Interleukin-16 is differentially expressed in viral co-infections.

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The SARS-CoV-2 pandemic has resulted in close to 1,000,000 deaths worldwide in less than one year¹ with an upcoming influenza season, raising the prospect of complications resulting from co-infections. Our understanding of gene expression in patients with viral co-infection is limited. We mined published microarray data² to identify transcriptional features most significantly associated with viral co-infection. We identified the cytokine interleukin-16 as among the most differentially expressed genes in the blood of patients with viral co-infections, including in a patient with co-infection of influenza A and human coronavirus OC43 and in a patient with co-infection of influenza A and human coronavirus 229E. Interleukin-16 may be relevant to the biology of viral co-infection.

Keywords: viral co-infection, SARS-CoV-2, coronavirus, systems biology of viral infection.

1 In the United States alone, nearly 6.5 million cases of infections from the Severe Acute
2 Respiratory Syndrome coronavirus SARS-CoV-2 have been reported with over 190,000 deaths in
3 less than one year³. Respiratory infections including influenza display peaks over specific times
4 of the year; influenza season is approaching raising the prospect of complications arising from
5 co-infections involving SARS-CoV-2 with influenza and other illnesses caused by respiratory
6 pathogens. A recent study of 1206 patients in Northern California demonstrated that co-infection
7 in patients with SARS-CoV-2 is a real clinical issue with 20.7% of patients positive for SARS-
8 CoV-2 also testing positive for a second viral pathogen, including rhinovirus, enterovirus,
9 respiratory syncytial virus, as well as non-SARS human coronaviruses⁴. Understanding of the
10 transcriptional biology of viral co-infections is limited.

11 We mined published microarray data² from the blood of patients infected with more than
12 one viral pathogen to determine in an unbiased fashion how gene expression most significantly
13 differs in viral co-infection. We identified significant differential expression of the cytokine
14 Interleukin-16 (IL-16) in the blood of patients with a variety of viral co-infections, suggesting
15 IL-16 may be important in the context of concurrent viral infection.

16 **Methods**

17 We used dataset GSE68310² for this differential gene expression analysis of the blood in
18 patients with viral co-infection. GSE68310 was generated using Illumina HumanHT-12 V4.0
19 expression beadchip technology; analysis was performed with platform GPL10558. We

1 compared the blood of $n=1$ patient with HCoV NL63 infection (ID: JR1447) to the blood of $n=1$
2 patient with HCoV NL63 and human rhinovirus co-infection (ID: JR1446). We compared the
3 blood of $n=1$ patient with influenza A infection (ID: JR0021) to the blood of $n=1$ patient with
4 influenza A and HCoV OC43 co-infection (ID: JR1829). We compared the blood of $n=1$ patient
5 with influenza A infection (ID: JR0021) to the blood of $n=1$ patient with influenza A and
6 HCoV-229E co-infection (ID: JR0173). We compared the blood of $n=1$ patient with respiratory
7 syncytial virus A (RSVA) virus infection (ID: JR0547) to the blood of $n=1$ patient with
8 RSVA and rhinovirus co-infection (ID: JR1145). We compared the blood of $n=2$ patients with
9 rhinovirus infection (ID: JR1242 and JR1292) to the blood of $n=1$ patient with rhinovirus and
10 enterovirus co-infection (ID: JR0209). We compared the blood of $n=4$ patients with influenza A
11 infection (ID: JR0021, JR0023, JR0025 and JR0053) to the blood of $n=4$ patients with influenza
12 A and rhinovirus co-infection (ID: JR0033, JR0147, JR0174, JR0199). We compared the blood
13 of $n=4$ patients with influenza B infection (IDs: JR1412, JR1491, JR1939 and JR1978) to the
14 blood of $n=5$ patients with influenza B and human rhinovirus co-infection (ID: JR1053, JR1120,
15 JR1275, JR1672, and JR1717). In the study from which this microarray data was obtained,
16 investigators collected peripheral blood from patients at baseline, day 0 of infection, correlating
17 with a visit to the clinic upon infection with a respiratory illness; day 2, day 4, day 6, and day 21
18 of infection following the clinic visit, as well as in the season following infection (“Spring”).

19 The Benjamini and Hochberg method of p -value adjustment was used for ranking of
20 differential expression but raw p -values were used for assessment of statistical significance of
21

global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used. A statistical test was used to evaluate the significance of difference in IL-16 gene expression between the blood of a patient with a single infection and the blood of a patient with co-infection using a two-tailed, unpaired t-test with Welch's correction. All statistical tests were performed with PRISM 8.4.0 (455).

