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Resolvin D1 (Rvd1) Attenuates *In Vitro* LPS-Stimulated Inflammation Through Downregulation of miR-155, miR -146, miR -148 and Krupple Like Factor 5

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Abstract

Background: Chronic inflammation is associated with many inflammatory diseases. Specialized pro-resolving mediators (SPMs) are well known for their crucial role in promoting the resolution phase of inflammation and restoring tissue homeostasis. Resolvin D1 (RvD1) is an endogenous omega-3-derived lipid mediator with pro-resolving activity. This study aimed to evaluate the effect of Resolvin D1 (RvD1) on some inflammatory miRNAs (mir-155-5p, miR146a-5p and miR148-3p) and Krüppel-like factors 5 (KLF5) in an LPS-stimulated THP-1 preclinical model of inflammation.

Methods: PMA-differentiated THP-1 cells (macrophages) were pre-incubated with or without various concentrations of RvD1 (10, 50, or 100 nM) for 2 h prior to stimulation by 1 µg/ml LPS. Un-stimulated PMA-differentiated THP-1 cells were as the control group. Then, the expression levels of target genes were evaluated by real-time PCR.

Results: Compared with untreated macrophages, stimulation with 1 µg/ml LPS increased mRNA expression levels of TNF-α, KLF5, miR-155-5p, miR-146-5p, and miR-148a-3p. When the cells were exposed to various concentrations (10, 50 and 100 nM) of RvD1 for 2 h prior to LPS stimulation, the TNF-α, KLF5, miR-155-5p, miR-146-5p, and miR-148a-3p mRNA expression levels were significantly downregulated in a dose-dependent manner, compared to the LPS group.

Conclusion: The results demonstrate that RvD1 can attenuate inflammatory response in LPS-stimulated macrophages. Our data also showed that RvD1 may exert anti-inflammatory effects by inhibiting miR-155-5p, miR-146a-5p, and miR-148-3p.

Keywords: Chronic inflammation, Krupple like factors (KLF), Micro-RNAs, Resolvin D1 (RvD1), Macrophages.

Introduction

Inflammation is a complicated immune response to harmful stimuli, such as pathogens, toxins, or tissue injury (1). Under normal circumstances, inflammation is a self-limiting process that promotes healing and restores homeostasis. Otherwise, persisted inflammation could become chronic, which is associated with many inflammatory diseases (2). M1 macrophages play a significant role in the development of choronic inflammation by releasing high levels of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) and chemokines (3). The nuclear factor-kappa B (NF-κB) signaling cascade has a central role in

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this process (4). However, outside of NF-κB signaling, regulation of acute inflammation can also occur through microRNAs (miRNAs) (5). MicroRNAs represent a class of small (20–25 nucleotides), non-coding RNAs that are key regulators of post-transcriptional gene expression by inhibiting mRNA translation (5). For example, some miRNAs, such as miR-146a, miR-148, and miR-155, are upregulated during inflammation and act as positive and/or negative regulators of inflammation by targeting genes involved in pro-inflammatory signaling pathways (6, 7). On the other hand, other miRNAs, such as members of the let-7 family and miR-21, are downregulated during inflammation and play a role in tissue repair and regeneration (8, 9). Furthermore, multiple facets of inflammation, including NF-κB and miR signaling, are regulated by Krüppel-like factors (KLFs) (10). The Krüppel-like factors (KLFs) are a family of transcription factors regulating the inflammatory response. They have been shown to promote or inhibit inflammation, depending on the specific KLF and the context in which it is expressed (10). The KLF5 is well known to regulate the expression of inflammatory genes in macrophages through NF-κB signaling (11-13). In addition, miRNA microarray analysis showed that KLF5 promotes pro-inflammatory miRNAs, such as miR-155 and miR-146a, in vascular smooth muscle cells (VSMCs) (14).

