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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Original article

Candesartan could ameliorate the COVID-19 cytokine storm

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ABSTRACT

Background: Angiotensin receptor blockers (ARBs) reducing inflammation and protecting lung and brain function, could be of therapeutic efficacy in COVID-19 patients.
Methods: Using GSEA, we compared our previous transcriptome analysis of neurons injured by glutamate and treated with the ARB Candesartan (GSE67036) with transcriptional signatures from SARS-CoV-2 infected primary human bronchial epithelial cells (NHBE) and lung postmortem (GSE147507), PBMC and BALF samples (CRA002390) from COVID-19 patients.
Results: Hundreds of genes upregulated in SARS-CoV-2/COVID-19 transcriptomes were similarly upregulated by glutamate and normalized by Candesartan. Gene Ontology analysis revealed expression profiles with greatest significance and enrichment, including proinflammatory cytokine and chemokine activity, the NF-kappa B complex, alterations in innate and adaptive immunity, with many genes participating in the COVID-19 cytokine storm.
Conclusions: There are similar injury mechanisms in SARS-CoV-2 infection and neuronal injury, equally reduced by ARB treatment. This supports the hypothesis of a therapeutic role for ARBs, ameliorating the COVID-19 cytokine storm.

1. Introduction

The highly infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current COVID-19 pandemic, a disease affecting not only the lung but multiple organs with devastating consequences, high mortality, and no available specific therapy. It is imperative to consider repurposing available drugs to treat and prevent SARS-CoV-2-induced multiorgan pathology that are well-tolerated and effective in the elderly, a vulnerable COVID-19 group. Ideal compounds will exert proven potent anti-inflammatory effects with amelioration of the cytokine storm, normalization of p53 pathway, demonstrated reduction of the SARS that follows pneumonia and other coronavirus infections, and protective effects in cardiovascular and metabolic disorders frequently comorbid with COVID-19.

The Angiotensin Receptor Blockers (ARBs) fulfill all these requirements. ARBs block the effects of excessive activation of Angiotensin II AT1 receptors (AT1R), a major injury factor participating in the development of disorders of the brain, the cardiovascular system, the kidney, lipid and glucose metabolism and the immune system, enhancing inflammation and viral injury in the lung and linearly associated with viral load and lung injury in COVID-19 patients [1–5].

ARBs, initially developed as antihypertensive compounds, exert multiple pleiotropic protective effects beyond their influence on blood pressure. ARBs reduce excessive inflammation, protect mitochondrial function, maintain insulin sensitivity and energy metabolism, and normalize the coagulation cascade [1,6,7]. These compounds are well-tolerated in the elderly and successfully used not only as first-line antihypertensives but also in the treatment of diabetes, kidney disease, congestive heart failure and cerebrovascular disorders, which are frequent COVID-19 comorbidities [8].

ARBs protect the lung from severe injury associated with pneumonia, sepsis, influenza and SARS-CoV [1,6,9,10]. Furthermore, mortality was reduced in patients previously treated with ARBs for cardiovascular disorders and later hospitalized for pneumonia [6].

In addition, ARBs protect cognition, cerebral blood flow and blood-brain barrier function, reduce brain inflammation, anxiety, and stress [11–15]. and normalize expression of multiple genes involved in the aging process including p53 signaling [16,17]. These findings are of interest because cerebrovascular complications are frequent in patients affected by COVID-19 and their prevalence increases in severe cases and

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in the elderly [18–23].

For these reasons it was reasonable to suggest that ARBs could be beneficial for the treatment of COVID-19 patients, by ameliorating inflammation, hypertension and other comorbidities and directly protecting the lung and other organs from the SARS-CoV-2 infection. Multiple clinical studies are in progress to determine the effect of ARB therapy in COVID-19 patients https://clinicaltrials.gov/ct2/results?cond=COVID-19&term=angiotensin+receptor+blockers&cntry=&state=&city=&dist= and preliminary evidence indicates a reduction of critical prognosis and a lower death rate in ARB-treated COVID-19 patients [24].

Recent transcriptomic analysis of samples from COVID-19 patients and SARS-CoV-2-infected primary human alveolar cells revealed unique inflammatory profiles with excessive inflammatory cytokine release, alterations in interferon responses, macrophage and neutrophil infiltration, increased apoptosis and p53 signaling associated with lymphopenia [25,26]. These results, at first glance, appeared to be similar to the ones we already reported in our neuronal cultures injured by excitotoxic glutamate concentrations, a major injury factor in the brain, and normalized by treatment with the ARB Candesartan [16,17]. We had previously reported that these changes in cultured neurons were strikingly correlated with those observed in aging, one of the most important risk factors for COVID-19, not only in the brain but also in peripheral tissues [16,17].

We hypothesized that there may be mechanisms of injury common to age-related disorders and those present after SARS-CoV-2 infection, both in the brain and the periphery. The recent transcriptome analyses of samples from COVID-19 patients [25,26] provided an opportunity to correlate their findings with those obtained earlier reporting ARBs anti-inflammatory and anti-aging protective effects [16,17].

2. Methods

2.1. Gene expression analysis

We analyzed our own raw data from a previous experiment (Elkahloun et al., 2016) submitted to Gene Expression Omnibus (GEO) under accession number GSE67036. In this experiment, we treated primary rat cerebellar granule cells (CGC) with either vehicle, candesartan, glutamate, or candesartan and glutamate. Four independent experiments were conducted for each group. Standard procedures such as extraction of total RNA, labeling, hybridization, washing, and staining were as per manufacturer's recommendation (Affymetrix, Santa Clara, CA). The raw data was submitted to GEO under accession GSE67036. Detailed procedures have been described previously [16].

2.2. Dataset description and microarray data mining

We used Gene Set Enrichment Analysis (GSEA) [27] (http://www.broadinstitute.org/gsea/) to compare our data to published datasets [26] (GSE147507) downloaded from the National Center for Biotechnology Information (NCBI) GEO database, and [25], CRA002390 downloaded from their supplemental data and the Genome Sequence Archive in BIG (Beijing Institute of Genomics) Data Center (https://bigd.big.ac.cn/), Chinese Academy of Sciences [28]. A complete description of these data sets is summarized in Table 1. Data from isolated cells from human fibrotic lung postmortem samples were taken from GSE122960 [29].

Datasets were imported into Partek Genomics Suite software (Partek, Inc., St. Louis, MI) or analyzed by the GEO2R, an online resource from GEO, that uses GEOquery and limma R packages from the Bioconductor project. We also used the supplemental tables provided by the authors of these two papers. For a more comprehensive description of the GSEA and the Broad Molecular Signatures Database v5.0 (MSigDB) consult the Broad Molecular Signatures Database v5.0 (MSigDB) http:// www.broadinstitute.org/gsea/) [30–32]. Ingenuity Pathway Analysis (IPA) (http://www.ingenuity.com) [33], Gene Ontology (http://geneontology.org/) [34], Metascape (https://metascape.org/gp/index.html#/main/step1) [35] and Jensen Compartments database (https://compartments.jensenlab.org/) [36] were used to identify gene expression profiles and canonical pathways associated with the differentially expressed genes.

