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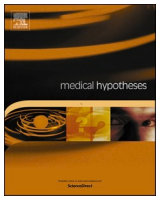

Adipocytes in obesity: A perfect reservoir for SARS-CoV-2?

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ABSTRACT

Research evidence suggests that adipocytes in obesity might facilitate SARS-CoV-2 replication, for it was only found in adipose tissue of individuals with overweight or obesity but not lean individuals who died from COVID-19. As lipid metabolism is key to adipocyte function, and viruses are capable of exploiting and manipulating lipid metabolism of host cells for their own benefit of infection, we hypothesize that adipocytes could not only impair host immune defense against viral infection, but also facilitate SARS-CoV-2 entry, replication and assembly as a reservoir to boost the viral infection in obesity. The latter of which could mainly be mediated by SARS-CoV-2 hijacking the abnormal lipid metabolism in the adipocytes. If these were to be confirmed, an approach to combat COVID-19 in people with obesity by taking advantage of the abnormal lipid metabolism in adipocytes might be considered, as well as modifying lipid metabolism of other host cells as a potential adjunctive treatment for COVID-19.

Introduction

COVID-19 severity and obesity

SARS-CoV-2 is a positive-sense, single-stranded RNA virus. By binding its spike (S) protein to the host membrane receptor – angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 enters host cells by endocytosis for replication and infection [1]. People with obesity are susceptible to acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with severe symptoms/complications and poor prognosis [2], and the consequently high hospitalization and mortality statistics should prioritize action for this particularly vulnerable population [3]. Obesity has long been associated with susceptibility to severe outcomes following respiratory viral infections such as influenza [4]. As the most significant character to define obesity – fat mass, can it promote SARS-CoV-2 infection [5]? Outside of the adipocyte, several lines of evidence suggest that excess adiposity could lead to impaired immune cell responses/defense against viral infection [6]. Inside of the adipocyte, can it actually facilitate SARS-CoV-2 replication to boost the infection quantitatively in patients with obesity? Body composition measurements indicate that the percentage of fat mass could exceed 40 % in people with severe obesity [5], and ACE2 (assisting SARS-CoV-2 entry into the host cell) gene expression at the mRNA level is present in human adipose tissue, although protein expression has not been confirmed [7]. However, it is interesting to note that viral replication was only found in adipose tissue of individuals with overweight or obesity who died from coronavirus disease 2019 (COVID-19), but not in those with a BMI < 25 Kg/m^2 [8].

SARS-CoV-2 and adipocytes in obesity

The key question is whether viral replication is associated with the quality of the adipocyte. Adipocytes are most specialized for lipid metabolism in terms of lipogenesis and lipolysis [9]. Even though SARS-

Abbreviations: ACE2, angiotensin-converting enzyme 2; ATP, adenosine triphosphate; COVID-19, coronavirus disease 2019; ER, endoplasmic reticulum; ERGIC, ER-to-Golgi intermediate compartment; FFAs, free fatty acids; LDs, lipid droplets; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S protein, spike protein; TAGs, triacylglycerols.

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CoV-2 replication was observed in cultured human adipocytes, the differentiation/lipid accumulation status was not examined in these adipocytes [10]. Further study indicated that SARS-CoV-2 replication was accompanied by high levels of intracellular lipid/ triacylglycerol (TAG) in human adipocytes [8], which is consistent with the observation that viral replication was only detected in adipose tissue of patients who died from COVID-19 with obesity and overweight [8]. However, we speculate that rather than the most obvious manifestation – very high intracellular TAGs, abnormal lipid metabolism in adipocytes may be the potential target for SARS-CoV-2 to hijack to promote its infection in obesity [11]. This is supported by RNA viruses rely heavily on other various host lipid metabolites such as free fatty acids (FFAs) and phospholipids for its replication and further assembly [12]. Moreover, it has long been established that viruses are extremely good at exploiting and even modifying lipid signaling, synthesis and compartmentalization of host cells for their own benefit of entry and infection [13]. Therefore, as the site where significant abnormal lipid metabolism occurs, adipocytes in obesity might facilitate SARS-CoV-2 replication in themselves to boost the subsequent infection.

