**PolyI:C Upregulated CCR5 and Promoted THP-1-Derived Macrophage Chemotaxis via TLR3/JMJD1A Signalling**

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**Abstract**

**Objective:** This study aimed to evaluate the specific roles of polyinosinic:polycytidylic acid (polyI:C) in macrophage chemotaxis and reveal the potential regulatory mechanisms related to chemokine receptor 5 (CCR5).

**Materials and Methods:** In this experimental study, THP-1-derived macrophages (THP1-Mφs) induced from THP-1 monocytes were treated with 25 μg/mL polyI:C. Toll-like receptor 3 (TLR3), Jumonji domain-containing protein (JMJD)1A, and JMJD1C small interfering RNA (siRNAs) were transfected into THP1-Mφs. Quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) was used to detect the expression levels of TLR3, CCR5, 23 Jumonji C domain-containing histone demethylase family members, JMJD1A, and JMJD1C in THP1-Mφs with different siRNAs transfections. Western blot was performed to detect JMJD1A, JMJD1C, H3K9me2, and H3K9me3 expressions. A transwell migration assay was conducted to detect THP1-Mφ chemotaxis toward chemokine ligand 3 (CCL3). A chromatin immunoprecipitation (ChIP) assay was performed to detect H3K9me2-CCR5 complexes in THP1-Mφs.

**Results:** PolyI:C significantly upregulated CCR5 in THP1-Mφs and promoted chemotaxis toward CCL3 (P<0.05); these effects were significantly inhibited by TLR3 siRNA (P<0.01), JMJD1A and JMJD1C expression was significantly upregulated in polyI:C-stimulated THP1-Mφs, while only JMJD1A siRNA decreased CCR5 expression (P<0.05). JMJD1A siRNA significantly increased H3K9me2 expression in THP1-Mφs but not in polyI:C-stimulated THP1-Mφs. The ChIP result revealed that polyI:C significantly downregulated H3K9me2 in the promoter region of CCR5 in THP1-Mφs.

**Conclusion:** PolyI:C can enhance THP1-Mφ chemotaxis toward CCL3 regulated by TLR3/JMJD1A signalling and activate CCR5 expression by reducing H3K9me2 in the promoter region of CCR5.

**Keywords:** Chemokine Receptor 5, Chemotaxis, Macrophages, Polyinosinic:polycytidylic Acid

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**Introduction**

Acute lung injury (ALI) is an inflammation characterized by the breakdown of the endothelial and epithelial lung barrier (1). Monocyte-derived macrophages are important in the pathogenesis of ALI. Under the pathological conditions of ALI, activated circulating monocytes infiltrate the alveolar space to form alveolar macrophages. Subsequently, alveolar macrophages may secrete several inflammatory mediators, such as cytokines and chemokines, to induce the migration of mature neutrophils and CD4+ T cells into the alveolar space, thereby prompting an inflammation response that may kill pathogenic microbes (2, 3). A previous study showed that the depletion of circulating monocytes and subsequently recruited alveolar macrophages significantly suppressed ALI in mice (4). Therefore, the function and activity of macrophages are extremely important in the development and prognosis of ALI.

Toll-like receptors (TLRs) are categorized as innate immune sensors, which play an important role in the process of antigen recognition for innate immune cells such as macrophages (5). It has been reported that TLR3 is upregulated in alveolar macrophages throughout the ALI pathogenesis (6). Chemokines comprise a class of cytokines that act as signalling molecules in the regulation of inflammatory response (7). Chemokine receptors (CCRs) are specific receptors for chemokines that are integral to the recruitment of alveolar macrophages (8). TLR3 and CCRs participate in ALI-induced inflammatory response through the recognition of pathogen-related molecular processes or the recruitment of macrophages; however, whether a direct regulating mechanism between CCRs and TLR3 exists in macrophages has not been thoroughly researched.

Histone demethylation is an important form of epigenetic modification that is regulated by Jumonji C domain-containing histone demethylases (JHDMs) (9). Histone demethylation is involved in the transcriptional repression and activation of target genes, and is closely associated with the inflammatory response of macrophages. It has been reported that Jumonji domain-containing protein 3 (JMJD3) influences transcriptional gene expression in lipopolysaccharide (LPS)-activated macrophages, and the regulatory role of JMJD3 is dependent upon H3K4me3.
The relative expression levels of target genes were calculated by $2^{-\Delta\Delta C_{\text{t}}}$ using GAPDH as an internal control. The primer sequences are shown in Table 1.

