Bioinformatic analyses suggest augmented interleukin-17 signaling as the mechanism of COVID-19-associated herpes zoster

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Abstract

Herpes zoster results from latent varicella zoster virus reactivation in the dorsal root ganglia, causing blistering rash along the dermatomal distribution and post-herpetic neuralgia. Increasing studies indicated that there may be a correlation between herpes zoster and COVID-19. Nevertheless, the detailed pathophysiological mechanism is still unclear. We used bioinformatic analyses to study the potential genetic crosstalk between herpes zoster and COVID-19. COVID-19 and herpes zoster were associated with a similar subset of genes involved in “cytokine-cytokine receptor interaction,” “Jak-STAT signaling pathway,” and “IL-17 signaling pathway,” including *TNF*, *IL10*, *ESR1*, *INFG*, *HLA-A*, *CRP*, *STAT3*, *IL6*, *IL7*, and *IL17A*. Protein-protein interaction network assay showed that the combined gene set indicated a raised connectivity as compared to herpes zoster or COVID-19 alone, particularly the potentiated interactions with *APOE*, *ARSA*, *CCR2*, *CCR5*, *CXCL13*, *EGFR*, *GAL*, *GP2*, *HLA-B*, *HLA-DRB1*, *IL5*, *TECTA*, and *THBS1*, and these genes are related to “cytokine-cytokine receptor interaction”. Augmented Th17 cell differentiation and the resulting enhanced IL-17 signaling were identified in both COVID-19 and herpes zoster. Our data suggested aberrant interleukin-17 signaling as one possible mechanism through which COVID-19 could raise the risk of herpes zoster.

Keywords SARS-CoV-2 · Varicella zoster virus · Cytokine · Jak-STAT

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the SARS-CoV-2, a positive-sense RNA virus containing a large genome of 30 kb in size likely originated from bats, has resulted in a huge death toll and an unprecedented economic loss worldwide (Beck da Silva Etges et al. 2021, Davillas and

Jones 2021, Dunne et al. 2021, Kumari 2021, Sood et al. 2020). As with 17 April 2020, over 139 million people globally have been diagnosed of COVID-19, causing nearly 3 million deaths (Lin et al. 2017). Although 40 to 50% of patients tested positive for COVID-19 are asymptomatic, some COVID-19 patients could develop severe symptoms, such as high fever, severe cough, and shortness of breath, and progress to acute respiratory distress syndrome and multiple organ failure (Harmon et al. 2021, Li et al. 2021, Yanes-Lane et al. 2020). The respiratory system is the primary site of attack by SARS-CoV-2, but growing number of evidences indicated that COVID-19 might influence other organ systems, including the skin and the nervous system (Birlutiu et al. 2021, Kyriakoudi et al. 2021, McMahon et al. 2021, Terzi et al. 2021). In this regard, COVID-19 may lead to cutaneous manifestations including widespread or localized urticaria, erythematous rash, or herpes zoster (Andina-Martinez et al. 2021, Pagali and Parikh 2021, Sachdeva et al. 2020). SARS-CoV-2 may also spread to the brain via both hematogenous and neural routes (El-Sayed et al. 2021b). Endeavors have been put forth to understand the pathogenic mechanism

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of SARS-CoV-2, especially the underlying factors triggering respiratory failure (El-Sayed et al. 2021a).

Herpes zoster (commonly known as shingles), common in middle age groups, is caused by the reactivation varicella zoster virus (VZV) and manifests as the painful vesicular rash along a dermatomal distribution (Nagel and Gilden 2013). VZV is also the causative agent of varicella (commonly known as chickenpox) that predominantly affects children under the age of 12 (Bérar et al. 2021, Shiraki et al. 2021). Following the initial infection, this virus remains latent in the ganglion cells of dorsal root or cranial nerve (Fukuyasu et al. 2021, Osman 2020, Zhu et al. 2020). Increasing age and immunosuppression are two major risk factors for VZV reactivation (Amaral et al. 2021). The most frequent complication of herpes zoster is post-herpetic neuralgia (Andrei and Snoeck 2021, Rahmatpour Rokni et al. 2020). Other complications include cutaneous (secondary bacterial infection, scarring), neurologic (motor neuropathy, meningoencephalitis), ocular (keratitis, iritis, retinitis), and visceral (pneumonitis, hepatitis) aspects (Nagel and Gilden 2013).

