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Cell Metabolism

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Letter

Replication of SARS-CoV-2 in adipose tissue determines organ and systemic lipid metabolism in hamsters and humans

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Population-based studies have found that obesity is an important and independent risk factor for hospitalization, ICU admission, and fatal outcome in individuals with coronavirus disease-19 (COVID-19) (Drucker, 2021). We read with great interest the recent publication in *Cell Metabolism* that provided evidence that SARS-CoV-2 (the virus that causes COVID-19) infection of adipocytes could trigger adipose tissue dysfunction and insulin resistance (Reiterer et al., 2021). This notion is supported by clinical data showing higher C-peptide concentrations and lower levels of the adipocyte-derived hormone adiponectin in individuals with COVID-19. To address a role of adipose tissue dysfunction caused by the virus, the authors studied SARS-CoV-2 infection in golden Syrian hamsters, an excellent animal model of COVID-19 (Sia et al., 2020). Importantly, they detected viral RNA and low adiponectin expression in hamster adipose tissue post infection, which may explain deteriorated metabolic homeostasis associated with SARS-CoV-2 infection (Reiterer et al., 2021). However, the study did not provide direct evidence of SARS-CoV-2 dissemination to adipose tissue in humans.

Here, we have extended the previous study by measuring SARS-CoV-2 RNA in adipose tissues, lung, and liver from 18 male and 12 female individuals who died from COVID-19 (Table S1). SARS-CoV-2 was found in at least one adipose tissue depot in 10 of the 18 male individuals. Although our study was not sufficiently powered for a conclusive statistical analysis, it is of note that the virus was found only in adipose tissue of male individuals who were overweight (BMI $\geq$ 25) or obese (BMI $\geq$ 30). It is also notable that in four males all with a BMI $\geq$ 30, SARS-CoV-2 RNA was additionally detected in liver samples, suggesting that hepatic fat accumulation frequently observed in obese individuals might additionally support SARS-CoV-2 replication in the liver. In 5 of the 12 female individuals, SARS-CoV-2 was detected, but with no clear correlation between BMI and virus mRNA levels. The expression of the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) was reported to be higher in adipose tissue of individuals with obesity compared with lean individuals (Ledford, 2020). In our study, however, no clear correlation between BMI, adipose ACE2 expression, and SARS-CoV-2 was observed (Table S1). Altogether, we provide direct evidence that adipose tissue depots, especially from male individuals with obesity, are susceptible to SARS-CoV-2 infection.

The study of Reiterer et al. showed replication of SARS-CoV-2 in cultured adipocytes, but without examining the relevance of adipocyte differentiation status for virus replication. We, therefore, performed infection experiments with human mesenchymal stem cells that were differentiated into mature adipocytes (Prawitt et al., 2008). After inoculation, we detected efficient multi-cycle replication of SARS-CoV-2 by determining infectious titers in the supernatants, whereas influenza A virus (H1N1) used as a control did not propagate in adipocytes (Figure S1A). Importantly, ACE2 expression was strongly induced upon adipocyte differentiation (Figure S1B). Consistent with this finding, efficient SARS-CoV-2 replication was only detected in lipid-laden adipocytes prior to infection, but not in adipocyte precursor cells or immature adipocytes (Figure S1C). In addition, we provide mechanistic insight that lipid droplet metabolism is critical for SARS-CoV-2 propagation, as blocking lipid breakdown using the lipase inhibitor tetrahydrolipstatin reduced viral replication by 100-fold in mature adipocytes (Figure S1D). Notably, concomitant administration with atorvastatin further suppressed replication (Figure S1D), which could be explained by drug-mediated lowering of ACE2 expression (Figure S1E). Together, these mechanistic studies provide the rationale for a novel

treatment strategy targeting SARS-CoV-2 propagation.

The study by Reiterer et al. showed clear evidence for adipose tissue infection with SARS-CoV-2 in hamsters. The authors focused on endocrine factors released by adipocytes; however, they did not explore infection kinetics or the consequences on adipocyte and systemic lipid metabolism. In our experiments, we detected infectious viral titers of SARS-CoV-2 in adipose tissues on days 1 and 3 post-infection, whereas no virus particles were present on day 6 (Figure S1F). The complete clearance of the virus from adipose tissue by day 6 indicated a proficient innate immune response. In line with this notion, a massive, transient induction of the classical type 1 interferon response gene *Isg15* was observed on day 3, but not on day 6, in adipose tissues (Figures S1G and S1H).

It is of note that, for yet unknown reasons, disease progression is highly variable among individuals with COVID-19. To identify risk profiles that predict the severity and outcome, a previous series of unbiased metabolomics studies found characteristic metabolite signatures in plasma that distinguish mild from severe disease states (Casari et al., 2021). For instance, higher levels of plasma free fatty acids are observed in individuals with COVID-19 compared with controls, suggesting higher basal lipolysis of triglycerides in adipose tissue (Thomas et al., 2020). Fatty acids released by adipose tissue include exogenous ones originally derived from the diet and such originating from endogenous synthesis. The latter metabolic pathway, termed *de novo* lipogenesis (DNL), is highly active in adipose tissue and is regulated mainly at the transcriptional level. Notably, the N-terminal non-structural protein 1 of beta-coronaviruses including SARS-CoV-2 has been shown to suppress host gene expression (Thoms et al., 2020). Thus, it is conceivable that viral infection not only reduces adiponectin expression, as shown by Reiterer et al., but also affects the expression of genes that regulate adipocyte lipid metabolism. Indeed, we observed that the expression levels of the key DNL enzymes *Acaca*, *Acly*, and *Fasn* were substantially lower in adipose tissues of SARS-CoV-2-infected hamsters (Figures S1I and S1J). This effect was not observed in controls treated with poly(I:C), arguing against the possibility that the induction of the type 1 interferon response is responsible for the reduced expression of lipid-related genes. To address whether this profound regulation affects systemic metabolite levels and lipid homeostasis, metabolomic analysis was performed in plasma samples of SARS-CoV-2-infected hamsters and individuals with COVID-19 (Figures S1K–S1M). Remarkably, the most significant inductions were found for triglyceride species enriched in polyunsaturated fatty acids (PUFAs) at days 3 and 6 post-infection (Figure S1L). In contrast and consistent with reduced expression of DNL genes in adipose tissues, triglycerides containing typical DNL-related fatty acids, including saturated fatty acids (SFAs) and monosaturated fatty acids (MUFAs), were profoundly reduced (Figure S1L). In humans, we found a trend toward higher triglycerides in the plasma of individuals with COVID-19 compared to a control cohort (Figure S1M). Of note, metabolomic analyses revealed that triglyceride species containing DNL-derived SFAs and MUFAs were lower in the plasma of individuals with COVID-19 (Figure S1N).

Extending the results of Reiterer et al., we show here that SARS-CoV-2 infection of adipose tissue profoundly affects organ and systemic lipid metabolism in hamsters and humans.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.cmet.2021.12.002.

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AUTHOR CONTRIBUTIONS

G.G. and J.H. designed the study. G.G., L.S., and J.H. wrote the manuscript. M.Z., S.S.-B., S.E., F.H., P.L., B.S., N.M.K., S.B., M.Y.J., O.M., S. Krasemann, M.S., D.J., A.N., S. Kluge, M.P., H.S., K.S., A.K., L.S., and B.O. researched data. All authors contributed to the data discussion and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPORTING CITATIONS

The following references appear in the Supplemental information: Otte et al. (2011); Schroeder et al. (2021).

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