Specialized pro-resolving mediators (SPMs) are a class of bioactive lipid molecules derived from essential fatty acids, including arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Given their structure differences, they are divided into four families: lipoxins, resolvins, protectins, and maresins. These play a crucial role in promoting the resolution phase of inflammation and restoring tissue homeostasis (15), SPMs dysregulation has been associated with several inflammatory diseases, including rheumatoid arthritis (16), pulmonary diseases (17), and Cardiovascular Disease (18).

Specialized pro-resolving mediators (SPMs) exert their functions by engaging specific G protein-coupled receptors (GPCRs) expressed on immune cells (15). In the post-capillary venules, SPMs limit neutrophil infiltration and stimulate the recruitment of non-phlogistic monocytes. At the inflammatory foci, it reduces pro-inflammatory cytokine production, enhances the clearance of apoptotic cells and debris, and facilitates the departure of inflammatory cells from tissues to resolve inflammation and tissue repair (15). It seems that part of the controlling activities of SPMs on the resolution of inflammation is done by microRNAs in a time-dependent manner. In a zymosan-induced inflammation model, RvD1 increases the IL-10 production by inducing miR-21 after 24h stimulation. Accordingly, RvD1 can also regulate the miR-146b, miR-208a, and miR-219 gene expression in a GPCR-dependent manner during the resolution phase (19).

This study aimed to investigate the anti-inflammatory properties of RvD1 in an LPS-stimulated THP-1-derived macrophage. we also examine the effect of RvD1 on some inflammatory-related miRNAs (miR-155, miR-146, and miR-148) and KLF5 in this model.

Materials and Methods

Cell culture

Human monocyte cell line, THP-1, were obtained from (Pasteur Institute, Tehran, Iran) and cultured in the RPMI 1640 (Biosera) supplemented with 10% inactivated fetal bovine serum (DNAbiotech) at 37 °C in the humidified incubator of 5% CO2. Then, THP-1 monocytes differentiated into macrophages by 48 h incubation with PMA (Sigma-Aldrich, Cat. No. 79346). Successful differentiation was confirmed by measuring the gene expression of markers CD11b using Real-Time PCR. Non-adherent cells were washed away and the remaining cells rested for 24 hours. Then macrophages were plated onto 24-well plates at a density of 1×10^6 cells/ml and primed with or without 1 µg/ml LPS (Sigma) for 1 or 2, or 4 hours for indicating appropriate stimulation times. Successful stimulation was determined by measuring the gene expression of TNF-α. Finally, macrophages were pre-incubated with or without RvD1 (10, 50 or 100

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nM) for 2 h prior to the addition of 1 μg/ml LPS. The control group was non-stimulated macrophage; vehicles were 100 nM RvD1 alone and Ethanol 100 nM. Each experiment was performed in triplicate.

RNA Extraction and RT-qPCR

The total RNA was isolated using FavorGen RNA isolation Kit (Favorgen Biotech corp, Taiwan, CAT No FAVNK 001) according to the manufacturer's instructions. To remove genomic DNA, the RNA was treated by DNase Free RNase (YTA, Tehran, Iran Cat No: YT9058) for 15 minutes. The Quantities and Quality of total RNA were examined using a Nanodrop-1000 spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). To determine the mRNA and lncRNA expression levels, the extracted RNA was then reverse-transcribed to cDNA by cDNA synthesis kit (Favorgen Biotech Corp., Taiwan) according to the manufacturer's recommendations. For miRNA, the reverse primer of the miRNAs was provided in the BONmiR first-Strand Synthesis Kit (Stem cell technology, Tehran, Iran) and cDNA was synthesized. The housekeeping gene Glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used to normalize the expression levels of the lncRNAs and mRNAs, and U6 was used to normalize the expression levels of miRNAs. Quantitative real-time PCR (qRT-PCR) was done using the Light cycler 96 device (Roche, Germany) and by SYBR green (Amplicon, Odense, Denmark) master mix. The primer sequences of the selected mRNAs and lncRNAs are listed in Table 1. The primers for miRNAs were purchased (Stem Cell Technology, Tehran, Iran). RT-qPCR was carried out in a 15-μL reaction mixture containing 7.5 μL 2 × iTaqTM Universal SYBR Green Supermix (BioRad, CA, United States), 1 μL cDNA, 6 μL ddH2O, and 0.5 μL forward and reverse primers. The following thermocycling program was used: 95 °C for 10 min; 45 cycles of 95 °C for 10 s, 60 °C for 20 s, followed by melting: 95 °C for 10 s, 65 °C for 60 s, and 97 °C for 1 s, and cooled in 37 °C for 30 s. All samples were analyzed in three independent reactions. The relative gene expression differences between controls and patients were calculated using the Pfaffl method.

