CytokineLink: a cytokine communication map to analyse immune responses in inflammatory and infectious diseases

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Abstract:
Intercellular communication mediated by cytokines is critical to the development of immune responses, particularly in the context of infectious and inflammatory diseases. By releasing these small molecular weight peptides, the source cells can influence numerous intracellular processes in the target cells, including the secretion of other cytokines downstream. However, there are no readily available bioinformatic resources that can model cytokine-cytokine interactions. In this effort, we built a communication map between major tissues and blood cells that reveals how cytokine-mediated intercellular networks form during homeostatic conditions. We collated the most prevalent cytokines from literature, and assigned the proteins and their corresponding receptors to source tissue and blood cell types based on enriched consensus RNA-Seq data from the Human Protein Atlas database. To assign more confidence to the interactions, we integrated literature information on cell-cytokine interactions from two systems immunology databases, immuneXpresso and
ImmunoGlobe. From the collated information, we defined two metanetworks: a cell-cell communication network connected by cytokines; and a cytokine-cytokine interaction network depicting the potential ways in which cytokines can affect the activity of each other. Using expression data from disease states, we then applied this resource to reveal perturbations in cytokine-mediated intercellular signalling in inflammatory and infectious diseases (ulcerative colitis and COVID-19, respectively). For ulcerative colitis, with CytokineLink we demonstrated a significant rewiring of cytokine-mediated intercellular communication between non-inflamed and inflamed colonic tissues. For COVID-19, we were able to identify inactive cell types and cytokine interactions that may be important following SARS-CoV-2 infection when comparing the cytokine response with other viruses capable of initiating a cytokine storm. Such findings have potential to inform the development of novel, cytokine-targeted therapeutic strategies. CytokineLink is freely available for the scientific community through the NDEx platform and the project github repository (https://github.com/korcsmarosgroup/CytokineLink).

**Introduction**

Cytokines are the key mediators of intercellular communication. Cytokines are low molecular weight peptides (5-20 kDa) released by a wide repertoire of cell types including immune cells, epithelial cells, endothelial cells, fibroblasts and other stromal cells. They enable coordinated autocrine, paracrine, and even endocrine homeostatic functions to occur within the body [1]. Cytokines exert these effects by binding to specific receptors that are expressed by target cells, which activate downstream intracellular signalling pathways and ultimately result in the expression of genes required for a particular process [2]. Cytokines effectively regulate all physiological processes in the human body ranging from embryonic development, to angiogenesis, to haemostasis, and innate and adaptive immunity. Cytokines are able to achieve such diverse and wide-ranging effects because they exhibit pleiotropy (i.e. a single cytokine can cause different biological effects and can act on different cell types) and redundancy (i.e. a variety of cytokines can activate the same signalling pathways) [3].

In addition, cytokine signalling is highly fine-tuned and regulated with cytokines themselves affecting the activity of each other through synergetic, antagonistic, or additive effects and feedback loops [4]. However, disturbances in the regulation of cytokine communication can
contribute to pathological processes including cancers, autoimmune disorders (e.g. inflammatory bowel disease (IBD), and cytokine storms as seen in response to certain infections (e.g. SARS-CoV-2) [5–7]. Although great progress has been made in identifying, characterising, and understanding the targets and functions of cytokines in the human body in health and disease, there is a lack of readily available resources that can computationally model cytokine-cytokine interactions [8,9]. Hence, we developed a novel biological network resource, CytokineLink. CytokineLink includes 10313 total interactions from 18 healthy human cell subsets and 24 tissue types. With CytokineLink two types of indirect or metanetworks were defined: 1) a cell-cell communication network connected by cytokines; and 2) a cytokine-cytokine interaction network depicting the potential ways in which cytokines can affect the activity of each other. To illustrate the utility and real-world applicability of this novel resource, we have demonstrated how CytokineLink can reveal important insights into cytokine signalling in IBD and following SARS-CoV-2 infection.

