Chemical exposures affect innate immune response to SARS-CoV-2

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Abstract

Severe outcomes of COVID-19 are associated with pathological response of the immune system to the SARS-CoV-2 infection. Emerging evidence suggests that interaction may exist between COVID-19 pathogenesis and a broad range of xenobiotics, resulting in significant increases in death rates in highly exposed populations. Therefore, a better understanding of the molecular basis of the interaction between SARS-CoV-2 infection and chemical exposures may open opportunities for better preventive and therapeutic interventions. We attempted to gain mechanistic knowledge on the interaction between SARS-CoV-2 infection and chemical exposures using *in-silico* approach, where we identified genes and molecular pathways affected by both chemical exposures and SARS-CoV-2 in human immune cells (T-cells, B-cells, NK-cells, dendritic, and monocyte cells). Our findings demonstrate for the first time that overlapping molecular mechanisms affected by a broad range of chemical exposures and COVID-19 are linked to IFN type I/II signaling pathways and the process of antigen presentation. Based on our data, we also predict that exposures to various chemical compounds will predominantly impact the population of monocytes during the response against COVID-19.

Introduction

In December 2019, a novel infectious disease was recognized [1]. The disease was named coronavirus disease 2019 (COVID-19) and it is known now to be caused by coronavirus SARS-CoV-2. As of 20th March 2021, the COVID-19 pandemic has recorded almost 122 million cases with 2,694,094 mortalities spanning 223 countries of the world [2]. Recently many SARS-CoV-2 vaccines have been developed, but global morbidity and mortality due to COVID-19 remain substantial. Additionally, the evolution of SARS-CoV-2 challenges existing vaccines and threatens the global population with new virus variants. Therefore, a better understanding of factors affecting COVID-19-caused morbidity and mortality is needed.

An emerging body of studies demonstrates that diverse chemical exposures can increase COVID-19 severity. For example, 1 $\mu\text{g}/\text{m}^3$ increase in particulate matter (PM_{2.5}) in air is responsible for a greater than 8% increase in the death rate from COVID-19 [3]. Exposure to air pollutants is the major culprit behind the significant COVID-19 mortalities in different countries of the world [4]. The major types of air pollutants that can increase the COVID-19 severity include ozone, carbon monoxides, sulphur dioxides, lead, volatile organic compounds, particulate matter (PM_{2.5} and PM₁₀), and nitrogen oxides [5–8].

Besides air pollutants, several other chemicals have also been associated with COVID-19 severity. For example, one study identified significant associations between COVID-19 infection fatality rates and toxic industrial chemicals in the United States [9]. Increased severity of COVID-19 was also reported because of the use of sanitizers and disinfecting chemicals [9–12]. Plasma levels of perfluorinated compounds were also associated with an increased risk of COVID-19 [13]. It has also been hypothesized that neuroinflammation induced by environmental chemicals may increase neurological symptoms in COVID-19 patients [14].

Thus, existing data demonstrate that a variety of chemical exposures increase the severity of COVID-19. A better understanding of the molecular basis of interaction between SARS-CoV-2 infection and chemical

exposures may open opportunities for better preventive and therapeutic interventions. Analysis of the interaction of SARS-CoV-2 infection with all chemicals humans are exposed to is however challenging if not an impossible task.

We propose to gain mechanistic knowledge on the interaction between SARS-CoV-2 infection and chemical exposures using *in-silico* approaches, which rely on existing data. In our recent study, we attempted to identify genes and molecular pathways most sensitive to chemical exposures using an unbiased big-data approach by overlying transcriptomic datasets from 2,169 individual studies [15]. This unbiased analysis demonstrated that immune response pathways, including interferon signaling and cytokine signaling, are pathways highly sensitive to chemical exposures [15]. Emerging data on SARS-CoV-2 indicate that the disease severity is linked to a highly dysregulated innate immune response characterized by a delayed interferon response and exuberant inflammatory response [16]. Thus, we hypothesize that specific immune response mechanisms may be synergistically affected by chemical exposures and SARS-CoV-2, resulting in increased severity of the disease.

To test this hypothesis, we used the *in-silico* approach to identify genes and molecular pathways affected by both chemical exposures and SARS-CoV-2 in major types of human immune cells. Our research predicts that chemical exposures and SARS-CoV-2 infection synergistically affect IFN type I/II signaling pathways and the process of antigen presentation.