Table 1. Sequences of primers used for real-time RT-PCR analyses.

Gene name	Sequence (5′ to 3′)	Product length (bp)
TNF-α (NM_000594.4)	F: AGAGGGAAGAGTTCCCCAGG	112
	R: GGGTTTGCTACAACATGGGC	
CD11b (NM_000632.4)	F: CTCCTTCCAGGTTCTGGCTC	75
	R: CATGACATAAGGTCAAGGCTGT	
GAPDH (NM_001256799)	F: GACCCCTTCATTGACCTCAAC	142
	R: GATCTCGCTCCTGGAAGATG	
U6 snRNA (NR_004394.1)	F: CTCGCTTCGGCAGCACA	94
	R: AACGCTTCACGAATTTGCGT	

Statistical Analysis

Statistical analyses were performed using the GraphPad Prism® 6.0 package for Windows (GraphPad Software Inc., San Diego, CA, USA) and *P* values < 0.05 were considered significant. Data are expressed as means ± standard deviation (SD). Comparisons between control, sham, and treatment groups were evaluated by one-way ANOVA followed by Kruskal-Wallis post hoc test.

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Results

THP-1 monocytes differentiation and stimulation

In order to induce terminal differentiation to macrophage-like cells, THP-1 cells were cultured in the presence of 100 nM PMA for 44 h. Real-time PCR analysis revealed that these cells expressed high levels of CD11b, a macrophage-specific differentiation antigen, compared to untreated THP-1 cells (Fig. 1A). For the stimulation of macrophages, they were cultured in the presence of 1 µg/ml LPS for 1, 2, and 4 h or medium. Real-time PCR analysis showed a significantly higher TNF-α gene expression at 1 and 2 h compared to the control group (Fig. 1B). Accordingly, macrophage was stimulated with 1 µg/ml LPS for 1 h in continue.

