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BRIEF CUTTING EDGE REPORT

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Fas (CD95) expression in adipocytes contributes to diet-induced obesity

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Abstract

Objective: Induction of browning in white adipose tissue (WAT) increases energy expenditure and may be an attractive target for the treatment of obesity. Since activation of Fas (CD95) induces pathways known to blunt expression of uncoupling protein 1 (UCP1), we hypothesized that Fas expression in adipocytes inhibits WAT browning and thus contributes to the development of obesity.

Methods: Adipocyte-specific Fas knockout ($Fas^{\Delta adipo}$) and control littermate ($Fas^{F/F}$) mice were fed a regular chow diet or a high-fat diet (HFD) for 20 weeks. Energy expenditure was assessed by indirect calorimetry, and browning was determined in subcutaneous WAT. In vitro, UCP1 was analyzed in subcutaneous murine adipocytes treated with or without Fas ligand. Moreover, *FAS* expression in WAT was correlated to *UCP1* and percentage of body fat in human individuals.

Results: HFD-fed $Fas^{\Delta adipo}$ mice displayed reduced body weight gain and blunted adiposity compared to control littermates. Concomitantly, whole-body energy

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expenditure and WAT browning were elevated. In cultured adipocytes, Fas ligand treatment blunted isoproterenol-induced UCP1 protein levels. In support of these findings in rodents, *FAS* expression in WAT correlated negatively with *UCP1* but positively with adiposity in human individuals.

Conclusions: Fas activation in adipocytes contributes to HFD-associated adiposity in rodents and may be a therapeutic target to reduce obesity and associated diseases.

INTRODUCTION

The activation of brown adipose tissue (BAT) and/or induction of white adipose tissue (WAT) browning may be attractive strategies to combat obesity and associated diseases [1–3]. The latter is characterized by increased expression of uncoupling protein 1 (UCP1), leading to energy dissipation via heat production [4]. In obesity, WAT browning may be suppressed by inflammatory cytokines. Of note, we previously found that activation of the tumor necrosis factor receptor superfamily member Fas (CD95 antigen) induces the latter [5], suggesting that Fas activation may negatively affect WAT browning. This finding is in line with the notion that Fas activation plays an important role not only in programmed cell death (apoptosis) but also in the induction of nonapoptotic signaling cascades such as inflammatory pathways [6, 7].

Since obesity is associated with elevated Fas expression in white adipocytes [5, 8], we hypothesized that Fas activation in adipocytes inhibits WAT browning and thus contributes to the development of obesity. To this end, experiments in high-fat diet (HFD)-fed adipocyte-specific Fas knockout ($Fas^{\Delta adipo}$) mice were performed. Moreover, we aimed to translate our findings in rodents to humans using WAT from individuals with or without obesity.

Study Importance

What is already known?

- Increasing browning of white adipose tissue (WAT) may be an attractive strategy to combat obesity and associated diseases.
- Activation of Fas (CD95) in adipocytes induces pathways that may reduce uncoupling protein 1 (UCP1) levels.

What does this study add?

- High-fat diet-fed adipocyte-specific Fas knockout mice displayed increased browning of WAT associated with reduced high-fat diet-induced adiposity and weight gain.
- In human WAT, *FAS* expression correlated negatively with the browning marker *UCP1* but positively with percentage body fat.

How might these results impact the direction of research or the focus of clinical practice?

- Blocking Fas activation in adipocytes may be a potential strategy to reduce obesity and associated diseases.

METHODS

Humans

In a cross-sectional study of 302 individuals (205 women, 97 men; body mass index [BMI] range: 16.9–85.5 kg/m^2; age range: 16–90 years), we investigated *FAS* and *UCP1* mRNA expression in subcutaneous and visceral WAT samples collected during elective laparoscopic abdominal surgery as described previously [9]. The study was approved by the Ethics Committee of the University of Leipzig (approval no: 159-12-21052012) and performed in accordance with the Declaration of Helsinki.

