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Proliferation-associated protein 2G4 promotes keratinocyte proliferation and survival in psoriasis

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Abstract

Background **Psoriasis is a noncommunicable inflammatory skin disease that affects approximately 2–3% of the world's population. Given its high impact on quality of life and the fact that a subset of patients exhibits suboptimal or secondary loss of response to current treatments, identifying new therapeutic strategies is crucial. Proliferation-associated protein 2G4 (PA2G4) is a transcription factor that has been exclusively studied in cancer research, where it promotes cell growth and enhances tumorigenesis by inhibiting apoptosis. However, its role in inflammatory skin diseases remains largely unknown.**

Objectives **To elucidate the pathophysiological and immunological functions of PA2G4 in psoriasis, and to evaluate its potential as a therapeutic target.**

Methods **Bulk, single-cell and spatial RNA sequencing (RNAseq) combined with immunohistochemistry were used to assess *PA2G4* expression in psoriatic skin compared with nonlesional control samples. Functional studies were performed in primary human keratinocytes and reconstructed human epidermis (RHE) models using the CRISPR/Cas9-mediated knockout of PA2G4 and pharmacological inhibition of PA2G4 with the small-molecule inhibitor WS6. The regulatory effects of PA2G4 on cellular processes, such as proliferation, differentiation and survival, were investigated using RNAseq, Western blot analysis, scratch assays and annexin V staining.**

Results ***PA2G4* was highly abundant in psoriasis, and its expression was predominantly restricted to basal proliferating keratinocytes. Its expression was positively correlated with psoriasis severity, the degree of acanthosis, neutrophil infiltration and genes that are upregulated in psoriasis. PA2G4 knockout in primary human keratinocytes activated differentiation pathways while suppressing proliferation pathways, resulting in the downregulation of proliferation- and inflammation-related genes (e.g. *MKI67*, *IL20*, *VEGFA* and *HIF1A*) and the upregulation of differentiation and cell adhesion markers (e.g. *KRT6C*, *LCE2C* and *DSG4*). Functionally, PA2G4 knockout reduced keratinocyte proliferation in scratch assays, attenuated interleukin-22-induced acanthosis in RHE models and promoted keratinocyte death. Pharmacological inhibition of PA2G4 using the small-molecule inhibitor WS6 similarly downregulated genes associated with proliferation and cell survival.**

Conclusions **PA2G4 could promote keratinocyte hyperproliferation and survival in psoriasis, thereby critically influencing epidermal homeostasis. Therefore, inhibition of PA2G4 may represent a new treatment option for psoriasis.**

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Lay summary

Psoriasis (pronounced 'suh-rye-uh-sis') is an inflammatory skin disease. It affects 2% to 3% of people worldwide. People with the disease have raised, scaly patches of skin all over the body. These symptoms are caused by excessive growth of skin cells and a decrease in dying skin cells. Immune cells are also involved. A few therapies work well in treating the disease. These treatments mainly target the immune cells in skin. However, they can stop working or do not work enough in some people.

We investigated the role of a protein called PA2G4 in psoriasis. PA2G4 increases the growth and progression of several cancerous tumours. Tumours share key features with psoriasis, including excessive growth and reduced cell death. We collected skin samples donated by people with psoriasis. Then, we used advanced laboratory techniques to analyse where and how much PA2G4 is produced in psoriasis compared with healthy skin. We found high levels of PA2G4 in skin samples from people with psoriasis compared with healthy donors. This was related to how severe their disease was. We were also able to identify skin cells as main producers of PA2G4. Next, we compared skin cells with normal and no levels of PA2G4. We found that a lack of PA2G4 resulted in lower levels of cell growth and inflammation. In addition, genes related to a process called cell differentiation (where a cell changes from a general, unspecialized form to a cell capable of carrying out a specific function) were found at higher levels. Finally, we looked at cell growth. We found that skin cells without PA2G4 had less ability to grow and reduced skin thickening, and did not die as often.

Our results highlight the role of PA2G4 in the development and progression of psoriasis. We suggest that inhibiting PA2G4 may be a possible new treatment option for people with psoriasis.

What is already known about this topic?

- Psoriasis is a chronic inflammatory skin disease characterized by keratinocyte hyperproliferation, aberrant differentiation and reduced cell death, leading to scaly plaques.
- Current treatments mainly target immune cells rather than keratinocytes, and some patients still show suboptimal responses to these therapies.
- In several malignancies, proliferation-associated protein 2G4 (PA2G4) has been identified as a promoter of cell growth, as well as tumorigenesis, by inhibiting cell death – cellular hallmarks shared with psoriasis.

What does this study add?

- PA2G4 is highly expressed in psoriatic skin and is correlated with disease severity and the histopathological features of psoriasis.
- PA2G4 was identified as a key regulator of keratinocyte proliferation, differentiation and survival.
- PA2G4 knockout reduced keratinocyte proliferation, decreased interleukin-22-induced acanthosis in reconstructed human epidermis models and increased cell death in primary human keratinocytes.
- Pharmacological inhibition of PA2G4 with WS6 reproduced these effects, further supporting its pathological role in psoriasis.

What is the translational message?

- Our complementary *in vivo* and *in vitro* findings highlight the pathological role of PA2G4, which disrupts skin homeostasis in psoriasis by promoting keratinocyte proliferation and survival.
- Inhibiting PA2G4 in keratinocytes, for example through topical or systemic treatment, represents a potential therapeutic strategy for psoriasis.

Psoriasis is a common immune-mediated inflammatory skin disease, affecting approximately 2–3% of the world's population.[1] It is a complex genetic disease with a high risk of multiple comorbidities, including psoriatic arthritis, cardiovascular diseases and metabolic syndromes, all of which substantially impair patients' quality of life.[2,3] Psoriasis is primarily driven by a T-cell immune response characterized by an exaggerated T helper (Th)17/Th1 axis.[4–6] Cytokines produced by Th17/Th1 cells promote keratinocyte hyperproliferation, aberrant differentiation and dysregulated cell death, leading to the formation of characteristic scaly plaques.[4] However, psoriatic keratinocytes actively contribute to the initiation and maintenance of psoriasis pathogenesis by amplifying a type 3 immune response.[7,8] These type 3 responses drive the histopathological features of psoriasis, including epidermal thickening (acanthosis), elongated rete ridges, a pronounced neutrophil infiltration and high metabolic activity.[4,9]

Given its high prevalence and profound impact on patients' quality of life, psoriasis imposes a substantial burden on global

health. While therapies targeting interleukin (IL)-17 and IL-23 have improved outcomes, a subset of patients exhibits suboptimal response, highlighting the need to better understand disease mechanisms.[10–16] Keratinocyte hyperproliferation is a hallmark of psoriasis, driven by transcription factors (TFs), such as the MYC family, Jun, signal transducers and activators of transcription (STAT) family members, and proliferating cell nuclear antigen (PCNA).[17–21] TF activity can be modulated through expression levels, subcellular trafficking, post-translational modification or targeted degradation, making TFs tractable hubs for elucidating pathogenic molecular networks. Understanding these regulatory circuits may decipher the mechanisms underlying keratinocyte hyperproliferation and pathogenic epidermal remodelling, while also identifying TFs as potential intervention points. Such strategies offer the potential to overcome cytokine pathway redundancies while maintaining a manageable safety profile. This suggests that targeting aberrantly expressed TFs may represent an alternative therapeutic approach for psoriasis, with the potential to restore pathogenic transcriptional programmes and improve outcomes in patients who do not benefit from current therapies.[17,22]