3. Results

3.1. Previous transcriptome analysis in cultured neurons

We had previously performed a transcriptome analysis of primary neurons (cerebellar granule cells, CGC) injured by excitotoxic concentrations of glutamate and compared gene expression in injured neurons with and without treatment with the ARB Candesartan (GSE67036), [16,17]. We have found that glutamate-induced upregulation of hundreds of pro-inflammatory and senescence related genes was normalized by Candesartan, indication of strong anti-inflammatory, anti-aging, and neuroprotective effects of ARB treatment [16,17].

3.2. GSEA analysis of SARS-CoV-2/COVID-19 transcriptomes

Using GSEA, we now asked the question whether this comparison would reveal normalization by Candesartan of gene signatures characteristic of COVID-19. We found a highly statistical positive correlation between the expression of a large number of genes upregulated by glutamate and those genes upregulated in four different SARS-CoV-2/COVID-19 human transcriptomes: a normal primary human bronchial epithelial (NHBE) cell culture infected with SARS-CoV-2 (Table 1, Fig. 1A), lung tissue post mortem samples from 2 COVID-19 patients and 2 lung biopsies from healthy controls (Table 1, Fig. 1B), peripheral blood mononuclear cells (PBMC) from 3 COVID-19 patients and 3 healthy

Table 1
Sample types, accession numbers, file names, links, and references of SARS-CoV-2/COVID-19 analyzed databases. Numbers of core enriched genes indicate the number of genes upregulated in SARS-CoV-2/COVID-19 human samples that were negatively correlated with genes normalized by Candesartan after glutamate upregulation in our neuronal cultures.

Sample type	Accession number	File	Number of core Enriched genes	Link	Reference
NHBE Primary human bronchial epithelial cells	GSE147507	GSE147507_SARS-COV-2_NHBE_CELLs_UP Fig. 1A	358	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147507	Blanco-Melo et al., 2020
Lung tissue autopsy from COVID-19 patient	GSE147507	GSE147507_PATIENT_SARS-COV-2_Table-S4_UP Fig. 1B	231	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147507	Blanco-Melo et al., 2020
Peripheral blood mononuclear cells (PBMC) fromCOVID-19 patients	CRA002390	YONG XIONG_2020_SUPPL2_PBMC_SARS-COV19_UP	459	https://bigd.big.ac.cn/gsa/browse/CRA002390	Xiong et al., 2020
Bronchoalveolar lavage fluid (BALF) from COVID-19 patients	CRA002390	YONG XIONG_2020_SUPPL2_BALF_SARS-COV19_UP Fig. 1D	273	https://bigd.big.ac.cn/gsa/browse/CRA002390	Xiong et al., 2020

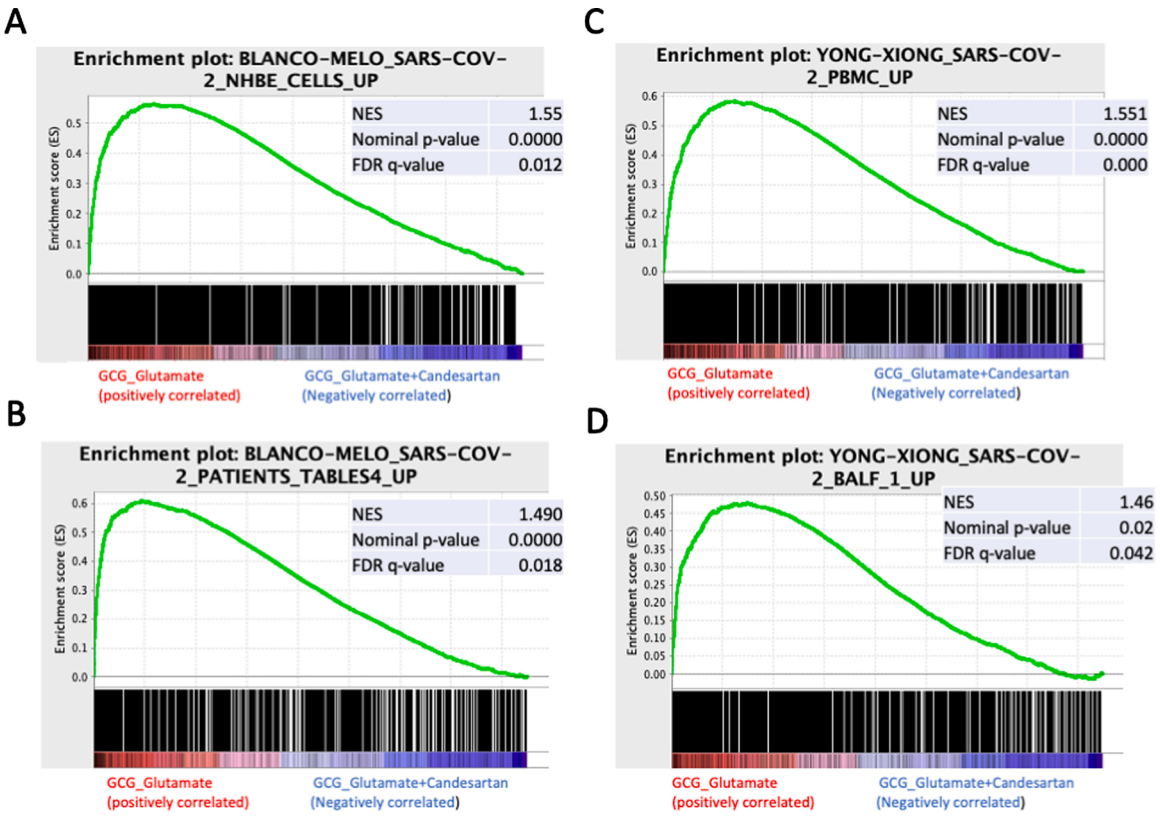

Fig. 1. Gene set enrichment plots from representative COVID-19 gene sets. The figure represents gene set enrichment analysis plots showing the positive correlations of genes upregulated by glutamate (in red) and normalized by Candesartan (in blue) in our neuronal cell culture with genes upregulated in primary human bronchial epithelial cells (NHBE) infected with SARS-CoV-2 (A), lung tissue post mortem samples from COVID-19 patients (B), peripheral blood mononuclear cells from COVID-19 patients (C) and bronchoalveolar lavage fluid (BALF) from COVID-19 patients (D) (see Supplemental Table 1 for complete GSEA output). NES, normalized enrichment score. FDR, False Discovery Rate. Gene sets with links and references are listed in Table 1.

controls (Table 1, Fig. 1C) and bronchoalveolar lavage fluid (BALF) from 2 COVID-19 patients and 3 healthy controls (Table 1, Fig. 1D).

