miRNA Profiling of Extracellular Vesicles Reveals Biomarkers for Psoriasis


TO THE EDITOR
Psoriasis is a chronic inflammatory skin disorder resulting from the complex pathogenic interactions of the immune system, keratinocytes, genetic susceptibility, and environmental factors. Moreover, psoriasis is regarded as a systemic disease that extends beyond the skin (Boehncke and Schön, 2015), and identification of blood-based biomarkers is of clinical and research significance to a certain extent.

MicroRNAs (miRNAs) are short single-stranded noncoding RNAs (21–24 nucleotides), which mediate posttranscriptional regulation by binding to the 3’ untranslated regions of targeting mRNAs, thus inhibiting their translation, accelerating turnover or degradation (Zibert et al., 2010). Several publications implicate that miRNAs play an important role in the pathogenesis of psoriasis by mediating inflammatory cytokine signaling, immune cell infiltration and differentiation, and keratinocyte hyperproliferation in psoriatic skin (Jiang et al., 2017; Srivastava et al., 2017; Wu et al., 2018; Yan et al., 2015). Serum levels of miR-369-3p and miR-1266 in patients with psoriasis (Pso) were considerably higher than those in healthy controls (HCs), and miR-1266 levels showed a positive correlation with PASI score (Guo et al., 2013; Seifeldin et al., 2016). Another study found that miR-125b, miR-146a, miR-203, and miR-205 were significantly decreased in the sera from Pso compared with the sera from normal subjects (Koga et al., 2014).

Previous evidence reveals that miRNA exchange between cells can be accomplished through extracellular vesicles (EVs) (Valadi et al., 2007). EVs are membrane-contained vesicles released by different cell types with the capacity to transfer intercellular information both locally and systemically. Cell-to-cell communication of EVs is realized by the complex cargo, including miRNAs, mRNAs, DNA, proteins, lipids (Robbins and Morelli, 2014; Witwer et al., 2013), and the unique package. Therefore, certain miRNA biomarkers of EVs are not only protected from degradation in the bloodstream but may reflect the characteristics of their parent cells (Cheng et al., 2014; Valentino et al., 2017). Thus, these features make EV-enclosed miRNA analysis superior to whole serum for exploring biomarkers in psoriasis.

To determine miRNA profiling of serum EVs in psoriasis, we examined paired sera from eight Pso and eight HCs (Supplementary Table S1) in the discovery set by small RNA sequencing. All donors provided written informed consent for this study. Research protocols were approved by the Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine. The small RNA sequencing demonstrated 1,075 and 1,066 known miRNAs in serum EVs from Pso and HCs, respectively (NCBI SRA, accession number: SRP250251). Among them, 913 miRNAs were simultaneously identified in both groups (Figure 1a). Moreover, we found 72 novel miRNAs expressed in at least one of the groups (Supplementary Table S2). According to the expression level in Pso, the top 10 most highly expressed miRNAs were miR-451a, let-7i-5p, miR-126-3p, miR-148a-3p, miR-26a-5p, miR-21-5p, miR-151a-3p, let-7g-5p, let-7f-5p, and let-7a-5p (Supplementary Table S3). Differential expression analysis of mature miRNA was conducted by DESeq (fold change > 1 and adjusted \( P < 0.05 \)). We identified 50 miRNAs with a significant change in expression level between Pso and HC, out of which 26 were upregulated and 24 were downregulated (Figure 1b–d, Supplementary Table S4). Figure 1c shows the top 10 highest log2-fold-change miRNAs differentially expressed in serum EVs of Pso versus HC, in which miR-11400 upregulated and miR-501-3p downregulated most significantly. The heatmap displays the patterns of miRNA expression between the experimental groups (Figure 1d).

To further confirm the miRNA signature found in the discovery set, we compared miRNA in serum EVs from Pso \( (n = 30) \) and \( HC \ (n = 18) \), and patients with pityriasis rosea \( (PR, n = 21; \text{Supplementary Table S5}) \), a common exanthematous erythematous skin disease manifested with typically herald patch followed by smaller scaly spots, by qRT-PCR. The expression level of miR-199a-3p was significantly upregulated in Pso than that in HC and PR (Figure 2a), and it had a relatively high receiver operating characteristic curve of 0.8647 (Figure 2b). In addition, the increase in the expression level of miR-199a-3p was positively correlated with PASI score and body surface area in Pso (Figure 2c and d). Furthermore, we tested 14 unpaired Pso who reached PASI90 after systemic treatment, and their miR-199a-3p decreased significantly (Figure 2e–g). However, there was no significant difference in miR-199a-3p in PBMCs (Supplementary Figure S1). Thus, miR-199a-3p may not only provide a clear distinction between psoriasis, pityriasis rosea, and HCs but also reflect the severity of psoriasis and therapeutic effect.

