$^{-/-}$ males and females had less body fat compared to WT mice (a decrease by 24%, $p < 0.05$, and 33%, $p < 0.0001$, respectively). The body mass index in 8.5 months old *Vim*$^{-/-}$ mice was lower in males (6.8 vs. 7.8, $p < 0.005$) and females (6.0 vs. 7.7, $p < 0.0001$) despite the slightly lower body length of *Vim*$^{-/-}$ mice. Increased mortality was observed in adult *Vim*$^{-/-}$ males. We conclude that vimentin is required for the normal accumulation of body fat.

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Keywords: body mass index; body weight; cellular stress; intermediate filaments; nanofilaments; stress proteins.

Introduction

The composition of cytoplasmic intermediate filaments (known also as nanofilaments), which consist of intermediate filament proteins, shows remarkable developmental and cell-type specificity, moreover, within a given cell type, an activation stage specificity is often reflected in the composition of intermediate filaments and appears in various pathophysiological situations, in particular those connected with cellular stress (Pekny and Lane, 2007; Toivola et al., 2010).

Vimentin is an intermediate filament protein expressed in a number of cell types of mesodermal and ectodermal origin. Mice lacking vimentin (*Vim*$^{-/-}$) survive into adulthood (Colucci-Guyon et al., 1994) and display a remarkable range of phenotypes, many of which reflect reduced levels of cell activation and reduced ability to counteract stress. Interestingly, depending on the context, these cell activation-modulating phenotypes can have either negative or positive effects, and they have been guiding our molecular and cellular understanding of the function of cytoplasmic intermediate filaments.

Vimentin is one of the main intermediate filament proteins in astrocytes, cells that control many functions of the central nervous system (CNS) in health and disease (Pekny and Pekna, 2014; Pekny et al., 2016, 2018), and *Vim*$^{-/-}$ mice show decreased reactivity of astrocytes after neurotrauma (Wilhelmsson et al., 2004), *Vim*$^{-/-}$ astrocytes exhibit decreased migratory speed (Lepekhin et al., 2001), and when on a *GFAP*$^{-/-}$ background [and hence having astrocytes completely devoid of cytoplasmic intermediate filaments (Eliasson et al., 1999; Pekny et al., 1999)], the *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice show slower wound healing after brain or spinal cord trauma (Pekny et al., 1999; Wilhelmsson et al., 2004), lower resistance of the CNS to mechanical stress (Lundkvist et al., 2004; Verardo et al., 2008), ischemic damage (Ding et al., 1998; Li et al., 2008; de Pablo et al., 2013; Wunderlich et al., 2015), or altered

astrocyte response to neurodegeneration and facilitated progression of Alzheimer's or Batten disease (Macauley et al., 2011; Kraft et al., 2013; Kamphuis et al., 2015). On the other hand, the absence of cytoplasmic intermediate filaments in astrocytes in *GFAP*$^{-/-}$*Vim*$^{-/-}$ mice results in increased basal (Larsson et al., 2004; Wilhelmsson et al., 2012), post-ischemic (Jarlestedt et al., 2010) and post-traumatic (Wilhelmsson et al., 2012) neurogenesis, leads to improved axonal and synaptic regeneration after neurotrauma (Menet et al., 2003; Wilhelmsson et al., 2004; Cho et al., 2005), and reduces the graft-induced reactive gliosis and improves the outcome of neural grafts and neural stem cell transplantations (Kinouchi et al., 2003; Widestrand et al., 2007).

Vimentin is expressed in many cells outside the CNS and vimentin ablation in mice leads to several revealing phenotypes. *Vim*$^{-/-}$ mice showed impaired transendothelial migration of lymphocytes (Nieminen et al., 2006) and delayed angiogenesis during embryonic development (Antfolk et al., 2017). *Vim*$^{-/-}$ fibroblasts show decreased stiffness, cell resilience and migratory capacity, which results in a slower migration into the wound site and delayed wound healing in *Vim*$^{-/-}$ embryos (Eckes et al., 1998, 2000). It was proposed that vimentin affects the wound healing and re-epithelialization via TGF-β1-Slug signaling that controls fibroblast proliferation and keratinocyte differentiation (Cheng et al., 2016).

