# Correlation of miR-150

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# Correlation of miR-150, hsa-let-7e, and miR-146a and gene expression of *IL-6*, *IL-8*, *IP-10*, and *MIP-1β* during dengue virus infection

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## Abstract

Growing evidence suggests that microRNAs (miRNAs) play a pivotal role in viral infection. The objective of this study was to assess the association between the expression of miR-150, hsa-let-7e, and miR-146a on cytokine expression during dengue infection. Dengue virus (DENV) strain SJN-006, a serotype 2 DENV strain of the Cosmopolitan genotype, isolated in Bali, Indonesia, was used to infect peripheral blood mononuclear cells (PBMCs) isolated from healthy individuals. The relative gene expressions of miR-150, hsa-let-7e, and miR-146a as well as the gene expression of cytokines (*IL-6, IL-8, IP-10,* and *MIP-1β*) were determined using quantitative real time - polymerase chain reaction (qRT-PCR) at 6, 12 and 24 hours post infection (hpi). Correlations between the microRNAs and cytokines were analyzed by means of causality tests. Our data suggests that miR-150 and hsa-let-7e were significantly higher in infected-PBMCs after 12 hpi compared to the uninfected-PBMCs ($p<0.05$). The causality tests demonstrated that miR-150 and hsa-let-7e were negatively correlated with *IL-8* expression, meanwhile miR-146a was the contrast. DENV infection was negatively and positively correlated with miR-150 and hsa-let-7e, respectively, after 24 hpi. In conclusion, our data demonstrates the vital role of miR-150, hsa-let-7e, and miR-146a in regulating *IL-8* expression with possible different pathways.

**Key words**: dengue, microRNA, miR-150, hsa-let-7e, miR-146a

## Introduction

Dengue fever (DF), caused by dengue virus (DENV) infection, is a global concern with 390 million cases reported each year [1]. DENV is a positive-strand RNA virus of the *Flaviviridae* family and there are four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) [2]. The severity of the disease varies from asymptomatic infection, dengue hemorrhagic fever (DHF) to dengue shock syndrome (DSS) with the mortality rate of DSS being potentially 50 times higher than DHF

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[3]. A systematic review found that the severity of DF is significantly higher in DENV-2 compared to other serotypes [4].

DHF and DSS are strongly correlated with the overexpression of an array of proinflammatory cytokines. The cascade of cytokine signaling is initiated by the recognition of pathogen-associated molecular patterns (PAMPs) by toll-like receptors (TLRs), followed by the activation of the transcription factor, nuclear factor kappa B (NFκB). The overexpression of proinflammatory cytokines leads to increased vascular permeability, plasma leakage and eventually abnormal bleeding [5]. Currently, there have been massive efforts in the scientific community to characterize the pathogenesis of cytokine-facilitated severe dengue and the involvement of microRNAs (miRNAs).

miRNAs are ubiquitously non-coding RNAs with a size of 18-25 nucleotides and play a vital role in a wide range of biological activities [6]. Recently, miRNAs have been noted to play a key role in immune regulation by inhibiting protein translation or by degrading the mRNA transcripts [7]. Several miRNAs were revealed to downregulate proinflammatory cytokines by directly binding to the 3′-untranslated region (UTR) of target mRNAs resulting in translation blockage or mRNA degradation [7]. miRNAs are also known to bind 5'-UTR of the mRNA which affects the post-transcriptional process [8]. In contrast to mRNA silencing, miRNA may induce proinflammatory cytokines by means of epigenetic modification [9]. Specific miRNAs may downregulate epigenetic regulators, such as histone deacetylases, DNA methyltransferases and polycomb-group genes [10]. Interestingly, in dengue infection, human miRNAs such as miR-21 [11] and miR-146a [12] may be hijacked by the virus to support viral replication.

