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COVID-19 and Obesity – A Tale of Two Pandemics

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Abstract

Viruses are insidious pathogens, which are unable to proliferate without co-opting the cellular machinery of their hosts. It is therefore vital that host metabolism is tightly regulated and controlled to protect against viral appropriation.

Obesity, on the other hand, is the result of dysregulated host metabolism, and obesity is frequently seen as a comorbidity in individuals infected with SARS-CoV-2. Unfortunately, obesity is associated with an unravelling of cellular regulation and control, which is likely to be conducive to infection from a virus such as SARS-CoV-2.

This review seeks to examine similar metabolic dysfunctions seen in both SARS-CoV-2

infection and obesity such as inflammasome activation, perturbed Ca^{2+} homeostasis, and loss of anti-inflammatory or antiviral mechanisms. The multiple metabolic dysfunctions that are common to both SARS-CoV-2 infection and obesity suggest that an obese SARS-CoV-2 patient has an increased risk of severe disease pathology.

Introduction

SARS-CoV-2 is the etiological agent of the ongoing COVID-19 pandemic that began in Wuhan, China in 2019.[1] SARS-CoV-2 infection leads to influenza-like symptoms and lung pathology that has the potential to become lethal.[1]

In parallel with the COVID-19 pandemic, there is also a non-viral pandemic, overlooked until recently, silently killing millions of people each year. This is the pandemic of chronic disease, where the pervasive Western diet and lifestyle has led to dramatic increases in conditions such as obesity, type 2 diabetes, and hypertension.[2] Patients infected with SARS-CoV-2 have significantly worse outcomes from the disease if they present with one or more comorbidity.[3] Analysis of American COVID-19 hospital admissions has revealed that almost 90% of people present with one or more comorbidity.[4]

There is a strong correlation between BMI, obesity, calorie-dense 'Western' diets, and deaths from SARS-CoV-2 infection.[5,6] Obese individuals have five times the risk of severe pneumonia when infected with SARS-CoV-2.[7] Frustratingly, lockdown restrictions may interfere with exercise regimes and, through boredom, people may resort to highly calorific foods and alcohol as a form of comfort.[8]

Below, multiple mechanisms that are common to both SARS-CoV-2 infection and obesity are analysed. These mechanisms are very likely to predispose an obese patient to viral infections such as SARS-CoV-2. Hopefully, this analysis will shed more light on the pathogenesis of both SARS-CoV-2 infection and a comorbidity such as obesity.

The NLRP3 inflammasome

The NOD, LRR and pyrin domain-containing protein 3 (NLRP3) inflammasome is a component of the innate immune response that defends against invading microbes, including viruses.

There is a struggle between host defenses and an invading virus such as SARS-CoV-2.[9] Appropriate NLRP3 inflammasome activation results in rapid viral elimination; however, if a virus is able to evade the immune system, it may exploit host defenses to further its replication. For example, chronic NLRP3 inflammasome activation can lead to pyroptosis, a type of programmed cell death, and a release of viral particles from dying or dead cells, thus allowing

the continued spread of an infection throughout the host.[10,11] If left unchecked, runaway inflammation induced by an aberrantly activated NLRP3 inflammasome can contribute to a 'cytokine storm', a potentially lethal complication seen in many infections, including coronavirus infection.[12,13]

In obese individuals, the production and release of excess inflammatory adipokines and cytokines lead to a state of low-grade chronic inflammation. Chronic inflammation subsequently drives an overload of toxic lipid metabolites described as lipotoxicity; toxic lipid metabolites are able to activate the NLRP3 inflammasome.[13] Obese individuals with an activated NLRP3 inflammasome have been found to be vulnerable to SARS-CoV-2 infection.[13]

The Cholinergic Anti-Inflammatory Pathway – Inflammasome Control

Due to an increased risk of a 'cytokine storm' in SARS-CoV-2 infection,[14] control of inflammation, via inhibition of the NLRP3 inflammasome, is essential to prevent progression of the infection and poor patient prognosis.

Obese individuals present with dysfunction of the autonomic nervous system with increased sympathetic tone and decreased parasympathetic tone.[15] Elevated sympathetic tone, seen in obesity, results in a blunting of the cholinergic anti-inflammatory pathway, a neuro-immune reflex essential for moderating excessive NLRP3 inflammasome and inflammatory cytokine activity.[16,17]

The cholinergic anti-inflammatory pathway operates via nicotinic acetylcholine receptors, which signal tristetraprolin, a protein that inhibits the NLRP3 inflammasome and degrades inflammatory cytokine mRNA.[18-20] Tristetraprolin mRNA is 4 to 5 times lower in adipose tissue of obese individuals.[20]

From the above, it can be seen that obesity can blunt the actions of both the cholinergic anti-inflammatory pathway and tristetraprolin, leaving an obese individual exposed to an increased risk of exaggerated inflammation.

