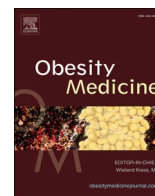




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## Review

## Single cell sequencing unraveling genetic basis of severe COVID19 in obesity



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## ABSTRACT

COVID-19 has shown a substantial variation in the rate and severity by which it impacts different demographic groups. Specifically, it has shown a predilection towards obese patients as well as other vulnerable groups including predilection of males over females, old age over young age and black races over Caucasian ones. Single cell sequencing studies have highlighted the role of cell polarity and the co-expression of proteases, such as Furin, along with ACE2 in the genesis of coronavirus disease rather than exclusively link tissue involvement with ACE2 levels thought previously. It has also forged a connection between the genetic and immune cellular mechanisms underlying COVID infection and the inflammatory state of obese patients, offering a more accurate explanation as to why obese patients are at increased risk of poor COVID outcomes. These commonalities encompass macrophage phenotype switching, genetic expression switching, and overexpression of the pro-inflammatory cytokines, depletion of the regulatory cytokines, in situ T cell proliferation, and T cell exhaustion. These findings demonstrate the necessity of single cell sequencing as a rapid means to identify and treat those who are most likely to need hospital admission and intensive care, in the hopes of precision medicine. Furthermore, this study underlines the use of immune modulators such as Leptin sensitizers, rather than immune suppressors as anti-inflammation therapies to switch the inflammatory response from a drastic immunological type 1 response to a beneficial type 2 effective one.

## 1. Introduction

Since the emergence of Severe Acute Respiratory Syndrome

Coronavirus 2 (SARS-COV2), the scientific community has been pushing the current boundaries of virology, in search of a widely anticipated breakthrough. The novel virus, Coronavirus Disease 2019 (COVID-19), responsible for more than 18 million infections and 700 000 deaths

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worldwide, is still ongoing. With the race for a vaccine intensifying, unraveling the reasons behind the variable immune response in COVID-

infection, (3) the likelihood of infection in certain subgroups of patients, namely, the elderly, obese, as well as the protective effect of female

Abbreviations			
ARDS	Acute respiratory distress syndrome	AMs	Alveolar Macrophages
ATM	adipose tissue macrophages	IL:	Interleukins
(BALF)	Bronchoalveolar lavage fluid	SPPN	alternatively called Osteopontin
CCL/CXCL:	chemokines ligands	HO-1	Hemo-Oxygenase
CCR2	chemokine receptor type 2	ROS	Reactive oxygen species
CD	Cluster of differentiation	TNF	tumor necrosis factor
COVID-19	Coronavirus disease 2019	JNK	c-JUN NH2-terminal kinase
FABP4	Fatty acid binding protein 4	IKK	IκB kinase
FCN-1	Ficolin-1	S6K	ribosomal protein S6 kinase 1
FSC	Forward Scatter	PBMCs	peripheral blood mononuclear cell
HOMA IR	Homeostatic Model Assessment for Insulin Resistance	MCS	monocytes
MCP-1	Monocyte Chemoattractant Protein-1	DCs	dendritic cells
PD-1	Programmed Death 1 cytokine	NK	natural killer cells
PPARγ	Peroxisome Proliferated Activated Receptor gamma agonists	TCs	T cells
SARS-COV2	Severe Acute Respiratory Syndrome Coronavirus 2	mRNA	messenger ribonucleic acid
ScRNA-seq	single cell sequencing of RNA	GIT	gastrointestinal tract
SPP1+	Osteopontin	ICU	intensive care unit
ACE2	Angiotensin Converting Enzyme 2	ER	estrogen receptor
TMPRSS2	Transmembrane protease serine 2	APC	antigen presenting cells
		CDC	centers for disease control and prevention
		AA	African American

19 patients has taken the research field by storm. Interestingly, COVID-19 patients show symptoms that are highly variable in intensity and severity, ranging from asymptomatic cases to hospitalization and intensive care treatment (Kim and Kim, 2020).

Researchers are striving to establish correlations between comorbid conditions and the exaggerated immune response to COVID-19, which often leads to poor prognosis. The possible genetic correlation that links the immune response to COVID-19 and obesity, proposes a new era in genetic testing and precision medicine that can drastically improve outcomes for patients with severe COVID-19.

ScRNA-seq (Single cell Ribonucleic Acid Sequencing) focuses on the analysis of individual cells, instead of bulk cell populations, and can lead to a more insightful characterization of local microenvironments than traditional sequencing methods (Hwang et al., 2018).

The first goal of this review is to elucidate the various benefits added by single cell sequencing to the current understanding of COVID-19 infection including: (1) the specific tropism of certain tissues, (2) the immunologic response that characterizes mild, moderate, and severe

gender in severe forms of infection.