Proliferation-associated 2G4 protein (PA2G4, also known as Ebp1), is a multifunctional TF that binds to RNA, DNA and proteins, regulating transcription, RNA biological activity, proteostasis and epigenetics.[23,24] It is ubiquitously expressed in epithelial and mesenchymal cells, and influences cell proliferation, differentiation and survival. Dysregulated expression of PA2G4 has been linked to abnormal cell development and oncogenesis, highlighting its importance as a regulator of pathogenic processes in various tissues and diseases, particularly cancer.[23,24] Alternative splicing generates two isoforms with opposing roles in cell growth and differentiation. PA2G4-p48 is the more predominantly expressed and localizes to both the cytoplasm and the nucleus, where it promotes cell growth and enhances tumorigenesis by inhibiting apoptosis. Accordingly, elevated PA2G4-p48 expression levels have been seen in several tumours, compared with healthy tissues, and are associated with tumour progression. In contrast, PA2G4-p42 is less abundant and primarily localizes to the cytoplasm. It functions as a tumour suppressor by inhibiting cell proliferation and promoting differentiation, similarly to thyroid or salivary gland cancer.[25–27] Overall, PA2G4 represents a promising therapeutic target in oncology, given its dual function in regulating proliferation, differentiation, cell survival and processes that are also dysregulated in psoriasis.

In this study, we aimed to investigate the pathophysiological and immunological role of PA2G4 in psoriasis and primary human keratinocytes. Further, we identified PA2G4 inhibition as a novel therapeutic approach in psoriasis treatment.

Materials and methods

Patient sample collection

Human skin samples (punch biopsies and keratinocytes isolated from suction blisters) were obtained from Biobank Biederstein. Punch biopsies (6 mm) of lesional and nonlesional skin from patients with psoriasis were obtained under local anaesthesia. For diagnostic accuracy, independent clinical and histological assessments were performed by a dermatologist and a dermatopathologist.

Cell culture

Primary human epidermal keratinocytes were obtained by suction blister and cultured in DermaLife K Keratinocyte Medium Complete Kit (LL-0007; Lifeline Cell Technology, Frederick, MD, USA) at 37 °C in 5% CO_2.[28] Details are provided in Appendix S1 (see Supporting Information).

Reconstructed human epidermis skin equivalents

Reconstructed human epidermis (RHE) skin equivalents were generated as previously described.[29] Details are provided in Appendix S1.

CRISPR/Cas9 knockout of PA2G4

CRISPR/Cas9 knockout of PA2G4 was performed by applying ribonucleoprotein complexes with the 4D-Nucleofector™ device (Lonza, Basel, Switzerland) using the P3 Primary Cell 4D-Nucleofector™ X Kit S (Lonza) as previously described.[30] Details are provided in the Appendix S1.

Inhibition of PA2G4 with WS6

PA2G4 inhibition was achieved after 24 h of treatment with WS6 (HY-12461; Hölzel, Köln, Germany). A concentration of 1 µmol L^{-1} was used, according to manufacturer's instructions and published data.[22] IC_{50} values of WS6 are 0.24 nmol L^{-1}, 0.21 nmol L^{-1} and 40.48 nmol L^{-1} in MV4-11, MOLM13 and K562 cells, respectively. Functional and molecular effects were assessed using real-time polymerase chain reaction and scratch assays, respectively.

Statistical analysis

Data were analysed using Prism 10 (GraphPad, La Jolla, CA, USA) and visualized as mean (SD) or as boxplots from a number of independent human donors (see figure legends for details). Details of statistical tests are provided in the figure legends.

Detailed information on bulk and single-cell RNA sequencing (RNAseq) and spatial transcriptomics of psoriatic skin biopsies, immunohistochemistry, bulk RNAseq of keratinocytes, the scratch-proliferation assay, IL-20 enzyme-linked immunosorbent assay (ELISA), annexin V staining, Western blot analysis, and RNA and real-time polymerase chain reaction (PCR) is provided in Appendix S1.

Results

PA2G4 is abundant in psoriatic skin and predominantly expressed in basal keratinocytes

Using bulk RNAseq, *PA2G4* was identified as being significantly upregulated in psoriasis ($n = 90$; $P < 0.001$) compared with autologous nonlesional skin (Figure 1a). Single-cell RNAseq (scRNAseq) revealed the strongest expression of *PA2G4* in keratinocytes, predominantly in proliferating (*CDK1*$^+$, *PCNA*$^+$, *KRT1*$^-$, *KRT10*$^-$) and differentiating cells (*KRT1*$^+$, *KRT10*$^+$) (Figure 1b).[31] Consistently, spatial transcriptomics confirmed abundant *PA2G4* expression in

psoriatic epidermis ($n = 12$) compared with nonlesional skin ($n = 5$), with marked enrichment in the basal and suprabasal layers, corresponding to the site of keratinocyte proliferation (Figure 1c, d). Immunohistochemistry further confirmed high PA2G4 protein expression in psoriatic skin [$n = 5$; mean (SD) 44.3 (13.7) cells per 10× field ($P = 0.02$)]. Conversely, nonlesional skin exhibited weak-to-no PA2G4 protein expression [$n = 5$; mean (SD) 1.6 (0.8) cells per 10× field] (Figure 1e, f).

