Expression and clinical significance of the m6A reader YTHDF2 in peripheral blood mononuclear cells from rheumatoid arthritis patients

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ABSTRACT
As an important m6A reader, the YT521-B homology domain family 2 (YTHDF2) has been shown to regulate mRNA degradation and translation, and to be involved in inflammation. However, little is known about the role of YTHDF2 in the autoimmune-based inflammatory disease rheumatoid arthritis (RA). To begin to ascertain any role for this reader, 74 RA patients and 63 healthy controls (HC) were recruited for this study. Blood was collected from each subject and peripheral blood mononuclear cells (PBMC) isolated. Thereafter, mRNA expression of YTHDF2, interleukin (IL)-1\textbeta, IL-6, IL-8, and tumor necrosis factor (TNF)-\textalpha in the cells was determined by quantitative reverse transcription-polymerase chain reaction (qRT-PCR). The harvested blood was also assessed for a variety of parameters, including levels of C-reactive protein (CRP), erythrocyte sedimentation rates (ESR), white blood cell counts (WBC), neutrophils counts (N)/neutrophils percentages (N\%), and neutrophil:lymphocyte ratios (NLR) - each markers of inflammation during RA. The results showed that YTHDF2 mRNA expression in RA patient PBMC was decreased significantly vs that in healthy control subject cells. Further, YTHDF2 mRNA expression in RA patient PBMC negatively-correlated with ESR, CRP levels, WBC counts, as well as neutrophils counts, percentages, and NLR values. In addition, it was seen that YTHDF2 mRNA expression in RA patient PBMC was associated with host serum RF levels and treatment. Moreover, it was found that mRNA expression of IL-1\textbeta, IL-6, IL-8, and TNF\textalpha was increased in PBMC from RA patients relative to in control subject cells; however, only the increased IL-1\textbeta expression was seen to be negatively-correlated with decreased YTHDF2 mRNA expression. In conclusion, the present study illustrated that YTHDF2 expression might have some regulatory role in the underlying mechanisms associated with the autoimmune disease RA and that this m6A reader could at some point represent a potential target for regulating inflammatory responses that occur during RA.

Introduction
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized primarily by joint damage (Schett and Gravallese 2012). Previous studies have found that genetic, infectious, environmental, and hormonal factors may play important roles in the development and progression of this disorder. It is clear, irrespective of which specific factor, that dysfunctions within the immune system, including aberrant lymphocyte, monocyte, and/or macrophages activation, are involved in the mechanisms that lead to the onset of RA (Pratt et al. 2009; Cascão et al. 2010; Klareskog et al. 2013). Even so, to date, a clear understanding of the etiology and the pathogenesis of RA remains incomplete (Scherer et al. 2020).

A role for N\textsubscript{6}-methyladenosine (m6A, methylation at N\textsubscript{6} of adenosine) in some altered biologic processes has been gaining attention in the past decade (Dominissini et al. 2012; Yang et al. 2018). m6A is the most abundant internal modification of mRNA in the majority of eukaryotes, and studies have increasingly focused on the potential role of methylation at N\textsubscript{6} of adenosine units in RNA in pathologies such as autoimmunity and inflammation (Lu et al. 2018; Rubio et al. 2018). The m6A modification affects multiple biological processes such as RNA splicing, translation, and degradation, through its impact on m6A readers, writers, and erasers (Wang et al. 2014; Adhikari et al. 2016; Coots et al. 2017; Li et al. 2017). One m6A reader, YTHDF2, is a member of the YTH (YT521-B homology) domain family (YTHDF) of proteins which comprise a group of cytoplasmic reader proteins that adjust the degradation and translation of mRNA (Li et al. 2014; Liao et al. 2018). In its capacity as a reader, YTHDF2 preferentially binds to m6A within a G(m6A)C consensus site (Zhu et al. 2014; Liu et al. 2018) leading to destabilization and degradation of target gene-derived RNA. It has also been determined that YTHDF2 activity seems to play a critical role in the expression of diverse functional signal agents and so can impact on normal health and diseases (Maity and Das 2016).
For example, Hou et al. (2019) demonstrated that YTHDF2 silenced in human hepatocarcinoma cells (HCC) or ablated in mouse hepatocytes could provoke inflammatory outcomes by impacting on the decay of the mRNA for m6A-containing IL-11 and serpin family E member 2. Another study showed changes in YTHDF2 expression could modulate lipopolysaccharide (LPS)-induced inflammatory responses by RAW 264.7 cells through effects on both MAPK and NF-κB signaling pathways (Yu et al. 2019). While those in vitro studies illustrate the potential impact of YTHDF2 expression on inflammation in the general sense, to date little is known about any potential role for this reader in actual immune-/inflammation-based pathologies.

