The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, 1799–1811
https://doi.org/10.1210/clinem/dgac137
Advance access publication 9 March 2022
Mini-Review

Obesity and COVID-19: Mechanistic Insights From Adipose Tissue

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Abstract

Obesity is associated with an increase in morbidity and mortality from coronavirus disease 2019 (COVID-19). The risk is related to the cytokine storm, a major contributor to multiorgan failure and a pathological character of COVID-19 patients with obesity. While the exact cause of the cytokine storm remains elusive, disorders in energy metabolism has provided insights into the mechanism. Emerging data suggest that adipose tissue in obesity contributes to the disorders in several ways. First, adipose tissue restricts the pulmonary function by generation of mechanical pressures to promote systemic hypoxia. Second, adipose tissue supplies a base for severe acute respiratory syndrome coronavirus 2 entry by overexpression of viral receptors [angiotensin-converting enzyme 2 and dipeptidyl peptidase 4]. Third, impaired antiviral responses of adipocytes and immune cells result in dysfunction of immunologic surveillance as well as the viral clearance systems. Fourth, chronic inflammation in obesity contributes to the cytokine storm by secreting more proinflammatory cytokines. Fifth, abnormal levels of adipokines increase the risk of a hyperimmune response to the virus in the lungs and other organs to enhance the cytokine storm. Mitochondrial dysfunction in adipocytes, immune cells, and other cell types (endothelial cells and platelets, etc) is a common cellular mechanism for the development of cytokine storm, which leads to the progression of mild COVID-19 to severe cases with multiorgan failure and high mortality. Correction of energy surplus through various approaches is recommended in the prevention and treatment of COVID-19 in the obese patients.

Key Words: obesity, COVID-19, chronic inflammation, cytokine storm, mitochondrial dysfunction

Coronavirus disease 2019 (COVID-19) is an infectious diseases caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) identified in 2019. As of February 1, 2022, the virus and its variants have infected more than 377 million people with 5.7 million deaths worldwide (https://coronavirus.jhu.edu/map.html). The COVID-19 pandemic has generated a huge challenge to the global healthcare community due to the high mortality rate. Although the infection and mortality have been effectively reduced by virus-targeting vaccinations, the threat remains serious as current vaccinations may lose efficacy to emerging mutant strains of virus, and a large portion of world's population remains unvaccinated. It is generally accepted that multiorgan failure is a major cause of the high mortality rate in COVID-19 with cytokine storm as the primary underlying event (1, 2).

Obesity is a well-established risk factor for severe COVID-19 with high mortality (3, 4), which was first reported in April 2020 and currently supported by epidemiological data from the World Health Organization (https://ourworldindata.org/). Based on World Health Organization data in 2016, obesity has become a pandemic, with 39% of adults (age > 18 years) being overweight or obese worldwide, leading to 4.7 million premature deaths each year (https://www.who.int/). The combination of the COVID-19 and obesity pandemics has resulted in a significant increase in the death rate in COVID-19 patients. The underlying mechanism linking obesity to the high death rate remains to be established; however, the chronic inflammation and tissue structure changes derived from obesity appear to be the major factors. For example, obesity may reduce the function of the respiratory system by complications, such as asthma, obstructive sleep apnea, and chronic obstructive pulmonary disease (5-7). The same applies to the H1N1 influenza virus infection (7).

In obesity, adipose tissue expansion induces multiple structural and functional changes in the body, which contribute to the development of severe COVID-19 (8, 9) (Fig. 1). The cellular and molecular events of adipose tissue dysfunction leading to severe COVID-19 will be discussed in this review.

Obesity Is a Strong Risk Factor for Severe COVID-19

Obesity, defined by a body mass index (BMI) over 30 kg/m^2, increases morbidity and mortality of COVID-19. The relationship was first reported by a French group in a study with a small sample size, in which obese patients (BMI > 35 kg/m^2) had a 7.36-fold increase in need for invasive mechanical ventilation over the lean patients (BMI < 25 kg/m^2). The first

Received: 8 December 2021. **Editorial Decision:** 2 March 2022. **Corrected and Typeset:** 27 April 2022
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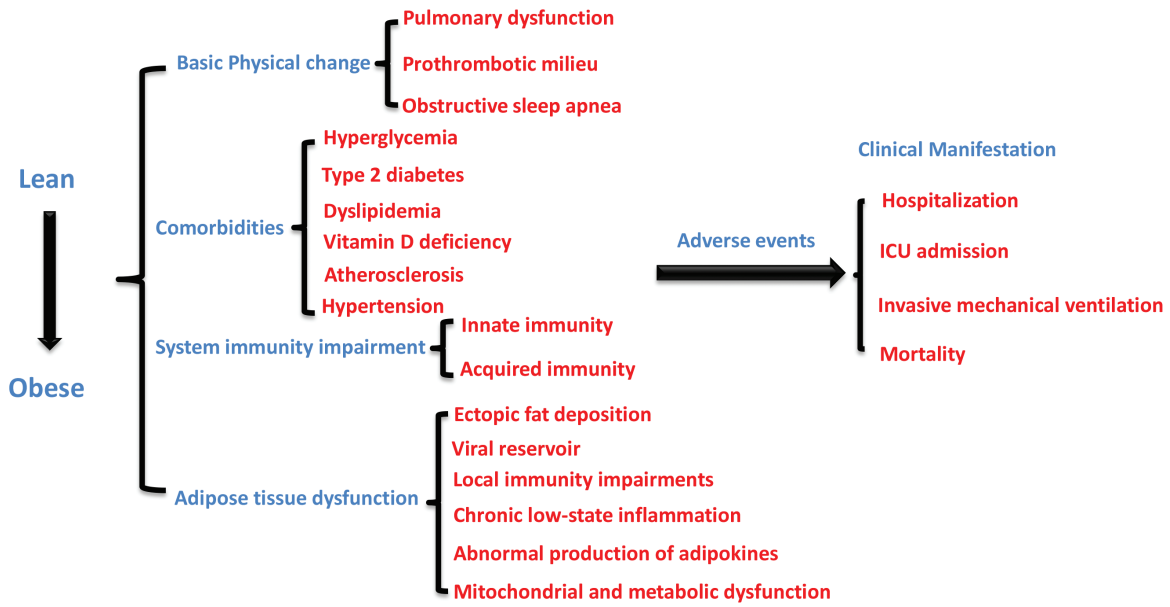