Results

According to our hypothesis, specific immune response mechanisms may be synergistically affected by chemical exposures and SARS-CoV-2, resulting in increased severity of the disease. To test this hypothesis, we first used data on the sensitivity of mammalian genes to chemical exposures identified in our previous research [15,17] by overlaying transcriptomic datasets from many individual toxicological genomic studies. This allowed the identification of genes that respond most often to a variety of chemical exposures (Fig. 1). At that step, the sensitivity of a gene to chemical exposure was expressed as the number of chemical-gene interactions (CGI). CGI reflects the number of individual toxicological studies in which the gene of interest was affected by exposure.

Genes sensitive to chemical exposures are not equally expressed in different cell types. If some cells have very low levels of expression of chemically-sensitive genes in normal physiological conditions, then it is reasonable to assume, that chemical exposures will not alter the physiology of these cells significantly. Contrary, cells expressing highly chemically-sensitive genes will respond to chemical exposure by the significant change in their physiology. Thus, to model cell response to xenobiotics we need to understand the levels of expression of chemically-sensitive genes in this specific cell type. Following this logic, we generated lists of genes with their chemical sensitivity values adjusted for the level of expression in different human immune cells. We call these adjusted values - cell-specific sensitivity of genes (CSSG).

At the next step, for different immune cells, we compared the lists of genes with the highest CSSG values with genes affected by SARS-CoV-2 in the same cell types, to identify synergistic effects of both stressors. Finally, we used genes with the highest CSSG values as well as genes affected by both chemical exposures and

SARS-CoV-2 in Metascape enrichment analysis to identify molecular mechanisms most sensitive to xenobiotics and both stressors in each cell type.

Below we provide an analysis of molecular pathways enriched with the top CSSG genes and with genes that are sensitive to both chemical exposures and SARS-CoV-2.

Monocytes

Top CSSG for monocytes

The list of top genes with the highest CSSG values in monocytes includes 409 genes (Supplemental file 1). Top Metascape enriched biological categories affected by chemical exposures are involved in the regulation of immune response, including cytokine signaling, degranulation and migration, phagocytosis, VEGFA-VEGFR2 signaling pathway, hemostasis, apoptosis, and response to toxic substance (Table 1, Supplemental file 2).

Table 1. Top biological functions most sensitive to chemical exposures in immune cells

	NK cells (649 top CSSG)	T cells (558 top CSSG)	Monocytes (409 top CSSG)	B cells (408 top CSSG)	Dendritic cells (510 top CSSG)
1	mRNA catabolic process	Ribosome, cytoplasmic	Leukocyte degranulation	Ribosome, cytoplasmic	Regulation of expression of SLITs and ROBOs
2	Cytokine Signaling in Immune system	Cytokine Signaling in Immune system	Cellular responses to external stimuli	VEGFA-VEGFR2 Signaling Pathway	Leukocyte activation involved in immune response
3	VEGFA-VEGFR2 Signaling Pathway	VEGFA-VEGFR2 Signaling Pathway	Cytokine Signaling in Immune system	TRBP containing complex	Oxidation-reduction process
4	Oxidation-reduction process	Oxidation-reduction process	VEGFA-VEGFR2 Signaling Pathway	Cytokine Signaling in Immune system	VEGFA-VEGFR2 Signaling Pathway
5	Leukocyte activation involved in immune response	positive regulation of cell death	Positive regulation of cell death	Nucleoside monophosphate metabolic process	Cytokine Signaling in Immune system
6	Ribonucleoprotein complex biogenesis	apoptotic signaling pathway	apoptotic signaling pathway	Ribosome assembly	TRBP containing complex
7	Protein processing in the endoplasmic reticulum	leukocyte activation involved in immune response	Oxidation-reduction process	Regulation of translation	Apoptotic signaling pathway
8	Regulation of apoptotic signaling pathway	ribonucleoprotein complex assembly	Nuclear Receptors Meta-Pathway	Protein folding	Response to toxic substance
9	Protein folding	regulation of cellular amide metabolic process	Cellular response to interleukin-12	Apoptotic signaling pathway	Mitochondrion organization
10	Regulation of cellular amide metabolic process	Epstein-Barr virus infection	Hemostasis	Positive regulation of cell death	Positive regulation of cell death