Previously, we investigated the changes of expression levels of hsa-let-7e, miR-30e*, miR-150, miR-146a, and hsa-miR-4290 using peripheral blood mononuclear cells (PBMCs) infected with DENV-2 [13]. The results revealed that miR-150, hsa-let-7e and miR-146a expression was elevated to 1.74, 1.49, and 2 times at 12 hours post-infection (hpi). miR-150 has been reported to affect the expression of a major immune response inducer and modulator, interferon gamma (IFN)-γ, by regulating suppressor of cytokine signaling 1 (SOCS-1) [14]. hsa-let-7e has also been reported to play a significant role in DF pathogenesis by regulating TNFα via enhancer of zeste homolog 2 (EZH2) [15]. The host proviral miR146a may suppress *IFN-β* expression to support viral replication [16]. We further investigated the correlation between miR-150, hsa-let-7e and miR-146a expression and the gene expression of *IL-6*, *IL-8*, *IP-10*, and *MIP-1β*. These cytokines have been widely suggested to contribute to DF and DHF pathogenesis [17-20], in particular IL-6 and IL-8, which are responsible for increased vascular permeability [21, 22].

## Materials and Methods

### Infection of PBMCs with DENV-2

The PBMC samples were isolated from healthy volunteers aged 18-25 years. The virus used, SJN-006 (GenBank: KY006142.1), was a DENV-2, Cosmopolitan genotype strain isolated from Bali, Indonesia [23]. The virus was propagated in C6/36 cells, based on a previously published protocol [24] with the titer determined by plaque assay employing baby hamster kidney cells (BHK21) [25].

PBMCs were infected with DENV-2 at multiplicities of infection (MOI) of 1, and incubated for a variation of infection times from 6, 12, to 24 hpi, in parallel. To confirm that the infection had been successful, NS1 antigen produced in the culture supernatant was assayed using the Panbio Dengue Early ELISA Kit (Panbio Diagnostics). The infected PBMCs were separated from supernatant and stored at -80°C for further use.

### Measurement of gene expression using qRT-PCR

The expression of miRNAs (miR-150, hsa-let-7e, and miR-146a) as well as *IL-6*, *IL-8*, *IP-10*, and *MIP-1β* were quantified using quantitative real-time RT-PCR (qRT-PCR). For miRNAs, RNA extraction was conducted using the miRCURY RNA Isolation Kit (Exiqon and its concentration was determined using Qubit RNA BR Assay Kit (Invitrogen). The cDNA synthesis step was performed using the Universal cDNA Synthesis Kit II (Exicon). To quantify gene expression, 100ng RNA was converted into a reverse transcription template – cDNA using GoScript Reverse Transcriptase, random primer (Promega), and primer Oligo(dT). The reaction temperatures were

adjusted at 25, 42, and 70°C, respectively for 5, 60, and 15 minutes. The cDNA amplification was conducted using 2x GoTaq qPCR master mix (Promega) with 10 µM forward and reverse primers (Macrogen) (**Table 1**). The gene expression of miRNAs was semi-quantified based on $2^{-[Ct(miRNA)-Ct(U6b)]}$ with an endogenous gene – snRNA U6 [9, 14] while the gene expressions of *IL-6*, *IL-8*, *IP-10*, and *MIP-1β* were normalized with endogenous gene - beta actin (β-actin).

Table 1. Primers used to determine the expression of miRNAs and cytokine genes using qRT-PCR

| Gene | Primer sequence |
|---|---|
| snRNA U6 | Forward: 5' CCCTGCGCAAGGATGAC-3' |
| | Reverse: 5'-GTCGGTGTCGTGGAGTCG-3' |
| miRNA-150e-5p | Forward: 5'-UCUCCCAACCCUUGUACCAGUG-3' |
| | Reverse: 5'-GGGGUUGGGGGAAGGGUUGGA-3' |
| hsa-let-7e | Forward:5'-GGGTGAGGTAGGAGGTTGTAT-3, |
| | Reverse: 5'-GTCGGTGTCGTGGAGTCGGTTAA-3', |
| miRNA-146a | Forward: 5'-UGAGAACUGAAUUCCAUGGGUU-3 |
| | Reverse:5'-AGCAGTGAGAACTGAATTCCATT-3 |
| *IL-6* | Forward: 5'-ATGAACTCCTTCTCCACAAGC-3' |
| | Reverse: 5'-CTACATTTGCCGAAGAGCCCTCAGGCTGGACTG-3' |
| *IL-8* | Forward: 5'-TGCCAAGGAGTGCTAAAG-3' |
| | Reverse: 5'-CTCCACAACCCTCTGCAC-3' |
| *IP-10* | Forward: 5'-TTCAAGGAGTACCTCTCTCTAG-3' |
| | Reverse: 5'-CTGGATTCAGACATCTCTTCTC-3' |
| *MIP-1β* | Forward: 5'-CTGTGCTGATCCCAGTGAATC-3' |
| | Reverse: 5'-TCAGTTCAGTTCCAGGTCATAGA-3' |
| β-actin | Forward: 5'-GCTCGTCGTCGACAACGGCTC-3' |
| | Reverse: 5'-CAAACATGATCTGGGTCATCTTCTC-3' |