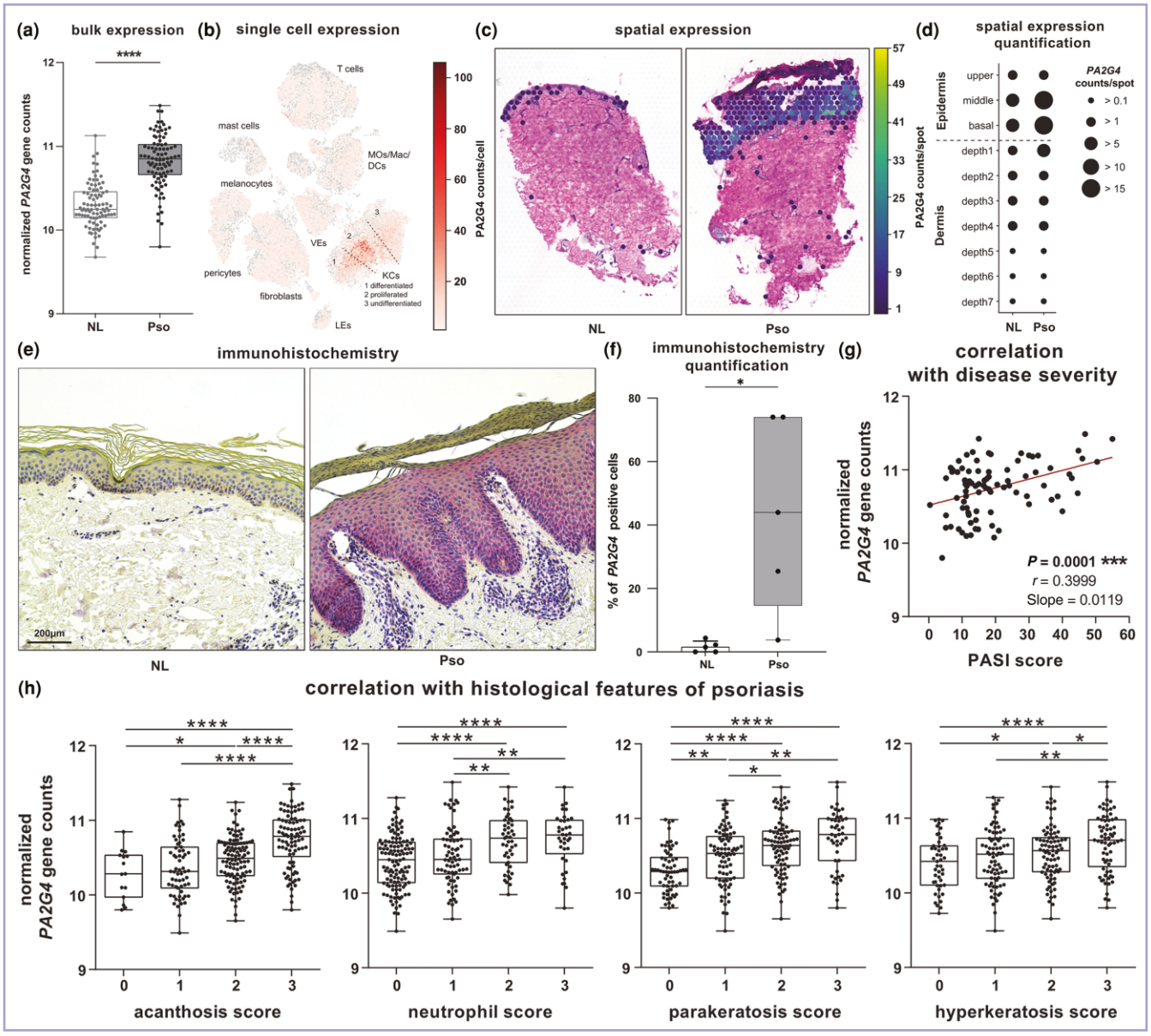

Figure 1 Proliferation-associated 2G4 (PA2G4) is abundant in psoriatic skin and positively correlates with disease severity and histological features of psoriasis. (a) Normalized *PA2G4* gene counts in nonlesional (NL) and lesional (Pso) skin of patients with psoriasis ($n = 90$) from bulk RNA sequencing (RNAseq). The adjusted *P*-value was extracted from DESeq2 analysis. (b) Cell type-specific expression of *PA2G4* from single-cell RNAseq analysis of lesional psoriasis skin ($n = 7$). *PA2G4* counts per cell are visualized as a uniform manifold approximation and projection (UMAP) plot. (c, d) Spatial expression of *PA2G4* in lesional (Pso, $n = 12$) and nonlesional (NL, $n = 5$) psoriatic skin analysed by spatial transcriptomics. (c) *PA2G4* total counts per spot (haematoxylin and eosin staining) of a representative patient. (d) Quantification of *PA2G4* counts per spot in the entire cohort, classified by upper, middle and basal epidermis, as well as seven different dermis depths. (e, f) PA2G4 protein expression in nonlesional (NL, $n = 5$) and lesional (Pso, $n = 5$) psoriatic skin analysed by immunohistochemistry. (e) Immunohistochemistry staining of PA2G4 of a representative patient with psoriasis. Scale bar = 200 µm. (f) Quantification of $PA2G4^+$ cells per 10× field using QuPath (version 0.6.0) with the positive cell detection workflow. (g) Correlation of normalized *PA2G4* gene counts to Psoriasis Area and Severity Index (PASI) scores of patients with psoriasis ($n = 85$). Significance for linear regression was calculated by Pearson correlation. (h) Association of normalized *PA2G4* gene counts in lesional skin of chronic inflammatory skin diseases ($n = 274$) with psoriasis-associated histological attribute scores for acanthosis, neutrophils, parakeratosis and hyperkeratosis. Attribute scores were determined by histological analysis and collected as categorical ordinary data represented as 0 (none), 1 (mild), 2 (moderate) or 3 (severe). Histological score groups were compared using an ordinary one-way ANOVA. *n* indicates the number of independent human donors. DCs, dendritic cells; KCs, keratinocytes; LEs, lymphatic endothelial cells; Mac, macrophages; MOs, monocytes; VEs, vascular endothelial cells. $^*P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$, $^{****}P \leq 0.0001$.

PA2G4 expression positively correlates with disease severity, histological features and proliferation/inflammation markers of psoriasis

To assess whether PA2G4 contributes to psoriasis pathogenesis, gene expression from bulk RNAseq data was correlated with disease severity and histological features. *PA2G4* expression was positively correlated ($r=0.3999$, $P<0.001$) with Psoriasis Area and Severity scores in patients with psoriasis ($n=85$; Figure 1g). Moreover, PA2G4 levels significantly increased with the intensity of acanthosis, neutrophils, parakeratosis and hyperkeratosis (intensity 0–3: $P<0.001$) in skin lesions of patients with inflammatory skin disease ($n=274$; Figure 1 h). Consistently, *PA2G4* expression correlated positively with promitogenic cytokine genes, including *IL20* ($r=0.54$, $P<0.001$) and *IL22* ($r=0.203$, $P=0.07$), in patients with psoriasis ($n=90$). Significant associations were also observed with genes encoding proliferation markers indicative of keratinocyte hyperproliferation, such as *MKI67* ($r=0.52$, $P<0.001$) and *PCNA* ($r=0.75$, $P<0.001$), and the keratinocyte TF encoded by *EHF* ($r=0.50$, $P<0.001$) (Figure S1a; see Supporting Information). Furthermore, *PA2G4* expression was strongly correlated with genes encoding type 3 inflammation markers, including *CXCL1* ($r=0.45$, $P<0.001$), *CXCL8* ($r=0.33$, $P=0.002$), *IL36G* ($r=0.62$, $P<0.001$), *HIF1A* ($r=0.58$, $P<0.001$) and *S100A9* ($r=0.52$, $P<0.001$), in patients with psoriasis ($n=90$) (Figure S1b). *IL17C* ($r=0.24$, $P=0.05$), *CXCL5* ($r=0.11$, $P=0.32$) and *VEGFA* ($r=0.20$, $P=0.07$) expression levels were not correlated with *PA2G4* expression (Figure 1Sc). Thus, PA2G4 probably contributes to psoriasis by regulating cell proliferation, differentiation and inflammation.