Conversely, we found a striking negative correlation between expression of these genes after Candesartan treatment and those genes upregulated in the SARS-CoV-2/COVID-19 human transcriptomes. There were high numbers of core enriched genes in each sample type: 358 genes for the SARS-CoV-2 infected NHBE, 231 genes for the lung post mortem samples, 459 genes for the PBMC, and 273 genes for the BALF samples (Table 1, Figs. 1A–D, Supplemental Table 1).

Table 2
GSEA Enrichment of SARS-CoV-2/COVID-19 samples. The table lists the top 20 genes with highest rank metric scores in each enrichment dataset. The complete list of enriched genes in each transcriptome is listed in Supplemental Table 1.

BLANCO_SARS-COV-2_NHBE		BLANCO-MELO_SARS-COV-2_PATIENTS		YONG-XIONG_SARS-COV-2_PBMC		YONG-XIONG_SARS-COV-2_BALF	
PROBE	RANK IN GENE LIST	PROBE	RANK IN GENE LIST	PROBE	RANK IN GENE LIST	PROBE	RANK IN GENE LIST
CXCL6	4	*CCL7*	2	*GPR34*	3	*CCL7*	2
CXCL10	7	*CXCL6*	4	*SERPINE1*	6	*CXCL6*	4
PTGS2	14	*CXCL10*	7	*CXCL10*	7	*CCL4*	8
CTSS	25	*CCL4*	8	*LILRB4*	12	*PTGS2*	14
CXCL1	45	*EVI2B*	13	*RSAD2*	22	*RSAD2*	22
IL1RN	49	*TLR7*	21	*CTSS*	25	*CXCL11*	26
EDN1	52	*RSAD2*	22	*MRC1*	33	*CCL3*	30
IER3	58	*CTSS*	25	*CYBB*	47	*CXCL1*	45
CTSC	62	*CXCL11*	26	*SLC11A1*	50	*AIF1*	53
IFITM1	63	*FCER1G*	28	*AIF1*	53	*IFITM1*	63
SQRDL	71	*CD53*	29	*CTSZ*	57	*CFH*	65
CXCL16	73	*CCL3*	30	*CSF1R*	68	*BIRC3*	84
SDC4	80	*LCP1*	31	*HMOX1*	69	*ASS1*	96
SLAMF9	81	*TYROBP*	37	*C3AR1*	76	*CD180*	101
BIRC3	84	*CD68*	39	*SDC4*	80	*ARHGAP29*	103
PGF	85	*EMR1*	40	*IL18*	93	*PMAIP1*	115
ICAM1	87	*RGS18*	41	*MSR1*	95	*GALNT3*	120
AMPD3	92	*CYBB*	47	*RGS16*	100	*IGSF6*	121
ANXA1	94	*FYB*	48	*CD180*	101	*SEMA3A*	127
ASS1	96	*IL1RN*	49	*ARHGAP29*	103	*EGR1*	138

3.3. Analysis of genes with highest metric scores

The top 20 genes with the highest rank metric scores in each enrichment dataset are listed in Table 2, that includes many genes related to cytokine and chemokine activity, chemokine receptor binding, cytokine-mediated signaling pathways, NF-κB complex, cellular response to type I interferon, type I interferon signaling pathway, response to interferon γ and response to virus, such as *CXCL1, CXCL6, CXCL10, CXCL11, CXCL16, CCL4, IL1RN, IFITM1, RSAD2, PTGS2, BIRC3, AIF1* and *ASS1*.

When the top 20 genes with the highest rank metric scores in each enrichment dataset were compared, each dataset revealed an apparent unique transcriptome signature, the result of different types of cells included in each transcriptome. The NHBE cells showed *ICAM1*, *IL6*, *EDNI*, *ANXA1*, *AMPD3*, *PGF* and *IER3* upregulation; lung postmortem samples displayed *EVI2B*, *FCER1G*, *CD53*, *LCP1*, *CD68*, *EMR1*, *FYB*, *TLR7* and *TYROBP*; PBMC samples presented *GPR34*, *SERPINE1*, *LILRB4*, *MRC1*, *SLC11A1*, *CTSZ*, *CSF1R*, *HMOX1*, *C3AR1*, *IL18*, *MSR1* and *RGS16* upregulation, and BALF samples showed *CFH*, *PMAIP1* and *SEMA3A* upregulation (Table 2).

3.4. Analysis of genes common to several SARS-CoV-2/COVID-19 transcriptomes

To reveal the genes most commonly associated with SARS-CoV-2 infection, we generated a list of 210 genes consistently upregulated and GSEA enriched in at least 2 out of the 4 SARS-CoV-2/COVID-19 human transcriptomes, that were also upregulated by glutamate and normalized by Candesartan in our neuronal culture. (Fig. 2 and Supplemental Tables 1 and 2). In addition, Supplemental Table 2 lists the individual gene associations with their dataset origin, the genes commonly upregulated in NHBE cells and PBMC, BALF and PBMC, and lung autopsies and PBMC databases. There were 112 genes enriched in the lung autopsies, 127 genes in the PBMC, 87 genes in the BALF, and 121 genes in the NHBE transcriptomes (Supplemental Table 2). The pair comparisons PBMC/lung biopsies, PBMC/BALF and PBMC/NHBE presented similar 40/60 % overlaps. This indicates that when the entire lists of enriched genes were compared, the enrichment was similar for all cells and tissues studied.

3.5. Gene ontology analysis

The list of the 210 genes was then analyzed using Gene Ontology (GO Molecular Function and GO Biological Process), GO Jensen Compartments and Metascape (Table 3, Figs. 3a and b, Supplemental Table 3). Using Gene Ontology, we found 47 highly significant Molecular Functions (p-value<0.05) and 89 Biological Processes (p-value<0.0001) modulating the activity of these 210 most upregulated genes. Some of the Molecular Functions with highest significance and with highest numbers of associated genes were those for chemokine receptor binding, chemokine activity, cytokine activity, ubiquitin-like protein ligase binding, kinase binding, endopeptidase activity and protein kinase activity (Table 3, Supplemental Table 3).

Some of the Biological Process with highest significance and highest numbers of associated genes were cytokine-mediated signaling pathway, cellular response to type I interferon, type I interferon signaling pathway, cellular response to interferon gamma, cellular response to cytokine stimulus, response to cytokine, response to interferon gamma, inflammatory response, neutrophil mediated immunity, neutrophil degranulation and neutrophil activation involved in immune response related to the cytokine-mediated signaling pathway, cellular response to type I interferon and type I interferon signaling pathway (Table 3, Supplemental Table 3).