### Statistical analysis

Distribution of the data was analyzed using Kolmogorov-Smirnov normality test. Gene expression data, with normal and non-normal distribution were comparatively analyzed using *t*-test and Mann-Whitney, respectively, at each infection time. The causal relationships were investigated with path analysis, correlation test, and regression tests. Direct correlation was represented by positive values, meanwhile an inverse correlation was represented by negative values.

## Results

### Effect of infection time against the expression of miRNAs

Expression levels of miRNAs in infected and control PBMCs are presented in **Table 2**. The relative expression of miR-150, hsa-let-7e and miR-146a were not significantly different within 6 and 12 hpi. The expression of miR-150 and hsa-let-7e were significantly lower in infected PBMCs compared to healthy PBMCs, 0.820 ± 0.312 *vs.* 1.077 ± 0.320 and 1.000 ± 0.932 *vs.* 1.016 ± 0.178, respectively.

### Correlation between DENV-2 infection and gene expression of miRNAs and cytokines

Correlations between DENV-2 infection and the relative expression of miRNAs (miR-150, hsa-let-7e, and miR-146a) and cytokine genes (*IL-6*, *IL-8*, *IP-10*, and *MIP-1β*) are presented in **Table 3**. Significant, but weak, inverse correlations between miR-150 and *IL-8* was found at 6 hpi (b=-0.396, p=0.011). However, this correlation was no longer found to be significant later in infection (i.e., at 12 and 24 hpi). At 12 h after infection, there was a significant correlation between miR-146a and *IL-8* expression (b=0.459, p=0.002). At 24 hpi, there was a weak negative correlation between miR-146a expression and *MIP-1β* expression with b=-0.264 and p=0.023. There was also a moderate correlation between hsa-let-7e expression and *IL-8* expression (b=0.551 and p=0.002).

Table 2. Expression of miRNAs and cytokine genes after 6, 12, and 24 hours post infection (hpi)

| MicroRNA | 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 |
| miR-150 | 0.954 ± 0.368 | 1.634 ± 1.530 | 0.323[a] | 1.178 ± 0.350 | 0.991 ± 0.280 | 0.139[b] | 0.820 ± 0.312 | 1.077 ± 0.320 | 0.043[a,*] |
| hsa-let-7e | 1.152 ± 0.453 | 1.030 ± 0.241 | 0.383[b] | 1.034 ± 0.279 | 1.161 ± 0.455 | 0.629[a] | 1.000 ± 0.932 | 1.016 ± 0.178 | 0.048[a,*] |
| miR-146a | 1.049 ± 0.392 | 1.047 ± 0.386 | 0.988[b] | 1.685 ± 1.613 | 0.934 ± 0.158 | 0.646[a] | 0.790 ± 0.375 | 1.029 ± 0.302 | 0.074[b] |

[a] Analyzed using Mann-Whitney test
[b] Analyzed using Student t-test
*Statistically significant at p=0.05