Second, we hypothesize that the inflammatory and immune mechanisms in response to COVID-19 are similar to those involved in the generalized inflammatory state of obese individuals, putting them at a greater risk of hospitalization and poor disease outcome. In this review, we analyze findings on the immune response to COVID-19 and correlate it to the activation of innate immunity in obesity, aiming to establish guidelines for predicting the genetic predisposition to severe COVID-19.

## 2. Specific tropism of certain tissues

Three proteins have been related to the cellular entry and activation of SARS-CoV-2, namely ACE2 (Angiotensin Converting Enzyme 2), TMPRSS2 (Transmembrane Protease 2), and Furin.

Studies based on the profiling of ACE2, TMPRSS2, and Furin mRNA (Messenger Ribonucleic acid) and protein expression, proposed multiple tissue cells as potential targets of SARS-CoV-2 virus, including cells from almost every important human system (Table 1). It was previously

**Table 1**

Basal levels of expression of Key entry and activation proteins in COVID-19 in different tissues.

	ACE2		FURIN		TMPRSS2	
	mRNA	Protein	mRNA	Protein	mRNA	Protein
Lung	Low	Low	Low	High	Low	Low
CNS	Low	Not detectable	High	High	Low	Not detectable
GIT	High	High	Low	Moderate	High	Low
Liver	Low	High	Moderate	Moderate	Low	Not detectable
Urinary system	Low	High	Low	High	High	High
Male Genital system	Low	High	Moderate	Moderate	High	Moderate
Female Genital S	Low	Not detectable	High	High	Low	Not detectable
Heart	Low	Not detectable	Low	Low	Not detectable	Not detectable
Endothelium	High	High	High	High	High	Moderate
Adrenal gland	Moderate	Moderate	Low	High	Low	Moderate

Abbreviations: ACE2: Angiotensin Converting enzyme 2, CNS: Central Nervous System, GIT: Gastrointestinal, mRNA: messenger Ribonucleic acid, Transmembrane Protease S2.

Note: mRNA and Protein expression were considered low when <30%, Moderate: 31–60%, and high when >60%.

References (Fagerberg et al., 2014; Pontén et al., 2008; Shulla et al., 2011; Thul et al., 2017; Thul and Lindskog, 2018; Zhou et al., 2020).

thought that lung expression of ACE2 receptors is the highest, being the most heavily involved organ. However, emerging evidence pointed to a discrepancy between the level of expression of such key proteins, and tissue involvement. Moreover, a mismatch was often found between both levels. The adrenal gland expresses little mRNA but showed a median level of ACE2 protein, while other tissues, such as the heart muscle and adipose tissue, showed a high level of expression of mRNA, but undetectable protein levels. Protein expression detection *in situ* is hence necessary beside mRNA expression analysis (Heialy et al., 2020).

Although the lungs are the most severely impacted organs in COVID-19, the degree of expression of the three key proteins was found to be low. Alveolar Type 2 cells, alternatively known as type 2 pneumocytes, were the only lung cells to express the Furin and ACE2, while other cells have been found with undetectable levels of ACE2. However, the lung endothelial cells were noted to highly express both ACE2 and Furin. This further demonstrates the vascular inflammatory origin and micro-thrombi induced damage causing the SARS-CoV-2 manifestations. An example of this is the identification of endotheliitis in postmortem samples from COVID patients and further explains the mounting rise of the use of blood thinners to treat them (Braun and Sauter, 2019; Xu et al., 2020).

Alternatively, the gastrointestinal tract (GIT) was found to be the most expressive organ of the three key proteins, raising the awareness of the GIT being a potential reservoir for the disease. Further claims have been made, albeit controversially, to the potential viability of COVID viral particles in the environment, enough for the possibility of faecal-oral transmission. Several studies not only noted the prolonged viral shedding from the gastrointestinal tract beyond that of the respiratory systems for up to 5 weeks, but also the perseverance of rectal swabs farther than nasopharyngeal swabs. Studies have also reported the often-underestimated associated diarrhea with regards to its onset (1–8 weeks after the onset of COVID), duration (1–14 days), severity (up to 9 bowel movements per day), and nature (34.3% watery diarrhea). The prognosis of SARS-CoV-2 patients with gastroenteric manifestations appears to be more adverse than those without, with almost half the percentage of recovered and discharged patients. Speculations have been made that the origin of COVID's pulmonary manifestations is a ramification of the gastrointestinal system's involvement. This is thought to be due to the communication of their microflora and to the role of the GIT in increasing the inflammatory cytokines responsible for inflammatory lung damage, owing to its high expression of ACE2 and Furin (Gu et al., 2020; Samanta et al., 2020).

A final finding is the high expression of Furin in the placenta. This goes in agreement with the results of the systematic review by our working group. We analyzed the pregnancy outcomes of more than 1700 pregnant mothers infected with COVID-19 and found out that placental abnormalities with subsequent fetal hypoxia are the most frequently encountered complication in pregnancies complicated by COVID-19 (Abdelmassih et al., 2020).