Genes affected by chemicals and COVID-19

We identified 635 genes that are affected by COVID-19. Out of these 635 genes, 124 genes (20%) were overlapping with top monocyte-specific sensitive genes (Fig. 2). The top overlapping genes include, for example, genes encoding cell cycle progression and differentiation (S100A8, S100A9), genes involved in suppression of apoptosis (PLAC8), several EEF genes serving a broad range of functions in monocytes such as protein synthesis and delivery of aminoacyl tRNA to the ribosome, CD14 and IFITM3 involved in response to bacterial and viral infections respectively, PABPC1 involved in ribosome recruitment and translation initiation, and NAPILI playing an important role in DNA replication (Table 2). Metascape enrichment analysis showed that overlapping genes are involved in essential functions of the immune system (cytokine signaling, antigen processing and presentation, positive regulation of reactive oxygen species, metabolic processes, platelet degranulation, response to bacterial and viral infections), respiratory diseases (pertussis, neutrophil degranulation), VEGFA-VEGFR2 signaling pathway, cell regulation and death (apoptotic signaling pathway, I-kappaB kinase/NF-kappaB signaling) (Table 3, Supplemental file 3).

Table 2. Top genes sensitive to COVID-19 and chemical exposures in immune cells

	NK cells	T cells	Monocytes	B cells	Dendritic cells
1	STAT1	TPT1	S100A8	MS4A1	HLA-DQB1
2	ISG15	EEF1A1	PLAC8	CD74	HSPA5
3	ACTB	STAT1	IFITM3	JCHAIN; IGJ	ISG15
4	GNLY	MX1	PABPC1	HSPA5	PABPC1
5	EEF2	EEF2	NAP1L1	CALR	EEF2
6	JAK1	PABPC1	S100A9	HSP90B1	TRIM22
7	SP100	EIF4B	EEF1A1	PDIA6	FKBP5
8	PABPC1	ISG15	EEF2	PDIA4	PLSCR1
9	TPT1	IL7R	CD14	CD79B	HSP90AB1
10	ISG20	PIM1	IFI6	CD79A	HSPA8

Table 3. Top biological functions most sensitive to chemical exposures and COVID-19 disease in immune cells

	NK cells (24 Gene Overlap)	T cells (55 Gene Overlap)	Monocytes (124 Gene Overlap)	B cells (65 Gene Overlap)	Dendritic cells (20 Gene Overlap)
1	Regulation of multi-organism process	Cytokine Signaling in Immune system	Neutrophil degranulation	Regulation of multi-organism process	Regulation of viral life cycle
2	Interferon Signaling	Chaperone Mediated Autophagy	Cytokine Signaling in Immune system	Protein folding	Antigen processing and presentation
3	T cell mediated cytotoxicity	Translation Factors	Regulation of multi-organism process	VEGFA-VEGFR2 Signaling Pathway	P2X7 receptor signaling complex
4	PID IL12 2PATHWAY	Regulation of multi-organism process	Defense response to other organisms	Translation Factors	Viral entry into host cell
5	Protein methylation	Antigen processing and presentation	Activation of immune response	Regulation of myeloid cell differentiation	Response to virus
6	Antigen processing and presentation	Regulation of hemopoiesis	Apoptotic signaling pathway	B cell activation	Translation Factors
7	Translation Factors	I-kappaB kinase/NF-kappaB signaling	Response to inorganic substance	Cytokine Signaling in Immune system	Response to interferon-gamma
8	Negative regulation of binding	Epstein-Barr virus infection	Regulation of cytokine production	Chaperone-mediated protein folding	Negative regulation of the cellular component organization
9	Homotypic cell-cell adhesion	Response to interferon-gamma	Pertussis	Translation	RNA degradation
10	Allograft Rejection	H2AX complex, isolated from cells without IR exposure	Antigen processing and presentation	Interaction with symbiont	Negative regulation of intrinsic apoptotic signaling pathway

NK cell

Top CSSG for NK-cells

Top CSSG genes in NK cells include 649 genes (Supplemental file 1). Top Metascape enriched biological categories affected by chemical exposures are involved in the regulation of protein synthesis and processing (mRNA catabolism and processing, protein processing in endoplasmic reticulum, protein folding, protein catabolism and proteolysis), immune response (cytokine signaling, VEGFA-VEGFR2 signaling, leukocyte

activation, interferon signaling, hemostasis), and mitochondria functions (mitochondrion organization, aerobic respiration, oxidation-reduction process). (Table 1, Supplemental 2).

