Discovering common pathogenetic processes between COVID-19 and diabetes mellitus by differential gene expression pattern analysis

Md. Rezanur Rahman, Tania Islam, Md. Shahjaman, Md. Rafiquil Islam, Salvo Danilo Lombardo, Placido Bramanti, Rosella Ciurleo, Alessia Bramanti, Andrey Tchorbanov, Francesco Fisicaro, Paolo Fagone, Ferdinando Nicoletti and Manuela Pennisi

Abstract

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the newly discovered coronavirus, SARS-CoV-2. Increased severity of COVID-19 has been observed in patients with diabetes mellitus (DM). This study aimed to identify common transcriptional signatures, regulators and pathways between COVID-19 and DM. We have integrated human whole-genome transcriptomic datasets from COVID-19 and DM, followed by functional assessment with gene ontology (GO) and pathway analyses. In peripheral blood mononuclear cells (PBMCs), among the upregulated differentially expressed genes (DEGs), 32 were found to be commonly modulated in COVID-19 and type 2 diabetes (T2D), while 10 DEGs were commonly downregulated. As regards type 1 diabetes (T1D), 21 DEGs were commonly upregulated, and 29 DEGs were commonly downregulated in COVID-19 and T1D. Moreover, 35 DEGs were commonly upregulated in SARS-CoV-2 infected pancreas organoids and T2D islets, while 14 were commonly downregulated. Several GO terms were found in common between COVID-19 and DM. Prediction of the putative transcription factors involved in the upregulation of genes in COVID-19 and DM identified RELA to be implicated in both PBMCs and pancreas. Here, for the first time, we have characterized the biological processes and pathways commonly dysregulated in COVID-19 and DM, which could be in the next future used for the design of personalized treatment of COVID-19 patients suffering from DM as comorbidity.

Key words: COVID-19; diabetes mellitus; blood gene expression; transcriptional signatures; molecular pathways
statistical inference, data science and deep learning with their application to big biological datasets such as biomarker identification from transcriptomics, metabolomics and other omics datasets.

Md. Rafiqul Islam is an Assistant Professor at the Department of Pharmacy, Jashore University of Science and Technology, Bangladesh. He has completed the B.Pharm and the M.Pharm from the University of Rajshahi, Bangladesh. Currently, he is pursuing PhD at the Queensland University of Technology, Australia. He is interested in genetics, genomics and bioinformatics research.

Salvo Danilo Lombardo graduated in medicine and surgery at the University of Catania, Italy (110/110 cum laude). He is currently a PhD student at the Menche's Lab at CeMM (Research Center for Molecular Medicine of the Austrian Academy of Sciences).

Placido Bramanti graduated in medicine and surgery at the University of Messina (1974), specialized in neurology (1978); he is a Full Professor of applied medical technical sciences at the Department of Biomedical Sciences and Morphological and Functional Imagery of the same university and, since 2006, a Scientific Director of the IRCCS Centro Neurolesi ‘Bonino-Pulejo’ of Messina. He is co-author of over 800 publications, numerous books, book chapters and patents.

Rosella Ciurleo graduated with honors in pharmaceutical chemistry and technology at the University of Messina, and then obtained a PhD in pharmaceutical sciences in 2009. Since 2009, she has been working at the IRCCS Centro Neurolesi Bonino-Pulejo. She is a PI of a research project sponsored by the Ministry of Health, which concerns the clinical application of Spectroscopic Magnetic Resonance, and the Head of the Technical-Scientific Secretariat of the Ethics Committee. She is in charge of the management, control and verification of the entire process of pharmacological and non-pharmacological clinical trials. She is the Co-PI of a project sponsored by the European Community (WEP).

Alessia Bramanti graduated at the University of Messina, where she also obtained her PhD. She is employed at the IRCCS Centro Neurolesi ‘Bonino-Pulejo’, Messina, Italy. She is a co-author of more than 150 international peer-reviewed journals, reaching an H of 26.

Andrey Tchorbanov is an Associate Professor. He has a renowned international experience obtained in Utrecht (Nederland), Taipei (Taiwan) and Budapest (Hungary). He is a group leader of projects financed by the National Science Fund of Bulgaria (L1304, TK-317, VU-L-306, VUH – 11, DO 02-312, TK-X-1611, DTK 02/19, DTK 02/78, DDVU 02/34), as well as of projects in the framework of bilateral agreements between Bulgarian Academy of Sciences and National Scientific Council (Taiwan) and Hungarian Academy of Sciences (Hungary). Dr. Tchorbanov is an expert in constructing hybrid antibody molecules by protein and genetic engineering, humanized SCID and other murine models and in vitro immunological studies. He holds a patent N108155 ‘A tool for selective suppression of pathological DNA-specific B cells’.