Figure 1. The potential mechanistic links between obesity and COVID-19 severity from physiologic changes, comorbidities, immune system impairment, and adipose tissue dysfunction.

large-scale clinical study of 5700 hospitalized COVID-19 patients in New York, USA, provided subsequent support that the most common comorbidities were obesity (41.7%), hypertension (56.6%), and diabetes (33.8%) (10). This relationship is consistently supported by later studies. A retrospective study containing 150 patients in China showed that a larger proportion of obese patients (33.3%) progressed to severe COVID-19 relative to the nonobese patients (11). Another retrospective study of 1158 patients in Kuwait also found obesity as an independent risk factor for severe COVID-19 (12). A cohort study in the United Kingdom reported a liner increase in hospitalization for COVID-19 patients with high BMI (13). A study of 1795 patients in Boston, Massachusetts, USA, found a relationship between high BMI, longer hospital stays, and intensive care unit admission rates in patients with acute respiratory distress syndrome (14). The relationship is also supported by a recent systematic review and meta-analysis that covered a total of 45 650 patients from 30 studies with obesity and 3 controlled studies with visceral obesity. Obesity not only aggravates COVID-19 but also promotes the occurrence of the entire course of COVID-19 (15). The impact of obesity is particularly pronounced in patients over the age of 60 (16). The relationship between COVID-19 and obesity is considered as "a pandemic within a pandemic" (17). These reports consistently support that obesity increases the risk of severe COVID-19.

Several factors have been proposed in the mechanism of severe COVID-19 in obese patients, which include anatomical changes and functional alterations derived from obesity (Fig. 1). Hyperlipidemia in obesity increases blood viscosity, which creates a prothrombotic environment to impair blood circulation. Thrombotic microangiopathy, arterial thrombosis, and venous thrombosis are major pathological changes seen in blood vessels of severe COVID-19 patients (18). Obstructive sleep apnea, a common complication in obesity with difficulties in breathing, causes systemic hypoxia, leading to severe hypoxemia following lung injury in COVID-19 patients. The hypoxemia may contribute to severe COVID-19 through cytokine storm (19). Other complications of obesity that may contribute to severe COVID-19 include hyperglycemia (20), type 2 diabetes mellitus (T2DM) (21), dyslipidemia (22), hypertension (23), atherosclerosis (24), and vitamin D deficiency (25). Obesity may dampen the innate and adaptive immune responses to virus, which contributes to viral spread across organs and failure of vaccinations (26). Obesity contributes to vaccination failure through induction of senescence in immune cells, such as natural killer (NK) cells (27), cytotoxic T cells (28), and B cells (29). These factors will not be extensively discussed here as they have been well documented in other reviews (30-32).

Mechanical Effects of Fat Depots in Severe COVID-19

White adipose tissues include subcutaneous and visceral fat depots. Excessive subcutaneous adipose tissue around the chest and abdomen restricts lung expansion during respiration. Lung activity is dependent on expansion of the chest cavity and intra-abdominal cavity. The subcutaneous fat depots physically limit chest cavity expansion, which decreases respiratory vital capacity to limit pulmonary function (7).

The visceral depots are mainly located in the abdominal cavity, which include omental, mesenteric, and retroperitoneal spaces. In obesity, there is huge expansion in visceral adipose tissue in addition to the subcutaneous fat. These fat depots increase peritoneal cavity pressure thereby restricting diaphragm movement and limiting lung activity. Both subcutaneous and visceral fat depots have been assessed in COVID-19 patients, and visceral fat depots were proven to increase the risk for severe COVID-19 (33). Therefore, visceral fat accumulation may serve as a predictive factor for intensive care admission in COVID-19 since fat depots contribute to pulmonary dysfunction and lung failure through the mechanical effects (34). In addition, visceral fat depots may contribute to severe COVID-19 through biological activities such as production of proinflammatory cytokines, which may be exacerbated by the virus infection contributing to the progression to cytokine storm.

Epicardial fat is ectopic fat deposition surrounding the myocardium and may fuel COVID-19-induced cardiac injury

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and myocarditis (35). Epicardial fat restricts the heart and lung functions through the mechanical effects, which local and systemic physiological effects (36). Epicardial fat quantified from chest computed tomography are independently associated with the extent of pneumonia and adverse outcomes in patients with COVID-19, supporting their application to clinical risk stratification (37). The fat volume of epicardial fat is a perfect indicator for severe COVID-19 in some obese patients (38).

Reservoir Effect of Adipose Tissue in COVID-19

The SARS-CoV-2 virus has a nonsegmented, positive single-stranded RNA genome with approximately 30 000 bases. The genome encodes 4 structural proteins, including the surface-located trimetric spike (S) protein, membrane (M) proteins, the nucleocapsid (N) combined with the RNA genome, and the envelope (E) proteins (39). SARS-CoV-2 is an obligate intracellular microorganism that uses the RNA genome as a template to encode the replicase and structural proteins for self-replication. The virus typically infects host cells by interacting with cell surface proteins, such as angiotensin-converting enzyme (ACE) and dipeptidyl peptidase 4 (DPP4), to enter the host cell and nucleus (Fig. 2). This propagation can interfere with normal cellular activities such as protein synthesis and energy metabolism, causing subcellular organ damage and, ultimately, cell death. Adipose tissue is a reservoir for other virus including influenza A virus, human adenovirus AD-36, and cytomegalovirus (40). Adipose tissue expresses ACE and DPP4 for SARS-CoV-2 virus infection, and the increased volume of adipose tissue in obesity may serve as a larger reservoir for SARS-CoV-2.

