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CCNB1 and CCNB2 involvement in the pathogenesis of psoriasis: a bioinformatics study

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Abstract

Objective: The cell cycle-related proteins cyclin B1 (CCNB1) and cyclin B2 (CCNB2) are potentially involved in the underlying mechanisms of psoriasis. The present study aimed to explore this possibility using bioinformatics approaches.

Methods: CCNB1 and CCNB2 protein levels were evaluated in 14 psoriasis patients and five healthy controls by enzyme-linked immunosorbent assays, and their mRNA levels were evaluated using data from four publicly available datasets (GSE53552, GSE41664, GSE14905, and GSE13355). Comparison of high- and low-expressing groups were performed to reveal CCNB1- and CCNB2-related differentially expressed genes, which were then assessed based on gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses. Correlation analyses between *CCNB1* and *CCNB2* levels and immune infiltration, as well as typical targets of psoriasis, were also performed.

Results: Overall, 12 CCNB1 and CCNB2 common immune-related targets potentially involved in psoriasis were identified. These could regulate the cell cycle of through multiple pathways. In addition, CCNB1 and CCNB2 were found to potentially support the release of key molecular targets of psoriasis through the regulation of mast cell activation and macrophage polarization.

Conclusions: These findings suggest that CCNB1 and CCNB2 may represent valuable molecular biomarkers of psoriasis, contributing to its onset and progression.

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Introduction

Psoriasis is a common, chronic, recurrent, immune-mediated, and genetic skin disorder that is histologically characterized by hyperproliferation and abnormal differentiation of keratinocytes. Approximately 125 million people worldwide have psoriasis, reaching an incidence of approximately 80 new cases per 100,000 persons per year. In the United States, approximately 3.2% of adults and 0.13% of children have psoriasis.[1] The pathological manifestations of psoriasis can vary, including parakeratosis and acanthosis of the epidermis, as well as immune cell infiltration of the dermis and epidermis.[2–4] Moreover, accelerated cell cycle and hyperproliferation of keratinocytes are among the main factors that cause psoriasis progression.[5] Therefore, a better understanding of how to prevent these abnormal molecular events is an important research direction to help identify potential new treatments for psoriasis. For example, Yang et al. found that nitidine chloride can inhibit the cell cycle and proliferation of keratinocytes by downregulating the expression of cell cycle-related proteins.[6] Moreover, Yin et al. demonstrated that high expression of *IL28RA* can activate downstream signaling pathways in keratinocytes with antiproliferative effects, whereas low *IL28RA* expression may contribute to the onset of psoriasis.[7]

Cyclin B1 (CCNB1) and cyclin B2 (CCNB2) are members of the cyclin family and are essential components of the cell cycle regulatory machinery.[8] Several studies have shown that CCNB1 and CCNB2 contribute to the proliferation and invasion of various cancer cell types, including hepatocellular carcinoma, lung adenocarcinoma, and bladder cancer.[9–11] Moreover, high expression of CCNB1 and CCNB2 can promote the proliferation and cell cycle progression of keratinocytes, further exacerbating psoriasis manifestations.[12,13] Bioinformatics analyses by Choudhary and Melero showed that CCNB1 is a core target in the onset mechanism of psoriasis and may contribute to the transformation of mild to severe psoriasis.[14,15] Furthermore, Li et al. showed that CCNB2 expression ameliorates the symptoms of psoriasis patients.[16] Indeed, bioinformatics analyses by Zou et al. further showed that CCNB1 and CCNB2 levels are correlated with several immune cell types, including $CD4^+$ T cells, $CD8^+$ T cells, B cells, neutrophils, and macrophages.[9] However, the immune-related mechanisms and role of CCNB1 and CCNB2 in psoriasis remain unclear.

In recent years, some bioinformatic algorithms, such as ESTIMATE and CIBERSORT, were developed for accurately assessing the abundance of immune cells in tumor and non-tumor diseases,[17–18] including in psoriasis,[19] lupus nephritis,[20] and osteoarthritis.[21] However, these algorithms are often used to comparatively assess immune infiltration between diseased and healthy individuals.

The present study aimed to verify the expression levels of CCNB1 and CCNB2 in clinical samples collected from psoriasis patients and explore their potential immune regulatory mechanism in this disease using

bioinformatics tools. We expect that the collected data will provide new insights into the pathogenesis of psoriasis, paving the way for the development of new targeted treatments for this common disease.

