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CGF therapy: bridging androgenetic alopecia observations to psoriasis treatment via IL-17 pathway

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Abstract

Introduction Concentrated Growth Factor (CGF), rich in CD34 + stem cells, is widely used in treatments for androgenetic alopecia and skin rejuvenation due to its immune-modulating properties. Psoriasis, a chronic inflammatory skin condition, presents significant treatment challenges, particularly for patients who cannot use biologics due to conditions such as cancer and lesions resistant to treatments. The potential of CGF in treating psoriasis is promising, given its broad immunoregulatory effects which confirmed in our previous androgenetic alopecia work.

Methods We evaluated the impact of CGF on IL-17 levels in two contexts: patients treated for androgenetic alopecia and a psoriasis mouse model. Twelve patients received three monthly injections of CGF, with serum IL-17 levels measured before and after treatment. In the psoriasis mouse model, groups were treated with CGF, and outcomes were assessed using the Psoriasis Area and Severity Index (PASI), skin barrier scores, histological analysis, and RNA sequencing. Additionally, in vitro experiments applied CD34 + cells from CGF to keratinocytes to measure levels of TNF-α, IFN-γ, IL-23, and IL-17.

Results In patients with androgenetic alopecia, three monthly CGF injections resulted in significantly reduced serum IL-17 levels. In the psoriatic mouse model, CGF-treated groups exhibited lower PASI scores and improved skin barrier scores compared to controls. Histological analysis revealed enhanced skin characteristics, while RNA sequencing demonstrated downregulated IL-17 and upregulated CD34 expression, as well as improved expression of barrier-related genes. In vitro, the application of CD34 + cells from CGF to keratinocytes led to a significant reduction in TNF-α, IFN-γ, IL-23, and IL-17 levels, indicating strong anti-inflammatory effects. A clinical case of a psoriasis patient unresponsive to IL-23 therapy (Guselkumab) showed significant improvement following CGF treatment.

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Conclusion These findings indicate that CGF could serve as an effective and versatile treatment for psoriasis, especially for patients who have already undergone biologic therapies but continue to experience resistant lesions.

Keywords Psoriasis, IL-17, CGF, CD34, Stem cell

Background

Psoriasis is a chronic inflammatory skin disease characterized by high recurrence and erythematous plaques [1]. The prevalence of psoriasis ranges from 0.47 to 6.6% among different countries [2]. Patients who suffer from psoriasis not only face a deteriorated skin barrier [3] but also experience elevated cardiovascular [4] and mental disorders [5], which all lead to a decrease in quality of life. Thus, various studies have investigated the possible mechanism of psoriasis. The IL-17 [6] axis plays a critical role in psoriasis. Treatment targeting the IL-17 axis, such as brodalumab and ixekizumab, can decrease the size of psoriatic skin lesions, increasing the popularity of this treatment for psoriasis [7]; however, psoriasis relapse can still occur, and resistant lesions often appears [8]. Certain parts of the psoriatic lesion, such as the head and groin fold [9], are reluctant to respond to biologics. Besides, most of the biologics may need months to reach PASI90 [10]. Long-term biologic treatment might always lead to a low response, which is attributed to "immune tolerance" [11]. From that point of view, it is urgent to discover another kind of treatment that does not lead to "immune tolerance".

What could be the possible treatment? First, possible treatments may include downregulating IL-17 expression. Second, because several biologists were given treatment once a month, it is better to not demand that patients attend the clinic frequently. Third, possible treatments should be accessible. This meant that a certain treatment that was already used in the clinic could be a candidate.

Concentrated growth factor (CGF) [12, 13], which upper part is platelet-rich plasma (PRP) and lower white cell layer contains CD34+cells (Fig. 1) [14–16], was used as a treatment for alopecia [17] and skin juveniles [18]. As a kind of regenerative medicine, CGF showed great potential in immune regulation [19]. Usually, the treatment was prepared once a month which does not patients attending the clinic frequently. Another reason that CGF treatment might be suitable for treating psoriasis is that the number of CD34+cells in the psoriatic skin of patients is inversely proportional to the severity of psoriasis [20–22]. The injection of CD34+cells into psoriatic lesions might contribute to regulating the microenvironment, which could lead to the remission of lesion skin. Furthermore, if CGF treatment downregulates IL-17, it might also become a solution for treating areas that are resistant to biologics, such as the scalp, because CGF treatment has been clinically proven to be applicable to the scalp for treating alopecia [17].

To evaluate whether CGF treatment could downregulate IL-17 expression as a candidate treatment for psoriasis, we enrolled 12 patients with androgenetic alopecia for whom CGF treatment was approved for androgenetic alopecia patients. The patients received CGF treatment once a month, and IL-17 expression in the peripheral blood was tested before the first and after the third treatment to determine whether CGF treatment could downregulate IL-17 expression. We also performed animal experiments using a CGF-treated imiquimod-induced psoriatic mouse model to confirm the potential of CGF treatment as a new approach for treating psoriasis.

