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Comprehensive Bioinformatics Analysis of the Immune Mechanism of Dendritic Cells Against Measles Virus

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: The purpose of this study was to explore the immune mechanism of dendritic cells (DCs) against measles virus (MV), and to identify potential biomarkers to improve measles prevention and treatment.

Material/Methods: The gene expression profile of GSE980, which comprised 10 DC samples from human blood infected with MV (RNA was isolated at 3, 6, 12, and 24 h post-infection) and 4 normal DC control samples, was obtained from the Gene Expression Omnibus database. Differentially expressed genes (DEGs) between the MV-infected DC samples and the control samples were screened using Genevestigator software. Gene ontology (GO) and Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses were performed using GenCLip 2.0 and STRING 10.5 software. The protein–protein interaction (PPI) network was established using Cytoscape 3.4.0.

Results: The gene expression profiles of MV-infected DCs were obviously changed. Twenty-six common DEGs (0.9%, MV-infected DCs *vs.* normal DCs) were identified at 4 different time points, including 14 down-regulated and 12 up-regulated genes (P=0.001). GO analysis showed that DEGs were significantly enriched in defense response to virus, type I interferon signaling pathway, et al. ISG15 and CXCL10 were the key genes in the PPI network of the DEGs, and may interact directly with the type I interferon signaling and defense response to virus signaling.

Conclusions: The DEGs increased gradually with the duration of MV infection. The type I interferon signaling pathway and the defense response to viral processes can be activated against MV by ISG15 and CXCL10 in DCs. These may provide novel targets for the treatment of MV.

MeSH Keywords: **Dendritic Cells • Gene Expression Profiling • Measles Virus • Neuroimmunomodulation**

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Background

Measles is a highly contagious acute respiratory tract infection caused by the measles virus (MV). Clinical manifestations include fever and rash, with encephalitis, bronchopneumonia and myocarditis among the more severe complications that can lead to death [1–3]. In 2012, the World Health Organization (WHO) launched the Measles and Rubella Global Strategic Plan. This aimed to eradicate both infectious diseases from at least 5 of the 6 WHO regions by 2020 [4]. At present, only the Americas have eliminated measles successfully, and the task of eradicating measles worldwide remains serious [5,6]. Improved understanding of the mechanisms underpinning MV infection may help resolve this problem. Early infection with the MV involves alveolar macrophages (AMs) and dendritic cells (DCs) as targets [7,8]. MV is inhaled via the respiratory tract to infect the local mature AMs and DCs directly. These infected cells then transport the virus to adjacent lymphatic vessels and subsequently to the draining lymph nodes. Here, MV infects monocytes, and T and B lymphocytes, and begins replicating and proliferating to cause primary viremia. MV proliferation results in spread to the tonsils, thymus and other secondary lymphoid organs, and then onto other sites such as the kidneys, gastrointestinal tract, liver and respiratory tract [9–11]. In the process of MV infection, the host usually mounts a strong immune response. Viral perception and activation of type I interferon exposure typically follows stimulation of 2 intracellular signal transduction pathways being the classical and the plasmacytoid dendritic cells pathways [12,13]. To date, there has been no investigation of the molecular mechanism for immature DC infection by MV. Therefore, the aim of this study was to explore the molecular basis for DC infection with MV using bioinformatics.

The microarray dataset, GSE980, was obtained from the Gene Expression Omnibus (GEO) database of the National Center for Biotechnology Information (NCBI; MD, USA). It contained 10 DC samples from human peripheral blood infected with MV (RNA was isolated at 3, 6, 12, and 24 h post-infection) and 4 normal DC control samples. This work comprised expression profile, differentially expressed gene (DEG), functional module, gene ontology (GO), Kyoto of encyclopedia genes and genomic (KEGG) pathway enrichment, and protein-protein interaction (PPI) network analyses.

Material and Methods

Data sources

We searched for human gene chip expression data related to the "measles virus" or "MV" in the GEO database (NCBI, MD, USA). We obtained the gene chip information dataset, GSE980, submitted by Zilliox MJ, Parmigiani G and Griffin DE in January 2004 and updated in June 2016. The dataset was obtained from Affymetrix Human Genome U95 Version 2 Array assay platform.