Methods

Clinical sample verification

Validation of clinical samples was performed at the Qingdao Huangdao District Central Hospital (Qingdao, China). Psoriasis patients and healthy controls were recruited at the Qingdao Huangdao District Central Hospital. Two professional dermatologists assessed the patients according to the psoriasis area severity index and dermatology life quality index.[22] The content of core targets was evaluated in serum samples using commercially available enzyme-linked immunosorbent assays (ELISAs) (Meimain, Wuhan, China) according to the manufacturer's instructions. The study protocol was approved by the Qingdao Huangdao District Central Hospital Ethics Committee and was conducted in accordance with the Declaration of Helsinki. Verbal informed consent was obtained from all participants prior to the study. Most participants provided written informed consent prior to the study, but those who only consented verbally gave written informed consent during the follow-up diagnosis and treatment periods.

Screening of CCNB1- and CCNB2-related immune targets

Four psoriasis-related datasets (GSE53552,[23] GSE41664,[24] GSE14905,[25] and GSE13355[26]) were obtained from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). Expression data of *CCNB1* and *CCNB2* in healthy volunteers and psoriasis patients were extracted and compared. Moreover, data from psoriasis patients were divided into high and low expression groups based on the median expression value of *CCNB1* and *CCNB2*. Next, differential expression analysis was performed between the high and low expression groups in each dataset using the "*limma*" R package (http://bioconductor.org/packages/release/bioc/html/lim ma.html), and CCNB1- and CCNB2-related differentially expressed genes (DEGs) were screened in each dataset. Immune gene information was obtained from the ImmPort database (https://www.immport.org/shared/home), and the Evenn tool (http://www.ehbio.com/test/venn/#/) was used to screen the intersection of common CCNB1- and CCNB2-related immune DEGs.

Protein–protein interaction (PPI) network construction and functional enrichment analysis

The STRING database (https://www.string-db.org/) was used to construct a PPI network based on the common CCNB1- and CCNB2-related immune DEGs. Moreover, gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the "*clusterProfiler*" (http://bioconductor.org/packages/release/bioc/html/clusterProfiler.html), "*org.Hs.eg.db*" (http://bioconductor.org/packages/release/data/annotation/html/org.Hs.eg.db.html), and "*enrichplot*" (http://bioconductor.org/packages/devel/bioc/html/enrichplot.html) R packages to explore the underlying molecular contribution of these common immune-related targets in psoriasis.

Immune infiltration analysis

Immune infiltration analysis was performed to calculate the abundance of multiple immune cells based on the four GEO

datasets using the "*preprocessCore*" R package (http://bioconductor.riken.jp/packages/3.0/bioc/html/preprocessCore.html). Moreover, the relationship between the abundance of immune cells and *CCNB1* and *CCNB2* expression was evaluated by correlation analysis. Principal component analysis (PCA) was performed to detect the differences between healthy and psoriasis samples in the GEO datasets.

Correlation analysis with targets of psoriasis

Expression data of *CCNB1*, *CCNB2*, and typical target genes of psoriasis (*IL17A*, *IL22*, *IL23R*, and *TNF*) were obtained from the GEO datasets to perform correlation analyses using the Spearman test.

Statistical analysis

All data are presented as mean ± standard deviation and were analyzed by Student's *t*-tests or one-way analysis of variance using Prism 9.0 (GraphPad Software, San Diego, CA, USA) and RStudio 1.2 software (RStudio PBC, Boston, MA, USA). *P*-values lower than 0.05 were considered statistically significant.

Results

CCNB1 and CCNB2 expression in psoriasis

Overall, 14 psoriasis patients (five men and nine women) and five healthy controls (two men and three women) were included in the study. ELISA assessment of CCNB1 and CCNB2 levels in the serum of primary psoriasis patients confirmed that secretion of these proteins was significantly increased compared with healthy individuals ($P = 0.0495$; Figure 1a, 1b). Further analysis of *CCNB1* and *CCNB2* expression levels in four publicly available datasets also confirmed that these genes were expressed significantly higher in psoriasis patients than in healthy controls ($P = 0.0072$; Figure 1c, 1d). Hence, these findings suggest that CCNB1 and CCNB2 may have a significant role in psoriasis.