From the Jensen Compartments database, we identified 50 highly significant gene expression profiles, and some of the most significant with highest numbers of genes were the NF-kappa B complex, interferon regulatory factor 7, interferon regulatory factor complex, interleukin-12 complex, interleukin-23 complex, S100A9 complex, extracellular space and Bcl-2 family protein complex (Table 3, Supplemental Table 3).

Metascape analysis identified 20 terms with high significance. The main GO identified categories with highest significance and number of genes were cytokine-mediated signaling pathway, response to virus, response to interferon gamma, regulation of cytokine production, response to bacterium, myeloid leukocyte activation, influenza A,

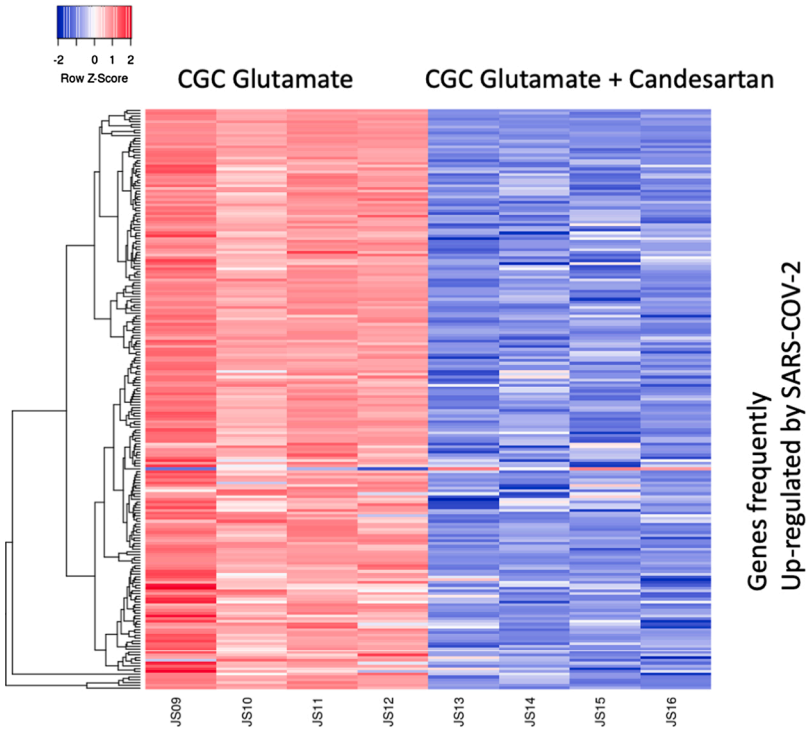

Fig. 2. Heatmap of the 210 genes that are most commonly upregulated in at least 2 out of 4 SARS-CoV-2 /COVID-19 transcriptome tissues and their expression in the CGC treated with glutamate or glutamate + Candesartan. Red is for greater gene expression (upregulation) positively correlated with the transcriptome of neurons injured by glutamate and blue is for lower gene expression (downregulation) in the transcriptome of neurons injured by glutamate and treated with Candesartan (negatively correlated).

Table 3
Selected Gene Ontologies (GO) of the 210 genes most upregulated in 4 COVID-19 infected tissues and negatively correlated with Candesartan. Enrichment and Metascape algorithms were used to generate the Gene Ontologies. A complete list of gene ontologies output is provided in Supplemental Table 3.

GO Molecular Function	
Terms	Genes
cytokine activity (GO:0005125)	*CXCL6;IL33;IL1RN;CXCL1;TNF;CXCL2;CXCL16; CXCL10;CXCL11;CCL7;IL1B;CCL4;CCL3;CCL2*
chemokine activity (GO:0008009)	*CXCL6;CXCL10;CXCL11;CCL7;CCL4;CCL3; CCL2;CXCL1;CXCL2;CXCL16*
chemokine receptor binding (GO:0042379)	*CXCL6;CXCL10;CXCL11;CCL7;CCRL2;CCL4; CCL3;CCL2;CXCL1;CXCL2;CXCL16*
GO Biological Process	
cytokine-mediated signaling pathway (GO:0019221)	*IFITM3;CXCL6;IFITM1;IL1RN;IFITM2;ITGB2; CXCL1;TNF;CXCL2;OASL;SOX2;MT2A;CASP1; TRIM21;RSAD2;ANXA2;IFNGR1;IL1R2;IFNGR2; IRAK3;OSMR;EREG;IL1B;IRF7;IRF5;IRF9;BIRC3; SP100;CEBPD;PTGS2;CCL7;CCL4;CCL3;CCL2; FCGR1A;IL33;STAT1;STAT2;MX1;FN1;ISG15; SOD2;PML;PSMB9;ISG20;CXCL10;CXCL11; LCN2;PLP2;XAF1;MYD88*
cellular response to type I interferon (GO:0071357)	*IFITM3;IFITM1;SP100;IFITM2;RSAD2;STAT1; STAT2;MX1;ISG15;OASL;ISG20;IRF7;IRF5; XAF1;IRF9;MYD88*
type I interferon signaling pathway (GO:0060337)	*IFITM3;IFITM1;SP100;IFITM2;RSAD2;STAT1; STAT2;MX1;ISG15;OASL;ISG20;IRF7;IRF5; XAF1;IRF9;MYD88*
GO_Jensen_COMPARTMENTS	
NF-kappa B complex	*CXCL6;CXCL1;TNF;CXCL2;CXCL16;IFIH1; CASP1;CYP1B1;CD38;TGM2;IFNGR1;DDX58; IL1R2;CYBB;IRAK3;F3;SLPI;IL1B;IRF7;TLR4; IRF9;BIRC3;CEBPD;RRBP1;PTGS2;THBS1; CCNB1;CCL7;CCL4;CCL3;CCL2;FCGR1A;LDLR; LYN;CD74;IL33;SMAD3;GADD45A;STAT1;VDR; STAT2;MX1;ISG15;SOD2;MAPK12;PSMB9; FOSL1;ISG20;CXCL10;CXCL11;BCL3;LCN2; MYD88*
Interferon regulatory factor 7 complex	*IL33;RSAD2;DDX58;STAT1;MX1;IFI44;ISG15; TNF;OASL;ISG20;IFIH1;CXCL10;MT2A;IRF7; CCL2;IRF5;PLP2;TLR4;CFB;MYD88;IRF9*
Interferon regulatory factor complex	*TNF;IFIH1;CCL4;CASP1;CCL3;CCL2;TRIM21; RSAD2;IFNGR1;STAT1;DDX58;IFNGR2;STAT2; MX1;IFI44;ISG15;ISG20;CXCL10;CXCL11;IL1B; IRF7;IRF5;PLP2;TLR4;MYD88;IRF9*

macrophage activation and positive regulation of defense response. (Figs. 3a and b, Table 4 and Supplemental Table 3).