The hypothesis

In addition to impairing host immune defense against viral infection, adipocytes could facilitate SARS-CoV-2 entry, replication and assembly intracellularly to boost the viral infection in obesity. This could mainly be mediated by SARS-CoV-2 hijacking the abnormal lipid metabolism in the adipocytes. Hence, adipocytes in obesity might be a perfect reservoir for SARS-CoV-2.

Evaluation of the hypothesis

Adipocytes play a crucial role in maintaining metabolic and immunologic homeostasis, especially by mobilizing FFAs from lipid droplets (LDs) to the extracellular environment – lipolysis [14]. Excess FFAs lipolyzed from adipocytes (abnormal lipid metabolism) in obesity are lipotoxic [15]. They could impair *T*-cells function, attenuate the adhesion and phagocytic activity of macrophages, and even induce their apoptosis, thereby weakening the host's immune defense against the viral infection [15,16]. In parallel, excess FFAs could systemically boost SARS-CoV-2 transmission by directly assisting membrane fusion between virus and other host cells (than adipocytes) in obesity [17]. This is realized by palmitoylation sites of viral S protein -covalent attachment of FFAs to the cytoplasmic side of viral S proteins in the endoplasmic reticulum (ER) [1,18].

Besides promoting the viral transmission among other host cells, how could adipocytes in obesity become a perfect reservoir for SARS-CoV-2 by facilitating the viral entry, replication and assembly?

Free fatty acids: bait, fuel or shield?

As the major fuel tank located in the nearly first line of defense [19], adipocytes are extremely susceptible to be hijacked by invading pathogens. Although adipocytes are capable of eliciting immune responses (as immune cells do) [20], the disadvantage of immobility (mobility is a significant feature of immune cells) may have prompted them to develop unusual defense strategies against invading pathogens, which is a research area worth exploring. As no SARS-CoV-2 replication was detected in the adipose tissue of lean individuals who died from COVID-19 [8], we speculate that adipocytes could adapt their lipid metabolism to defend against SARS-CoV-2 infection. For instance, flux of FFAs from plasma lipoproteins (hydrolyzed by lipoprotein lipase secreted by adipocytes) or the lipolysis – a 'bait' [21], might lure and assist SARS-CoV-2 entry into adipocytes by palmitoylation mediated-membrane fusion for its later destruction (discussed in Lipid droplets: Nemesis).

By contrast, SARS-CoV-2 entry into adipocytes could be boosted in obesity either by overexpression of *ace2* or excess lipolysis induced-membrane fusion [22]. Once inside the adipocytes, abundant 'ready to use' intracellular FFAs resulted from lagged lipogenesis – turnover of intracellular FFAs to TAGs stored in LDs (another key feature of abnormal lipid metabolism in obesity) [23], might directly be exploited by SARS-CoV-2 for phospholipid synthesis and S protein modification, thereby intensifying its assembly in adipocytes. Recent studies have demonstrated that SARS-CoV-2 replication could be extensively reduced by reducing content of FFAs in host cells [24]. In terms of fueling SARS-CoV-2 replication and assembly in adipocytes, these abundant intracellular FFAs might be subject to β-oxidation in the mitochondria before channeling into the tricarboxylic acid cycle for adenosine triphosphate (ATP) production. This tremendous workload of energy generation might explain high levels of oxidative stress in SARS-CoV-2-infected host cells of individuals with obesity [25]. Moreover, inhibition of mitochondrial β-oxidation of FFAs using trimetazidine has been suggested as a potential treatment for COVID-19-induced acute cardiac injury [26], as FFAs are the primary energy source for cardiomyocytes (similar to adipocytes) function and metabolism [27,28].

It is intriguing to note that SARS-CoV-2 might also use adipocytes in obesity as a hideout for immune evasion. Though immune cell infiltration is a hallmark of adipose tissue in obesity [29], the abundant intracellular FFAs (resulting from lagged lipogenesis) might disrupt lipid rafts in cytokine signal transduction [30], thereby blocking the immune response against SARS-CoV-2 in adipocytes in obesity.

Lipid droplets: Nemesis or culprit?