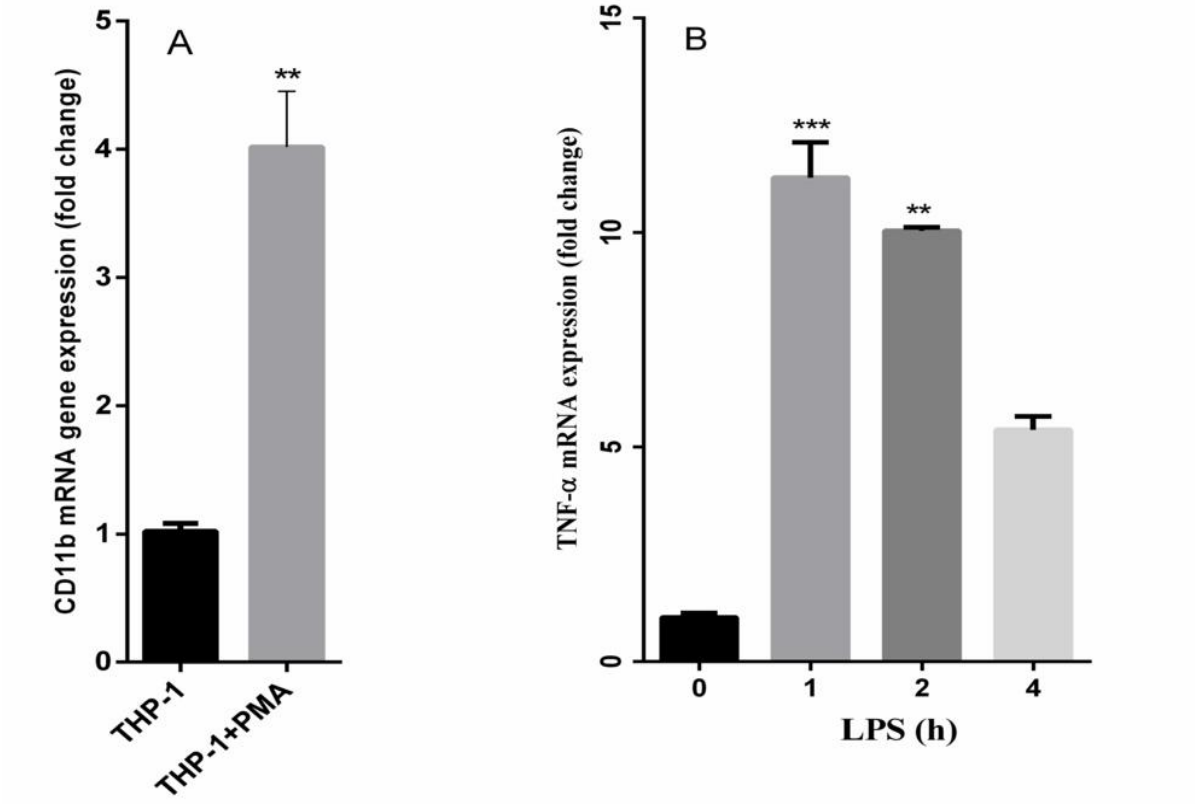

Fig. 1. THP-1 monocytes differentiation and stimulation. (A) THP-1 monocyte cells were differentiated into macrophages by 48h incubation with 100 nM PMA. Successful differentiation was confirmed to be significantly higher CD11b gene expression than untreated THP-1 cells. (B) To determine the optimal stimulation time, macrophages were cultured in the presence of 1 µg/ml LPS for 1, 2, and 4 h or medium, and then subsequently, TNF-α mRNA levels were determined at the indicated times by quantitative PCR analysis. Representative experiments of at least three individual experiments are shown. Data are expressed as mean values ± S.D. of three individual replicates.

RvD1 attenuates LPS-induced mRNA miRNAs of Target genes

In the present study, differentiated THP-1 cells were exposed to 1 µg/ml LPS for 1 h, then the mRNA expression levels of TNF-α, KLF5, miR-155-5p, miR-146-5p, and miR-148a-3p were detected by RT-qPCR. Compared with untreated macrophages, stimulation with 1 µg/ml LPS resulted in increased mRNA expression levels of TNF-α, KLF5, miR-155 5p, miR-146-5p, and miR-148a-3p c (Fig. 2). When the cells were exposed to various concentrations (10, 50, and 100 nM) of RvD1 for 2 h prior to LPS stimulation, the TNF-α, KLF5, miR-155-5p, miR-146-5p, and miR-148a-3p mRNA expression levels were significantly inhibited in a dose-dependent manner, compared to the LPS group (Fig. 2).