The first virus receptor found in adipose tissue is ACE2. SARS-CoV-2 uses the viral S protein for host cell entry. The protein consists of 2 subunits with distinct functions. The surface subunit (S1) binds to ACE2 on the host cell membrane, whereas the transmembrane subunit (S2) facilitates fusion of the viral membrane with the host cell membrane (41). The S protein binds to ACE2 through the receptor-binding domain region (42). Transmembrane protease serine 2 cleaves the S protein to facilitate the fusion of SARS-CoV-2 and host cell membranes. Because of this, the S protein is a major target in exploration of antivirus vaccines worldwide. Interestingly, ACE2 is expressed by adipocytes in the adipose tissue (43, 44). ACE2 gene expression is higher in the visceral and subcutaneous adipose tissues than lung tissue in the human body according to gene expression profile (44). Moreover, an increase in transcription, expression, and enzymatic activity of ACE2 was observed in adipose tissue in obese mice (45). A study of a large cohort of obese patients with COVID-19 revealed serum ACE2 elevation (46). The high adipose ACE2 expression was reported with more mortality in obese COVID-19 patients (44). These studies suggest that adipose tissue may contribute to the severity of COVID-19 through expression of high expression of ACE2 (47). However, mechanism of the ACE2 action remains unknown.

Glucose may increase the binding activity of ACE2 to SARS-CoV-2 in obesity (48). Glycosylation of ACE2 and the viral S protein under hyperglycemic conditions was found to increase the affinity and interaction of the 2 proteins promoting virus entry into host cells (49-51). Glycosylation of the human ACE2 receptor contributes substantially to virus binding. The glycan at the N322 site in ACE2 interacts tightly with the receptor-binding domain of the S protein to strengthen the complex (50). Cryoelectron microscopy indicates that the viral S protein is extensively glycosylated to facilitate binding to the ACE2 receptor (49). Uncontrolled hyperglycemia might induce glycosylation of ACE2 and the S protein of SARS-CoV-2; however, the stable glucose adducts require long-term exposure to hyperglycemia. The glycosylation effect remains to be verified as the exposure time to hyperglycemia is only few weeks in COVID-19. However, clinical studies have demonstrated that hyperglycemia independently increased the

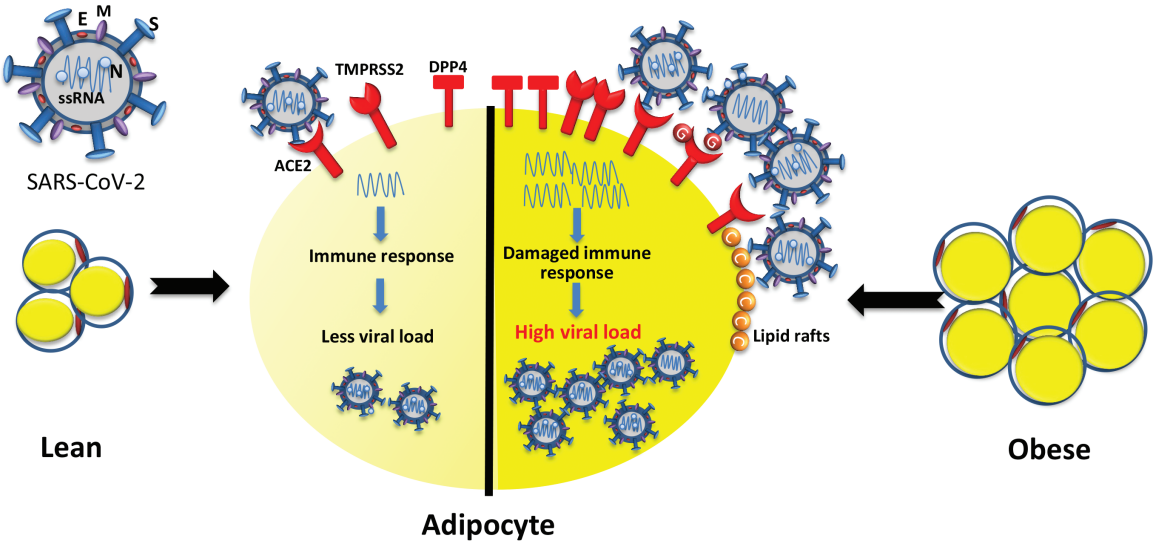

Figure 2. SARS-CoV-2 and surface receptors on adipocytes. The main structural proteins of SARS-CoV-2 include the spike (S), membrane (M), nucleocapsid (N), and envelope I proteins. The cellular angiotensin-converting enzyme 2 (ACE2) exopeptidase acts as a receptor for SARS-CoV-2 S protein binding. Subsequent cleavage of the S protein by cellular transmembrane serine protease 2 (TMPRSS2) results in membrane fusion and viral entry. DPP4 acts as another receptor for SARS-CoV-2 cell entry. Obesity-induced overexpression of ACE2, TMPRSS2, and DPP4 result in more virus entry into adipocytes. Glycosylation (G) of ACE2 on adipocytes and S proteins on viruses increases the binding activity. Augmented lipid rafts supplied by cellular cholesterol also increase binding between ACE2 and the S protein further facilitating viral entry.

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through formation of a complex with mitochondrial antiviral signaling (MAVS) protein at mitochondrial-associated endoplasmic reticulum membranes to activate IRF3/IRF7 (86) (Fig. 3). This complex represents a crosstalk between the RNA and DNA sensing pathways. Adipocytes may use several pathways, such as TLR7/8, MDA5, RIG-I, and the noncanonical STING pathway to sense SARS-CoV-2 and initiate production of IFNs.

SARS-CoV-2 uses multiple strategies to antagonize the IFN system (74, 84), which include the viral nonstructural proteins (Nsp) 16, Nsp3, and Nsp1. NspP16 suppresses global messenger RNA (mRNA) splicing to diminish viral RNA recognition by intracellular helicase receptors. Nsp16 encodes 2'-O-methyltransferase for posttranscriptional modification of the 5′-terminal RNA cap to a methylated 5′-cap-1, allowing viral RNA to mimic the host cell's mRNA (87). Therefore, the viral RNA is capable of escaping detection by TLR-7/8 and MDA5. Nsp3 inhibits the innate immune response by inhibiting phosphorylation, dimerization, and nuclear translocation of the transcription factor IRF7 or IRF3 (88). Nsp1 is found in the closest portion of the 5′ end encoded by ORF1a/b. Nsp1 inhibits IFN-β production by accelerating degradation of IFN-β mRNA (Fig. 3). Expression of IFN-stimulated genes is significantly decreased in obesity, contributing to impaired immune responses. These studies suggest that adipocytes have an innate immune activity against SARS-CoV-2 and a defect in this activity occurs in obesity, increasing the risk of severe COVID-19.