Experimental design and mRNA extraction

Human CD14$^+$ monocytes were first isolated from human peripheral blood using standard methods, and grown in colony stimulating factor 2 (GMCSF) and interleukin 4 (IL-4) for 6 days before infection with MV (Chicago-1 strain). After infection for 3, 6, 12 and 24 h [14], mRNA was extracted from macrophages for subsequent analysis, using an mRNA extraction kit (Thermo Fisher Scientific, America).

GSE980 contained data on the gene expression profiles of CD14$^+$ monocytes from 14 human subjects. These comprised CD14$^+$ monocytes without interventions for use as the control group (n=4), and CD14$^+$ monocytes infected with MV for 3 h (n=2), 6 h (n=3), 12 h (n=2) and 24 h (n=3). The dataset contained expression information from 12625 genes detected by microarray.

Data preprocessing and differentially expressed gene screening

After downloading the GSE980 dataset, R software (*https://www.r-project.org/*) and Genevestigator (*https://genevestigator.com/*) were used to conduct the normalization (μ=0, s=1) to improve data comparability and reliability. The 4 independent MV-infected CD14$^+$ mononuclear cells groups and the control group were tested using the unpaired Student's t-test, and the DEGs were screened out (P<0.05, false discovery rate <0.05, fold change >1.2).

GO and KEGG enrichment analysis

We considered that the common DEGs at all 4 time points would be a sensitive and stable biomarker for CD14$^+$ cells infected with MV, and would play an important role in this process. Therefore, we selected the common DEGs from the CD14$^+$ mononuclear cells at the 4 time points and analyzed their biological functions using human gene functional analysis software GenCliP 2 (*http://ci.smu.edu.cn/GenCLiP2/analysis.php*) and Cytoscape 3.5.1 platform. The corresponding analysis parameters were then established to obtain the biological functions and signal pathways enriched among the DEGs.

Establishment of the PPI network

The name of the protein corresponding to the common DEGs at 4 time points was uploaded to STRING 10.0 (*http://string-db.org/*) and online software (*https://www.intomics.com/inbio/map/#hom*) to establish the PPI network. Parameter values

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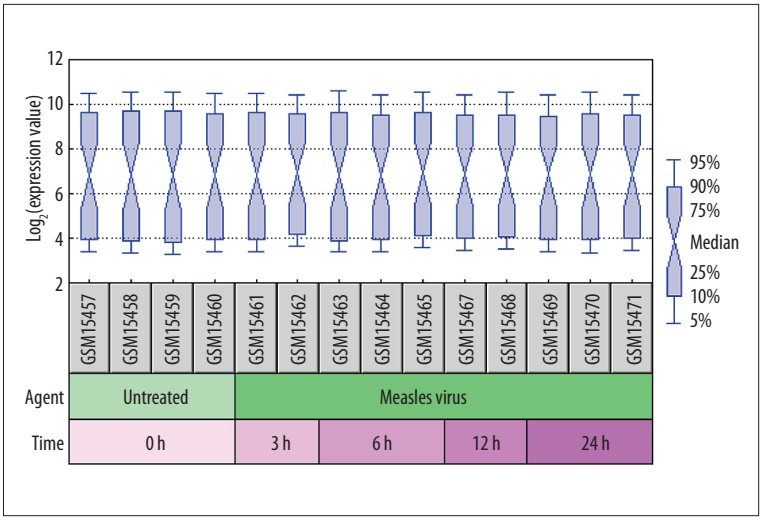

Figure 1. Distribution features of the expression data after sample normalization. (After preprocessing, the median value of the sample data was essentially the same as the mean value, which indicated normality, which showed good stability and ensured that subsequent analyses were reliable).

such as reliability and attachment nodes were adjusted and the appropriate PPI network of the DEGs obtained. The core protein of CD14+ mononuclear cells against MV was screened according to the PPI nodes.

Construction of the gene-pathway interaction network

To further explore the potential role of the above core protein, the gene-pathway interaction network for the common DEGs was established. This was done using the GLUGO platform of Cytoscape software (*http://cytoscape.software.informer.com/*) to investigate the interactions among the core protein and pathways in CD14+ against MV.