3.6. Individual gene analysis

Individual analysis of the list of 210 genes upregulated in at least 2 out of 4 SARS-CoV-2/COVID-19 human transcriptomes, that were also upregulated by glutamate and normalized by Candesartan in our neuronal culture (Fig. 2 and Supplemental Tables 1 and 2) revealed some genes encoding for pattern recognition receptors (PRRs) for viral entry or regulating their function (*RIG-1* (*DDX58*), *TLR4*, *MYD88*, *HERC6*). Many genes encoded for pro-inflammatory chemokines and cytokines (*CXCL6*, *CXCL1*, *CXCL2, CXCL16, CCL2, IL1B, IL1R2, TNF, TNFAIP6* and *CD74*), regulated their pro-inflammatory effects *or* were biomarkers of systemic inflammation (*LCN2/NGAL*) or were NF-kappa B targets in response to inflammatory cytokines (*IGFBP3*, *BCL3*).

Enrichment and Metascape algorithms were used to generate the Gene Ontologies. A complete list of gene ontologies is provided in Supplemental Table 3.

There were many genes contributing to regulation of the interferon response or directly regulated by interferon (*IFITM1, IFITM3, ISG15, ISG20, IRF5*, *IRF7, IRF9, MX1, STAT1, STAT2, IFIH1* and *IFI44*). Other genes regulate mitochondrial function and are important for viral progression (*PLP2, GLDC, HTRA1, LGALS9, SLPI* and *ZC3H12A/MCPIP1*). Other groups of genes are sensors of DNA damage and activate p53 (*PML, PARP9, SLC43A3),* are involved in the TGFβ signaling pathways (*LFM2/noelin2*), play important roles in ameliorating or increasing superoxide production (*SOD2, NCF2, PLBD1, FAM72A)* or contribute to regulate the coagulation system (*CFB*, Factor V, *KPTN*).

3.7. GSEA analysis of lung fibrosis transcriptomes

We used GSEA to compare gene expression profiles from single-cell RNA-Seq from postmortem samples from patients with lung fibrosis with our global gene expression profile from primary cortical neurons (Supplemental Table 4). We found striking and highly statistically positive correlations of genes upregulated in these conditions with genes upregulated by glutamate, and negative correlations with genes normalized by Candesartan in our neuronal cultures (Supplemental Table 4).

3.8. IPA upstream regulation

We used the IPA upstream regulator function to generate a potential list of drugs and transcription factors that may be used to reverse the upregulation of gene expression in the SARS-CoV-2/COVID-19 transcriptomes analyzed. These drugs include dexamethasone, immunoglobulin, beta-estradiol, MAPK1, simvastatin, anti-inflammatory and immune-suppressing drugs, and several kinase inhibitors (Supplemental table 5). Conversely, up-stream regulators that positively correlate with COVID-19 upregulated genes are many proinflammatory cytokines, PRRs and inflammation-inducing chemical drugs (Supplemental table 5).

4. Discussion

4.1. GSEA analysis of SARS-CoV-2/COVID-19 transcriptomes

We previously showed that Alzheimer's disease, aging, and senescence transcriptomes revealed a striking positive correlation with gene expression upregulated by glutamate and a remarkable negative correlation with gene expression after Candesartan treatment in our neuronal cultures [16,17].

Excessive inflammation with a cytokine storm and innate and adaptive immune alterations are hallmarks of COVID-19 [25,26], a disorder more severely affecting the elderly and involving not only the lung but many other organs, including the brain [37]. Because of the above, we asked the question whether the strong anti-inflammatory effects and normalization of the immune response by Candesartan could be in any way related to a relief of the cytokine storm and immune alterations associated with SARS-CoV-2 infection, and we compared, using GSEA, our results with the recently reported gene signature samples obtained from SARS-CoV-2 infected human cells and COVID-19 patients [25,26]. In all cases, we found striking and highly significative positive correlations between the upregulation of hundreds of genes associated with SARS-CoV-2 infection [25,26] and those upregulated by neuronal injury, that were negatively correlated with genes normalized by Candesartan in our neuronal cultures [16,17].

4.2. Unique transcriptome signatures

As expected, because of the different source of the materials examined, each of the datasets studied revealed unique transcriptome signatures when only the top 20 genes with highest rank metric scores in each enrichment dataset were reported (Table 2). The NHBE transcriptome included *ICAM1*, important for recruitment of inflammatory immune cells and participating in the COVID-19 response [38], and *IL-6*, a pro-inflammatory cytokine associated to poor COVID-19 response [39, 40]. The transcriptome from COVID-19 post mortem samples contained *CYBB* (*NOX2*) [41] a super-oxide generating enzyme forming excessive