### 3. Striking similarity of lung milieu in severe COVID-19 and adipose tissue changes in obesity

Liao et al. compared the cellular immune response in mild and severe COVID-19 cases. The study, using single cell sequencing of RNA (scRNA-seq) analysis, compared the bronchoalveolar lavage fluid (BALF) from three cases with moderate infection and six cases with severe COVID-19 (Liao et al., 2020). To date, there is no single study describing the specific cellular changes by single cell sequencing occurring in the lung milieu of obese COVID-19 patients compared to lean subjects. However, it is well established that obesity is characterized by an overactive innate immunity, which stems from nutrient overload and results in a hyper-inflammatory state. This low-grade inflammation extends over a number of organs involved in energy homeostasis including the liver, adipose tissue, pancreas, and skeletal muscles. (Saltiel and Olefsky, 2017). Of the brilliantly complex and intertwined inflammatory

mechanisms, surprisingly, there is an intriguing similarity between the immune cellular landscape occurring in the lung milieu of severe COVID-19 patients, and the immune cellular alterations occurring in the adipose tissue.

#### 3.1. Lung macrophages

##### 3.1.1. Macrophage phenotyping switching

Macrophages manifest distinct phenotypes according to the organs in which they reside. They also flexibly switch their character to adapt to changing environments. One of the commonest interchanges of the macrophage phenotype is between M1 (pro-inflammatory) and M2 (regulatory) macrophage phenotypes.

A comparison of macrophage subphenotypes in the lung milieu in severe COVID-19 patients has revealed that the expressed macrophages showed predominant features of M1 macrophages with high Forward Scatter (FSC) closer to that seen in M1. Though very similar to the M1 phenotype, the macrophage phenotype encountered in severe cases of COVID-19, also shows some features of M2 macrophages such as the expression of Proliferated Activated Receptor gamma agonists (PPAR $\gamma$ ). (Halaney et al., 2015).

It was previously widely accepted that macrophage switching in obese states occurs in favor of M1 pro-inflammatory macrophages until Castoldi et al. (Castoldi et al., 2016) outlined the presence of a third phenotype sharing features of both types. This third phenotype mimics the one found in the lung micro-environment in COVID-19, which is also sensitive to inhibition by PPAR  $\gamma$  agonists as suggested by Ciavarella et al. (Ciavarella et al., 2020). The balance of pro-versus anti-inflammatory activation determines the protective versus the deleterious impact on the host. The persistence of M1-like macrophages in severe COVID-19 not only increases short term mortality, but can also lead to long term complications due to delayed recovery of affected tissues. Rodriguez and colleagues profiled the course of resolving versus persistent inflammation, with special reference to IL-1 (Interleukin 1) family molecules. An independent single cell mRNA analysis of peripheral blood mononuclear cells during early recovery of COVID-19 infection revealed an increased ratio and level of classical CD14++ (Cluster of differentiation) IL-1 $\beta$ + monocytes. It is worth mentioning that those receptors are another evidence of macrophage polarization toward M1 macrophages in COVID-19 (Rodriguez et al., 2020).

##### 3.1.2. 2-Macrophage gene expression switching

Of the different macrophage subtypes, lung Alveolar Macrophages (AMs), which harbor Fatty Acid Binding Protein 4 (FABP4), constitute the majority of the macrophage population in lungs under physiological conditions (Hussell and Bell, 2014). Patients with mild COVID-19 symptoms showed this profile, while severe COVID-19 patients showed an almost total loss of lung AMs. In addition, the loss of lung AMs in severe COVID-19 patients was accompanied by an overpopulation of monocyte-derived macrophages expressing Ficolin-1 (FCN-1), and profibrotic macrophages with increased cellular levels of Osteopontin (SPP1+).

Such profibrotic macrophages express a number of chemokine ligands (CCL/CXCL), and Interleukins (IL) (CCL2, CCL3, CCL5, IL-8, CXCL9, CXCL10, and CXCL11), which makes them heavily involved in an exaggerated deleterious inflammatory reaction.

The combined effect of FABP4 depletion and FCN1+ overexpression in severe COVID-19 cases leads to the deterioration of lung function (Liao et al., 2020) due to over activation of the complement classical and alternative pathways. Surprisingly, one of the macrophages' clusters characteristic of better outcomes in the lung milieu of COVID-19 patients is the pro-fibrotic cluster. This finding goes in agreement with the clinical findings outlined by Spagnolo and colleagues that recovering cases from COVID-19 are liable to develop long-standing pulmonary fibrosis (Spagnolo et al., 2020).