Screening of CCNB1- and CCNB2-related immune targets

CCNB1-related genes were screened out from 9936 DEGs in GSE53552 (Figure 2a), 5,358 DEGs in GSE41664 (Figure 2b), 2828 DEGs in GSE14905 (Figure 2c), and 1762 DEGs in GSE13355 (Figure 2d). CCNB2-related genes were screened out from 9438 DEGs in GSE53552 (Figure 2e), 1580 DEGs in GSE41664 (Figure 2f), 2334 DEGs in GSE14905 (Figure 2g), and 1703 DEGs in GSE13355 (Figure 2h). Overall, 49 CCNB1- and 14 CCNB2-related immune DEGs were identified (Figure 3a, 3b), of which 12 genes were both CCNB1- and CCNB2-related immune DEGs (Figure 3c).

PPI network and functional enrichment analysis

A PPI network was constructed based on the identified CCNB1 and CCNB2 common immune-related DEGs to reveal the potential relationship between them (Figure 3d). GO enrichment analysis of these genes concerning their biological processes showed that the common immune-related DEGs were mainly associated with positive regulation of fibroblast proliferation, regulation of fibroblast proliferation, fibroblast proliferation, and mitotic nuclear envelope disassembly (Figure 3e). Cellular component analysis also suggested that the common immune-related DEGs were involved in cyclin-dependent protein kinase holoenzyme complex, serine/threonine protein kinase complex, protein kinase complex, and condensed chromosome kinetochore

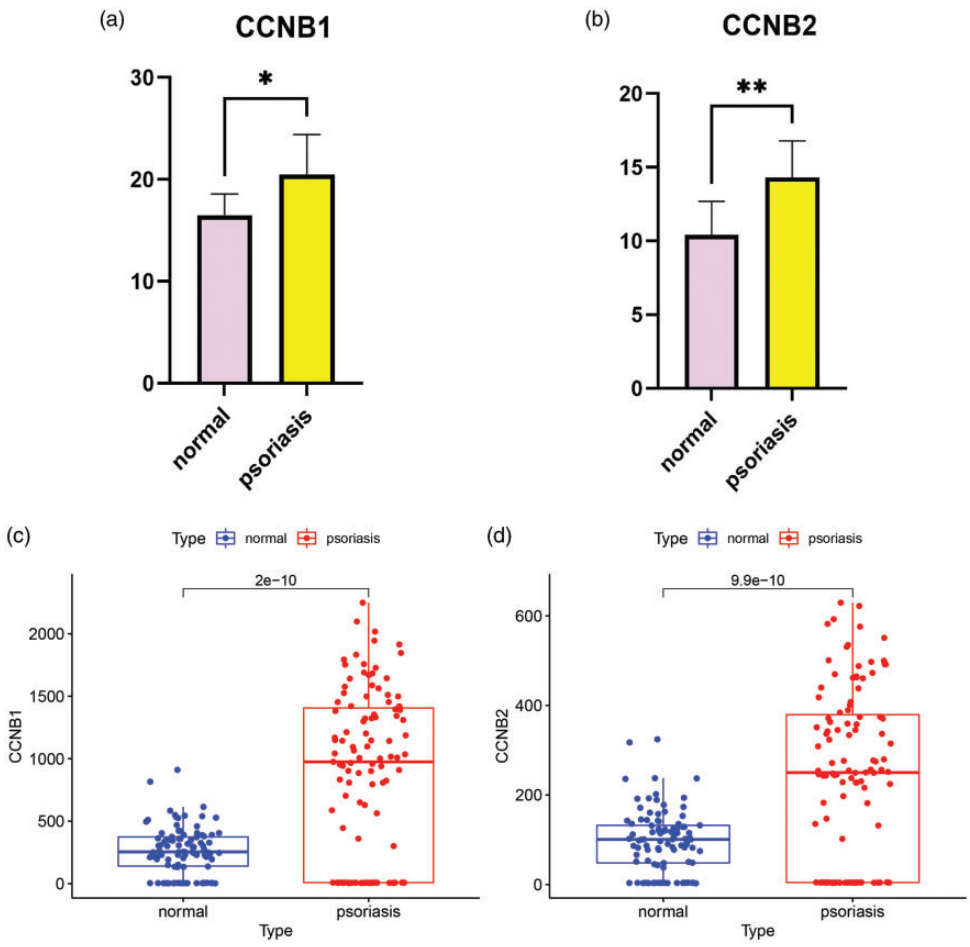

Figure 1. Verification of the protein and mRNA expression of cyclin B1 (CCNB1) and cyclin B2 (CCNB2). (a,b) Protein levels of (a) CCNB1 and (b) CCNB2 were measured in the serum of psoriasis patients and healthy individuals by enzyme-linked immunosorbent assays (ELISAs) ($P = 0.0495$ and 0.0072, respectively). (c,d) mRNA expression profiles of (c) *CCNB1* and (d) *CCNB2* were determined in psoriasis patients and compared with those of healthy individuals using data from four publicly available Gene Expression Omnibus (GEO) datasets ($P = 2 \times 10^{-10}$ and 9.9×10^{-10}, respectively).