The interesting findings of attenuated inflammation, fibrosis and improved survival in response to acute lung injury in *Vim*$^{-/-}$ mice (dos Santos et al., 2015) suggest that a reduced level of cell activation and reactivity as a consequence of vimentin absence may in certain contexts be advantageous and help to identify maladaptive cell activation responses in specific diseases. Another mechanism seems to increase the resistance of *Vim*$^{-/-}$ mice to bacterial infection: increased production of reactive oxygen species and nitric oxide by *Vim*$^{-/-}$ phagocytes leads to more efficient bacterial killing and better control of *Escherichia coli* peritonitis and to decreased extravasation of intestinal bacteria in dextran sodium sulfate-induced colitis (Mor-Vaknin et al., 2013).

Vim$^{-/-}$ mice exhibit impaired vascular adaptation to partial nephrectomy, which is normally followed by immediate and sustained vasodilation of the renal vascular system allowing survival of wildtype (WT) mice but results in a renal failure and death in *Vim*$^{-/-}$ mice (Terzi et al., 1997). This lethality was rescued by the administration of endothelin receptor antagonist implying that vimentin modulates vascular tone, possibly via the endothelin-nitric oxide axis (Terzi et al., 1997; Mor-Vaknin et al., 2013).

Vimentin in adipocytes forms a scaffold around lipid droplets (Franke et al., 1987; Heid et al., 2014). We recently demonstrated that vimentin deficiency confers partial resistance to atherosclerosis (Haversen et al., 2018) induced either by transplantation of *Vim*$^{-/-}$ bone marrow to lethally irradiated mice deficient for low-density lipoprotein receptor or by infecting *Vim*$^{-/-}$ mice with the PCSK9 virus (Bjorklund et al., 2014), in both cases also fed an atherogenic diet. *Vim*$^{-/-}$ macrophages showed increased expression of markers of oxidative stress and higher secretion of proinflammatory cytokines despite decreased subendothelial accumulation of lipids in the aortic wall (Haversen et al., 2018). Prompted by these findings and by the fact that vimentin was shown to affect lipolysis (Shen et al., 2010) and that vimentin absence resulted in smaller adipocytes (Shen et al., 2010) and lipid droplets (Shen et al., 2012), here we compared the body weight and the amount of body fat tissue between *Vim*$^{-/-}$ and WT mice kept on a standard diet. We report that as they age, *Vim*$^{-/-}$ mice put on progressively less body weight compared to their WT controls and that this difference is largely due to a lower accumulation of body fat.

Results

Adult *Vim*$^{-/-}$ mice kept on a standard diet exhibit lower body weight and *Vim*$^{-/-}$ males have increased mortality

We followed the body weight over time in *Vim*$^{-/-}$ and WT mice, kept on a standard diet, both males and females (mixed C57BL/6-129Sv-129Ola genetic background), starting at the age of 45 days (Figure 1A and B). While at 45 days of age the body weight of *Vim*$^{-/-}$ and WT mice did not differ, at 3.5, 5.5 and 8.5 months of age, both *Vim*$^{-/-}$ males and females had lower body weight compared to WT controls. In a separate experimental cohort, we investigated mice on a pure C57BL/6 genetic background, and we also detected reduced body weight of *Vim*$^{-/-}$ compared to WT mice (Figure 1C). Interestingly, we observed an increased mortality in *Vim*$^{-/-}$ males (Figure 1D). At 8.5 months of age, 38% of the initial group of *Vim*$^{-/-}$ males (six out of 16) had died, compared to 7% of the WT males (one out of 15). There were no deaths in the female groups (Figure 1D). Thus, the *Vim*$^{-/-}$ mice exhibit reduced age-related increase in body weight and *Vim*$^{-/-}$ males show increased mortality.