Flow cytometry

Flow cytometry was performed to detect chemokine receptor 5 (CCR5) expression in THP1-Mφs. Simply, cells were suspended in fresh RPMI-1640 medium and incubated with CCR5-PE antibody (R&D Systems, USA) in the dark for 30 minutes at room temperature. Data were collected using the FACSCalibur flow cytometer (BD Biosciences, San Jose, CA, USA) and analysed with CellQuest software (BD Biosciences).

siRNA transfection

siRNAs targeting TLR3, Jumonji domain-containing protein 1A (JMJD1A), and JMJD1C were obtained from Shanghai GeneChem Company (Shanghai, China), as follows:

- **TLR3 siRNA:** 5′-CCUGAGCUGCAAGCCACUACCUUU-3′
- **JMJD1A siRNA:** 5′-GCAAUUGGCUUGGGUUACUU-3′
- **JMJD1C siRNA:** 5′-GCAAUUGGCUUGGGUUACUU-3′.

After 6 hours of incubation with 100 ng/mL PMA, THP1-Mφs were incubated with specific siRNAs and Lipofectamine 2000 reagent (ThermoFisher, Waltham, MA, USA) for 6 hours. Transfected cells were treated with 25 μg/mL polyI:C for an additional 42 hours. The efficacy of the TLR3 transfection was detected using qRT-PCR and flow cytometry as described above, while the efficacy of JMJD1A and JMJD1C siRNA-mediated gene silencing was monitored using Western blotting.

Transwell migration assay

THP1-Mφ chemotaxis toward chemokine ligand 3 (CCL3) was detected using transwell inserts. Transwell inserts with a pore size of 8 μm were placed into 24-well plates. Cells were suspended in serum-free RPMI-1640 medium and inoculated into the upper chamber at a density of $1\times10^5$ cells/mL. RPMI-1640 medium that contained 100 ng/mL recombinant human CC chemokine ligand 3 (rhCCL3; #270-LD, R&D Systems, USA) and 10% FBS was added into the lower chamber. Following 12 hours of incubation at 37°C, the non-migrated cells were removed from the upper chamber, and migrated cells in the lower chamber were fixed with methanol and stained with eosin. Five random fields of each well were observed using light microscopy, and the number of migrated cells was counted.

Chromatin immunoprecipitation assay

The chromatin immunoprecipitation (ChIP) assay was performed to detect H3K9 methylation in THP1-Mφs. After being fixed in 1% formaldehyde, the chromatin was extracted from THP1-Mφs using sonication. Then, the chromatin was immunoprecipitated with H3K9me2 (Abcam, Cambridge, MA, USA) or H3K9me3 antibody (Abcam, USA) pre-bound Protein G-plus Agarose beads, overnight at 4°C. Precipitated protein-DNA complexes were eluted in Tris-EDTA buffer that contained 2% sodium dodecyl sulfate (SDS), and the crosslink was reversed through a 16 hour incubation period at 65°C. The precipitated DNA fragments were analysed by qRT-PCR as described above. The primer sequences of CCR5-ChIP are shown in Table 1. qRT-PCR was performed...
on a LightCycler 2.0 Instrument (Roche, Germany) using TB Green Fast qPCR Mix (Code No. RR430S/A/B, TaKaRa, Japan).

Table 1: Sequences of specific primers used in quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR)