Genes affected by chemicals and COVID-19

A total of 779 genes were affected by COVID-19 in NK cells. Out of these, 24 genes (3%) were overlapping with the list of top NK-cell specific chemically-sensitive genes (CSSG) (Fig. 2). The top overlapping genes include, for example, genes encoding interferons - antiviral signaling molecules (ISGI5, ISG20), proteins involved in cytokine signal transduction (STAT1 and JAK1), antimicrobial protein of cytotoxic granules of NK-cells (GNLY), proteins involved in the regulation of viral gene expression (SP100), beta-actin involved in cell motility (ACTB), and proteins involved in the regulation of protein synthesis (TPT1, EEF2, PABPC1) (Table 2). Metascape enrichment analysis revealed that overlapping genes are involved in the VEGFA-VEGFR2 signaling pathway, immune responses (interferon signaling, antigen processing and presentation, cytotoxicity), and apoptosis (Table 3, Supplemental file 3).

T-cells

Top CSSG for T-cells

A total of 558 genes were identified as top CSSG genes for T-cells (Supplemental file 1). Top Metascape enriched biological categories affected by chemical exposures are involved in the regulation of protein synthesis and processing (ribosome, protein folding, protein processing in endoplasmic reticulum, and others), immune response (cytokine signaling, VEGFA-VEGFR2 signaling, leukocyte activation, response to viral infection), response to stress (response to toxic substance, transcriptional regulation by TP53, regulation of cellular stress response) and apoptosis (Table 1, Supplemental file 2).

Genes affected by chemicals and COVID-19

743 genes were affected by COVID-19. Out of these, 55 genes (7.4%) were overlapping with top T-cell-specific sensitive genes (CSSG) (Fig. 2). The top overlapping genes include, for example, genes involved in antiviral interferon signaling cascade (MX1, ISGI5), genes involved in lymphocytes development, proliferation, and survival (IL7R, PIM1), genes involved in protein synthesis (EEF1A1, EEF2, PABPC1), and STAT1, involved in response to cytokines and growth factors, (Table 2). Metascape analysis showed that the top overlapping genes are involved in immune response (cytokine signaling and production, response to interferon-gamma, antigen processing and presentation, I-kappaB kinase/NF-kappaB signaling, P2X7 receptor signaling complex), hemopoiesis, chaperone-mediated autophagy, and cell cycle/apoptosis regulation (MYC signaling). (Table 3, Supplemental file 3).

B-cells

Top CSSG for B-cells

The shortlist of the top CSSG genes for B-cells included 408 genes (Supplemental file 1). Top Metascape biological categories affected by chemical exposures are involved in protein synthesis (ribosome, ribosome assembly, regulation of translation, and others) and processing (protein ubiquitination, protein folding, response to topological incorrect proteins), DNA biosynthesis, immune response (leucocyte activation, cytokine signaling, VEGFA-VEGFR2 signaling), hemopoiesis, apoptotic signaling and response to toxic substances. (Table 1, Supplemental file 2).

Genes affected by chemicals and COVID-19

A total of 660 genes were affected by COVID-19. Out of these, 65 genes (9.8%) overlapped with the top B-cell-specific chemically-sensitive genes (CSSG) (Fig. 2). The top overlapping genes include, for example, genes encoding for chaperones (HSPA5, PD1A4, PD1A6, CALR, CD74), genes involved in the development and differentiation of B-cells into plasma cells (MS4A1), genes encoding components of B lymphocyte antigen receptor (CD79A, CD79B), and JCHAIN, a protein component of the antibodies IgM and IgA (Table 2). Metascape analysis showed that the top overlapping genes are involved in translation, protein folding, different components of immune system development and immune response, including myeloid cell differentiation B-cell activation, cytokine signaling, antigen processing and presentation, I-kappaB kinase/NF-kappaB signaling, VEGFA-VEGFR2 signaling, and response to viral, bacterial, and parasitic infections among others (Table 3, Supplemental file 3).