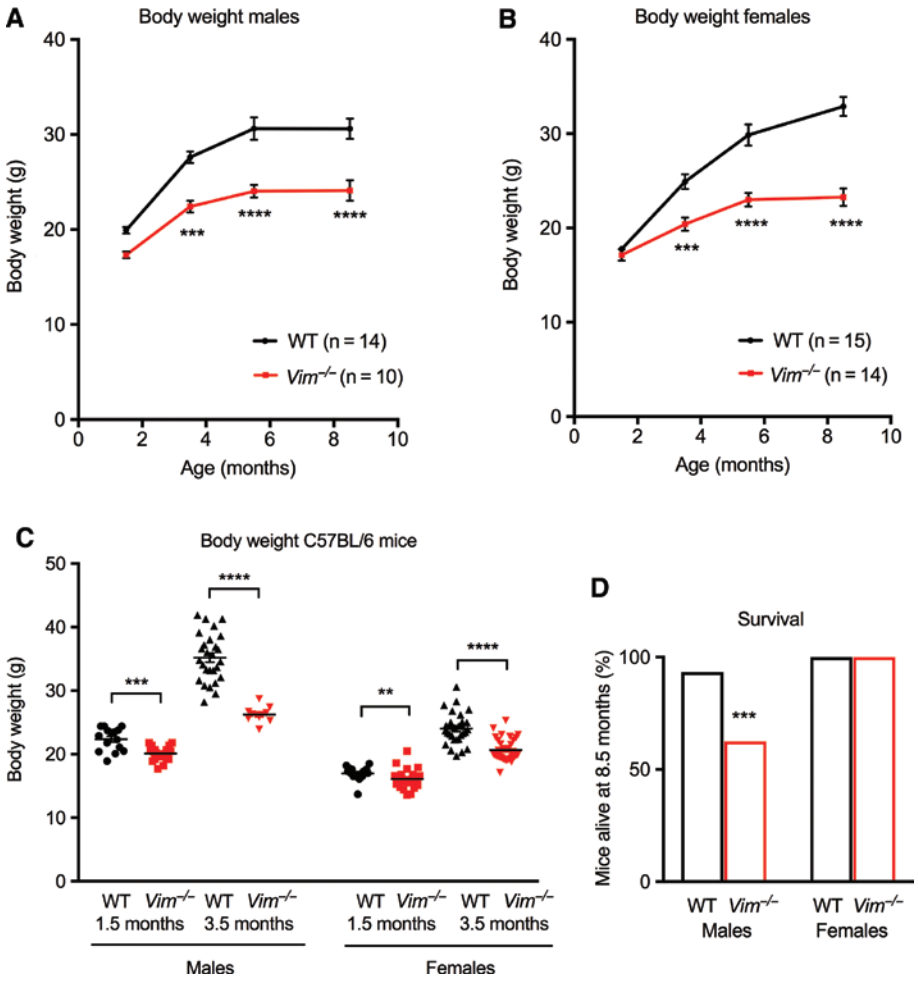

Figure 1: The body weight of *Vim*$^{-/-}$ mice is lower than of wildtype (WT) mice.
The growth curves of male (A) and female (B) mice showed decreased body weight of *Vim*$^{-/-}$ compared to WT mice from the age of 3.5 months and onwards, when on mixed genetic background (C57BL/6-129Sv-129Ola). The difference in body weight between *Vim*$^{-/-}$ and WT mice was present also in males and females on pure C57BL/6 genetic background (C, n = 11–36 mice per group). The mortality of *Vim*$^{-/-}$ males up to the age of 8.5 months was increased compared to WT males (D; n = 15 and 16 for WT and *Vim*$^{-/-}$ males, respectively, n = 15 and 14 for WT and *Vim*$^{-/-}$ females, respectively). $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$ by two-way ANOVA repeated measures followed by Sidak's post hoc test (A and B), by two-tailed Mann-Whitney test (C), and by binominal χ^2 test (D). Means ± SEM and exact *p*-values for data in A–D are presented in Table S1 in the online supplementary material.

