Downregulation of Caveolae-Associated Proteins in Psoriasis: A Case Series Study

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We have previously identified that a structural membrane protein Caveolin-1 (Cav1) is involved in the regulation of aberrant keratinocyte proliferation and differentiation. The aim of this study was to elucidate the role of Cav1, Caveolin-2 (Cav2), and Cavin-1 in the pathogenesis of psoriasis vulgaris and between psoriasis subtypes. We utilized human biopsies from validated cases of psoriasis vulgaris (n = 21) at the University of Miami Hospital and compared the expression of Cav1, Cav2, and Cavin-1 by immunohistochemistry staining with that in normal healthy age-/sex-/location-matched skin (n = 15) and chronic spongiotic dermatitis skin samples (as control inflammatory skin condition) and quantified using QuPath. Distinct subtypes of psoriasis included guttate, inverse, nail, plaque, palmoplantar, and pustular. All biopsy samples exhibited a trend toward downregulation of Cav1, with nail, plaque, and palmoplantar psoriasis exhibiting the most pronounced effects. Only nail and pustular psoriasis samples exhibited significant downregulation of Cav2 and Cavin-1, suggesting Cav1 to be the main caveolar contributor to the pathogenesis of psoriasis. Together, these data support caveolae as pathophysiological targets in nail and pustular psoriasis, whereas Cav1 seems to be a general biomarker of multiple subtypes of psoriasis.

Keywords: Caveolae, Caveolin, Lipid rafts, Psoriasis

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INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disease characterized by well-defined, erythematous plaques with a silvery scale. It is a common skin disorder affecting approximately 3.0% of the general United States population, affecting nearly 7.5 million individuals (Armstrong et al, 2021). The exact pathogenesis is currently unknown; however, recent studies have shown psoriasis to affect the human body as a chronic inflammatory systemic disorder rather than localized insults to the skin (Späh, 2008). Large epidemiological studies from Germany and Taiwan indicate an increased association of other inflammatory systemic comorbidities such as rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus in patients with psoriasis that support the pathophysiology of psoriasis to be rooted in chronic systemic inflammation (Augustin et al, 2010; Tsai et al, 2011). The elevated inflammatory profile of psoriasis and associated comorbidities may lead to a decreased life expectancy of 3−4 years because a population-based cohort study from the United Kingdom assessed patients with severe psoriasis to have approximately a 50% increased risk of mortality (Gelfand et al, 2007). Although aberrant keratinocyte proliferation is a key hallmark of psoriasis, increased infiltration of T cells within the epidermis and release of inflammatory cytokines (IL-12, IL-22, IL-23) may be driving epidermal hyperplasia (acanthosis) (Torti and Feldman, 2007; Zheng et al, 2007).

Subtypes of the disease include plaque, guttate, pustular, erythrodermic, palmoplantar, nail, and inverse psoriasis. Plaque psoriasis is the most common subtype, affecting approximately 80% of patients with psoriasis (Brunasso et al, 2013). Guttate psoriasis is characterized by an acute onset of multiple, small red papules and plaques ranging from 0.5 to 1.5 cm commonly associated with a preceding viral upper respiratory illness. Palmoplantar psoriasis, on the other hand, is characterized by plaque or pustular lesions primarily or exclusively located on the palms and soles of patients, affecting approximately 12% of patients with psoriasis (Balan et al, 2021). Pustular psoriasis is characterized by white, pus-filled, painful bumps primarily located on the hands, feet, and fingertips. Histological findings of pustular psoriasis differ from those of plaque psoriasis, with the presence of superficial dermis edema with diffuse parakeratosis rather than confluent features and neutrophil-filled pustules (Li et al, 2017). Patients with pustular psoriasis also exhibited higher serum levels of IL-36α than patients with plaque psoriasis and healthy controls (Jiaravuthisan et al, 2007). Nail psoriasis has varying clinical presentations beyond its pustular variant and can be observed as an isolated finding in 5−10% of patients, although concurrent nail involvement affects up to 50% of patients with psoriasis with a lifetime incidence of 80−90%

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Abbreviations: Cav1, Caveolin-1; Cav2, Caveolin-2; CSD, caveolin scaffolding domain

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(Taylor et al, 2006). Inverse psoriasis is an uncommon form of psoriasis and is characterized by smooth, tender, erythematous skin primarily located in the intertriginous and flexural zones of the body.