PA2G4 regulated keratinocyte proliferation, differentiation and inflammation

Following the identification of abundant PA2G4 expression in psoriasis, we characterized its transcriptional landscape and elucidated its function. Highly efficient PA2G4 knockouts at the gene [log2 fold change (FC) $=-2.4$; $P<0.001$] and protein levels (expression relative to the control: 0.049 vs. 0.42; 88.3% reduction) were generated in keratinocytes using CRISPR/Cas9 ribonucleoprotein complexes (Figure 2a). PA2G4 knockout and pulsed wildtype control keratinocytes ($n=6$) were cultured under unstimulated or chronic type 3 inflammatory [IL-17A + tumour necrosis factor (TNF)-α] conditions for 24 h and analysed by bulk RNAseq. Transcriptomic profiling by DESeq2 analysis identified 88 downregulated and 129 upregulated genes in PA2G4 knockout keratinocytes under basal conditions, relative to wildtype keratinocytes ($\log2FC \geq |0.5|$; $P \leq 0.05$) (Figure 2b). Under type 3 conditions, the number of downregulated genes increased to 145, whereas 137 genes were upregulated (Figure S2a; see Supporting Information). Gene Set Enrichment Analysis (GSEA) provided a global overview of PA2G4-regulated processes. Under basal conditions, GSEA revealed suppression of proliferation- and inflammation-related pathways (e.g. 'positive regulation of cell population proliferation', 'regulation of cell growth', 'cytokine production involved in inflammatory response', 'response to type I IFN [interferon] and IFN-γ'). By contrast, pathways linked to epidermal differentiation (e.g. 'keratinocyte and epidermal cell differentiation') and skin development were activated (Figure 2c). Moreover, suppression of the 'negative regulation of programmed cell death' pathway indicated activation of cell death processes. A comparable pathway enrichment was observed under type 3 conditions (Figure S2b). Hyperproliferation-associated genes were significantly downregulated in PA2G4 knockout cells, including those encoding inflammatory cytokines: *IL20* ($\log2FC=-0.97$; $P=0.04$), *VEGFA* ($\log2FC=-0.56$; $P<0.001$) and *TGFB1* ($\log2FC=-0.20$; $P=0.03$), as well as TFs: *TP63* ($\log2FC=-0.34$; $P<0.001$), *MKI67* ($\log2FC=-0.90$; $P=0.01$) and *E2F8* ($\log2FC=-0.54$; $P=0.007$) (Figure 2d, Figure S2c). By contrast, genes associated with skin homeostasis, epidermal differentiation, cell adhesion and tissue remodelling were significantly upregulated. These included keratin genes *KRT6B* ($\log2FC=0.59$; $P=0.02$) and *KRT6C* ($\log2FC=0.79$; $P=0.002$), cell adhesion genes *FLG* ($\log2FC=0.75$; $P<0.0001$) and *DSG4* ($\log2FC=1.36$; $P<0.001$), extracellular matrix gene *DCN* ($\log2FC=1.67$; $P=0.04$) and late cornified envelope gene *LCE2C* ($\log2FC=1.32$; $P=0.02$) (Figure 2e, Figure S2c). Inflammation-associated genes such as that encoding the TNF superfamily member lymphotoxin β (*LTB*) ($\log2FC=-1.48$; $P=0.02$), as well as *IL33* ($\log2FC=-0.47$; $P=0.03$) and *CXCL10* ($\log2FC=-1.20$; $P=0.004$), were suppressed in PA2G4 knockout cells. Likewise, IFN-related genes, including *IFNGR2* ($\log2FC=-0.28$; $P<0.001$), *IFITM1* ($\log2FC=-0.79$; $P<0.001$) and *IRF1* ($\log2FC=-0.66$; $P<0.001$), and the matrix metalloproteinase-encoding *MMP2* ($\log2FC=-0.89$; $P<0.001$), were significantly downregulated (Figure 2f, Figure S2c). By contrast, typical psoriasis-associated cytokines and chemokines (encoded by *CXCL1*, *CXCL5*, *CXCL8*, *TNF*, *IL6* and *IL23A*) remained unchanged (Figure S3; see Supporting Information). Overall, PA2G4 promoted proliferation and inflammation, while suppressing differentiation, adhesion and epidermal remodelling in the skin.

PA2G4 promotes keratinocyte proliferation capacity and acanthosis induction in reconstructed human epidermis

Functional proliferation-related assays were performed using PA2G4 knockout keratinocytes. In scratch-proliferation assays ($n=7$), PA2G4 knockout keratinocytes showed a significantly impaired proliferation capacity ($P=0.003$) with a mean (SD) closing gap of 0.88 (0.66) mm^2 compared with 1.44 (0.89) mm^2 in wildtype cells, which nearly closed the scratch (Figure 3a, b). In line with this, PA2G4 knockout cells secreted significantly reduced levels of the proliferative cytokine IL-20 [mean (SD) 68.5 (67.5) pg mL^{-1} vs. 643.3 (917.2) pg mL^{-1} in wildtype cells; $P=0.007$] (Figure 3c). Western blot analysis further revealed decreased hypoxia-inducible factor (HIF)-1α protein expression in PA2G4 knockout keratinocytes [mean (SD) 0.31 (0.36) arbitrary units (a.u.) vs. 0.69 (0.11) a.u. in wildtype cells], suggesting that PA2G4 supports hyperproliferation through HIF-1α regulation (Figure 3d). Consistently, cell cycle phase analysis of scRNAseq data from patients with psoriasis ($n=7$) showed highest *PA2G4* expression in keratinocytes in the DNA synthesis (S) phase, indicating its involvement in DNA replication during mitosis and further underscoring its contribution to keratinocyte proliferation (Figure 3e).

