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Original Article

The role of mediator suppressor of cytokine signaling (SOCS), toll-like receptor 3 (TLR-3) and nuclear factor kappa B (NFκB) on cytokine production during dengue virus infection

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Abstract

Inability to understand the pathogenesis of severe dengue, in particular the control mechanism of immune responses, has led to high mortality rate for patients with dengue shock syndrome (DSS). The aim of this study was to determine the control mechanism of cytokine production by mediator suppressor of cytokine signaling (SOCS), toll-like receptor 3 (TLR-3) and nuclear factor kappa B (NFκB) during DENV infection. Peripheral blood mononuclear blood cells (PBMC), isolated from healthy individuals, were infected with dengue virus (DENV)-2 strain SJN-006 Cosmopolitan genotype (isolated from Bali, Indonesia). The relative gene expression of SOCS-3, TLR-3, NFκB, and the cytokine genes (interleukin (IL)-6, IL-8, interferon inducible protein 10 (IP-10), and macrophage inflammatory protein-1 beta (MIP-1β)) were measured using qRT-PCR at 6, 12 and 24 hours post infection (hpi). Student t-test and Mann-Whitney test were used to compare the gene expressions while causal correlations were analyzed using regression test and path analyses. DENV-2 infection increased the gene expression of SOCS-3, TLR-3, and NFκB after 12 and 24 hpi. The expression of IL-6, IL-8, IP-10, and MIP-1β genes was increased and peaked at different times post-infection. NFκB and SOCS-3 genes likely have role in the upregulation of IL-8 and IL-6 gene expression, respectively. MIP-1β gene expression was significantly induced by both NFκB and SOCS-3. In conclusion, our study suggested that SOCS-3, TLR-3, and NFκB are important in regulating the production of IL-6, IL-8, IP-10, MIP-1β during early phase of DENV-2 infection. This enriches our understanding on pathogenesis pathway of DENV-associated cytokine storm.

Keywords: Dengue, SOCS-3, TLR-3, NFκB, cytokine storm



Introduction

Since its first case reported in Indonesia in 1968, the incidence rate (IR) of dengue virus (DENV) infection keeps increasing in the country [1]. Globally, there are approximately 390 million dengue cases annually, of which 96 million are symptomatic [2]. DENV infection have a wide spectrum of disease, ranging from asymptomatic or a self-limiting dengue fever (DF) to life-threatening dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [3]. The mortality of DENV infection is mostly contributed from patients with DSS, which is 50 times higher than those without DSS [4]. Among four DENV serotypes (DENV-1 to -4), a meta-analysis study revealed that DENV-2 serotype is a significantly associated with DSS [4].

Clinical manifestation of DENV infection may be affected by variety of either exogenous or endogenous factors [5]. Complex interactions between DENV with innate or adaptive immunity has led to investigation on differential expression of cytokines such as interleukin (IL)-6, IL-8, interferon (IFN) inducible protein 10 (IP-10), and macrophage inflammatory protein-1 beta (MIP-1 β) and other soluble mediating factors such as suppressor of cytokine signaling 3 (SOCS-3), toll-like receptor 3 (TLR-3), and nuclear factor kappa B (NF κ B) [6-12].

Upon its attachment to the surface of a dendritic cell or macrophage, DENV will be recognized by TLRs, mainly TLR-3 and TLR-7, followed by retinoic acid-inducible gene-I-like receptors (RIG-1) or melanoma differentiation-associated gene-5 (MDA-5). This leads the activation of transcription factor, NF κ B, and regulating the production of cytokines as innate immune response. Host immune response to DENV generates a cascade of cytokine releases and it has been suggested as the primary contributor of increasing vascular permeability, followed by plasma leakage and abnormal bleeding in DENV infection [3]. In severe dengue, the levels of cytokines such as tumor necrosis factor (TNF)- α , IL-1 β , IL-6, IL-8, IL-10, IFN- γ , c-c motif chemokine ligand (CCL)-2, CCL-3, CXCL-8, CXCL-10, IP-10, MIP-1, and monocyte chemoattractant protein-1 (MCP-1) are increased [8, 14-16].