NK Cells and Lymphocytes

Immune cells are subject to metabolic reprogramming in the circulation, lymph nodes, and adipose tissue in obesity. The metabolic changes decease the activities of NK, iNKT, T, and B cells, which compromise the antiviral immune response in COVID-19.

NK cells are effector lymphocytes of the innate immune system, which recognize and destroy infected cells through production of cytotoxic molecules, such as granzymes and perforins, fragment receptor ligand, and tumor necrosis factor (TNF)-related apoptosis-inducing ligand. NK cells recognize infected cells marked with antibodies through Fc receptors and destroy them through antibody-dependent cellular cytotoxicity (Fig. 4). In obesity, the number of NK cells is increased in visceral adipose tissue due to local cell

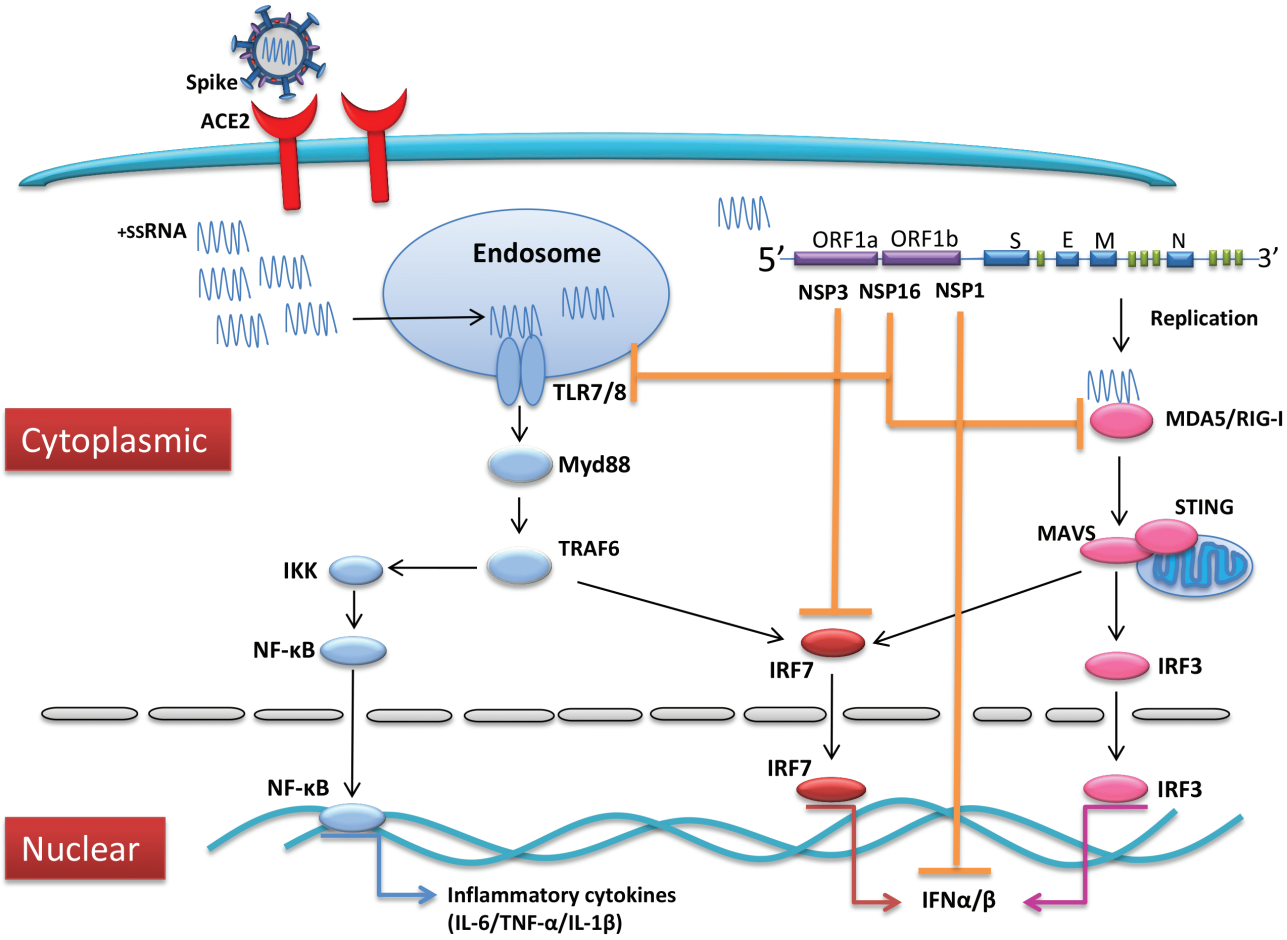

Figure 3. Suppression of antivirus responses by viral components in adipocytes. Various pattern recognition receptors, including toll-like receptor (TLR) 7/8, melanoma differentiation-associated antigen 5 (MDA5)/retinoic acid-inducible gene I (RIG-I), and stimulator of interferon genes (STING), mediate innate antiviral responses. TLR7/8 senses single-stranded RNA leading to activation of interferon regulatory factor 7 (IRF7) and expression of interferon (IFN)-α/β through the Myd88-dependent pathway; RIG-I and MDA5 detect double-stranded RNA during viral replication leading to activation of IRF3 and IRF7 and expression of IFN-α/β through mitochondrial antiviral signaling protein (MAVS); STING binds with MAVS to activate IRF3/IRF7, thereby allowing crosstalk between the RNA and DNA sensing pathways. These processes can be inhibited by SARS-CoV-2–derived nonstructural protein (Nsp) 16, Nsp3, and Nsp1.

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proliferation (89); however, NK cells activity is reduced (90). There is reduced expression of activating receptors KIR2DS4 and NKp46, increased expression of inhibitory NK cell receptor NKG2A (NK group 2 member A), and decreased TNF-related apoptosis-inducing ligand expression on NK cells (91). This suppression is related to the energy metabolism disorder in NK cells in obesity (27, 92). NK cell activity is highly dependent on glycolysis, which is inhibited in obesity by the increased activity of peroxisome proliferator-activated receptors (27). Glycolysis inhibition, together with other changes such as excessive exposure to free fatty acids and interleukin (IL)-6, may inhibit NK cell production of granzyme B and perforin in obesity (93). In summary, NK cell function is reduced in obesity through metabolic reprogramming and glycolysis inhibition.

iNKT cells are a subset of T lymphocytes that coexpresses NK-lineage receptor and an invariant T-cell receptor. iNKT cells are in high abundance in adipose tissue and sense lipid-related antigens presented by adipocyte. iNKT cells produce perforin and Fas ligand to generate cytotoxic effects on virus-infected cells (94) (Fig. 4). iNKT cells may secret cytokine IL-4 to regulate other immune cells. In obesity, the number of iNKT cells is decreased in adipose tissue (95), contributing to impaired virus immunity in obesity.