Recently, a growing number of studies showed that herpes zoster might be associated with COVID-19. Recalcati reported for the first time that varicella-like vesicles could be a cutaneous manifestation of COVID-19 (Recalcati 2020). In a later multicenter case series, Marzano et al. reported that 22 patients with a COVID-19-positive nasopharyngeal swab developed varicella-like papulovesicular exanthem with a predominant trunk involvement (Marzano et al. 2020). Fernandez-Nieto et al. also reported that among 53 COVID-19 patients who developed vesicular rashes, 15 patients presented typical clinical lesions and symptoms of herpes simplex/zoster (Fernandez-Nieto et al. 2020). Ertugrul and Aktas also reported that the number of patients with herpes zoster seeking medical attention in Turkey was remarkably increased in May and June 2020 during the COVID-19 outbreak as compared to the same period in 2019 (Cao et al. 2020). By searching the diagnostic code from the hospital automation system, Maia et al. also reported an increased number of herpes zoster cases in Brazil during the pandemic period (Maia et al. 2021). As the COVID-19 pandemic continues, these clinical characteristic of COVID-19-dependent herpes zoster may continue to be expound. However, the detailed pathological mechanisms about the disease entity remain undefined. In our research, we utilized bioinformatic method to clarify the potential crosstalk between herpes zoster- and COVID-19-associated genes.

Materials and methods

Identification of herpes zoster- and COVID-19-associated genes

The genes information related to these two disease entities (COVID-19, disease id: C000657245, version 5, N.PMIDs $\geq$

10; herpes zoster, disease id: C0019360, Gene-Disease Association Score ≥ 0.01) was searched from DisGeNET, a platform about disease genomics, on 17 April 2021.

Protein-protein interaction networks of herpes zoster- and COVID-19-associated genes

The abovementioned gene sets, alone or in combination, were chosen to functional protein correlation networks assay by STRING. Protein-protein interactions were visualized with minimum interaction score of 0.900 (and the highest confidence) and disconnected nodes hidden in this network. Only “databases,” “experiments,” “co-occurrence,” and “co-expression” were used as the active interaction sources. The MLC (Markov Cluster) algorithm with the inflation parameter of 3 was then utilized for the network clustering.

Pathway enrichment analysis

KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment assay was utilized with the STRING built-in function to clarify the biological functions of COVID-19- and herpes zoster-correlated gene networks.

Results

Protein-protein interaction networks of COVID-19- and herpes zoster-associated genes indicated common enrichment in cytokine-cytokine receptor interaction

We first defined the list of genes involved in the pathogenesis of COVID-19 and herpes zoster using a disease-based pathway analysis. A total of 114 and 51 genes correlated with COVID-19 (disease id: C000657245, version 5; N.PMIDs ≥ 10) and herpes zoster (disease id: C0019360; Gene-Disease Association Score ≥ 0.01), respectively, were choose from DisGeNET (Table 1). Disease-related genes overlapped between COVID-19 and herpes zoster are *TNF*, *IL10*, *ESR1*, *INFG*, *HLA-A*, *CRP*, *STAT3*, *IL6*, *IL7*, and *IL17A*, which are enriched in the KEGG pathways “cytokine-cytokine receptor interaction,” “Jak-STAT signaling pathway,” and “IL-17 signaling pathway.” We reconstructed the protein-protein correlation networks among genes using STRING and identified connecting genes (Figure 1A for COVID-19; Figure 1B for herpes zoster). Notably, STAT3 indicated a high connectivity in the both herpes zoster- and COVID-19-associated gene networks with number of interacting partners of 21 and 8, respectively. The functional prediction further showed that “cytokine-cytokine receptor interaction,” “Jak-STAT signaling pathway,” “hematopoietic cell lineage,” “antigen processing and presentation,” “IL-17 signaling pathway,” “T cell receptor signaling pathway,” “intestinal

Table 1 Disease-associated genes retrieved from DisGeNET. Genes associated with both COVID-19 and herpes zoster are bolded. *COVID-19*, coronavirus disease 2019

