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Cross-talk between SARS-CoV-2 infection and the insulin/IGF signaling pathway: Implications for metabolic diseases in COVID-19 and for post-acute sequelae of SARS-CoV-2 infection

The pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that causes coronavirus disease 2019 (COVID-19) has had a devastating impact on humanity. SARS-CoV-2 infection affects the function of several human tissues including metabolically active and endocrine tissues to induce several metabolic abnormalities such as insulin resistance and diabetes [1–4]. However, the mechanisms underlying how SARS-CoV-2 induces metabolic disease remain to be fully elucidated. In a study published in *Metabolism*, Shin et al. showed that SARS-CoV-2 infection impairs insulin-like growth factor 1 (IGF)/insulin signaling pathway in respiratory, metabolic and endocrine cells and tissues [5]. Herein, we discuss the role of the IGF/insulin signaling pathway in SARS-CoV-2 infection (Fig. 1). We then identify critical areas for future work to fill gaps in existing knowledge on the pathogenesis of SARS-CoV-2-induced insulin impairment in COVID-19 and potentially post-acute sequelae of COVID-19 infection (PASC).

1. Impaired glucose homeostasis is related to increased incidence of COVID-19 and associated morbidity

Altered glucose metabolism is associated with increased prevalence of SARS-CoV-2 infection ranging between 8 and 43 % in different studies [1–4,6,7]. Diabetes and its complications can increase the risk of morbidity and mortality during coronavirus infections [8–10] including COVID-19 [6,11]. Patients with diabetes have impaired innate immune functions such as neutrophil chemotaxis, phagocytic cell function and recruitment of inflammatory macrophages in tissues [12]. In addition, diabetic patients have impaired adaptive (T cell-mediated) immune functions [12] and alterations of cytokines [13–16] and host proteins that facilitate SARS-CoV-2 replication such as ACE2 [17,18] and furin [19]. Collectively, these perturbations in host cellular responses in diabetic patients may contribute to their increased risk to develop severe SARS-CoV-2 infection. Although host proteins that are entry factors for SARS-CoV-2 such as ACE2 and TMPRSS2 are present not only in epithelial but also in pancreatic endocrine β-cells [20], the molecular mechanisms that drive the cross-talk between SARS-CoV-2 and metabolic perturbations, have not yet been fully elucidated.

2. SARS-CoV-2 alters signaling of insulin in several tissues

Shin et al. focused on addressing this gap in our knowledge and were among the first to provide scientific evidence that SARS-CoV-2 alters the IGF/insulin signaling pathway, not only in the respiratory tract but also in metabolic (liver, adipose tissue) and endocrine pancreatic cells and tissues, in association with impairment of several metabolic pathways and excessive interferon responses such as IRF1 [5]. Signaling of insulin and IGF is critical for cellular survival, proliferation [21], function [22] and the control of cell damage and death in non-metabolic organs and tissues, including the lung [21–23]. Preclinical mechanistic experimental studies have shown that impairment of the insulin/IGF signaling in adipose tissue and pancreatic beta cells triggers early onset of hyperglycemia, insulin resistance, diabetes, ketoacidosis [24–26], loss of adipose tissue and severe metabolic syndrome [27]. Thus, the findings from Shin et al. may improve our understanding in metabolic dysregulation in COVID-19 [5].

3. SARS-CoV-2 directly infects pancreatic endocrine cells that produce insulin

The presence of ketoacidosis during SARS-CoV-2 infection indicates a lack of insulin due to dysfunction or loss of β-cells [1–4]. Viruses can induce direct damage to pancreatic cells or drive inflammation and potentially β-cell-specific autoimmunity [20]. Other studies have shown that SARS-CoV-2 infects cells of the human pancreatic exocrine and endocrine (β-cells, islets of Langerhans) cells *ex vivo* and *in vivo* [20]. Thus, independent studies have identified the human pancreas as a target of SARS-CoV-2 infection that may contribute to the metabolic dysregulation observed in patients with COVID-19 [5,20]. However, since Shin et al. did not utilize state-of-the art molecular virology assays or antivirals such as remdesivir in their *ex vivo* studies [5], it remains unknown whether the observed changes in the IGF/insulin signaling pathway in pancreatic endocrine cells are specific to SARS-CoV-2 infection *per se* or reflect SARS-CoV-2-induced inflammatory injury of pancreatic endocrine cells.