Francesco Fisicaro graduated in medicine and surgery at the University of Catania and then obtained his Residency in Neurology. He is currently a PhD student in basic and applied biomedical sciences at the University of catania, Italy.

Paolo Fagone is an Assistant Professor at the Department of Biomedical and Biotechnological Sciences at the University of Catania, Italy. He obtained his MS degree in health biology at the University of Catania in 2006 (110/110 um laude). Afterwards, he completed his Residency training in Microbiology and Virology. He has been a Research Fellow at the Stellor-Chance Laboratories at the University of Pennsylvania, Philadelphia, for 2 years, after which he attended the School of Medicine of the University of Catania and graduated in medicine and surgery in 2018 (110/110 cum laude). He has published more than 100 papers in peer-reviewed journals and has reached an H-index of 27.

Ferdinando Nicoletti is a Full Professor of general pathology at the Department of Biomedical and Biotechnological Sciences at the University of Catania, Italy. He graduated in medicine and surgery at the University of Catania and obtained his Residency in Allergology and Clinical Immunology at the Institute of Internal Medicine, Infectious Diseases and Immunopathology at the University of Milan in 1990. Ferdinando Nicoletti has been working in the field of cellular and molecular immunology, immunopharmacology, toxicology and experimental oncology. He has published more than 350 papers in peer-reviewed journals and has reached an H-index (google scholar) of 66. Prof. Nicoletti serves in the Editorial Board of several international journals including Antioxidants, Antioxidant and Redox Signaling, Basic and Clinical Pharmacology and Toxicology, European Journal of Pharmacology, International Journal of Molecular Medicine and Journal of Clinical Medicine. Ferdinando Nicoletti is inventor of 5 patents (granted) and has cofounded 5 biotech companies, namely Ganial Immunotherapeutics (Delaware, USA), OncoNox ApS (Copenhagen, Denmark), Aura Biopharm (Oslo, Norway), Roxiant (Copenhagen, Denmark) and Censence (Oslo, Norway).

Manuela Pennisi graduated in medicine and surgery (110/110 cum laude) at the University of Catania in 2004. In 2009, she obtained the Residency in Neurology (70/70 cum laude). She obtained the PhD in neurobiology in 2014. From 2018, she is an Assistant Professor at the Department of Biomedical and Biotechnological Sciences, University of Catania, Italy.

Introduction

SARS-CoV-2 is responsible for the novel coronavirus disease 2019 (COVID-19), which has become a massive threat for humanity worldwide [1, 2]. Many factors influence the outcome of the disease, such as age, diabetes, hypertension and lung disease [3].

Diabetes mellitus (DM) is a chronic metabolic disease characterized by elevated blood glucose levels, due to the lack of insulin production, the resistance to insulin signaling or both. There are two main conditions, namely type 1 DM (T1D) and type 2 DM (T2D), with pathogenic and clinical differences. T1D is characterized by the destruction of pancreatic beta cells by T cells of the immune systems [4]. On the other hand, although subchronic immune-inflammatory pathways are implicated in the pathogenesis of T2D, the primary culprits in the development of the disease seem to depend on peripheral insulin resistance, which is often secondary to obesity.

The prevalence of DM has increased worldwide with changing lifestyles and rising obesity. Approximately, 90% of all cases of diabetes regards T2D, and another around 10% of cases are classified as T1D. According to the International Diabetes Federation, in 2019, around 463 million people aged between 20 and 79 years had DM [5]. People with both T1D and T2D may experience diabetes-related complications, including cardiovascular disease, kidney disease, neuropathy, blindness and lower extremity amputation [6].

As expected, patients with DM and especially those with long-lasting disease and related complications [7, 8] have been shown to exhibit a more severe course of COVID-19 than nondiabetic individuals [7, 8]. It has also been proposed that COVID-19 exposure can precipitate T1D onset [9].

The synergistic effect of hyperglycaemia and COVID-19-related hyperinflammation might predispose DM patients to increased vulnerability and lethal outcomes in SARS-CoV-2 infection [10, 11].