Materials and methods

Detection of peripheral IL-17 expression in CGF-treated patients

We recruited 12 patients who were only diagnosed with androgenetic alopecia. Participants who met the following criteria were excluded: pregnancy or lactation, a diagnosis of hypertension, hyperlipidaemia, diabetes, malignancy, thyroid dysfunction, infectious disease, autoimmune disease, bleeding disorder, platelet dysfunction syndrome, a PLT < 150,000/μL, a history of drug allergy, anticoagulant therapy, or any acute or chronic medical or laboratory abnormalities that increased the risk of participating in the study. Written informed consent was obtained from all participants. Ethics Committee approval was obtained from the Institutional Ethics Committee of Shanghai East Hospital prior to the commencement of the study. Each patient was given CGF treatment on the scalp 3 times. Peripheral blood was collected before the first and after the third treatment. Sera were separated from venous peripheral blood samples. Then, IL-17 A levels were measured by ELISA using an ELISA kit for IL-17 A (Shanghai ExCell Biology, Shanghai, China).

CGF and PRP preparation

Six milliliters of venous blood was collected from the elbow vein. Blood was prepared with standard CGF extraction protocols (2700 r/min for 2 min, 2400 r/min for 4 min, 2700 r/min for 4 min, and 3000 r/min for 3 min).

Surgical procedure

Scalp disinfection and anaesthesia were achieved using 5.0 g/L iodophor and 2% lidocaine, respectively. After

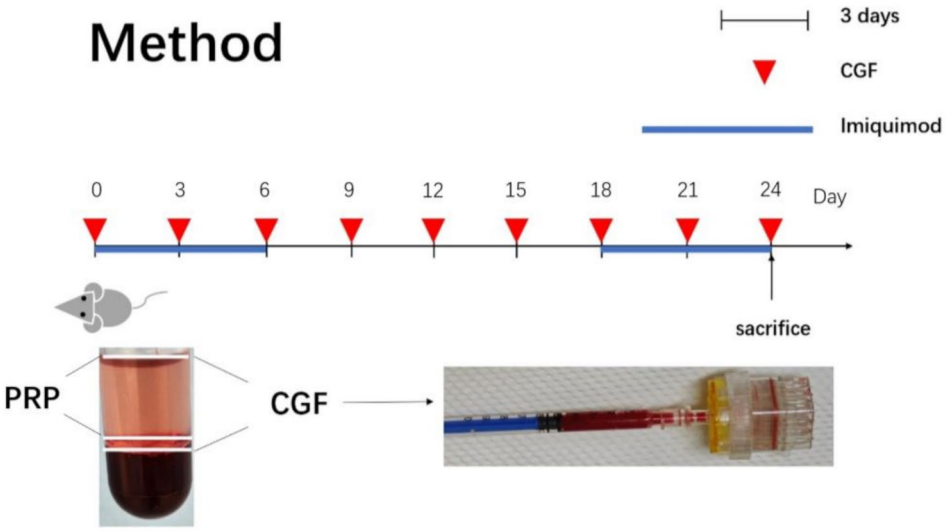

Fig. 1 Methods of the mouse experiment

anaesthesia, CGF was injected into the scalp according to previous methods [23].

Statistical analysis

Statistical analysis was performed using Prism 9.0 (GraphPad Software). The results are reported as the mean ± standard deviation (SD). The statistical tests used, number of animals, and *P* values are described in the legend for each figure or indicated as dots in the figures.

Mouse experiment

The Institutional Animal Care and Use Committee of the Experimental Animal Welfare and Ethics Management Committee of Shanghai East Hospital (Shanghai, China) approved the animal experiments titled "The effect of CGF microneedle injection on the imiquimod induced psoriatic mouse model". The work has been reported in line with the ARRIVE guidelines 2.0. Seven-week-old male C57BL/6 mice (obtained from JSJ Experimental Animal Company, Shanghai, China) were divided into four groups (n=3/group). The groups included the control group, CGF group, IMQ group and IMQ+CGF group. The control group and the IMQ group were given saline through MNs every 3 days on the dorsal skin, while the CGF group and the IMQ+CGF group were given CGF treatment through MNs at the same pace. Imiquimod was applied on the dorsal surface of the mice in the IMQ and IMQ+CGF groups on the first week and fourth week. All the treatment were prepared following the induction of anaesthesia with isoflurane. At the end of week 4, the mice were injected with an overdose of ketamine (180 mg/kg)+xylazine (30 mg/kg) immediately for euthanasia. The appearance of the back skin was photographed, and the skin barrier score (GPSKIN) was recorded. Dorsal skin was biopsied, and IL-17 expression was tested through PCR. In addition, pathological examination of the biopsied skin samples was also performed (Fig. 1).

Mouse psoriatic lesion severity assessment

The severity of skin inflammation was assessed using the Psoriasis Severity Index (PSI), which was recognized as the PASI of mice experiment [24]. Skin erythema, scaling, and thickness were the indicators, and each was scored independently on a scale of 0 to 4: 0–none, 1–slight, 2–moderate, 3–marked, and 4–very marked. The total PSI was determined by the cumulative score of all indicators.