SOCS family proteins are attenuators of proinflammatory cytokines upon the generation of cytokine release cascade concomitant to host antiviral mechanism. Among the eight family members, SOCS-1 and SOCS-3 have been identified as potent inhibitors in Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathways [17, 18]. Previously, SOCS-1 is reported to be more potent inhibitor of JAKs compared to SOCS-3 [19]. However, a research on human immunodeficiency virus-1 (HIV-1)-infected cells suggests the JAK/STAT-free suppression of NF- κ B by SOCS-3, which is central for the inflammatory stimuli [20]. SOCS-3 also has been reported to have high selectivity against JAK-1, JAK-2 and tyrosine kinase (TYK)-2 [21]. Unfortunately, amidst these conflicting findings of its importance, SOCS-3 has been underreported for its role in the pathogenesis of DHF/DSS [10, 22-25]. The data on the role of SOCS-3 on regulation of cytokine production in DENV infection is lacking. The objective of this study was to assess the role of SOCS-3, TLR-3 and NF κ B in regulating the production of cytokines during the early course of DENV-2 infection in peripheral blood mononuclear cells (PBMC). Understanding on the regulation of proinflammatory cytokines through their regulators is important to have a better understanding on the pathogenesis of DHF or DSS. Therefore, the aim of this study was to determine the role of SOCS, TLR-3 and NF κ B in controlling cytokine production during the early phase of DENV infection.

Methods

Study design and the virus

An experimental study with randomized post-test control group design was used. Peripheral blood mononuclear blood cells (PBMCs) were collected from seven healthy volunteers (18-25 years old) and the PBMCs from each individual were divided into two groups: (1) infected with DENV strain SJN-006 of Cosmopolitan genotype (GenBank: KY006142.1) and (2) uninfected control. The virus originated from Bali and received from Eijkman Institute for Molecular Biology (now known as Eijkman Research Center for Molecular Biology), Jakarta, Indonesia. The virus was propagated in *Aedes albopictus* cells (C6/36) as described previously [15]. The titer of the virus was determined using plaque assay using baby hamster kidney cells (BHK21) as previously

used [26]. In the present study, the independent variable was DENV2 infection; the mediating variables were the gene expression of SOCS-3, TLR-3 and NFκB; while the dependent variables were the gene expression of IL-6, IL-8, IP-10, and MIP-1β. All gene expressions were measured using quantitative real time-polymerase chain reaction (qRT-PCR).

DENV-2 infection in PBMCs

PBMCs were infected at multiplicities of infection (MOI) of 1 plaque-forming units (pfu)/cell. Samples were then incubated at 37°C and 5% CO₂ for 6, 12, and 24 hours post infection (hpi), in parallel. PBMC-infected cells and the supernatant were harvested by centrifugation at 8,000 rpm and then stored at -80°C before used for RNA extraction, enzyme linked immunosorbent assays (ELISA) and qRT-PCR.

Detection of non-structural 1 protein (NS1) antigen using ELISA

To ensure the success of infection, the production of NS1 antigen in the culture supernatants were assayed using Panbio Dengue Early ELISA kit (Standard Diagnostics, Yongin, Korea), according to the manufacturer's protocol. In brief, after the supernatant from each well was incubated at 37°C for 1 h, the plate was washed and the horseradish peroxidase (HRP)-conjugated anti-NS1 monoclonal antibody (MAb) (100 μL) was added. The measurement of absorbance was conducted at 450 nm wavelength using a microplate photometer (Thermo Scientific, Waltham, USA).

Measurement of gene expression using qRT-PCR

The gene expression of SOCS-3, TLR-3, NFκB and the cytokines (IL-6, IL-8, IP-10, and MIP-1β) were measure using qRT-PCR. Briefly, 100 ng RNA was converted into a reverse transcription template – cDNA using GoScript Reverse Transcriptase, primer Oligo(dT), and random primer (Promega, Madison, USA). The reaction condition was maintained at 25°C for 5 min, 42°C for 60 min, and 70°C for 15 min. The amplification of the cDNA was carried out using 2x GoTaq qPCR master mix (Promega, Madison, USA) and 10 μM forward and reverse primers (Macrogen, Singapore). The endogenous gene, beta actin (β-actin), was used for normalization of gene expression. The detailed primer sequences are presented in **Table 1**.