4. Altered molecular signatures of the insulin pathway are associated with severity of COVID-19

Observational human studies performed by Shin et al., showed that the higher basal expression of IRF1 was associated with increased age in male lung tissue, and with obesity and diabetes [5], which are all well-established risk factors for the severity and mortality of COVID-19. The IRF1 intron variant rs17622656-A was also associated with the prevalence of COVID-19 [5]. Notably, the higher expression of IRF1 and the lower expression of mediators of the IGF/insulin signaling pathway were significantly associated with adverse critical outcomes in patients with COVID-19 [5] and worse molecular signatures of disease such as increased IL1-b and IL-6 signaling, cell damage and death, and metabolic abnormalities [5]. However, observational studies do not prove

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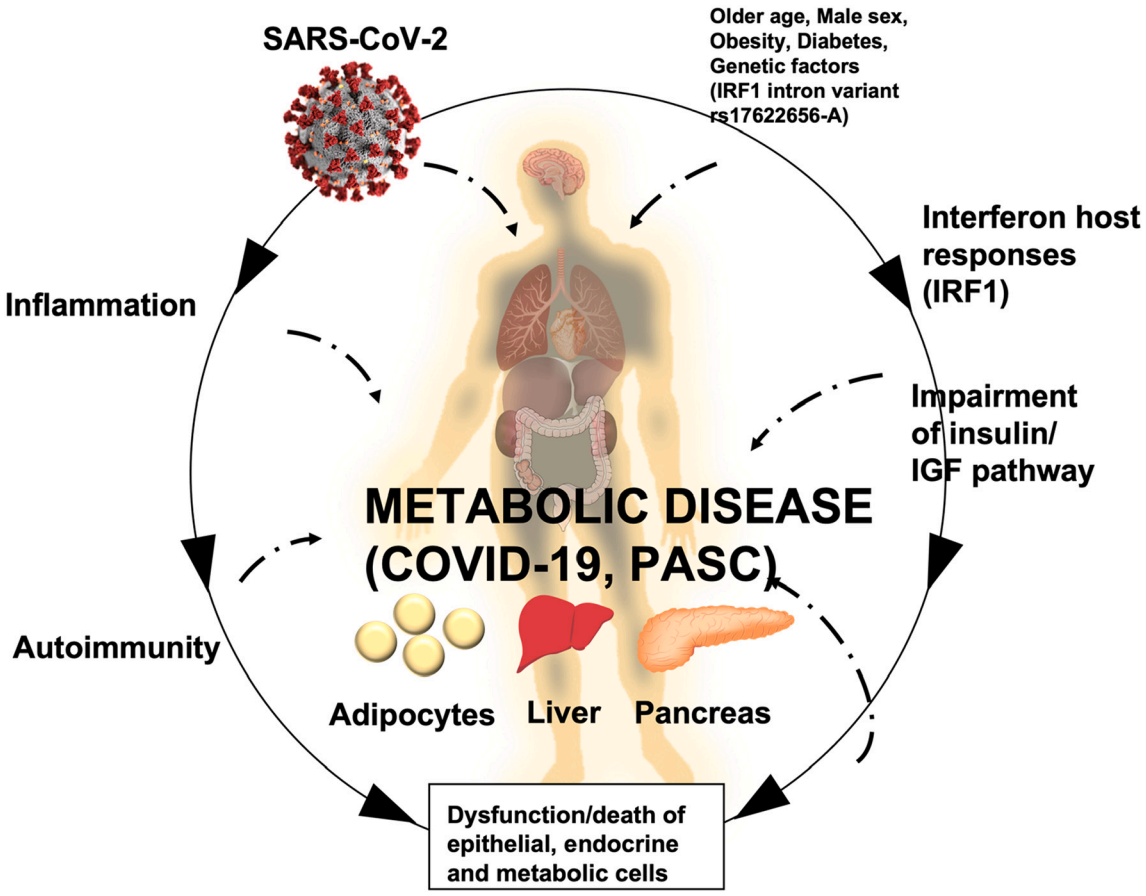

Fig. 1. Overview of hypothesis. Insulin/IGF signaling is critical for cellular survival and function. Preclinical mechanistic experimental studies have shown that impairment of the insulin/IGF signaling in adipose tissue and pancreatic beta cells triggers early onset of hyperglycemia, insulin resistance, diabetes, ketoacidosis, loss of adipose tissue and severe metabolic syndrome. SARS-CoV-2 impairs the insulin/IGF signaling pathway not only in the respiratory tract but also in metabolic (liver, adipose tissue) and endocrine pancreatic cells and tissues in association with downregulation of various metabolic pathways and excessive interferon responses such as the interferon-gamma-induced interferon regulatory factor-1 (IRF-1). Risk factors such as older age, male sex, obesity, diabetes and genetic factors are associated with increased metabolic abnormalities and impaired insulin/IGF signaling pathway in COVID-19. SARS-CoV-2 can directly infect the pancreatic endocrine cells and also induce indirect inflammatory and autoimmune responses that may further damage the endocrine cells. Collectively, the SARS-CoV-2 induced impairment of the insulin/IGF signaling may contribute to metabolic disease in COVID-19 and post-acute sequelae of COVID-19 (PASC).

causality. Further mechanistic studies with overexpression of IRF1 and inhibition of IRF1 in *ex vivo* cell culture models of metabolically active cells and pancreatic endocrine cells, in the presence of SARS-CoV-2 infection, are warranted to establish the pathogenetic role of IRF1 in SARS-CoV-2-induced metabolic alterations.