| Gene | Primer sequence (5'-3') |
|------|------------------------|
| CCR1 | F: CGAAAGCCTACGAGATGGGA A R: CGGACAGGTTTGGATTCTTCT |
| CCR2 | F: GAGCCATAACCTGTAATGCC R: GAGCCGAAATACGTAATTG |
| CCR4 | F: CATGAAACCCACGGATATAGCA R: CTACTCCCCAATGCTTTCGT |
| CCR5 | F: TGTCCCTCTTGCGTGCTCATTAT R: TGGACGACAGGGTCACCCCT |
| CCR6 | F: TGGACGACAGGGTGCTTGTGTA R: TGGACGACAGGGTCACCCCT |
| CCR7 | F: CCTGGGGAACCAATGAAAAAGC R: GAGCATGCCATGGCGAGGAAC |
| CCR8 | F: TTCTCTGCCCACCATGTAGTC R: TCGATGCTGATCCCAATGTA |
| CXCR4 | F: TTAGCTGCCACCATGCTGAC R: TCGATGCTGATCCCAATGTA |
| FBXL10 | F: CAGTGGGTGGAGGGCTAAA R: ACTGAGGTGGAGCTTGGAGA |
| FBXL11 | F: ATACAACACGTTCACACTGTCA R: TGGCCATGCCATCTATCTCC |
| JMJD1A | F: ATGCCCAACAGACCTACCTTTAC R: TGGCCATGCTGACTATTAC |
| JMJD1B | F: AATTCCTCCCAAACCCCTTTCG R: CCCATACCACATCTCTTC |
| JMJD1C | F: TCGAGAACTGACCTGAGTCCAG T: TGGCCATGCTGACTATTAC |
| JMJD2A | F: CAGAGGACAAACCCCTTTCG R: CCCATACCACATCTCTTC |
| JMJD2B | F: GGGGGAAGAATGTTGAGTGA R: CTATGGGGGCTCCTTTC |
| JMJD2C | F: TGCCCTGACGTTCTGAGTT C: TGGCCATGCTGACTATTAC |
| JMJD2D | F: AAAATGTTGCGCCGGGACCAAC R: TGGCCATGCTGACTATTAC |
| JMJD3 | F: CTCTAGTGCAAGCGCTGCAAG R: TGGCCATGCTGACTATTAC |
| JMJD4 | F: ACTGGGTCAATGGGCTTCAAC R: TGGCCATGCTGACTATTAC |

Western blot

THP1-Mφs were lysed in RIPA buffer. Total proteins were separated by SDS-polyacrylamide gel electrophoresis on 10% polyacrylamide gels and transferred to nitrocellulose membranes (Bio-Rad, Hercules, CA, USA). The membrane was blocked with 5% skim milk in TBST for 2 hours and incubated with special primary antibody (anti-H3K9me2, anti-H3K9me3, Abcam, USA) at 4˚C for 12 hours. After there were washed three times with TBST, the membrane was incubated with horseradish peroxidase-conjugated secondary antibody (Abcam, USA) at 25˚C for 2 hours. Protein bands were visualized with the Image Station IS2000 (Kodak, Rochester, NY, USA).
Statistical analysis

All experiments were performed in triplicate, and all data are presented as means ± standard deviation. The statistical analysis conducted in this study was performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk was used to test the normality of the distribution. For the data presenting a normal distribution, the mann-withney (two groups) and kruskal-wallis (more than two groups) were used to compare results among different groups. The Wilcoxon rank-sum test was used for non-normally distributed data. P<0.05 denoted statistically significant results.

Results

Polyinosinic:polycytidylic acid upregulated chemokine receptor 5 expression in THP-1-derived macrophages through toll-like receptor 3 signalling

The expression levels of diverse CCRs in THP-1 monocytes and THP1-Mφs were detected. As shown in Figure 1A, CCR1, CCR4, CCR5, and CCR6 were expressed in both THP-1 monocytes and THP1-Mφs. CCR1 expression was significantly higher in THP1-Mφs than in THP-1 monocytes (P=0.031). CCR2, CCR7, and CXCR4 expressions at the mRNA level were not detected in THP-1 monocytes and THP1-Mφs (Fig.1A). Then, the effects of polyI:C on CCR1, CCR4, CCR5, and CCR6 expressions were evaluated in THP-1 monocytes and THP1-Mφs. qRT-PCR demonstrated that CCR5 expression was significantly elevated by polyI:C treatment in THP1-Mφs, while CCR5 expression was not significantly changed by polyI:C treatment in THP-1 monocytes (Fig.1B). The remarkably increased CCR5 expression in polyI:C-stimulated THP1-Mφs was also confirmed by flow cytometry (45.9% vs. 20.8%, P=0.017, Fig.1D).

Since macrophages can recognize polyI:C stimulation through TLR3 signalling. The effects of TLR3 silencing on CCR5 expression were detected in polyI:C-stimulated THP1-Mφs. Flow cytometry and qRT-PCR showed that TLR3 siRNA transfection significantly inhibited TLR3 expression in polyI:C-stimulated THP1-Mφs (80.2% vs. 48.8%, P=0.011, Fig.1C, E). CCR5 expression was significantly inhibited by TLR3 siRNA transfection in polyI:C-stimulated THP1-Mφs (P=0.044, Fig.1F).