Results

Data preprocessing and stability

The gene dataset, GSE980, was subjected to standard normalization treatment using R software. After preprocessing, the median value of the sample data was essentially the same as the mean value, which indicated normality. The data showed good stability and ensured that subsequent analyses were reliable (Figure 1).

DEG screening

After infection of CD14+ monocytes with MV for 3 h, 31 genes were significantly changed (18 down-regulated, 13 up-regulated) compared with the controls. After MV infection of CD14+ monocytes for 6 h, the expression of 565 genes also had obvious changes (294 down-regulated, 271 up-regulated) compared with the control group. After 12 and 24 h, there were 1114 (726 down-regulated, 388 up-regulated) and 1505 (956 down-regulated, up to 549 up-regulated) genes, respectively, that were significantly altered in MV-infected CD14+ monocytes compared with controls (Figure 2).

To obtain the most sensitive and stable DEGs of CD14+ monocyte against MV, we used a Venn diagram to obtain the 24 most common DEGs at the 4 time points (Figure 3). The 26 common DEGs are shown in Supplementary Table 1.

GO and KEGG enrichment

The results of GO functional enrichment analysis of 26 common DEGs are shown in Figure 4 and in Supplementary Table 2. The functional enrichment analysis was divided into 3 categories: biological processes, molecular functions and cellular components. Figure 4 shows 5 molecular functions, 1 cellular component, and 26 biological processes were involved in these 26 common DEGs. This shows that the main function of the DEGs in the process of CD14+ monocytes against MV is through the interferon I signaling and the antiviral reaction pathways.

PPI (protein-protein interaction) network of DEGs

The PPI network of the 26 common DEGs was established and showed that the topology network contained 3 typical sub-networks, mainly related to biological functions such as protein synthesis (Figure 5). Both ISG15 and CXCL10 proteins interacted with many other proteins. Deletion of these 2 proteins would result in the entire network structure being obviously scattered, indicating that ISG15 and CXCL10 were important link nodes in the most typical sub-network. The CXCL10 cluster was related to chemokine and interferon induction. The ISG15 cluster was related to the antiviral function of the interferon signaling pathway.

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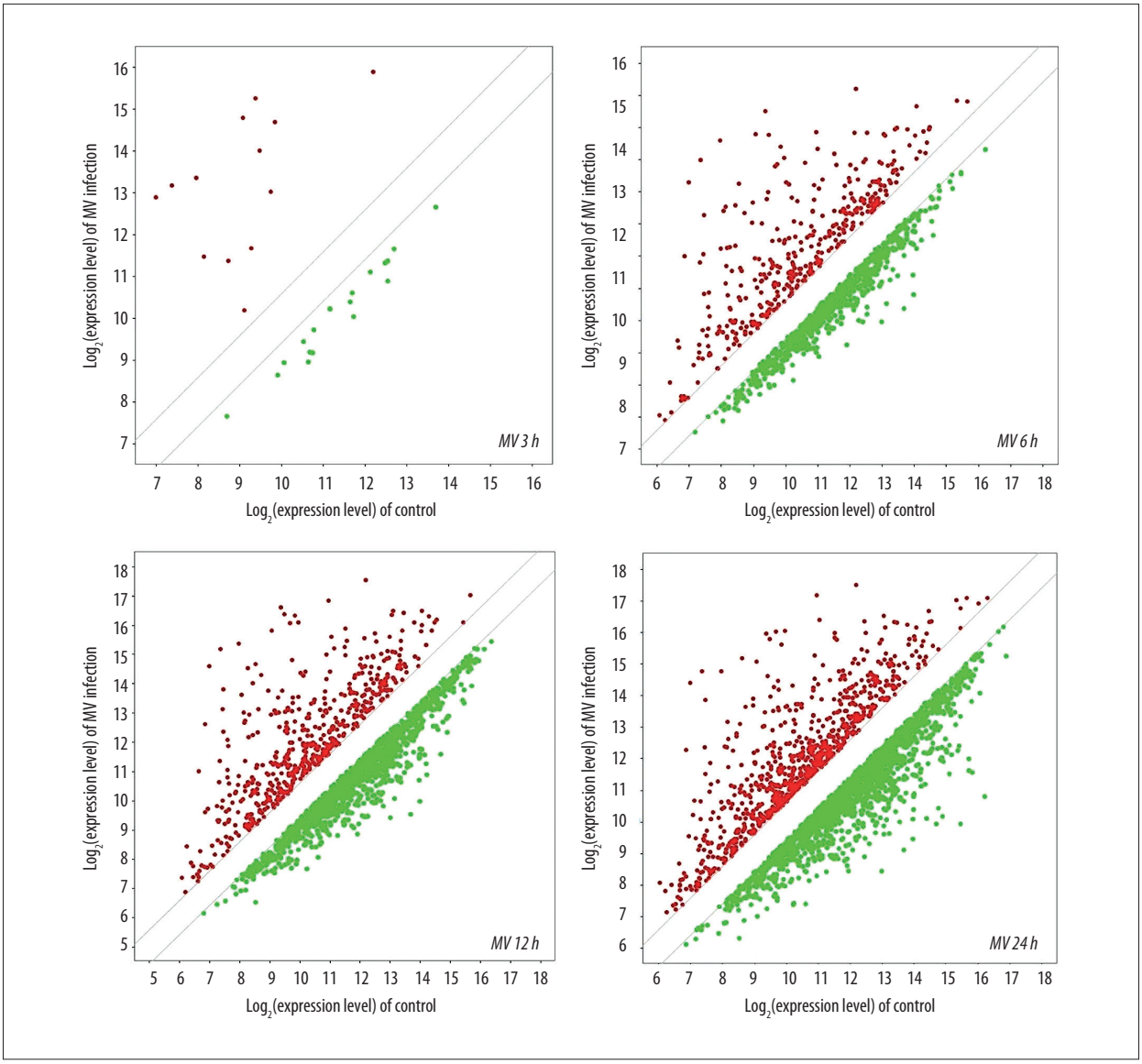