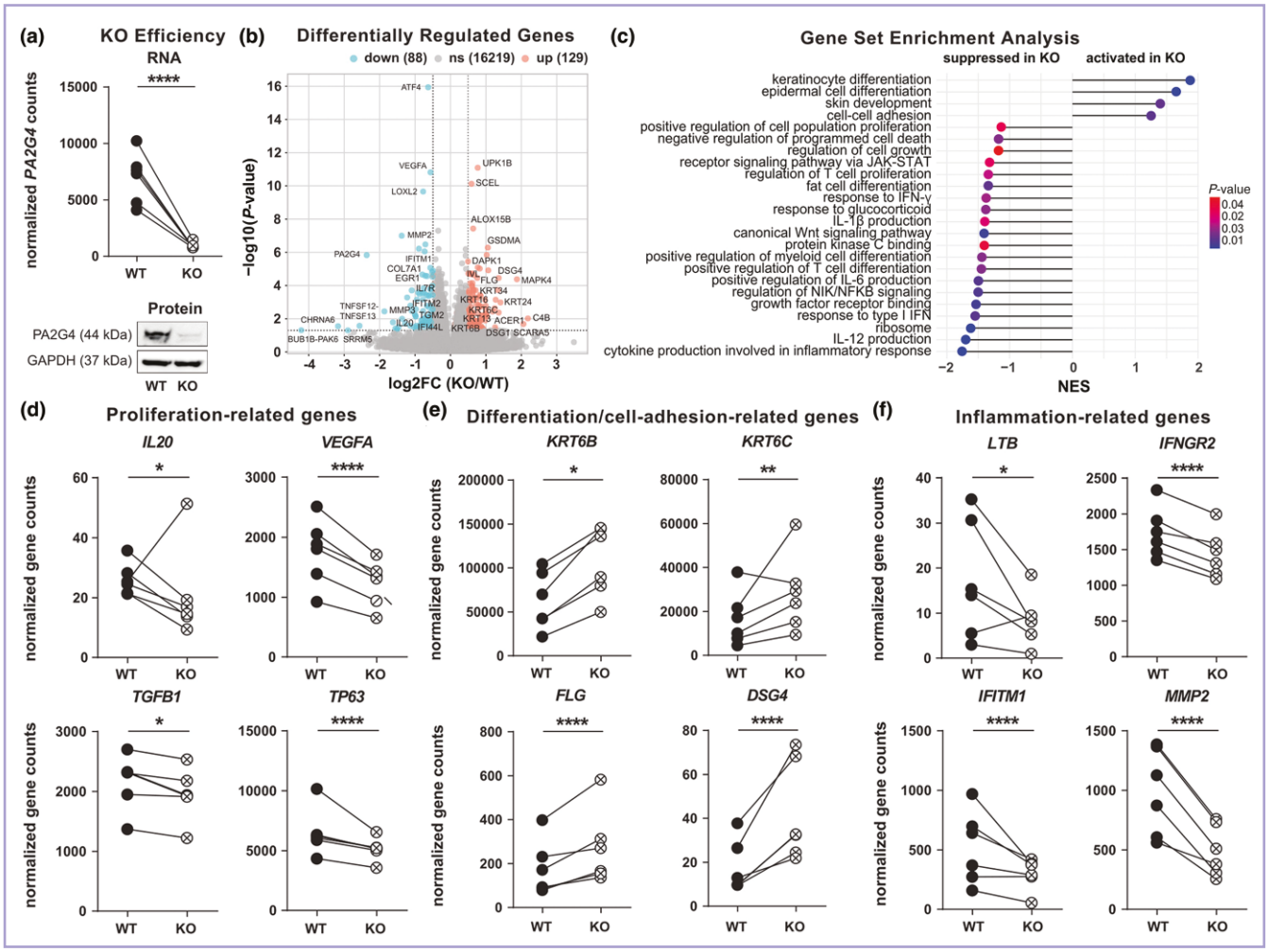

Figure 2 Proliferation-associated 2G4 (PA2G4) regulates keratinocyte proliferation, differentiation and inflammation. PA2G4 was knocked out (KO) via CRISPR/Cas9 in primary human keratinocytes under basal conditions. Subsequently, changes at the transcriptome level under basal (unstimulated, $n=6$) or interleukin (IL)-17A + tumour necrosis factor-stimulated ($n=6$; see Figure S1) conditions were analysed by bulk RNA sequencing. (a) Knockout efficiency of PA2G4 on RNA level (top) and protein level analysed by Western blot analysis (bottom) under basal conditions. (b) Volcano plot displaying differentially regulated genes in PA2G4 knockout compared with wildtype (WT) keratinocytes under basal conditions analysed with DESeq2 ($\log2FC \geq |0.5|$, $P \leq 0.05$). Blue indicates downregulated, orange indicates upregulated and grey indicates not statistically significant (ns; i.e. $P > 0.05$). (c) Suppressed and activated pathways in PA2G4 knockout compared with wildtype keratinocytes under basal conditions ($P \leq 0.05$) analysed by Gene Set Enrichment Analysis. (d–f) Normalized gene expression in PA2G4 knockout and wildtype keratinocytes under basal conditions of (d) proliferation-related; (e) differentiation, cell adhesion and extracellular matrix-related; and (f) inflammation-related genes regulated by PA2G4. Significant values for differences in normalized gene expression were extracted from DESeq2 analysis. *n* indicates the number of independent human donors. FC, fold change; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; IFN, interferon; IL, interleukin; JAK, Janus kinase; NES, normalized enrichment score; NFKB, nuclear factor-κB; NIK, nuclear factor-κB-inducing kinase; STAT, signal transducers and activators of transcription. $^*P \leq 0.05$, $^{**}P \leq 0.01$, $^{****}P \leq 0.0001$.

Finally, IL-22-induced acanthosis in RHE was markedly reduced in PA2G4 KO keratinocytes [mean (SD) 33.9 (3.1) µm vs. 17.0 (2.7) µm in wildtype cells; $P=0.03$], with a tendency towards reduced epidermal thickness under basal conditions (Figure 3f, g). Therefore, PA2G4 was identified as a key regulator of keratinocyte proliferation and demonstrated its contribution to the development of acanthosis in psoriasis.

PA2G4 suppressed cell death and apoptosis in keratinocytes

Bulk RNAseq initially indicated that PA2G4 may suppress cell death in keratinocytes, as reflected by the suppression of the ‘negative regulation of programmed cell death’ (Figure 2c). Therefore, we examined the effect of PA2G4 on keratinocyte survival. PA2G4 knockout keratinocytes showed significant upregulation of proapoptotic genes such as *CASP9* ($\log2FC=0.41$; $P=0.02$), *DAPK1* ($\log2FC=0.67$; $P<0.001$) and *HRK* ($\log2FC=2.49$; $P=0.07$), the pyroptotic effector gene *GSDMA* ($\log2FC=1.00$; $P<0.001$) and inflammasome-related genes, such as *IL18* ($\log2FC=0.33$; $P=0.02$) and *NLRP10* ($\log2FC=0.67$; $P=0.01$). Conversely, the antiapoptotic protein-encoding *BCL11A* ($\log2FC=-0.38$; $P=0.02$), the ferroptosis inhibitor-encoding *GPX4* ($\log2FC=-0.32$; $P=0.001$) and the complement inhibitor-encoding *CFH* ($\log2FC=-1.55$; $P=0.02$) were downregulated (Figure 4a), further supporting the role of PA2G4 in restraining cell death. To functionally validate PA2G4 effects on cell death, annexin V and propidium iodide (PI) staining