Although there have been some recent breakthroughs in treatment of psoriasis that centered around IL-23/T helper 17 axis and TNFα signaling, which have demonstrated some efficacy, a lack of understanding about the multifactorial pathogenesis of psoriasis causes it to remain a treatable rather than curable disease. The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. We have recently identified a structural membrane protein Caveolin-1 (Cav1), the primary structural component of caveolae, to be involved in regulating both and thus may serve as a potential therapeutic target in the treatment of psoriasis (Yamaguchi et al, 2015). Caveolae are specialized lipid rafts with immunomodulatory functions located in the plasma membrane of different cell types (Yamaguchi et al, 2015). They play important roles in cell signaling transduction by sequestration of receptors and signaling intermediates and provision of transendothelial transportation for macromolecules (Yamaguchi et al, 2015). Caveolae are dependent on the expression of structural coat proteins named caveolins, which vary with different specialized vascular and inflammatory functions depending on the cell type. Given the important role of caveolins in inflammation, genetic deletion of caveolins impairs caveolae function and ultimately signal transduction, rendering the innate immune system unable to respond adequately to inflammation. Although primarily known for their function as structural components of caveolae and its role in endocytosis, Cav1 plays important roles in multiple cellular processes fundamental to development of psoriasis, including chronic inflammation, pathogen colonization, and cellular migration, in addition to proliferation and differentiation (Yamaguchi et al, 2015).

Exploration surrounding the contribution of caveolins in the pathogenesis of psoriasis is relatively new. Recent studies have demonstrated the downregulation of Cav1 in small animal models with psoriasiform inflammation induced by imiquimod and proposed that Cav1 aberration leads to the activation of the Jak–signal transducer and activator of transcription pathway, ultimately driving the characteristic hyperproliferation of keratinocytes and associated chemokine/cytokine inflammatory profile of psoriasis (Campbell and Gumbleton, 2000). This significant downregulation in Cav1 is also observed in studies evaluating its levels in human biopsy skin samples compared with those in its controls, further strengthening Cav1's important role in the negative feedback loop regulating epidermal keratinocyte differentiation and proliferation (Takamura et al, 2019). Interestingly, follow-up studies exploring the systemic implementation of caveolin scaffolding domain (CSD), a synthetic Cav1 mimetic, showed that CSD in murine models effectively decreased macrophage infiltration, epidermal thickness, and improved clinical skin phenotype (Watanabe et al, 2020). Previous studies have demonstrated that the increased levels of leptin in patients with psoriasis who have obesity downregulates Cav1 in epidermal keratinocytes, leading to activation of keratinocytes and T helper 17 cells by upregulation of IL-6 (Fitch et al, 2007).

Although there are reports of Cav1's role in pathogenesis of hyperproliferative and inflammatory skin diseases (Kruglikov and Scherer, 2019a, 2019b), there is limited documentation exploring the role, if any, of other structural caveolae components, including Caveolin-2 (Cav2) and Cavin-1 in the development or progression of dermatological disorders. The question follows whether it is a specific component of caveolae or downregulation of all caveolae structural components that contributes to the pathogenesis of psoriasis and whether this differs between subtypes of psoriasis.