Figure 2. DEGs between MV-infected CD14+ monocytes and controls at different time points. After infection of CD14+ monocytes with MV for 3 h, 18 DEGs were down-regulated and 13 DEGs up-regulated comparing with the controls; At 6 h, 294 were down-regulated and 271 were up-regulated comparing with the control group. After 12 and 24 h, there were 1114 (726 down-regulated, 388 up-regulated) and 1505 (956 down-regulated, up to 549 up-regulated) genes, respectively. The red dots represent up-regulated DEGs and the green dots represent down-regulated DEGs comparing with the control group.

Gene-pathway network

To further explore the specific pathways of ISG15 and CXCL10 protein involvement in the antiviral process of DCs, we established a gene-pathway network (Figure 6). As shown in Figure 6, the change in expression of ISG15 could directly activate the type I interferon signaling pathway, and CXCL10 could directly activate the defense response to the virus signaling pathway.

Expression of key genes at different time points of DC antiviral activity

The changes in expression of ISG15 and CXCL10 at different antiviral time points are shown in Figure 7. Both genes showed a significant increase after CD14+ cells were infected with MV, which suggested that elevated expression of the 2 key genes might activate the critical pathway in CD14+ cells against MV (A: * *vs.* 0 h: $P<0.05$, # *vs.* 3 h: $P<0.05$; B: * *vs.* 0 h: $P<0.05$).

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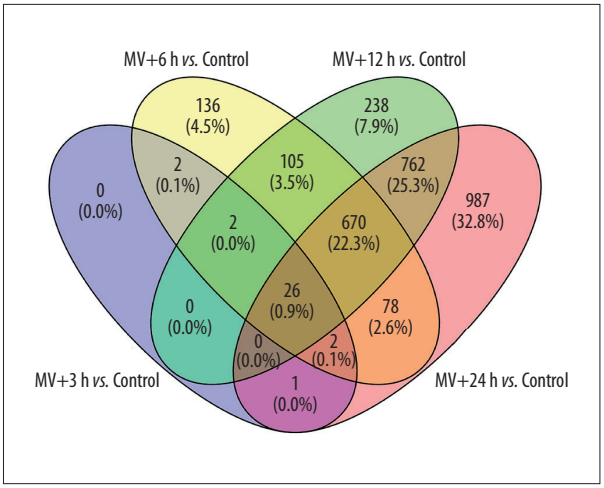

Figure 3. Venn diagram of Figure 3. Venn diagram of DEGs between MV-infected CD14⁺ monocytes and controls at different time points. 26 is the number of common DEGs among the samples at 4 time points.