Table 1. Primers used to determine the gene expression of mediator suppressor of cytokine signaling (SOCS), toll-like receptor 3 (TLR-3) and nuclear factor kappa B (NFκB) and cytokines using qRT-PCR

Gene	Sequence
SOCS-3-F	5'-CCTGCGCCTCAAGACCTT-3'
SOCS-3-R	5'-GTCAGTGGCTCCAGTAGAA-3'
TLR-3-F	5'-GATCTGTCTCATAATGGCTTGT-3'
TLR-3-R	5'-GGCAAAGATATCCAGTTCTCA-3'
NFκB-F	5'-CCTGGATGACTCTTGGGAAA-3'
NFκB-R	5'-TCAGCCAGCTGTTTCATGTC-3'
IL-6-F	5'-ATGAACTCCTTCTCCACAAGC-3'
IL-6-R	5'-CTACATTTGCCGAAGAGCCCTCAGGCTGGACTG-3'
IL-8-F	5'-TGCCAAGGAGTGCTAAAG-3'
IL-8-R	5'-CTCCACAACCCTCTGCAC-3'
IP-10-F	5'-TTCAAGGAGTACCTCTCTAG-3'
IP-10-R	5'-CTGGATTCAGACATCTCTCTC-3'
MIP-1β-F	5'-CTGTGCTGATCCCAGTGAATC-3'
MIP-1β-R	5'-TCAGTTCAGTTCAGGTCATAGA-3'
β-actin-F	5'-GCTCGTCTCGACAACGGCTC-3'
β-actin-R	5'-CAAACATGATCTGGGTCATCTTCTC-3'

Statistical analysis

Distribution of the data was tested with Kolmogorov-Smirnov normality test. Comparative analysis of gene expressions was conducted for each hpi observation using Student t-test and Mann-Whitney for normal and non-normal distribution, respectively. Correlation test, regression test, and path analysis were conducted to investigate the causal relationship between variables. Positive coefficient means direct correlation; while negative coefficient means inverse correlation. The correlation was classified as very weak (coefficient <0.1), weak (coefficient 0.10–0.49), moderate (coefficient 0.50–0.74), strong (coefficient 0.75–0.90), and very strong (coefficient ≥0.90).

Results

Effect of infection time on expression of SOCS-3, TLR-3, NFκB and cytokine genes

In this study, PBMCs from seven healthy volunteers were included and were divided into two infected and uninfected control groups. The gene expression of SOCS-3, TLR-3 and NFκB as well as the cytokines for both DENV-2 infected and control PBMC are presented in **Table 2**. The expression of SOCS-3, TLR-3, and NFκB were significantly higher in DENV-2-infected PBMCs at 6, 12 and 24 hpi compared to non-infected PBMCs at 6, 12 and 24 hpi.

The gene expression of IL-8, IP-10, and MIP-1β were significantly higher in DENV-2-infected group than non-infected PBMCs at 6, 12 and 24 hpi. IL-6 expression was only statistically significant at 12 hpi, where it was 1.86 times higher in infected PBMCs compared to uninfected cells (**Table 2**). The presence of DENV-2 in the culture was confirmed in all samples collected at different time points by the positive NS1 ELISA result (index value >1.1 or Panbio Unit >11).