Overall, these observations forge the hypothesis that DM patients are more susceptible to COVID-19 infection [12]. As COVID-19 patients with DM have an elevated risk of complicated outcomes, it becomes essential to identify eventual synergetic biomolecular pathways triggered by COVID-19 and DM, which could lead to a tailored approach for the treatment of diabetic patients with COVID-19. However, the molecular alterations in common between COVID-19 with DM have not yet been investigated. The characterization of the molecular pathways is crucial to identify therapeutic targets or drug repurposing for DM patients infected with COVID-19. Recently, several studies have
COVID-19 in DM is still not completely clear. Figure 1 of the study layout is presented as ways and regulators that underlie COVID-19 and DM (a summary of the datasets generated by RNA sequencing (RNA-Seq) [17], GSE25724, GSE38642).

In order to identify suitable datasets generated from peripheral blood mononuclear cells (PBMCs) from COVID-19 and T2D patients, we queried the NCBI Gene Expression Omnibus (GEO) and the ArrayExpress databases. We retrieved the GSE152418 microarray dataset containing whole-genome transcriptomic data from human pancreas organoids infected in vitro with SARS-CoV-2 at an MOI of 0.1 for 24 h. For the determination of the T2D pancreas signature, the GSE20966 [22], GSE25724 [23] and GSE38642 [24] datasets were obtained, which comprised a total of 25 T2D and 71 controls islet data. For T1D, the GSE27492 [25] and the E-MEXP-1140 [26] dataset were found, which included whole-genome mRNA data from a total of 24 T1D and 13 controls. The characteristics of the datasets included in this study are summarized in Table 1.

Data processing and differential expression analysis

The two datasets of COVID-19 PBMCs (with accession number: GSE152418 and CRA002390) were first analyzed using the DESeq2 R package, using as statistical threshold an absolute log-fold change (logFC) ≥ 1 and Benjamini–Hochberg corrected P-value (false discovery rate—FDR) < 0.05. Then, we meta-analyzed these two RNA-seq datasets using Fisher's inverse method, using the metamRNASeq R package (designed for meta-analysis of RNA transcriptomic datasets).

For the meta-analysis of the microarray datasets, we used the Network Analyst (NA) web utility tool [27]. For the normalization of the datasets, we employed variance stabilizing normalization algorithm [28], followed by the quantile normalization [29]. ComBat procedure embedded into NA was also performed to adjust study batch effect in meta-analysis. Finally, the meta-analysis of the datasets was performed using the Fisher's P-value combination method.

Since we had only one T2D PBMCs gene expression dataset (GSE9006) and one for SARS-CoV-2 infected pancreas organoids (GSE151803), the significant genes were selected using the R package LIMMA (linear models for microarray data) [50], considering an FDR < 0.05.

Functional insights into the DEGs

The enrichment analysis was performed using the widely utilized tool ‘Metascape’ [31]. Compared with other GO-based enrichment methods, it includes additional, optimized ontology databases, such as MSigDB, and clusters corresponding terminology to eliminate repetition [31]. By default, the Metascape gene functional enrichment makes use of several databases, including gene ontology (GO), KEGG, Reactome, and MSigDB databases. Metascape uses hypergeometric tests and the Benjamini–Hochberg P-value correction algorithm to classify all ontological parameters containing a substantially higher P-adjusted value.
set of genes common to an input list than expected casually. The pairwise similarity between any two enriched terms is computed based on a Kappa-test score. The matrix of similarity computes the similarity between the input gene expression terms were selected using as threshold a Bonferroni-corrected $q$-value $< 0.05$. The pathways that were significantly enriched by the downregulated DEGs, 32 were found to be commonly modulated in COVID-19 and T2D ($P < 0.05$) (Figure 2A), while 10 DEGs were commonly downregulated (Figure 2B).

### Identification of common transcriptional signatures between COVID-19 and T1D PBMCs
To determine the transcriptional signature common between COVID-19 and T1D in PBMCs, we first meta-analyzed three T1D PBMCs datasets (GSE9006, GSE72377, GSE55100) comprising 162 samples of which 111 cases and 51 healthy controls. The meta-analysis identified 370 significant DEGs (FDR $< 0.05$) characterizing T2D PBMCs. Among the upregulated DEGs, 29 DEGs commonly downregulated in COVID-19 and T1D ($P < 0.05$) (Figure 2B), while 10 DEGs were commonly upregulated in COVID-19 and T2D.