Vim$^{-/-}$ mice kept on a standard diet accumulate less fat

To address a possible connection between the reduced body weight of *Vim*$^{-/-}$ mice and fat accumulation, we used dual-energy X-ray absorptiometry (DEXA) to determine the amount of body fat as well as the body length in 8.5-month-old mice on a mixed C57BL/6-129Sv-129Ola genetic background. Both male and female *Vim*$^{-/-}$ mice had a shorter body length compared to WT (Figure 2A). The calculated body mass index (BMI), that relates body weight to body length, also showed lower values for both *Vim*$^{-/-}$ males and females (Figure 2B). DEXA imaging revealed a clear reduction of fat tissue in both *Vim*$^{-/-}$ males and females compared to WT controls (Figure 2C). These data show that the *Vim*$^{-/-}$ mice are leaner because they accumulate less fat tissue than WT mice.

Discussion

Here, we report that *Vim*$^{-/-}$ mice have lower body weight and show decreased accumulation of body fat compared to WT mice. Although *Vim*$^{-/-}$ mice have been extensively studied for the last 25 years, this important phenotype has not yet been reported. One reason might be that the difference in

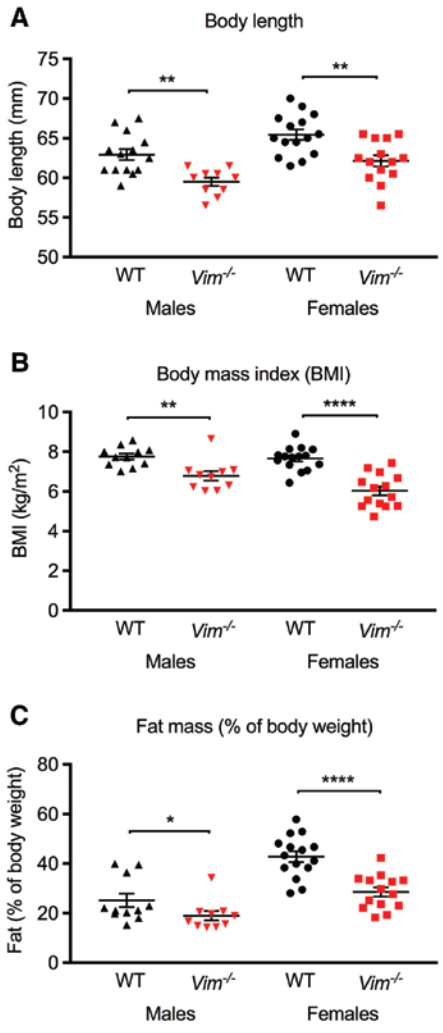

Figure 2: *Vim*$^{-/-}$ mice show shorter body length, lower BMI and reduced amount of body fat compared to wildtype (WT) mice. Eight and half-month-old *Vim*$^{-/-}$ mice on mixed genetic background (C57BL/6-129Sv-129Ola) showed shorter body length compared to WT mice (A), as well as lower BMI (B). DEXA analysis of fat tissue content showed reduced fat accumulation in *Vim*$^{-/-}$ compared to WT mice (C). n = 10–15 mice per group (A–C); *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$ by two-tailed Mann-Whitney test (A–C). Means ± SEM and exact *p*-values for data in A–C are presented in Table S1 in the online supplementary material.

body weight and accumulation of body fat is not present in young adult mice and only appears at the age when the rate of fat accumulation normally increases. Also, this phenotype might depend on the amount and composition of food. Indeed, we recently demonstrated that 4-month-old *Vim*$^{-/-}$ and WT mice in which atherosclerosis was induced by a combination of infection with PCSK9 virus and atherogenic diet had comparable body weight (Haversen et al., 2018).

Vimentin is the only intermediate filament protein expressed in preadipocytes and based on its association with lipid globules, vimentin was proposed to play a role in adipogenesis (Franke et al., 1987). The findings that *Vim*$^{-/-}$ adipocytes (Shen et al., 2010) and lipid droplets in the *Vim*$^{-/-}$ adrenals are smaller (Shen et al., 2012), provide further support to the contention that vimentin participates in adipogenesis through lipid droplet formation or homeostasis. Our observation of lower body weight and reduced body fat accumulation with age are fully in line with such a conclusion.