LDs are paramount in regulating adipocyte metabolism including buffering FFA-elicited lipotoxicity by lipogenesis [31]. As TAGs are accumulated between the two leaflets of the endoplasmic reticulum (ER) membrane, nascent LDs are proposed to emerge by budding from the outer leaflet or by excision of the outer and inner leaflets of the ER membrane [32], either of which processes could temporarily interrupt membrane integrity, thereby decreasing the surface tension of ER membrane [33]. As a result, vigorous formation of LDs in adipocytes could significantly loosen the ER membrane [34], which might be fatal for the formation of SARS-CoV-2 replication organelles, for high surface tension is indispensable for its tethering on the ER membrane [35]. Although these organelles consist of complex membrane structures that might potentially increase the surface tension of the ER membrane to facilitate tethering of double-membrane vesicles for viral replication [36], once lured inside the adipocytes, SARS-CoV-2 viral nucleic acids might be susceptible to intracellular destruction. The nemesis – vigorous formation of LDs, will disrupt the ER membrane and inhibit the formation of the replication organelles. Without this protective microenvironment, the viral nucleic acids exposed to the cytosol will be rapidly destroyed by triggering innate immune responses [37], which might imply why no evidence of SARS-CoV-2 replication was detected in adipose tissue of lean individuals who died from COVID-19 [8].

By contrast, besides copious material and energy (excess intracellular FFAs), lagged formation of LDs in adipocytes in obesity could also provide the ER membrane with proper tension for SARS-CoV-2 to tether its replication organelles and indulge in replication. Paradoxically, inhibition of formation of LDs was observed to suppress SARS-CoV-2 propagation in host cells [38]. However, it should be noted that in these experiments, the net effects of inhibiting synthesis of lipid mediators to interrupt formation of LDs was lowering intracellular content of FFAs [38], which matches increasing formation of LDs in adipocytes.

Adipocytes: medium?

Secretory autophagy is exploited by various positive-sense RNA viruses for assembly and transmission [39]. Even though it is increased adipocyte degrative autophagy with which obesity is associated [40], SARS-CoV-2-induced oxidative stress might switch the increased degrative autophagy to secretory autophagy by altering the crosstalk