RNA isolation and library preparation

Total RNA was extracted using TRIzol reagent (Invitrogen, CA, USA) according to the manufacturer's protocol. RNA purity and quantification were evaluated using a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA). RNA integrity was assessed using an Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). Then, the libraries were constructed using the VAHTS Universal V6 RNA-seq Library Prep Kit according to the manufacturer's instructions. Transcriptome sequencing and analysis were conducted by OE Biotech Co., Ltd. (Shanghai, China).

RNA sequencing and differentially expressed genes analysis

The Illumina NovaSeq 6000 platform was used to sequence the libraries, generating 150 bp paired-end reads. The raw reads in fastq format were processed using fastp [25], and low-quality reads were removed to obtain clean reads. HISAT [26] was used to map the clean reads

to the reference genome. FPKM [27] values were calculated for each gene, and the read counts of each gene were obtained using HTSeq-count [28]. To assess the biological duplication of samples, PCA was performed using R (v 3.2.0). DESeq2 [29] was used for differential expression analysis, with a Q value < 0.05 and a fold change > 2 or < 0.5 set as the thresholds for significantly differentially expressed genes (DEGs). Hierarchical cluster analysis of DEGs was conducted using R (v 3.2.0) to show the expression patterns of genes in different groups and samples. The expression of upregulated or downregulated DEGs is shown in heat map of the top 10 genes according to the R package ggradar.

Flow cytometry sorting and treatment group preparation

To investigate the therapeutic effect of CD34+stem cells within Concentrated Growth Factor (CGF) on psoriasis, a cell-based experiment was conducted using the PAM212 mouse keratinocyte cell line (1×10^6 cells/mL). CGF was extracted from the peripheral blood of mice and treated with red blood cell lysis buffer to remove erythrocytes, resulting in a single-cell suspension. The cells were washed twice with PBS and incubated with an anti-CD34 antibody (RAM34, FITC, eBioscience) at 4 °C for 30 min. After incubation, the cells were washed again with PBS, resuspended, and prepared for flow cytometry sorting.

During flow cytometry, CD34+cells were identified and excluded, resulting in a negatively sorted CD34- cell population. This CD34- cell population was resuspended in mouse platelet-rich plasma (PRP) at a concentration of 1×10^6 cells/mL, constituting the CGF non-CD34+cell group (Treatment C). Conversely, the CD34+cells collected through flow cytometry were similarly prepared in mouse PRP at a concentration of 1×10^6 cells/mL, forming the CD34+cell CGF group (Treatment B).

Cytokine expression analysis

Psoriasis-related inflammatory inducers (a cocktail containing IL-17 A, IL-22, Oncostatin M, IL-1α, and TNF-α) were applied to PAM212 cells, which were then cultured for 24 h. The stimulated cells were divided into four groups: Group A (control, treated with 10 μL of culture medium), Group B (treated with 10 μL of CD34+cell CGF, Treatment B), Group C (treated with 10 μL of CGF non-CD34+cells, Treatment C), and Group D (treated with 10 μL of mouse PRP).

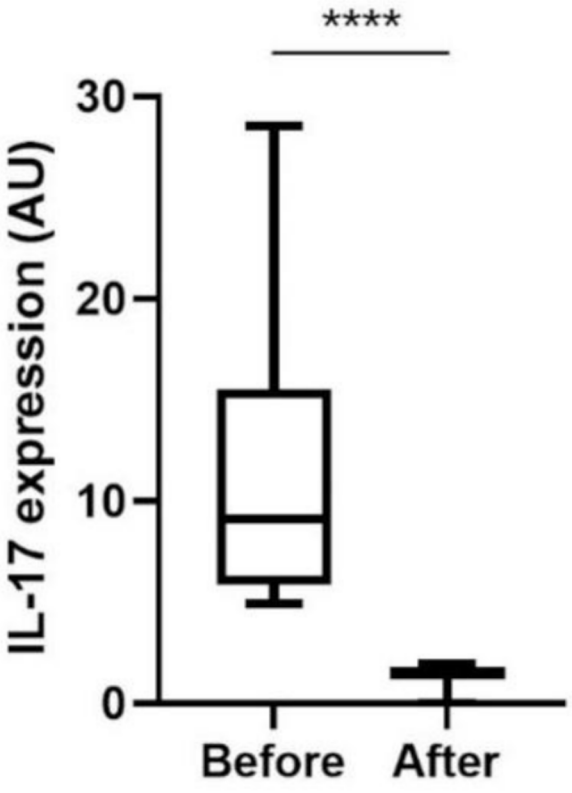

Fig. 2 IL-17 expression in peripheral blood before and after 3 rounds of CGF treatment. The data are presented as the mean ± standard deviation (SD), $n = 12$. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.001$ compared with the line-indicated group

Results

Expression of peripheral IL-17 before and after 3 scalp CGF injections

The peripheral blood IL-17 levels in 12 patients before and after 3 rounds of CGF treatment were 11.05±7.00 and 1.36±0.54, respectively. The IL-17 level in patients before CGF treatment was significantly greater than that in patients after 3 rounds of CGF treatment. (Fig. 2).