Dendritic cells

Top CSSG for Dendritic Cell

Top CSSG genes for dendritic cells include 510 genes (Supplemental file 1). Top enriched biological categories affected by chemical exposures are involved in the regulation of protein synthesis and processing (TRBP containing complex, protein folding, protein processing in endoplasmic reticulum, and others), immune response (leukocyte activation, cytokine signaling, VEGFA-VEGFR2 signaling, response to viral infection), response to stress (response to toxic substance, response to oxidative stress, fluid shear stress), mitochondria function (oxidation-reduction process, mitochondrion organization, aerobic respiration, monocarboxylic acid metabolism), SLIT and ROBO cascade which may be involved in the regulation of cell migration and angiogenesis, and apoptosis (Table 1, Supplemental file 2).

Genes affected by chemicals and COVID-19

623 genes were affected by COVID-19. Out of these 623 genes, 20 genes (3.2%) are overlapping with the top dendritic-cell-specific chemically-sensitive genes (CSSG) (Fig. 2). The top overlapping genes include, for example, genes encoding chaperones (HSPA5, FKBP, HSP90AB1, HSPA8), major histocompatibility complex protein (HLA-DQB1), TRIM22 which mediates interferon's antiviral effects, EEF2 and PABPC1 genes involved in protein synthesis (Table 2). Metascape analysis showed that the top overlapping genes are involved in response to viral infection (regulation of viral life cycle, viral entry into host cell, response to virus, response to interferon-gamma, RNA degradation), antigen processing and presentation, P2X7 receptor signaling complex which senses ATP released by dying cells and plays role in inflammation, IL-18 signaling and apoptotic signaling. (Table 3, Supplemental file 3).

Top sensitive overlapping genes in multiple cell-types

Eight genes were identified as the topmost genes sensitive to chemical exposures and COVID-19 in more than one cell type. They include genes involved in the regulation of protein synthesis (EEF2, EEF1A1, PABPC1, TPT1), chaperones (HSPA5 and HSP90B1), and key players in interferon signaling cascade (ISG15 and STAT1).

Biological functions sensitive to chemical exposures across different cell types include cytokine signaling, VEGFA-VEGFR2 signaling, apoptotic signaling pathway, oxidation and reduction processes, protein synthesis, and folding. Biological functions most sensitive to chemical exposure and COVID-19 in more than one cell type include cytokine signaling, antigen processing and presentation.

Discussion

This study is the first to provide an overview of overlapping molecular mechanisms affected by COVID-19 and a broad range of chemical exposures. Previous research suggested that exposure to chemicals can increase COVID-19 disease severity [18–20]. The molecular mechanisms underlying the adverse effect of chemical exposures on the COVID-19 progression remain mostly unknown. Our study allows the prediction of molecular mechanisms affected by chemical exposures, which may be responsible for severe progression of COVID-19.

Today COVID-19 severity is linked to abnormal behavior of an innate immune system, characterized by a delayed IFN response and excessive inflammatory response [16,21].

IFN-mediated signaling plays a central role in anti-viral defense mechanisms [22]. Response to SARS-CoV-2 starts from activation of pattern recognition receptors (PRRs) primary in epithelial and endothelial cells, alveolar macrophages, NK cells, dendritic cells, and inflammatory monocyte-macrophages [16]. PRRs then activate IFN production pathway via a cascade of adaptors and IRF proteins. IFNs bind to their specific

receptors leading to phosphorylation of STAT1 and STAT2 by JAKs. This phosphorylation results in a formation of an IFN-stimulated gene factor 3 (ISGF3) complex containing STAT1, STAT2, and a transcription factor IRF9. Further translocation of ISGF3 to the nucleus results in its binding to IFN-stimulated response elements (ISREs) in promoters of IFN stimulated genes and induction of their transcription.

IFN stimulated genes are involved in many lines of antiviral defense, such as suppression of protein synthesis to prevent replication of pathogens, promotion of apoptosis of virus-infected cells via p53 pathway, activation of major histocompatibility complexes I (MHC I, all IFNs) and II (MHC II, IFN γ) to increase antigen presentation, increase of immunoproteasome activity to boost the process of antigen loading to MHC I, suppression of angiogenesis and activation of other immune cells. It is important to mention here that positive regulation of antigen presentation by IFNs results in activation of the adaptive branch of the immune system, as both T-cells and B-cells are activated by antigen presentation by dendritic cells and macrophages.