Animals

To obtain adipocyte-specific Fas depletion ($Fas^{\Delta adipo}$), mice with floxed exon IX of Fas [5, 10, 11] were crossed to mice expressing Cre under the adiponectin promoter (AdipoqCre). All protocols conformed to the Swiss animal protection laws and were approved by the Cantonal Veterinary Office in Zurich, Switzerland (ZH111/2021).

RESULTS

Reduced body weight gain and adiposity in HFD-fed $Fas^{\Delta adipo}$ mice

To investigate whether Fas expression in adipocytes affects body weight gain, male adipocyte-specific Fas knockout ($Fas^{\Delta adipo}$) and floxed control littermate ($Fas^{F/F}$) mice were fed a regular chow diet or HFD for 20 weeks. As intended, Fas protein levels were markedly reduced in isolated white adipocytes but not in other tissues of $Fas^{\Delta adipo}$ mice compared to control littermates (Figure 1A; Figure S1A).

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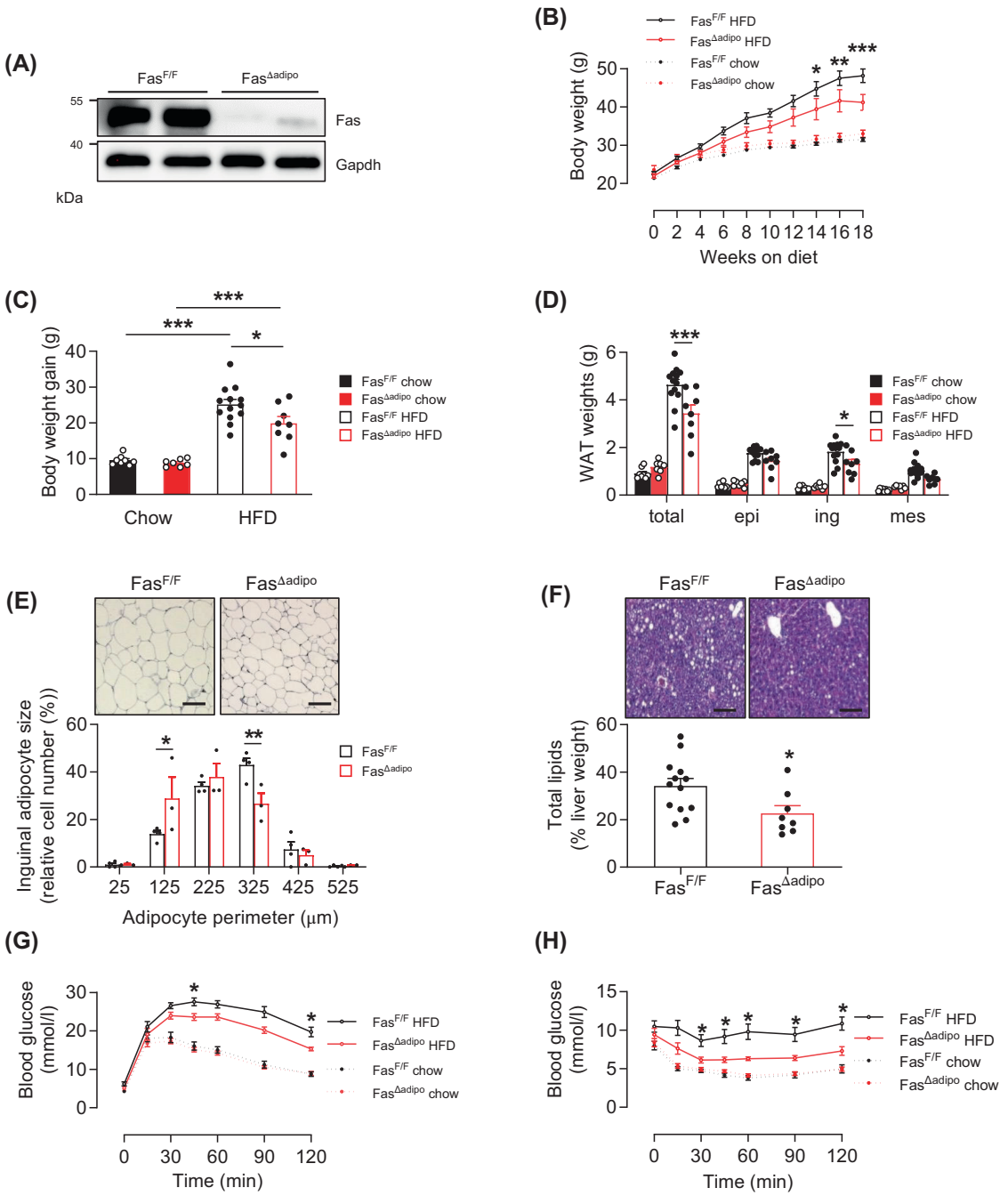