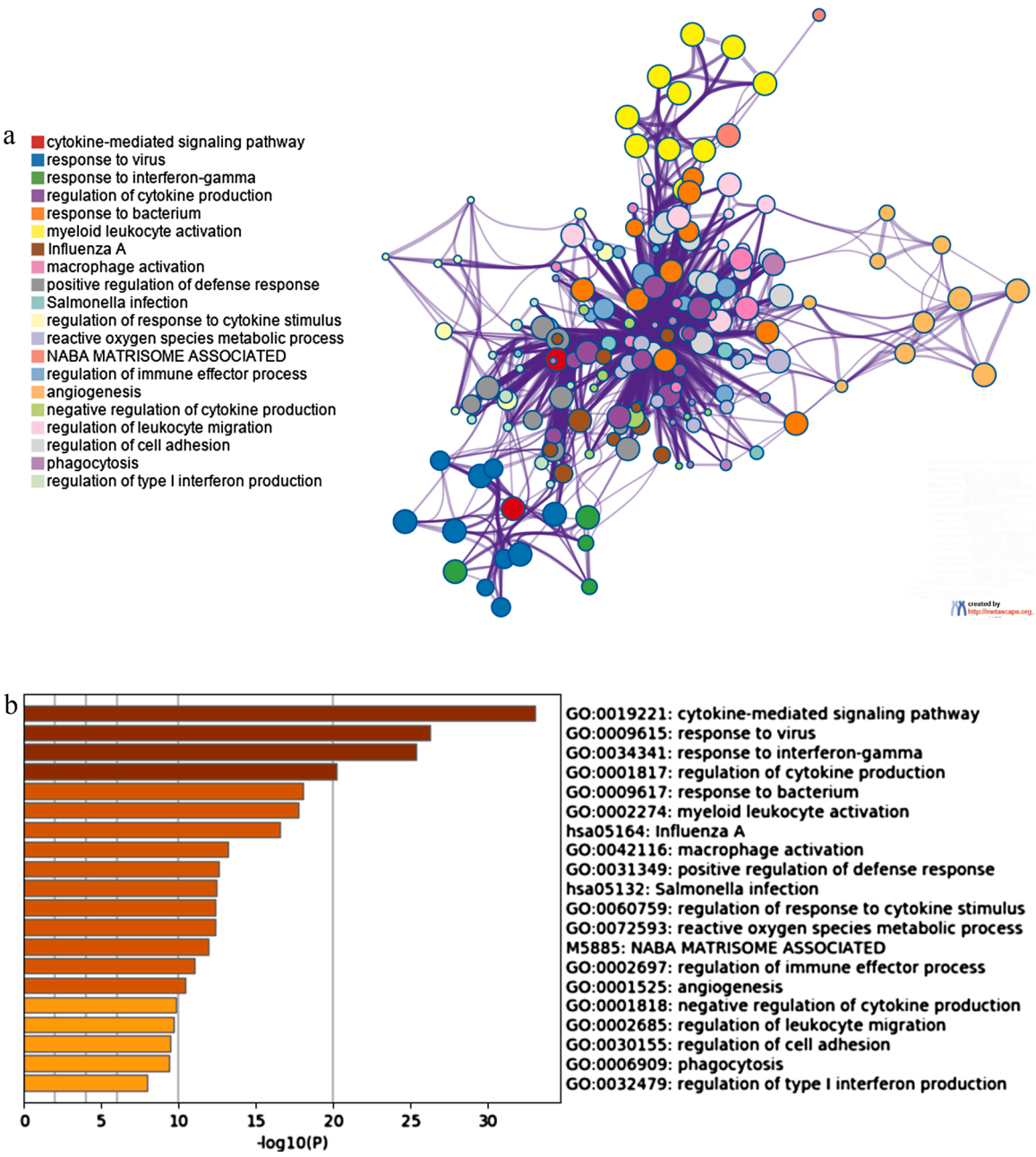

Fig. 3. a. **Network of enriched terms colored by GO category similarities.** Nodes that share the same cluster ID are typically close to each other and the size of the nodes are associated with their statistical significance (Supplemental Table 3). b. **Metascape Gene Ontologies (GO) enrichment for the 210 genes most commonly up-regulated in 4 COVID-19 infected tissues.**

reactive oxygen species (ROS) and involved in SARS-CoV-2 infection [42] and *TLR7*, a Toll-like receptor essential for antiviral immunity, including the response to SARS-CoV-2 [43–45]. The PBMC transcriptome revealed *HMOX1*, with anti-inflammatory properties [46,47], and *IL18*, a proinflammatory cytokine reported to play an important role in COVID-19 [48–50]. The BALF transcriptome included upregulated *CFH*, reported to increase pathogen virulence [51], and *PMAIP1* (Noxa) proapoptotic member of the Bcl-2 protein family, involved in p53-mediated apoptosis [52]. However, when the entire lists of enriched genes were compared (Table 1 and Supplemental Table 2) we found hundreds of enriched genes in each of the datasets studied.

4.3. Common gene signatures

To determine whether there was a gene signature common to COVID-19 we identified 210 genes upregulated in at least 2 out of the 4 different tissues infected by SARS-CoV-2/COVID-19 and GSEA enriched (glutamate upregulation and Candesartan downregulation). Gene Ontology analysis (Tables 3 and 4, Fig. 3a and b, Supplemental Tables 1–3) revealed a highly significant enrichment for all principal pathways associated with the host response to SARS-CoV-2 infection. These pathways included multiple genes related to cytokine and chemokine production, activity and signaling pathways, the NF-kappa B complex, reactive oxygen species, myeloid leukocyte and macrophage activation, response to virus, cellular response to type I interferon and interferon-gamma and interferon response and regulatory pathways, immune effectors activity, response to virus and regulation of extracellular matrix proteins. Supplemental Table 2 includes the specific genes associated with each of the transcriptomes studied, revealing that the number of enriched genes is similar for each transcriptome.

Table 4
Selected Gene Ontologies (GO) of the 210 genes most upregulated in 4 COVID-19 infected tissues and negatively correlated with Candesartan.

Go Metascape	
Terms	Genes
Cytokine-mediated signaling pathway (GO:0019221)	*ANXA2,BIRC3,CASP1,CD74,CEBPD,ECM1, EREG,F3,FCGR1A,FN1, CXCL1,CXCL2,IFNGR1,IFNGR2,IL1B,IL1RN, CXCL10,IRF5,IRF7,ISG20, ITGB2,KRT18,LCN2,MT2A,MX1,MYD88, PLP2,PML,PSMB9,ROBO1, CCL2,CCL3,CCL4,CXCL6,CXCL11,SOD2, SP100,TRIM21,STAT1,STAT2, TNF, IL1R2,IFITM1,OASL,CCRL2,ISG15,IRF9, IFITM3,IFITM2,IRAK3, XAF1,PARP9,IL33,RSAD2*
Response to virus (GO:0009615)	*BIRC3,BCL3,IFNGR1,IFNGR2,IL1B,CXCL10, IRF5,IRF7,ISG20,LCN2, LGALS9,MX1,PML,HTRA1,CCL4,STAT1, STAT2,TNF,FOSL1,IFITM1, OASL,ISG15,IRF9,IFITM3,IFI44,IFITM2, IRAK3,DDX58,IFIH1,ZC3H12A, PARP9,IL33,RSAD2,DTX3L*
Response to interferon-gamma (GO:0034341)	*AIF1,ASS1,CASP1,FCGR1A,GCH1,IFNGR1, IFNGR2,IRF5,IRF7,LGALS9, MT2A,PML,CCL2,CCL3,CCL4,SP100, TRIM21,STAT1,TLR4,IFITM1,OASL, IRF9,IFITM3,IFITM2,CXCL16,PARP9,GBP5, SIRPA*

4.4. Individual gene analysis of commonly upregulated genes

4.4.1. Pattern recognition receptors (PRRs) and associated genes

Individual analysis of the 210-gene list revealed many genes playing major roles in COVID-19 pathology. There were several commonly upregulated genes associated with viral entry, such as *TLR4*, *MyD88*, *DDX58* (*RIG-I*) [53]. *TLR4*, encoding for the PRR TLR4, a Toll-like receptor 4 [54], recognizes molecular patterns from SARS-CoV-2 to induce inflammatory responses [55]. *TLR4* and *MyD88* are major components of the *MyD88*-dependent pathway, regulating early NF-kappa B activation and downstream inflammatory cytokine production such as TNF-α, and IL-1, and activating the innate immune system [56]. *MyD88* plays an important role in *IL-6* induction during COVID-19 [57]. *RIG-I* is a PRR sensing RNA virus, upregulated by viral infection [58] and has been implicated in the induction of early antiviral immune responses in COVID-19 [59].

