Efficacy of dupilumab in palmoplantar pustulosis treatment highlights the role of Th2 inflammation

Yu-Xin Zheng[1,2]*, Xi-Bei Chen[1]*, Zhao-Yuan Wang[1]*, Sui-Qing Cai[1], Min Zheng [1], Li Fang Koh [2], John E Common [2¶], Xiao-Yong Man [1¶]

[1] Department of Dermatology, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China.

[2] A*STAR Skin Research Labs (A*SRL), Agency for Science, Technology and Research (A*STAR), Republic of Singapore.

*Contributed equally

¶Correspondence

Xiao-Yong Man

Mailing address: No.88 Jiefang Road, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, 310009.

Phone number: +86 13600516219

Email address: manxy@zju.edu.cn

John Common

Mailing address: A∗STAR Skin Research Labs (A∗SRL), 8A Biomedical Grove, #06-06, Immunos, Singapore, 138648.

Phone number: +65 64070508

Email address: john_common@asrl.a-star.edu.sg.

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Author Contribution statement: YXZ conceptualized, planned, and executed the study, researched the data, performed statistical analyses, and wrote the first draft of the manuscript. XBC and ZYW planned, and executed the study, researched the data, and edited the manuscript. JC, XYM, SQC, MZ conceptualized the study, provided funding, and revised the manuscript. LFK revised the manuscript.

Key words:

Palmoplantar pustulosis, dupilumab, atopic dermatitis, psoriasis, Olink, serum

Palmoplantar pustulosis is a chronic, recurrent skin disorder characterized by sterile pustul

similarities between PPP and atopic dermatitis based on serum Olink proteomics.

Abbreviations:

PPPASI (palmoplantar Psoriasis Area and Severity Index)

PPPASI75 (≥75% improvement in the PPPASI score from the baseline)

To the Editor:

Palmoplantar pustulosis (PPP) is a chronic, recalcitrant skin disease characterized by sterile pustules and erythematous scaling on the palms and soles[1]. Emerging treatments, including IL-12/23, TNF, IL-17A, IL-8, IL-36, and phosphodiesterase-4 inhibitors, were evaluated in PPP patients[2]. Some PPP patients were reported to benefit from targeted therapies, however, through a network meta-analysis, no drug was found to be more effective than placebo for disease improvement and clearance[1].

Bulk RNAseq of lesions in PPP patients revealed unexpected upregulation of Th2 gene expression, which is common in atopic dermatitis (AD)[3]. Dupilumab is a recombinant IgG4 antibody that targets IL-4Rα and inhibits IL-4 and IL-13 signaling[4]. Based on the emerging pathogenesis of PPP and successful experience treating sporadic PPP patients with dupilumab[4,5], we conducted a targeted study with 10 patients.

In our cases, we carefully selected only PPP patients for inclusion and no patients had concomitant psoriasis (PSO) lesions or a family history of PSO. All ten Asian Chinese patients received 300 mg dupilumab every 4 weeks after a 600 mg loading dose. Nine patients achieved PPPASI75 (≥75% reduction) at week 16, with the non-responder switched to guselkumab with PPPASI75 subsequently reached. Among the 9

complete-response patients, the average time to reach PPPASI75 was 9.2 weeks, were followed up for at least 52 weeks and reported no reoccurrence of disease flare or adverse events (**Table 1)**.

To further understand the pathogenesis of PPP and mechanistic response to dupilumab, we profiled serum biomarkers. Serum samples from 11 PPP patients, 15 AD patients, 14 PSO patients, and 19 healthy controls (HCs) were collected at baseline and evaluated with Olink® target 96 inflammation panel (Olink Proteomics AB, Sweden). Additionally, serum from 7 PPP patients who underwent dupilumab treatment was analyzed at week 16 time point (**Table E1-4** for patients' demographic).

First, we compared the protein expression of PPP patients with that of HCs. A total of 17 differentially expressed proteins (DEPs) were identified (4 upregulated and 13 downregulated). CCL19, MCP-4, CCL11, and CXCL5 expression was upregulated in PPP patients **(Figure 1a)**. Protein biomarkers most upregulated in our study have been associated with allergic diseases[6-8]. CCL11 (eotaxin-1) is a critical eosinophil chemoattractant that is associated with Th2-mediated AD[6]. Similarly, MCP-4 (CCL13) is a monocyte chemoattractant protein related to asthma and AD[7] and CCL19 plays an important role in a murine asthmatic model[8]. McCluskey D *et al*.[3] have previously observed a marked Th2 signature in PPP non-lesion skin, and MCP-4 and CCL19 were significantly increased in PPP patient skin from bulk RNAseq data

analysis and strongly connecting with our results herein.