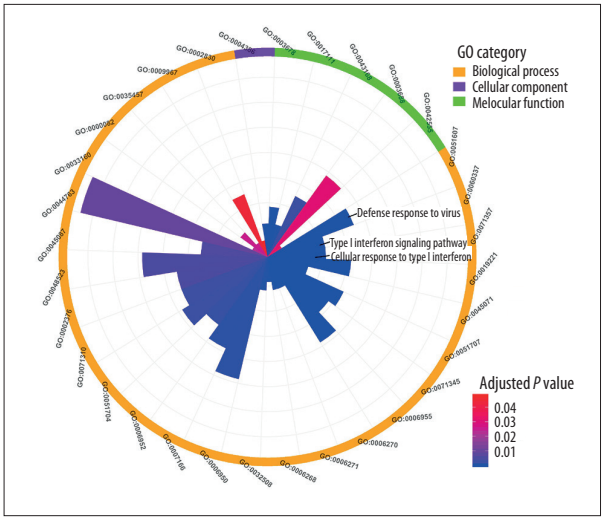

Figure 4. Results of GO and KEGG enrichment analysis for the 26 common DEGs. Five molecular functions, 1 cellular component, and 26 biological processes were involved in these 26 common DEGs.

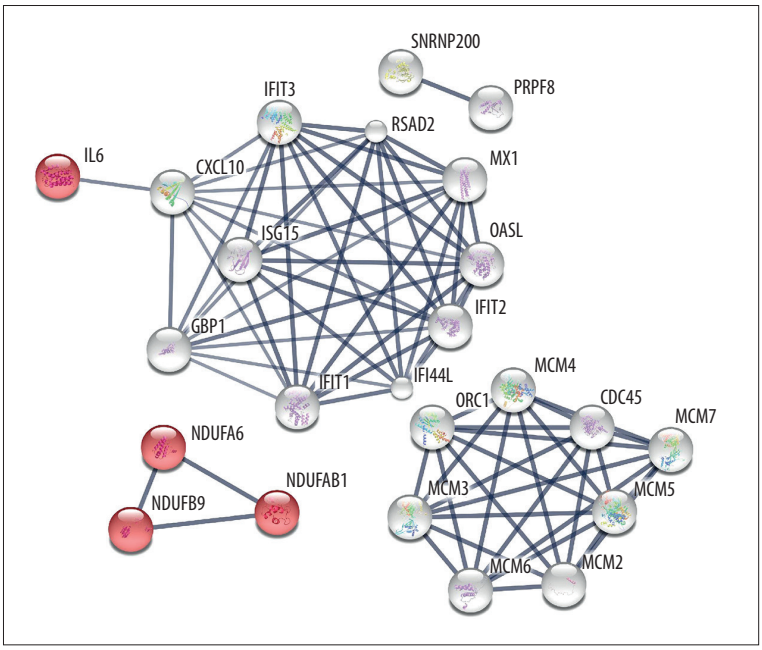

Figure 5. PPI network (confidence ≥0.70) of 26 DEGs generated with STRING. The topology network contained 3 typical sub-networks, mainly related to biological functions such as protein synthesis. Both ISG15 and CXCL10 proteins interacted with many other proteins, indicating that ISG15 and CXCL10 were important link nodes in the most typical sub-network.

We further explored the co-expression of ISG15 and CXCL10 in human tissue samples using STRING. The results showed that ISG15 and CXCL10 were co-expressed in humans (including CD14⁺), suggesting that these 2 genes have an interactive relationship in the fight of CD14⁺ cells against MV infection (Figure 8).

Discussion

In the past, measles was a typical acute respiratory tract disease that was very prevalent in children and highly contagious. The widespread uptake of the measles vaccine has led to a significant reduction in the incidence of this disease. However, in some geographical areas, especially where vaccines are not widely available, the incidence of measles remains high and poses significant threat to child health [15–17]. To actively prevent and treat measles, we should actively explore its pathogenesis to assist in the control of this disease.