Cytotoxic $CD8^+$ T lymphocytes play an important role in the adaptive immune response by eliminating virus-infected cells through perforin and granzyme released in an antigen-specific manner (Fig. 4). However, the numbers of $CD8^+$ T and $CD4^+$ T lymphocytes are decreased in the circulation of patient with severe COVID-19. $CD8^+$ T cells require INF-γ and IL-2 secreted from $CD4^+$ T lymphocytes to activate and proliferate. Decreased numbers of $CD4^+$ T lymphocytes in obese patients with COVID-19 leads to lower levels of circulating INF-γ and IL-2 cytokines and decreased activation of $CD8^+$ T cells (96, 97). $CD4^+$ T cell alterations from metabolic disorders in obesity along with increased T cell exhaustion and reduced T cell proliferation lead to reduced levels of circulating T cells (98). Therefore, obesity impairs the adaptive immune responses in COVID-19 by causing metabolic disorders in $CD4^+$ and $CD8^+$ T cells.

B lymphocytes produce antibodies in the humoral immune response to virus infection. The antibodies mark virus

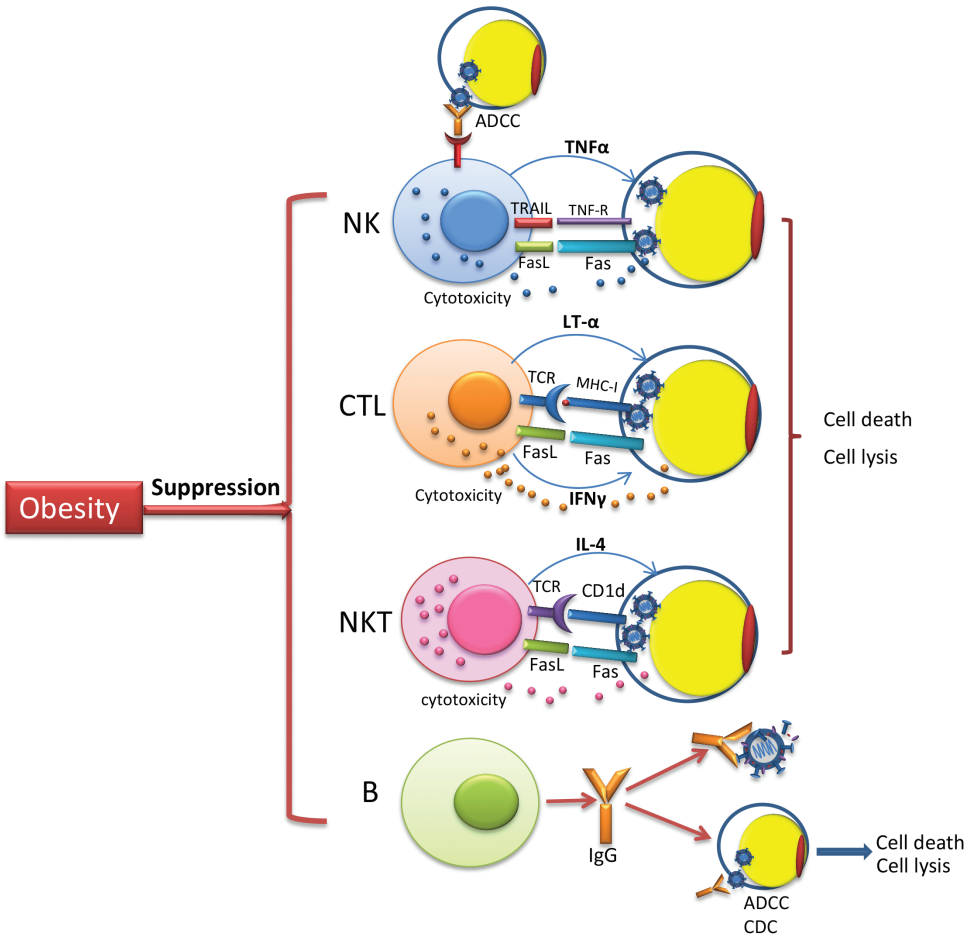

Figure 4. Obesity suppresses the crosstalk between infected adipocytes and immune cells. Various immune cells including natural killer (NK), invariant natural killer T (iNKT), T and B cells, reside in the extracellular matrix of adipocytes to constitute local antiviral immunity. NK recognize virus-infected adipocytes through activating receptors and destroy the cells through cytotoxicity, fragment receptor ligand (FasL), tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), and antibody-dependent cellular cytotoxicity (ADCC). Cytotoxic T cells recognize antigens presented by MHC-I molecules on virus-infected cells in an antigen-specific manner. They kill the infected cells by releasing cytotoxic enzymes and induce TRAIL and FasL to bind with targets. Natural killer T cells sense lipid-related antigens presented by CD1 in adipocyte and produce cytotoxic effects and FasL to promote virus-infected cell death. The antiviral function of B cells is dependent on antibody secretion. Antibodies neutralize antigens and mark them for elimination, through the process of complement-dependent cytotoxicity and ADCC. The functions and numbers of these cells are suppressed by obesity.

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antigens for neutralization and elimination and involve complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity in the clearance of infected cells (Fig. 4). In obesity, there is inhibition of deaminase activation, leading to B-cell inability to produce antibodies, compromising humoral immunity (99). In addition, B cells produce more proinflammatory cytokines in obese subjects, further contributing to immune disorder in COVID-19 (100, 101). B cells suffer functional deficiency in obesity, increasing the risk for severe COVID-19 infection and cytokine storm.