Table 2. Gene expression of mediator suppressor of cytokine signaling (SOCS), toll-like receptor 3 (TLR-3), nuclear factor kappa B (NFκB) and cytokines after 6, 12, and 24 hours post infection (hpi) with DENV-2

Gene	Gene expression								
	6 hours post infection			12 hours post infection			24 hours post infection		
	Infected (± SD)	Control (± SD)	p-value	Infected (± SD)	Control (± SD)	p-value	Infected (± SD)	Control (± SD)	p-value
SOCS-3	1.529 ± 1.60	1.020 ± 0.28	0.613 ^b	2.421 ± 2.55	1.007 ± 0.43	0.006 ^a	2.196 ± 2.21	1.016 ± 0.48	0.041 ^a
TLR-3	0.906 ± 0.39	0.801 ± 0.29	0.215 ^b	1.453 ± 0.72	0.927 ± 0.31	0.026 ^a	2.629 ± 3.79	0.876 ± 0.32	0.007 ^a
NFκB	1.178 ± 0.62	0.899 ± 0.42	0.180 ^b	1.954 ± 1.06	0.986 ± 0.25	0.003 ^b	12.32 ± 23.05	1.018 ± 0.30	0.00 ^a
IL-6	0.976 ± 0.58	1.035 ± 0.30	0.505 ^a	1.650 ± 1.43	0.889 ± 0.28	0.013 ^a	1.816 ± 1.74	0.982 ± 0.48	0.395 ^a
IL-8	1.407 ± 0.55	0.855 ± 0.51	0.011 ^b	2.984 ± 1.84	0.906 ± 0.47	0.000 ^a	8.993 ± 10.02	1.091 ± 0.63	0.00 ^a
IP-10	7.776 ± 12.56	0.940 ± 0.33	0.009 ^a	37.316 ± 52.97	0.968 ± 0.45	<0.001 ^a	301.16 ± 333.60	1.018 ± 0.42	<0.001 ^a
MIP-1β	1.504 ± 0.52	0.951 ± 0.20	0.001 ^b	3.176 ± 2.98	1.034 ± 0.20	<0.001 ^a	7.761 ± 7.17	0.899 ± 0.46	0.001 ^b

^a Analyzed using Mann-Whitney test

^b Analyzed using Student t-test

Correlation between DENV-2 infection and expression of SOCS-3, TLR-3, NFκB and cytokine genes

Correlations between independent variable (DENV-2 infection), mediating variables (SOCS-3, TLR-3, NFκB) and dependent variables (IL-6, IL-8, IP-10, and MIP-1β) are presented in **Table 3**. Significant correlations at 6 hpi were observed between infection → IL-8 (moderate), infection → IP-10 (weak), and infection → MIP-1β (moderate), SOCS-3 → IL-6 (weak), SOCS-3 → MIP-1β (weak), NFκB → IL-8 (moderate), and NFκB → MIP-1β (weak) (**Figure 1**).

After 24 h post infection, there were significant correlations between infection → SOCS-3 (weak), infection → TLR-3 (weak), infection → NFκB (weak), infection → IL-8 (moderate), infection → IP-10 (moderate), infection → MIP-1β (moderate), SOCS-3 → IL-6 (strong), SOCS-3 → MIP-1β (strong) (**Figure 1**).

Discussion

Our data suggest that the expression of SOCS-3, TLR-3, NFκB, IL-8, IL-6, IP-10, and MIP-1β were higher in the DENV-2 infected cells than in control. It was similar to the previous studies [6, 8-11]. DENV infection induced the expression or secretion of IL-8 through at least three mechanisms: non-structural protein (NS) 5 hyperphosphorylation of DENV-2 [7], recognition of DENV RNA by TLR-3 [27], and interaction between activator protein-1 (AP-1) and NFκB or c/EBP [28, 29]. Overexpression of IL-8 and IL-6 might be associated with the manifestation of DENV infection, where their consistent increment upon infection time is linked to the severity of

the disease [6, 7]. SOCS-3, TLR-3, NFκB, IP-10, and MIP-1β also had similar trend and have been suggested as biomarker for the severity [8-11] and acute stage of DENV infection [12].