Table 3. Correlation of DENV-2 infection, expression of miRNAs and expression of cytokine genes at 6, 12, and 24 hours post infection (hpi)

| Correlation | 6 hours post infection | | 12 hours post infection | | 24 hours post infection | |
|---|---|---|---|---|---|---|
| | b coefficient [a] | p-value [b] | b coefficient [a] | p-value [b] | b coefficient | p-value [b] |
| DENV-2 infection → miR-150 | -0.303 | 0.117 | 0.287 | 0.139 | -0.389 | 0.041* |
| DENV-2 infection → hsa-let-7e | 0.171 | 0.383[c] | -0.171 | 0.383c | 0012 | 0.048[b,*] |
| DENV-2 infection → miR-146a | 0.003 | 0.988 | 0.322 | 0.095 | -0.343 | 0.074 |
| miR-150 expression → *IL-6* expression | 0.331 | 0.067 | 0.004 | 0.952 | -0.066 | 0.623 |
| miR-150 expression → *IL-8* expression | -0.396 | 0.011* | 0.123 | 0.360 | -0.200 | 0.280 |
| miR-150 expression → *IP-10* expression | -0.087 | 0.661 | -0.026 | 0.896 | -0.092 | 0.642 |
| miR-150 expression → *MIP-1β* expression | -0.217 | 0.205 | -0.016 | 0.911 | -0.066 | 0.583 |
| hsa-let-7e expression → *IL-6* expression | -0.029 | 0.883 | -0.086 | 0.090 | 0.212 | 0.102 |
| hsa-let-7e expression → *IL-8* expression | -0.080 | 0.612 | -0.193 | 0.076 | 0.551 | 0.002* |
| hsa-let-7e expression → *IP-10* expression | 0.017 | 0.932 | -0.085 | 0.666 | -0.107 | 0.587 |
| hsa-let-7e expression → *MIP-1β* expression | 0.140 | 0.418 | 0.007 | 0.952 | -0.033 | 0.771 |
| miR-146a expression → *IL-6* expression | 0.228 | 0.233 | -0.108 | 0.038 | -0.120 | 0.361 |
| miR-146a expression → *IL-8* expression | 0.054 | 0.739 | 0.459 | 0.002* | -0.211 | 0.210 |
| miR-146a expression → *IP-10* expression | 0.042 | 0.832 | -0.024 | 0.903 | -0.142 | 0.472 |
| miR-146a expression → *MIP-1β* expression | -0.045 | 0.794 | -0.025 | 0.837 | -0.264 | 0.023* |

[a] Path coefficient, very weak if <0.1; weak if 0.10≥ b <0.50; moderate if 0.50 ≤ b < 0.75; strong if 0.75 ≤ b < 0.90; and very strong if b ≥ 0.90
[b] Otherwise stated, all analyses conducted using a linear regression
[c] Analyzed using Mann-Whitney test
*Statistically significant at p=0.05

## Discussion

Cytokine expression has been suggested to be a good predictor of DENV disease development, since disease pathogenesis is based on the dysregulation of cytokines [17-21]. Some interesting findings have suggested the important role of miRNAs in DENV infection and are potentially to be screened to identify suitable miRNAs as DENV biomarkers [26, 27].

### miR-150

A study has highlighted the critical role of miR-150 in the pathogenesis of DENV diseases by regulating the expression of SOCS-1 [14]. We observed the significant reduction of miR-150 in the infected PBMCs after 24 hpi. Previously, the expression of miR-150 was significantly higher in DENV2-infected peripheral blood cells of patients with DHF compared to those with DF [28]. A similar trend was also observed in another study using DENV2-infected PBMCs after 24 hpi [14]. A study based on A/H1N1 infection revealed that the upregulation of miR-150 did not occur in patients with moderate illness; only in those with severe illness [29]. Additionally, screening of miRNA from blood samples of sepsis patients revealed a reduction of miR-150 in peripheral blood leukocytes [30, 31], and was found to be correlated with pro-inflammatory cytokines [31]. Our study substantiates the potential of miR150 as a biomarker for the development and progression of DENV infection.

The suppression of miR-150 has been reported to be due to the DNA hypermethylation of its promoter, based on a study using piglet livers treated with 2-hydroxy-(4-methylthio) butanoic acid [32]. Gene expression involving miR-150 is possibly regulated via epigenetic modification [33]. Our study suggests the potential role of miR-150 as a negative regulator for *IL-8* expression. Suppression of *IL-8* by SOCS-3 has been reported in multiple reported cases of inflammation [34-36]. It is further corroborated by the results of the previous investigation, that revealed SOCS-1 mRNA as a hypothetical gene target of miR-150 that reduces the expression of *IFN-γ* gene [14].