Diseases	Disease-associated genes
COVID-19	<i>ACE2</i> , <i>CRP</i> , <i>IL6</i> , <i>ACE</i> , <i>REN</i> , <i>TNF</i> , <i>TMPRSS2</i> , <i>CD4</i> , <i>CD8A</i> , <i>AGT</i> , <i>ALB</i> , <i>IL1B</i> , <i>GPT</i> , <i>F2</i> , <i>IL10</i> , <i>LOC102724971</i> , <i>LOC102723407</i> , <i>INS</i> , <i>IFNG</i> , <i>IFNA1</i> , <i>FURIN</i> , <i>CSF2</i> , <i>DPP4</i> , <i>TNNI3</i> , <i>F3</i> , <i>IL2</i> , <i>GOT1</i> , <i>CRX</i> , <i>IFNB1</i> , <i>NFKB1</i> , <i>AGTR1</i> , <i>RPGR</i> , <i>IL6R</i> , <i>PLAT</i> , <i>CALCA</i> , <i>IL17A</i> , <i>SERPINA13P</i> , <i>HLA-C</i> , <i>HBA1</i> , <i>CENPJ</i> , <i>IL2RA</i> , <i>NELFCD</i> , <i>MB</i> , <i>CXCL10</i> , <i>VWF</i> , <i>CTSL</i> , <i>NLRP3</i> , <i>CTRL</i> , <i>CTSB</i> , <i>IL4</i> , <i>SPECC1</i> , <i>MAS1</i> , <i>ZFYVE9</i> , <i>MS4A1</i> , <i>PDCD1</i> , <i>RTN1</i> , <i>RTN4</i> , <i>BSG</i> , <i>MTOR</i> , <i>VEGFA</i> , <i>PLG</i> , <i>KRT20</i> , <i>F8</i> , <i>JAK1</i> , <i>SERPINA5</i> , <i>CD19</i> , <i>IFNA2</i> , <i>PSMD1</i> , <i>STAT3</i> , <i>TTR</i> , <i>KNG1</i> , <i>NPPB</i> , <i>EMSLR</i> , <i>AGTR2</i> , <i>CSF3</i> , <i>IL7</i> , <i>IL18</i> , <i>PROS1</i> , <i>LINC01672</i> , <i>ESR1</i> , <i>NFE2L2</i> , <i>EEF1A2</i> , <i>ERBB2</i> , <i>G6PD</i> , <i>GGT1</i> , <i>NCAM1</i> , <i>ADAM17</i> , <i>TLR4</i> , <i>GGTLC5P</i> , <i>GGRLC3</i> , <i>GGT2</i> , <i>GGTLC4P</i> , <i>FCGR3A</i> , <i>FCGR3B</i> , <i>HSPA5</i> , <i>IL1RN</i> , <i>INSRR</i> , <i>JAK2</i> , <i>CCL3</i> , <i>CCL5</i> , <i>TLR3</i> , <i>KLK4</i> , <i>SH2D3C</i> , <i>WDC1</i> , <i>PGR-AS1</i> , <i>C3</i> , <i>CD14</i> , <i>F10</i> , <i>HIF1A</i> , <i>HLA-A</i> , <i>SERPINF2</i> , <i>SLC5A2</i> , <i>ADAMTS2</i> , <i>TLR7</i>
Herpes zoster	<i>HLA-B</i> , <i>LRRC32</i> , <i>LINC02785</i> , <i>HCP5</i> , <i>FAM110B</i> , <i>TMC7</i> , <i>TNF</i> , <i>IL10</i> , <i>CPS1</i> , <i>HLA-DRB1</i> , <i>ESR1</i> , <i>APOE</i> , <i>IFNG</i> , <i>HLA-A</i> , <i>ARSA</i> , <i>CRP</i> , <i>RBM45</i> , <i>PART1</i> , <i>GAL</i> , <i>ENOSF1</i> , <i>STAT3</i> , <i>TECTA</i> , <i>THBS1</i> , <i>CCR2</i> , <i>TRPV1</i> , <i>CCR5</i> , <i>TMPRSS13</i> , <i>LMLN</i> , <i>LINC02605</i> , <i>IL33</i> , <i>BOD1</i> , <i>RECQL4</i> , <i>MUC1</i> , <i>MTX1</i> , <i>MST1</i> , <i>GP2</i> , <i>ETFA</i> , <i>CXCL13</i> , <i>EGFR</i> , <i>CYP17A1</i> , <i>CYP11A1</i> , <i>IL5</i> , <i>IL6</i> , <i>IL7</i> , <i>CTLA4</i> , <i>IL17A</i> , <i>MBL2</i> , <i>MECP2</i> , <i>MIP</i> , <i>MSMB</i> , <i>CD34</i>