Results

We mined published microarray data² to determine in an unbiased fashion and at the transcriptome level genes most differentially expressed in the blood of patients with viral co-infection.

IL-16 is differentially expressed in the blood of a patient with influenza A and HCoV OC43 co-infection.

We observed significant differential expression of the interleukin-16 cytokine (IL-16) in the blood of a patient with co-infection of influenza A and human coronavirus HCoV OC43 when compared to that of a patient with infection of influenza A only. When sorting all transcripts measured based on significance of change in expression between blood from a patient with co-infection of influenza A and HCoV OC43 and blood from a patient with infection of influenza A only, IL-16 ranked 212 out of 47254 total transcripts. Differential expression of IL-16 in influenza A and HCoV OC43 co-infection was statistically significant (Table 1; $p=5.94E-04$).

IL-16 is differentially expressed in the blood of a patient with co-infection of respiratory syncytial virus A and human rhinovirus.

We then asked whether IL-16 differential expression was specific to human coronavirus co-infections or could be observed in other viral co-infections. Analysis of a separate patient revealed significant differential expression of IL-16 in the blood of a patient with co-infection of respiratory syncytial virus A (RSVA) and human rhinovirus when compared to that of a patient with infection of RSVA only. When sorting all transcripts measured based on significance of change in expression between blood from a patient with co-infection of RSVA and human rhinovirus and blood from a patient with infection of RSVA only, IL-16 ranked 94 out of 47254 total transcripts (Table 2). Differential expression of IL-16 in RSVA and human rhinovirus co-infection was statistically significant (Table 2; $p=1.43E-06$).

IL-16 is differentially expressed in the blood of a patient with co-infection of HCoV NL63 and human rhinovirus.

IL-16 was also differentially expressed in the blood of a patient with co-infection of HCoV NL63 and human rhinovirus when compared to the blood of a patient with infection of HCoV NL63 only. When sorting all transcripts measured based on significance of change in expression between blood from a patient with co-infection of HCoV NL63 and human rhinovirus and blood from a patient with infection of HCoV NL63 only, IL-16 ranked 1821 out of 47254 total transcripts (Table 3). Differential expression of IL-16 in HCoV NL63 and human rhinovirus co-infection was statistically significant (Table 3; $p=3.58E-03$).

IL-16 is differentially expressed in the blood of a patient with co-infection of HCoV-229E and influenza A.

We also observed significant differential expression of IL-16 in the blood of a patient with co-infection of HCoV-229E and influenza A when compared to the blood of a patient with infection of influenza A only. When sorting all transcripts measured based on significance of change in expression between blood from a patient with co-infection of HCoV-229E and influenza A and blood from a patient with infection of influenza A only, IL-16 ranked 879 out of 47254 total transcripts (Table 4). Differential expression of IL-16 in HCoV-229E and influenza A co-infection was statistically significant (Table 4; $p=4.28E-03$).

IL-16 is differentially expressed in the blood of a patient with co-infection of human rhinovirus and enterovirus.

Further analysis revealed significant differential expression of IL-16 in the blood of a patient with co-infection of human rhinovirus and enterovirus when compared to the blood of a patient with infection of enterovirus only. When sorting all transcripts measured based on significance of change in expression between blood from a patient with co-infection of human rhinovirus and enterovirus and blood from a patient with infection of enterovirus only, IL-16 ranked 523 out of 47254 total transcripts (Table 5). Differential expression of IL-16 in human rhinovirus and enterovirus co-infection was statistically significant (Table 5; $p=1.24E-03$).

IL-16 is differentially expressed in the blood of patients with co-infection of influenza A and human rhinovirus.

IL-16 was again among the most differentially expressed genes in the blood of patients

with viral co-infection; here, in the blood of four patients with influenza A and human rhinovirus co-infection when compared to the blood of four patients with influenza A infection only (Table 6). When sorting all transcripts measured based on significance of change in expression between blood from patients with co-infection of influenza A and human rhinovirus and blood from patients with infection of influenza A only, IL-16 ranked 1600 out of 47254 total transcripts (Table 6). Differential expression of IL-16 in influenza A and human rhinovirus co-infection was statistically significant (Table 6; $p=9.08E-03$).

IL-16 is not differentially expressed in the blood of patients with co-infection of influenza B and human rhinovirus.