### hsa-let-7e

As a biomarker, the hsa-let-7 miRNA family is most notable for cancer and tumor diagnosis and prognosis [37]. Recently, hsa-let-7i is among the potent therapeutic molecules used against SARS-CoV-2 infection, targeting host angiotensin-converting enzyme 2 (ACE-2) [38]. In the case of DENV infection, hsa-let-7c has been found to be overexpressed in infected human hepatoma Huh-7 cells [39]. A previous study also found different levels of hsa-let-7e expression in DENV-infected PBMCs [9]. Nonetheless, the hsa-let-7e was upregulated only at the second and fourth day after the fever onset and downregulated at the third day [28]. The regulation pattern of hsa-let-7e is similar to our finding and our previously reported preliminary study [40]. Although after 24 hpi the expression level of hsa-let-7e was significantly lower, a further investigation is required regarding its differential expression.

It is reported that hsa-let-7e may interact with EZH2, which eventually initiates the inhibition of TNFα [15]. EZH2 is an epigenetic regulator with a critical role in histone methylation in downstream genes. *NFκB* was speculated to be downregulated by the EZH2-induced inhibition of NFκB activation [15]. In this regard, *IL-8* can also be suppressed by hsa-let-7e since NFκB mediates the activity of *IL-8* promoter [41]. Furthermore, a study reported the role of EZH2 in downregulating *TNFα*, *IFN-β*, and *IL-8* during influenza A virus (IAV) strain A/WSN/33 (WSN) virus infection [42]. In the present study, our data demonstrates the possible downregulation of *IL-8* by hsa-let-7e after 24 hpi.

### miR-146a

Although, the expression of miR-146a in DENV-2-infected PBMCs was not significantly different to the control PBMCs miR-146a has been reported to be one of the only two known human pro-DENV miRNAs [16]. A previous study found that miR-146a was upregulated in THP-1 cells and primary monocyte cells, targeting tumor necrosis factor receptor-associated factor 6 (TRAF-6) and consequently suppressed *IFN-β* [16]. The exploitation of miR-146a is not unique to DENV infection and is observed in vesicular stomatitis virus infection by similarly targeting TRAF-6 and several other innate immune-related molecules [12].

Our data suggests the possibility of miR-146a to indirectly downregulate the expression of *MIP-1β*, that is induced by signal transducers and activators of transcription 1 (STAT-1) pathway [43]. This is further substantiated by the findings of a previous study [44] where IFN regulatory factor 5 and STAT-1 were shown to be the possible gene target of miR-146a.

## Conclusion

The expression of miR-150 and hsa-let-7e were significantly lower in DENV-2 infected PBMCs compared to the uninfected PBMCs after 24 hpi. Our data suggest that the expression of proinflammatory cytokine IL-8 is associated with miR-150, has-let-7e and miR-146a. Therefore, further investigations are required to elucidate the regulation pathways.

## Declarations

### Ethics approval

The approval of the research protocol was granted by Ethical Review Boards of Universitas Udayana (No. 2072/UN.14.2/KEP/2017). All PBMC donors signed the informed consent prior to the enrolment.

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### Conflict of interest

The authors declare that they have no competing interests.