Pityriasis rosea is sometimes difficult to distinguish from psoriasis. Of note, the levels of miR-500a-3p, miR-484, miR-185-3p, miR-27a-5p, and let-7f-5p in serum EVs from Pso and HC were significantly lower than those from PR (Figure 2h–m), whereas miR-1255b-5p level was less in PR (Figure 2n). In addition, the differentially expressed miRNAs in PR provided fairly good area

Abbreviations: EV, extracellular vesicle; HC, healthy control; miRNA, microRNA; PR, patients with pityriasis rosea; Pso, patients with psoriasis

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Figure 1. The miRNA signature of serum EVs. (a) Venn diagram showing the unique and overlapping miRNAs in serum EVs between Pso (n = 8) and HC (n = 8). (b) Volcano plot diagram for 50 miRNAs with significant change in expression level. (c) The top 10 highest log2-fold-change miRNAs differentially expressed in serum EVs of Pso versus HC. (d) Unsupervised hierarchical clustering and heatmap of differential miRNA expression in serum EVs between Pso and HC. EV, extracellular vesicle; HC, healthy control; miRNA, microRNA; Pso, patients with psoriasis; vs., versus.
under the curve values to discriminate them from Pso (for miR-500a-3p, 0.9557; for miR-484, 0.8762; for miR-185-5p, 0.7915; for miR-27a-5p, 0.7964; for miR-1255b-5p, 0.8183; Figure 2o). The abovementioned results indicated that these miRNAs in serum EVs had specific expression levels in pityriasis rosea, suggesting that they may serve as diagnostic biomarkers for psoriasis and pityriasis rosea.

In addition to the above miRNAs differentially expressed in Pso and PR, there was no statistical difference in some other miRNAs, including miR-21-5p, let-7a-5p, let-7e-5p, miR-148a-3p, and miR-374b-5p (Supplementary Figure S2a–e). Furthermore, the levels of the remaining miRNAs were too low to allow analysis, such as miR-11400 and miR-501-3p.

Next, we searched bioinformatics miRNA target databases to explore the potential functions of these miRNAs.
Using miRNet, 114 mRNAs were found to be predicted targets of miR-199a-3p (Figure 2p). Kyoto Encyclopedia of Genes and Genomes pathway analysis indicated that 17 targets marked with green dots were significantly enriched in the focal adhesion pathway and mammalian target of rapamycin pathway (Figure 2q). Moreover, we found 16 mRNAs as shared putative targets for the six miRNAs significantly changed in PR. Then, we mapped the miRNA-mRNA regulatory network (Figure 2q).

By comparison, the differential expression of miR-199a-3p between Pso and HC found in the validation set was consistent with small RNA sequencing, but other miRNAs had no significant change that was different from the sequencing results. The relatively small sample size and the variation of miRNA profiling among samples might be the cause of these inconsistencies.

A recent publication has demonstrated that circulating EV miRNAs, let-7b-5p and miR-30e-5p, were reduced in patients with psoriatic arthritis compared with patients with psoriasis vulgaris (Pasquali et al., 2020). The study performed small RNA sequencing on the above two types of patients. The most abundant miRNAs included miR-451a and several members of the let-7 family, partially consistent with our results. However, HCs were not included in the study, making it difficult to compare the differentially expressed miRNAs with those of our study.

In conclusion, this study provides evidence that serum EVs contain specific miRNAs with potential diagnostic value for psoriasis and pityriasis rosea. The results of this study underscore the involvement of circulating EVs in psoriasis and pityriasis rosea and may contribute to a better definition of their pathogenesis through deep investigation.

**Data availability statement**
Small RNA sequencing data are openly available at the National Center for Biotechnology Information Sequence Read Archive (https://www.ncbi.nlm.nih.gov/sra/), accession number: SRP250251.

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**CONFLICT OF INTEREST**
The authors state no conflict of interest.