Energy from the fat tissue is utilized via lipolysis, a process controlled mainly by the sympathetic nervous system and insulin, and hormone-sensitive lipase is the main enzyme responsible for the mobilization of free fatty acids from fat tissue and facilitates the transfer of cholesterol to mitochondria (Shen et al., 2003). Vimentin was shown to interact with hormone-sensitive lipase in a hormonally-dependent manner and facilitate lipolysis (Shen et al., 2010). *Vim*$^{-/-}$ mice show decreased movement of cholesterol to mitochondria in adrenals and ovaries, resulting in the decreased production of corticosterone and progesterone (Shen et al., 2012). Vimentin was also shown to be an interacting partner of stimulated β3-adrenergic receptors, important for ERK activation and stimulation of lipolysis (Kumar et al., 2007). These data point to the importance of vimentin in the mobilization of cholesterol from lipid droplets in the cytoplasm to mitochondria for steroidogenesis and for maintaining lipid droplet homeostasis in general (Shen et al., 2012). Thus, the role of vimentin in lipid homeostasis is likely complex and warrants further investigation.

Another finding in this study is the increased mortality detected among adult *Vim*$^{-/-}$ males but not females. Interestingly, *Vim*$^{-/-}$ mice were reported to have decreased production of corticosterone, which in rodents is the main glucocorticoid involved in the regulation of energy, immune reactions and stress responses (Shen et al., 2012), so this apparent sudden death affecting some adult or aging *Vim*$^{-/-}$ males might reflect an increased sensitivity of the male sex to a particular stress that remains to be identified.

In conclusion, we show that compared to WT, *Vim*$^{-/-}$ adult mice put on less body weight and accumulate less body fat, and *Vim*$^{-/-}$ males show increased mortality throughout adult life.

Materials and methods

Mice

Vim$^{-/-}$ and WT mice were on a C57BL/6-129Sv-129Ola mixed genetic background. A single colony of mice was used for all the experiments,

vimentin heterozygotes were used for backcrosses, and the experimental groups were generated from littermates or within the next generation. Additional groups of *Vim*$^{-/-}$ and WT mice on a pure C57BL/6 genetic background were also used for assessments of body weight as presented in Figure 1C. Genotypes were determined by polymerase chain reaction (PCR) as described (Colucci-Guyon, 1994). Mice were housed in the barrier facility of the University of Gothenburg and held on a standard chow diet with free access to water. Experiments were performed according to guidelines approved by Gothenburg Ethics Committee.

Growth assessment and body composition analysis

The body weight of the mice was repeatedly determined at 1.5, 3.5, 5.5 and 8.5 months of age (with the precision of ±0.05 g). At 8.5 months of age, the mice were anesthetized using isoflurane (Baxter, Deerfield, IL, USA) and the total body fat content as well as the body length were assessed by scanning by DEXA using Lunar PIXImus (GE Lunar Corp., Chicago, IL, USA). BMI was calculated as kilograms of body weight per (meter body length)^2.

Statistical analysis

Prism 7.0 (GraphPad Software, San Diego, CA, USA) was used for statistical analyses of the data. The data are presented as a mean ± standard error of the mean (SEM). After testing for normality, the data were analyzed by two-way analysis of variance (ANOVA) repeated measures followed by Sidak's post-hoc test, two-tailed Mann-Whitney test or binominal chi-square (χ^2) test as indicated in the figure legends. Data are presented graphically in Figures 1 and 2, and in Table S1 in the online Supplementary material. Differences were regarded statistically significant at $p < 0.05$.

Acknowledgments: The authors wish to thank Dr. Marcela Pekna for her comments on the manuscript. This work was supported by Swedish Medical Research Council (2017-02255), ALF Gothenburg (146051), AFA Research Foundation, Söderbergs Foundations, Sten A. Olsson Foundation for Research and Culture, Hjärnfonden, Hagströmer's Foundation Millennium, Amlöv's Foundation, E. Jacobson's Donation Fund, VINNOVA, the Swedish Stroke Foundation, NanoNet COST Action (BM1002), EuroCellNet COST Action, EU FP 7 Program EduGlia (237956), and EU FP 7 Program TargetBraIn (279017).

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/hsz-2019-0170).