Table 3. Results of causality test of DENV-2 infection on gene expression of mediator suppressor of cytokine signaling (SOCS), toll-like receptor 3 (TLR-3), nuclear factor kappa B (NFκB) and cytokines

Variable	6 hours post infection		12 hours post infection		24 hours post infection	
	b/η	p-value	b/η	p-value	b/η	p-value
Infection → SOCS-3	NA	NA	0.390	0.006*	0.377	0.041*
Infection → TLR-3	0.155	0.430	0.461	0.026*	0.322	0.007*
Infection → NFκB	NA	NA	0.627	0.003*	0.440	<0.001*
Infection → IL-6	NA	NA	0.364	0.013*	NA	NA
Infection → IL-8	0.554	0.011*	0.666	<0.001*	0.509	0.004*
Infection → IP-10	0.422	0.009*	0.460	<0.001*	0.560	<0.001*
Infection → MIP-1β	0.661	0.001*	0.486	<0.001*	0.577	0.001*
SOCS-3 → IL-6	0.402	0.028*	1.000	<0.001*	0.754	<0.001*
SOCS-3 → IL-8	0.190	0.189	0.017	0.880	0.032	0.850
SOCS-3 → IP-10	-0.169	0.389	0.191	0.329	0.185	0.345
SOCS-3 → MIP-1β	0.367	0.037*	0.814	<0.001*	0.798	<0.001*
NFκB → IL-6	0.229	0.194	0.032	0.612	0.156	0.234
NFκB → IL-8	0.529	0.001*	0.499	0.001	0.219	0.295
NFκB → IP-10	0.300	0.121	0.264	0.174	0.103	0.604
NFκB → MIP-1β	0.349	0.026*	0.133a	0.261	0.049	0.664
TLR-3 → NFκB	0.031	0.875	0.224	0.252	-0.065	0.743

The arrow indicates the causal relationship between variables.

*Statistically significant at $p=0.05$.

We suspect TLR-3 to be suppressed at the early stage of infection (6 hpi) because the significant difference was observed only afterward. The suppression of TLRs (including TLR-3) is also exhibited by hepatitis C virus in HepG-2 cells [30]. Similarly, DENV infection downregulates TLRs expression during the entry of DENV into monocytes via Fc receptor [31]. Significant correlation between DENV infection and TLR-3 was observed at 12 and 24 hpi, which corresponds to the significant increase of its expression.

Direct induction of MIP-1β by DENV-2 in PBMC has been previously reported; deduced from the absence of correlation between MIP-1β and other possible mediating factors [32]. Nonetheless, our data suggest the correlation between MIP-1β induction with NFκB and SOCS-3. Correlation between NFκB and MIP-1β that was identified in our study, in line with the previous study in hepatocytes, in which NFκB silencing yields to downregulation of MIP-1β mRNA [33]. Furthermore, SOCS-3-induced NFκB expression has been reported by a study using influenza A virus-infected A549 cells [34]. Hence, it contributes to the strong correlation between SOCS-3 and MIP-1β.

Upon infection, IP-10 is induced by IFN-γ and produced by multiple cell types (endothelial cells, monocytes, keratinocytes, and dendritic cells) as innate immune response [35, 36]. Along with MIP-1β, IP-10 plays a key role in the recruitment of leukocytes at the DENV-infected tissues or organs [32, 37-39]; explaining their significant correlations with the infection. Additionally, it was further found that IP-10 limits the viral replication through competitive binding to heparan sulphate on the cell surface [39].

In line with the results of our study, upregulation of SOCS-3 expression is a common viral resistance mechanism against host immune response that inhibits JAK/STAT pathway [40]. A study using DENV-antibody-dependent enhancement (ADE)-infected macrophages revealed the role of IL-6 in SOCS-3 induction [22]. Correlation between infection and IL-6 can be explained through the upregulation of IL-6 by DENV NS1 through TLR-2 and TLR-6 expressions [41]. The correlation was recorded at 12 hpi, when the IL-6 expression was significantly higher than control. At the same time, SOCS-3 was at the peak of expression; further confirming IL-6-mediated SOCS-3 induction.