Accordingly, to begin to address this issue, in the present study the mRNA expression of YTHDF2 in peripheral blood mononuclear cells (PBMC) from both RA patients and control counterparts was quantified. Further, any relationship between YTHDF2 mRNA expression and host inflammatory level/disease activity was also evaluated. Lastly, any correlation between the expression of YTHDF2 in the blood and levels of a variety of pro-inflammatory cytokines in these cells was also investigated. It was hoped that such analyses would help to shed light on what role, if any, changes in YTHDF2 expression could have in the emergence and progression of RA in humans.

### Material and methods

#### Patient variables and controls

Potential subject patients for the present study were consecutively enrolled between September 2018 and June 2020 at the First Affiliated Hospital of Nanchang University. The RA patients ultimately included herein all fulfilled the revised American College of Rheumatology (ACR) 2010 criteria for RA (Aletaha et al. 2010); those RA patients with other autoimmune, inflammatory, or hormonal diseases, cancers, or mental disorders, were excluded. All RA cases were new-onset and the subjects not yet received corticosteroids or immunosuppressive drugs prior to blood sample collection. At study start, a total of 74 RA subjects were evaluated. Healthy age-matched control subjects not yet received corticosteroids or immunosuppressive drugs prior to blood sample collection. At study start, a total of 74 RA subjects were evaluated. Healthy age-matched control subjects not yet received corticosteroids or immunosuppressive drugs prior to blood sample collection. At study start, a total of 74 RA subjects were evaluated. 

Effect of patient treatment on measured parameters

To ascertain if changes in RA status could be reflected by changes in PBME YTHDF2 mRNA status, six random new-onset RA subjects underwent therapeutic regimens with cortico-steroids/immunosuppressive drugs. Each subject received 15mg prednisone (once a day), 200mg hydroxychloroquine sulfate (twice a day), and 12.5mg methotrexate (once/week) for at least 15 days. At 24h after the final treatment, blood was re-sampled and both the same sets of blood parameters as before, and PBMC-related measurements, were repeated. Values post-treatment for each endpoint were then compared to the Day 0 (before treatment) values.

#### Quantitative real-time polymerase chain reaction analysis (QRT-PCR) analysis

After determination of cell concentrations in each isolated sample, RNA was isolated from 2 × 10^6 PBMC/patient using TRIzol reagent (Invitrogen, Waltham, MA) according to manufacturer protocols. The concentration and purity of each total RNA isolate was determined (using A260/A280, A260/A230 ratios) in a NanoDrop ND-1000 spectrophotometer (Invitrogen). For PCR analyses, 1μg total RNA/isolate was used to synthesize cDNA by reverse transcription using a PrimeScript™ RT reagent kit (Takara) according to manufacturer protocols. The product, in turn, was used as a template for PCR in an ABI 7500 Real-time PCR System (Invitrogen) that employed SYBR® Premix Ex Taq™ II (Takara). The amplification primers sequences for YTHDF2, IL-1β, IL-6, IL-8, TNFα, and GAPDH (housekeeping gene) are listed in Table 1. Relative expression of each gene was derived using the 2^−ΔΔCt method (Livak and Schmittgen 2001).

