Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A data-driven hypothesis on the epigenetic dysregulation of host metabolism by SARS coronaviral infection: Potential implications for the SARS-CoV-2 modus operandi

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ABSTRACT

COVID-19, the disease caused by the novel SARS-CoV-2, a betacoronavirus structurally similar to SARS-CoV. Based on both structural and syndromic similarities with SARS-CoV, a hypothesis is formed on SARS-CoV-2 potential to affect the host's metabolism as part of its lifecycle. This hypothesis is evaluated by (a) exploratory analysis of SARS-CoV/human transcriptomic interaction data and gene set enrichment analysis (b) a confirmatory, focused review of the literature based on the findings by (a). A STRING Viruses (available search for human – SARS-CoV (NCBI taxonomy Id: 9606 vs. NCBI taxonomy Id: 694009) genomic interactions reveals ten human proteins, interacting with SARS-CoV: SGTA, FGL2, SPECC1, STAT3, PHB, BCL2L1, PPP1CA, CAV1, JUN, XPO1. Gene set enrichment analyses (GSEA) with STRING on this network revealed their role as a putative protein – protein interaction network (PPI; Enrichment p-value = 0.0296) mediating, viral parasitism, interleukin as well as insulin signaling, diabetes and triglyceride catabolism. In the literature, SARS-CoV has been known to cause de novo diabetes by ACE2-dependent uptake on pancreatic isle cells, and furthermore dysregulate lipid autophagy in favor of the viral lifecycle. Conversely, currently there are only non-causative, observational evidence of worse outcomes for COVID-19 patients with comorbid diabetes or hyperglycemia. No study has reported on the lipid profiles of COVID-19 patients; however, lipid-targeting molecules have been proposed as agents against SARS-CoV-2. Future studies, reporting on lipid and glucose metabolism of COVID-19 patients could help elucidate the disease's seculae and aid drug design.

Background

Since its emergence in on December 2019, the COVID-19 pandemic has evolved as a global health emergency [1]. COVID-19 is caused by the novel SARS-CoV-2, a betacoronavirus structurally similar (approximately 79%) to SARS-CoV [2]. In a recent study by Hoffmann et al. [3], the similarities between the SARS viruses extend to ACE2 dependent host cell entry. At present, SARS-CoV-2 has shown significant similarities with SARS-CoV, both in clinical characteristics and exploited host intracellular functions [4,5]. Due to these commonalities, SARS-CoV remains an attractive substitute for the yet to be determined specifics of the SARS-CoV-2/Human protein interaction [6] and its consequences.

Among the first studies to report clinical data on COVID19 was a recent publication by Yang and colleagues [6]. Their study provided the foundation for a hypothesis put forth by Fang and colleagues indicating that diabetic and hypertensive patients exposed to ACE2 inhibitors may be at an increased risk of more severe COVID-19 [7].

Hypothesis

Based on the structural and proteomic similarities between SARS coronaviruses, a hypothesis is formed on viral epigenetic remodeling of host cell metabolism, as a result of SARS-CoV-2 infection.

Evaluation of the hypothesis

The evaluation of this hypothesis relies on (a) exploratory analysis of transcriptomic interaction data, between SARS-CoV and human cells (b) a confirmatory review of the literature based on the results of (a), comparing current knowledge on SARS-CoV and SARS-CoV-2.

A STRING Viruses [8] (available from: http://viruses.string-db.org/

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Table 1
Selected, significantly enriched pathways by the SARS-Cov / Human interaction.