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## References

1. Bhatt S, Gething PW, Brady OJ *et al.* The global distribution and burden of dengue. Nature 2013; 496(7446):504-507.
2. Holmes EC. Molecular epidemiology and evolution of emerging infectious diseases. Br Med Bull 1998;5 4(3):533-543.
3. WHO. Handbook for Clinical Management of Dengue. Geneva, Switzerland: WHO Press; 2012.
4. Huy NT, Van Giang T, Thuy DH *et al.* Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS Negl Trop Dis 2013; 7(9):e2412.
5. Srikiatkhachorn A, Mathew A, Rothman AL. Immune-mediated cytokine storm and its role in severe dengue. Semin Immunopathol 2017; 39(5):563-574.
6. An JH, Ohn JH, Song JA *et al.* Changes of microRNA profile and microRNA-mRNA regulatory network in bones of ovariectomized mice. J Bone Miner Res 2014; 29(3):644-656.
7. Gracias DT, Katsikis PD. MicroRNAs: key components of immune regulation. Adv Exp Med Biol 2011; 780:15-26.
8. Gu W, Xu Y, Xie X *et al.* The role of RNA structure at 5' untranslated region in microRNA-mediated gene regulation. RNA 2014; 20(9):1369-1375.
9. Qi Y, Li Y, Zhang L *et al.* microRNA expression profiling and bioinformatic analysis of dengue virus infected peripheral blood mononuclear cells. Mol Med Rep 2013; 7(3):791-798.
10. Sato F, Tsuchiya S, Meltzer SJ *et al.* MicroRNAs and epigenetics. FEBS J 2011; 278(10):1598-1609.

11. Kanokudom S, Vilaivan T, Wikan N *et al.* miR-21 promotes dengue virus serotype 2 replication in HepG2 cells. Antiviral Res 2017; 142:169-177.
12. Hou J, Wang P, Lin L *et al.* MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. J Immunol 2009; 183(3):2150-2158.
13. Masyeni S, Hadi U, Kuntaman K *et al.* Profiling of microRNA expression within the cells of peripheral blood mononuclearafter an infection with serotype-2 of dengue virus: preliminary study. Biomed Pharmacol J 2018; 11(2):923-927.
14. Chen RF, Yang KD, Lee IK *et al.* Augmented miR-150 expression associated with depressed SOCS1 expression involved in dengue haemorrhagic fever. J Infect 2014; 69(4):366-374.
15. Zhang Y, Zhang Q, Gui L *et al.* Let-7e inhibits TNF-alpha expression by targeting the methyl transferase EZH2 in DENV2-infected THP-1 cells. J Cell Physiol 2018; 233(11):8605-8616.
16. Wu S, He L, Li Y *et al.* miR-146a facilitates replication of dengue virus by dampening interferon induction by targeting TRAF6. J Infect 2013; 67(4):329-341.
17. Patro ARK, Mohanty S, Prusty BK *et al.* Cytokine signature associated with disease severity in dengue. Viruses 2019; 11(1):34.
18. Bozza FA, Cruz OG, Zagne SM *et al.* Multiplex cytokine profile from dengue patients: MIP-1beta and IFN-gamma as predictive factors for severity. BMC Infect Dis 2008; 8:86.
19. Flores-Mendoza LK, Estrada-Jimenez T, Sedeno-Monge V *et al.* IL-10 and SOCS3 are predictive biomarkers of dengue hemorrhagic fever. Mediators Inflamm 2017:5197592.
20. Balakrishna Pillai A, Cherupanakkal C, Immanuel J *et al.* Expression pattern of selected toll-like receptors (TLR's) in the PBMC's of severe and non-severe dengue cases. Immunol Invest 2020; 49(4):443-452.
21. Butthep P, Chunhakan S, Yoksan S *et al.* Alteration of cytokines and chemokines during febrile episodes associated with endothelial cell damage and plasma leakage in dengue hemorrhagic fever. Pediatr Infect Dis J 2012; 31(12):e232-238.
22. Medin CL, Fitzgerald KA, Rothman AL. Dengue virus nonstructural protein NS5 induces interleukin-8 transcription and secretion. J Virol 2005; 79(17):11053-11061.
23. Megawati D, Masyeni S, Yohan B *et al.* Dengue in Bali: Clinical characteristics and genetic diversity of circulating dengue viruses. PLoS Negl Trop Dis 2017; 11(5):e0005483.
24. Yohan B, Kendarsari RI, Mutia K *et al.* Growth characteristics and cytokine/chemokine induction profiles of dengue viruses in various cell lines. Acta Virol 2014; 58(1):20-27.
25. Warnasih S. Induksi ekspresi gen sitokin/kemokin pada sel makrofag manusia yang dipapar virus dengue isolat Indonesia. Current Biochemistry 2014; 1(3):146-157.
26. Tambyah PA, Ching CS, Sepramaniam S *et al.* microRNA expression in blood of dengue patients. Ann Clin Biochem 2016; 53(Pt 4):466-476.
27. Chen X, Liu MX, Yan GY. RWRMDA: predicting novel human microRNA-disease associations. Mol Biosyst 2012; 8(10):2792-2798.
28. Hapugaswatta H, Amarasena P, Premaratna R *et al.* Differential expression of microRNA, miR-150 and enhancer of zeste homolog 2 (EZH2) in peripheral blood cells as early prognostic markers of severe forms of dengue. J Biomed Sci 2020; 27(1):25.
29. Moran J, Ramirez-Martinez G, Jimenez-Alvarez L *et al.* Circulating levels of miR-150 are associated with poorer outcomes of A/H1N1 infection. Exp Mol Pathol 2015; 99(2):253-261.
30. Essandoh K, Fan GC. Role of extracellular and intracellular microRNAs in sepsis. Biochim Biophys Acta 2014; 1842(11):2155-2162.
31. Vasilescu C, Rossi S, Shimizu M *et al.* MicroRNA fingerprints identify miR-150 as a plasma prognostic marker in patients with sepsis. PLoS One 2009; 4(10):e7405.
32. Jia Y, Ling M, Zhang L *et al.* Downregulation of miR-150 expression by DNA hypermethylation is associated with high 2-hydroxy-(4-methylthio)butanoic acid-induced hepatic cholesterol accumulation in nursery piglets. J Agric Food Chem 2016; 64(40):7530-7539.
33. Ghorpade DS, Holla S, Sinha AY *et al.* Nitric oxide and KLF4 protein epigenetically modify class II transactivator to repress major histocompatibility complex II expression during Mycobacterium bovis bacillus Calmette-Guerin infection. J Biol Chem 2013; 288(28):20592-20606.