### Table 1. Amplification primer sequences.

| Gene     | Sequence (5’→3’) |
|----------|------------------|
| YTHDF2   | F: GCGCACTCGGAGTTGGA<br>R: CCCTGGGACCCAAGGTTTA |
| IL-1β    | F: CGTCTCGCACTACTCATT<br>R: CACCTGCTTCTGGCAGCT |
| TNFα     | F: GCTCTCTCCTCTGAGCTTG<br>R: CAGAGACTGATGGCTGCTC |
| IL-6     | F: AGTTGAGAAAGCCACGAC<br>R: GATGGTAGAGAGTTCTGAGG |
| IL-8     | F: TCTCACCTCAATCCTC<br>R: GTGTTGACAGTGGCAGCT |
| GAPDH    | F: GAAGATGGTAAGTGTTGTTG<br>R: GCATCGAGAAGATGATGGTA |

*IL-1β*: Interleukin 1β; *IL-6*: interleukin-6; *IL-8*: interleukin-8; *TNFα*: tumor necrosis factor-α; *YTHDF2*: YT521-B homology domains family 2.
Table 2. Clinical details of study patients.

| Clinical characteristic | RA \((p < 0.05\) vs. HC) | HC |
|-------------------------|--------------------------|----|
| Number of subjects      | 74                       | 63 |
| Sex [male/female] (female%) | 8/66 (89.2)      | 10/53 (84.1) |
| Age (year)              | 50.41 ± 12.67           | 50.24 ± 13.02 |
| Duration (year)         | 3.99 ± 6.41             |     |
| ESR [mm/h]              | 95.1 ± 7.72             |     |
| TJC                     | 12.92 ± 7.04            |     |
| VAS                     | 32.72 ± 31.90           |     |
| RF [IU/mL]              | 369.97 ± 456.72         |     |
| Anti-CCP [RU/mL]        | 557.60 ± 805.82         |     |
| C3 [g/L]                | 0.24 ± 0.09             |     |
| C4 [g/L]                | 1.01 ± 0.32             |     |
| HCT [g/dL]              | 0.30 ± 0.04             |     |
| HGB [g/dL]              | 121.30 ± 168.88         |     |
| PLT [10^9/L]            | 1.25 ± 0.25             |     |
| WBC [× 10^9/L]          | 20.38 ± 27.23           |     |
| N [× 10^9/L]            | 4.20 ± 1.17             |     |
| M [× 10^9/L]            | 1.52 ± 0.54             |     |
| N%                      | 36.88 ± 7.23            |     |
| M%                      | 62.3 ± 1.66             |     |
| L%                      | 3.29 ± 2.46             |     |
| C3 [g/L]                | 17.98 ± 10.19           |     |
| NLR                     | 0.44 ± 0.17             |     |
| PLR                     | 127.90 ± 38.65          |     |
| LMR                     | 4.63 ± 5.15             |     |

anti-CCP: anti-cyclic citrullinated peptide antibodies; C3: complement 3; C4: complement 4; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HCT: hematocrit; HGB: hemoglobin; L: lymphocyte count; Lym: lymphocyte percentage; LMR: lymphocyte:monocyte ratio; M: monocyte count; N: monocyte percentage; NLR: neutrophil:lymphocyte ratio; PLR: platelet:lymphocyte ratio; RBC: red blood cell; RF: rheumatoid factors; SJC: swollen joint count; TJC: tender joint count; VAS: visual analogue scale; WBC: white blood cell.

Statistical analysis

All data are expressed in terms of means ± SE. For the analyses, a Student’s t-test or a Mann-Whitney U-test was used to compare the data according to the normality. The Spearman method was used for correlation analysis. A paired t-test was performed for evaluation of changes related to patient treatment. All data were analyzed using Prism v.5.0 (GraphPad, San Diego, CA) and SPSS v.17.0 (SPSS Inc., Chicago, IL) software. A p-value ≤ 0.05 was considered statistically significant.

Results

Characteristics of study population

This study enrolled a total of 137 participants, i.e. 74 RA patients and 63 HC (healthy controls). Population characteristics are detailed in Table 2. The groups were matched for age and gender for all analyses.