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**AUTHOR CONTRIBUTIONS**
Conceptualization: ZYW, XYM, SQC, MZ; Data Curation: ZYW, YZ; Formal Analysis: ZYW, XYM; Funding Acquisition: SQC, MZ, YYM; Investigation: ZYW, YZ, BXY, YXC, JZ; Methodology: ZYW, XYM, SQC; Project Administration: ZYW, YXM, MZ; Resources: YXM, MZ, SQC; Supervision: YXM, MZ, SQC; Validation: BXY, YZ, YXC; Visualization: ZYW, YXM; Writing - Original Draft Preparation: ZYW, YZ; Writing - Review and Editing: ZYW, YXM, XYM, MZ, SQC.

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**SUPPLEMENTARY MATERIAL**
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2020.04.021.

**REFERENCES**
Acne Eligibility Criteria Related to Hormones: A Systematic Review

TO THE EDITOR

Hormones play a complex role in acne pathogenesis and treatment. Androgens typically increase the size and secretion of sebaceous glands, worsening acne, whereas estrogen counters androgen effect by direct local opposition, inhibition of androgen production, and gene regulation (Barros and Thiboutot, 2017; Beinenfeld et al., 2019). Despite multiple guidelines on acne management, there is a paucity of high-quality data on the treatment of acne among patients receiving hormone therapy (Beinenfeld et al., 2019; Del Rosso et al., 2015; Zaenglein et al., 2016). In the United States, this potentially impacted the treatment of acne among at least 9.1 million women using oral contraceptive pills in 2015–2017 and 2.3 million cisgender and transgender men receiving testosterone replacement therapy (Daniels and Abma, 2018; U.S. Food and Drug Administration, 2018). We sought to examine the inclusion and exclusion criteria of acne clinical trials to identify potential barriers to the enrollment of patients receiving hormone therapy.

We queried ClinicalTrials.gov for interventionalal studies from 1 January 2009 to 16 May 2019 using the search term acne. All age groups and sexes were included, including those with healthy volunteers. The inclusion and exclusion criteria of acne interventions with a focus on those related to hormone therapy and contraception were analyzed.

Of 121 studies identified, 86 were included (2 duplicates, 8 not related to acne, 25 targeted acne scar appearance) (Table 1). A total of 33 studies (38%) had exclusion criteria related to hormone therapy, including recent changes in therapies such as oral contraceptives, estrogen, and antiandrogenic medications within specified time ranges (ranging from 4 weeks to 1 year). Patients with hormone disorders were excluded in four studies (4.7%). Other exclusion criteria included current use of oral contraceptives (3.5%), androgen blockers (4.7%), and hormone replacement therapy (2.3%). Overall, patients receiving consistent oral contraceptives, androgen blocker therapy, or hormone replacement therapy would be excluded from nine trials (10.5%). Contraceptive requirements were specified in 36 studies (41.9%), which were listed based on gender, sexual behavior, and/or reproductive potential.

Nearly half of acne clinical trials had exclusion criteria that presented potential barriers to patients receiving hormone therapy, including women receiving hormone contraception and men receiving testosterone replacement therapy. In general, women over the age of 25 years with acne tend to have acne that is refractory to conventional therapies and related to androgen production regardless of whether they have clinical signs of hyperandrogenism (Barros and Thiboutot, 2017; Beinenfeld et al., 2019; Del Rosso et al., 2015). Men may experience increased sebum production and acne from testosterone replacement for hypogonadism or gender-affirming hormone therapy, and hormone-related exclusion criteria further contribute to the dearth of evidence on optimizing testosterone-related acne treatment for cisgender and transgender men (Yeung et al., 2019). In some cases, the practice of excluding patients on hormone therapy may be reasonable; clinical trials typically restrict patients newly placed on hormone replacement therapy would be excluded from nine trials (10.5%).
SUPPLEMENTARY MATERIALS AND METHODS

Serum samples from patients and healthy donors
For the whole study, we prepared two independent sample sets to discover and validate potential microRNA (miRNA) biomarkers for psoriasis in serum extracellular vesicles (EVs). In both sets, sera from patients with psoriasis (Pso, n = 52), patients with pityriasis rosea (PR, n = 23), and healthy controls (HCs, n = 26) were collected at Dermatology Department, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China. PASI and body surface area were determined at the time of sample collection.

Research protocols were approved by the Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China. PASI and body surface area were determined at the time of sample collection.

In the discovery set, paired sera from Pso (n = 8) and HC (n = 8) were chosen for small RNA sequence. Paired sera from Pso (n = 30), PR (n = 21), and HC (n = 18) were designated as the validation set. The above patients with Pso were untreated with systemic drugs for at least 1 month. In addition, sera from Pso (n = 14) who reached PASI 90 after systemic treatment were tested.