Methods

Network generation

We built the CytokineLink network resource based on cytokine-receptor interactions found in the literature [1] and the integrated OmniPath resource [10]. To achieve a broad coverage of cytokines, all cytokines listed in the ImmuneXpresso and ImmunoGlobe systems immunology databases were selected. To define the tissue or cell type specific expression properties for all these cytokines and their receptors, we downloaded the consensus RNA-Seq data from the Human Protein Atlas (HPA) website [11,12]. We used the enrichment of consensus expression from the downloaded HPA data as designated by HPA. HPA was selected as the source of expression data due to its expansive coverage, both in terms of the queried cytokines and receptors, and the available expression data from blood cells and tissues. The cytokine - receptor interactions, and the tissue/cell associations of all cytokines and cytokine receptors was merged into an integrated edge list. This edge list enabled us to reconstruct a base network describing the chain of cytokine signalling events occurring between a source cell and target tissue types, connected by the included cytokine - cytokine-receptor interactions.

From the reconstructed base network, we created two metanetworks. The metanetworks were created by generating all shortest paths of length five in the base network, with the
get_simple_paths() function of the NetworkX (version: 2.5) python library (python version: 3.8.6). The resulting list of shortest paths were then filtered to contain only the paths capturing the adequate chain of events (i.e. Cell₁, Cytokine₁, Receptor, Cell₂, Cytokine₂). These paths, containing the underlying signalling events, were used to generate the cell-cell and cytokine-cytokine meta-interactions, as seen on Figure 1.

**Figure 1** The construction steps and main sources of CytokineLink. Cytokine-receptor data was obtained from OmniPath and a relevant literature source. RNA enrichment data was downloaded from the Human Protein Atlas to assign cytokines and cytokine receptors to source tissue and cell types. The combination of cytokine - receptor interactions, and tissue/cell - cytokine/receptor interactions was used to generate base networks containing tissue-cytokine-receptor interactions, from which abstracted meta-edges were created. The
cell-cytokine associations were further annotated using information from two systems immunology databases, immuneXpresso and ImmunoGlobe. The cell-cell metaedges show the intercellular interactions mediated by the individual cytokines. The cytokine-cytokine edges indicate the potential ways by which the production of a cytokine can alter the production of another, by binding to its receptor carried by a cell type expressing the secondary cytokine.

Annotation

The systems immunology databases, immuneXpresso and ImmunoGlobe curate interaction data collated from the literature, between cell types and cytokines, both as sources and targets (i.e. both the cytokines and cells can be actors and can be acted upon). The curated cell-cytokine and cytokine-cell interaction annotations from immuneXpresso and ImmunoGlobe were included in CytokineLink, assigning literature enrichment to the cell-cytokine associations to the underlying edges in the general network the metaedges were created from. In practice, following the example on Figure 1, this means that for every metaedge (e.g. myeloid DC → memory B-cell) users can see if the cytokine-cell interaction annotations establishing the metaedge (i.e. myeloid DC → TNFSF13) has been reported in the literature previously. Supplementary Table 1 contains the combined cytokine-cell interaction annotations from the ImmuneXpresso and ImmunoGlobe databases.

Assessing the translational relevance of the cytokine-cytokine interactions

To measure the relevance of cytokine-cytokine interactions, we compared the differentially expressed genes signatures from experiments where patients were treated with cytokine inhibitor drugs. The effects of infliximab and golimumab (two TNF-α inhibitors) and tocilizumab (an IL6 inhibitor) were investigated. The significance of differentially expressed cytokines regulated by TNF-α or IL6 following inhibitor treatment was determined using a chi square test of independence, via the chisq.test() R language function. Expression data was downloaded from GEO and analysed using GEO2R. The cutoff for differential expression was a fold-change of 2, with an adjusted p-value of less than 0.05. The R scripts used for establishing differential gene expression and the subsequent statistical analysis can be found in our GitHub repository: https://github.com/korcsmarosgroup/CytokineLink. Table 1 lists and briefly describes the datasets we used.
Table 1: Datasets used to investigate the reliability of cytokine-cytokine interactions.

| Dataset  | Reference                  | Drug      | Inhibited cytokine | p-value |
|----------|----------------------------|-----------|--------------------|---------|
| GSE16879 | [14]                       | infliximab| TNF-α              | 0.01504 |
| GSE92415 | (Li et al., 2018, unpublished data) | golimumab | TNF-α              | 0.01525 |
| GSE93777 | [15]                       | tocilizumab| IL6                | 0.00587 |

Gene expression datasets following cytokine inhibitor treatment were used to determine the significance of the cytokine-cytokine interactions captured by CytokineLink for a subset of cytokines.