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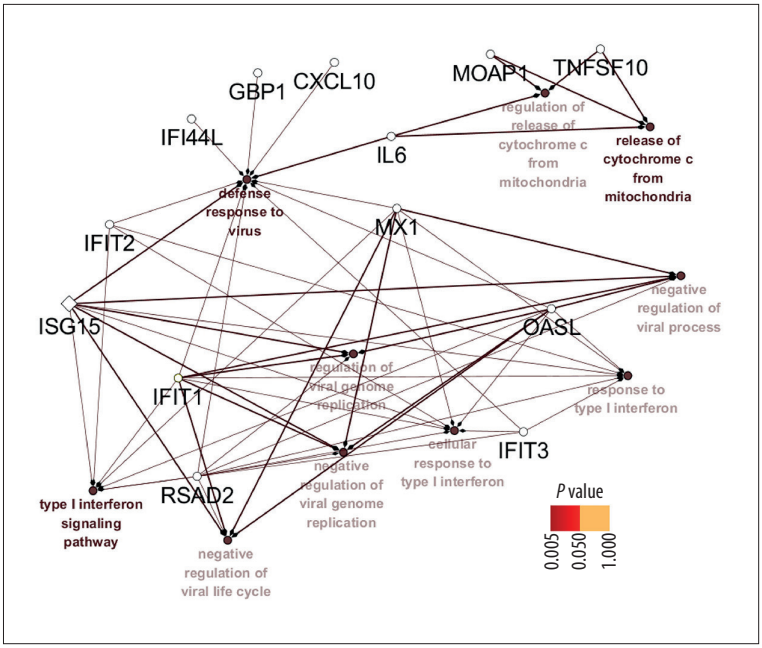

Figure 6. Gene-pathway network of 26 DEGs. The change in expression of ISG15 could directly activate the type I interferon signaling pathway, and CXCL10 could directly activate the defense response to the virus signaling pathway.

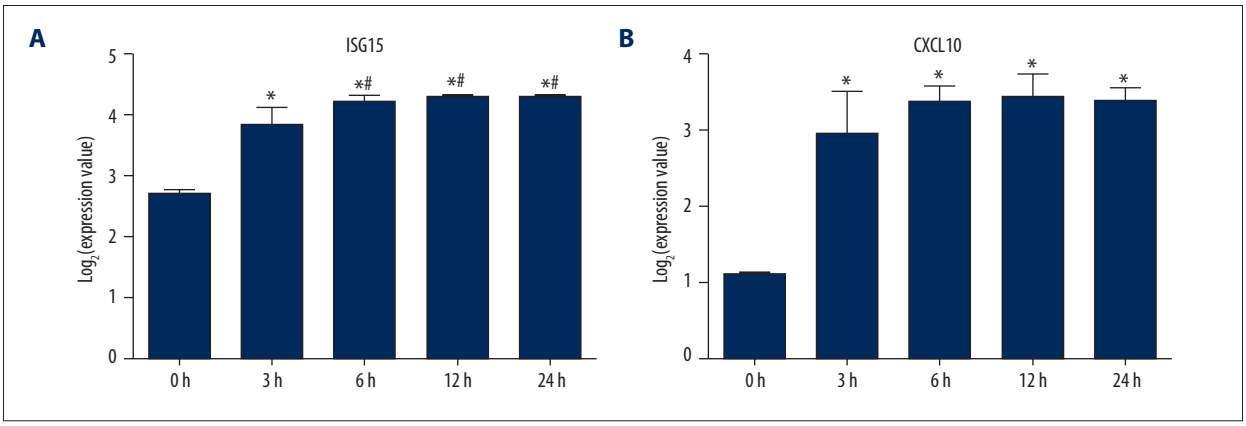

Figure 7. ISG15 and CXCL10 expression at different time points after CD14⁺ cell infection with MV virus. ISG15 and CXCL10 showed a significant increase after CD14⁺ cells were infected with MV, which suggested that elevated expression of the 2 key genes might activate the critical pathway in CD14⁺ cells against MV (A: * *vs.* 0 h: $P<0.05$, # *vs.* 3 h: $P<0.05$; B: * *vs.* 0 h: $P<0.05$).