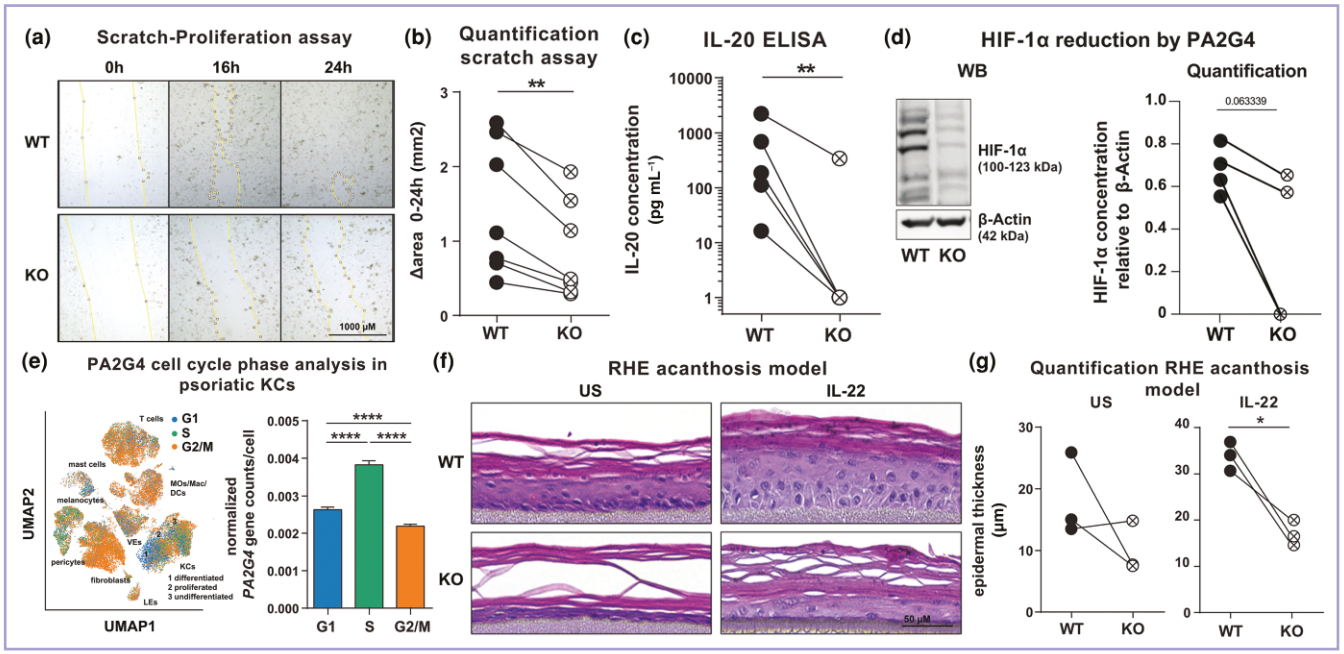

Figure 3 Proliferation-associated 2G4 (PA2G4) promotes keratinocyte proliferation capacity and acanthosis induction in reconstructed human epidermis (RHE). PA2G4 was knocked out (KO) via CRISPR/Cas9 in primary human keratinocytes, followed by functional assays to analyse the effects on proliferation capacity. (a, b) Scratch-proliferation assay ($n = 7$). Confluent keratinocytes under basal conditions were scratched using a pipette tip and proliferation capacity was observed within 24 h. (a) Representative pictures after 0, 16 and 24 h of scratching. Scale bar = 1000 µm. The scratched area is outlined with a yellow line and quantified in (b). The Δarea 0–24 h was calculated. (c) Released interleukin (IL)-20 concentrations from keratinocytes after IL-17A + tumour necrosis factor stimulation for 24 h ($n = 5$), analysed by enzyme-linked immunosorbent assay (ELISA). ELISA measurements were performed in technical replicates. (d) Western blot analysis of hypoxia-inducible factor (HIF)-1α in basal keratinocytes (left). Relative protein intensity was quantified to β-actin (right, $n = 4$). The intensity of the bands was calculated using ImageJ (NIH, Bethesda, MD, USA). (e) Cell cycle phase analysis on single-cell RNA sequencing data of patients with psoriasis ($n = 7$). Cell cycle phases G1, S and G2/M are highlighted for each cell in a uniform manifold approximation and projection (UMAP) plot (left) and correlated to the respective *PA2G4* gene counts per cell in keratinocytes (right). (f, g) Acanthosis model of RHE ($n = 3$). Keratinocytes were grown in an air–liquid interface to form an RHE. Acanthosis was induced by stimulation with recombinant IL-22 for 72 h or left unstimulated (US) as a control. Representative haematoxylin and eosin stainings are shown in (e) and epidermal thickness is quantified in (f). Scale bar = 50 µm. Mean knockout and wildtype (WT) values were compared using a paired two-sided *t*-test. *n* indicates the number of independent human donors. $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{****}P \leq 0.0001$.

were performed under basal and type 3 inflammatory conditions. Flow cytometric analysis revealed a marked increase in the frequency of total dead cells (annexin V^+ PI^+) (IL-17A + TNF, $P = 0.004$; IL-22, $P = 0.03$) and apoptotic cells (annexin V^+ PI^-) (IL-17A + TNF, $P = 0.06$; IL-22, $P = 0.03$) in PA2G4 knockout keratinocytes. (Figure 4b, c). Thus, PA2G4 could suppress keratinocyte death.

Targeting PA2G4 by WS6 inhibitor treatment reduced psoriasis features

We next investigated the potential of pharmacological PA2G4 inhibition using the selective PA2G4 inhibitor WS6 as a possible treatment approach for psoriasis.[22] WS6, a tyrosine kinase inhibitor that primarily targets PA2G4, was initially shown to regulate cell proliferation in diabetes and,[32,33] more recently, has been reported to exert tumour-suppressive effects in MYCN-driven cancers and acute myeloid leukaemia (AML).[34,35] To investigate the effects of WS6 treatment in psoriasis context, keratinocytes were treated with low-dose WS6 (1 µmol L^{-1}), according to the manufacturer's instructions, as well as previous reports.[22] The expression of psoriasis-associated genes (upregulated in psoriasis; Figure 5a) was measured using real-time PCR. WS6 treatment significantly reduced *PA2G4* expression (61%, $P = 0.04$) and *MYC* (44%, $P = 0.05$); similar trends were found for *MKI67* (61%, $P = 0.16$) and *PCNA* (80%, $P = 0.29$). In addition, WS6 markedly downregulated the expression of *HIF1A* (51%, $P = 0.08$), *S100A7* (23%, $P = 0.01$) and *CXCL8* (67%, $P = 0.19$) (Figure 5b). Consistent with these transcriptomic findings, functional scratch proliferation assays confirmed the severely impaired proliferative capacity of WS6-treated keratinocytes (Figure 5c). WS6 treatment reduced proliferation capacity ($P = 0.06$), with minimal mean (SD) gap closure of 0.07 (0.04) mm^2 to 0.95 (0.58) mm^2 in untreated cells, which completely closed the gap (Figure 5d). Overall, WS6 treatment suppressed keratinocyte proliferation and downregulated psoriasis-related inflammatory genes involved in metabolic activity, thereby supporting PA2G4 as a promising therapeutic target for psoriasis.

Discussion

PA2G4 is a multifunctional TF involved in transcriptional regulation, RNA biology, proteostasis and epigenetic modulation, highlighting its critical function in maintaining cellular homeostasis.[23] To our knowledge, this study is the first to functionally characterize PA2G4 in psoriasis, identifying it as a regulatory hub of