### Identification of common functional GO terms in COVID-19 and DM PBMCs
Several GO terms were found in common between COVID-19 and DM (Figure 3A, Supplementary Table 1, see Supplementary Data available online at http://bib.oxfordjournals.org/). The terms significantly enriched by the upregulated DEGs in common between COVID-19 and T2D, but not with T1D, were related to the mRNA metabolism, sub-cellular organelle organization and nucleotide synthesis (Figures 3B and 4).

The pathways that were significantly enriched by the downregulated DEGs, and in common between COVID-19 and T2D, but not in T1D were related to the mRNA metabolism and immune responses (Figures 3B and 4). On the other hand, the
autophagy process was found to be enriched among the upregulated DEGs in T1D and COVID-19, but not in T2D (Figure 3B and Figure 4).

**Prediction of TF overlapping between COVID-19 and DM PBMCs**

Determination of the putative TFs involved in the regulation of the DEGs implicated in COVID-19 and DM showed that SPI1 and RELA are involved in the expression of commonly upregulated genes in COVID-19, T1D and T2D. On the other hand, no significant enrichment was observed for TFs controlling the downregulated DEGs (Figure 5).

**Drug prediction for COVID-19 patients suffering from DM**

To predict drugs potentially helpful in treating COVID-19 patients with DM comorbidity, we used the L1000FWD web-based utility. For T1D, the top five drugs with the most anti-similar signature were: WAY-213613; gitoxigenin; fatostatin; BRD-K63425657 and emetin (Table 2).
No drug anti-signature was found to be significantly enriched when considering the DEGs overlapping the COVID-19 and T2D PBMCs profiles (data not shown).

Analysis of pancreas-related processes in COVID-19 and DM

Identification of common functional GO terms and TFs in COVID-19 and DM pancreas

Comparative analysis revealed that 35 DEGs were commonly upregulated in COVID-19 infected organoids and T2D islets, while no overlapping was found for T1D. Among the downregulated DEGs in COVID-19 infected organoids, 14 overlapped with the downregulated DEGs in T2D islets. No overlapping was instead found for T1D.

GO term enrichment analysis revealed several common processes characterizing both SARS-CoV-2 infection and T2D, including ‘transmembrane receptor protein tyrosine kinase signaling pathway’, ‘regulated exocytosis’ and ‘apoptotic signaling pathway. The ‘regulation of secretion’ and ‘inorganic ion homeostasis’ terms were enriched by both the up- and down-regulated DEGs characterizing COVID-19 infection and T2D (Figure 6A, Supplementary Table 2, see Supplementary Data available online at http://bib.oxfordjournals.org/). Two GO terms were commonly enriched by the downregulated DEGs charaterizing both COVID-19 infection and T2D: ‘plasma membrane bounded cell projection assembly’ and ‘response to glucose’ (Figure 6, Supplementary Table 2, see Supplementary Data available online at http://bib.oxfordjournals.org/). A network showing the relationships among the genes belonging to the ‘response to glucose’ term is presented as Figure 7A. Finally, our analysis revealed a disruption of the pathways related to insulin signaling, in both T2D pancreas ans SARS-CoV-2-infected pancreas organoids (Figure 7B, Supplementary Table 2, see Supplementary Data available online at http://bib.oxfordjournals.org/).

Analysis of the putative TFs involved in the regulation of the DEGs modulated in COVID-19 and DM revealed that MYC, HDAC1, STAT1, JUN, STAT3, CEBP, AESR1, USF1, SP1, NFkB1, RELA and HIF1A were commonly involved in the expression of the upregulated DEGs in COVID-19 and T2D islet. No overlapping enrichment was instead observed T1D and neither for the downregulated DEGs in COVID-19, T1D and T2D (Figure 6B).

Drug prediction for COVID-19 and DM pancreas

Analysis of drugs potentially useful for the treatment of COVID-19 patients concomitantly suffering from T2D was performed using the L1000FWD web-based utility, on the 35 upregulated and 14 downregulated genes in common between COVID-19 infected pancreas organoids and T2D islets. The top three drugs with the most anti-similar signature were: vemurafenib, milnacipran and erbstatin-analog (Table 3). No drug was found to be significantly enriched when considering the DEGs overlapping the COVID-19 and T1D pancreas profiles (data not shown).