CD14, the lipopolysaccharide (LPS) receptor, was initially a leukocyte differentiation antigen that existed on the surface of monocytes and macrophages. Experimental work involving the addition of LPS to the supernatant of endothelial cells cultured *in vitro* showed obvious endothelial cell activation with the addition of normal human serum (including sCD14) or recombinant human sCD14. This involved induction of the endothelial lymphocyte adhesion molecules, IL-1 and IL-6, along with other cytokines. In contrast, addition of anti-CD14 antibodies could inhibit activation of these cytokines [18–20]. Therefore, under the action of LPS, CD14 could mediate the cell reaction, and play an anti-inflammatory and antiviral role.

This study systematically analyzed the chip dataset, GSE980, to explore the mechanism of CD14 cells undergoing antiviral activity. Our study showed that compared with normal CD14 cells, the gene expression profiles of CD14 cells infected with MV were significantly changed, and the number of DEGs was significantly increased with longer infection times. Further analysis showed that the initial effects of CD14 cells against MV infection involved activation of the interferon I signaling and the antiviral response pathways. Our PPI analysis showed that the activation of these pathways was accomplished mainly by ISG15 and CXCL10. Our establishment of the gene-pathway interaction network further confirmed these findings.

The type I interferon pathway is a major component of natural immunity, and plays an important role in the process of controlling and scavenging pathogens. IRF3 is a key transcription factor of the interferon I pathway. The currently recognized major

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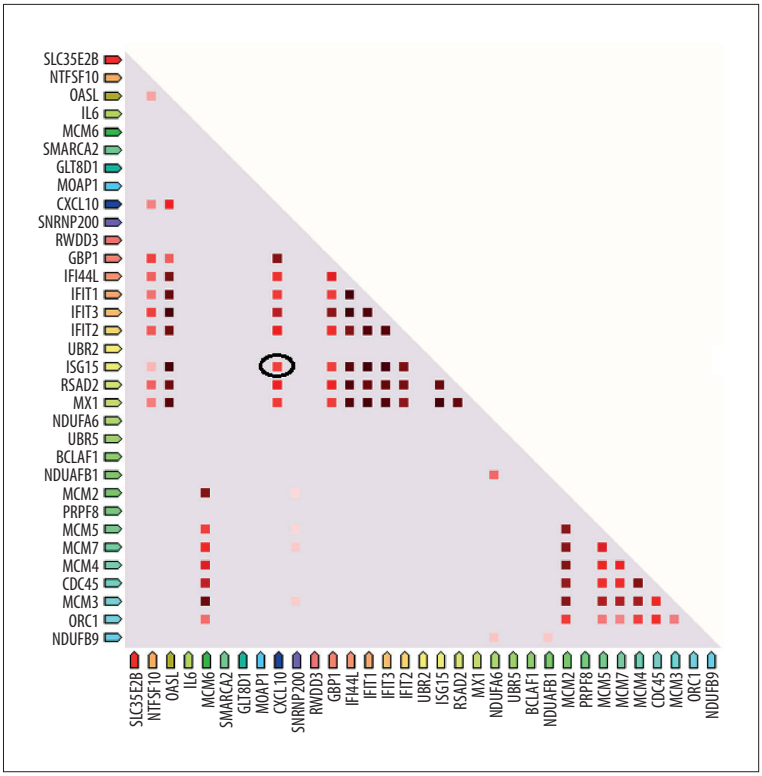

Figure 8. Co-expression relationship of ISG15 and CXCL10 in humans. The results showed that ISG15 and CXCL10 were co-expressed in humans.

mechanism for negative regulation of IRF3 is degradation of IRF3 protein caused by viral infection [21–23]. Other studies have reported that ISG15 enhanced the congenital antiviral response by inhibiting IRF3 degradation [24,25]. Experiments conducted *in vitro* showed that the signaling pathway involved in IRF3 could effectively activate and regulate the expression of the promoter region of CXCL10. The result being activation of the antiviral effect of the type I interferon pathway [26,27]. ISG15 is a 17 kDa protein secreted and encoded by the ISG15 gene in humans. ISG15 has antiviral activity that is tightly regulated by specific signaling pathways with a role in innate immunity. ISG15 was identified as an interferon stimulated gene (ISG) since its expression was induced in response to type I interferon or LPS treatment [28].