FIGURE 1 Reduced body weight gain and adiposity in high-fat diet (HFD)-fed Fas$^{\Delta adipo}$ mice. (A) Protein levels of Fas in isolated adipocytes harvested from HFD-fed Fas$^{F/F}$ and Fas$^{\Delta adipo}$ mice. (B) Body weight course in mice fed a chow diet (Fas$^{F/F}$, $n = 8$ mice; Fas$^{\Delta adipo}$, $n = 7$ mice) or HFD (Fas$^{F/F}$, $n = 13$ mice; Fas$^{\Delta adipo}$, $n = 8$ mice) for 20 weeks. (C) Body weight gain in mice fed a chow diet (Fas$^{F/F}$, $n = 8$ mice; Fas$^{\Delta adipo}$, $n = 7$ mice) or HFD (Fas$^{F/F}$, $n = 13$ mice; Fas$^{\Delta adipo}$, $n = 8$ mice) for 20 weeks. (D) Total as well as epididymal (epi), inguinal (ing), and mesenteric (mes) WAT fat pad mass (chow-fed: Fas$^{F/F}$, $n = 8$ mice; Fas$^{\Delta adipo}$, $n = 7$ mice; HFD-fed: Fas$^{F/F}$, $n = 13$ mice; Fas$^{\Delta adipo}$, $n = 8$ mice) in mice at 26 weeks of age. (E) Representative hematoxylin and eosin–stained sections and quantification of adipocyte size in inguinal WAT harvested from HFD-fed Fas$^{F/F}$ ($n = 4$) and Fas$^{\Delta adipo}$ ($n = 3$) mice. Scale bar represents 100 μM. (F) Representative hematoxylin and eosin–stained histological liver sections and total liver lipid levels in HFD-fed mice (Fas$^{F/F}$, $n = 13$ mice; Fas$^{\Delta adipo}$, $n = 8$ mice). Scale bar represents 100 μM. (G) Glucose tolerance test in 26-week-old mice (chow-fed: Fas$^{F/F}$, $n = 8$ mice; Fas$^{\Delta adipo}$, $n = 7$ mice; HFD-fed: Fas$^{F/F}$, $n = 11$ mice; Fas$^{\Delta adipo}$, $n = 8$ mice). (H) Insulin tolerance test in 26-week-old mice (chow-fed: Fas$^{F/F}$, $n = 8$ mice; Fas$^{\Delta adipo}$, $n = 7$ mice; HFD-fed: Fas$^{F/F}$, $n = 11$ mice; Fas$^{\Delta adipo}$, $n = 8$ mice). Data are expressed as mean ± SEM. Statistical tests used: Student t test for panel F; two-way ANOVA for panels B, C, D, E, G, and H. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ (differences between HFD-fed groups). WAT, white adipose tissue. [Color figure can be viewed at wileyonlinelibrary.com]

HFD-induced body weight gain was significantly decreased in $Fas^{\Delta adipo}$ mice, resulting in significantly lower body weight (Figure 1B,C). Moreover, total and subcutaneous (inguinal) WAT mass as well as inguinal adipocyte size was significantly reduced in HFD-fed knockout mice (Figure 1D,E), whereas these parameters were not significantly lower in the intra-abdominal epididymal and mesenteric fat depots (Figure 1D; Figure S1B,C).