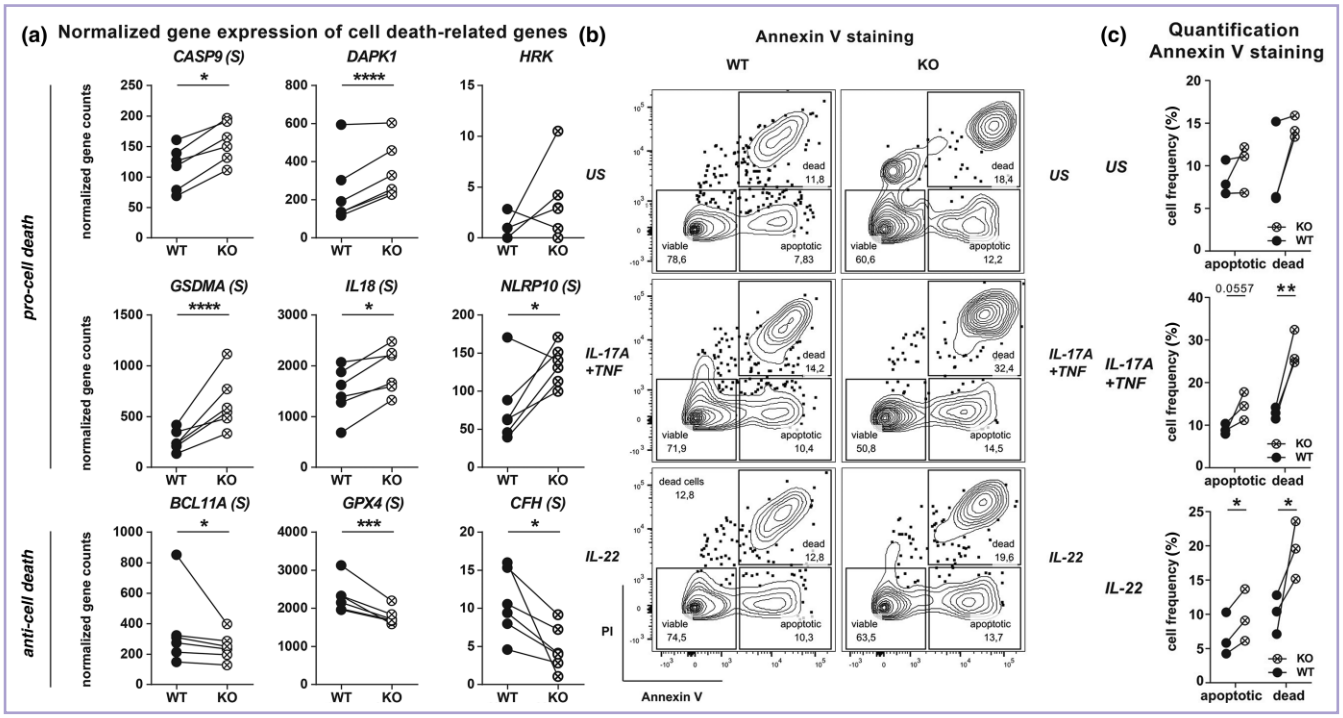

Figure 4 Proliferation-associated 2G4 (PA2G4) suppresses cell death and apoptosis of keratinocytes. PA2G4 was knocked out (KO) via CRISPR/Cas9 in primary human keratinocytes, followed by functional assays to analyse the effects on cell death and apoptosis. (a) Bulk RNA sequencing ($n = 5$). Normalized gene expression in PA2G4 knockout (KO) and wildtype (WT) keratinocytes under basal or interleukin (IL)-17A + tumour necrosis factor (TNF)-stimulated (S) conditions of cell death-related genes regulated by PA2G4. Significant values for differences in normalized gene expression were extracted from DESeq2 analysis. (b, c) Annexin V staining ($n = 3$). Keratinocytes were stimulated for 72 h with IL-17A + TNF and then stained with annexin V and propidium iodide (PI). Frequency of apoptotic (annexin V^+ PI^-) and dead (annexin V^+ PI^+) cells was determined by flow cytometry. Representative scatter plots (b) and quantification of all donors (c) are shown. Mean values of knockout and wildtype cells were compared using a paired two-sided *t* test. *n* indicates the number of independent human donors. $^*P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$, $^{****}P \leq 0.0001$.

keratinocyte proliferation, differentiation, inflammation and survival, positioning it as a therapeutic target in psoriasis.

PA2G4 was first identified in 2000 in a yeast two-hybrid screen, and has since attracted considerable interest for its role in tumour progression and poor clinical outcomes.[26,27,36–39] Herein, we demonstrated that PA2G4 was markedly upregulated in psoriasis at the RNA and protein levels, with spatial enrichment in basal keratinocytes, aligning with Skin Atlas proteomics maps, showing predominant epidermal expression.[40] Moreover, PA2G4 expression was positively correlated with disease severity, acanthosis and neutrophil infiltration, supporting its involvement in psoriasis.

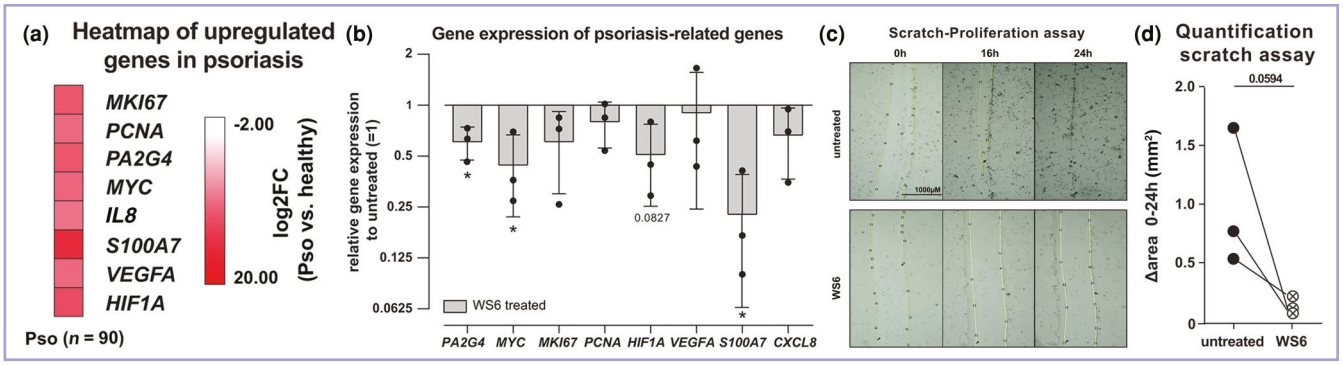

Figure 5 Targeting proliferation-associated 2G4 (PA2G4) by WS6 inhibitor treatment reduces features of psoriasis. Primary human keratinocytes were treated with 1 µmol L^{-1} WS6 inhibitor or left untreated as controls (0.1% dimethyl sulfoxide), followed by functional assays to analyse the effects on proliferation and inflammation. (a) Heatmap of selected upregulated genes in lesional compared with nonlesional skin [log2 fold change (FC)] of patients with psoriasis ($n = 90$) from bulk RNA sequencing. (b) Relative gene expression of psoriasis-related markers in keratinocytes 24 h after WS6 treatment compared with untreated cells ($n = 3$). (c, d) Scratch-proliferation assay ($n = 3$). Confluent keratinocytes were scratched using a pipette tip directly after WS6 treatment and proliferation capacity was observed within 24 h. (b) Representative pictures after 0, 16 and 24 h of scratching. Scale bar = 1000 µm. The scratched area is outlined with a yellow line and quantified in (c). The Δarea 0–24 h was calculated. WS6 and untreated mean values were compared using a paired two-sided *t*-test. *n* indicates the number of independent human donors. Pso, psoriasis.