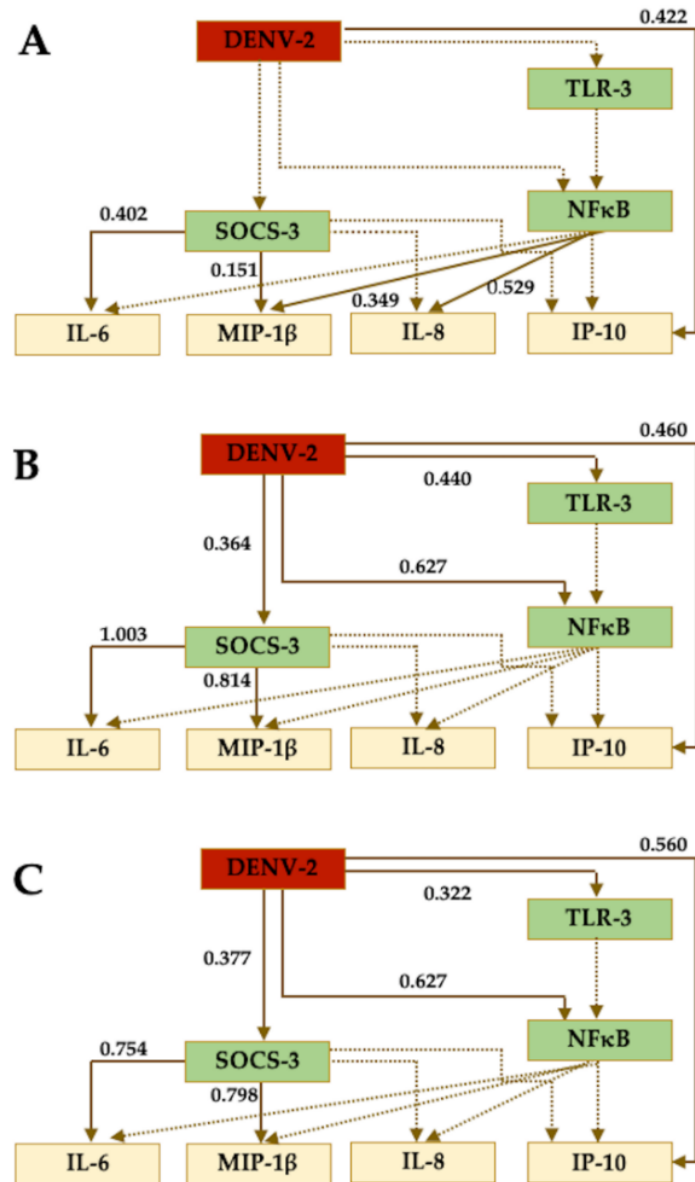


Figure 1. Proposed regulatory pathways of SOCS-3, TLR-3 and NFκB in regulation of cytokines during DENV-2 infection in 6 (A), 12 (B) and 24 hours (C) post-infection. The numbers are the co-efficient of the significant correlations. Continuous lines indicate significant correlation at $p < 0.05$ while dashed-lines indicate non-significant correlation. Coefficient < 0.1 (very weak), $0.10-0.49$ (weak), $0.50-0.74$ (moderate), $0.75-0.90$ (strong), and ≥ 0.90 (very strong).

There are some limitations of this study. The gene expressions of SOCS-3, TLR-3, NFκB and the cytokines were measured using qRT-PCR. Since there is post-transcriptional attenuation phenomenon in which not all the mRNA will be translated into protein, a study to measure both RNA and the protein concentration will provide better evidence. In this present study, only one serotype was used, DENV-2. The effects of other DENV serotypes might also worth to be assessed.

Conclusion

DENV-2 infection induces the overexpression of SOCS-3, TLR-3, NFκB, IL-6, IL-8, IP-10, and MIP-1β. SOCS-3 involved in the dysregulation of IL-6 and MIP-1β; while NFκB involved in induction of IL-8 and MIP-1β. Further studies are required to confirm the proposed and reveal other feasible mechanisms.

Ethics approval

The protocol of this study was approved by Ethical Review Boards of Universitas Udayana (No. 2072/UN.14.2/KEP/2017). All PBMC donors were voluntarily required to sign informed consent prior to the study.

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Conflicting of interest

All the authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results can be requested from the corresponding author (SM).

How to cite

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