We next identified 14 DEPs that were differentially expressed in AD patient serum compared to that of HCs (p-value < 0.05). Interestingly, when comparing these DEPs with the 17 that were differentially expressed in PPP patient's serum, we noticed a significant overlap ($p < 0.0001$). There was also an overlap between the PPP DEPs and the 17 proteins that were differentially expressed in PSO serum compared to that of HCs (P=0.0139) **(Figure 1b, c).** Therefore, the serum biomarkers of PPP patients were similar to that of AD and PSO patients, although there were fewer similarities with the latter.

Finally, we compared the serum of PPP patients before and after treatment with dupilumab. Following dupilumab treatment, serum IL-4 increased and IL-17A decreased significantly **(Figure 1d**). Consistent with previous reports using IL-4Rα blockade, serum IL-4 and IL-13 was increased after dupilumab treatment. A possible explanation for the decrease in serum IL-17A is that there is an indirect response caused by improvement in the skin phenotype and concomitant reduction in systemic inflammation in PPP patients.

In conclusion, our study provides new insight into the treatment and pathogenesis of PPP. PPP patients showed a strong positive response to dupilumab indicating that characteristics of PPP are related to Th2 inflammation. Future studies with larger cohorts and more comprehensive

multiomics analysis will deepen our pathomechanistic understanding of this disease and guide the diagnosis and treatment of PPP.

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Table 1. Demographic and clinical information about palmoplantar pustulosis patients

Patient No.	1	2	3	4	5	6	7	8	9	10
Sex	F	F	F	F	M	M	F	F	F	F
Age, year	32	52	32	55	61	39	23	60	44	28
Disease course, year	1	0.5	10	10	1	0.5	8	1	4	0.5
Baseline PPPASI	6.0	22.8	7.2	8.1	4.2	7.4	4.1	3.0	3.7	12.8
Plaque psoriasis	N	N	N	N	N	N	N	N	N	N
Previous treatments	TC AH SEC	TC AH AC	TC TVD	TC AC AH	TC AH	TC AH	TC AC	TC TVD AH	TC TVD AC SEC	TC TVD AH
Time to reach PPPASI75, week	16	6	8	5	9	12	11	Fail	8	8
PPPASI75 Response after 16 weeks	CR	CR	CR	CR	CR	CR	CR	NR	CR	CR
Adverse events	N	N	N	N	N	N	N	N	N	N
Months of follow-up	28	20	18	15	21	15	12	15	28	16

TC, topical corticosteroids; TVD, topical vitamin D derivatives; AC, acitretin; AH, antihistamine; SEC, secukinumab; CR, complete-response; NR, nonresponse

Figure Legend

Figure 1. Serum characteristics of PPP patients based on Olink proteomics. (a) Boxplots show the normalized protein expression in serum of HCs and PPP patients. Welch's t test. (b-c) Overlap between the proteins differentially expressed in the serum of PPP, AD, and PSO patients. Fisher’s exact test. (d) Boxplots show normalized protein expression in the serum of patients with PPP before (n=11) and after (n=7) dupilumab treatment. Welch's t test. PPP_D, palmoplantar pustulosis dupilumab treatment group.

Online Supplementary file

Methods

Study participants

This study complied with the principles of the Helsinki Declaration, and written informed consent was obtained from participants.

Our clinical study enrolled 10 PPP patients in the dermatology department of the Second Affiliated Hospital of Zhejiang University from January 2021 to September 2023. The inclusion criteria were typical PPP clinical presentation and pathological evidence. There were 2 males and 8 females with a mean age of 43 years. Moreover, the patients were resistant to conventional medication for over 3 months. Two of the patients did not respond to secukinumab. Demographic information and response to dupilumab are presented in Table 1.

The demographic data of PPP, AD, and PSO patients and healthy controls whose samples were included in the Olink proteomics assay are shown in **Tables E1-4**. No significant difference was found in age or sex among the four groups (p value> 0.05). The average age of the 11 PPP patients (3 males and 8 females) was 42 years, and the mean PPPASI was 8.1. The mean age of the 14 psoriasis patients (6 males and 8 females) was 36 years, and the mean PASI and BSA were 26.0 and 44.8, respectively. The mean age of the 15 patients with AD (6 males and 9 females) was 33 years, and the mean EASI and SCORAD were 15.6 and 55.9, respectively. The average age of the 19 healthy controls (8 males and 11 females) was 32 years, and conditions such as tumors, cardiovascular disease, autoimmune disease, and infection were excluded.