We sought to determine whether there were any viral co-infection settings in which IL-16 was not differentially expressed. IL-16 was not significantly differentially expressed in the blood of patients with co-infection of influenza B and human rhinovirus (Table 7; $p=8.57E-01$); IL-16 was the 41811th most differentially expressed transcript out of 47254 total measured transcripts in influenza B and human rhinovirus co-infection when compared to that of influenza B infection only.

IL-16 is expressed at significantly lower levels in the blood of a patient with influenza A and HCoV OC43 co-infection when compared to that of a patient with influenza A infection only.

We obtained exact mRNA expression levels for IL-16 in the blood from each patient to directly compare IL-16 expression in influenza A and HCoV OC43 co-infection and in influenza A infection only. IL-16 expression was lower in the blood of a patient with co-infection of

influenza A and HCoV OC43 as compared to that of a patient with influenza A infection only; this difference was statistically significant (Figure 1). We calculated a mean fold change in IL-16 expression of 0.9829 ± 0.0066 in influenza A and HCoV OC43 co-infection in the blood (Table 1).

IL-16 is expressed at significantly higher levels in the blood of a patient with RSVA and rhinovirus co-infection when compared to that of a patient with RSVA infection only.

We also obtained exact mRNA expression levels for IL-16 in the blood to directly compare IL-16 expression in Respiratory Syncytial Virus A (RSVA) and human rhinovirus co-infection and in RSVA infection only. In this case, IL-16 expression was higher in the blood of a patient with co-infection of RSVA and rhinovirus as compared to that of a patient with RSVA infection only; this difference was statistically significant (Figure 2). We calculated a mean fold change in IL-16 expression of 1.0232 ± 0.0069 in RSVA and rhinovirus co-infection in the blood (Table 2).

Thus, we found that IL-16 was among the genes most differentially expressed in the blood of patients with a spectrum of viral co-infections, including co-infections with human coronaviruses. While IL-16 expression was higher in RSVA and rhinovirus co-infection as compared to RSVA infection only, IL-16 expression was lower in influenza And HCoV OC43 co-infection as compared to influenza A infection only.

Discussion

IL-16, originally known as lymphocyte chemoattractant factor (LCF), was identified from supernatant of human peripheral blood mononuclear cells following concanavalin A mitogen stimulation based on the ability to induce migration of non-adherent lymphocytes⁵, and characterized as a 14 kilodalton protein which possessed chemotactic properties in tetrameric form⁶. IL-16 can also stimulate migration of eosinophils⁷, monocytes⁸, and CD25+ CTLA-4+ regulatory T-cells⁹, and induce the expression of the IL-2 receptor and HLA-DR on CD4+ T-lymphocytes⁸. Membrane-bound CD4 is required for IL-16-induced migration in T-lymphocytes¹⁰ and in eosinophils⁷.

IL-16 can be produced by both cytotoxic CD8+ T-lymphocytes as well as mast cells¹¹. Production of IL-16 by B-lymphocytes has also been reported¹². While IL-16 can activate the tyrosine kinase p56^{lck}, interactions between CD4 and p56^{lck} but not p56^{lck} catalytic activity are required for IL-16-induced T-lymphocyte migration¹³. In CD4+ T-lymphocytes, IL-16 stimulation results in an increase in intracellular calcium and inositol triphosphate levels; these IL-16-stimulated signaling events require the intracytoplasmic domain of CD4¹⁴. IL-16 induces the translocation of protein kinase C (PKC) from the cytosol to the plasma membrane and inhibitors of PKC block T-lymphocyte migration induced by IL-16¹⁵.

Experiments using peptides modeled after the immunoglobulin-like domain 4 (D4 domain) of CD4 suggested direct interactions between IL-16 and CD4 through a binding site which overlapped with the binding site of CD4 for the class II major histocompatibility complex

(MHC-II)¹⁶. Consistent with overlapping binding sites of IL-16 and MHC-II for CD4, IL-16 can inhibit mixed lymphocyte reactions *in vitro*, and the inhibitory effect of IL-16 on mixed lymphocyte reactions can be blocked by addition of soluble CD4¹⁷. In addition to its functions in chemotaxis of lymphocytes, monocytes and eosinophils, stimulation of CD14⁺ monocytes but not T-lymphocytes with IL-16 induces secretion of the cytokines IL-6, IL-15, IL-1 β and tumor necrosis factor alpha (TNF- α)¹⁸. Interestingly, despite a number of studies emphasizing a requirement for CD4 in the induction of lymphocyte chemotaxis by IL-16, cells from CD4-deficient mice are functionally equivalent to wild-type in chemotaxis and cytokine production in response to IL-16¹⁹.

