Insights into the Immunopathophysiology of Severe COVID-19 in Metabolic Disorders

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Abstract

Coronavirus disease 2019 (COVID-19) has affected millions of people across the world but disproportionately and severely affects persons with metabolic disorders such as obesity, diabetes mellitus, and hypertension. In this brief review, we discuss the pathways of immune dysregulation that may lead to severe COVID-19 in persons with metabolic conditions.

Keywords
- COVID-19
- diabetes mellitus
- hypertension
- obesity

Introduction

Coronavirus disease 2019 (COVID-19) is an unprecedented global pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that has affected over 5 million persons globally at the time of this review.[1] Strikingly, it disproportionately affects persons with underlying endocrine conditions such as obesity, diabetes mellitus, and hypertension. In the United States, the most common co-existing condition affecting patients with COVID-19 is hypertension (49.7%) followed by obesity (48.3%) and diabetes mellitus (28.3%).[2] These conditions are also associated with an increased risk of poor outcomes including mortality.[3-5] In light of these risks, it is prudent to explore the pathophysiological mechanisms that account for the observed trends. In this brief review, we discuss the molecular basis of COVID-19 risks in obesity, diabetes mellitus, and hypertension with a focus on immune dysregulation.

Common Immune Dysregulation Pathways

The human body has multiple protective mechanisms against viral infections. Broadly, viruses gain cellular entry by attaching to viral cell surface receptors. Following this, viral antigens are presented via the major histocompatibility complex to trigger counteractive cellular and humoral immune responses. If immunological mediators are expressed abnormally due to comorbid conditions, the resulting immunological response can be catastrophic. The abnormal expression of immunological mediators appears to be the predominant mechanism in dysregulated immune responses to COVID-19 in metabolic disease that may result in a cytokine storm (►**Fig. 1**).

SARS-CoV-2, a betacoronavirus and the causative agent of COVID-19, gains cellular entry by binding to the cell membrane bound angiotensin-converting enzyme 2 (ACE2).[6] SARS-CoV-2 related coronaviruses such as Middle

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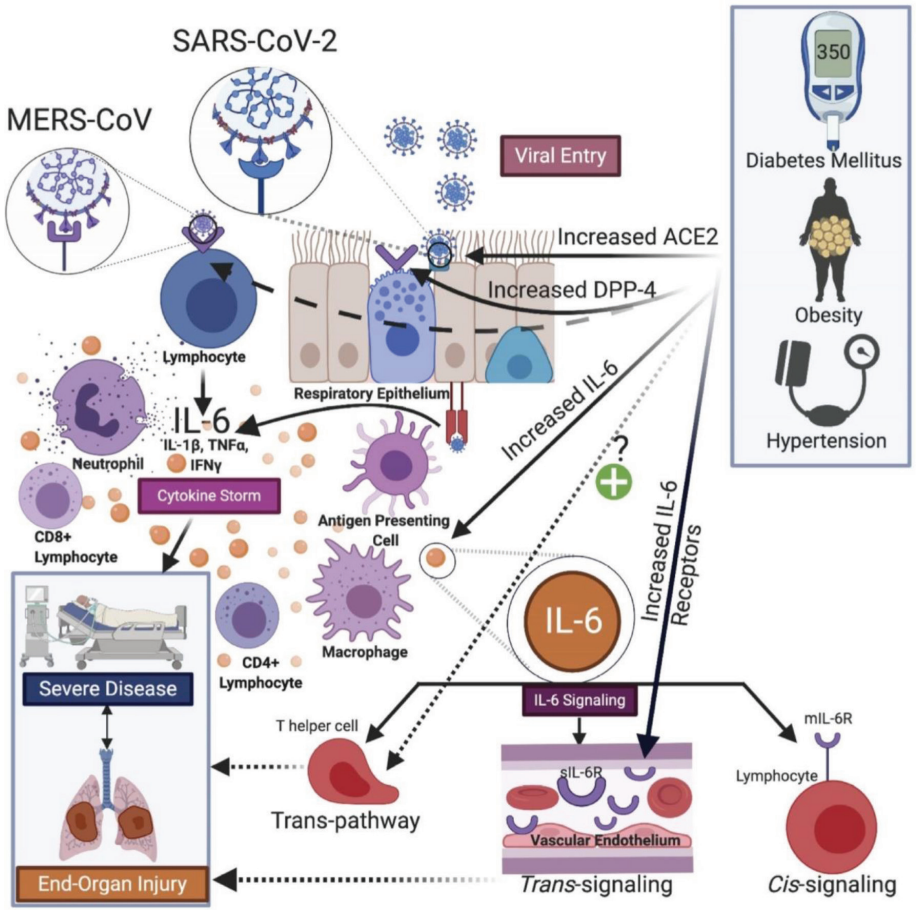