Cutaneous status of mice that underwent CGF treatment

Photograph of the dorsal skin of the mice on day 24 revealed elevated erythema and scale in the IMQ group compared with the control group, CGF group and IMQ+CGF group (Fig. 3A). Compared with that in the control group, slight darkness was observed in the CGF group, possibly due to the faster hair growth in the CGF group [23]. The PSI of the IMQ group was significantly greater than that of the IMQ+CGF group (Fig. 3B). Hematoxylin and eosin (HE)-stained dorsal skin sections from the IMQ group showed greater epidermal thickness than those from the IMQ+CGF group (Fig. 3C and D). The barrier score of the IMQ group was the lowest of the four groups, and there was a significant difference in the barrier score between the IMQ group and the IMQ+CGF group.

Transcriptional portraits of mouse skin after treatment with different regimens

RNA-seq analysis of skin samples from mice treated with different regimens was performed on day 24. The

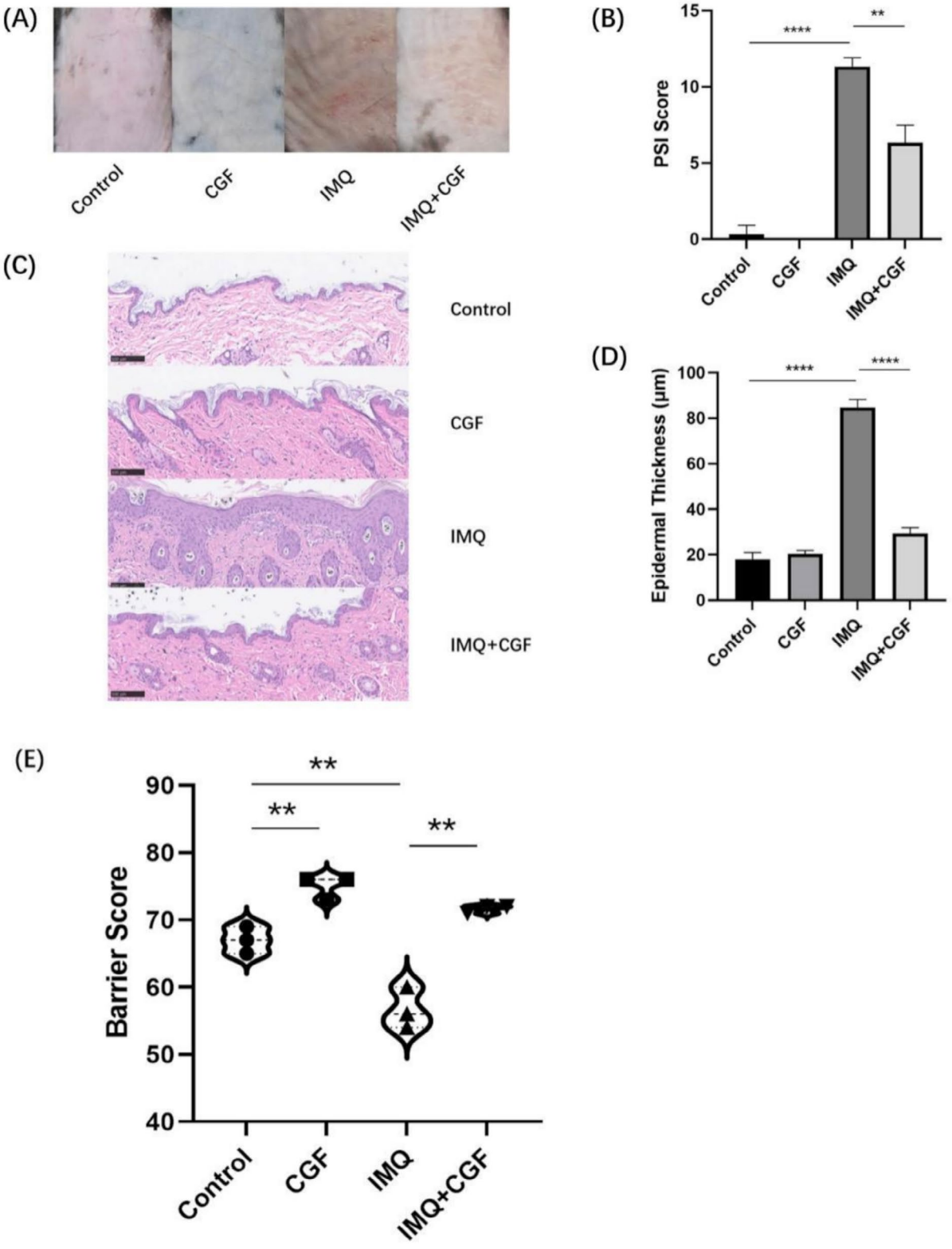

Fig. 3 Cutaneous status of mice underwent CGF treatment. (**A**) Photographs of mice dorsal skin on day 24 of Group Control, Group CGF, Group IMQ and Group IMQ + CGF, from left to right, respectively. (**B**) Hematoxylin and eosin (HE) stained dorsal skin sections from Group Control, Group CGF, Group IMQ and Group IMQ + CGF, from up to down, respectively. Bar indicated 100 μm. (**C**) Barrier score of the dorsal skin of mice. Data are presented as the mean ± standard deviation (SD), $n = 3$ mice/group. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with line indicated group