Macrophages Contribute to the Cytokines Storm

Chronic low-grade inflammation is a well-established characteristic of obesity, in which white adipose tissues, especially visceral fat deposits, are the major players (102). The inflammation is featured by an increased number of macrophages, regulatory T cells, and eosinophils in the adipose tissue. Subpopulations of macrophages are altered with a decrease in M2-like macrophages (alternatively activated macrophages) and an increase in M1 macrophages. This alteration leads to a reduction in anti-inflammatory cytokines, such as IL-10, IL-4, and IL-13 (Fig. 5) and an elevation in proinflammatory cytokines, contributing to sustained low-grade inflammation. The response induces neutrophil infiltration followed by accumulation of proinflammatory $CD8^+$ T cells and $CD4^+$ Th1 cells. These cells further increase the levels of TNF-α, IL-1, IFN-γ, and IL-6 to exacerbate the existing inflammatory state to culminating into cytokine storm (Fig. 5).

A cytokine storm is a quick and robust release of proinflammatory mediators following an inappropriate immune response to antigens. Severe COVID-19 cases are associated with an uncontrolled immune response leading to an immense elevation of proinflammatory (INF-γ, TNF-α, IL-6, IL-8, etc) and anti-inflammatory cytokines (IL-10, IL-4, etc) (103). The cytokine storm is closely associated with severe COVID-19 and responsible for multiorgan failure (104, 105). Infection further adds to the already elevated levels of cytokines in obesity and increases the risk of cytokine storm in severe COVID-19.

Adipokines in Severe COVID-19

Several studies suggest significant roles of adipokines/hormones in severe COVID-19 (106). Adipokines, such as leptin and adiponectin, are produced by adipocytes to maintain the energy homeostasis in physiological conditions.

Leptin levels are elevated in the circulation of obese subjects, resulting in hyperleptinemia and leptin resistance (107). Leptin is a proinflammatory adipokine that activates macrophages and T cells resulting in expression of TNF-α, IL-1β, and IL-6 (108). The protein structure of leptin is similar to that of other proinflammatory cytokines including IL-6, IL-11, IL-12, granulocyte colony-stimulating factor, etc, which may permit crosstalk of these cytokines with the leptin receptor (108, 109). Increased leptin contributes to chronic low-grade inflammation in obesity (Fig. 5) and obesity-related complications. A study found that COVID-19 patients with higher levels of serum leptin were more likely to require mechanical ventilation over the control group (110). The hyperleptinemia may increase the risk of cytokine storm by induction of superactivation of immune cells. However, this role of leptin remains to be tested in experiments. If proven, pharmacological interference of leptin may be considered in the treatment of obese COVID-19 patients.

Adiponectin is 1 of the most abundant proteins in the serum. Its level is reduced in obesity. In contrast to leptin, adiponectin has an anti-inflammatory activity, which induces expression of anti-inflammatory cytokine IL-10 and inhibits expression of proinflammatory cytokines such as TNF-α and IL-6. Adiponectin deficiency in obesity is associated with an exaggeration of inflammation. A study for screening glucoregulatory hormones revealed that adiponectin level is also reduced in the circulation of COVID-19 patients (80). Hamsters infected with SARS-CoV-2 exhibited a strong antiviral response in adipose tissue with a reduced expression of adiponectin (80). The exact role of adiponectin remains to be investigated in COVID-19 although it is considered beneficial in the control of severe COVID-19 (111).

Dysfunctional Mitochondria in Cytokine Storm

Mitochondria produce 90% of the adenosine 5′-triphosphate (ATP) and reactive oxygen species (ROS) in cells for execution of various cellular activities (112). According to classical biochemical principles, ATP is produced on demand, and intracellular ATP levels are maintained at a set point between 1.5 and 2.5 mM in a cell type-dependent manner. However, oversupply of energy materials including glucose, fatty acids, and amino acids in obesity leads to "mitochondrial overheating" and ATP overproduction in cells (113). The extra ATP causes mitochondrial dysfunction by inhibiting mitochondrial biogenesis and mitophagy, which are essential in the maintenance of the quality and quantity of mitochondria. Dysfunctional mitochondria predispose to more mitochondrial ROS (mtROS) production, oxidative stress, and exposure of mtDNA in the cytoplasm. mtROS and mtDNA both promote inflammatory responses and immune dysregulation (Fig. 6).

In the course of SARS-CoV-2 infection, oxygen supply is reduced in the peripheral tissues due to structural damage in the lungs by the viral infection. Hypoxia causes energy metabolism reprogramming in mitochondria with a shift from oxidative phosphorylation toward glycolysis (112). The mechanism is related to activation of the hypoxia signaling pathway including the hypoxia inducible factor 1. The metabolic reprogramming may lead to an increased production of mtROS and mtDNA through hypoxia inducible factor 1 activation, which in turn promotes the inflammasomal activation for IL-1β and IL-18 release, all contributing to the pathogenesis of cytokine storm. The NLR family pyrin domain-containing protein 3 (NLRP3) inflammasome, containing NLRP3, is activated by several mitochondrial ligands, such as mtDNA, ATP, and mtROS (114). After NLRP3 activation, an adaptor protein of apoptosis-associated speck-like (ASC) protein containing a C-terminal caspase recruitment domain recruits pro-caspase-1 to the inflammasome. Caspase-1 cleaves pro-IL-1β and pro-IL-18 to generate the mature cytokines for secretion (Fig. 6).

Mitochondrial damage-associated molecular patterns (DAMPs; mtROS and mtDNA) are important factors in the cell detection of infection. However, the pathway may cause an undesirable immune response resulting in unwanted