Extraction of total RNA from exoRNeasy-enriched EVs
EV RNA was extracted from serum with exoRNeasy Serum-Plasma Midi Kit and exoRNeasy Serum-Plasma Maxi Kit (Qiagen, Hilden, Germany), which were designed for the direct purification of total vesicular RNA without the intermediate isolation of EVs, according to the manufacturer’s instructions. Briefly, 1 volume of serum (1 ml with the midi format and 4 ml with the maxi format) was mixed with 1 volume of buffer XB and added onto the exoEasy spin column to bind the EVs on the basis of the principle of membrane affinity. After centrifugation (500g for 1 minute at 20 °C), the flow-through was discarded. Buffer XWB was added to the column to remove residual material by another centrifugation (5,000g for 5 minutes at 20 °C) and discarding of the flow-through. Then, we added 700 μl QIAzol Lysis Reagent (Qiagen) to the membrane and collected the lysate through centrifugation. After the addition of chloroform and centrifugation, the lysate was separated into aqueous and organic phases. The upper aqueous phase was recovered and mixed with ethanol. The mixture was added to the RNeasy MinElute spin column and centrifuged, followed by buffer RWT and buffer RPE washing. Finally, 14 μl RNase-free water was used to elute the RNA. RNA samples were frozen at −80 °C before further use. RNA amount and integrity were analyzed by Qubit 2.0 Fluorometer (Life Technologies, Foster City, CA) and Agilent Bioanalyzer 2100 system (Agilent Technologies, Santa Clara, CA).

Library preparation and small RNA sequencing
Sequencing libraries were generated by NEBNext Multiplex Small RNA Library Prep Set for Illumina (NewEngland Biolabs, Ipswich, MA) following the manufacturer’s recommendations. Briefly, NEB 3’ SR Adaptor was specifically ligated to the 3’ end of small RNA. After the 3’ ligation reaction, the SR RT Primer was applied to hybridize to the excess of 3’ SR Adaptor and transform the single-stranded DNA adaptor into a double-stranded DNA molecule, which was important to prevent adaptor-dimer formation. Then, we added 5’SR Adaptor to ligate to 5’ end of small RNA, followed by the reverse transcription reaction using M-MuLV Reverse Transcriptase (RNase H–). PCR amplification was performed using LongAmp Taq 2X Master Mix, SR primer for Illumina, and index (X) primer. Subsequently, PCR products were separated on an 8% polyacrylamide gel to purify DNA fragments corresponding to 140–160 base pairs. Finally, libraries were dissolved in 8 μl elution buffer and assessed on the Agilent Bioanalyzer 2100 system (Agilent Technologies). Libraries were sequenced on the HiSeq 2500 platform (Illumina, San Diego, CA).

Sequencing data analysis
After sequencing, raw reads in fastq format were filtered for possible technical artifacts and biological contaminants. At the same time, Q30 values and GC-content of the raw data were calculated. Then, the filtered reads were mapped to the reference sequence by Bowtie2 (Langmead and Salzberg, 2012). Alignments of known miRNA were retrieved from miRBase 20.0. The available software miRevo (Wen et al., 2012) and mirdeep2 (Friedländer et al., 2012) were integrated to predict novel miRNA by exploring the secondary structure, the Dicer cleavage site, and the minimum-free energy of the small RNA tags unannotated in the former steps. MiRNA expression level was estimated by transcript per million. Differential expression analysis was conducted with the DESeq R package (1.8.3). The P-values were adjusted using the Benjamini-Hochberg method, with a false discovery rate of 0.05. The above small RNA sequence and data analysis were performed by Novogene Bioinformatics Technology (Beijing, China).

PBMC separation and total RNA extraction
Human PBMCs were prepared from the blood of Pso (n = 12) and HC (n = 10). A total of 4 ml of whole blood was diluted with 4 ml PBS, layered onto 4 ml of Ficoll (Sigma-Aldrich, St. Louis, MI), and centrifuged at 800g for 20 minutes at room temperature. The PBMC interface was carefully recovered and washed with PBS by centrifugation (250g for 5 minutes at 4 °C). Total RNA was extracted from PBMCs using the miRNeasy Mini Kit (Qiagen), following the manufacturer’s instructions.

