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ORIGINAL RESEARCH

Kinases Associated with Herpes Zoster Virus Infection Unveiled by Phosphoromics Profiling

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Introduction: Reactivation of varicella-zoster virus (VZV) causes herpes zoster (HZ) in humans and elicits a VZV-specific immune response. However, the effect of VZV on host protein post-translational modifications (PTMs) remains largely unknown.

Objective: In this study, we investigated global changes in phosphorylation levels in HZ patients with postherpetic neuralgia (PHN) compared to healthy controls.

Methods: Using publicly available datasets, we found that the serine/threonine protein kinase and phosphatase pathways are significantly regulated by VZV infection, suggesting that VZV infection might globally alter the phosphorome of the host. To test this hypothesis, the phosphoproteomes of peripheral blood collected from HZ patients with PHN were profiled and differentially phosphorylated proteins were identified.

Results: The enhanced phosphorylated proteins were involved in pathways including complement activation, coagulation cascades, and endoplasmic reticulum protein processing. Variations in the phosphorylation levels of several proteins were highly consistent with a previously published proteomic study, indicating the synergistic regulation of protein translation and post-translational modification.

Conclusion: Notably, kinase-substrate enrichment analysis identified CSNK2A1 and PRKACA as potential response kinases, whereas their transcription and protein levels were experimentally validated to be significantly altered after VZV infection, showing the same trend. Furthermore, Mendelian randomization (MR) analysis revealed that decreased expression of CSNK2A1 may lead to a higher risk of HZ, indicating a vital role of this kinase during anti-VZV infection. Collectively, our findings provide valuable insights into the molecular mechanisms underlying VZV infection and highlight potential therapeutic targets for further investigation.

Keywords: Varicella-zoster virus, phosphoproteome, kinase, CSNK2A1, PRKACA

Introduction

VZV is a human-specific virus that causes HZ, and is distributed worldwide.[1] Approximately one-third of the global population experiences VZV infection during their lifetime, and the incidence and severity of the disease are associated with age.[2] During primary infection, VZV establishes a lifelong latency in the dorsal root sensory ganglion, which may recover and induce HZ.[3] The occurrence of HZ and its complications greatly impair quality of life. The most common complication is PHN, which persists long after resolution of HZ and manifests as chronic neuropathic pain and sensory dysesthesia.[4] In recent years, significant progress has been made in understanding the immune response to VZV infection, shedding light on the regulatory mechanisms of immunity during VZV reactivation.[1,5] However, the PTMs mediated regulation of host cells following VZV infection remains poorly understood.

Phosphorylation is a critical cellular PTM mechanism that dynamically regulates protein function, signal transduction, and responses to diseases.[6] A key component of VZV' s ability to replicate and evade the host immune response is the

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activation of several host and viral kinase, such as ERK1/2, p38, JNK, and viral kinase like ORF47 and ORF66.[7–9] These kinase play critical roles in the regulation of viral propagation, apoptosis, and immune evasion, making them attractive targets for the development of antiviral treatments. Kinase-mediated protein phosphorylation can inhibit viral replication,[10] whereas viruses evade host immune responses by regulating specific phosphorylation events. For instance, VZV blocks type I interferon (IFN-I) signaling by inhibiting the phosphorylation of STAT family protein and down-regulating the levels of Janus kinase 2 (JAK2) and IRF9 via itself protein ORF63;[11] while calcineurin is a key host factor regulating VZV-induced cell fusion, which is crucial for VZV pathogenesis.[12] Viruses can also hijack host-specific kinases to phosphorylate viral proteins, thereby promoting replication. Consequently, inhibitors targeting specific kinases exhibit promising antiviral potential.[13,14] Despite several studies identifying the roles of certain phosphorylation-related proteins during VZV infection, there is a lack of direct assessment of global protein phosphorylation changes in patients with HZ.

In this study, we performed a phosphoproteomic analysis of peripheral blood from clinical HZ patients to evaluate changes in protein phosphorylation levels. Our findings revealed certain kinases maybe particular important in response to VZV infection, providing novel insights into the immunological mechanism of HZ.

Materials and Methods

Sample Collection and Protein Digestion

Blood samples (10 mL) were collected from three patients with HZ and three healthy controls at Chongqing Traditional Chinese Medicine Hospital in China, incubated at room temperature for 2 h, centrifuged at 7000×g for 20 min (Supplementary Table 1). The pallet was washed three times with 40 mL of acetone. After removing the residual acetone, 50 mg of the resulting white powder from each sample was resuspended in 1 mL SDT lysis buffer. The suspension was heated in a water bath at 100°C for 15 min followed by sonication for 100 s. The lysate was centrifuged at 12000×g for 15 min, and the protein concentration in the supernatant was quantified using the bicinchoninic acid (BCA) assay. The quality was assessed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis. For protein digestion, residual SDS was removed using a filter-aided sample preparation (FASP) method prior to digestion. The concentrated proteins were digested with 8 μg of trypsin at 37 °C for 16 h. The resulting peptide solution was purified using a Microcon filter device, and the peptide concentration was determined by measuring the OD280.