However, mRNA expression of inflammatory and immune cell markers such as interleukin 1 beta (*Il1b*), *Il6*, tumor necrosis factor α (*Tnfα*), *Cd11b* (also known as integrin alpha M *[Itgam]*), and *Cd11c* (also

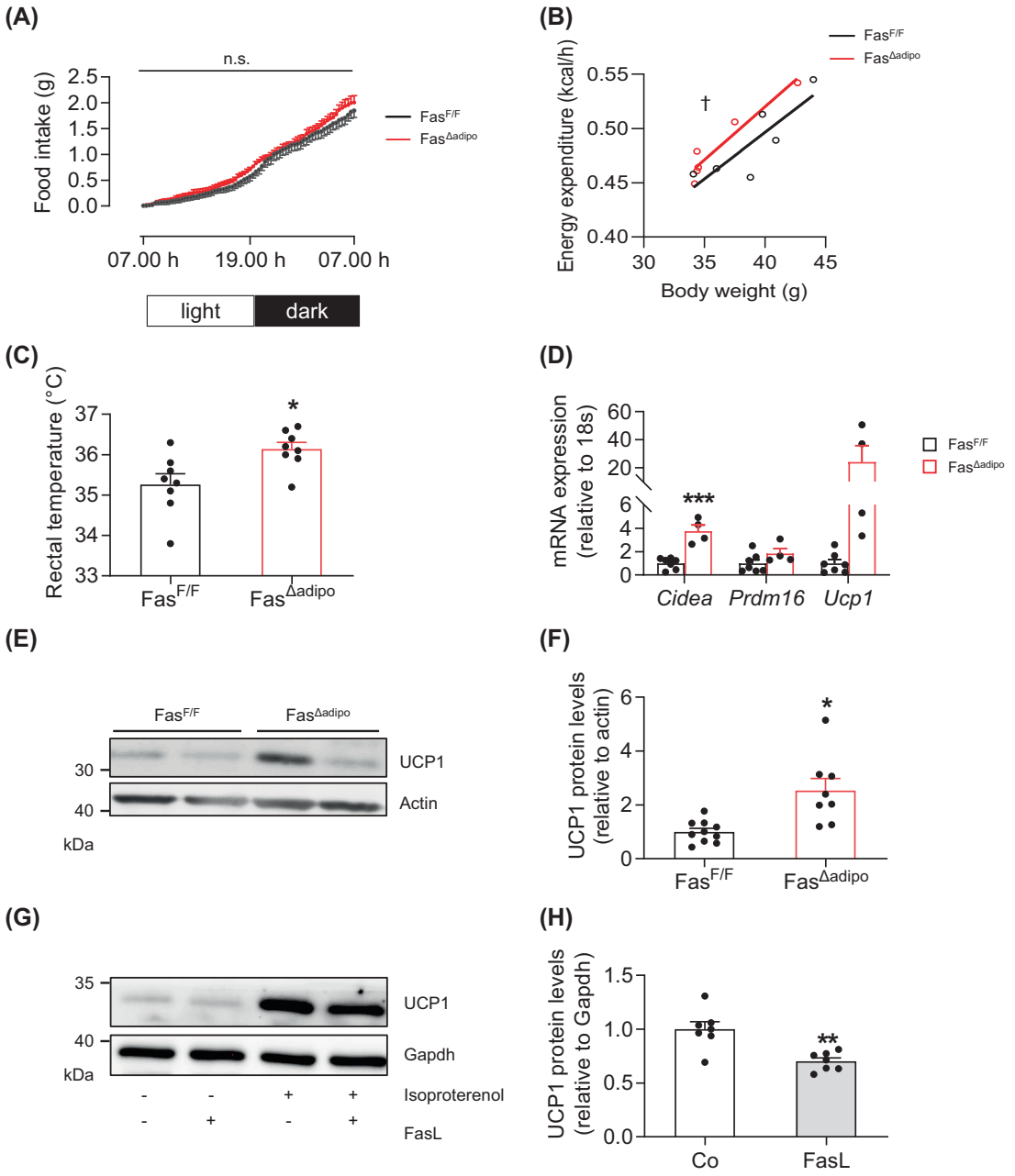

FIGURE 2 Increased energy expenditure in high-fat diet (HFD)-fed $Fas^{\Delta adipo}$ mice. (A) Food intake and (B) linear regression analysis of energy expenditure during the light phase (kcal/h) in HFD-fed $Fas^{F/F}$ ($n = 6$) and $Fas^{\Delta adipo}$ ($n = 6$) mice. $^{\dagger}p = 0.078$. (C) Rectal temperature measured in HFD-fed $Fas^{F/F}$ ($n = 8$) and $Fas^{\Delta adipo}$ ($n = 8$) mice. (D) mRNA expression of respective genes relative to 18s (ΔΔCt) in inguinal adipose tissue of HFD-fed $Fas^{F/F}$ ($n = 7$) and $Fas^{\Delta adipo}$ ($n = 4$) mice. (E) Representative Western blot and (F) quantification of UCP1 protein levels in inguinal adipose tissue harvested from HFD-fed $Fas^{F/F}$ ($n = 10$) and $Fas^{\Delta adipo}$ ($n = 8$) mice. (G) Representative Western blot and (H) quantification of UCP1 protein levels of subcutaneous adipocytes cultured with or without 0.4-ng/mL FasL for 72 h followed by 6 h of isoproterenol stimulation. $n = 7$ cell culture wells of four independent experiments. Data are expressed as mean ± SEM. Statistical tests used: two-way ANOVA for panel A; ANCOVA for panel B; Student *t* tests for panels C, D, F, and H. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. FasL, Fas ligand; n.s., not significant; UCP1, uncoupling protein 1; Cidea, cell death-inducing DNA fragmentation factor, alpha subunit-like effector A; Prdm16, PR domain containing 16. [Color figure can be viewed at wileyonlinelibrary.com]

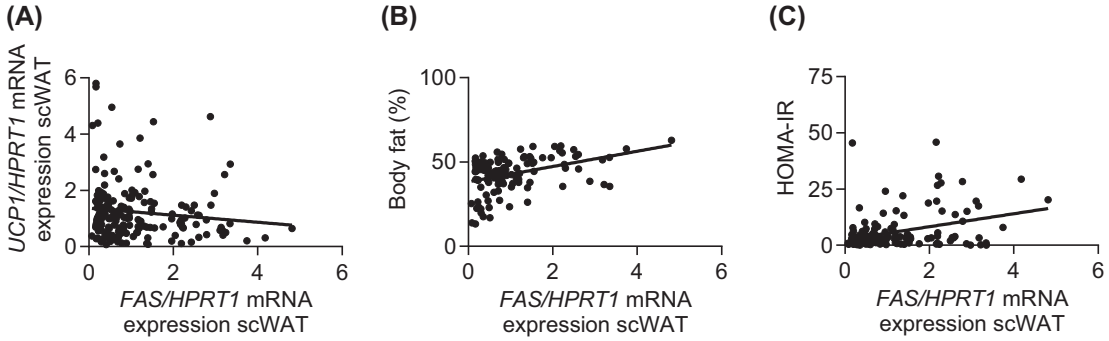

FIGURE 3 *FAS* correlates positively with percentage body fat and HOMA-IR in female human individuals. Scatterplot of subcutaneous WAT *FAS* mRNA expression and (A) subcutaneous *UCP1* mRNA expression ($n = 186$, $r = -0.146$, $p < 0.05$), (B) percentage body fat ($n = 115$, $r = 0.336$, $p < 0.001$), and (C) HOMA-IR ($n = 138$, $r = 0.248$, $p < 0.01$) in female human individuals. HOMA-IR, homeostatic model assessment of insulin resistance; UCP1, uncoupling protein 1; WAT, white adipose tissue; HPRT, hypoxanthine phosphoribosyltransferase 1; scWAT, subcutaneous WAT.

known as integrin alpha X *[Itgax]*) was significantly reduced in epididymal WAT of HFD-fed $Fas^{\Delta adipo}$ mice (Figure S1D). Moreover, liver steatosis was reduced in HFD-fed $Fas^{\Delta adipo}$ mice as inferred by histological examination and a ~35% decrease in total liver lipid content (Figure 1F).