Use cases

For the evaluation of cytokine communication in ulcerative colitis (UC), single-cell expression data from patients containing 51 colonic cell subsets were used and processed from the seminal study by Smillie et al [16]. All genes with RNA counts of 0 were removed, and normalised log2 counts across all samples (separately for each cell type) were fitted to a gaussian kernel [17]. Only the genes falling into the top quintile of expression ranges were considered expressed, both for cytokines and receptors, respectively. From the processed data, 13 cell subsets that are especially important in inflamed ulcerative colitis (out of 51 cell subsets) were selected [18–20]. The cell type names were used as presented in Smillie et al [16]: inflammatory fibroblasts, myofibroblasts, goblet cells, immature goblet cells, M cells, CD8+ IEL, CD8+ LP, CD8+ IL17+, DC1, DC2, inflammatory monocytes, and Tregs.

To evaluate the applicability of the tool for infectious diseases, we used cytokines elevated in COVID-19 patients collected for our previous work [21]. The elevated cytokine list contained: CCL2, CCL4, CSF2, CXCL10, CXCL8, IL6, IFNG, IL1B. A complemented cytokine list containing cytokines elevated in viral infections capable of causing cytokine release syndrome (CRS), but not elevated in COVID-19, contained IL4 and IL5, also from our previous work [21].
Results

A novel network resource of cytokine communication

To deconvolute the effects of cytokines on intercellular communication, we built a new network resource that aimed to depict all possible indirect interactions (i.e. regulatory interactions) of the most prevalent cytokines from the literature, and overlaid it using consensus expression data the HPA [22]. CytokineLink was built using 18 blood cell types and 24 tissues, using 115 cytokines with 260 cytokine-receptor pairs. To add more confidence to the interactions, annotation data from two systems immunology databases (immuneXpresso, and ImmunoGlobe) was added that contains literature enrichment scores, signage (i.e. stimulatory/inhibitory) data and literature references for interactions [11,12]. Table 2 lists the number of interactions and degree of literature annotation in CytokineLink. The annotated interactions section in the table refers to at least one of the two cell-cytokine interactions in the chain of signalling events (i.e. Cell1-Cytokine1-Receptor-Cell2-Cytokine2) being listed in the literature as per the ImmunoGlobe and immuneXpresso databases.

| Tissues                  | 24 |
|--------------------------|----|
| Blood cell types         | 18 |
| Cytokines                | 115|
| Cytokine - receptor pairs| 260|

| Interactions                              |     |
|-------------------------------------------|-----|
| All interactions between two cells        | 581 |
| regardless of receptor usage              |     |
| All interactions listed between two cells | 1118|
| mediated by different receptors           |     |
### Table 2: Interaction data and annotations in CytokineLink

Annotated interactions refer to that at least one part of the underlying cell → cytokine interactions being listed in the literature in the ImmunoGlobe and immuneXpresso databases.

| Type               | Description                                                                 | Count |
|--------------------|----------------------------------------------------------------------------|-------|
| **cytokine - cytokine** | All interactions between two cytokines regardless of receptor usage | 2818  |
|                    | All interactions listed between two cytokines, mediated by different receptors | 9195  |
| **Annotated interactions** | Number of cell-cell interactions with annotated cell - cytokine relationships | 74    |
| **cell - cell**     | Percentage of cell-cell interactions with annotated cell - cytokine relationships | 6.7%  |
| **cytokine - cytokine** | Number of cytokine - cytokine interactions with annotated cell - cytokine relationships | 1673  |
|                    | Percentage of cytokine - cytokine interactions with annotated cell - cytokine relationships | 18.2% |

Cytokine - cytokine metaedges capture the possible ways cytokines affect each other

To capture the validity of cytokine - cytokine metaedges, we analysed publicly available gene expression datasets of cytokine inhibitors (infliximab, golimumab and tocilizumab) for two important proinflammatory cytokines, TNF-α and IL6. The chosen gene expression datasets measured the abundance of RNA in patients suffering from chronic illnesses where cytokine communication is often disrupted (inflammatory bowel disease, rheumatoid arthritis) [23,24]. Analysing the differential expression between treatment and control groups, we investigated whether there is a significant association between the differential expression of cytokines in the selected datasets, and the cytokines captured by our model. In other words, we tested if there was a significant association in differentially expressed cytokines between the targets
of one of the inhibited cytokines (e.g. IL-6), and differentially expressed cytokines that were not targeted by the inhibited cytokine in CytokineLink. We were able to confirm a significant relationship for IL-6 and TNF-α using a chi-square test of independence, as we found a statistically significant difference between the presence of differentially expressed cytokines that were not targeted by the respective cytokines, compared to the differentially expressed cytokines that were targets of IL-6 (tocilizumab p value = 0.00587), and TNF-α (infliximab p value = 0.01504, golimumab p value = 0.01525) in our model. These results highlight that CytokineLink is able to capture physiologically relevant cytokine - cytokine interactions for two important proinflammatory cytokines. For detailed steps, and scripts used please refer to the Methods section.