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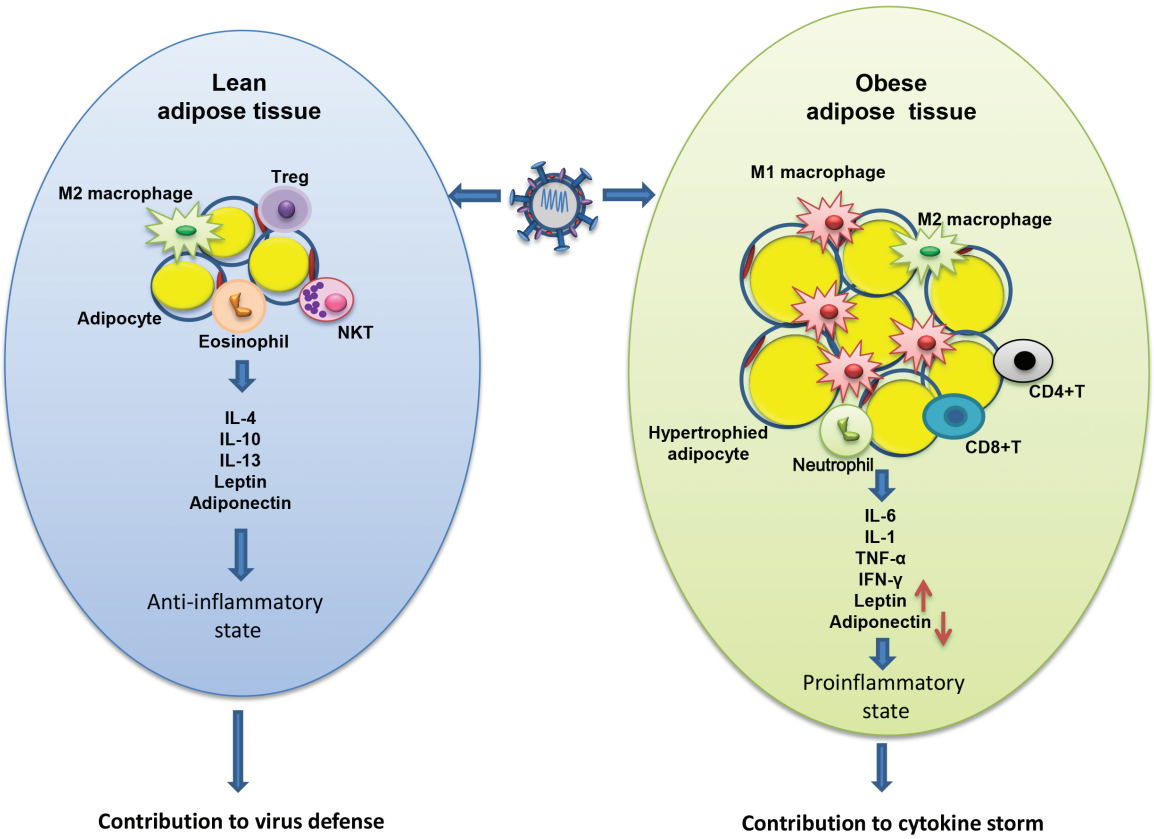

Figure 5. Obesity-associated chronic inflammation and adipokines contribute the cytokine storm in COVID-19. In the lean state, the adipose tissue microenvironment is a well-balanced crosstalk between the adipocyte and immune cells, including regulatory T cells, eosinophils, and invariant natural killer T cells. M2-like resident macrophages predominate to maintain the homeostasis. These cells secrete anti-inflammatory cytokines, such as interleukin (IL)-10, IL-4, and IL-13. Balanced levels of leptin and adiponectin suppress proinflammation in an anti-inflammatory state. In obesity, hypertrophic adipocytes are characterized by a proinflammatory phenotype. Early transient infiltration of neutrophils is followed by infiltration and accumulation of proinflammatory CD8 + T cells, CD4 + Th1 cells, and M1 macrophages. The increased release of proinflammatory cytokines (tumor necrosis factor-α, IL-1, interferon-γ, IL-6) in the obese state adipose tissue microenvironment, increased leptin, and decreased adiponectin leads to a high inflammatory state and results in chronic low-grade systemic inflammation.

inflammation in certain conditions, such as obesity. In obesity, mitophagy is defective, leading to accumulation of damaged mitochondria and release of mitochondrial DAMPs into the cytosol. Accumulation of DAMPs triggers an uncontrolled proinflammatory response in obesity, which is further enhanced in COVID-19. This may contribute to progression to severe cases with cytokine storm in obese COVID-19 patients.

The mitochondrial dysfunction may also contribute to cytokine storm through production of intermediate metabolites of the tricarboxylic acid cycle. One example is α-ketoglutarate (α-KG), which plays an important role in the proinflammatory response. α-KG is found to be elevated in macrophages after lipopolysaccharide stimulation and plays a role in the production of cytokines. Elevation of α-KG levels have been reported in T cells in rheumatoid arthritis (115). Lipopolysaccharide levels in the circulation and α-KG levels in the liver of obese mice are elevated (116), which supports a role of α-KG in the proinflammatory response in obesity. Succinate is another example of a proinflammatory metabolite of the tricarboxylic acid cycle. Succinate elevation promotes macrophage activation and production of proinflammatory cytokines (117). Succinate is elevated in the circulation of obese mice and patients with T2DM and promotes inflammation through succinate receptor 1 (118). In addition, protein modification by succinylation is another mechanism in the regulation of the inflammatory response. Therefore, the increased levels of mitochondrial metabolites (α-KG and succinate) may contribute to cytokine storm in the pathogenesis of severe COVID-19 in obese patients.

Impact of Obesity in the Treatment and Prevention of COVID-19

Given the strong impact of obesity in the immune system, obesity may negatively affect the treatment and prevention of COVID-19. To control the negative effects, weight loss is the first choice, which may be achieved through behavioral modifications including calorie restriction, physical activity, or exercise training.

Adequate nutritional status is an essential element for antiviral defense. In a systematic review, vitamins (A, C, D, and E), omega 3 fatty acids, and minerals (zinc and iron) were found to be fundamental for an adequate antiviral immune response to SARS-CoV-2 (119). Obesity is recognized as a vitamin-deficient state despite energy surplus. In particular, the prevalence of vitamin D deficiency is 35% greater in obese individuals (120). Vitamin D deficiency

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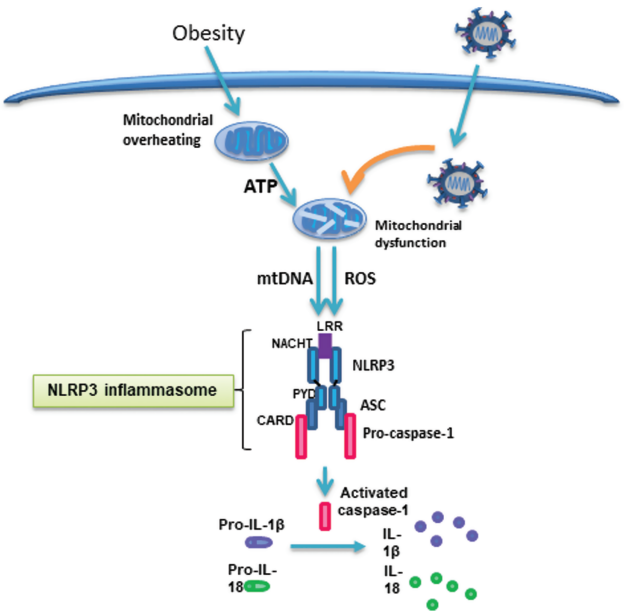