Fig.1: Polyinosinic:polycytidylic acid (PolyC) upregulated chemokine receptor 5 (CCR5) expression in THP-1-derived macrophages (THP1-Mφs) through toll-like receptor 3 (TLR3) signalling. A. Expression profile of chemokine receptors in THP-1 monocytes and THP1-Mφs by quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) (fold change at the mRNA level), B. CCR1, CCR4, CCR5, and CCR6 expressions in polyC-stimulated THP-1 monocytes and THP1-Mφs by qRT-PCR, C. CCR5 expression in polyC-stimulated THP1-Mφs by flow cytometry, D. TLR3 expression in THP1-Mφs with TLR3 siRNA by flow cytometry, E. Knockdown efficiency of TLR3 siRNA by qRT-PCR, and F. CCR5 expression in polyC-stimulated THP1-Mφs transfected with TLR3 siRNA. *; P<0.05 and **; P<0.01
Polyinosinic:polycytidylic acid promoted THP-1-derived macrophage chemotaxis toward chemokine ligand 3 through toll-like receptor 3 signalling

Since CCR5 can be activated by CCL3, THP1-Mφ chemotaxis toward CCL3 was analysed. As shown in Figure 2A, THP1-Mφs easily migrated to rhCCL3 (P=0.0005). PolyI:C significantly increased THP1-Mφ chemotaxis toward rhCCL3 (P=0.0006, Fig.2A). In addition, TLR3 siRNA transfection significantly inhibited polyI:C-stimulated THP1-Mφ chemotaxis toward rhCCL3 (P=0.0029, Fig.2B).

Polyinosinic:polycytidylic acid upregulated Jumonji domain-containing protein 1A and JMJD1C in THP-1-derived macrophages

Since histone methylation is involved in the inflammatory response of macrophages, the expression levels of 23 JHDM family members were observed in polyI:C-stimulated THP1-Mφs by qRT-PCR. As shown in Figure 3A, polyI:C significantly increased JMJD1A, JMJD1C, JMJD2A, JARID1A, and HSPBAP1 expressions in THP1-Mφs (all P<0.01, Fig.3A). Notably, two JHDM2 subgroup members, JMJD1A and JMJD1C, were highly expressed and abundant in polyI:C-stimulated THP1-Mφs. In addition, TLR3 siRNA transfection significantly reversed the upregulatory effect of polyI:C on JMJD1A and JMJD1C on THP1-Mφs (JMJD1A, P=0.002; JMJD1C, P=0.018, Fig.3B). Therefore, JMJD1A and JMJD1C were chosen as the targets for the following investigative processes.

Fig.2: Polyinosinic:polycytidylic acid (PolyI:C) promoted THP-1-derived macrophage (THP1-Mφ) chemotaxis to chemokine ligand 3 (CCL3) via toll-like receptor 3 (TLR3) signalling. A. THP1-Mφs migration toward CCL3 by polyI:C treatment and B. PolyI:C-stimulated THP1-Mφ migration toward CCL3 by TLR3 siRNA transfection. **: P<0.01.
Regulatory Effects of polyI:C on Macrophages

Polyinosinic:polycytidylic acid-mediated Jumonji domain-containing protein 1A upregulated chemokine receptor 5 by inhibiting H3K9me2

In order to investigate whether the promoted expression of JMJD1A and JMJD1C is involved in the regulation of CCR5 expression, JMJD1A and JMJD1C were silenced in THP1-Mφs. As shown in Figure 4A, the protein expressions of JMJD1A and JMJD1C were significantly reduced in THP1-Mφs with JMJD1A or JMJD1C siRNA transfection. In addition, JMJD1A siRNA transfection significantly decreased CCR5 expression in both THP1-Mφs (P=0.007, Fig.4B) and polyI:C-stimulated THP1-Mφs (P=0.013, Fig.4B). However, CCR5 expression was not significantly influenced by JMJD1C siRNA transfection (Fig.4B). The downregulation of CCR5 expression induced by JMJD1A siRNA was also confirmed in polyI:C-stimulated THP1-Mφs by flow cytometry (43.8 vs. 32.6%, P<0.05, Fig.4C).