Genetic switching in obesity mirrors what is observed in severe

**Table 2**  
Macrophages' subsets in lung milieu of COVID-19 patients.

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Mainly expressed Receptor	FCN1	FCN1/SPP1	SPP1	FBP4
Main Macrophage phenotype and function	M1 Proinflammatory	M1 Proinflammatory	M2 Profibrotic	M2 Immuno-regulatory
State of Dendritic cells	–	–	++	++
Antigen Presentation	Inefficient	Inefficient	Efficient	Efficient
Mild	–	–	++	++
Severe	++	++	–	–

Abbreviations: FBP4: Fatty acid binding protein 4, FCN1: Ficolin, SPP1: Osteopontin, –: Decreased, ++: Increased. (Liao et al., 2020; Mathew et al., 2020).

**Table 3**  
T cell subsets in different immunotype (1: Severe clinical spectrum, 2: Mild clinical spectrum) of COVID-19.

	Mild Infection	Severe Infection
Proliferating T cells	–	++
CD8 T cells	++	–
T regulatory cells	++	–
Innate T cells	++	–
NK cells	++	–
CCR7+ cells	++	–
PD cells	–	++

Abbreviations: CD: Cluster of Differentiation, Natural Killer cells, CCR: Chemokine receptor, PD: Programmed death, –: Decreased, ++: Increased. References (Liao et al., 2020, 2020; Mathew et al., 2020).

COVID-19 cases. Queipo-Ortuño et al. (Queipo-Ortuño et al., 2012) outlined a depletion of FBP4 gene expression in adipose tissue macrophages (ATM) in obesity. Inversely, Osteopontin and Ficolin-1 gene expression is markedly elevated in obese states. Kaye et al. has shown in his cross-sectional study that, FCN-1 gene expression is elevated in the AT in cases of acquired obesity, while Tardelli et al. suggested that SPPN-1 (alternatively called Osteopontin), is a key inducer of inflammatory changes seen in the AT of obese individuals (Tardelli et al., 2016, Table 2).

### 3.1.3. Lymphocytes

T cell behavior in the lung micro-environment in COVID-19 patients and in the AT of obese individuals passes through two stages:

**3.1.3.1. Stage 1: Predominance of effector vs. proliferating resident T cells.** It has been thought that any respiratory virus-specific CD8 cells are primed in the lung draining lymph nodes, where they undergo multiple rounds of division. It remained unclear, however, if such cells would continue to proliferate after reaching the lung or not, and if such proliferation was associated with a good or bad prognosis. McGill et al. was the first to outline such proliferation in mice infected with influenza (McGill and Legge, 2009).

Intriguingly enough, severe COVID-19 cases showed a proliferation of resident T cells in the lung environment, constituting the major proportion of the T cell population as opposed to CD8<sup>+</sup> effector cells in mild cases. CD8<sup>+</sup> effector cells showed an upregulation of signaling molecules involved in T-cell activation and migration. Proliferating cells, on the other hand, appeared to overexpress virus response and energy generation molecules to support the proliferation process. This particular finding suggests that effector CD8<sup>+</sup> cells in mild cases are more active in clearing viral particles than the proliferating cells in severe cases (Liao et al., 2020).

Misumi and colleagues outlined a very similar behavior of resident T lymphocytes in obesity to that previously mentioned in the lung micro-environment of critical COVID-19 patients. Resident T cells of the adipose tissue continue to proliferate in situ, with the production of pro-inflammatory and pro-fibrotic chemokines (Misumi et al., 2019).

**3.1.3.2. Stage 2: T cell exhaustion.** Following the proliferation of resident T cells in the lung and adipose tissue micro-environments, a supposedly regulatory protein, programmed death 1 protein (PD-1), is over-secreted by proliferating T cells, and other immune cells. In severe cases, it acts in a paracrine manner by inhibiting T cell receptors; this mechanism progressively leads to T cell depletion and exhaustion (Z. Chen and John Wherry, 2020) (Kado et al., 2019; Wang et al., 2019, Table 3).

## 4. Overexpressed cytokines

As mentioned earlier, Liao and colleagues (Bourgonje et al., 2020; Liao et al., 2020; Xiong et al., 2020; Z. Zhou et al., 2020) outlined the cellular changes that are encountered in the micro-environment of severe COVID-19 cases, which are linked to a higher likelihood of mechanical ventilation and ARDS (acute respiratory distress syndrome). In their series, they also demonstrated the upregulation of several genes linked to cellular entry or cytokine expression in severe COVID-19 cases.

In the previous section, two of those genes were overexpressed by lung macrophages, namely **FCN-1** and **SPPN**. The latter two genes were also linked to the augmented inflammation seen in the adipose tissue of obese individuals.

In this section, we attempt to elucidate the genes involved in severe COVID-19 worst clinical picture, surprisingly most of these genes are also implicated in the pathogenesis of metabolic syndrome and its complications as follows:

**IL-6** is the chemokine mediating the cytokine storm in COVID-19; its levels have been suggested by our working group to predict severe outcomes in COVID-19 cases. IL-6 was also found to be elevated in plasma and adipose tissue in obesity. The role of IL-6 in obesity has been suggested to be partially protective. IL-6 overexpression in skeletal muscle stimulates energy expenditure and reduces food intake and its low levels lead to obesity and insulin resistance. Exercise is important to control weight gain since, as a myokine, IL-6 is secreted by contracting muscle and is elevated two to threefold in the circulation during exercise (exercise-induced lipolysis in adipose tissue) (de Gieseinski et al., 2003).