34. Fukushima A, Kajiya H, Izumi T *et al.* Pro-inflammatory cytokines induce suppressor of cytokine signaling-3 in human periodontal ligament cells. J Endod 2010; 36(6):1004-1008.
35. Gao A, Van Dyke TE. Role of suppressors of cytokine signaling 3 in bone inflammatory responses. Front Immunol 2014; 4:506.
36. Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signalling and immune regulation. Nat Rev Immunol 2007; 7(6):454-465.
37. Chirshev E, Oberg KC, Ioffe YJ *et al.* Let-7 as biomarker, prognostic indicator, and therapy for precision medicine in cancer. Clin Transl Med 2019; 8(1):24.
38. Chauhan N, Jaggi M, Chauhan SC *et al.* COVID-19: fighting the invisible enemy with microRNAs. Expert Rev Anti Infect Ther 2021; 19(2):137-145.
39. Escalera-Cueto M, Medina-Martinez I, del Angel RM *et al.* Let-7c overexpression inhibits dengue virus replication in human hepatoma Huh-7 cells. Virus Res 2015; 196:105-112.
40. Masyeni S, Hadi U, Kuntaman *et al.* Detection of micro-RNA hsa-let-7e in peripheral blood mononuclear cells infected with dengue virus serotype-2: preliminary study. OP Conf Ser Earth Environ Sci 2018; 125: 012010.
41. Elliott CL, Allport VC, Loudon JA *et al.* Nuclear factor-kappa B is essential for up-regulation of interleukin-8 expression in human amnion and cervical epithelial cells. Mol Hum Reprod 2001; 7(8):787-790.
42. Chen S, Sheng C, Liu D *et al.* Enhancer of zeste homolog 2 is a negative regulator of mitochondria-mediated innate immune responses. J Immunol 2013; 191(5):2614-2623.
43. Dai X, Sayama K, Tohyama M *et al.* The NF-kappaB, p38 MAPK and STAT1 pathways differentially regulate the dsRNA-mediated innate immune responses of epidermal keratinocytes. Int Immunol 2008; 20(7):901-909.
44. Tang Y, Luo X, Cui H *et al.* MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. Arthritis Rheum 2009; 60(4):1065-1075.

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