RESULTS

In this study, we analyzed protein levels of Cav1, Cav2, and Cavin-1 in different forms of psoriasis by immunohistochemical staining, followed by quantification of positive cells per mm^2 using QuPath image analysis software (Figure 1). As expected, in normal trunk or leg skin, we observed that Cav1 localized to the basal epidermal cells, as previously demonstrated by our laboratory and others (Castellanos et al, 2020; Jozic et al, 2021a, 2021b; Jozic et al, 2019; Sawaya et al, 2019), and as such, we utilized only basal epidermal cells for quantification of Cav1 levels in normal versus psoriatic skin samples. It should be noted that endogenous levels of Cav1 fluctuated on the basis of body location, with plantar foot skin exhibiting much higher levels than trunk or leg skin, which exhibited similar levels of Cav1 (Figure 2). Subsequently, when comparing expression of Cav1 in subtypes of psoriasis, we utilized location-matched normal skin samples ($n = 15$) from abdominal, breast, thigh, back, and plantar foot skin, whereas nail psoriasis samples were compared with normal nail bed samples (Table 1). The results of our study revealed a general trend of downregulation of Cav1 in multiple subtypes of psoriasis ($n = 21$), with nail, palmoplantar, plaque, and pustular all exhibiting a statistically significant decrease in Cav1-positive cells, in comparison with their location-matched control skin (Figure 2). Conversely, chronic spongiotic dermatitis samples ($n = 3$) did not exhibit any changes in Cav1 expression in comparison with their location-matched normal skin samples (Figure 2).

Moreover, other structural components of caveolae, namely Cav2 and Cavin1, both exhibited a similar localization that was not restricted to basal epidermal cells but also included several layers of the differentiated keratinocytes of the spinous layer (Figures 3 and 4). Thus, when quantifying their levels in normal and psoriatic samples, we compared their levels in the viable epidermis (rather than restricting analysis only to basal epidermal cells). Interestingly, these structural components of caveolae displayed downregulation only in nail and pustular forms of psoriasis, with guttate, inverse, palmoplantar, and plaque samples exhibiting levels similar to those of their location-matched control skin samples (Figures 3 and 4). It should be noted that Cav2 exhibited a trend toward downregulation in palmoplantar psoriatic samples; however, this was not statistically significant. Moreover, we did not observe major differences in expression of either Cav1, Cav2, or Cavin-1 in the endothelial or other dermal cells in any form of psoriasis in comparison with their