Discussion

Comorbidities are associated to a higher risk of develop severe forms of COVID-19, with consequent need of mechanical ventilation and increased death rate [34]. Among the comorbidities that affect the prognosis of COVID-19 patients, DM has emerged as a potential risk factor [10]. This may in part be related to the observation that SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in metabolic organs and tissues, such as pancreatic beta cells, adipose tissue, the small intestine and the kidneys [35]. Therefore, elucidating the key genes and pathways in COVID-19 and DM is crucial to decipher the molecular association and mechanisms shared by these pathologies. The use of whole-genome transcriptomic analyses has been largely exploited by ourselves and others to study autoimmune diseases, cancer and neurodegenerative disorders [36–40], as well as to characterize potential pathogenetic mechanisms and novel therapeutic targets [41–43]. Here, we have comprehensively studied the pancreas and blood transcriptomic changes occurring in DM and COVID-19.
Discovering common pathogenetic processes between COVID-19 and diabetes

Figure 5. Putative TFs regulating the DEGs in PBMCs from COVID-19 and T1D and T2D patients. The TFs are visualized as a hierarchical clustering. The heatmap is colored by the P-values, and grey cells indicate the lack of significant enrichment.

Figure 6. Functional analysis on the DEGs in COVID-19 and DM pancreas. (A) Hierarchical clustering of the top 20 most enriched terms. The heatmap is colored by the P-values, and grey cells indicate the lack of significant enrichment. (B) Putative TFs regulating the DEGs in COVID-19 and DM datasets (both type 1 and type 2) pancreas. The TFs are visualized as a hierarchical clustering. The heatmap is colored by the P-values, and grey cells indicate the lack of significant enrichment.
by using integrative bioinformatics approaches. We detected 10 common down-regulated genes and 32 common upregulated genes between COVID-19 and T2D in PBMCs. Among them, it is worth noting TSPYL4 (Testis-specific Y-encoded-like protein 4), for which a genetic variants has been associated with chronic pulmonary obstructive disorder [44], and ACSL1 (Acyl-CoA Synthetase long chain family member 1) that encodes for the isozyme of the long-chain fatty-acid-coenzyme A ligase family. It has been shown that the inflammatory phenotype in rat model of T1D is linked to increased expression of ACSL1, and deletions of this gene prevent the acquisition of the inflammatory phenotype of macrophages associated with T1D [45]. Along the same lines, our study revealed altered immune response signaling pathways modulated in both COVID-19 and T2D PBMCs. In a recent study, Codo et al. [46] suggested that increased levels of blood glucose in T2D patients and glycolysis may promote the replication of the SARS-CoV-2 and higher production of cytokines by monocytes via mitochondrial ROS/hypoxia-inducible factor-1a-dependent

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Table 2. Top 25 drugs predicted for the use in COVID19 patients with T1D comorbidity

| Drug                  | Similarity score | P-value | q-value | Z-score | Combined score |
|-----------------------|------------------|---------|---------|---------|----------------|
| WAY-213613            | −0.1463          | 1.03E−04| 6.29E−01| 1.68    | −6.7           |
| gitoxigenin           | −0.122           | 7.10E−04| 8.61E−01| 1.84    | −5.78          |
| fatostatin            | −0.122           | 7.47E−04| 8.61E−01| 1.78    | −5.56          |
| BRD-K63425657         | −0.122           | 8.08E−04| 8.61E−01| 1.74    | −5.37          |
| emetine               | −0.122           | 6.41E−04| 8.61E−01| 1.8     | −5.76          |
| GSK-2126458           | −0.122           | 1.01E−03| 8.61E−01| 1.6     | −4.79          |
| hynemecromone         | −0.122           | 7.85E−04| 8.61E−01| 1.81    | −5.62          |
| BRD-K83509924         | −0.0976          | 5.45E−03| 8.61E−01| 1.66    | −3.76          |
| PF-562271             | −0.0976          | 4.91E−03| 8.61E−01| 1.71    | −3.95          |
| podophyllotoxin       | −0.0976          | 5.85E−03| 8.61E−01| 1.65    | −3.69          |
| lestaurtinib          | −0.0976          | 5.45E−03| 8.61E−01| 1.73    | −3.91          |
| BRD-K65904652         | −0.0976          | 7.22E−03| 8.61E−01| 1.65    | −3.53          |
| VU-0418939-2          | −0.0976          | 8.14E−03| 8.61E−01| 1.73    | −3.61          |
| digoxigenin           | −0.0976          | 5.85E−03| 8.61E−01| 1.83    | −4.09          |
| sunitinib             | −0.0976          | 5.54E−03| 8.61E−01| 1.73    | −3.9           |
| CFM-1571              | −0.0976          | 5.33E−03| 8.61E−01| 1.87    | −4.26          |
| BRD-K59556282         | −0.0976          | 5.81E−03| 8.61E−01| 1.73    | −3.87          |
| fenbendazole          | −0.0976          | 8.37E−03| 8.61E−01| 1.78    | −3.7           |
| SA-1447005            | −0.0976          | 6.18E−03| 8.61E−01| 1.76    | −3.88          |
| vincristine           | −0.0976          | 6.56E−03| 8.61E−01| 1.67    | −3.65          |
| ALW-II-38-3           | −0.0976          | 5.67E−03| 8.61E−01| 1.74    | −3.91          |
| EI-346-erlotinib-analog| −0.0976         | 6.08E−03| 8.61E−01| 1.73    | −3.84          |
| BRD-K14027855         | −0.0976          | 6.18E−03| 8.61E−01| 1.76    | −3.9           |
| triciribine           | −0.0976          | 6.61E−03| 8.61E−01| 1.7     | −3.71          |
| VU-0418933-1          | −0.0976          | 5.85E−03| 8.61E−01| 1.75    | −3.9           |