Incubation of T-lymphocytes with IL-16 prior to *in vitro* CD3-stimulation resulted in 80% reduction in T-cell activation as assessed by induction of IL-2R expression, suggesting that IL-16 could inhibit CD3-induced T-cell activation²⁰. IL-16 can cooperate with IL-2 in expansion of CD4⁺ T-lymphocytes from peripheral blood mononuclear cells *in vitro*²¹. IL-16 has inhibitory effects on HIV-1 replication by nearly 99% at the level of messenger RNA expression, which is independent of viral entry as proviral DNA was present in equal amounts following transfection of IL-16 or empty vector²². One mechanism for IL-16 interference with the HIV-1 life cycle could be IL-16 repressive activity on core enhancer sequences at the HIV-1 promoter²³.

In summary, by mining a published microarray dataset² we found that the cytokine interleukin-16 was among the most differentially expressed genes in the blood of patients with

viral co-infections, including co-infections involving multiple human coronaviruses and influenza A. IL-16 may be important to the biology of viral co-infection in humans.

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Rank	ID	p-value	t	B	FC	Gene	Gene name
212	ILMN_2290628	5.94E-04	-4.4582013	-0.2009	0.9829 ± 0.0066	IL16	interleukin 16

Table 1: Differential expression of IL-16 in the blood of a patient with influenza A and HCoV OC43 co-infection.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, fold change in expression of IL-16 in the blood of a co-infected patient, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	FC	Gene	Gene name
94	ILMN_2290628	1.43E-06	8.06	5.66073	1.0232 ± 0.0069	IL16	interleukin 16

Table 2: Differential expression of IL-16 in the blood of a patient with co-infection of respiratory syncytial virus A and human rhinovirus.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, fold change in expression of IL-16 in the blood of a co-infected patient, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
1821	ILMN_1813572	3.58E-03	3.5033508	-2.02142	IL16	interleukin 16

Table 3: Differential expression of IL-16 in the blood of a patient with co-infection of HCoV NL63 and human rhinovirus.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
879	ILMN_1813572	4.28E-03	3.4244145	-2.1857	IL16	interleukin 16

Table 4: Differential expression of IL-16 in the blood of a patient with co-infection of HCoV-229E and influenza A.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
523	ILMN_1813572	1.24E-03	3.7389538	-1.16457	IL16	interleukin 16

Table 5: Differential expression of IL-16 in the blood of a patient with co-infection of human rhinovirus and enterovirus.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
1600	ILMN_2290628	9.08E-03	-2.7095818	-3.682248	IL16	interleukin 16

Table 6: Differential expression of IL-16 in the blood of patients with co-infection of influenza A and human rhinovirus.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
41811	ILMN_2290628	8.57E-01	0.1807633	-7.18006	IL16	interleukin 16

Table 7: IL-16 is not differentially expressed in the blood of patients with co-infection of influenza B and human rhinovirus.

The rank of differential expression with respect to all transcripts measured, probe ID, p-value with respect to global differential expression, t, a moderated t-statistic, B, the log-odds of differential expression between the two groups compared, gene and gene name are listed in this chart.

Figure 1: IL-16 is expressed at significantly lower levels in the blood of a patient with co-infection of influenza A and HCoV OC43 when compared to that of a patient with influenza A infection only.

The mRNA expression level of IL-16 in $n=1$ patient with influenza A infection (left) and $n=1$ patient with influenza A and HCoV OC43 co-infection (right) is graphically depicted with mean IL-16 level marked and the result of a statistical test evaluating significance of difference in IL-16 expression between patients, a p -value, listed above. Each patient is represented by 7 samples from baseline, day 0, day 2, day 4, day 6, day 21 and Spring post-infection.

Figure 2: IL-16 is expressed at significantly higher levels in the blood of a patient with co-infection of RSV and human rhinovirus when compared to that of a patient with RSV infection only.

The mRNA expression level of IL-16 in $n=1$ patient with RSV infection (left) and $n=1$ patient with RSV and human rhinovirus co-infection (right) is graphically depicted with mean IL-16 level marked and the result of a statistical test evaluating significance of difference in IL-16 expression between patients, a p -value, listed above. Each patient is represented by 7 samples from baseline, day 0, day 2, day 4, day 6, day 21 and Spring post-infection.