Phosphorylated Peptides Enrichment and TMT Labeling

Phosphorylated peptides were enriched using TiO_2 microbeads. Acidification of the labeled peptides was performed using 50 μL of DHB buffer. The acidified peptides were incubated with 25 μg TiO_2 microbeads (10 μm diameter, Sangon Biotech) at room temperature for 40 min. After incubation, TiO_2 microbeads were pelleted by centrifugation and transferred to a pipette tip for further processing. The peptide-TiO_2 complexes were washed three times with 20 μL mix of 20% acetic acid, 300 mm sodium p-toluenesulfonate, and 20 mg/mL DHB, followed by three washes with 20 μL mix of 70% water and 30% acetonitrile. Phosphorylated peptides were eluted using freshly prepared 50 mm ammonium phosphate. The eluted peptides were lyophilized and re-dissolved in 20 μL of 0.1% TFA solution. For each sample, 100 μg of peptide was labeled using TMT 10plex reagent according to the manufacturer's instructions.

LC-MS/MS Analysis

Aliquots (5 μg) of the phosphopeptide solution were loaded onto a Q Exactive hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific) coupled with a two-dimensional EASY-nLC 1000 system. Prior to sample loading, a Thermo EASY SC200 trap column (RP-C18, 3 μm, 100 mm × 75 μm) was pre-equilibrated for 30 min with 95% mobile phase A consisting of an aqueous solution containing 0.1% formic acid. Phosphopeptides were transferred to a Thermo Scientific EASY column (2 cm × 100 μm, 5 μm-C18) and separated on a trap column for 200 min. The column was subsequently washed with 100% mobile phase B, which contained 84% acetonitrile with 0.1% formic acid, for 8 min, followed by re-equilibration to the initial conditions over 12 min. The flow rate throughout the procedure was maintained at 0.25 μL/min. Mass spectrometry data were acquired over a range of 350–1800 m/z, with a resolution of

70000. Raw data were extracted using Mascot (v2.2) and analyzed with Proteome Discoverer 1.4 (Thermo Scientific). To quantify phosphopeptides, Spectronaut software (v15.7) was used to search the human protein sequence database from UniProt, employing default parameters with a false discovery rate of less than 0.01.

Transcriptomic and Phosphoproteomic Analysis

For public transcriptomic analysis, the GSE79396 and GSE141932 datasets were downloaded from the NCBI GEO database. Differential expression analysis of GSE141932 was performed using the limma package, with thresholds set at $|\log2FC| > 1$ and $FDR < 0.05$.[15] For GSE79396, time-series analysis was conducted using the Mfuzz package to evaluate data before vaccination and at 1, 3, and 7 days post-vaccination with the live attenuated varicella-zoster vaccine, with the number of clusters set to 10.[16] For phosphoproteomic analysis, differentially phosphorylated sites were identified using thresholds of $P < 0.05$, and $|\log2FC| > 0.3$. KEGG and GO enrichment analyses were performed using the ClusterProfiler package[17] with $FDR < 0.05$, as the significance threshold. Protein-protein interaction (PPI) network was constructed using the STRINGdb package, with an interaction score of > 600. Kinase-substrate enrichment analysis (KSEA) was conducted using the KSEAapp package.[18]

RNA Extraction and qRT-PCR

Total RNA was extracted from blood samples using the RNAprep Pure High-Performance Blood Total RNA Extraction Kit (Tiangen, DP443), and cDNA was synthesized using a reverse transcription kit (Takara). cDNA amplification for quantification was performed using a Bio-Rad PTC-200 fluorescence quantitative PCR machine. Gene expression levels were normalized to those of GAPDH and quantification was performed using the ΔΔCt method. The *t*-test was used for statistical analysis of the qPCR results between the groups. ***$P < 0.001$.

Enzyme Linked Immunosorbent Assay

ELISA for CSNK2A1 (#E10177h, EIAab) and PRKACA (#E1918h, EIAab) was performed according to the manufacturer's instructions. Serum samples were appropriately diluted with the provided sample diluent and immune detection was performed according to the manufacturer's guidelines. Absorbance was recorded in triplicate at 450 nm using a Multiskan GO plate reader (Thermo Fisher Scientific). Protein levels of the two kinases in the blood of healthy individuals and patients with herpes zoster were compared using the Wilcoxon rank-sum test.