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Figure 7. (A) Network constructed using the genes belonging to the ‘response to glucose’ (GO:0009749) term, enriched among the downregulated DEGs in both SARS-CoV-2 infected pancreas organoids and T2D islets. The network has been built using the GeneMania software (https://genemania.org/) and visualized in Cytoscape. (B) Hierarchical clustering of the enriched terms related to the insulin pathways. The heatmap is colored by the P-values, and grey cells indicate the lack of significant enrichment.
pathway, which may result in T cell dysfunction and epithelial cell death. These observations suggest that metabolic inflammation in T2D patients may be favorable for viral replications and could enhance the release of cytokines.

Our results also suggested crucial pathways involved in T1D and COVID-19, such as lymphocyte activation, cellular protein catabolic process, immune response and autophagy. It has been previously shown that higher activity of lymphocytes is observed in T1D [47]; however, lymphocytes and immunoinflammatory events play a role in T2D, as well [48]. Our results suggest the ‘activation of immune response’ and ‘signaling by interleukins’ as crucial GO terms in COVID-19 and T1D, which is consistent with previous observations confirming the dysregulation of immune systems in response to viral infections [49]. The impairment of innate immunity has been linked to the increased prevalence of infections in DM patients [49]. Similarly, in an animal model, comorbid DM results in immune dysregulation and increases the severity of the diseases following infection with the other coronavirus, MERS-CoV [50].

It is also believed that metabolic inflammation compromises the immune systems in DM patients, which corroborates our results that systemic immune alterations in PBMCs could play a crucial role in both COVID-19 and T1D [51]. The impairment of the innate immunity has been also linked to the increased prevalence of infections in DM patients [49]. Moreover, the ‘cytokine storm’ occurring in COVID-19 results from uncontrolled host immune responses, which are believed to be associated with increased complications and critical conditions in COVID-19 patients. Therefore, clinical trials on antibodies/drugs that target these pathways might be conducted to identify potential use in COVID-19 patients with comorbid DM.

The two main TFs that regulate the shared DEGs between COVID-19 and DM are ‘SPI1’ and ‘RELA’. While SPI1 is involved in the inflammatory process and modulates host immune systems [52], RELA is implicated in NF-kB development and regulates proliferative and inflammatory cell responses [53]. We have previously detected these two TFs as critical regulators of the DEGs identified from transcriptomic analysis of COVID-19 infected lung tissue, suggesting that these two TFs might represent both biomarkers and pharmacological targets in COVID-19 [16].

Next, we profiled the gene expression signature of pancreas organoids infected with SARS-CoV-2 to detect transcriptional alterations characterizing the response to COVID-19 infection and to compare with T1D and T2D-associated transcriptomic pancreas profiles. Our analysis identified the dysregulated process involved in the ‘regulation of secretion’, which indicates that COVID-19 alters the secretory pathways of the pancreas, likely affecting the insulin secretion and impacting the prognosis of DM patients.

Glycaemic deterioration is often observed in COVID-19 patients with DM or with impaired glucose homeostasis [54]. Accordingly, SARS-CoV-2 infection was associated with need for higher doses of insulin [54]. Moreover, although ketoacidosis typically occurs in T1D patients, it was observed that more than 75% of COVID-19 patients who developed ketoacidosis had T2D [55].