4.4.2. Genes associated with the COVID-19 cytokine storm, reactive oxygen species and interferon responses

Many genes are associated to the COVID-19 cytokine storm. *IL1B is* markedly increased during SARS-CoV-2 infection associated with rapid activation of the innate immune response, epithelial and endothelial apoptosis and vascular leakage [60–62] *CASP1*, encoding for Caspase-1/interleukin-1 converting enzyme (ICE) forms part of the inflammasome complex activating IL-1β and IL-18 [63,64]. *CXCL6*, *CXCL1*, and *CXCL2* encode for pro-inflammatory chemokines, attracting neutrophils, monocytes, memory T cells and dendritic cells to the site of injury during SARS-CoV infection [65–67]. They activate oxidative and endoplasmic reticulum stress, amplify acute lung injury and SARS, subsequently triggering innate immune responses [67,68]. *CXCL10* is a chemokine attracting macrophages and promoting T cell adhesion in response to interferon [69] and is part of the COVID-19 cytokine storm [70].

CCL2 encodes MCP1,recruiting monocytes, memory T cells, and dendritic cells to the sites of inflammation and is part of the distinct host inflammatory cytokine profile to SARS-CoV-2 infection [25,44]. *CCL2* activates apoptosis and the p53 signaling pathway that may cause patient's lymphopenia [25]. *CCL4* and *CCL7* are chemokines attracting macrophages and with major proinflammatory properties [71,72],

CXCL16 is induced by interferon gamma and TNF-α [73], that interacts with SARS-CoV N protein in and out of the cell [74]. *CCL2* stimulates neuroinflammatory processes [66]. CD74 encodes the HLA class II histocompatibility antigen gamma chain (CD74) mediating the macrophage migration inhibitory factor proinflammatory effects, viral replication and IFN-γ production during the acute phase of brain SARS-CoV. *STAT1* is activated by interferon and IL-6, polarizing the immune response specifically in macrophages, resulting in a worsened COVID-19 outcome [75–78]. *TNF* is produced by activated macrophages, promoting the acute inflammatory response. Increased TNFα production and release, associated with IL-1α and IL-β and inversely correlated with lymphopenia and decreased IFN-γ expression, is characteristic of severe COVID-19 [79–82]. *PTGS2*, encoding COX2, plays an important role in SARS-CoV infections. SARS-CoV N protein causes lung inflammation by activating COX2 and stimulating multiple COX2 inflammatory cascades [83].

CF2 is a subunit of the NADPH oxidase complex and produces a burst of ROS in neutrophils [84]. *IRAK3*, an interleukin-1 receptor associated kinase, is involved in excessive production of reactive oxygen species [85]. *SOD2* is a crucial regulator of antiviral signaling, clearing mitochondrial reactive oxygen species (ROS), protecting against cell death, [86] inhibiting the RIG-I-like receptor induction of innate immune responses, and activating interferon regulatory factor-3 [87]. *CN2/NGAL,* encoding lipocalin-2, is a biomarker of systemic inflammation [88,89].

Other genes, such as *IFITM1 and IFITM3* encoding interferon-induced transmembrane protein 1 and 3, respectively, have been previously associated with SARS-CoV infections. They are restriction factors for virus, including SARS-CoV [90–94]. *MX1* encodes interferon-induced GTP-binding proteins Mx1 (MxA) and is prominently induced by interferon-beta after SARS-CoV infection [95]. *PLP2* encodes for proteolipid protein 2, a coronavirus protease increasing virulence factors and antagonizing the host innate immune response, inhibiting the p53-*IRF7*- mediated antiviral response including that to SARS-CoV [96–99]. *HTRA1* encodes serine protease HTRA1; its overexpression enhances papilloma virus cell proliferation [100].

4.4.3. Genes associated with coagulation abnormalities

Genes part of the complement complex, such as *CFB* and *F5*, stimulate recruitment and infiltration of inflammatory cells, contributing to lung injury [101] and predisposing to thrombosis [102]. Their upregulation may play a role in the high risk of thrombosis of COVID-19 patients [103,104].

4.4.4. Effects of ARB treatment on COVID-19-related genes

The anti-inflammatory effects of ARB treatment have been extensively documented in the literature, and ARBs normalize the upregulation of expression of several genes in our 210-gene selected list. *LCN2/NGAL* is increased in hypertensive patients and downregulated by ARB treatment [105]. ARB blockade reduces *STAT1* phosphorylation induced by inflammation and IL-1β, leading to a predominant M2 macrophage phenotype [106]. ARBs downregulate *TLR4, MyD88* and NF-kappa B expression [107,108] as well as the inflammasome [109,110].

There is extensive evidence for a reduction of inflammatory cytokines such IL-1β, encoded by *IL-1B* after ARB treatment, both in the periphery and in the brain [13,111]. Beneficial effects of ARB treatment, reducing inflammation including TNFα production and release have been extensively documented in disorders where excessive inflammation and increased AT1R receptor activity play a fundamental role, including but not limited to diabetes [112], cerebral ischemia [113], hypertension [114] and cardiovascular disease [115]. COX2, a powerful proinflammatory enzyme, is inhibited by ARBs [116,117].

ARB treatment reduced the effects of *CXCL1* and *CXCL2* upregulation and increased oxidative stress [118–120]. *CXCL16* is involved in Angiotensin II associated metabolic disorders and atherosclerosis, and its secretion is blocked by ARBs [121,122]. ARB treatment reduces MCP-1 upregulation during lung injury, inhibits monocyte recruitment

and reduces lung fibrosis development [123,124]. ARBs downregulate the proinflammatory chemokines *CCL4*, *CCL7* and *CXCL10* [125–128].

4.4.5. Genes associated with pulmonary fibrosis

The beneficial effect of ARB treatment may not be limited to acute SARS-CoV-2 infection and COVID-19 severity but may extend to ameliorate long-term consequences of the disease. Pulmonary fibrosis leading to pulmonary arterial hypertension and irreversible respiratory failure is likely to occur in patients recovered from acute respiratory distress syndrome (ARDS) associated with critically severe COVID-19 [57,129,130]. We found highly significant negative correlations between genes upregulated by glutamate and normalized by Candesartan in our neuronal cultures with transcriptome signatures of alveolar cells, fibroblasts and macrophages from post mortem human fibrotic lungs, indicative of alterations in mitochondrial biogenesis and enhanced oxidative stress, inflammation and senescence [29] (Supplemental Table 4).

It has been previously established that Angiotensin II increases lung fibrosis and chronic obstructive pulmonary disease [131] in animal models, and this is suppressed by ARB treatment [123,132–135]. Examples of genes from our 210-gene list and previously reported to play a role in the development of lung fibrosis include *SOX2*, [75–78,136] and *HTRA1*, a gene repressing signaling by TGF-β family members, preventing vascular fibrosis and extracellular matrix protein synthesis, effects similar to those of ARB treatment [137].