Xiong and colleagues demonstrated an important role for **Monocyte Chemoattractant Protein-1 (MCP-1)** in the lung milieu of severe COVID-19 cases. MCP-1 plays a role in the previously explained macrophage phenotypic polarization. It is also known as an insulin responsive gene. Additionally, in vivo studies proved that MCP-1 is excessively expressed in mice with obesity in comparison with lean controls, and that white adipose tissue is an essential source of MCP-1 (Cranford et al., 2016; Deshmane et al., 2009).

One of the major hallmarks of macrophages is their heterogeneity, which is reflected by their specialized function in a particular micro-environment. Besides their heterogeneity, macrophages are known to display remarkable plasticity. In response to different micro-environmental stimuli, a fully differentiated macrophage can adopt a polarized phenotype with specific functional characteristics. As mentioned earlier, the classic phenotypic switching of macrophages from M1 to M2, and the reverse, is mainly driven through a cross-talk of paracrine mediators, namely Chemokine receptor type 2 (**CCR2**). A statistically vital correlation was found between CCR2 expression in



monocytes with body weight and fat mass, and also with insulin and HOMA IR. The affiliation of CCR2 expression with insulin resistance has been previously noticed in subjects having more developed metabolic disorder, where higher monocyte CCR2 expression was encountered in diabetic patients in comparison to non-diabetic. (Ruytinx et al., 2018; Weisberg et al., 2006), 2018; Weisberg et al. (2006)).

**TNF- $\alpha$**  (a pro-inflammatory cytokine primarily produced by resident macrophages) which is upregulated in severe COVID-19, was reported to participate in the pathogenesis of insulin resistance. It inhibits insulin signaling through the activation of several serine kinases including JNK (c-JUN NH2-terminal kinase), IKK, and S6K (ribosomal protein S6 kinase 1). (Alzamil, 2020).

The above findings converge with the previous findings of Mathew et al., who unleashed two distinct types of immune responses; immunotype 1 characterized by pro-inflammatory macrophage polarization, excessive release of pro-inflammatory cytokines resulting in exhausted and depleted CD 8 cells, and immunotype 2 characterized by less severe disease, balance between M1 and M2 phenotypes, and more efficient CD 8 effector function. The landscape of immune cells in obesity states seems to prepare COVID-19 towards the immunotype 1 response, with more disease severity and worst disease outcome (Mathew et al., 2020).

## 5. The beneficial effects of the inflammatory response in obesity

The occurrence of low-grade inflammation in obesity has been considered for years as a therapeutic target to improve various aspects of obesity and metabolic syndrome, such as insulin resistance. However, there is recent evidence that this low-grade inflammation is rather beneficial.

The anti-inflammation therapies (anti-TNF, anti-IL-1, and anti-IL-6) have shown very limited efficacy in improving insulin action and glucose homeostasis. So, it was assumed that the idea of inflammation, having only negative effects on insulin action and glucose homeostasis, might not be correct. There might be some beneficial effects of inflammation in obesity (Ye and McGuinness, 2013), which explains why anti-inflammation therapy has largely failed in improving the outcome of obesity. (Wang and Ye, 2015; Ye and McGuinness, 2013).

Recently, COVID-19 patients have been undergoing treatment with drugs suppressing IL-6 inflammatory activity. The principle underlying this intervention covers the interpretation of inflammatory-induced lung damage in COVID-19 patients and the hypothesis of IL-6 playing an integral role as a pro-inflammatory molecule. It has been demonstrated that drastic outcomes in patients are correlated with high IL-6 levels, therefore drugs inhibiting the action of IL-6 may improve the patients' conditions. Paradoxically, IL-6 has considerable anti-inflammatory characteristics that will make the usage of anti-IL-6 drugs doubtful in inhibiting inflammatory cascade in COVID-19 patients. Besides, the role of IL-6 has expanded into being a part of the host's response to infection, which will consequently oppose the approach of anti-IL6 as a line of COVID-19 treatment. In studies involving the injection of recombinant IL-6 into human volunteers, IL-6 levels showed a considerable rise compared to the levels of COVID-19 patients, with insignificant pulmonary or other organ affection. These outcomes challenge the reliability of using anti-IL6 drugs such as Tocilizumab in treatment. Clinical incidences with Tocilizumab showed a surge in the rates of developing opportunistic infections, increasing the uncertainty of using anti-IL6 as a main approach of treating COVID-19 (Scherger et al., 2020).