Fig. 1 Immune dysregulation in metabolic disease leading to a pathological immunological coronavirus disease 2019 response. Upstream secretion of interleukin-6 (IL-6) leads to downstream activation of the *trans*-signaling and *trans*-pathway modes of IL-6 action resulting in severe end-organ injury. ACE2, angiotensin-converting enzyme 2; DPP-4, dipeptidyl peptidase-4; MERS-CoV, Middle East respiratory syndrome-coronavirus; mIL-6R, membrane bound interleukin-6 receptor; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; sIL-6R, soluble interleukin-6 receptor; TNF-α, tumor necrosis factor-alpha (image created using BioRenderTM).

East respiratory syndrome-coronavirus (MERS-CoV) and SARS-CoV also directly affect immune cells including monocytes, dendritic cells, and T-cells.[7] The cellular entry of these betacoronaviruses is mediated by a glucose homeostasis intermediary—dipeptidyl peptidase-4 (DPP-4)—an enzymatic cleaver of glucagonlike peptide-1 (GLP-1).[8] Following SARS-CoV-2 infection, immune cell releases interleukin-6 (IL-6), a proinflammatory cytokine.[9] IL-6 has two main pleiotropic signaling pathways—*cis*- and *trans*-signaling. In *cis*-signaling, IL-6 initially binds to its membrane bound receptor (mIL-6R), found predominantly on the surface of immune cells, followed by recruitment and activation of T-cells, B-cells, and natural killer cells.[7] IL-6 secretion by recruited cells is enhanced and its exaggerated release is hypothesized to trigger the onset of the cytokine release syndrome. When IL-6 binds to its soluble receptor (sIL-6R) present on the vascular endothelium, it leads to the activation of the *trans*-signaling pathway that in turn causes the release of vascular endothelial growth factor (VEGF) and monocyte chemoattractant protein-1 (MCP-1). Vascular endothelial E-cadherin levels decline as a consequence of *trans*-signaling, which in combination with elevated VEGF and MCP-1, can lead to increased vascular permeability and leakage (►**Fig. 1**). Ultimately, these effects result in syndromes such as acute respiratory distress syndrome and hypotensive shock. A third, less dominant, pathway of IL-6 signaling known as *trans*-pathway (different from *trans*-signaling) pathologically activates T-helper cells, a prelude to lung injury and shock.[7]

The pathological mediators of virus-triggered immune responses are elevated in metabolic diseases such as obesity, diabetes mellitus, and hypertension. As an example, IL-6 levels are chronically elevated in obesity and progressively increase with increments in body mass index.[10,11] This is thought to be consequent to the secretion of IL-6 by adipocytes in response to chronic adipose tissue hypoxia.[12] C-reactive protein (CRP), a downstream product of IL-6 and a prognosticator of poor COVID-19 outcomes, is also elevated in obesity.[11,13] Similarly, IL-6 levels are elevated in diabetes mellitus and insulin resistance states.[14] Further, IL-6 receptors are also upregulated in type 1 diabetes mellitus, predisposing T-cells to be more sensitive to circulating IL-6.[15] This leads to a consequent elevation in CRP that is also common in diabetes mellitus.[16] Equally, IL-6 levels are elevated in hypertension that was well illustrated by Luther et al, who demonstrated the role of angiotensin II as a direct stimulator of IL-6 production.[17,18] Luther et al also

reported that the stimulatory effect of IL-6 on angiotensin II was blocked by the use of angiotensin receptor blockers (ARBs) and mineralocorticoid receptor antagonists such as spironolactone.[17] Another study of diabetic mice infected with the betacoronavirus, MERS-CoV, reported a prolonged course of severe infection.[19] This was accompanied by a reduction in CD4+ T-cells and a pathological elevation of IL-17α, a proinflammatory cytokine, confirming the presence of immune dysregulation in diabetes mellitus.[19]