Mendelian Randomization Analysis

MR analysis was performed using the R package TwoSampleMR.[19] For exposure data, the cis-expression quantitative trait locus (cis-eQTLs) dataset from eQTLGen were downloaded,[20] and SNPs significantly ($P < 5\times10e\text{-}6$) associated with the expression of CSNK2A1 and PRKACA were selected. The retained single nucleotide polymorphisms (SNPs) were clumped to obtain independent genetic variants, ensuring linkage disequilibrium (LD) with $r^2 < 0.001$. For the outcome data, the Finn-b-AB1_ZOSTER genome-wide association study (GWAS) dataset from the OpenGWAS database was used. The harmonized data underwent genetic pleiotropy and heterogeneity tests before MR analysis.

Result

VZV Infection Remodel Phosphorylation-Related Pathways of Host Cells

To determine whether VZV infection leads to global changes in the phosphorylation modifications of host cells, we analyzed two publicly available datasets related to VZV infection. Enrichment analysis revealed that, following VZV infection, differential phosphorylated genes (DPGs) in the host cells were significantly enriched in the p53 signaling and MAPK pathways (Figure 1a and b). For the herpes zoster vaccination dataset, we performed a time-series analysis and clustered all genes based on their expression changes over time into 10 clusters. Among them, the genes in one cluster were upregulated on day one after vaccination and recovered in the following days (Figure 1c). This cluster was also significantly enriched in the serine/threonine protein kinase and phosphatase regulatory pathways (Figure 1d and e).