PCA plot (Fig. 4A) indicates that the different treatments contributed to the variance among the four experimental groups, with three mice analysed for each group. The Il17 expression in the IMQ group was significantly greater than that in the IMQ+CGF group (Fig. 4B). Differential gene analysis between the IMQ group and the IMQ+CGF group revealed that the expression of inflammation-associated genes, such as Il20 and Cxcl5, was significantly greater in the IMQ group (Fig. 4C). Gene Ontology (GO) enrichment analysis revealed that the top ten pathways upregulated in the IMQ+CGF group compared with the IMQ group in terms of biological processes and cellular components were mostly distributed among the skin barrier and hair circle (Fig. 4D).

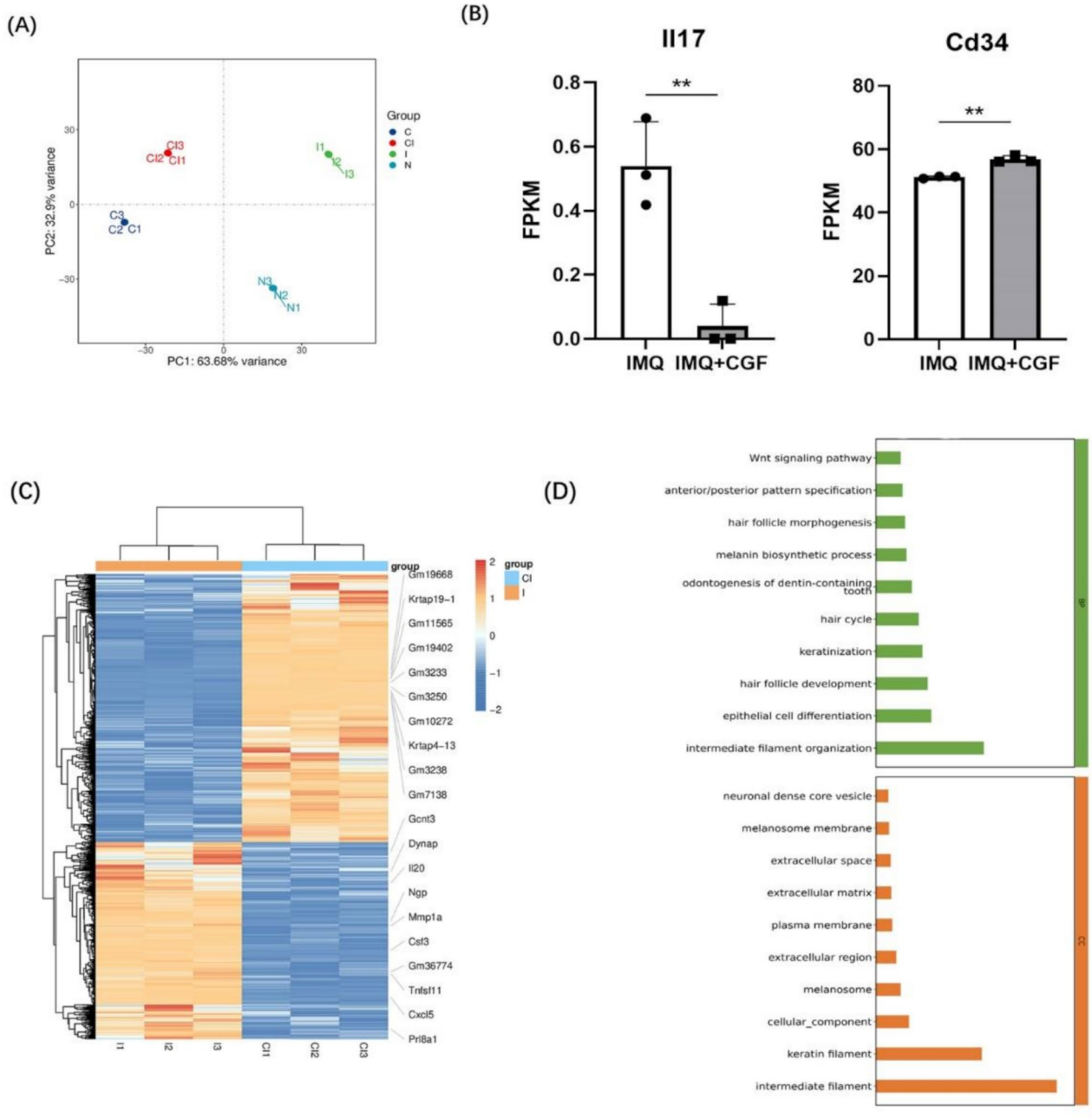

Fig. 4 The results of RNA-seq analysis of skin samples from mice treated with different regimens on day 24. (**A**) The PCA plot shows the variance contributed by different treatments to the four groups ($n=3$). (**B**) Bar plots showing the FPKM expression levels of Il17 and Cd34 from left to right. (**C**) Heatmap showing the DEGs between the IMQ group and the IMQ+CGF group, with red indicating upregulated genes and blue indicating downregulated genes. The top ten genes are labelled. (**D**) The bar plots display the top ten pathways upregulated in the IMQ+CGF group compared with the IMQ group in terms of biological processes and cellular components