This brief overview of molecular mechanisms involved in the IFN I/II cascade and biological functions regulated downstream, suggests that chemical exposures may increase the severity of COVID-19 due to their interaction with IFN signaling cascade. Indeed, majority of genes and enriched molecular pathways affected by both stressors, COVID-19 and xenobiotics, are relevant to IFN signaling. Key IFN signaling genes were identified as sensitive to COVID-19 and chemical exposures in all analyzed cells (not all of them are shown in tables in the text; see Supplemental File 1 for more detail). For example, IFN gamma receptor was among the top TSSG genes in monocytes and dendritic cells, STAT1 was sensitive to COVID-19 and xenobiotics in monocytes, NK-cells, and T-cells. Additionally, IFN-signaling pathway was highly enriched in NK cells, and response to IFN-gamma was enriched in dendritic cells and T-cells. Similarly, biological categories regulated downstream of IFN were enriched in most cells, including protein synthesis, apoptosis, antigen processing and presentation, cell cycle, and angiogenesis pathway (VEGFA-VEGFR2).

It is interesting that among genes sensitive to chemical exposures and COVID-19 we did not find genes involved in the regulation of IFN production in response to viral infection. In other words, our data suggest that IFN signaling is disrupted at some downstream steps, following IFN binding to their receptors.

Given that severe progression of COVID-19 is associated with a dysregulated inflammatory response, many studies suggested that SARS-CoV-2 may cause a “cytokine storm” responsible for increased morbidity and mortality [23–26]. Several studies attempted to identify inflammatory molecules associated with severe COVID-19 [21,27–29]. Although the profile of inflammatory markers is highly variable between patients, a general phenotype of severe COVID-19 is characterized by elevated IL-6, IL-8, IL-10, TNF-alpha, CCL2, CCL3, and CXCL8 [16]. All these genes were not members of the lists of most chemically-sensitive genes in all analyzed immune cells, except CCL2, which was among the top CSSG genes for monocytes. Thus, it is likely that chemical exposure does not play a significant role in promoting an excessive inflammatory response – “cytokine storm”.

In our analysis, we observed the highest overlap (20%) between the top CSSG genes and genes affected by SARS-CoV-2 in monocytes. This observation suggests that functions of monocytes may be compromised in COVID-19 patients exposed to high doses of various chemicals. Monocytes are professional antigen presenters providing the link between innate and adaptive branches of the immune system. Delayed response of T-cells and B-cells due to disrupted antigen presentation by monocytes may constitute the molecular mechanism responsible for severe COVID-19 progression in patients exposed to high doses of chemicals. For example, antigen presentation is required for differentiation of effector T cells: cytotoxic T cells are critical for elimination of virally infected host cells; T helper cells are responsible for stimulation of antibody class switching in B cells and activation/recruitment of macrophages, neutrophils, and other innate cells.

The approach used in our study is based on a high level of generalization, which masks the complexity and diversity of individual chemical-gene interactions. Additionally, the direction of change in gene expression was not considered when sensitivities of genes to chemical exposures were calculated. In fact, our previous study demonstrated that the absolute majority of highly chemically-sensitive genes are induced and suppressed by almost equal number of compounds [15]. Similarly, high level of generalization does not allow accounting for individual differences in patients' response to COVID-19, including differences determined by age, sex, race, comorbidities, and other factors. Future experimental studies are needed to validate our *in-silico* predictions.

Materials And Methods

Sensitivity of genes to chemical exposures

The unbiased approach for the identification of genes sensitive to chemical exposures was developed in our previous studies [15,17]. A database was created by extracting data on chemical-gene interactions from the Comparative Toxicogenomics Database CTD [30] (Fig. 1A) using the following filtering criteria. First, data was extracted only from experiments that used high-throughput approaches for gene expression analysis. In addition, we selected data only from experiments that used human, rat, or mouse cells or tissue for gene expression analysis in *in-vitro* and *in-vivo* studies. Further, we removed from the database all genes that are not present in the genomes of all 3 species (human, rat, and mouse). The resulting database included 591,084 entries, each representing one CGI. At the next step, the number of CGI was calculated for every gene to represent its sensitivity to chemical exposures (Fig. 1B). Our previous study has shown that ranked sensitivities of genes to chemical exposures do not depend on the composition of chemicals used in original studies – sources of transcriptomic data [15], suggesting that our method provides unbiased results.