MiRNA expression analysis by qRT-PCR
The reverse transcription reaction was performed using the miScript II RT kit (Qiagen) according to the manufacturer’s instructions. Briefly, 12 μl isolated RNA was added to the cDNA master mix, composed of miScript Reverse Transcription Mix, 10× miScript Nucleics Mix, and 5× miScript HiiSpec Buffer (mature miRNA detection only), to a total volume of 20 μl. The reaction mixture was incubated at 37 °C for 60 minutes, followed by 5-minute incubation at 95 °C. The cDNA was diluted 10 times to serve as a template for further analysis.
The expression levels of candidate miRNAs were validated by qRT-PCR using FastStart Universal SYBR Green PCR Master (Roche Holdings AG, Basel, Switzerland) and miRNA-specific primers in a QuantStudio 5 Real-Time PCR system (Applied Biosystems, Waltham, MA), following the amplification procedures recommended by the manufacturer (15 minutes at 95 °C, followed by 40 cycles of 15 seconds at 94 °C, 30 seconds at 55 °C, and 35 seconds at 70 °C). The primers were designed by miRprimer2.0 (Busk, 2014).

For miRNAs in EVs, geNorm software was used to select the optimal set of reference genes for normalization (Vandesompele et al., 2002). After geNorm analysis, the geometric mean of miR-126-3p, miR-26a-5p, and let-7i-5p was considered as the optimal normalization factor for our experimental conditions. For miRNAs in PBMCs, RNU6 was used as the reference gene. The relative expression level of miRNAs was calculated by the $2^{-\Delta\Delta C_t}$ method.

**miRNA target gene prediction**
Bioinformatics miRNA target prediction, regulatory network visualization, and Kyoto Encyclopedia of Genes and Genomes pathway analysis were performed using miRNet platform, which integrates data from 11 different miRNA databases (http://https://www.mirnet.ca/miRNet/home.xhtml/) (Fan et al., 2016).

**Statistical analysis**
The comparisons of means were analyzed by Mann-Whitney test and one-way ANOVA, the latter including Kruskal-Wallis test and Dunn Multiple Comparison test. The associations between miR-199a-3p expression level and PASI score or body surface area were confirmed by linear regression. $P$-value was calculated by $R^2$ statistic. The area under the receiver operating characteristic curve (area under the curve) was calculated. All these statistical analyses were performed using GraphPad Prism 8 (GraphPad Software, San Diego, CA). $P < 0.05$ was considered statistically significant.

**SUPPLEMENTARY REFERENCES**
Supplementary Figure S1. The expression level of miR-199a-3p in PBMCs. PBMCs were prepared from the blood of Pso (n = 12) and HC (n = 10). Significance was determined by Mann-Whitney test. \(* P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001\). HC, healthy control; Pso, patient with psoriasis.

Supplementary Figure S2. Expression analysis of candidate miRNAs in serum EVs by qRT-PCR. (a–e) qRT-PCR expression analysis of miR-21-5p, let-7a-5p, let-7e-5p, miR-148a-3p, and miR-374b-5p in serum EVs from Pso (n = 30), PR (n = 21), and HC (n = 18). Significance was determined by Kruskal-Wallis test. \( * P < 0.05, ** P < 0.01, *** P < 0.001, **** P < 0.0001\). EV, extracellular vesicle; HC, healthy control; miRNA, microRNA; PR, patient with pityriasis rosea; Pso, patient with psoriasis.
### Supplementary Table S1. The Characteristics of Pso and HC Studied in the Discovery Set

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<th>Gender</th>
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<th>HCs</th>
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<td>51</td>
<td>90</td>
</tr>
<tr>
<td>Female</td>
<td>35</td>
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Abbreviations: BSA, body surface area; HC, healthy control; Pso, patient with psoriasis.

### Supplementary Table S3. The Top 10 Most Highly Expressed miRNAs in Serum EVs from Pso and HC on the Basis of the Expression Levels of Pso

<table>
<thead>
<tr>
<th>miRNA ID</th>
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<th>Pso</th>
<th>Fold change</th>
<th>Adjusted P-value</th>
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<td>hsa-miR-451a</td>
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<td>hsa-miR-148a-3p</td>
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<td>hsa-miR-26a-5p</td>
<td>70160.0</td>
<td>46630.0</td>
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<td>hsa-miR-21-5p</td>
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Abbreviations: EV, extracellular vesicle; HC, healthy control; miRNA, microRNA; Pso, patient with psoriasis.