Metabolism related pathways		
Pathway	Description	FDR
HSA-163560	Triglyceride catabolism	0.0066
hsa04933	AGE-RAGE signaling pathway in diabetic complications	0.0109
hsa04931	Insulin resistance	0.0109
Hsa04024	cAMP signaling pathway	0.0163
hsa05418	Fluid shear stress and atherosclerosis	0.0131
KW-0219	Diabetes mellitus	0.0106
Infection related pathways		
Pathway	Description	FDR
HSA-6785807	Interleukin-4 and Interleukin-13 signaling	0.0171
KW-0945	Host-virus interaction	0.0027
hsa05164	Influenza A	0.0150
hsa05168	Herpes simplex infection	0.0161
hsa05166	HTLV-I infection	0.0109

HSA- prefix pathways are retrieved from the Reactome database; KW- prefix pathways are retrieved from the Kyoto Encyclopedia for Genes and Genomes (KEGG). All analyses were perfomed by STRING gene set enrichment analyses.

cgi/; accessed March 15, 2020) search for human – SARS-CoV (NCBI taxonomy Id: 9606 vs. NCBI taxonomy Id: 694009) genomic interactions reveals ten human proteins, interacting with SARS-CoV: SGTA, FGL2, SPECC1, STAT3, PHB, BCL2L1, PPP1CA, CAV1, JUN, XPO1. Gene set enrichment analyses (GSEA) with STRING [8] (available from: https://string-db.org; accessed March 20, 2020) on this network revealed their role as a putative protein – protein interaction network (PPI; Enrichment p-value = 0.0296) mediating, among other functions, viral parasitism (including but not limited to influenza A viruses and HTLV-1), interleukin as well as insulin signaling, diabetes and triglyceride catabolism.

Discussion

Meta-analyses on SARS cohorts have indicated that both a history of diabetes and hyperglycemia were independent factors of worse outcomes including more severe respiratory symptoms and death, regardless of medication [9]. In another study, SARS-CoV was shown to cause diabetes by ACE2-dependent infection of pancreatic isle cells [10]. Interestingly, the significantly enriched “cAMP signaling” pathway is an indirect link between diabetes and ACE2 signaling, based on experimental evidence associating cAMP levels and ACE2 activity in diabetic patients [11] (False Discovery Rate (FDR) < 0.05); Table 1. Following entry to host cells, lipid metabolism is a subsequent important target of single strand RNA viruses, critical for the formation of the viral envelope in subsequent lifecycles [12]. Autophagy mediated triglyceride and lipid droplet catabolism is one such mechanism, as identified in DENV infection [13]. Hijacking the host cells’ lipid metabolism has been shown to be a critical step in establishing HCoV-22E and MERS – coronavirus latency [14]. In SARS-CoV patients, alterations in lipid metabolism have been detected as far as 12 years after the initial infection [15].

Evidence on COVID-19’s interplay with diabetes is only recently emerging, and can currently only be considered within the context of epidemiological studies, determining diabetes mellitus (DM) as frequent comorbidity. Furthermore, DM has recently been characterized as a determinant of more severe respiratory syndrome, along with other comorbidities [16]. Aside from DM, novel hyperglycemia was recently associated with an increased with worse outcomes in COVID-19 patients, however this association was not independent of other predictors in the multivariate model [17].

Epidemiological associations between COVID-19 and lipid metabolism are currently not possible, since even large scale cohorts do not report on relevant measurements [18]. On the experimental level, lipid metabolism on the cellular level has been proposed as a treatment target for COVID-19; specifically, both interactions between SARS-CoV’s spike protein with lipid rich membrane compartments, as well as the epigenetic modulations in lipid metabolism were considered as the end-point targets for the development of small molecules, aiming to prevent SARS-CoV-2 infection [19].

Barring actual proteomics SARS-CoV-2, SARS-CoV based in silico analyses of the SARS-CoV – Human interaction partially support the hypothesis of Fang and colleagues, insofar as to warrant further scrutiny on COVID19 patient's metabolic states and concomitant medication. While the approach presented here is inherently limited due to setting its basis on the SARS-CoV proteomic interactions, it nevertheless presents in silico and literature evidence supporting SARS-CoV-2 potential to affect human metabolism. Furthermore, as genes affected by SARS-CoV infection are significantly enriched for other infections, they may represent a common interface, targeted by viruses. Future studies should determine SARS-CoV-2 interaction and effect on the human transcriptome, further identifying drug targets using pharmacogenomic enrichment analyses.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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