So, the idea is not to tame the inflammatory response in COVID-19 or obesity states, but rather switching it from a deleterious ineffective immune response to a beneficial effector one. The role of leptin in this switching seems like an important and understudied target. Leptin, released from adipocytes seems to orchestrate the low-grade inflammation seen in obesity. It is widely accepted that leptin can directly link nutritional status and pro-inflammatory T helper 1 immune response and that a decrease of leptin plasma concentration during food deprivation can lead to an impaired immune function. Additionally, several

studies have implicated leptin in the pathogenesis of chronic inflammation, and the elevated circulating leptin levels in obesity appear to contribute to the low-grade inflammatory background seen in those patients. Leptin induces satiety and increases energy expenditure to minimize weight gain. On the other hand, insulin induces energy accumulation leading to weight gain. There is also increasing evidence of adipokine-myokine crosstalk via Leptin. Leptin is able to stimulate the skeletal muscles to release IL-6 following exercise, which in turn improves tissue response to insulin (Chellappa et al., 2019).

Despite the beneficial effects of leptin in obesity, excessive leptin increase in obesity is driven by central leptin resistance, which impairs control of food intake and energy expenditure. Central leptin resistance does not only halt the beneficial cardiometabolic effects of leptin, but is also responsible for the more severe immunologic switch previously described in obesity (Iikuni et al., 2008).

Excessive levels of leptin induce the expression of the previously mentioned pro-inflammatory cytokines in macrophages and T cells, stimulate macrophage phagocytosis and monocyte proliferation, and activate some other signaling pathways used by pro-inflammatory cytokine receptors. (Crunkhorn, 2016).

This explains why there was a paradigm shift in the treatment of obesity and the slowing down of obesity-related complications. The change from taming inflammation to modulating it has shifted trials from failing anti-inflammatory therapy to Leptin sensitizers. Several experimental products notably Withaferin A and celastrol have reversed obesity in mice. Further studies are needed to ensure its safety for human trials and to explore its effects on the immune landscape encountered in obese patients. The potential immunomodulatory role of leptin and leptin sensitizers in COVID-19 should be explored, to check if leptin sensitizer can achieve the previously mentioned immunologic switch from a deleterious immune response to an efficient one (Abu Bakar et al., 2019).

### 5.1. Single cell sequencing in vulnerable groups to COVID-19

#### 5.1.1. Old age

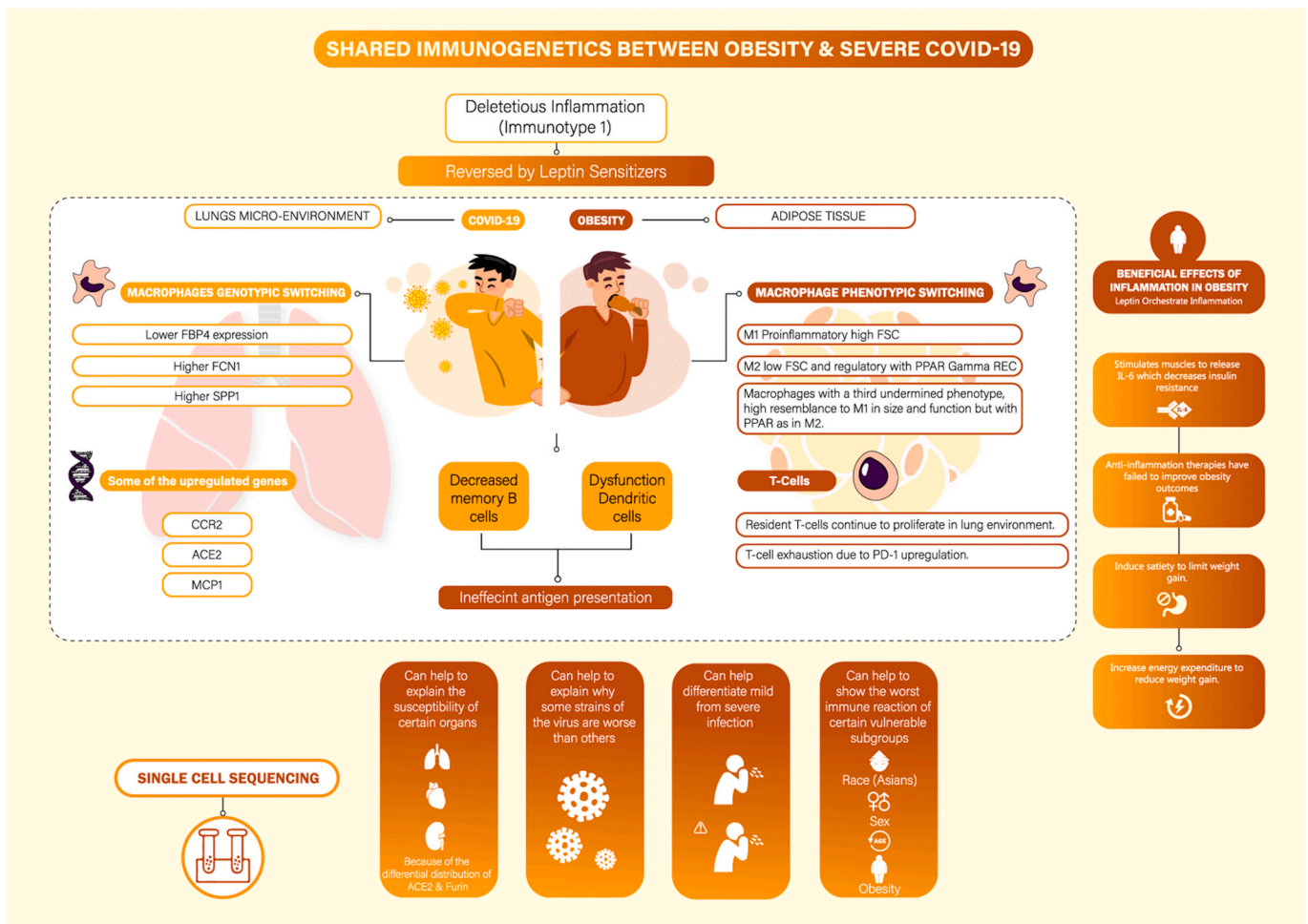
Single cell sequencing performed by Zheng and colleagues of the lung microenvironment in old and young COVID-19 patients revealed that aging plays a major role in reprogramming the human immune cell landscape, as well as increasing the susceptibility and vulnerability to COVID-19 related mortality. In young healthy individuals, homeostasis of the immune landscape allows for the effective and timely clearance of infection. On the other hand, aging was found to; (1) decrease T cells and increase monocytes, (2) promote the polarization of T cells into effector, exhausted, and regulatory subtypes, (3) increase the number of age-associated B cells, NK cells, and inflammatory monocytes, (4) increase dysfunctional dendritic cells and induce the loss of their antigen-presenting ability with the promotion of an inflammatory state. Aging was also found to increase the expression of genes related to SARS-CoV-2 susceptibility which further explains their increased susceptibility to COVID-19 (Zheng et al., 2020).