Cytokine signalling in Ulcerative Colitis (UC)

Ulcerative colitis (UC) is one of the two main clinical subtypes of IBD, which is characterised by chronic inflammation of the intestinal mucosa that begins in the rectum and extends proximally along the colon [25]. It is a relapsing and remitting condition which can cause significant morbidity to patients. The incidence as well as prevalence of UC has been increasing globally over the past few decades [25,26]. Although the aetiology of the disease is unclear, complex interactions between multiple genetic risk loci, environmental factors, and the gut microbiota are thought to give rise to dysregulated immune responses in the colon, resulting in chronic inflammation. Whilst UC can be successfully treated through surgical removal of the colon (i.e. colectomy), many patients wish to preserve the function of their colons and avoid the complications of surgery, and hence opt for medical management which aims to induce and maintain remission [27,28].

The advent of biologic therapies targeting cytokine signalling (e.g. Infliximab targeting TNF-α or Ustekinumab targeting the p40 subunit of IL12 and IL23) has transformed the medical management of UC in the past decade, and has led to fewer patients undergoing colectomies and better treatment outcomes [18,29–31]. Nevertheless, approximately 20% of UC patients fail to respond to medical therapies and eventually undergo surgical intervention for their disease [18]. One important reason for this is that certain subgroups of UC patients may possess distinct pathogenic pathways and cytokine signalling networks which are not targeted by the existing armamentarium of biologic therapies [32]. Thus, further disentangling the cytokine signalling networks driving the pathomechanisms in UC patients is a pressing need. Over the past three years, a number of landmark single-cell RNA
sequencing (scRNAseq) studies have been performed in IBD patients, that have revealed critical and novel insights into the likely cell types mediating the pathogenic processes involved during non-inflamed and inflamed states of the disease [16,33–35]. However, these studies did not focus on cytokine-specific intercellular signalling networks. This would be important for better understanding dysregulation of cytokine signalling in UC and revealing potential new therapeutic targets for patients.

Therefore, we applied CytokineLink to a recently published scRNAseq dataset obtained from inflamed and non-inflamed tissues of UC patients [16]. This analysis revealed novel insights into the differences in cytokine signalling between non-inflamed and inflamed UC conditions. We first mapped cell-cell interactions between 13 cell types in both inflamed and non-inflamed UC conditions (Figure 2a). We then filtered these interactions by individual cytokines, which led to the emergence of disease-status specific differences in the patterns of intercellular cytokine communication (Figure 2b). This faceted visualization approach can highlight cytokine-specific signalling differences occurring between disease states and cell types. For example, the generally anti-inflammatory cytokine IL10 was found to be produced by regulatory T cells (Treg cells) in both conditions, but in non-inflamed tissues additional interactions arose involving innate lymphoid cells (ILCs) and type 1 dendritic cells (DC1s), stemming from an increase in the expression of the IL10 receptor (IL10R) in these cell types. The difference in interactions between disease states was even more apparent in the case of TGFB1, where there was only a small overlap between TGFB1-mediated intercellular signalling in both inflamed and non-inflamed UC tissues. In non-inflamed UC conditions, TGFB1 was found to drive multiple interactions involving CD8+ intraepithelial cells and a number of cell types including inflammatory fibroblasts, myofibroblasts, inflammatory monocytes, and type 2 dendritic cells (DC2s). However, in inflamed UC conditions, TGFB1 signalling shifted towards interactions largely between type 1 dendritic cell cells (DC1s) and inflammatory fibroblasts, myofibroblasts, DC2s, and CD8 lamina propria (LP) T cells.
**Figure 2: Cytokine specific rewiring of intercellular interactions in ulcerative colitis.**