It has been proposed an association between ACE2 and glucose homeostasis. ACE2 knockout mice are more susceptible than the wild-type counterpart to high-fat diet-induced β-cell dysfunction [56]. This observation and the expression of ACE2 in the endocrine pancreas support the notion that coronaviruses could damages the pancreatic islets, leading to hyperglycaemia [57]. Notably, it was previously shown that hyperglycaemia in SARS patients persisted for up to 3 years after recovery, indicating long-term damage to β-cells upon coronavirus infection.

In our analysis, a disruption of the regulation of insulin secretion has been observed among the DEGs characterizing COVID-19 and DM. Also, among the GO terms commonly enriched by

**Table 3.** Top 25 drugs predicted for the use in COVID-19 patients with T2D comorbidity

| Drug            | Similarity score | P-value | q-value | Z-score | Combined score |
|-----------------|------------------|---------|---------|---------|----------------|
| vemurafenib     | -0.2245          | 5.95E-10| 5.34E-06| 1.82    | -16.75         |
| milnacipran     | -0.2041          | 1.43E-08| 3.08E-05| 1.76    | -13.81         |
| erbstatin-analog| -0.2041          | 8.79E-09| 3.08E-05| 1.69    | -13.63         |
| TPCA-1          | -0.1837          | 1.30E-07| 1.38E-04| 1.84    | -12.64         |
| MV-STK33-2A     | -0.1837          | 2.63E-07| 1.46E-04| 1.66    | -10.93         |
| cinobufagin     | -0.1837          | 1.54E-07| 1.38E-04| 1.72    | -11.71         |
| dasatinib       | -0.1837          | 3.78E-07| 1.90E-04| 1.6    | -10.28         |
| enzastaurin     | -0.1837          | 2.87E-07| 1.55E-04| 1.69    | -11.03         |
| pifithrin-mu    | -0.1837          | 1.83E-07| 1.38E-04| 1.7    | -11.15         |
| RAN-03          | -0.1633          | 1.99E-06| 5.79E-04| 1.76    | -10.02         |
| BRD-K42499654   | -0.1633          | 3.53E-06| 6.41E-04| 1.74    | -9.48          |
| rotterlin       | -0.1633          | 7.69E-06| 1.29E-03| 1.75    | -8.96          |
| PD-98059        | -0.1633          | 2.31E-06| 5.79E-04| 1.65    | -9.33          |
| XMD-132         | -0.1633          | 2.50E-06| 5.79E-04| 1.7    | -9.5           |
| atracurium      | -0.1633          | 5.05E-06| 8.75E-04| 1.7    | -8.98          |
| BRD-K89486464   | -0.1633          | 2.80E-06| 5.99E-04| 1.75    | -9.72          |
| bosutinib       | -0.1633          | 1.71E-06| 5.79E-04| 1.73    | -9.98          |
| daunorubicin    | -0.1633          | 2.80E-06| 5.99E-04| 1.79    | -9.95          |
| CYT-997         | -0.1633          | 3.22E-06| 6.16E-04| 1.78    | -9.76          |
| MW-STK33-1C     | -0.1633          | 1.37E-06| 5.46E-04| 1.71    | -10.04         |
| BRD-A18725729   | -0.1633          | 2.06E-06| 5.79E-04| 1.78    | -10.11         |
| BRD-K9576153    | -0.1633          | 1.60E-06| 5.79E-04| 1.77    | -10.27         |
| BRD-K9493764    | -0.1633          | 1.27E-06| 5.46E-04| 1.77    | -10.45         |
| BRD-K48654774   | -0.1633          | 1.62E-06| 5.79E-04| 1.79    | -10.34         |
| amoxapine       | -0.1633          | 3.07E-06| 6.08E-04| 1.69    | -9.32          |
the downregulated DEGs characterizing both COVID-19 infection and T2D, we found ‘response to glucose’. Overall, our data suggest the hypothesis that SARS-CoV-2 tropism for the β-cell could cause acute impairment of insulin secretion and/or destruction of β-cells causing deterioration of the metabolic control in people with pre-existing DM or leading to the development of new-onset DM.