These changes bring to mind the immunotype 1 response seen in cases with severe COVID-19 infection.

#### 5.1.2. Gender

Gender is a risk factor for higher severity and mortality in patients with COVID-19, independent of age and susceptibility. Several studies have pointed to the effect of gender as a predictor of COVID-19 worst outcome. Jin and colleagues concluded that males were twice at risk of dying from COVID-19 than females (Jin et al., 2020). Vahidy and colleagues found that 56% of hospital admission and 66% of ICU admissions were males. The reasons behind this gender disparity remain largely elusive due to the lack of single cell sequencing studies comparing the immune landscape of COVID-19 male vs. female patients (Vahidy et al., 2020).

Gemmati and colleagues have shown that among ethnic groups,



**Fig. 1.** Applications of Single cell sequencing in COVID-19 and Shared immunogenetics between Obesity and severe COVID-19. Abbreviations: CCR2: chemokine receptor type 2; COVID-19: Coronavirus disease 2019; FABP4: Fatty acid binding protein 4; FCN-1: Ficolin-1; FSC: Forward Scatter; MCP-1: Monocyte Chemoattractant Protein-1; PD-1: Programed Death 1 cytokine; PPARγ: Peroxisome Proliferated Activated Receptor gamma agonists; REC: Receptor; SPP1+: Osteopontin.

Asian females had exceptionally high basal levels of ACE2, as well as an age-dependent decrease in ACE2 levels more significant in males than females. These findings contradict the epidemiologic data previously reported by Wadman et al., which highlighted the increased susceptibility of males to COVID-19. The lack of significant ACE2 levels in the lung milieu and the conflicting ACE2 levels in males suggests that the attempts to relate the severity of COVID-19 infection to circulating ACE2 levels are questionable (Gemmati et al., 2020).

Sexual dimorphisms in immune function are important but have been largely ignored by the field of immunotherapy. Differences in innate and adaptive immune responses lead to functional diversity between males and females. These include the number and activity of immune cells and the orchestrating signals between the two branches of immunity. In females; (1) Antigen presenting Cells (APC's) play their role more vigorously neutrophils and macrophages have higher phagocytic activity, and (2) show a higher frequency of progenitors and mature group 2 innate lymphoid cells (ILC's), key regulators of type 2 inflammatory response. Males, on the other hand, have (1) rapidly proliferating but exhausted CD8<sup>+</sup> cells, (2) macrophage phenotype switching towards M1 macrophages, and (3) changes that mimic the more severe immunotype 1 observed in patients with COVID-19 (Jaillon et al., 2019).