Global cell-cell interaction (a) and cytokine-specific cell-cell interaction (b) networks in inflamed and non-inflamed UC tissues. **a)** Global cell-cell interaction networks showed only a few differences in the cell types interacting with each other between non-inflamed and inflamed UC states. More interactions between inflammatory fibroblasts and type 1 dendritic cells (DC1s) were present in inflamed UC compared to non-inflamed UC. The size of the nodes corresponds to the degree. **b)** Cytokine-specific cell-cell interaction networks revealed more notable differences between non-inflamed and inflamed UC states, particularly with the cytokines IL10 and TFB1. IL-10 was found to be produced by regulatory T cells (Tregs) in both inflamed and non-inflamed UC tissues. However, in inflamed UC, TGFβ1 signalling shifted to interactions mostly between DC1s and inflammatory fibroblasts, myofibroblasts, DC2s, and CD8 lamina propria (LP) T cells.
Cytokine signalling following SARS-CoV-2 infection

During the COVID-19 pandemic, it has become apparent that the development of a cytokine storm can lead to increased mortality in a subset of patients infected by SARS-CoV-2 [36]. The cytokine storm is caused by the overactivation of adaptive and innate immune cells, which can lead to a positive feedback loop of pro-inflammatory cytokines [37]. To further study pro-inflammatory cytokine signalling occurring between various cell types in COVID-19, we applied CytokineLink to a literature curation dataset containing cytokines that are upregulated following SARS-CoV-2 infection in patients [21]. Using this metanetwork, we uncovered important connections in the cytokine communication of COVID-19 patients.

We found that the majority of cell types included in CytokineLink are activated by the elevated cytokines during SARS-CoV-2 infection (Figure 3a). However, in our previous work we noted that the levels of certain cytokines were not always elevated in COVID-19, compared to infections by other cytokine storm-causing viruses (SARS-CoV, MERS-CoV, H5N1, H7N9) [21].

Figure 3b highlights the differences in metanetworks caused by the compared cytokine profiles. This approach lets users study the systems level changes inflicted by the addition of just a few cytokines. In this instance we complemented the system with cytokines that are found induced in other virus-induced cytokine storms (i.e. IL4 and IL5) to show what parts of the intercellular and cytokine-cytokine communication network were affected based on literature curated data. The complemented model further increases the connectivity of basophils in the network by connecting them to multiple members of the innate immune system, and connects memory B-cells to eosinophils and basophils.
**Figure 3: Metanetworks of cytokines increased in COVID-19 patients.** a) intercellular interactions involving cytokines elevated in COVID-19 patients. b) intercellular interactions mediated by IL4 and IL5. c) Combined intercellular network of cytokines elevated in COVID-19 patients, and intercellular interactions mediated by IL4 and IL5. d) Cytokine-cytokine involving cytokines elevated in COVID-19 patients. e) Cytokine - cytokine interactions involving IL4 and IL5. f) Combined cytokine - cytokine network. The IL4 - IL12 interaction is highlighted with dashed lines. IL4 has been shown to be increased in severe COVID-19, potentially repressing IL12, whose levels are comparable to healthy controls in severe cases [38,39]. Mutual edges were collapsed, shown with arrows on both ends to reduce complexity.

On the level of cytokine - cytokine interactions the difference is more apparent, as IL5 and especially IL4 act as hubs, further increasing the connections between the elevated cytokines. The CytokineLink analysis provides a possible mechanistic link to the lack of one of the key anti-inflammatory cytokines, IL12. The low levels of IL12 are comparable to healthy controls in severe COVID-19 patients, while the levels of IL4 are significantly higher in severe patients [38,39]. We note that the basis of using IL4 to complement the system was based on our previous work involving literature curation. At the time one research article was available that had measured serum IL4 levels in SARS-CoV-2 infected patients. These patients had mild symptoms and therefore low levels of IL4 [40]. Comparing the SARS-CoV-2 specific and complemented network models, there is a missing interaction between basophils and naive B-cells, mediated by the cytokine IL4. IL4 is capable of repressing Th1 responses, including the production of IL12 and IFN-γ [41]. Thus, the
increase in the levels of IL4 in severe COVID-19 patients can offer an explanation for the low levels of observed IL12, through the previously described IL4 - IL12 interaction captured by our model. IL12 is an important stimulator of IFN-γ and the type II interferon response. This response is critical for leading the innate immune response into the adaptive one and eliminating viral infection. It also has an important role in facilitating the differentiation of naive B cells into plasma cells. In our analysis, we found that IL12 levels remain low in patients with severe COVID-19 likely due to an increase in IL4. IL4 is a potent inhibitor of Th1 responses, including the production of IL12 and IFN-γ. Thus, the diminished IL12 levels in a certain subgroup of COVID19 patients may explain the reason why they experience more severe disease. Further work is needed to investigate this potential causal link [42–45].