PBMC YTHDF2 mRNA expression as a function of age or sex and disease state

The analyses here revealed that PBMC YTHDF2 mRNA expression among HC and RA subjects > 40 year-of-age were significantly lower compared with younger counterparts (p = 0.006, Figure 1(A) for HC, and p = 0.007, Figure 1(B) for RA). Furthermore, PBMC YTHDF2 mRNA expression was negatively associated with age in HC (r = −0.3467, p = 0.005; Figure 1(C)). On the other hand, there was no correlation between PBMC YTHDF2 mRNA expression among the RA subjects (r = −0.0883, p = 0.4544; Figure 1(D)). No correlation between PBMC of YTHDF2 mRNA expression and sex was observed in either the RA or HC populations (data not shown).

When the RA patients were compared with their controls, it was seen that the presence of the disease state resulted in a significant lowering of YTHDF2 mRNA expression in the PBMC of the RA subjects (p < 0.0011, Figure 2).

Decreased PBMC YTHDF2 mRNA expression correlates with markers of inflammation

Spearman analyses were used to investigate correlations between decreases in PBMC YTHDF2 mRNA expression in samples from RA subjects and corresponding host markers of inflammation, including ESR, CRP, WBC, N, N%, NLR, PLR, LMR in RA. As shown in Figure 3, YTHDF2 mRNA expression in PBMC from RA patients negatively correlated with ESR (r = −0.387, p = 0.001), CRP (r = −0.316, p = 0.006), WBC (r = −0.290, p = 0.012), N (r = −0.278, p = 0.017), N% (r = −0.272, p = 0.019), and NLR (r = −0.268, p = 0.021), while expression in RA patient PBMC did not correlate with PLR (r = −0.152, p = 0.200), LMR (r = 0.160, p = 0.177).

Decreased PBMC YTHDF2 mRNA expression correlates with changes in serum RF levels

Serum levels of anti-CCP and RF, important autoantibodies in RA, were evaluated for their potential associations with PBMC YTHDF2 mRNA expression. The results shown in Figure 4, illustrate that YTHDF2 mRNA expression in PBMC from RA patients negatively-correlated with RF (r = −0.335, p = 0.005) levels, but did not correlate with anti-CCP (r = 0.160, p = 0.177) levels.

Decreased PBMC YTHDF2 mRNA expression correlates with treatment effects on RA

YTHDF2 mRNA expression in PBMC was compared in six new-onset RA cases before and after corticosteroid/immunosuppressant therapy. When compared to pretreatment values, PBMC YTHDF2 mRNA expression increased as a result of the 15-day treatment regimen (Figure 5, p = 0.048). To investigate if decreased YTHDF2 mRNA expression might be related to disease severity and host activity, correlations between PBMC YTHDF2 mRNA expression were analyzed. Ultimately, it was seen that PBMC YTHDF2 mRNA expression did not correlate with any of the clinical measures (data not shown).

Decreased PBMC YTHDF2 mRNA expression correlates with increased cell IL-1β mRNA

The aforementioned results demonstrate that the decreased YTHDF2 mRNA expression in PBMC correlated with several markers of inflammation. To explore whether any decrease in YTHDF2 mRNA expression could potential correlate with inflammatory responses in part by up-regulating pro-inflammatory cytokine expression during RA, PBMC mRNA levels of IL-1β, TNFα, IL-6, and IL-8 were measured. As shown in Figure 6,
PBMC mRNA levels of pro-inflammatory IL-1β (p = 0.005), TNFα (p = 0.017), IL-6 (p = 0.004), and IL-8 (p < 0.0001) were seen as significantly increased in patients with RA compared to in cells from the HC. Correlation analyses showed that of the four, only expression of PBMC YTHDF2 mRNA from RA patients was seen to negatively-correlate with same-cell IL-1β expression ($r_s = -0.4773$, $p = 0.016$). The YTHDF2 mRNA expression in these same PBMC did not correlate with mRNA levels for TNFα ($r_s = 0.228$, $p = 0.262$), IL-6 ($r_s = 0.030$, $p = 0.885$), or IL-8 ($r_s = -0.141$, $p = 0.492$).