Effect of CGF treatment on cytokine expression in PAM212 cells

The expression of TNF-α, IFN-γ, and IL-17 was significantly downregulated in Groups B and C compared to Group A ($p<0.05$). There was no significant difference in IL-23 levels between Group A and Group B, whereas elevated IL-23 expression was observed in Groups C and D compared to Group A ($p<0.05$). (Fig. 5)

CGF treatment in a patient with persistent psoriasis lesion on IL-23 antibody therapy

A 57-year-old patient with a history of moderate to severe plaque psoriasis had been undergoing treatment with an IL-23 antibody (Guselkumab) for two years. Despite this therapy, which generally managed the condition effectively, the patient exhibited a persistent psoriatic lesion on the left lower limb that failed to achieve remission. With informed consent, the patient received a single intralesional injection of concentrated growth factor (CGF) into the resistant psoriatic plaque. The CGF was prepared following standard protocols. The lesion was photographed at baseline (prior to CGF administration) and one month post-treatment. One month after the CGF injection, the lesion showed significant improvement, characterized by reduced erythema, scaling, and thickness (Fig. 6).

Discussion

Psoriasis is a chronic inflammatory skin disease, and its treatment faces many difficulties [30]. One of the dilemmas was that although new biologics and small molecule treatments could greatly lead to lesion remission, patients with tumors or certain backgrounds might not be suitable for treatments such as these [31]. Furthermore, psoriatic lesions in typical areas, such as the scalp [32], might need other treatments because they might not respond to frequently used treatments, such as biologics. CGF treatment, a new therapeutic approach for treating alopecia and skin aging, is now widely used in dermatologic clinics [23] and is also useful for patients with certain conditions, such as patients with tumors. Our previous study showed that cosmetic approaches, such as topical MN insertion, could contribute to downregulated IL-17 expression, which raised the question of whether CGF treatment, another cosmetic approach, might downregulate IL-17 expression in patients who are eligible for psoriasis treatment. Our observation confirmed our hypothesis. CGF treatment of the scalp can downregulate systemic IL-17 expression, which is consistent with the finding that widely used biologics can downregulate IL-17 expression in peripheral blood [30]. Further experiments in psoriatic mice also corroborated our findings. The psoriatic lesions of the mice