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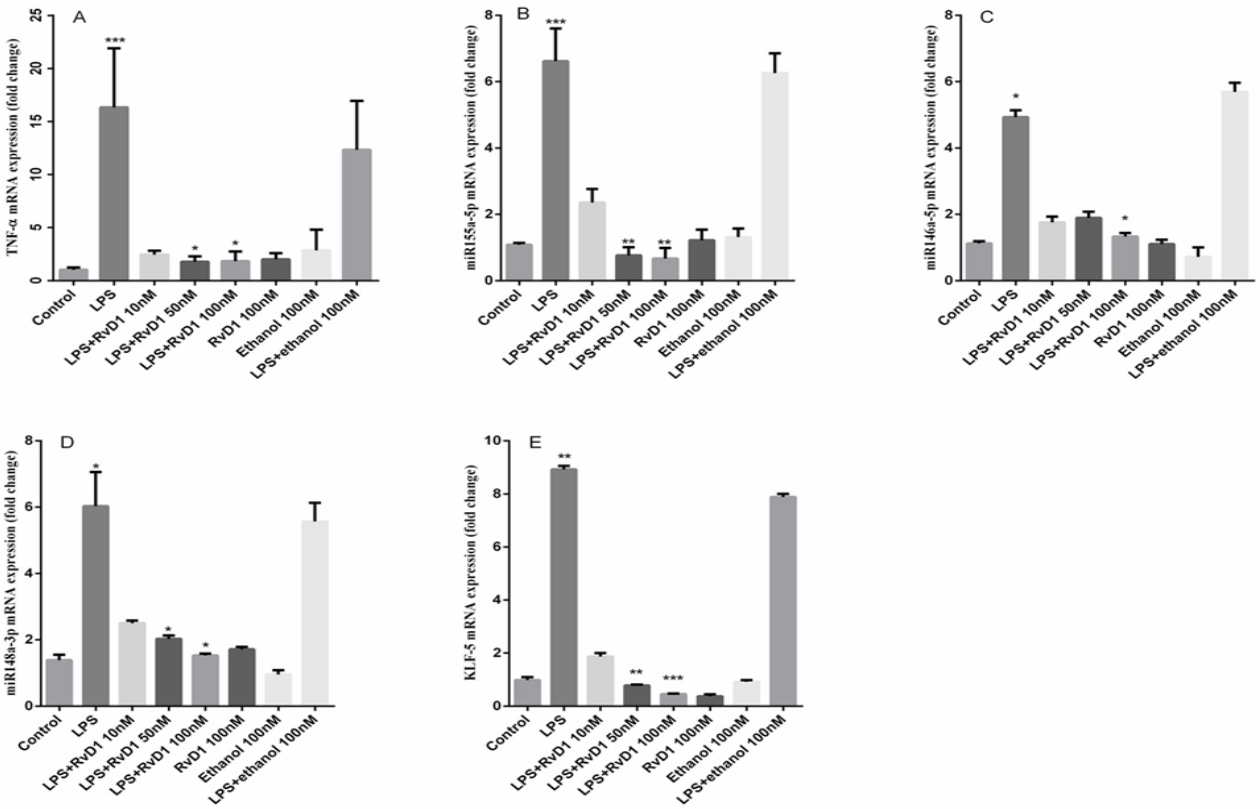

Fig. 2. Relative gene expression levels of TNF-α (A), miR-155-5p (B), miR-146-5p (C), miR-148-3p (D), and KLF5 (E) in LPS stimulated macrophages. After 1 h stimulation by 1 µg/ml LPS, the expression levels of target gene compared with unstimulated macrophages significantly increased. When the cells were exposed to various concentrations (10, 50 and 100 nM) of RvD1 for 2 h prior to LPS stimulation, the TNF-α, KLF5, miR-155-5p, miR-146-5p, and miR-148a-3p mRNA expression levels were significantly downregulated in a dose-dependent manner, compared to the LPS group. Representative experiments of at least three individual experiments are shown. Data are expressed as mean values ± S.D. of three individual replicates.

Discussion

Unresolved inflammation is a significant feature of the pathogenesis of several inflammatory disorders (16-18). The present study investigates the anti-inflammatory properties of resolving D1 (RvD1) in an LPS-stimulated THP-1 preclinical inflammation model. The results showed that RvD1 significantly attenuated LPS-induced TNF-α mRNA expression in a dose-dependent manner, which is consistent with previous studies. RvD1 has been shown dose-dependently downregulated IL-1β, IL 6 andTNF α expression levels in LPS-induced MG 63 cells (20). *In vivo* studies also showed that RvD1, in a dose-dependent manner, down-regulated the level of TNF-α and IL-6 in BALF of mice with LPS-induced acute lung injury and experimental acute pancreatitis (21-22). Furthermore, RvD1 has been shown to reduce levels of TNF-α and IL-6 in mouse models of colitis and D-galactosamine-sensitized endotoxin shock (23, 24). In addition, the aspirin-triggered epimer of RvD1 (AT-RvD1; 7S,8R,17R-trihydroxy-4Z,9E,11E,13Z,15E, 19Z-docosahexaenoic acid) has been shown to decrease levels of TNF-α and IL-6 in a mouse model of hydrochloric acid-induced acute lung injury (25). The nuclear factor kappa B (NF-κB) is ubiquitously expressed transcription factor that regulates proinflammatory cytokines expression in response to LPS (26-27). RvD1 seems to exert its anti-inflammatory and pro-resolving effects by inhibiting the NF-κB signaling pathway. Recent researches have shown that RvD1 markedly inhibited the activation of NF-κB in a mouse model of LPS-