4.4.6. Genes associated with old age

Old age is a major risk factor for COVID-19 progression and death [5,18,138]. As we previously reported, ARBs normalize expression of multiple genes involved in the aging process [16,17], and ARB blockade prevents the premature senescence produced by excessive Angiotensin II activation [139,140]. It has been recently shown that one Alzheimer's risk gene correlates with risk for severe COVID-19 [141]. Within our 210-gene list, a genetic variant of *IFITM3* has been recently associated with age-dependent COVID-19 severity [142], and *ADAP2* has been proposed to participate in Alzheimer's disease progression [143]. Downregulation of *SOD2*, a gene with antiaging effects that ameliorates DNA damage and protects against cellular senescence [144] is normalized by ARB treatment in a rodent model of Alzheimer's disease [145].

4.4.7. Genes highly expressed in the brain, and effects of ARB treatment on brain disorders

SARS-CoV-2 infection not only affects the lung but extends to many other organs, including the brain, and age-related cerebrovascular disorders such as cerebral hemorrhage and stroke are not only frequent comorbidities but also novel and critical events in the presentation, progress and prognosis of COVID-19 [18,19,21–23,146,147]. It has also been established that ARB administration is strongly neuroprotective, regulating cerebral blood flow, blood-brain barrier function, reducing brain inflammation and protecting cognition in hypertensive patients and in the elderly [5,11–13,15,17]. Some of the genes included in our 210-gene list are widely expressed in brain, such as *SLC43A3,* encoding the solute carrier family 22 member 3 and a biomarker of sensitivity to DNA damage [148], specifically expressed in the microvasculature [149,150]. Increased *CXCL1* expression in the brain was associated with increased mortality and demyelination [151].

4.5. Up-stream regulators

Our IPA upstream regulator analysis identified many factors that may downregulate COVID-19 upregulated genes in our study, including dexamethasone, immunoglobulin, beta-estradiol, and simvastatin. Dexamethasone has been proposed for acutely ill COVID-19 patients, but its use carries severe risks and needs to be carefully evaluated [152]. Immunoglobulin was reported to be effective in severely ill COVID-19 patients [153]. The use of beta-estradiol and simvastatin is currently being evaluated in interventional clinical trials [154]. Not surprisingly, many proinflammatory cytokines (TNF, IL1B, IL6, IL13), PRRs such as TLR4 and TLR7, and inflammation-inducing drugs such as lipopolysaccharide were found to positively correlate with COVID-19 upregulated genes.

4.6. Additional literature support

It could be argued that given that cells and tissues analyzed here are very different from neurons, Candesartan inhibition of neuronal inflammation does not necessarily correlate with similar effects of this compound in the lung and PBMC.

However, there is convincing literature demonstrating a role for AT1R in lung function [155–158], lung injury as a result of excessive AT1 receptor activation [133,159–165] and protective effects of ARB treatment in lung injury [10,135,166–175].

It has also been reported that ARBs ameliorate pneumonia in COVID-19 patients [176–179], after viral infections [6,180–186], in diabetic patients [187] and in chronic obstructive pulmonary disease [188–190]. Improved clinical outcome after ARB treatment of COVID-19 patients is associated with reduced IL-6 in peripheral blood, increased CD3 and CD8 T cell counts and reduced peak viral load [178] and lower concentrations of high-sensitivity C-reactive protein (hs-CRP) and procalcitonin (PCT) [24].

Reported molecular mechanisms of ARBs protective effects in lung function include reduction of MCP-1 upregulation, CCR2 signaling, monocyte recruitment and lung fibrosis [123,124], downregulation of pro-inflammatory chemokines CCL4, CCL7 and CXCL10, and autoimmune inflammation [125,126], attenuation of sepsis-induced acute lung injury, TNF-alpha, IL-6, IL-1beta, NF-kappaB, degradation of IkappaB-alpha, inhibition of p38MAPK phosphorylation, extracellular signal-regulated kinase ½,and c-Jun N-terminal kinase, critical for cytokine release as well as protecting from ALI/ARDS [171]. The direct efficacy of ARB treatment in coronavirus infections has been demonstrated by their reduction of lung injury and pulmonary edema in a SARS-CoV infection mouse model and after SARS-CoV spike protein injection in mice, a clinically relevant post-infection model [9].

In addition, Candesartan decreases the innate immune response to endotoxin administration in human monocytes, including reduction of gene expression of CD14, the pro-inflammatory cytokines TNF-alpha, IL-1beta, IL-6, and the lectin-like oxidized low-density lipoprotein receptor, and well as a reduction of NF-kappaB activation, TNF-alpha and IL-6 secretion and oxygen radical production [191]. These findings support the present correlation of our neuronal transcriptome with that of PBMC in COVID-19 patients.

From the above, the present demonstration of effects of Candesartan on multiple genes associated with inflammation and alterations in innate and adaptive immune responses affected by neuronal injury but also characteristic of COVID-19 adds a strong argument in favor of the therapeutic use of Candesartan to ameliorate COVID-19 cytokine storm, as well as other potentially deleterious effects of SARS-CoV-2 infection.

4.7. Counter-regulatory mechanisms

AT1R inhibition by ARBs may activate counterbalance mechanisms such as Ang II AT2 receptor stimulation. Activation of AT2 receptors was reported to produce anti-inflammatory effects in an animal model [192]. However, the role of AT2 receptor activation in COVID-19 patients has not been studied.

4.8. Summary

In summary, the present results and those of the literature, strongly suggest that ARB treatment, by amelioration of excessive inflammation, oxidative stress, lung fibrosis, and expression of pro-senesce genes, normalization of mitochondrial function, interferon production and

innate and adaptive immunity, could be beneficial for the treatment of acute SARS-CoV-2 infection and its long-term complications, be particularly effective in the elderly and protect not only lung function but that of the brain as well.

5. Conclusions

Our goal was to test the hypothesis of common mechanisms leading to excessive inflammation and immune alterations in injured neurons associated to neurodegenerative disorders, aging/senesce and SARS-CoV-2 infection that could be responsive to ARB treatment, and in particular if the powerful anti-inflammatory properties of Candesartan could be considered to relieve the cytokine storm characteristic of severe COVID-19. The present results and the preexisting clinical literature strongly suggest that this is the case, supporting the proposal not only to continue ARB therapy in patients affected with COVID-19 comorbidities or SARS-CoV-2 infection, but also to perform carefully designed data analysis and conclusive clinical studies to establish whether these compounds may be considered as additional therapeutic tools in COVID-19 patients.

Authors contributions

AGE performed and interpreted the bioinformatic analysis, wrote the analytical methods and contributed to write the manuscript.

JMS conceived of the presented idea, described the role of the genes involved, and wrote the manuscript.

Both authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors reported no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopha.2020.110653.

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