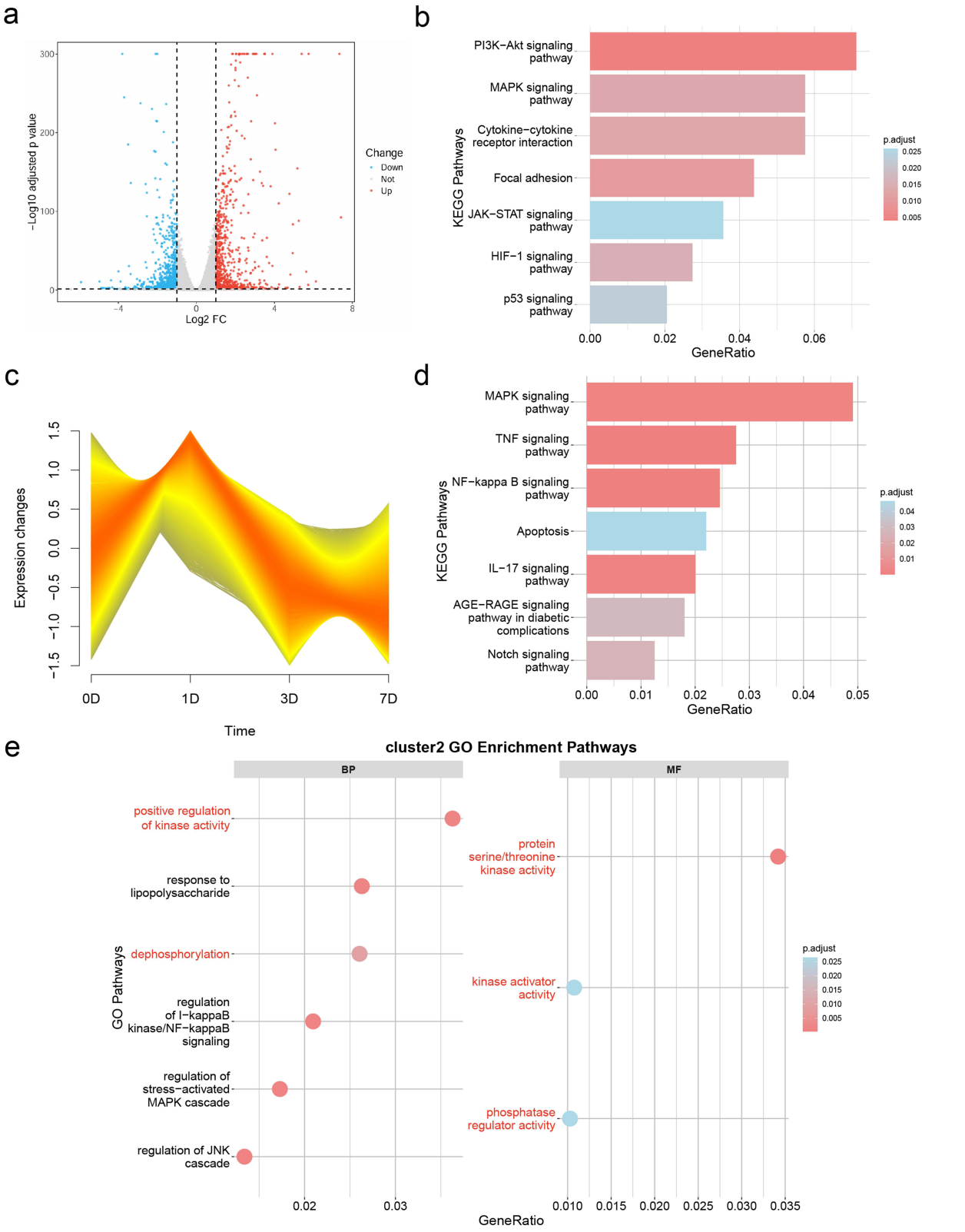

Figure 1 VZV infection induce global phosphorylation changes in host cells. (**a**) Volcano plot of differential expressed genes (DEGs) (|log2FC| > 1 and FDR < 0.05) under VZV infections in the GSE141932 dataset. (**b**) KEGG pathway enrichment of DEGs. (**c**) Cluster of genes enriched by phosphorylation related (**d**) KEGG and (**e**) GO pathways through time series analysis from a HZ-vaccine cohorts. Pathways colored in red represent direct phosphorylation pathways.
Abbreviations: BP, biological process; MF, molecular function.

Alterations of Protein Phosphorylation Levels in HZ Patients

Peripheral blood samples were collected from patients with HZ and from healthy controls for phosphoproteomic sequencing. A total of 1558 peptides and 322 modified peptides were identified. In general, 308 modification sites were identified in 180 proteins, with 287 sites in 166 proteins containing quantitative information. Differential analysis revealed that patients with HZ exhibited four downregulated phosphorylation sites and 48 upregulated phosphorylation sites compared to HC (Figure 2a, Supplementary Table 2). These sites corresponded to 37 genes, with phosphorylation levels of VTN, PLG, PRKACB, and CHGB being significantly downregulated, while the phosphorylation levels of the other proteins were significantly upregulated. KEGG enrichment analysis indicated that these DPGs were highly enriched in pathways, such as complement and coagulation cascades and protein processing in the endoplasmic reticulum (Figure 2b). GO enrichment analysis revealed significant changes in all three categories, with biological processes including complement activation and plasma lipoprotein particle assembly (Figure 2c). PPI network analysis also showed that most DPGs were highly interconnected (Supplementary Figure 1). Motif analysis revealed a high enrichment of glutamic acid downstream of phosphorylated serine (Figure 3), whereas amino acids near phosphorylated threonine did not show a specific pattern.