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induced acute lung injury (21, 28), LPS-induced kidney injury (29), experimental pancreatitis (22), STZ-induced diabetic retinopathy rats (30), and MG 63 cells treated with LPS (20).

Studies have shown that miRNAs play roles in governing pro-inflammatory type-1 macrophages (M1) and anti-inflammatory type-2 macrophages (M2) polarization (6). In the present study, our results indicate that RvD1 could prevent the induction of pro-inflammatory miR-155-3p, 146a-5p, and 148a-3p in LPS-stimulated THP-1. Dysregulations in miRNAs have been implicated in various diseases, including diabetes, cancer, cardiovascular, renal, and autoimmune disorders (31). Interestingly, it has been shown that *miR-155,* miR-146a, and miR-148a upregulation promotes macrophage proinflammatory M1 polarization (7, 32). *In vitro,* miR-155 and miR-146a were upregulated in THP1 cells, macrophages, and human monocytes when stimulated with LPS (32, 33). On the other hand, the Polarization of PBMC-derived macrophages (32) THP-1 cells and BMDMs (34) to the M1 phenotype also increased miR-155 expression. In addition, *in vivo,* upregulation of miR-155 has been observed in chronic alcohol consumption, contributing to alcohol-induced elevation in TNF-*α* production via NF- *κ*B signaling (35). Furthermore, In a BALB/c mouse model, it has been observed that LPS stimulation increases microRNA-155 expression in the liver (36). In addition, anti-miR-155 has been reported to polarize M2 macrophages by restraining NF-κB (37). MiR-146a is also in a NF-κB signaling pathway dependent induced in response to TLR4 signaling in activated monocytes (38, 39). Furthermore, i.p. administration of miR-146a-5p induced acute peritonitis with robust monocyte/neutrophil (40). Also, miR-148a-3p have been shown promoted M1 and inhibited M2 polarization of macrophages (7). MiR-148a Suppression led to decreased mRNA levels of proinflammatory M1-like markers (Nos2, IL-6, Cox2, and TNF-α) and increased the expression of anti-inflammatory genes (Arg1, Retlna, and Mrc1) in murine primary macrophages (41).

The present study showed that RvD1 can significantly prevent the induction of KLF5 in LPS-stimulated THP-1. The transcription factor KLF5 has been demonstrated to associate with NF-κB regulates inflammation-related genes (11, 12). The evidence suggests that KLF5 exerts pro-inflammatory actions. *In vitro,* knockdown of KLF5 by siRNA inhibits tumor necrosis factor alpha (TNF-α)-induced expression of the monocyte chemoattractant protein-1 (MCP1) in human umbilical vein endothelial cells (HUVECs) (42) and LPS-induced NF-κB expression and its downstream target genes, including TNF-α and interleukin 6 (IL6) (43). *In vivo,* KLF5 initiates the accumulation of M1 macrophages. It regulates the inflammation of tubulointerstitium in the unilateral ureteral obstruction (UUO) mouse (13). The overexpression of KLF5 in distal tubule cells is associated with increased production of pro-inflammatory cytokines in kidney tissues of young rats fed with melamine and cyanuric acid (44).

In conclusion, our data demonstrate that RvD1 is capable of attenuates inflammatory response in LPS-stimulated macrophages. Our data also showed RvD1 exerts anti-inflammatory effects by inhibiting miR-155-5p, miR-146a-5p, and miR-148-3p. We conclude from the present data and the literature that RvD1 may be a potential innovative therapeutic approach for chronic inflammatory diseases.

Conflicts of interest

The authors declare that they have no conflicts of interest regarding this manuscript.

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