(Figure 3e). Moreover, molecular function analysis revealed that the chromobox (CBX) family and correlated genes were enriched in calcium-dependent protein binding, platelet-derived growth factor receptor binding, growth factor activity, and receptor ligand activity (Figure 3e). KEGG pathway enrichment analysis further revealed that the common immune-related DEGs were enriched in multiple pathways, including melanoma, the p53 signaling pathway, cell cycle, cellular senescence, and the FoxO signaling pathway (Figure 3f).

Immune infiltration analysis

Immune infiltration analysis revealed a differential abundance of multiple immune cell populations in psoriasis patients, including naïve B cells, $CD4^+$ memory-activated

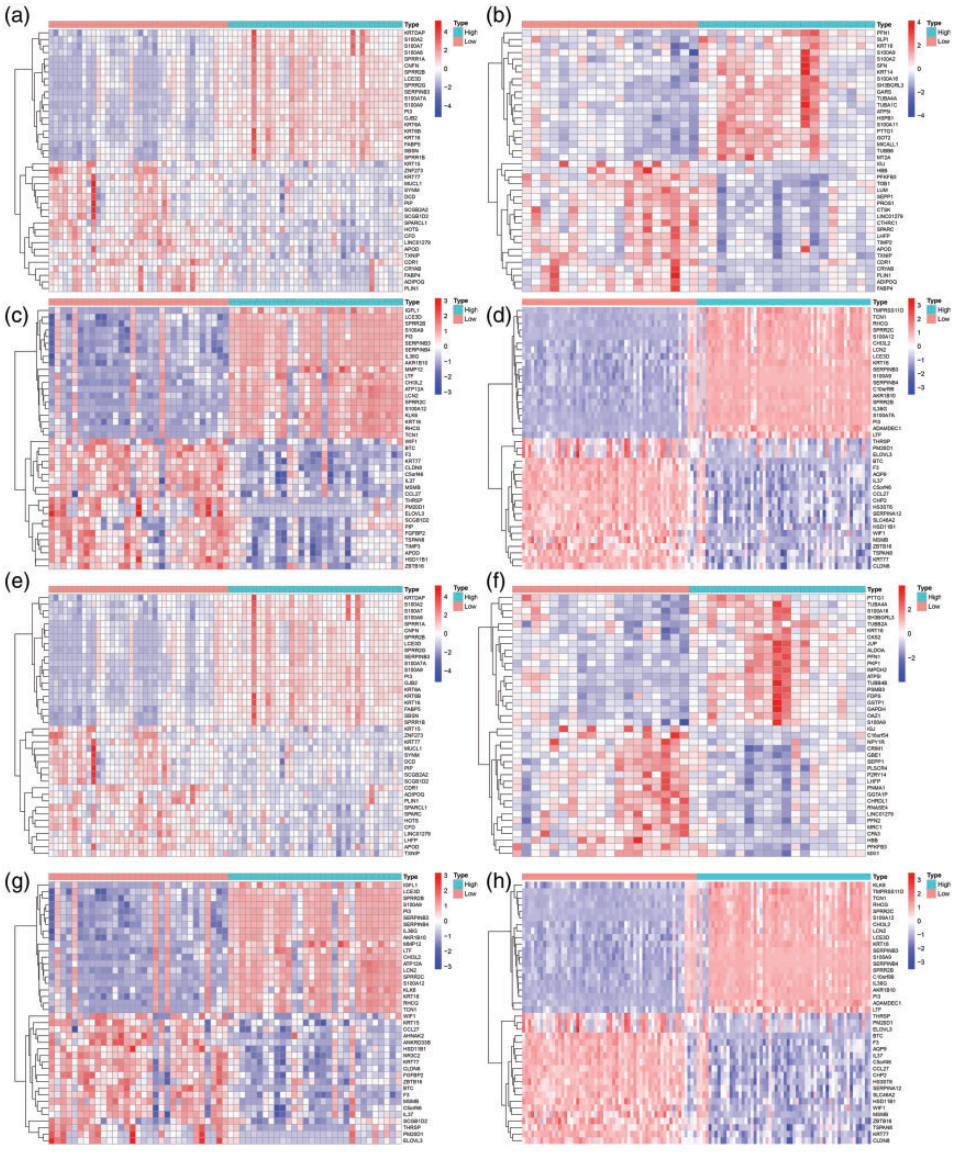

Figure 2. Heatmap of the differential gene expression profile between psoriasis patients with high and low (a–d) *CCNB1* and (e–h) *CCNB2* levels. The following publicly available datasets were analyzed: (a, e) GSE53552, (b, f) GSE41664, (c, g) GSE14905, and (d, h) GSE13355. Red and blue rectangles represent high and low expression, respectively.

T cells, T follicular helper cells, T regulatory cells, resting and activated natural killer cells, monocytes, M0 and M1 macrophages, activated dendritic cells, resting and activated mast cells, and eosinophils (Figure 3g, h). Correlation analysis further showed that *CCNB1* and *CCNB2* levels were negatively associated with the abundance of most of the immune cell populations. In particular, they were significantly negatively correlated

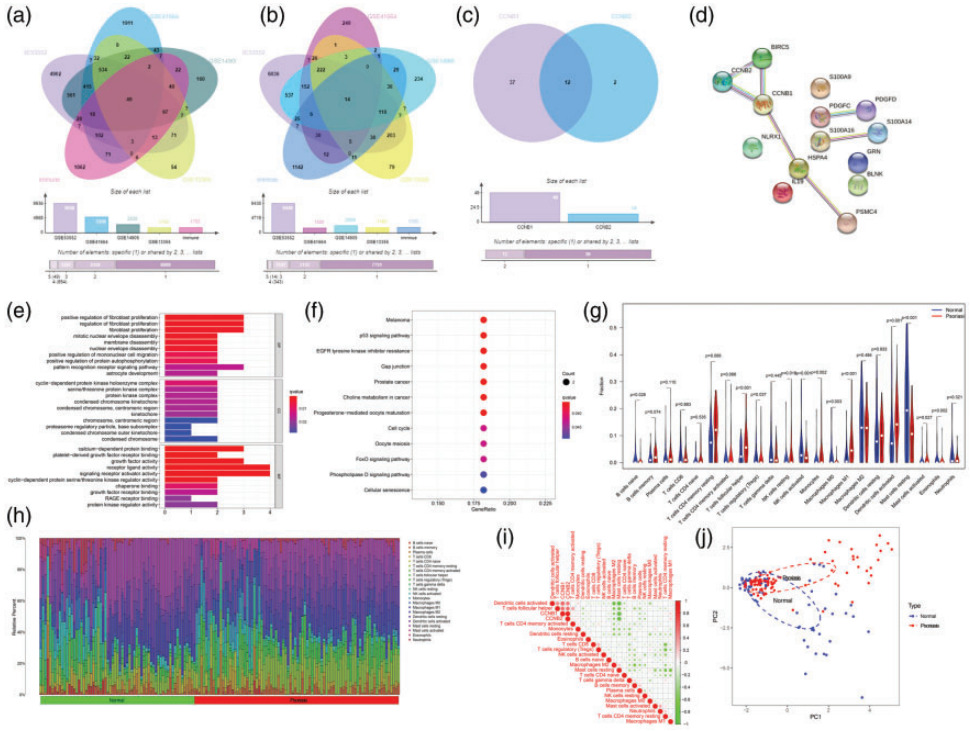

Figure 3. Identification and characterization of the *CCNB1*- and *CCNB2*-immune related differentially expressed genes (DEGs) involved in psoriasis. (a, b) Determination of the (a) *CCNB1*- and (b) *CCNB2*-related immune DEGs among the four Gene Expression Omnibus (GEO) datasets. (c) Determination of the common *CCNB1*/*CCNB2* immune-related DEGs. (d) Protein–protein interaction (PPI) network, (e) gene ontology (GO) enrichment analysis, and (f) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the common *CCNB1*/*CCNB2* immune-related DEGs. Darker red indicates more significant differences. The *q*-value indicates the adjusted *P*-value. (g) Violin plot of the proportion of 22 types of immune cells. (h, i) Heatmap of the (h) proportion and (i) correlation of 22 types of immune cells. Squares represent the strength of the correlation. Green and red colors represent negative and positive correlations, respectively and (j) Principal component analysis (PCA) cluster plot of immune cell infiltration between psoriasis and control samples.