Sensitivities of genes to chemical exposures normalized for expression in different cell types

Normalized Gene Expression (NGE) values for human T-cells, B-cells, NK-cells, dendritic, and monocyte cells were extracted from the Human Protein Atlas [31] (Fig. 1C) and used to adjust the chemical sensitivity of genes for the level of expression in different immune cells. For this adjustment, CGI values were magnified by NGE values for corresponding cells (CSSGs = CGI × NGE) (Fig. 1D) (Supplemental file 4). To select top genes with the highest CSSG values for enrichment analysis, we used an approach of cutoff point identification in descriptive high-throughput –omics studies described in detail elsewhere [32]. In short, the cutoff point was

identified as a point of transition from exponential to super-exponential phases of the curve of ranked CSSG values. The major assumption of that approach is that the small number of genes with high CSSG values dominate changes in biological processes and functions in response to chemical exposures.

Genes affected by SARS-CoV-2 in human immune cells

The Coronascope database was used as a source of information on gene expression changes in human tissues in response to COVID-19 exposures (Fig. 1E). This database contains 390 datasets representing 29 tissues and cell lines collected from 22 individual studies. Only datasets where the effect of COVID-19 was analyzed in immune cells of human patients were used (Table 4). In-vitro studies were excluded from the analysis.

Table 4. Total number of COVID-19 data sets for each cell type

Cell type	Number of datasets	Genes affected by COVID 19 in more than one dataset	Sources
Dendritic cells	14	53	[33]
NK cells	19	81	[34] [33]
B-cells	23	248	[34] [33] [35]
Monocytes	32	278	[34] [33]
T-cells	35	116	[34] [33]

Overlap of top CSSG genes with genes affected by COVID-19

To identify genes that are sensitive to both chemicals and COVID-19, we overlapped top CSSG genes for each cell type with genes affected in Coronascope datasets in the same cell types (Table 1). Percent overlap was calculated as follows: % overlap = number of top CSSG genes/COVID-19 affected genes (Fig. 2).

Enrichment analysis

Top genes with high CSSG values for each cell type as well as genes affected by chemical exposures and COVID-19 in immune cells were analyzed using Metascope analysis (Fig. 1F) with default settings [36]. For enrichment analysis, we selected only chemically-sensitive genes affected in a specific cell type in more than one patient-specific COVID-19 dataset.

Conclusion

This study demonstrates that overlapping molecular mechanisms affected by a broad range of chemical exposures and COVID-19 are linked to IFN type I/II signaling pathways and to the process of antigen presentation. These pathways are essential components of the immediate response of innate immunity against viral infections. Synergistic impairment of these mechanisms by environmental factors and SARS-CoV-2 infection may affect the magnitude of the adaptive immune response and result in severe progression of the COVID-19. Based on our data we predict that exposures to various chemical compounds will predominantly impact the population of monocytes during the response against COVID-19. Our data do not provide any support of a hypothesis that chemical exposures may exacerbate COVID-19 induced “cytokine storm”.

Declarations

Author Contributions : OA - methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization. AS - conceptualization, methodology, validation, formal analysis, investigation, resources, data curation, writing—original draft preparation, writing—review and editing, visualization, supervision, project administration. LP - conceptualization, formal analysis, investigation, writing—review and editing. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: All data used in this study are available from published sources and public databases. Information on genes’ sensitivity to chemical exposures was published previously [17]. Normalized Gene Expression (NGE) values for human immune cells is available from the Human Protein Atlas [31]. Information on gene expression changes in human tissues in response to COVID-19 exposures is available from the The Coronascope database.

Conflicts of Interest: The authors declare no conflict of interest.

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Figures

Figure 1

Flow chart of the study approach: transcriptomic information from 2,169 studies was extracted from the Comparative Toxicogenomic Database (A) and used to calculate the sensitivity of every gene to chemical exposures (B) [15]. Information on the expression of every gene in different types of immune cells was extracted from the Human Protein Atlas (C) and used to normalize sensitivities of genes to chemical exposures for the level of expression in different cell types (D). Information on changes in gene expression in different immune cells in response to SARS-CoV-2 was extracted from Coronascope (E). Metascope (F) was used to identify molecular pathways enriched with genes highly sensitive to chemical exposures in immune cells and genes affected in these cells by both chemical exposures and SARS-CoV-2.

Figure 2

Overlap in genes affected by chemical exposures and SARS-CoV-2 infection in different types of human immune cells.

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