Given that acanthosis reflects dysregulated cell cycle control, a hallmark of tumour biology, we investigated the role of PA2G4 in keratinocyte proliferation. PA2G4 has been shown to promote proliferation by interacting with histone deacetylase 2 and Sin3A to regulate E2F-mediated transcription.[41–45] Consistent with this, our bulk RNAseq of PA2G4 knockout keratinocytes demonstrated the downregulation of cell cycle genes (E2F members, *AURKB*, and *BUB1*), underscoring the importance of PA2G4 in cell cycle progression. scRNAseq data further showed the highest expression in proliferating keratinocytes enriched in the S phase, supporting its involvement in DNA replication and proliferation. Similar effects have been reported in tumour models, where PA2G4 overexpression increased S-phase entry and knockdown impaired cell cycle progression.[24,46]

Beyond cell cycle control, PA2G4 promotes proliferation by stabilizing PCNA through MDM2 (mouse double minute 2 homolog) binding, mediating p53 degradation and inhibiting MDM2 self-ubiquitination by enhancing Akt activity.[26,47,48] Moreover, the interaction with transcription initiation factor-1A promotes the transcription of PCNA, enhancing rRNA synthesis in T cells.[49] Accordingly, genetic or pharmacological inhibition of *PA2G4* reduced *MKI67, MYC*, *HIF1A*, *TP63* and *PCNA* expression at the RNA and protein levels. We further determined that genes encoding cytokines that drive hyperproliferation, including *IL20*, *VEGFA* and *TGFB1*, were likewise reduced, and that *PA2G4* expression correlated positively with proliferation-related genes in psoriasis. The loss of PA2G4 impaired keratinocyte proliferation in scratch assays and reduced IL-22-induced acanthosis in RHE models. Supporting our data, Li *et al*. have reported that loss of the post-translation modification lysine 2-hydroxyisobutyrylation (Khib) on PA2G4 enhances its hyperproliferative function in psoriasis.[50]

PA2G4 modulates adaptive immune responses,[49,51,52] suggesting its involvement in shaping inflammatory responses in psoriasis. We showed that its loss reduced *TGFB1*, a central driver of Th17 differentiation and tissue remodelling, and *LTB*, which contributes to lymphoid tissue organization,[53,54] whereas canonical Th17 cytokines remained unaffected. Instead, IFN-related genes *IL33* and *MMP2* were significantly downregulated, indicating modulation beyond the IL-23/IL-17 axis. Although the IL-23/IL-17 axis and tissue-resident memory T cells drive psoriasis chronicity, our findings highlight PA2G4 as a potential link between IFN signalling and chronic inflammation. The role of PA2G4 in the psoriatic microenvironment warrants further investigation, which our group will address in a follow-up study.

Psoriasis pathogenesis is driven by accelerated epidermal turnover and reduced keratinocyte death, processes to which PA2G4 contributes.[4] In our PA2G4 knockout keratinocytes, GSEA revealed activation of epidermal differentiation and skin development pathways, with upregulation of keratins, adhesion molecules and ECM genes critical for terminal differentiation and skin homeostasis.[54–58] Consistent with this, PA2G4 has been linked to cellular differentiation, including pancreatic cancer where its expression correlates with tumour size.[46,59–62] Moreover, PA2G4 knockout keratinocytes showed increased frequencies of apoptotic and dead cells, alongside upregulation of proapoptotic and inflammasome-related genes, including the pyroptosis gene *GSDMA*. Conversely, the antiapoptotic gene *BCL11A*, the ferroptosis inhibitor gene *GPX4* and the complement inhibitor gene *CFH* were downregulated, indicating a survival-promoting function in keratinocytes, consistent with its protein kinase Cδ–Akt-mediated antiapoptotic signalling.[46,63–65]

Given its predominant epidermal expression and multifaceted contribution to psoriatic features, PA2G4 is a promising target for topical interventions. Pharmacological blockade with the tyrosine kinase inhibitor WS6 reduced keratinocyte proliferation and suppressed inflammatory genes linked to metabolic activity and neutrophil recruitment. WS6 targets PA2G4 primarily by interfering with PA2G4–MYC binding,[33] reducing MYCN stability and tumorigenicity *in vitro* and *in vivo*.[34,66] Tumour-suppressive functions have been demonstrated in AML and MYCN-driven cancers,[39,40] where systemic administration decreased proliferation without major toxicity.[22] While potential off-target effects of WS6 cannot be completely excluded,[67] several studies have reported outcomes consistent with on-target inhibition,[22,34,68] and PA2G4 knockout in our study also confirmed WS6-induced phenotypes. The absence of major off-target readouts (e.g. histone deacetylase activity assays) further strengthens the argument that WS6 is acting through its intended mechanism.[22] Recent structure–activity optimizations of WS6 have broadened the therapeutic window and reduced nonspecific activities,[34] indicating that current limitations are compound specific and do not compromise the translational potential of targeting PA2G4.

In summary, this study implicates the TF PA2G4 as an important factor in psoriasis pathogenesis that could promote proliferation, aberrant differentiation, cell survival and inflammation. PA2G4 may be an interesting target for psoriasis treatment.

Author contributions

Theresa Raunegger (Investigation, Methodology, Writing—review & editing [lead], Visualization, Writing—original draft [equal]), Sophia Wasserer (Investigation, Writing—review & editing [supporting], Visualization [equal]), Jessica Eigemann (Investigation, Methodology, Writing—review & editing [supporting]), Christina Hillig (Investigation, Visualization, Writing—review & editing [supporting]), Görkem Aydin (Investigation, Writing—review & editing [supporting]), Nils Kurzen (Writing—review & editing [supporting]), Carsten B. Schmidt-Weber (Writing—review & editing [supporting]), Michael P. Menden (Funding acquisition, Supervision, Writing—review & editing [supporting]), Natalie Garzorz-Stark (Conceptualization, Writing—review & editing [supporting]), Inga Wessels (Supervision, Writing—review & editing [supporting]), Stefanie Eyerich (Writing—review & editing [supporting]), Kilian Eyerich (Writing—review & editing [supporting]), Tilo Biedermann (Writing—review & editing [supporting]), Felix Lauffer (Funding acquisition [lead], Supervision, Writing—review & editing [equal]), and Manja Jargosch (Conceptualization [lead], Investigation, Methodology, Supervision, Visualization, Writing—original draft, Writing—review & editing [equal])

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Conflicts of interest

F.L. has been an advisor and/or has received speaker’s honoraria and/or has received grants and/or has participated in clinical trials for the following companies: AbbVie, Almirall, Amgen, Biogen,

Bristol Myers Squibb (BMS), Galderma, Hexal, Incyte, Johnson & Johnson, LEO Pharma, Lilly, Novartis, Regeneron, Sanofi and UCB. C.B.S.-W. gave advice to and/or has received grants from the following companies: Allergopharma, LETI Pharma, law firms and Zeller. T.B. gave advice to or received honoraria for talks or research grants from AbbVie, ALK-Abelló, Boehringer Ingelheim, Celgene-BMS, LEO Pharma, Lilly, Novartis, Sanofi-Genzyme, Regeneron, and Viatris. K.E. has received grants and honoraria from and served as a speaker, investigator, consultant/or advisor for AbbVie, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, LEO Pharma, Eli Lilly, Johnson & Johnson, Novartis, MoonLake, Sanofi, UCB and Sitryx. S.W. has received grants and/or funding and/or speaker's honoraria from Almirall, BMS, Janssen, LEO Pharma, Lilly, Novartis, Sanofi and Regeneron. J.E. was partially funded by the Deutsche Forschungsgemeinschaft (GRK2668). The rest of the authors declare no conflicts of interest.

Data availability

Bulk RNA sequencing data of the skin related to this article can be obtained from the Gene Expression Omnibus (GEO; https://0-www-ncbi-nlm-nih-gov.brum.beds.ac.uk/geo/) under accession number GSE154200. All other data will be shared on reasonable request to the corresponding author.

Ethics statement

The study design was approved by the local ethics committee (Klinikum Rechts der Isar 44/16S, 5590/12).

Patient consent

Human skin samples were collected after written informed consent was obtained from Biobank Biederstein, in accordance with the Declaration of Helsinki protocol and local ethics committees.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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