Olink® target 96 inflammation panel and statistical analysis

After standing, blood samples were centrifuged at 3000 rpm for 15 minutes to obtain serum samples. The collected serum was analyzed by LC-Biotechnology (Hangzhou) CO., Ltd. All samples passed the quality control checks. Olink multiplex proximity extension assay (PEA) panels were used to quantify serum proteins. The readout was given as normalized protein expression (NPX) on a log2 scale, which is Olink's arbitrary unit. R version 4.1.2 software and GraphPad 9 were used for statistical analyses and data visualization. *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

Table E1. Olink Proteomics, information for palmoplantar pustulosis patients.

Patient No.	Sex	Age, year	Baseline PPPASI	Baseline serum acquisition (pre-treatment)	Dupilumab Treatment	Serum acquisition after treatment (16 weeks)
1	F	32	6.0	√	√	√
2	F	52	22.8	√	√	√
3	F	32	7.2	√	√	√
4	F	55	8.1	√	√	√
5	M	61	4.2	√	√	√
6	M	39	7.4	√	√	√
7	F	23	4.1	√	√	√
8	F	60	3.0	√	√	
11	M	59	14.6	√		
12	F	24	6.0	√		
13	F	27	5.6	√		

Patient 9 and 10 were not included in the Olink proteomics study as they did not donate blood. Patients 11, 12 and 13 were not included in the dupilumab trial.

Table E2. Olink Proteomics, information for psoriatic patients.

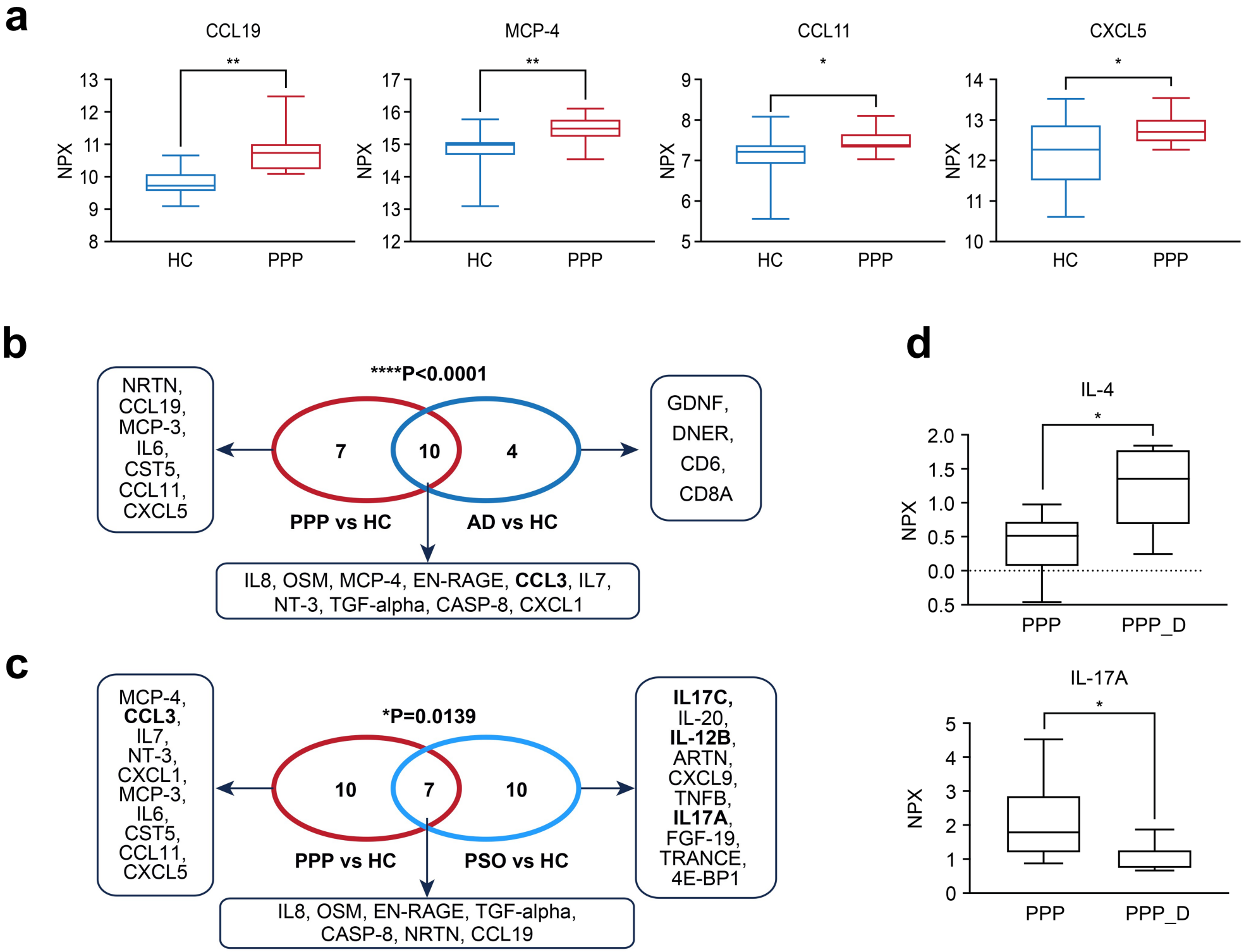
Patient	Sex	Age	PASI	BSA
1	F	38	27.9	65
2	F	42	21.6	30
3	F	10	17	65
4	F	26	29	44
5	F	36	12	28
6	F	29	10.6	25
7	M	37	12.4	21
8	M	58	25.6	30
9	M	46	25.9	35
10	M	34	36.9	55
11	M	36	18.6	14
12	M	52	43.6	70
13	F	35	51.6	85
14	F	30	31.2	60