Discussion

The current study examined mRNA expression of YTHDF2 in PBMC from RA patients and healthy counterparts. The analyses indicated that YTHDF2 mRNA expression in PBMC from RA patients was significantly lower than in cells from the health controls (HC). These results were inconsistent with those in a report from Wang and colleagues who noted that PBMC YTHDF2 mRNA expression in RA subjects did not significantly differ from values in cells from normal controls (Wang et al. 2019). A cause for this discrepancy in outcomes could possibly be due to differences in the patient populations evaluated, patient numbers, the region where the subjects reside in, and the level of disease progression. Specifically, here, the RA subjects were 74 cases from south China (Jiangxi), all diagnosed as early-onset and the disease duration was short (4.0 ± 6.4 year); in the Wang et al. study, the RA subjects were 47 cases from Northern China (Weifang) and disease duration of the RA subjects was far longer (16.6 ± 5.2 year). In addition, the level of RF differed between the two studies, the level of RF (370.0 ± 456.7 IU/mL) in this study was higher than in the Wang et al. study (191.6 ± 5.7 IU/mL), which was consistent with the result in the current study, i.e. that YTHDF2 mRNA expression in PBMC from RA patients was lower and the level of RF was higher compared to in control PBMC.

Previous studies clearly showed that YTHDF2 could help to regulate LPS-induced inflammatory responses in cultured cells. Specifically, it was seen that YTHDF2 knockdown significantly increased LPS-induced IL-6, TNFα, and IL-1β expression in RAW264.7 cells (Yu et al. 2019). This is important to the pathogenesis of RA in that many inflammatory mediators including IL-1β, TNFα, IL-6, and IL-8 contribute to arthritis and articular deformity (Brennan and McInnes 2008). The current results showed that PBMC YTHDF2 mRNA expression by RA patients was negatively correlated with whole-blood markers of inflammation, e.g. ESR, CRP, WBC, N, N% and NLR. This indicated that PBMC YTHDF2 mRNA expression, at least in RA patients,
was likely to be associated with inflammatory responses in these hosts. To discern if decreased YTHDF2 might promote inflammation by up-regulating PBMC pro-inflammatory cytokine expression in the RA subjects, mRNA levels of IL-1β, TNFα, IL-6, and IL-8 were evaluated. It was seen that the mRNA levels of these cytokines were each significantly increased in the PBMC of the RA

Figure 3. Correlation of inflammation markers with PBMC YTHDF2 mRNA expression. With RA patients, PBMC YTHDF2 mRNA expression negatively-correlated with (A) ESR, (B) CRP, (C) WBC, (D) N, (E) N%, and (F) NLR. Expression did not correlate with (G) PLR or (H) LMR. C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); lymphocyte-to-monocyte ratio (LMR); neutrophil count (N); neutrophil percentage (N%); neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); White blood cell count (WBC).

Figure 4. Correlation of autoantibodies with PBMC YTHDF2 mRNA expression. With RA patients, PBMC YTHDF2 mRNA expression (A) negatively-correlated with serum RF levels, (B) did not correlate with serum anti-CCP levels. Anti-cyclic citrullinated peptide antibodies (anti-CCP), Rheumatoid factors (RF).
(as compared to in HC cells). Of note, the mRNA expression of \textit{YTHDF2} in RA patient PBMC was specifically found to negatively correlated with mRNA levels of IL-1\(\beta\). These results demonstrated that \textit{YTHDF2} mRNA expression, at least in the PBMC of RA patients, may help to regulate inflammatory responses \textit{in situ} in these subjects. Further study is clearly warranted.