Whereas glucose and insulin tolerance were not affected by adipocyte-specific Fas depletion in chow-fed mice, glucose levels during intraperitoneal glucose and insulin tolerance tests were significantly lower in $Fas^{\Delta adipo}$ mice compared to control ($Fas^{F/F}$) littermates fed an HFD for 20 weeks (Figure 1G,H; Figure S1E,F).

Increased energy expenditure and WAT browning in HFD-fed $Fas^{\Delta adipo}$ mice

Next, food intake and energy expenditure were assessed in metabolic cages after 8 weeks of HFD, a time point when body weight was not yet significantly different between genotypes (Figure 1B). Whereas food intake was similar between control and knockout mice (Figure 2A), linear regression analysis revealed a statistical trend toward a body-weight-independent increase in energy expenditure in the light phase of knockout mice (Figure 2B; Figure S2A) [12]. While locomotor activity and respiratory exchange ratio were similar (Figure S2B,C), rectal temperature was significantly elevated in HFD-fed $Fas^{\Delta adipo}$ mice (Figure 2C), further suggesting increased heat production and energy dissipation in knockout mice.

Increased energy expenditure in HFD-fed $Fas^{\Delta adipo}$ mice may result from increased browning of (subcutaneous) WAT and/or higher activity of BAT. Indeed, mRNA expression of the browning markers cell death-inducing DNA fragmentation factor, alpha subunit-like effector A (*Cidea)* and *Ucp1* were elevated in inguinal WAT of HFD-fed $Fas^{\Delta adipo}$ mice (Figure 2D), paralleled by higher protein levels of UCP1 (Figure 2E,F). In contrast, no significant differences in mRNA and protein abundance of UCP1 and other markers of thermogenesis were detected in BAT (Figure S2D,E).

Next, in vitro experiments in murine subcutaneous white adipocytes were performed [13]. Whereas high Fas ligand (FasL) concentrations induced cleavage of poly (ADP-ribose) polymerase as expected, lower concentrations (0.4 ng/mL) did not affect cleavage, either after 24 or after 72 h (Figure S2F,G), indicating that lower Fas concentration did not induce apoptosis. However, treatment with 0.4-ng/mL FasL for 72 h significantly blunted isoproterenol-induced nuclear peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) content (Figure S2H,I) and UCP1 protein levels (Figure 2G,H). Such a finding may suggest that Fas activation directly reduces UCP1 concentration, potentially via blunting PGC1α-mediated *Ucp1* expression.

FAS expression in WAT correlates negatively with *UCP1* but positively with adiposity in humans

Consistent with our data in murine adipocytes, we found a negative correlation between *FAS* and *UCP1* mRNA expression in female human abdominal subcutaneous as well as visceral WAT (Figure 3A; Figure S3A), suggesting that the negative effect of Fas on *UCP1* expression may be conserved between species and different WAT depots. Importantly, *FAS* mRNA expression in subcutaneous WAT correlated positively with percentage body fat as well as homeostatic model assessment of insulin resistance (HOMA-IR) (Figure 3B,C). While similar results were found in men, correlations were only significant between *FAS* and HOMA-IR (Figure S3B–E).

DISCUSSION

The presented experiments in mice and humans suggest that adipocyte-expressed Fas contributes to the development of obesity, potentially via reducing WAT browning. In fact, HFD-fed male mice with adipocyte-specific Fas depletion displayed increased browning of WAT, which was paralleled by increased energy expenditure as well as reduced adiposity and reduced body weight gain. Conversely, Fas activation reduced UCP1 protein levels in cultured subcutaneous

murine adipocytes. Moreover, *FAS* expression negatively correlated with *UCP1* expression in WAT and positively with adiposity in humans, suggesting that the negative effect of Fas may be conserved between species. Stronger correlations between *FAS* and *UCP1* in WAT of women versus men indicate that the negative effect of Fas is more pronounced in women. Alternatively, lower sample size in men may explain the difference. Moreover, despite the observed correlations, the clinical relevance remains to be confirmed. Because female mice were not analyzed in this study and (adipose tissue) metabolism differs between sexes [14], future studies are warranted.