Table E3. Olink Proteomics, information for atopic dermatitis patients.

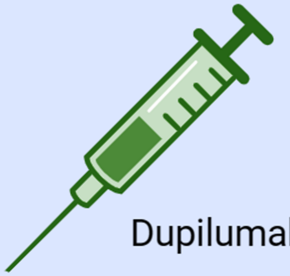
Patient	Sex	Age	EASI	SCORAD
1	M	64	28.1	73
2	F	34	5.8	42
3	M	27	33.3	91.5
4	M	19	12.35	58
5	F	32	5.4	30.5
6	F	21	13.5	57
7	F	41	12.6	52
8	M	59	11.55	58.5
9	M	30	6.85	44.2
10	F	32	6.4	39.5
11	M	49	28.1	67
12	F	28	20.4	49
13	F	19	18.75	56.5
14	F	21	16.1	63.5
15	F	18	14.4	56

Table E4. Olink Proteomics, information for healthy contributors.

Normal	Sex	Age
1	M	23
2	M	41
3	F	35
4	M	34
5	F	23
6	F	34
7	F	56
8	M	27
9	M	34
10	M	32
11	M	29
12	M	24
13	F	23
14	F	44
15	F	24
16	F	42
17	F	36
18	F	22
19	F	23


a
CCL19
MCP-4
CCL11
CXCL5
NPX
HC
PPP
**
*
b
****P<0.0001
NRTN, CCL19, MCP-3, IL6, CST5, CCL11, CXCL5
7
10
4
GDNF, DNER, CD6, CD8A
PPP vs HC
AD vs HC
IL8, OSM, MCP-4, EN-RAGE, CCL3, IL7, NT-3, TGF-alpha, CASP-8, CXCL1
c
*P=0.0139
MCP-4, CCL3, IL7, NT-3, CXCL1, MCP-3, IL6, CST5, CCL11, CXCL5
10
7
10
IL17C, IL-20, IL-12B, ARTN, CXCL9, TNFB, IL17A, FGF-19, TRANCE, 4E-BP1
PPP vs HC
PSO vs HC
IL8, OSM, EN-RAGE, TGF-alpha, CASP-8, NRTN, CCL19
d
IL-4
IL-17A
PPP
PPP_D

Dupilumab treatment in PPP patients results in clinical improvement



Dupilumab

Palmoplantar pustulosis (n=10)

9 patients achieved PPPASI75 at week16

Proteomics of PPP shows evidence of Th2 inflammation and overlap with AD and PSO

Dupilumab

Healthy control (n=19)

Psoriasis (n=14)

Atopic dermatitis (n=15)

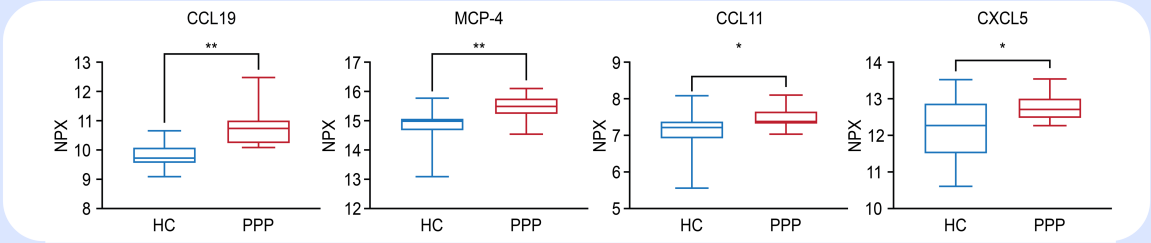
Palmoplantar pustulosis (n=11)

Palmoplantar pustulosis after Dupilumab treatment (n=7)

Serum sample collection

Olink® target 96 Inflammation panel

Th2 inflammation in PPP cohort



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