with the abundance of resting mast cells, M2 macrophages, and plasma cells (Figure 3i). PCA of immune cell infiltration also suggested that there were differences between healthy and psoriasis tissues; however, no difference was observed between the two groups in some individual samples (Figure 3j). Thus, these findings suggest that CCNB1 and CCNB2 may be associated with mast cell activity in psoriasis.

Correlation analysis with typical psoriasis targets

Next, mRNA expression data of currently recognized disease-related targets (*IL17A*, *IL22*, *IL23R*, and *TNF*) were collected from publicly available GEO datasets, and their relationships with *CCNB1* and *CCNB2* were independently evaluated. Overall, *CCNB1* and *CCNB2* were found to be positively correlated with the

expression of these target genes ($P < 0.05$; Figure 4).

Discussion

The onset and progression of psoriasis involve multiple factors, including genetic, autoimmune, and inflammatory factors.[27] Abnormal proliferation and differentiation of keratinocytes is one of the principal pathophysiological features of psoriasis, with enhanced cell cycle being responsible for the abnormal proliferation of keratinocytes.[28] Owing to the chronic and recurrent nature of psoriasis, treatments need to be continuously administrated to ensure that psoriasis symptoms are adequately managed.[29] Therefore, further research to obtain a better understanding of the underlying molecular mechanisms of psoriasis is still warranted to identify more effective therapeutic targets.

The present study confirmed that the mRNA and protein levels of CCNB1 and CCNB2, which are closely related with cell cycle regulation,[30,31] are increased in psoriasis patients compared with those in healthy controls. Therefore, CCNB1 and CCNB2 may play an important role in psoriasis by regulating cell cycle progression of keratinocytes. In agreement with our findings, previous investigations also suggested that CCNB1 and CCNB2 could partake in the pathogenesis of psoriasis.[13,32] Indeed, Choudhary et al. even demonstrated that CCNB1 is one of the central targets of severe psoriasis.[14] However, to date, the potential pathological mechanisms of CCNB1 and CCNB2 in psoriasis remain unclear.

Herein, DEG analysis was performed to identify CCNB1- and CCNB2-related targets potentially involved in psoriasis onset. Moreover, functional enrichment analysis was also conducted to explore their potential molecular and cellular mechanisms in psoriasis. Overall, 26 common immune-related targets were identified, and