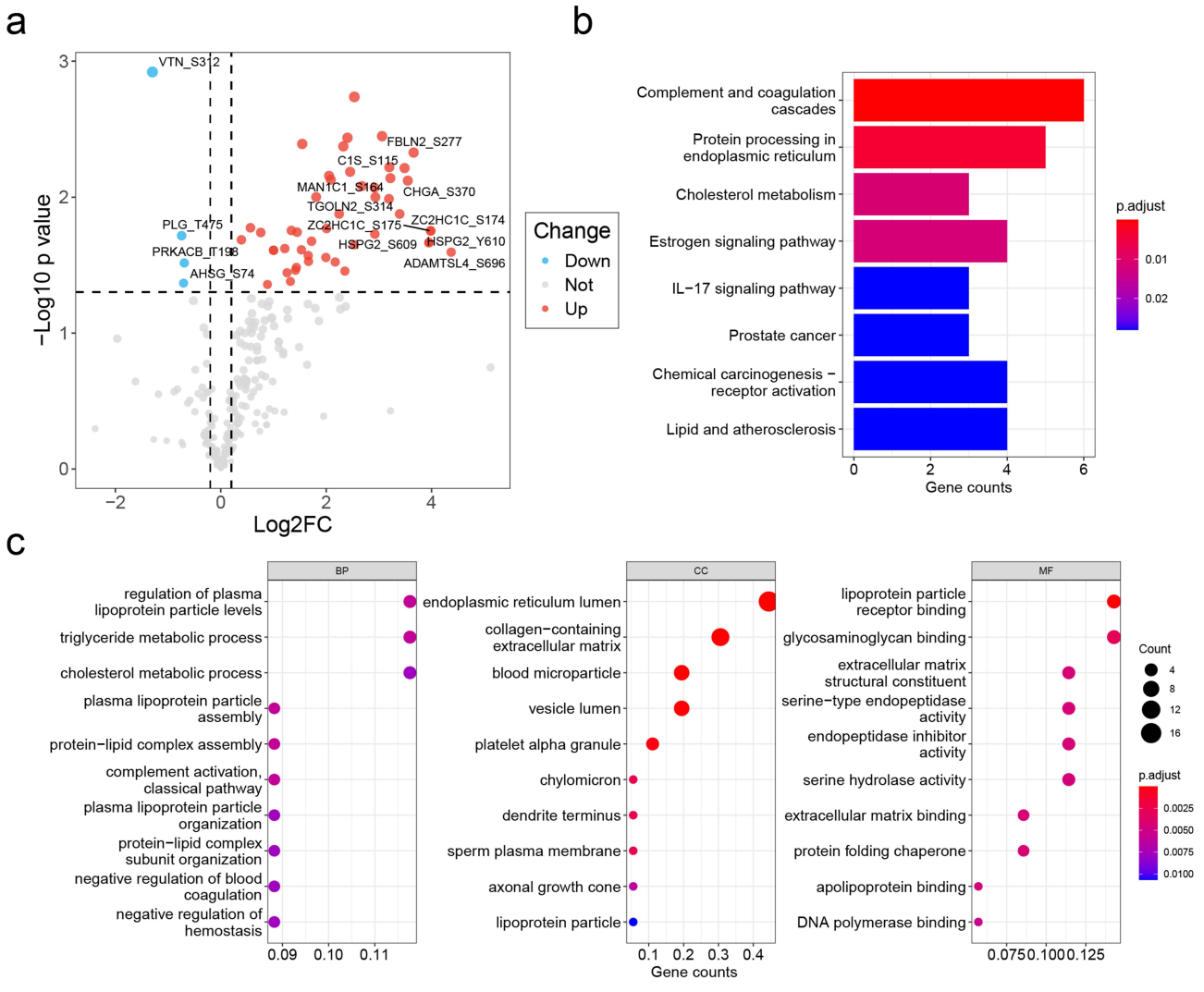

Figure 2 Phosphorylation events altered in HZ patients. (**a**) Volcano plot of differentially phosphorylated sites (P < 0.05, |log2FC| > 0.3). (**b**) KEGG enrichment analysis of differentially phosphorylated genes. (**c**) GO enrichment analysis of differentially phosphorylated genes.
Abbreviation: CC, cell component.

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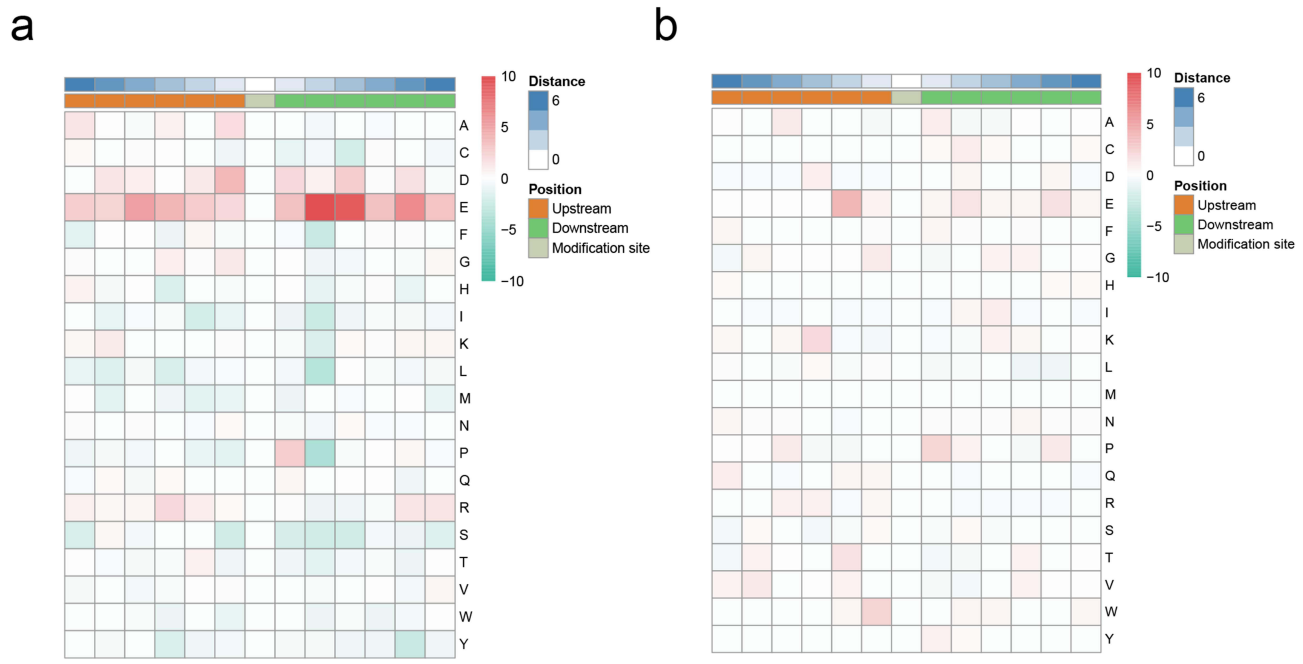

Figure 3 Motif analysis of phosphorylated sites. Six amino acid codon were shown upstream and downstream phosphorylated (**a**) serine and (**b**) threonine sites.