Since H3K9 is known to be the substrate of JMJD1A, we sought to determine if the regulatory role of JMJD1A in CCR5 expression was dependent on H3K9 methylation. As shown in Figure 4D, H3K9me2 expression was decreased in polyI:C-treated THP1-Mφs, while H3K9me3 expression was not significantly changed. In addition, H3K9me2 was significantly upregulated by JMJD1A siRNA transfection in THP1-Mφs. However, H3K9me3 expression was not influenced by JMJD1A siRNA transfection in polyI:C-stimulated THP1-Mφs (Fig.4E). In addition, polyI:C treatment downregulated H3K9me2 expression in the promoter region of CCR5 in THP1-Mφs (Fig.4F).
Fig. 4: Polyinosinic:polycytidylic acid (PolyI:C)-mediated Jumonji domain-containing protein 1A (JMJD1A) upregulated chemokine receptor 5 (CCR5) by reducing H3K9me2. A. JMJD1A and JMJD1C expression in THP-1-derived macrophages (THP1-Mφs) treated with JMJD1A or JMJD1C siRNA by Western blot. B. CCR5 expression in polyI:C-stimulated THP1-Mφs transfected with JMJD1A siRNA and JMJD1C siRNA by quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) (fold change at the mRNA level). C. CCR5 expression in polyI:C-stimulated THP1-Mφs transfected with JMJD1A siRNA by flow cytometry. D. H3K9me2 and H3K9me3 expression in polyI:C-stimulated THP1-Mφs transfected with JMJD1A siRNA by Western blot (protein level). E. H3K9me2 and H3K9me3 expressions in polyI:C-stimulated THP1-Mφs transfected with JMJD1A siRNA by Western blot (protein level), and F. H3K9me2 expression in the promoter region of CCR5 in THP1-Mφs by chromatin immunoprecipitation (ChIP) analysis. *; P<0.05 and **; P<0.01.
Discussion

Macrophage chemotaxis is an important component of ALI pathogenesis. It is known that viral infections can induce alveolar macrophage recruitment, but the regulatory mechanisms of viral infection (polyI:C) on monocyte-derived macrophages are still unclear. Thus, in this study, we have explored the regulatory mechanisms of polyI:C on THP1-Mφs. The results showed that polyI:C significantly upregulated CCR5 in THP1-Mφs and promoted THP1-Mφ chemotaxis toward CCL3 via TLR3 signalling. In addition, polyI:C-upregulated CCR5 was mediated by JMJD1A, and H3K9me2 was downregulated in the promoter region of CCR5 in THP1-Mφs.

Since CCRs are important in macrophage chemotaxis, the expression levels of diverse CCRs were examined in THP1-Mφs after polyI:C treatment. Our results demonstrated that only CCR5 was significantly upregulated by polyI:C treatment in THP1-Mφs. CCR5 is a cell surface G protein-coupled receptor that is involved in inflammatory response via interaction with specific chemokine ligands, including CCL3, CCL4, and CCL5 (14-16). The activation of CCR5 and CCL5 is required to prevent the apoptosis of virus-infected macrophages (17). In addition, CCR5 is involved in obesity-induced adipose tissue inflammation via regulation of macrophage recruitment (18, 19). Moreover, it has been reported that polyI:C-treated macrophages can promote CCR5 expression (20), which is consistent with the findings of our study. It was supposed that CCR5 is involved in polyI:C-induced inflammation in THP1-Mφs. Subsequently, THP1-Mφ chemotaxis toward CCL3 (a ligand of CCR5) was investigated. The results suggest that polyI:C significantly increased THP1-Mφ chemotaxis toward CCL3. A previous study reported that CCL3 expression was significantly elevated in the lung of a murine model of LPS-induced ALI and mediated an enhanced inflammatory injury-possibly by recruiting macrophages (21). Therefore, polyI:C-upregulated CCR5 contributes to the promotion of macrophage chemotaxis by interacting with CCL3.

Moreover, our results also suggest that TLR3 siRNA transfection significantly suppressed CCR5 expression in polyI:C-stimulated THP1-Mφs and inhibited chemotaxis toward CCL3. TLR-3 is responsible for anti-viral immunity against several virus infections via double-stranded RNA recognition and the activation of multiple antiviral factors in macrophages (20). Similarly, TLR-3 is activated in macrophages in response to encephalomyocarditis infection via type I IFN production. It has been reported that CCR5 may participate in virus replication and acts as the primary receptor for regulating encephalomyocarditis infection in mediating inflammatory response-related genes in macrophages (22). These results indicate that macrophages may recognize polyI:C stimulation through TLR3 signalling. PolyI:C may upregulate CCR5 expression and promote THP1-Mφ chemotaxis toward CCL3 through TLR3 signalling.