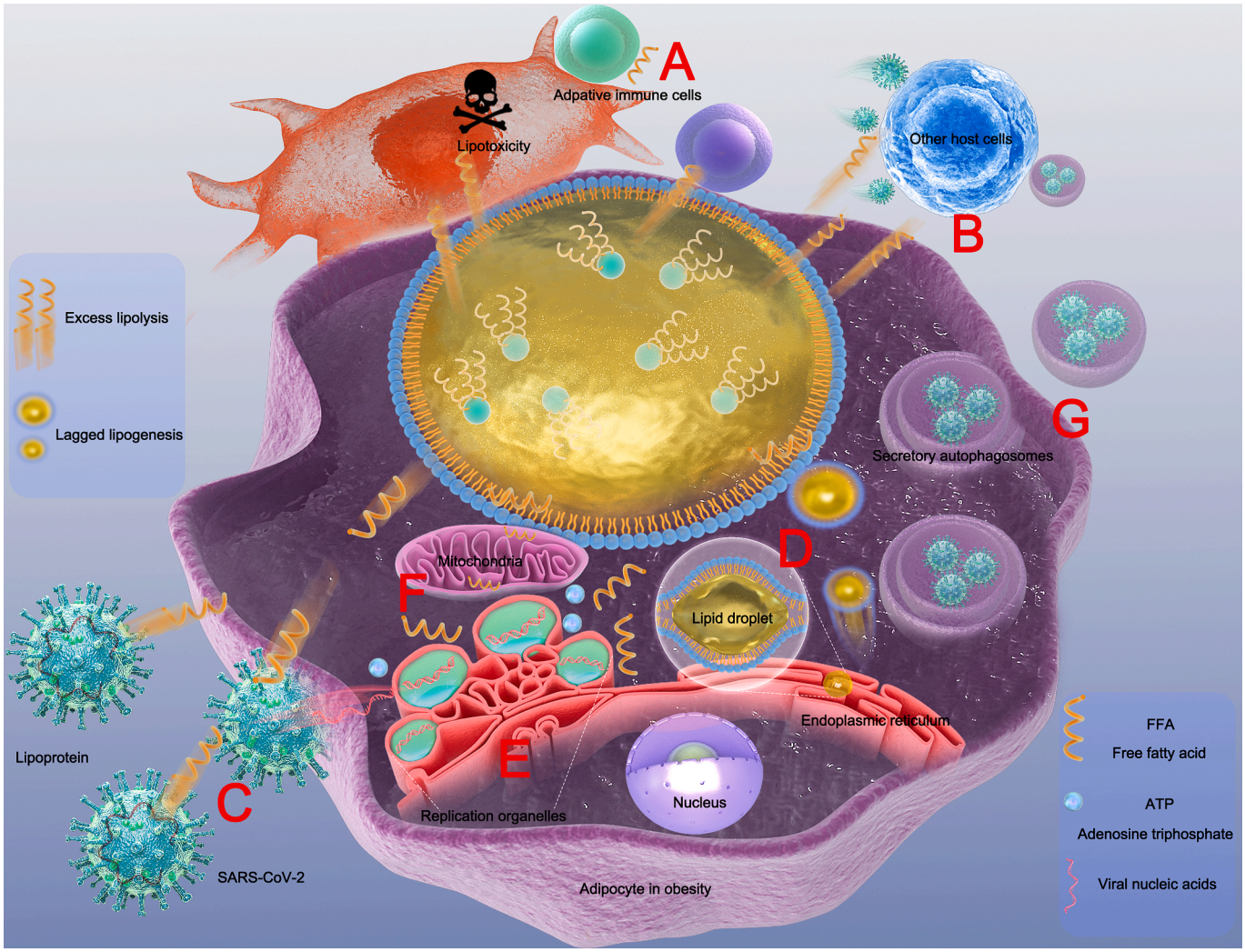

Fig. 1. In obesity **(A)** adipocytes could protect SARS-CoV-2 against host immune defense. **(B)** SARS-CoV-2 could hijack excess lipolysis to boost its transmission systemically as well as **(C)** entry into the adipocytes. **(D)** Lagged lipogenesis could supply SARS-CoV-2 with **(E)** the ER membrane with proper tension to tether its replication organelles; **(F)** FFA and ATP for its replication and assembly. **(G)** SARS-CoV-2 could promote secretory autophagy-mediated exocytosis.

between the mitochondria and lysosomes [41,42]. SARS-CoV-2 exocytosis/infectivity can thus be boosted, for the traditional 'one assembly processed by the ER-to-Golgi intermediate compartment at a time' being bypassed by multiple virus assemblies being packed in a single secretory autophagosome.

Conclusion

We hypothesize that in obesity adipocytes could protect SARS-CoV-2 against host defense by inducing lipotoxicity in immune cells. Concurrently, SARS-CoV-2 could hijack the abnormal lipid metabolism in the adipocytes, specifically excess lipolysis and lagged lipogenesis, to boost its entry (as well as into other host cells), replication, assembly and even immune evasion. Furthermore, SARS-CoV-2 could promote secretory autophagy-mediated exocytosis to enhance the viral infectivity. Taken together, the adipocytes in obesity can be a perfect reservoir for SARS-CoV-2 (Fig. 1).

Tackling obesity has never been an easy task, but reflected on excess (*e.g.*, saturated) FFAs lipolyzed from adipocytes in obesity systemically boosting SARS-CoV-2 entry by palmitoylation mediated-membrane fusion, taking advantage of this abnormal lipid metabolism with unsaturated FA supplementation could be a potential therapy, as unsaturated FFAs could block the viral entry into host cells by interfering its S protein binding to ACE2 [43]. Modifying lipid metabolism of other host cells might be another promising adjunctive treatment for COVID-19, as activation of peroxisome proliferator-activated receptor γ in immune cells could induce lipogenesis/reduce intracellular FFAs to orchestrate host defense against SARS-CoV-2 infection [44–46].

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Consent statement/Ethical approval

Not required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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