The sexual dysmorphism of the immune responses is driven by endocrine and genetic factors. The 17β-estradiol (E2) –estrogen receptor α (ER) axis is a key player of the observed gender-based disparity of

immunologic responses. The E2 receptor interacts with dendritic cells to stimulate more efficient antigen presentation, balancing phenotypic switching between M1 and M2 macrophages. Additionally, many immune regulated genes, such as FOXP3 (Forkhead box P3) and CD40L, are located on the X chromosome and many T cells carry Estrogen response elements in their promoter genes. Therefore, sex-biased T cell differences exist in females, characterized by inflammatory and cytotoxic effector genes. Moreover, on the X chromosome, micro-RNA can inhibit the transcription and action of PD cytokine thereby preventing the exhaustion and depletion of T cells (Capone et al., 2018).

### 5.1.3. Racial

Several studies have outlined the racial disparities of mortality from COVID-19. Most of those studies have evolved starting from April 2020 originating from multinational communities, especially in the USA. Hooper et al. observed higher COVID19 mortality rates among African American persons (184 per 100,000), in comparison with white citizens (93 per 100 000). (Webb Hooper et al., 2020). The CDC and COVID19 Associated Hospitalization Surveillance Network have performed a study supporting the latter findings by declaring that 33% of hospitalized patients were AA (African American), compared to 13% of the Caucasian population. Furthermore, a study conducted by Boulware and colleagues deduced that individuals of black races are four times more prone to death from COVID19 than other races. In Norway and Sweden, immigrants with African ethnicity, notably Somalians, were more at risk

of ICU admission, hospitalization and mortality from COVID-19. (Boulware, 2020).

Despite underlying socioeconomic differences underlying such findings; there seem to be several genetic and immunologic factors underlying the severity of manifestations in Black races. There is to date no study to compare the immune landscape in the peripheral bloodstream or lung milieu between black and Caucasian races. However, several previous studies have used single cell sequencing to explain the augmented severity of some tumors in black races. Prostate cancer is one such example of race-associated disparity of immune response, with African Americans having higher mortality and more aggressive disease. Literature continues to suggest strong evidence for the disparities in immune response among races. In African Americans, genetic predisposition in immune modifiers contributes to their poorer prognosis. Additionally, alleles that regulate pro-inflammatory cytokines, including IL-6, are significantly higher in African Americans (Chaudhary et al., 2020; Thomas et al., 2019).

IL-6 drives the unbalanced phenotype switching of macrophages towards M1, leading to inefficient antigen presentation and uncontrolled activation of CD8 cells. AA also have a higher expression of the lymphocyte depleting Programmed death receptor. These, again, are changes that are largely similar to immunotype 1 of COVID-19. (Chen et al., 2018).

## 5.2. Single cell sequencing and Furin, is Furin mutation a key to milder or more severe manifestations?

Single cell sequencing studies are scarce regarding Furin in the context of COVID-19. Furin has been widely accepted as an important determinant of endothelial tropism of COVID-19. Our working group showed that Furin inhibitors can be an efficient strategy against COVID-19. (AbdelMassih et al., 2020). To date, the only relevant single cell sequencing study involving Furin was not performed on human cells to study Furin expression, but was focused on studying the Furin cleavage site between different strains of SARS-CoV-2 to outline if the severity of manifestations between a viral strain and another is related to the Furin cleavage site. Jin et al. noticed that the patients affected with COVID-19 from Zhejiang province displayed milder manifestations than those from Wuhan, the initial epicenter of the virus. They attributed this finding to an evolution of the initial virus, thus becoming less pathogenic. This evolution was mediated by mutations in the Furin cleavage site of the S protein, rendering the Zhejiang strain less able to bind to Furin (Jin et al., 2020, Fig. 1).

## 6. Conclusion

In conclusion, single cell sequencing has led to more understanding of several aspects in the context of COVID-19 infection. One of the unleashed mechanisms is the relative independence of organ involvement to ACE2 concentration in such organs; Furin seems a better predictor of organ involvement. Furin affinity also seems to be the key differentiating factor between mild and severe strains of the virus. Moreover, there seem to be two distinct immune responses to COVID-19; a deleterious type 1 response and a beneficial type reaction. Type 1 response is characterized by an extremist phenotypic switch of macrophages towards M1, dysfunctional dendritic cells with inefficient antigen presentation, and uncontrolled proliferation of CD8 cells, with resulting exhaustion and depletion of its effector function. Surprisingly, obesity, old age, male gender, and African American race seem to have a likelihood to develop this immunotype 1 response due to complex interplay between genetic and endocrinal factors, thus, explaining the higher mortality observed in such subgroups. The establishment of guidelines for a predictive genetic test is a huge milestone in precision medicine concerning COVID-19 and can surely lead to more efficient and tailored treatment protocols. Also developing treatments that can reprogram the immune response from type 2 to type 1 response in

COVID-19, such as leptin sensitizers, can be a game-changer in the prognosis of affected cases.

## Declaration of competing interest

Authors declare that there is no conflict of interest.

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