immune network for IgA production,” and “Th17 cell differentiation” were then enriched in both these gene networks (Table 2).

Potentiating and additive interactions of COVID-19- and herpes zoster-correlative gene networks

To study the potential interactions between the herpes zoster- and COVID-19-correlated gene networks, two genes sets were subject and combined to the STRING assay. The network of combined genes indicated a better integration than that of herpes zoster- and COVID-19-correlated genes alone, with many clusters previously divorced from the major network now rejoined (e.g., *CTSB*/*TLR7*-*CTSL*/*TLR3*, *TLR4*-*CD14*, *FCGR3B*-*FCGR3A* clusters in COVID-19; *HLA-A*-*HLA-B*-*HLA-DRB1* cluster in herpes zoster) or expanded (*TECTA*-*GP2* cluster in herpes zoster) (Figure 2A). To quantitatively study the impact of the COVID-19 on herpes zoster-correlated gene networks, the amount of these genes connecting with 51 herpes zoster-correlated genes were

calculated in herpes zoster-alone, COVID-19-alone, and COVID-19-herpes zoster-correlated networks. The 51 GBS-correlated genes were connected to significant genes in combined network as compared to 2 disease entities alone (Figure 2B). Clustering and visualization of this connectivity with the heap map indicated two distinct patterns of interactions, namely additive (e.g., *HLA-A*, *IL10*, *IL6*, *IL7*, *IFNG*, *MUC1*, *STAT3*, *TNF*) and synergistic (e.g., *APOE*, *ARSA*, *CCR2*, *CCR5*, *CXCL13*, *EGFR*, *GAL*, *GP2*, *HLA-B*, *HLA-DRB1*, *IL5*, *TECTA*, *THBS1*) interactions (Figure 2C). The latter are significantly enriched in “cytokine-cytokine receptor interaction.”

Discussion

Emerging evidence supports that herpes zoster might be a cutaneous manifestation of COVID-19 (Brancaccio et al. 2021, Jamshidi et al. 2021). In this regard, it has been postulated that COVID-19-associated immunosuppression (e.g., suppressed T cell-mediated immunity) or the psychological

Table 2 Significantly enriched “KEGG Pathways” in COVID-19- and herpes zoster-associated gene networks. KEGG pathways are ranked according to the false discovery rate (all < 0.0001) in an ascending order.

Diseases	KEGG pathways of disease-associated gene networks
COVID-19	Cytokine-cytokine receptor interaction, hematopoietic cell lineage, Jak-STAT signaling pathway, Th17 cell differentiation , PI3K-Akt signaling pathway, Toll-like receptor signaling pathway, complement and coagulation cascades, NOD-like receptor signaling pathway, HIF-1 signaling pathway, necroptosis, cytosolic DNA-sensing pathway, natural killer cell mediated cytotoxicity, IL-17 signaling pathway , renin-angiotensin system, antigen processing and presentation , T cell receptor signaling pathway , AGE-RAGE signaling pathway in diabetic complications, EGFR tyrosine kinase inhibitor resistance, Th1 and Th2 cell differentiation, phagosome, osteoclast differentiation, TNF signaling pathway, RIG-I-like receptor signaling pathway, intestinal immune network for IgA production , NF-kappa B signaling pathway, renin secretion, Insulin resistance
Herpes zoster	Cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, hematopoietic cell lineage, antigen processing and presentation, IL-17 signaling pathway, T cell receptor signaling pathway, Th17 cell differentiation, intestinal immune network for IgA production

Pathways under the category of “human diseases” were omitted. Pathways associated with both COVID-19 and herpes zoster are bolded. *COVID-19*, coronavirus disease 2019