Discussion

In this study, we have introduced a new biological network resource, CytokineLink enabling the detailed analysis of intercellular communication mediated by cytokines. We integrated data from various interaction and expression databases, and used the available literature to strengthen and demonstrate the reliability of the interactions in CytokineLink. CytokineLink is freely available for the scientific community on the NDEx platform [46].

The CytokineLink database stores cytokine interactions in two ways. The intercellular interaction meta-edges convey the interactions of the individual cell types and tissues included in the analysis, mediated by enriched cytokines. Cytokine-cytokine meta-edges indicate the potential pathways through which cytokines can affect the production of other cytokines. These two meta-interaction layers place the underlying chain of events in two different contexts using the cell - cell and cytokine - cytokine metaedges, elucidating as to how cytokines are involved in immune responses following infection, or in inflammatory diseases. These metanetworks are a context-specific interpretation of the underlying signalling events, depicting the flow of information mediated by intercellular cytokine communication.

The chain of events consisting of the binding and release of cytokines between various cell types of the body have been well documented in the scientific literature [47,48]. In recent years, interest has grown in the study of intercellular interactions occurring between immune cell subtypes [16,49–51]. However, these studies had a broader selection of ligand - receptor
interactions, and used differential expression and/or marker genes describing the cell subsets to generate their interactions. CytokineLink provides metanetworks built from healthy human consensus expression data, enriched with literature annotation information previously present in separate, unconnected resources. Our methods use the underlying chain of signalling events to generate the metanetworks, and because of this every metaedge can be led back to the exact signalling sequence it was created from, the information content of the generated metaedges matches those of the original signalling events. As such, the interactions in CytokineLink represent a novel, context specific signalling format, allowing for focused analyses involving cell-cell or cytokine-cytokine interactions. Our analyses using the CytokineLink platform highlight the rewiring of cell-cell communication between disease states in a cytokine-centered way, mediated by specific cytokines in UC, a form of IBD, and COVID-19. Similar analyses involving multi-omics data could help researchers shortlist potential therapeutic targets, through the integrated analysis of the expression, proteomic or regulatory status of tracked cytokines [16,34,52].

The introduction of cytokine-cytokine interactions provides a novel metaedge for the functional study of signalling between the elements of the immune system. Due to the limited amount of available experimental data on cytokine inhibitors we were only able to confirm a significant relationship for a small subset of cytokines, but future studies could further establish the reliability of such interactions, especially using more refined modelling steps, involving intracellular signaling as well. Our use case involving elevated cytokines in COVID-19 elucidated how the approach can be used to capture known cytokine - cytokine interactions, and use the data as a starting point for subsequent studies. The advantage and purpose of these cytokine focused metaedges is that they could enable the identification of previously unknown drug targets by focusing on upstream cytokines, especially if direct intervention on a downstream cytokine would be unavailable or not preferable. In addition, it could allow researchers to predict the potential ways an administered drug could alter downstream cytokine responses and the associated cell types involved in intercellular communication.

In conclusion, we have developed a novel network resource aimed at capturing the most prevalent cell-cell and cytokine-cytokine interactions in healthy individuals. Furthermore, this resource can be overlaid with disease-specific expression data from patients to reveal changes occurring in cytokine-mediated intercellular communication during disease states. Hence, CytokineLink can act as a powerful platform for hypothesis-generation i.e. for deconvoluting the complexities of cytokine signalling in inflammatory and infectious diseases.
to reveal potential cytokine drug targets, or for predicting the downstream effects of drugs on cytokine responses.

Data Availability Statement

The original contributions presented in the study are included in the article's Supplementary Material and available at https://github.com/korcsmarosgroup/CytokineLink.

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a. inflamed

b. TGFB1

non-inflamed

IL10

inflamed

non-inflamed

both

- DC2
- DC1
- CD8_LP
- CD8_IL17
- ILCs
- ImmatureGoblet
- InflammatoryFibroblasts
- InflammatoryMonocytes
- Myofibroblasts
- Mcells

- Goblet
- CD8IELs
Cell - cell interactions

Cytokine - cytokine interactions

Elevated in COVID-19

Elevation of IL4 and IL5

Complemented model