Ca^{2+} Homeostasis

Ca^{2+} is employed as a signalling molecule in many biological processes within the nervous system, the immune system, and muscle. In viral infections, increased Ca^{2+} influx in a cell can provide an opportunistic mechanism for a virus to enhance its infectivity by promoting virus entry, assembly, replication, and thus disease progression.[21] The vulnerability of a host cell to viral exploitation of Ca^{2+} suggests supporting intracellular Ca^{2+} homeostasis could be an important antiviral strategy.

Obesity leads to perturbed intracellular Ca^{2+} homeostasis, which negatively impacts metabolic tissue and immune cells, increasing the risk of adipose and systemic inflammation.[22] Interestingly, the voltage gated calcium channel blocker verapamil has been reported to have both antiviral[23] and anti-obesity effects.[24] Calcium channel blockers amlodipine and nifedipine have both demonstrated the potential to inhibit SARS-CoV-2 growth *in vitro.*[25]

Lipid droplet accumulation and disrupted autophagy are two pathologies associated with obesity, which are reduced by calcium channel blocker verapamil *in vitro*.[24] As opportunists, coronaviruses are thought to exploit both lipid droplets[26] and autophagy to enhance their replication.[27] Furthermore, lipid droplets are a rich source of cholesterol,

a lipid that increases viral infectivity. Cholesterol accounts for 44% of virus lipid content and 11-12% of their weight[28]; and cholesterol reduction, through statin use, is associated with an improved clinical outcome for COVID-19 patients.[29]

Ca^{2+}-Dependent Enzymes

Calpain is a Ca^{2+}-dependent cysteine protease with characteristics similar to the Ca^{2+}-dependent enzyme calmodulin and papain, a protease in papaya fruit. Calpain plays an important role in normal cell metabolism[30]; however, elevations of intracellular Ca^{2+} can overactivate calpain,[31] which can then allow the protein to promote inflammation,[32] virus entry and replication.[33,34] Calpain inhibitors II and XII are chemical compounds which block the protease activity of calpain and have been found to help defend against SARS-CoV-2 *in vitro*.[33]

Calpain inhibition has been shown to protect against lung fibrosis in both *in vitro* and *in vivo* models.[34] As fibrosis is seen in SARS-CoV-2-infected lung tissue biopsy,[35] calpain inhibition might protect an infected lung against fibrosis, driven by virus dependent immune dysregulation. Therefore, analysis of whether calpain inhibition can block lung fibrosis during SARS-CoV-2 infection is warranted.

NLRP3 inflammasome-induced pyroptosis, which occurs during SARS-CoV2 infection, is dependent on calpain-associated degradation of the cytoskeleton – leaving a cell susceptible to rupture.[14,36] As described previously, pyroptosis leads to the release of viral particles from dying or dead cells and so accelerates the rate of infection.[10]

In animal models of obesity, a high fat diet results in calpain overexpression, mediating adipose tissue inflammation and remodelling.[37] Additionally, elevated blood glucose, observed in type 2 diabetes mellitus and obesity, increases calpain activity in blood vessels and promotes endothelial dysfunction.[38]

Cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) is a Ca^{2+}-dependent phospholipase found to increase the cellular concentration of lysophospholipid—a lipid which coronavirus replication/transcription complexes (RTCs) bind with, thus accelerating viral proliferation.[39] Similar to calpain, $cPLA_2\alpha$ activity is upregulated by increased intracellular Ca^{2+} levels.[40] Inhibition of $cPLA_2\alpha$ has been found to slow coronavirus replication in cell culture by reducing lysophospholipid concentration, thus limiting the availability of this phospholipid platform for coronavirus proliferation.

$cPLA_2\alpha$ activity is increased in obesity. For example, a short-term high fat diet in mice was found to trigger $cPLA_2\alpha$ driven infiltration of neutrophils into adipose tissue[41]; and $cPLA_2\alpha$ is also considered to be necessary for adipose and liver lipid storage in obesity.[41]

Vitamin D

Vitamin D helps modulate cytosolic Ca^{2+}*, an effect that reduces excessive inflammatory cytokine expression.[42] Cathelicidins and defensins are vitamin D-dependent proteins with direct-acting antiviral properties.[43] Importantly, a review of 79 studies has concluded that lowered vitamin D status was associated with increased risk of SARS-CoV-2 infection and poorer*

outcomes, once an individual is infected.[44]

Vitamin D deficiency is common in obesity, and higher doses of vitamin D are needed to attain sufficiency compared to non-obese individuals. Weight loss in obese patients normalizes vitamin D status and corrects deficiency.[45]

***Sirtuins and* NAD⁺ – Host Antiviral Factors**

Nicotinamide adenine dinucleotide (NAD^+) is a cofactor that operates in many metabolic pathways, including energy production and regulation of inflammation. Obesity is a state of energy abundance found to deplete NAD^+.[46]

NAD^+ is an essential substrate for the sirtuin family of enzymes, which induce post-translational modifications to multiple target proteins.[47] Sirtuins are now known to act as antiviral factors, modifying host metabolism to help defend against many viruses, including RNA viruses.[48] Calorie restriction,[49] exercise,[50] and the Mediterranean diet[51] all increase the activity of sirtuins. Conversely, obesity reduces the expression of SIRT1,[52] one of the most studied sirtuins. Therefore, a healthy diet and lifestyle, acting through the sirtuins, provides a robust antiviral defense. Obesity, on the other hand, depletes the sirtuin SIRT1 and its substrate NAD^+, increasing the risk of an RNA virus infection such as SARS-CoV-2.