Histone demethylation, dynamically regulated by JHDMs, is implicated in the regulation of inflammatory response of macrophages (23). Previous studies have reported that JMJD3 is over-expressed in LPS-activated macrophages, which regulates diverse genes involved in LPS-induced immune and inflammatory responses (10, 24). However, few studies have focused on the regulatory mechanisms of polyI:C in histone demethylation in macrophages. In this study, the expression levels of 23 JHDM family members were detected in polyI:C-stimulated THP1-Mφs. The expression levels of JMJD1A, JMJD1C, JMJD2A, JARID1A, and HSPBAP1 were significantly increased by polyI:C in THP1-Mφs, while that of JMJD3 was not significantly changed. These results indicated that the effects of polyI:C on inflammatory responses of macrophages might differ from LPS. Since JMJD1A and JMJD1C could be regulated by TLR3 in polyI:C-stimulated THP1-Mφs, the regulatory roles of JMJD1A and JMJD1C on CCR5 were further analysed in this study. It was revealed that CCR5 was significantly downregulated by JMJD1A siRNA transfection in polyI:C-stimulated THP1-Mφs, while CCR5 expression was not significantly influenced by JMJD1C siRNA transfection. The regulatory role of JMJD1A has been found to affect the proliferation, migration, and invasion of cancer cells in various cancer types (25-27). It has been reported that JMJD1A inhibition suppresses tumour growth by downregulating angiogenesis and macrophage infiltration (28). Our findings indicate that polyI:C treatment may induce a similar macrophage inflammatory response with cancer; PolyI:C may enhance CCR5 expression by upregulating JMJD1A in THP1-Mφs.

Since JMJD1A is a H3K9 demethylase, the H3K9 methylation state of CCR5 was analysed in polyI:C-stimulated THP1-Mφs. Our results showed that H3K9me2 expression was significantly decreased by polyI:C treatment in THP1-Mφs. H3K9me2 downregulation might have attributed to the upregulation of JMJD1A. However, H3K9me3 expression was not significantly influenced by polyI:C treatment. Our findings indicate that the regulatory role of JMJD1A on CCR5 was dependent on H3K9me2. In addition, H3K9me2 was upregulated by JMJD1A siRNA transfection in THP1-Mφs, while H3K9me2 expression was not significantly influenced by JMJD1A siRNA in polyI:C-stimulated THP1-Mφs. This may be explained by the fact that some other upregulated JHDMs induced by polyI:C, such as JMJD1C, and JMJD2A may share a target with JMJD1A. JMJD1C and JMJD2A exhibit redundant effects on H3K9me2 expression. The presence of H3K9me2 in the promoter region of target genes typically results in reduced expressions of its targets. A previous study has reported that H3K9 exhibits a low methylation level in response to the activation of dendritic cells and is erased from the promoters of some activated inflammatory genes (29). Consistent with the results of that study, our results reveal that H3K9me2 expression was significantly reduced by polyI:C treatment in the promoter region of CCR5 in THP1-Mφs. We suspected that polyI:C-mediated JMJD1A upregulation may
upregulate CCR5 by reducing H3K9me2 in the promoter region of CCR5. Interestingly, JMJD1A is also a hypoxia-inducible gene that has been found to be upregulated in hypoxia-stimulated macrophages. However, hypoxia treatment decreases CCR5 expression via H3K9me2 upregulation in the promoter region of CCR5 (20). This may be explained by the effects of hypoxia-induced repressive JMJDs, which can overwhelm the effects of JMJD1A.

Conclusion

The present study revealed that polyIC upregulated JMJD1A expression in THP1-Møs, thereby elevating the CCR5 expression by reducing H3K9me2 in the promoter region of CCR5 via TLR3 signalling. However, this study is still limited to the cellular level, and the validation of these results in animal models is required in future research.

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Authors’ Contributions

X.Y., H.W.; Participated in study design, data collection and evaluation, drafting, and statistical analysis. H.S., C.Z., X.J.; Performed the study and contributed extensively in interpreting data and developing conclusions. J.Y.; Participated in study design, data analysis and responsible for overall supervision. All authors participated in the editing and finalization of the manuscript and approved the final draft for submission.

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