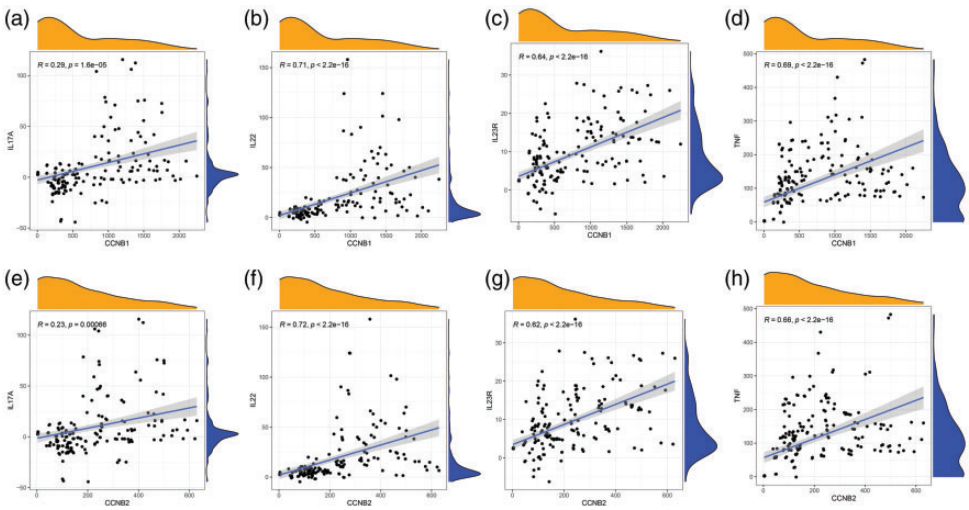

Figure 4. Correlation analysis between (a–d) *CCNB1* and (e–h) *CCNB2* levels and the expression of typical psoriasis-associated targets. (a, e) *IL17A* ($R = 0.29$, $P = 1.6 \times 10^{-5}$; and $R = 0.23$, $P = 6.66 \times 10^{-4}$, respectively), (b, f) *IL22* ($R = 0.71$, $P < 2.2 \times 10^{-16}$; and $R = 0.72$, $P < 2.2 \times 10^{-16}$, respectively), (c, g) *IL23R* ($R = 0.64$, $P < 2.2 \times 10^{-16}$; and $R = 0.62$, $P < 2.2 \times 10^{-16}$, respectively), and (d, h) *TNF* ($R = 0.69$, $P < 2.2 \times 10^{-16}$; and $R = 0.66$, $P < 2.2 \times 10^{-16}$, respectively).

CCNB1 and CCNB2 were found to be potentially involved in multiple biological process and signaling pathways. According to KEGG analysis results, CCNB1 and CCNB2 may function through the melanoma, p53 signaling pathway, cell cycle, cellular senescence, and FoxO signaling pathways in psoriasis. The p53 signaling pathway has been demonstrated to be involved in the regulation of the cell cycle of keratinocytes,[32] with Yazici et al. showing that p53 may be an important factor for psoriasis progression.[33] Zhang et al. and Fischer et al. also suggested that CCNB1 and CCNB2 have a potential relationship with the p53 signaling pathway to regulate the cell cycle of multiple cell types.[30,34] Moreover, the FoxO signaling pathway can work together with the PI3K-AKT and TGF-β signaling pathways to regulate the cell cycle, with inhibition of FoxO signals directing impacting keratinocyte proliferation.[35,36]

To understand the potential immune-related mechanisms triggered by CCNB1 and CCNB2 in psoriasis, immune infiltration analysis was performed and revealed significant differences in the abundance of several immune cell populations between healthy individuals and psoriasis patients. Moreover, correlation analysis showed that *CCNB1* and *CCNB2* levels are negatively correlated with the abundance of resting mast cells and M2 macrophages, whereas they are significantly positively correlated with the expression of recognized biomarkers of psoriasis, including *IL17A*, *IL22*, *IL23R*, and *TNF*. Hence, high expression of *CCNB1* and *CCNB2* may inhibit resting mast cells and promote mast cell activation. Furthermore, *CCNB1* and *CCNB2* may also promote the secretion of interleukin (IL)-17, IL-22, and tumor necrosis factor (TNF).[37–39]

In psoriasis, M1 macrophages produce proinflammatory cytokines, while M2 macrophages produce anti-inflammatory cytokines.[40] This agrees with the present correlation analysis results. Indeed, *CCNB1* and *CCNB2* levels were found to be positively correlated with the abundance of M1 macrophages, but negatively with M2 macrophages abundance. Thus, CCNB1 and CCNB2 may play a role in the polarization of macrophages in psoriasis. A previous study showed that decreased expression of the M2 macrophages marker *CD200R* was associated with enhanced production of IL-23.[41] Moreover, high expression of *IL17A* can shift macrophages from the M2 to the M1 phenotype in the skin of mice with psoriasis.[42] Noteworthily, correlation analysis indicated that *CCNB1* and *CCNB2* levels were positively correlated with the expression of *IL17A*. Lin et al. demonstrated that inhibition of TNF-α can rectify M1 macrophage polarization in patients with psoriasis.[43] In addition, *IL22* expression can enhance the abundance of M2 macrophages.[44] Herein, we found that both *CCNB1* and *CCNB2* were positively correlated with *TNF* and *IL22* levels in psoriasis.

In summary, the present study revealed for the first time the CCNB1- and CCNB2-related complex potential mechanisms involved in psoriasis. Based on the collected knowledge, CCNB1 and CCNB2 may not only regulate the cell cycle of keratinocytes through multiple pathways, but also support the release of critical signaling molecules by regulating immune cells, such as macrophages and mast cells, to participate in and promote the onset and progression of psoriasis. Nonetheless, further in vitro and in vivo studies are required to fully describe and support the roles of CCNB1 and CCNB2 in keratinocytes, macrophages, and mast cells contributing to the development and progression of psoriasis.

Data availability statement

The genetic data that support the findings of this study are publicly available from the Gene Expression Omnibus (GEO) database. Patient

data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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