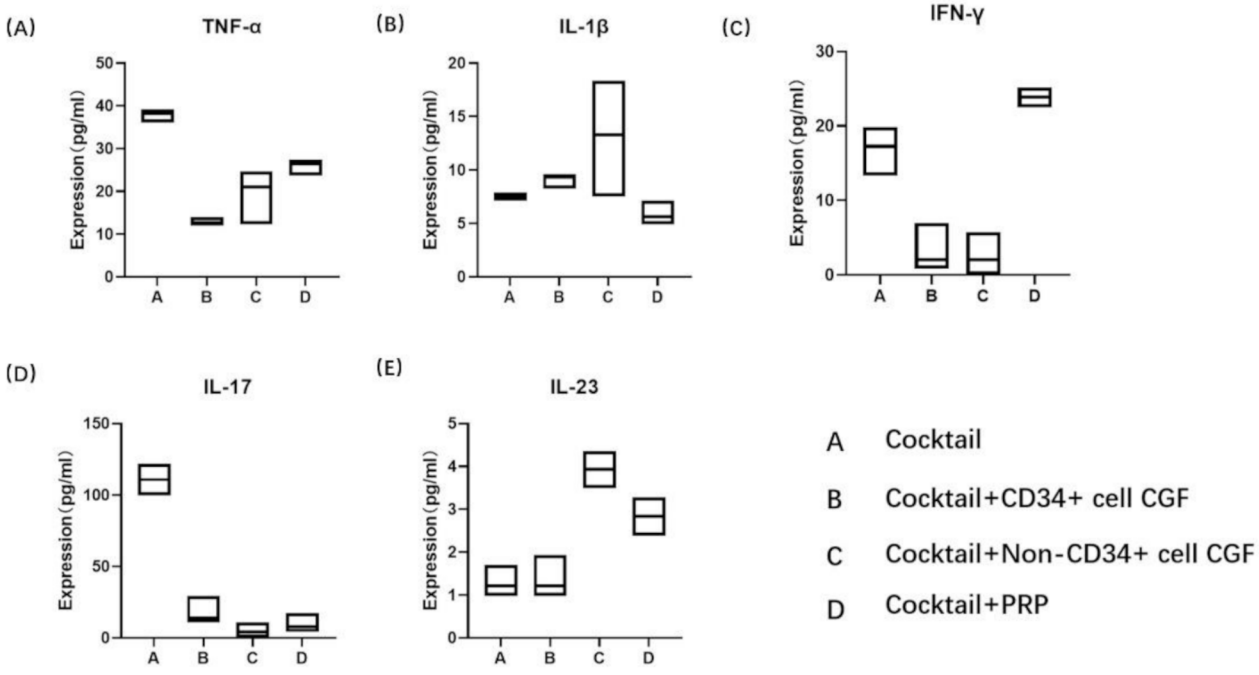

Fig. 5 Cytokine Expression in PAM212 Cells After Treatment with CGF Fractions. Bar graphs depicting the levels of TNF-α (**A**), IL-1β (**B**), IFN-γ (**C**), IL-17 (**D**), and IL-23 (**E**) in the supernatant of PAM212 cells treated with various fractions of CGF
Group A (Control): Cells treated with 10 µL culture medium
Group B (CD34 + CGF): Cells treated with 10 µL CD34 + cell fraction from CGF
Group C (CD34- CGF): Cells treated with 10 µL CD34- cell fraction from CGF
Group D (PRP Control): Cells treated with 10 µL mouse platelet-rich plasma (PRP)

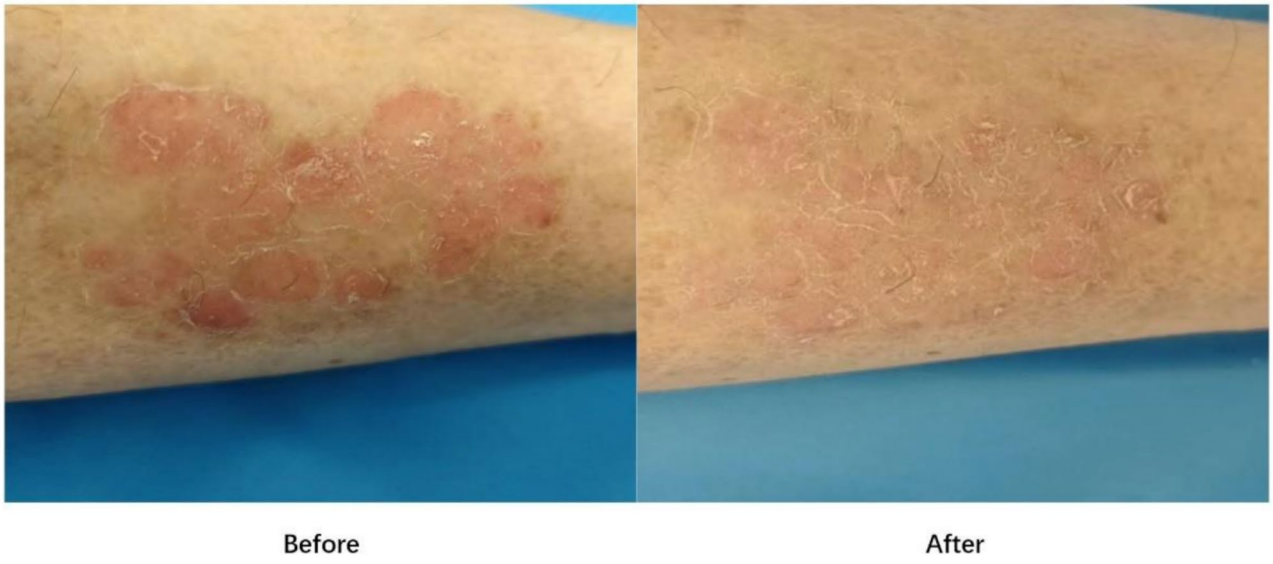

Fig. 6 Clinical Images of Psoriatic Lesion Before and After CGF Treatment Left, before the treatment. Right, one month after the treatment