5. Hormonal interventions may attenuate cellular alterations in the IGF/insulin signaling pathway under inflammatory conditions

Interventional studies in humans with therapeutic agents that target specific molecular pathways may complement observational studies to further establish the physiological relevance of these pathways in humans. Shin et al. showed that hormonal interventions, such as dexamethasone and dihydrotestosterone (DHT), effectively enhanced the IGF/insulin signaling pathway in epithelial cells and adipocytes and reduced the gene expression of IRF1 [5]. Dexamethasone also effectively attenuated TNF-mediated insulin resistance in HEK293T cells. Dexamethasone has well-established favorable impact on inflammatory responses that contribute to worse clinical outcomes in COVID-19 [28] and also induce metabolic abnormalities in several tissues. However, dexamethasone may also worsen hyperglycemia and have adverse metabolic impact. The roles of androgens in the pathogenesis of COVID-19 still remain controversial [29–31]. Notably, the *ex vivo* studies performed by Shin et al. were done in cells that were not infected with SARS-CoV-2 [5]. Thus, detailed studies with careful titration of the concentration of dexamethasone and the duration of treatment in SARS-CoV-2 infected epithelial cells, adipocytes and hepatocytes are needed to elucidate whether hormonal interventions may have a favorable effect on the IGF/insulin signaling pathway and metabolic abnormalities in SARS-CoV-2 infection.

6. Elucidating the role of the IGF/insulin signaling pathway in PASC

Other coronaviruses such as SARS-CoV-1 have been shown to induce a transient damage to beta cells for 3 years after recovery from acute infection [32]. One small study of 25 persons who recovered 12 years after SARS-CoV infection showed altered glucose and lipid metabolism and blood metabolomes compared to age-matched healthy controls [33]. SARS-CoV-2 infection may also be a risk factor for development of autoimmune-mediated diabetes mellitus even years after recovery [34]. Experimental studies have shown that SARS-CoV-2 infection triggers aberrant cytokine and interferon responses in human islets and epithelial cells [20,35]. It remains to be further explored whether increased basal levels of aberrant interferon host proteins such as IRF1 in association with morbidity in SARS-CoV-2 infection, as shown by Shin et al. [5], could potentially be relevant to metabolic abnormalities in PASC.

Thus, it is of paramount importance to monitor blood glucose levels and cardiometabolic sequelae of SARS-CoV-2 infection in both COVID-19 and during long-term follow up in PASC [36]. Identifying altered IGF/insulin signaling pathway as a molecular signature across distinct metabolic organs such as liver, pancreas and adipose tissue in PASC may set the foundation for future interventions to reduce the long term adverse detrimental metabolic sequelae of SARS-CoV-2 infection.

7. Gaps in knowledge that require further investigation regarding the role of SARS-CoV-2-induced cellular alterations in the IGF/insulin signaling pathway

Appropriately controlled large studies are needed to determine whether associations between severity of COVID-19 and alterations in the IGF/insulin signaling pathway are causal or due to underlying confounding and colinearity between overlapping molecular cardiometabolic and inflammatory pathways. Experimental studies that consider the direct impact of SARS-CoV-2 infection in the presence of antivirals and appropriate controls with overexpression and inhibition of key proteins of the IGF/insulin signaling pathway are warranted to establish the pathogenetic role of the IGF/insulin in SARS-CoV-2 induced metabolic alterations. SARS-CoV-2 induced alterations in the expression level of genes of the IGF/insulin signaling pathway by Shin at al [5] were not confirmed at the protein and cell level and further experimental studies are needed to address this limitation. High-quality, rigorous observational studies and clinical trials that also consider the genetic background of target populations, virulence of SARS-CoV-2 variants, clinical comorbidities and disease severity are of vital importance to clarify and further explore the findings of the observational studies by Shin et al. A more in-depth evidence-based information and understanding of the role of the IGF/insulin signaling pathway in COVID-19 is crucial for the development of potent therapeutic strategies for SARS-CoV-2 induced metabolic abnormalities.

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Declaration of competing interest

All authors have declared that no conflict of interest exists.

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