Figure 1 Functional protein-protein correlation networks of the COVID-19 (A) and herpes zoster-related (B) genes were determined using STRING. Genes correlated with these 2 disease entities (herpes zoster, disease id: C0019360, Gene-Disease Association Score ≥ 0.01 ; COVID-19, id: C000657245, version 5, N.PMIDs ≥ 10) were retrieved from the

DisGeNET, a platform for the disease genomics. Only highly confident interactions with minimum required interaction score of 0.900, derived from “databases,” “co-occurrence,” “co-expression,” and “experiments,” were counted. Network clustering was done with the MLC (Markov cluster) algorithm with an inflation parameter of 3

stress inflicted by the pandemic might promote VZV reactivation and thus account for the escalating number of herpes zoster cases (Pona et al. 2020). In this study, by bioinformatic analysis of COVID-19- and herpes zoster-associated genes, we found that both diseases are associated with “cytokine-cytokine receptor interaction,” “Jak-STAT signaling pathway,” and “IL-17 signaling pathway,” in which STAT3 acts as a central hub in the protein-protein interaction networks of both diseases. To this end, STAT3 is known to mediate the differentiation of naive CD4⁺ T cells into T helper 17 (Th17) cells, which secretes IL-17A, IL-21, and IL-22 to promote inflammatory processes, such as recruitment of neutrophils (Egwuagu 2009).

IL-17 signaling is important for the clearance of bacterial and fungal infections but its role in viral infection remains poorly defined (Lin et al. 2021, Xue et al. 2021). In COVID-19, lymphocytes isolated from these cases were demonstrated to secrete more IL-17 (De Biasi et al. 2020). In herpes zoster, a recent study showed that patients had a higher number of circulating Th17 cells without alteration of the number of regulatory T cells (Kim et al. 2017). Concordantly, the serum level of IL-17 was reported to be higher in patients with herpes zoster (Zajkowska et al. 2016). These findings collectively

suggest that deregulated cytokine responses, particularly the differentiation of Th17 cells and IL-17 signaling, were linked to pathogenesis of COVID-19-correlated herpes zoster. Nevertheless, it is still unclear if IL-17 elevation is the cause or consequence of VZV reactivation. In this connection, a recent study showed that IL-17A could directly support reactivation and de novo lytic infection of γ -herpesvirus (whereas VZV belongs to the α -herpesvirus family) (Jondle et al. 2021). Our present study thus suggests that COVID-19 might induce excessive Th17 differentiation to increase the circulating level of IL-17A, which in turn triggers VZV reactivation to increase the risk of herpes zoster.

By defining the genes involved in COVID-19 and herpes zoster, we delineated the protein-protein interaction networks of these two diseases, in which Th17 cell differentiation and IL-17 signaling were found to play a common role. Although zoster vaccine and antiviral therapy (e.g., acyclovir started within 72 h after the onset of the rash) have been proven effective for preventing and treating herpes zoster, respectively (Gershon et al. 2015, Rosamilia 2020), the best strategies to clinically manage COVID-19-associated herpes zoster remained undefined. To this end, our data suggested that the augmented Th17 cell differentiation and IL-17

Figure 2 STRING analysis of combined COVID-19/herpes zoster gene sets. **A** Interaction map shows better integration of COVID-19- and herpes zoster-associated clusters. **B** Herpes zoster-associated genes showed higher connectivity with other genes in the combined network as compared to COVID-19- or herpes zoster-alone network. **C** Heap map visualizes the additive and synergistic effects of incorporating COVID-19-

signaling might underlie the increased risk of herpes zoster among patients with COVID-19. It is therefore worthwhile to investigate in the future if modulation of IL-17 signaling could be of any prophylactic and therapeutic value to this disease entity.

Data availability statement Research data will be shared upon request.

Author contribution XY and LL conceptualized the study and analyzed the data. WKKW performed the bioinformatic analysis. XY, MTVC, and WKKW revised the manuscript.

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Declarations

Ethical approval This study was approved by the Clinical Ethics Committee of Beijing Friendship Hospital.

Consent to participate Not applicable.

Consent to publish Not applicable.

Conflict of interest The authors declare no competing interests.

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