Figure 6. Dysfunctional mitochondria in obesity stimulate inflammasome activation. Obesity induces mitochondria overheating to cause extra adenosine 5′-triphosphate (ATP) production, which eventually results in mitochondrial dysfunction. Dysfunctional mitochondria predispose to more mitochondrial reactive oxygen species (mtROS) production and exposure to mitochondrial DNA (mtDNA). Mitochondrial ligands, such as mtDNA, ATP, and mtROS induces the activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome , which contains three parts: receptor, ASC and pro-caspase-1. The receptor includes the leucine rich repeats domain, NACHT domain and pyrin domain. After NLRP3 activation, an apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (CARD) adaptor protein recruits pro-caspase-1 to the inflammasome. After activation, caspase-1 cleaves pro-interleukin (IL)-1β and pro-IL-18 to IL-1β and IL-18, leading to their secretion.

also increases the risk of severe COVID-19, especially in the obese population (121). However, vitamin D supplementation as prevention and adjuvant therapy for COVID-19 is controversial. Studies have concluded that there is no evidence to support taking vitamin D supplements in COVID-19 (122), and at present, there is no consensus for vitamin D supplementation in the prevention or treatment of COVID-19. Adherence to existing public health advice on vitamin D supplementation is recommended to prevent vitamin D deficiency and maintain bone and muscle health during the COVID-19 pandemic.

Vaccination is the best choice for the prevention and control of COVID-19. In fact, obesity may reduce the efficacy of vaccination against SARS-CoV-2 because of immune cell dysfunction. Reduced efficacy of the influenza vaccine has been observed in obese individuals. One study including 21 patients suggests that obesity is associated with a reduced adaptive immune response to a COVID-19 mRNA vaccine, which can be reversed with weight loss (123). Current evidence shows that 3 major brands of SARS-CoV-2 vaccines, Pfizer-BioNTech BNT162b2, Moderna mRNA-1273, or Janssen/Johnson & Johnson Ad26.CoV2.s, have similar efficacy between obese and nonobese individuals (124). However, analysis of the efficacy of SARS-CoV-2 vaccines in obesity and selection of adequate vaccines should continue to be considered in the future.

For COVID-19 patients with obesity, guidelines for supportive treatment and intensive care have been well established (125). Efficacy of antiviral medication may be reduced in obese patients. Hydroxychloroquine was reported to interfere with the replication cycle of SARS-CovV2 and reduce viral entry. However, recent studies did not show that hydroxychloroquine administration was associated with a significant reduction in the end point of incubation or death rate during COVID-19 treatment (126). Lopinavir/ritonavir, inhibitors of 3-chymotrypsin-like protease, which is involved in viral ribonucleic acid processing, was previously used as the first-line antiviral agent in the treatment of COVID-19. The medicines have side effects including lipodystrophy and hyperlipidemia. However, the efficacy of lopinavir/ritonavir has come into question as multiple studies did not find it to reduce mortality significantly (127). The conclusion that lopinavir/ritonavir combination was no better than standard care in the treatment of COVID-19 patients still remains (128). However, favipiravir shows promising efficacy in COVID-19 patients with improvement in clinical parameters such as length of hospitalizations and clinical recovery, although the results were not confirmed in some studies (125). In this case, antidiabetic agents such as DDP4 inhibitors, GLP-RA, and antiviral agents (eg, favipiravir) are all considered for COVID-19 treatment.

Concluding Remarks

In this review, we discuss mechanisms by which obesity contributes to the high mortality of obese COVID-19 patients with a focus on adipose tissue. Accumulation of adipose tissue around the chest and in the peritoneal cavity generates a mechanical pressure that restricts the respiratory capacity of the lungs. The restriction promotes systemic hypoxia in the presence of parenchyma damage by viral infection. The hypoxia exuberates the metabolic and immunologic disorders that preexist in obesity, such as accumulation of intermediate metabolites, chronic inflammation, and hyperleptinemia. Hypoxia inhibits mitochondrial respiration and promotes metabolite accumulation inside of cells. This induces gene transcription and enhances the inflammatory response through adipocyte secretion of leptin. The elevated levels of the metabolites leptin and cytokines may amplify the hypoxia signal in macrophages and T cells leading to cytokine storm. ATP overproduction in multiple cell types in obesity leads to inhibition of autophagy by inactivation of AMP-activated kinase. This leads to mitochondrial degeneration, more production of mtROS, and more exposure of mtDNA. The TLR and STING pathways may sense mtDNA in macrophages and T cells to favor cytokine production. Metabolic disorders in adipocytes and immune cells cause restriction of their immune responses to viruses such as SARs-CoV-2. In endothelial cells and platelets, metabolic disorders in combination with the cytokine storm may cause circulation defects for multiorgan failure. Additionally, adipose tissue may serve as a reservoir for the SARS-CoV-2 virus and promote virus spreading. ACE2 and DPP4 elevation in obesity may promote virus entry into host cells for increasing risk for severe infection. In summary, metabolic disorders from energy surplus occur in various cell types in obesity and serve as a foundation for the increased risk of cytokine storm and multiorgan failure in severe COVID-19. Correction of energy surplus by weight loss through various

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approaches is recommended in the prevention and treatment of COVID-19 in obese patients.

Funding

This work was supported by grants from the Natural Science Foundation of China (grant nos. 81500675 and 82070895), research and training funds of School of Basic Medical Sciences (JCYXYKY202023) to L.Y. and the National Key Research and Development Program of China (2018YFA0800603) and a project (19ZR1439000) of the Shanghai Association for Science and Technology to J.Y.

Conflict of Interest Disclosure

The authors have declared that no competing interests exist.

Data Availability

The data used to support the findings of this study are included within the article.

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