Common Kinase of Differential Phosphosites

We used KSEA to identify the common substrates recognized by these DPGs. The results indicated that CSNK2A1, PRKCA, CSNK2A2, AKT1, PRKCD, and PRKACA were potential kinases for these DPGs (Figure 4a). Among these, CSNK2A1 and PRKACA were significantly enriched and exhibited the highest absolute kinase z-scores. CSNK2A1 is activated during phosphorylation, whereas PRKACA is deactivated. qPCR analysis revealed that the transcription levels of CSNK2A1 were significantly upregulated compared with those in healthy controls ($P<0.001$), whereas the transcription levels of PRKACA were significantly downregulated ($P<0.001$) (Figure 4b). Similarly, ELISA tests showed that protein levels of CSNK2A1 were significantly increased in patients ($P<0.001$), whereas PRKACA displayed the opposite trend ($P<0.001$) (Figure 4c).

MR Analysis of eQTLs of Kinase with VZV Infection Risk

To further explore the roles of CSNK2A1 and PRKACA in VZV infection, 49 eQTLs significantly associated with CSNK2A1 expression were extracted and used as exposure data, and 7 eQTLs after clumping were included in further analysis (Figure 5a). However, none of significant eQTLs of PRKACA were observed in VZV infection data, thus further analysis was not conducted. All five MR models consistently indicated a significant negative association between CSNK2A1 and the outcome (Figure 5b). The causal effect estimates for the MR Egger and inverse variance weighted (IVW) methods are −1.71 (95% CI: −2.92 - −0.50, P = 0.02) and −0.95 (95% CI: −1.03 - −0.87, P = 4.36e-6). Causal effect estimates for all SNPs included in the analysis were less than zero.

Discussion

Phosphorylation is one of the key PTMs that regulate cellular physiology and pathology. VZV has been shown to hijack host phosphorylation regulatory circuits in multiple ways to establish successful infection. VZV viral proteins IE62 and ORF47 kinase inhibit IRF3 phosphorylation, thus preventing host interferon-mediated immune response in infected cells.[21,22] The p53 pathway plays a key role in controlling cell cycle progression and apoptosis, which are essential for limiting viral replication and maintaining host cell survival.[23] Dysregulation of p53 signaling may compromise the host's antiviral defense, potentially facilitating VZV latency and reactivation. Additionally, the MAPK pathway, which governs inflammation, immune responses, and cell survival, is likely activated during VZV infection to modulate inflammatory