DPP-4, a proinflammatory molecule and a coronavirus receptor, is also elevated in obesity, diabetes mellitus, and hypertension.[20] DPP-4 is directly proportional to measures of visceral adiposity such as intra-abdominal fat and waist-hip ratio.[21] In persons with diabetes mellitus, DPP-4 levels correlate linearly with glycemic control.[22] DPP-4 has also been identified as a therapeutic target in diabetes, suggesting a critical role for DPP-4 in the pathophysiology of diabetes.[23] Finally, the *trans*-pathway of IL-6 may be overactive in obesity, diabetes mellitus, and hypertension and may represent the final common pathway in the causative pathophysiology of acute end-organ injury. Taken together, the enhanced secretion and activity of these immune mediators in metabolic diseases are key to understanding the risk of severe COVID-19 (see ►**Fig. 1**).

Specific Immune Dysregulation Pathways

Obesity

Obesity is also linked to increased levels of interleukins such as IL-1 and tumor necrosis factor-alpha (TNF-α) that may exacerbate the IL-6-mediated immune dysregulation. This is worsened by hyperinsulinemia-induced T-cell dysfunction, a consequence of increased body adiposity. Additionally, obesity is associated with an increased propensity for risks including diabetes mellitus, hypertension, obstructive sleep apnea, and obesity hypoventilation syndrome that further enhance the risks of severe disease by both immune and nonimmune-mediated mechanisms. While DPP-4 inhibition as a therapeutic target to reduce COVID-19 severity remains speculative, GLP-1 receptor analogues have been proven to be immunoregulatory and lung protective in animal models.[24]

Diabetes Mellitus

Immune dysregulation is multifactorial in diabetes mellitus. In addition to the aforementioned-effects, ACE2 levels are augmented in diabetes mellitus that presumably facilitates viral entry into respiratory and other tissues.[25] A disintegrin and metallopeptidase domain 17 (ADAM17), the enzymatic cleaver of ACE2, is lower in mouse models of diabetes mellitus, which may increase the risk of COVID-19 infection.[24,25] Co-existing complement deficits, impaired antigen presenting cell function, elevated TNF-α and IL-8, and compromised T-cell function all independently contribute to the dysregulated immune milieu of diabetes mellitus.[27-29] In addition, the co-existence of other risk factors including obesity and hypertension further amplifies the pre-existing immunological dysfunction in diabetes.

Hypertension

Hypertension has additional features of immune dysregulation, manifesting as elevated IL-17 and diminished T-cell and natural killer cell function.[30,31] Hypertension is also associated with an overactive sympathetic drive and elevated angiotensin II, both of which contribute to a compromised immune response.[32] While sympathetic overdrive has indirect pleiotropic effects on immunity, angiotensin II directly stimulates the secretion of IL-6, which orchestrates the pathological host immune response as detailed above.[17,33] ACE inhibitors (which are inhibitors of ACE1) and ARBs have been speculated to raise COVID-19 risks through a potential increase in ACE2, but emerging clinical evidence refutes this theory.[34-37]

Conclusion

Patients with COVID-19 infection in the setting of metabolic diseases such as obesity, diabetes mellitus, and hypertension independently have a significantly worse outcome than those without these diseases. As each of these diseases is associated with dysregulation of the immune system leading to cytokine storm and consequent severe COVID-19. Further research is needed to elucidate the specific immune-deregulatory mechanisms that lead to severe COVID-19 in patients with metabolic disorders.

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Conflict of Interest

None declared.

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