Finally, we have used an anti-signature-based approach [16] that aimed to detect candidate drug molecules that could reverse the DEGs signatures identified from DM PBMCs and pancreas. Interestingly, when considering the PBMCs gene expression profiles, we only found drugs potentially reverting the T1D/COVID-19, but not the T2D/COVID-19, signature. This is likely to be ascribed to the predominant immunoinflammatory processes underlying T1D pathogenesis, characterizing the autoimmune destruction of the β cells of the endocrine pancreas, but not T2D, where insulin resistance and reduced secretion of insulin by the β cells are the main culprit of the disease [58]. On the other hand, when investigating the pancreas data, we found drugs with a signature reverting the T2D/COVID-19 profile, but none for the T1D/COVID-19 common gene expression profile. This is in line with the GO analysis, which showed prevalent metabolic alterations in COVID-19 and T2D pancreas, and not common immunoinflammatory processes. In particular, on the top three predicted drugs, we have found vemurafenib, an FDA approved drug that can induce cellular apoptosis in melanoma cells that contained BRAF mutation via interfering B-raf/MEK/ERK pathway [59]. Also, we found Milancipran, an anti-depressant of serotonin-norepinephrin class, which is used for the treatment of psychotic disorders and fibromyalgia with dubious results [60, 61], and an erbsatin-analog, which is a EGFR inhibitor [62]. It is known that many growth factor receptors are associated with viral infections, and previous studies have suggested their repurpose for COVID-19 pandemic [63, 64]. However, despite the importance of the bioinformatics and systems biology-based analyses, the clinical validation of these findings is crucial before establishing them as biomarkers and/or interventional targets for the management of COVID-19 patients.

Conclusions

The present study aimed at discovering gene expression signatures, TFs, and dysregulated molecular pathways, which were in common between COVID-19 and T1D and T2D. Our analysis revealed common dysregulated immune-related pathways in COVID-19 and both T1D and T2D PBMCs. Accordingly, the top predicted TFs that regulate the shared DEGs between COVID-19 and DM were SPI1 and RELA, which are involved in the regulation of the inflammatory processes. However, as expected, we have observed different DEGs shared between COVID-19 and T1D and T2D.

In addition, several pathways, including those associated to the response to glucose and insulin pathways, were enriched by the DEGs in COVID-19 and DM, as observed in the pancreas-related transcriptomic profiles. This observation supports the hypothesis that SARS-CoV-2 could directly determine an impairment of insulin secretion, with consequent disruption of the metabolic control in people already suffering from DM or leading to the development of new-onset DM.

However, it should be pointed out that there are some limitations to the present study. Indeed, although the molecular pathways commonly dysregulated in COVID-19 and either of the two forms of diabetes may help to better understand the pathophysiology of the increased vulnerability of DM patients to COVID-19, the mechanisms by which DM affects COVID-19 susceptibility, severity, prognostic, mortality and long-term complications require more in-depth analysis to associate gene expression changes with respective traits. In addition, there are other major organs that are involved in the pathology of DM, which may be affected upon SARS-COV-2 infection, including kidneys, heart and blood vessels. Hence, it will be important to evaluate whether these extrapulmonary tissues are affected by pathogenetic pathways in common between COVID-19 and DM.

Notwithstanding the above-mentioned limitations, our work represents the first effort to characterize the overlapping gene expression profiles that may explain the negative prognostic association between COVID-19 and DM and, hence, may set the basis for future tailored pharmacological strategies for the better management of COVID-19 patients.

Key Points
- Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the newly discovered coronavirus, SARS-CoV-2. Increased severity of COVID-19 has been observed in patients with diabetes mellitus (DM).
- This study implemented a bioinformatic framework to detect common transcriptional signatures, regulators and pathways between COVID-19 and DM.
- We have integrated human whole-genome transcriptomic datasets from COVID-19 and DM, followed by functional assessment with gene ontology and pathway analyses.
- We observed 32 differentially expressed genes (DEGs) were found to be commonly modulated in COVID-19 and type 2 diabetes (T2D), while 10 DEGs were commonly downregulated in peripheral blood mononuclear cells. As regards type 1 diabetes (T1D), 21 DEGs were commonly upregulated, and 29 DEGs commonly downregulated in COVID-19 and T1D.
- We also found 35 DEGs were commonly upregulated in SARS-CoV-2 infected pancreas organoids and T2D islets.
- Here, for the first time, we have characterized the biological processes and pathways commonly dysregulated in COVID-19 and DM, which could be in the next future used for the design of personalized treatment of COVID-19 patients suffering of DM as comorbidity.

Supplementary Data

Supplementary data are available online at https://academic.oup.com/bib.

Data Availability Statement

All data here analyzed are publicly available on NCBI Gene Expression Omnibus (GEO) and the ArrayExpress databases.

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Discovering common pathogenetic processes between COVID-19 and diabetes

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