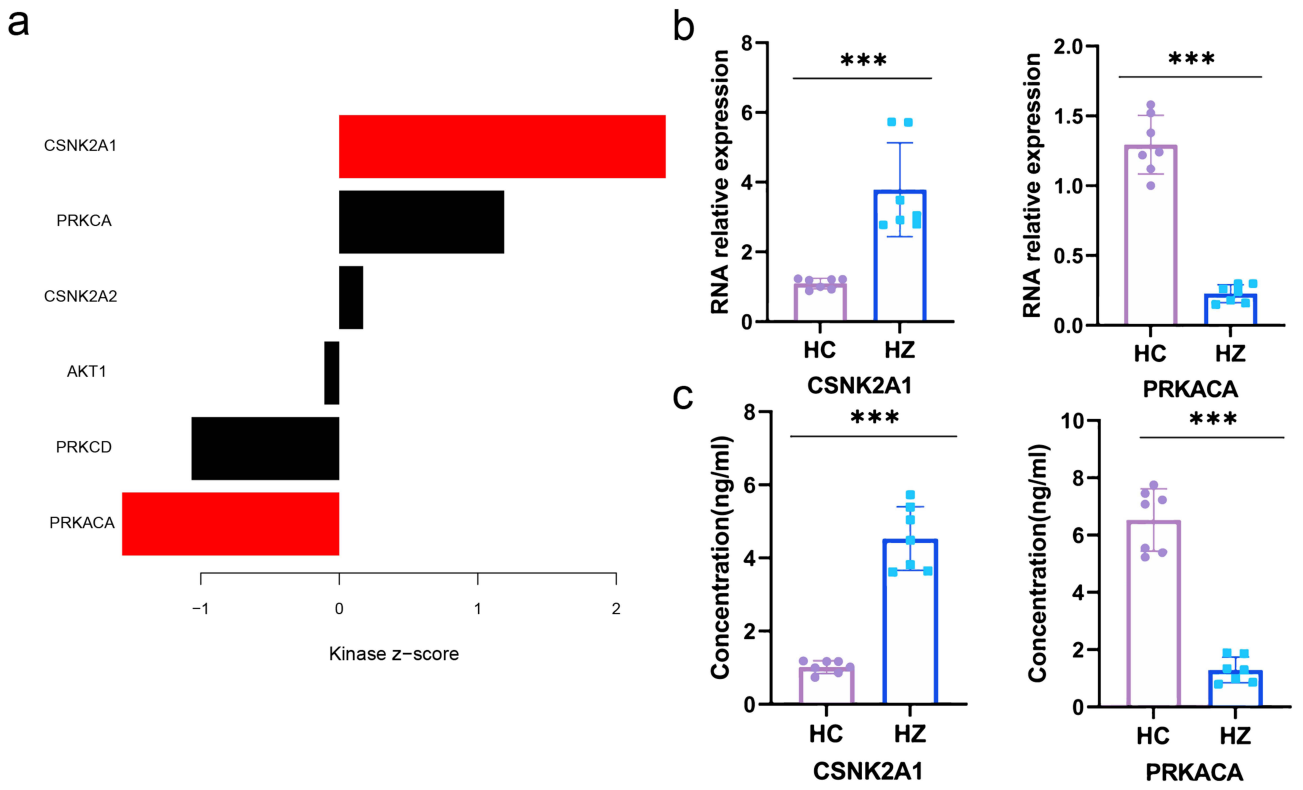

Figure 4 Common kinases involved in differentially phosphorylated genes. (**a**) KSEA analysis revealed that CSNK2A1 and PRKACA are key kinases in HZ patients. (**b and c**) qPCR and ELISA assays demonstrated significant differences in both the transcriptional activity and protein level of CSNK2A1 and PRKACA between HZ patients and healthy individuals. ***, P < 0.001.

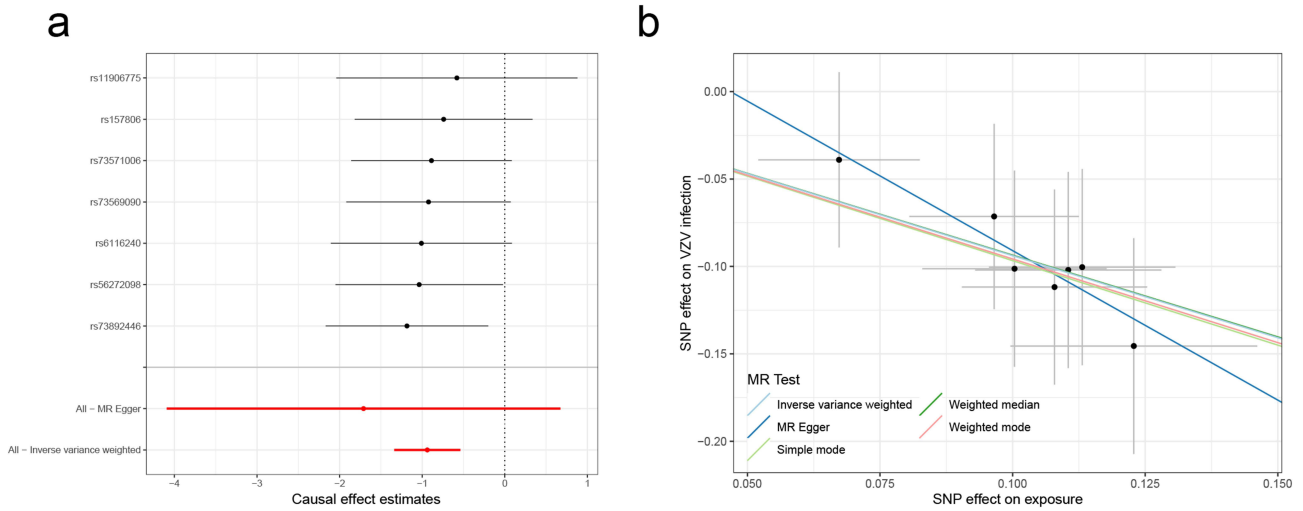

Figure 5 The expression of CSNK2A1 is associated with HZ risk. (**a**) Effects of CSNK2A1 eQTLs on VZV infection. (**b**) All of MR tests showed negative impact of CSNK2A1 expressions on VZV infection.

reactions.[24] Perturbations in MAPK signaling may reflect the host's attempt to suppress viral spread, but aberrant activation could also contribute to complications such as PHN. We also found that both HZ vaccination and VZV infection could significantly regulate the host's serine/threonine protein kinase- and phosphatase-related pathways, suggesting that VZV drives global reprogramming of the host protein phosphorylation landscape. Through phosphoproteomic analysis of HZ patients, we identified significant changes in the phosphorylation status of several proteins