We previously observed that adipocyte-specific Fas knockout mice were protected from the development of intra-abdominal WAT inflammation and insulin resistance induced by an HFD for 6 weeks [5]. Mechanistically, activation of Fas induced the release of inflammatory cytokines (i.e., IL-6) as well as free fatty acids from adipocytes, promoting hepatic steatosis and insulin resistance [5, 15]. In that study [5], expression of the Cre recombinase was under the control of the fatty acid-binding protein 4 (Fabp4)-promotor, which may induce Fas deletion not only in adipocytes but also in other cells or tissues such as macrophages, heart, kidney, muscle, or pancreas [16, 17]. Although we did not have evidence of such unspecific Fas deletion [5], data obtained using Fabp4-Cre mice need to be interpreted with caution and should be confirmed in mice using alternative strategies to knock down the gene of interest specifically in adipocytes [18].

Whereas previous data obtained in Fabp4-Cre crossed mice were analyzed after 6 weeks of HFD [5], $Fas^{\Delta adipo}$ mice were studied after 20 weeks of HFD feeding in the current study. In both mouse models, body weight was not significantly different between control and knockout mice after 6 weeks of HFD. However, our current data reveal that Fas depletion significantly reduced fat mass and body weight in long-term HFD-fed mice. In parallel, browning of subcutaneous WAT was elevated. These findings are in agreement with a previous observation that total body Fas-deficient mice revealed increased *Ucp1* expression in WAT [19]. Future studies may help to decipher whether the inhibitory effect of Fas on UCP1 is mediated via inflammatory, mitochondrial, and/or other metabolic pathways. Besides UCP1, other energy-expending "futile" cycles in other organs and/or in WAT, such as calcium or creatine cycling, may have contributed to increased energy dissipation in Fas-depleted mice. Of note, differences in energy expenditure were small and therefore are hardly responsible for the observed phenotypic differences. Rather, other factors like decreased food intake over the whole 20-week period (despite similar food intake observed after 8 weeks of HFD) and/or reduced intestinal absorption may have contributed to the reduced body weight gain in HFD-fed knockout mice.

We previously found that *FAS* (*CD95*) and Fas ligand (*FASLG*) expression differs between visceral and subcutaneous WAT but that they increased in depots of both patients with obesity and those with type 2 diabetes compared to lean or normal glucose-tolerant controls [8]. Moreover, *FAS* expression in both depots positively correlated with BMI and percentage body fat. Herein, we confirm a positive correlation between *FAS* expression in human abdominal subcutaneous WAT and percentage body fat in an independent larger cohort and in both sexes. Moreover, we reveal a negative correlation between *FAS* and *UCP1* expression in human visceral and subcutaneous WAT.

In conclusion, our study identifies a role for adipocyte-expressed Fas in the development of diet-induced obesity in rodents. Moreover, *FAS* expression in WAT of human individuals was positively associated with percentage body fat. Thus, Fas may be a novel pharmacological target to combat obesity and its associated diseases.

AUTHOR CONTRIBUTIONS

Stephan Wueest designed and performed experiments, analyzed data, and wrote the manuscript. Chiara Scaffidi, Pim P. van Krieken, Nils K. Konrad, Christian Koch, Michael S. F. Wiedemann, Anne Goergen, Marcela Borsigova, Ioannis G. Lempesis, Jonas Fullin, Konstantinos N. Manolopoulos, Steffen Böttcher, Gijs H. Goossens, and Matthias Blüher performed experiments. Daniel Konrad designed experiments, analyzed data, and wrote the manuscript. All authors reviewed and commented on the manuscript and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declared the following relationships to entities: NovoNordisk (Daniel Konrad) and Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Lilly, NovoNordisk, Novartis, Sanofi, and Pfizer (Matthias Blüher). All other authors declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article, its online Supporting Information file, or from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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