Lastly, the current study also evaluated whether the PBMC \textit{YTHDF2} mRNA expression could be used to potentially reflect the current severity of RA in the test subjects. Using a subpopulation who had undergone a 15-day regimen of corticosteroids/immunosuppressants, it was found that PBMC \textit{YTHDF2} mRNA increased after treatment when compared to before treatment. It was also seen that PBMC \textit{YTHDF2} mRNA expression in all RA patients was negatively correlated with serum RF levels. From these two sets of findings, we could assume that \textit{YTHDF2} was associated with the production of RF and participated in the pathogenicity of RA. It is well-known that RF is the landmark autoantibody of RA and is involved in the occurrence and development of RA.

It has become increasingly understood that m6A methylation might play an important role in many pathologies (see Malovic et al. 2021). Considering these emerging roles for m6A methylation, the results from this study showing that \textit{YTHDF2} mRNA expression in autoimmune disease RA was abnormal and that its expression was related to host drug treatment, this study appears to confirm that \textit{YTHDF2} and m6A methylation each likely play critical roles in the onset/progression of some

\begin{figure}[h]
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\caption{PBMC \textit{YTHDF2} mRNA expression and changes in RA status. PBMC \textit{YTHDF2} mRNA expression among six RA patients increased after the 15-day corticosteroid/immunosuppressant treatment regimen when compared with levels prior to treatment.}
\end{figure}

\begin{figure}[h]
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\caption{Correlation of PBMC cytokine mRNA levels with \textit{YTHDF2} mRNA expression. PBMC mRNA levels of (A) IL-1\(\beta\), (B) TNF\(\alpha\), and (C) IL-6 in RA patient cells was significantly increased compared to in HC cells. (D) mRNA levels of IL-8 (\(p < 0.0001\)) were also significantly increased in RA patients PBMC compared with HC cells. (E) PBMC \textit{YTHDF2} mRNA levels with RA patients cells negatively-correlated with cell IL-1\(\beta\) mRNA levels. \textit{YTHDF2} mRNA expression in RA patient PBMC did not correlate with cell mRNA levels for (F) TNF\(\alpha\), (G) IL-6, or (H) IL-8.}
\end{figure}
immunopathologies. Nevertheless, there are several limitations to the present study. The first is the relatively small sample size and that all the samples were selected from only one hospital; this restricted the number and representativeness of the subjects. Second, although mRNA expression is often considered indicative of protein expression, the actual YTHDF2 reader protein turnover in HC and RA patients remains unclear and will be explored in greater detail in our ongoing studies. Lastly, the m6A methylation status of the YTHDF2 mRNA should be investigated to see if this modification process also impacted on the YTHDF2 reader protein status in PBMC and/or other cells (i.e. by performing meRIP-qPCR analyses in our next round of studies).

Conclusions
It is well-established that RA occurs primarily among people aged 40–60 years, with a slightly greater predominance in women than in men. When analyzed in the context of age and sex, the data revealed that YTHDF2 mRNA expression in PBMC from both RA and HC subjects >40 year-of age were significantly lower compared with levels in PBMC from younger counterparts (i.e. <40 year-of age). Interestingly, there seemed to be no association between PBMC YTHDF2 mRNA expression and sex among either the RA or HC populations. Thus, YTHDF2 mRNA expression was clearly associated with age, regardless of disease status. By comparing across age-matched groups, the study here found that in general, the PBMC mRNA expression of YTHDF2 was decreased in RA patients. In addition, decreased YTHDF2 expression was associated with changes in the values for markers of inflammation and PBMC mRNA levels for some key pro-inflammatory cytokines. These data indicate that YTHDF2 could play a regulatory role in the onset/progression of RA. This present research provides a novel target for RA research and opens new avenues to gain insight into underlying inflammatory mechanisms associated with RA.

Author contributions
All authors were involved in revising the text critically for important intellectual content, and all authors approved the final version to be published. QL, JML and FYY are responsible for the study conception and design. CXX, YJG, BQF, LZ, ZKH and YG collected the samples and clinical parameters. QL, FYY, CXX, XZW, and JML are responsible for the analysis and interpretation of data. QL and JML drafted the article.

Disclosure statement
The authors declare no conflict of interest. The authors alone are responsible for the content of this manuscript.

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Data availability statement
Data used to support findings in the present study are available from the corresponding author, upon reasonable request.

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