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following infection. Owing to the sample size and technical limitations, we speculate that the actual number of differentially phosphorylated proteins after VZV infection may have been underestimated in our study. Pathway enrichment analysis of these DPGs revealed several known pathways, which is consistent with previous reports. The complement and coagulation cascade pathways were significantly enriched, which corresponds with previous findings that VZV infection activates the complement system.[24,25] We found that C3 phosphorylation status was significantly elevated in patients with HZ. C3 is central to the complement system and is responsible for the activation of both classical and alternative complement pathways; phosphorylation mediated by CK2 increases C3 sensitivity to proteolytic cleavage, enhancing its activity and promoting a more effective immune response.[26] ADAMTSL4 and SERPINA10 were the proteins with the highest increases in phosphorylation levels in our study. The former is involved in angiogenesis, while the latter is directly related to coagulation.[27,28] These proteins may be associated with bleeding in the HZ, corresponding to the enrichment of blood microparticle components. Several phosphorylation sites on the HSP90 family members (HSP90AA1, HSP90AB1, and HSP90B1) were significantly upregulated. HSP90 is a member of the heat shock protein family, which is related to rapid replication of the virus as it facilitates protein assembly.[29] All three genes participate in the IL-17 signaling pathway, which plays a central role in the host defense against infections and the development of inflammatory diseases.[30] Interestingly, protein processing in endoplasmic reticulum (ER) pathway was also significantly enriched. Previous studies have reported that VZV infection induces ER stress and ER-associated degradation (ERAD), which typically promote autophagy.[31,32] Moreover, the VZV-derived ORF68 protein may interact with human insulin degradation enzymes and be involved in ERAD.[31] Since IL17 can induce the expression of the key ERAD factor HRD1,[33] future studies should further explore the complex interactions between these two pathways following VZV infection. We also observed that the phosphorylation levels of some proteins, including VTN and PLG, were downregulated in these patients. Importantly, the protein levels of VTN and PLG were also downregulated in a previous proteomic study,[34] suggesting that changes in their phosphorylation levels were synchronized with their expression. VTN is an adhesive glycoprotein that promotes cell adhesion or migration and regulates coagulation and tissue remodeling, whereas both VTN and PLG promote wound healing and recruitment of inflammatory cells.[35,36] Thus, we speculate that these two genes could be used as diagnostic biomarkers for HZ.

Protein kinases play widespread roles in cellular signal transduction. Several protein kinases have been shown to play vital roles in herpes virus infections,[37] while some kinases may be affected by viral proteins to promote the reproduction of the virus.[38] KSEA revealed that CSNK2A1 and PRKACA are the most important kinases regulating downstream phosphorylation events, indicating that these two enzymes are highly responsive to VZV infection. Importantly, both qPCR and ELISA results confirmed that the changes in the expression levels of these two kinases were consistent with alterations in the phosphorylation levels of their substrates. PRKACA is a catalytic subunit of protein kinase A (PKA). This kinase has a broad range of phosphorylation substrates and can activate the viral helicase nsp13. PRKACA knockdown inhibits SARS-CoV-2.[39] One of PRKACA's phosphorylated substrates of PRKACA, LCP1, has been shown to reduce neuroinflammation and immune suppression in knockout models and improve neurobehavioral outcomes in mice.[40] Thus, changes in PRKACA expression may be associated with neurological complications of HZ.[40] CSNK2A1 is a subunit of the protein kinase CK2, which is constitutively active and regulates cell cycle progression, apoptosis, and viral infection. CSNK2A1 mutations have been linked to various neurodegenerative diseases.[41–43] Several viruses promote replication by increasing host CK2 expression to phosphorylate their own proteins.[44–46] In our study, CSNK2A1 was identified as a kinase with several upregulated phosphorylation sites (HSP90AA1 S263, HSP90AB1 S226/S255, IGFBP1 S1, and FGA S609). Interestingly, the MR results suggest that decreased CSNK2A1 expression may significantly increase VZV infection risk, indicating that the role of CSNK2A1 in VZV infection may differ from that of other viruses. These findings suggest a potential protective role of CSNK2A1 during VZV infection. The observed negative correlation between CSNK2A1 expression levels and disease susceptibility may indicate that reduced CSNK2A1 activity could compromise host defense mechanisms, thereby increasing vulnerability to VZV.

Our study had several limitations. We were unable to validate the differentially phosphorylated sites or detect direct phosphorylation events of the two kinases identified in our analysis using biochemical experiments. However, the consistency between the expression of the two kinases and the changes in the phosphorylation levels of the corresponding proteins strengthens the reliability of our findings. Future work should test whether these two kinases are decisive factors in phosphorylation regulation in VZV-infected patients, and a multicenter, prospective cohort to test the diagnostic and

prognostic value of the two kinases in patients is worthwhile. Meanwhile, while we observed coordinated changes in kinase activity and phosphorylation patterns, our study design cannot distinguish whether these modifications represent direct viral manipulation or indirect host responses. Thus, further study are requested to demonstrate the real significance of these phosphorylated proteins.

Data Sharing Statement

The datasets generated in this study can be found in PXD058933 in the ProteomeXchange database.

Ethics Statement

All participants provided written informed consent prior to sample collection. Studies involving human participants were reviewed and approved by the Ethics Committee of Chongqing Traditional Chinese Medicine Hospital (2021-ky-67). All participants provided written informed consent prior to participating in the study. All patients provided written informed consent to participate in the study. The study complies with the Declaration of Helsinki in Ethics Statement.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that there is no conflict of interest in this work.

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