Three examples of SIRT1-dependent target proteins of interest, in the context of SARS-CoV-2 infection and obesity, are ADAM17, the vitamin D receptor (VDR), and tristetraprolin.

ADAM17. Disintegrin and metallopeptidase domain (ADAM)17 is a protein that cleaves angiotensin-converting enzyme 2 (ACE2), the receptor identified as the binding site for SARS-CoV-2. Cleavage of the ACE2 receptor by ADAM17 supports SARS-CoV-2 virus entry into host cells.[53] NAD^+-dependent SIRT1 downregulates ADAM17[54] and protects host cells from virus entry.

Vitamin D and vitamin D receptor (VDR). Vitamin D has to operate through its nuclear receptor VDR to enable viral, and therefore SARS-CoV-2, protective gene expression.[55] VDR requires NAD^+ dependent SIRT1 for its activation.[56]

Tristetraprolin. As mentioned above, tristetraprolin is a protein that inhibits the NLRP3 inflammasome and degrades inflammatory cytokine mRNA.[18,20] Tristetraprolin requires deacetylation by NAD^+ dependent SIRT1 for its activation.[57]

Interferons

Interferons are not direct-acting antiviral agents, but instead induce multiple effector genes that alter cellular metabolism in ways that are less hospitable to viruses. Appropriate activation of interferons place a cell in an 'antiviral state'.[58]

A central antiviral action of interferons is to constrain cellular lipid metabolism to limit the availability of lipids, which could potentially be used as platforms for viral replication. However, obesity undermines interferon expression and efficacy, in part due to perturbed lipid metabolism.[58]

The importance of the antiviral potential of interferons has been observed in phase 2 pilot trials in the UK. Nebulised interferon beta-1a administered to COVID-19 patients for 14 days was found to increase the probability of patient symptom improvement and recovery.[59]

Mitochondrial Antiviral Signalling (MAVS) Protein

MAVS is protein that plays a vital role in mounting an immune response against many viruses, including RNA viruses such as SARS-CoV-2. MAVS enables the innate immune system to mount an antiviral defense through the activation of interferons.[60]

Mitochondria continually fuse and divide in dynamic processes called fusion and fission. However, to mount an effective antiviral response, mitochondria are required to undergo fusion to promote the aggregation of active MAVS complexes.[61] Mitochondrial dysfunction, seen in obese individuals, can compromise mitochondrial fusion, leading to an increased number of dysfunctional, fragmented mitochondria.[62] Consequently, obese individuals are very likely to present with compromised MAVS and interferon expression.

Conclusion

A virus is an opportunistic pathogen that will thrive in a host that does not have an appropriately controlled metabolism. In COVID-19 patients presenting with a comorbidity such as obesity, intracellular mechanisms and inflammation will have been perturbed even before SARS-CoV-2 infection. A patient's metabolic dysfunction is therefore likely to leave him or her extremely vulnerable to viral infection.

Inflammation is an immune system process found to be overactive in both viral infection and obesity. Excess NLRP3 inflammasome activity, vitamin D deficiency, and loss of intracellular Ca^{2+} homeostasis can all play their part in driving up inflammation – and importantly, all occur in viral infection and obesity. Additionally, innate anti-inflammatory mechanisms are compromised in viral infection and obesity, putting an obese SARS-CoV-2 patient at risk of a life-threatening cytokine storm.

Interferons are required to trigger the gene expression needed to put a cell into an 'antiviral state'. Cellular metabolic efficiency and control are qualities amplified by interferons to ensure that a virus cannot easily infect and appropriate cellular replication mechanisms. Therefore, the loss of interferon expression in obese individuals is catastrophic for their defense against SARS-CoV-2 infection, leading them to be at much higher risk of infection and disease-related complications.

In a similar way to interferons, sirtuin enzymes act as antiviral factors, through improvements in metabolic efficiency, to make a cell less hospitable to an RNA virus such as SARS-CoV-2. Sirtuins modify host metabolism via post-translational mechanisms rather than direct gene expression; however, sirtuin expression is suppressed through poor diet and lifestyle and obesity.

Obesity is endemic throughout much of the developed world. Obesity is a condition largely induced via poor diet and

lifestyle choices and is therefore highly preventable when armed with sound advice and knowledge. There is now an urgent need for health authorities and governments throughout the world to support anti-obesity campaigns, with an emphasis on the antiviral effects of weight loss. In this way, many people can improve their long-term health, and simultaneously, put their metabolism into a fully prepared antiviral state.

Conflict of interest statement

Ray Griffiths is the sole author of this work. The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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