In this study, gene expression profiles in the infection and control groups were distinctly different in the initial 24 h, and the immune mechanism of the DCs against MV varied with infection time. The expression of the type I interferon signaling pathway along with the other key genes (ISG15 and CXCL10) are integral in the immune response's fight against MV of the DCs. As such, they provide a reference for the diagnosis and treatment of MV infection.

Conclusions

In conclusion, our findings explained, from a bioinformatics perspective, the potential immune mechanism of DCs in MV infection within the first 24 hours of infection, and suggested that key signaling pathways (such as type I interferon signaling pathway) and key genes (ISG15 and CXCL10) played an important role in the anti-infective process. Similar reports are still rare. These potential biomarkers will also enhance the early diagnosis and treatment of MV infection. Unfortunately, independent validation experiments were not carried out in this study. Therefore, more rigorous experiments will be designed and conducted to verify the above findings in our future studies.

Conflict of interests

None.

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Supplementary Tables

Supplementary Table 1. The 26 common DEGs.

AASDHPPT	MOAP1
ANP32A	MX1
BCLAF1	NDUFA6
CXCL10	OASL
GBP1	RSAD2
GLT8D1	RWDD3
IFI44L	SLC35E2B
IFIT1	SMARCA2
IFIT2	SNRNP200
IFIT3	TMEM56-RWDD3
IL6	TNFSF10
ISG15	UBR2
MCM6	UBR5

Supplementary Table 2. The results of GO functional enrichment analysis of 26 common DEGs.

Pathway ID	Pathway description	Count in gene set	False discovery rate	Founctional category
GO:0051607	Defense response to virus	11	6.51E-13	Biological process
GO:0060337	Type I interferon signaling pathway	7	6.47E-09	Biological process
GO:0071357	Cellular response to type I interferon	7	6.47E-09	Biological process
GO:0019221	Cytokine-mediated signaling pathway	10	4.41E-08	Biological process
GO:0045071	Negative regulation of viral genome replication	5	5.28E-06	Biological process
GO:0051707	Response to other organism	10	6.81E-06	Biological process
GO:0071345	Cellular response to cytokine stimulus	9	1.24E-05	Biological process
GO:0006955	Immune response	12	2.01E-05	Biological process
GO:0006270	DNA replication initiation	4	4.15E-05	Biological process
GO:0006271	DNA strand elongation involved in DNA replication	4	6.78E-05	Biological process
GO:0006268	DNA unwinding involved in DNA replication	3	0.000172	Biological process
GO:0032508	DNA duplex unwinding	4	0.000402	Biological process
GO:0006950	Response to stress	15	0.00122	Biological process
GO:0007166	Cell surface receptor signaling pathway	12	0.00122	Biological process
GO:0006952	Defense response	10	0.00198	Biological process
GO:0051704	Multi-organism process	12	0.00235	Biological process
GO:0071310	Cellular response to organic substance	11	0.00275	Biological process

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Pathway ID	Pathway description	Count in gene set	False discovery rate	Founctional category
GO:0002376	Immune system process	11	0.00515	Biological process
GO:0048523	Negative regulation of cellular process	15	0.00519	Biological process
GO:0045087	Innate immune response	8	0.00549	Biological process
GO:0044763	Single-organism cellular process	23	0.00975	Biological process
GO:0033160	Positive regulation of protein import into nucleus, translocation	2	0.0217	Biological process
GO:0000082	G1/S transition of mitotic cell cycle	4	0.0253	Biological process
GO:0035457	Cellular response to interferon-alpha	2	0.0253	Biological process
GO:0009967	Positive regulation of signal transduction	8	0.0438	Biological process
GO:0002830	Positive regulation of type 2 immune response	2	0.0478	Biological process
GO:0004386	Helicase activity	6	8.10E-05	Molecular function
GO:0003678	DNA helicase activity	4	0.000294	Molecular function
GO:0017111	Nucleoside-triphosphatase activity	8	0.00256	Molecular function
GO:0043168	Anion binding	12	0.0307	Molecular function
GO:0003688	DNA replication origin binding	2	0.0332	Molecular function
GO:0042555	MCM complex	4	3.20E-07	Cellular component

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