were alleviated after CGF treatment. The severity of skin lesions in mice improved according to gross, pathological, inflammatory cytokine and gene expression data. The possible mechanism by which CGF treatment contributes to psoriasis treatment might involve the activation of CD34+stem cells because patients with psoriasis exhibit an increase in CD34+cells compared with healthy individuals, which is negatively correlated with disease severity [21]. Furthermore, the key pathogenic factor IL-17 was downregulated in the lesioned skin of CGF-treated psoriatic mice. Inflammation-associated genes such as Il20 [33] and Cxcl5 [34] were downregulated in CGF-treated psoriatic mice, which suggested that CGF treatment could reduce the inflammatory status of the skin. In addition, the upregulated barrier score of CGF-treated psoriatic mice and elevated skin barrier-associated GO terms such as keratin filament and plasma membrane showed that CGF might contribute to psoriatic treatment through skin barrier recovery [35], which plays an important role in psoriatic lesion remission. Our work showed that CGF treatment downregulated IL-17 expression in peripheral blood and could be a potential treatment for psoriasis. In addition, our work revealed that GO terms such as hair circle and hair follicle development were upregulated in CGF-treated psoriatic mice, which is consistent with the clinical findings that CGF is effective at treating alopecia. Pathways associated with vitiligo, such as the melanosome membrane pathway [36] and Wnt signalling pathway [37], were also upregulated in the CGF-treated group, which indicated the potential of CGF for treating vitiligo. Furthermore, our data support that CGF has a barrier recovery ability, which indicates that CGF might be suitable for treating not only psoriasis but also dermatologic diseases caused by barrier disruption, such as atopic dermatitis [38] and acne rosacea [39]. Our current study investigated the effects of CD34+and CD34- cell fractions from concentrated growth factor (CGF) on cytokine expression in a mouse keratinocyte cell line (PAM212), with the aim of exploring their potential therapeutic roles in psoriasis. Our results indicate that both CD34+and CD34- components of CGF modulate inflammatory cytokine levels, highlighting the complex interplay between different cellular constituents of CGF in the context of inflammatory skin conditions. A key finding of this study is the significant downregulation of TNF-α, IFN-γ, and IL-17 in the supernatants of PAM212 cells treated with both CD34+ (Group B) and CD34- (Group C) fractions compared to the control (Group A). These cytokines are well-established mediators in the pathogenesis of psoriasis, contributing to keratinocyte proliferation and immune cell activation. The observed reduction in these cytokines suggests that CGF, regardless of its specific cellular composition, possesses anti-inflammatory properties that may help mitigate the inflammatory cascade characteristic of psoriasis. Interestingly, IL-23 levels did not show a significant difference between the control and the CD34+treated group (Group B), while an increase in IL-23 was observed in the CD34- treated group (Group C) and the PRP control group (Group D). The findings from this study support the potential utility of CGF, including its CD34+and CD34- cell fractions, as a complementary treatment for psoriasis. The significant reduction in key inflammatory cytokines such as TNF-α, IFN-γ, and IL-17 aligns with the therapeutic goals of current biologic treatments, which aim to downregulate these mediators while CD34+cells in CGF showed

a greater potential as it could also downregulated IL-23. Our clinical findings support our results. A patient, with a chronic psoriatic lesion unresponsive to two years of IL-23 antibody therapy, showed significant remission after a single intralesional CGF injection, as evidenced by clinical photographs taken one month post-treatment. These findings suggest that CGF has the potential to modulate inflammatory cytokines relevant to psoriasis and CD34+cells in CGF which could downregulated IL-23 could be the key factor that leading the remission of the psoriatic lesion. Besides,

CGF therapy may enhance the effectiveness of existing psoriasis treatments, particularly in patients who have not achieved full remission with standard biologic therapies like IL-23 inhibitors. Furthermore, the incorporation of green nanomaterials in CGF preparation could enhance its therapeutic potential while aligning with sustainable and eco-friendly biomedical practices. This approach not only offers a novel therapeutic avenue but also emphasizes the importance of integrating green technologies in the development of next-generation treatments [40]. Relevant studies, such as the effects of saffron in epilepsy [41], and the use of natural oils [42] in health and cosmetics, supporting the potential for CGF's integration with natural products for enhanced therapeutic effects. But there is still limitation of our study, which including a small sample size, reliance on in vitro models, and a lack of longitudinal data, which restricts the generalizability and depth of findings. Additionally, the study did not fully explore the mechanisms of CGF's effects or establish a strong clinical correlation. Future research should involve larger, in vivo studies and controlled clinical trials to validate the efficacy and mechanisms of CGF in psoriasis treatment.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

Q.X. (Qiannan Xu) generated the study and designed the study. N.X., Y.L., Q.X. (Qin Xiao) and Q.X. (Qiannan Xu) funded the study. Q.X. (Qiannan Xu), J.G. (Jing Guo), Y.L. and J.G. (Jin Gao) collected the peripheral blood samples. Q.X. (Qiannan Xu) analysed the data and wrote the original paper. Q.X. (Qiannan Xu), M.H., W.Y. and W.C. revised the paper. Q.X. (Qiannan Xu), J.G. (Jing Guo) and Q.X. (Qin Xiao) prepared the mouse experiments. Q.X. (Qiannan Xu) and W.C. recruited the psoriasis patient. Q.X. (Qiannan Xu) prepared the microneedle CGF procedure.

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Data availability

https://data.mendeley.com/datasets/76mdvzw7fg/1.

Declarations

Ethics approval and consent to participate

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Shanghai East Hospital (Shanghai, China; Title of the approved project: Cytokine Change After CGF treatment; Approval No: 2022YS-238) on 2022.12.30. Written informed consent was obtained from individual or guardian participants. All experiments involving mice were approved by the Institutional Animal Care and Use Committee of Tongji University (Shanghai, China; Title of the approved project: Animal Experiment Approval "The effect of CGF microneedle injection on the imiquimod induced psoriatic mouse model"; Approval No: SYXK 2020-0002) on 2020.2.14.

Consent for publication

Not applicable.

Competing interests

The authors declare that no conflicts of interest exist.

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