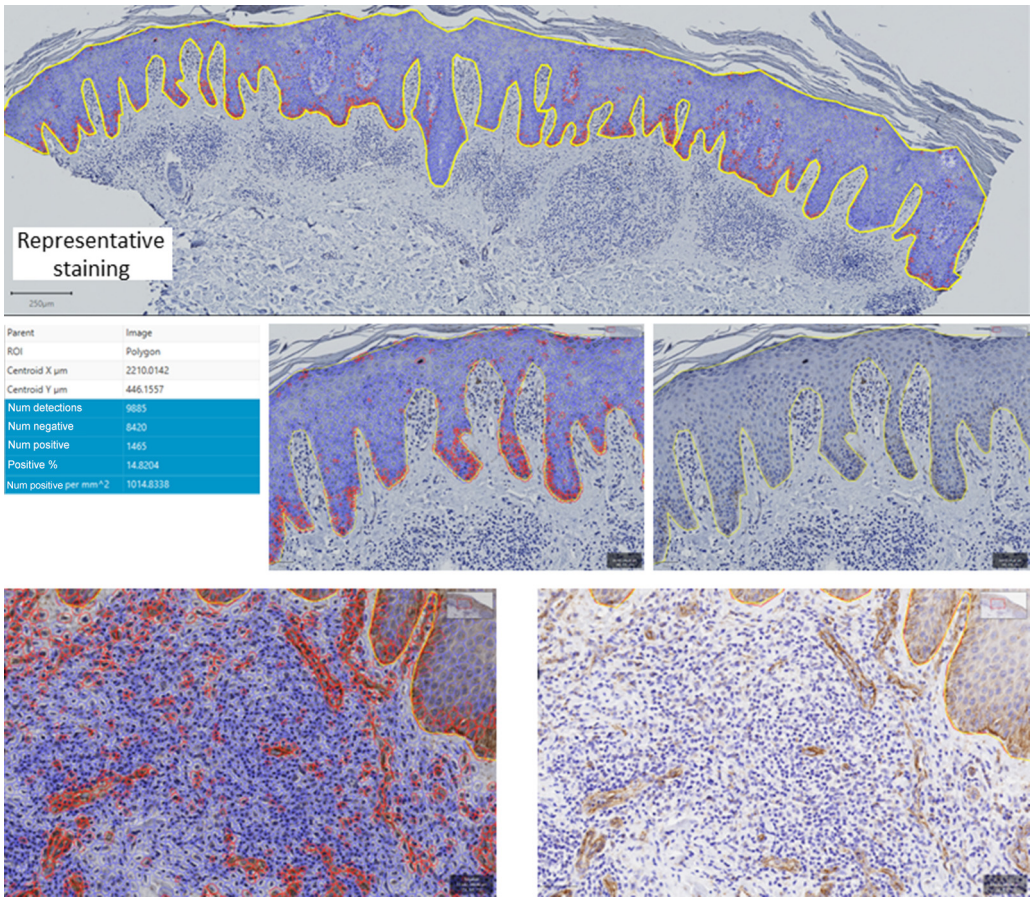

Figure 1. Sample quantification of DAB-positive cells using QuPath image analysis software. The upper segment demonstrates outlining the epidermis using polygon feature (in yellow) in QuPath, after which positive cell detection/mm^2 is determined (blue represents negative, red represents positive). Insets demonstrate a close-up of the same image with and without DAB quantification. Similarly, the number of DAB-positive cells can be determined as seen in the bottom panels (bar = 250 μm). DAB, 3,3′-diaminobenzidine; ROI, region of interest.

healthy control counterparts. Finally, we utilized a publicly available psoriasis dataset (Nattkemper et al, 2018) to evaluate transcriptional levels of caveolar structural genes in psoriatic samples in comparison with those in normal skin (Figure 5). We found that indeed Cav1, Cav2, and Cavin1 all exhibited a trend toward downregulation, in addition to Caveolin-3 and Cavin2, which were beyond the scope of our analysis. Together, these data suggest a generally conserved deregulation of caveolae structural components for nail and pustular psoriasis, with palmoplantar and plaque psoriasis exhibiting a Cav1-centered pathophysiology.

DISCUSSION

The current understanding of the exact pathogenesis of psoriasis remains unknown despite more recent breakthroughs in knowledge surrounding the IL-23/T helper 17 pathway and its major contribution to the eruption of psoriasiform dermatitis (Chen et al, 2018). This has led to the use of systemic biologics targeting this pathway and its associated inflammatory cytokines, resulting occasionally in significant improvement to complete resolution of hyperkeratotic plaques and associated symptoms of pruritus and burning. However, these systemic agents are typically reserved for patients with severe psoriasis affecting either a large body surface area or exhibiting associated psoriatic arthritis that negatively impedes daily functioning. Despite the efficacy of these systemic agents, access and availability remain difficult, especially for patients of low socioeconomic status or without insurance because the average annual cost of biologics ranges from $10,000 to $30,000 (Campbell et al, 2002). Other modalities of treatment for patients with psoriasis include methods of maintenance rather than cure, including topical corticosteroids, vitamin D analogs, and phototherapy. We have previously discussed the important role of caveolins in the field of dermatology, ranging from its significant upregulation in diabetic and venous foot ulcers to its influence on keratinocyte proliferation (Yamaguchi et al, 2015). Although previous studies have shown a downregulation of Cav1 in murine models of psoriasis and validated human biopsy samples (Ma et al, 2012; Zhang et al, 2014), there are limited documented reports of how other structural components of caveolae, namely Cav2 and Cavin-1, may also play in the pathophysiology of psoriasis and how this differs between subtypes. The results from our Cav1 immunohistochemical staining and quantification strengthen our hypothesis that similar to the results revealing downregulation of Cav1 in isolated RNA assessed by qRT-PCR in imiquimod-induced psoriasiform murine models, Cav1 plays an important role in the pathogenesis of psoriasis across all subtypes (Takamura et al, 2019; Yamaguchi et al, 2015).

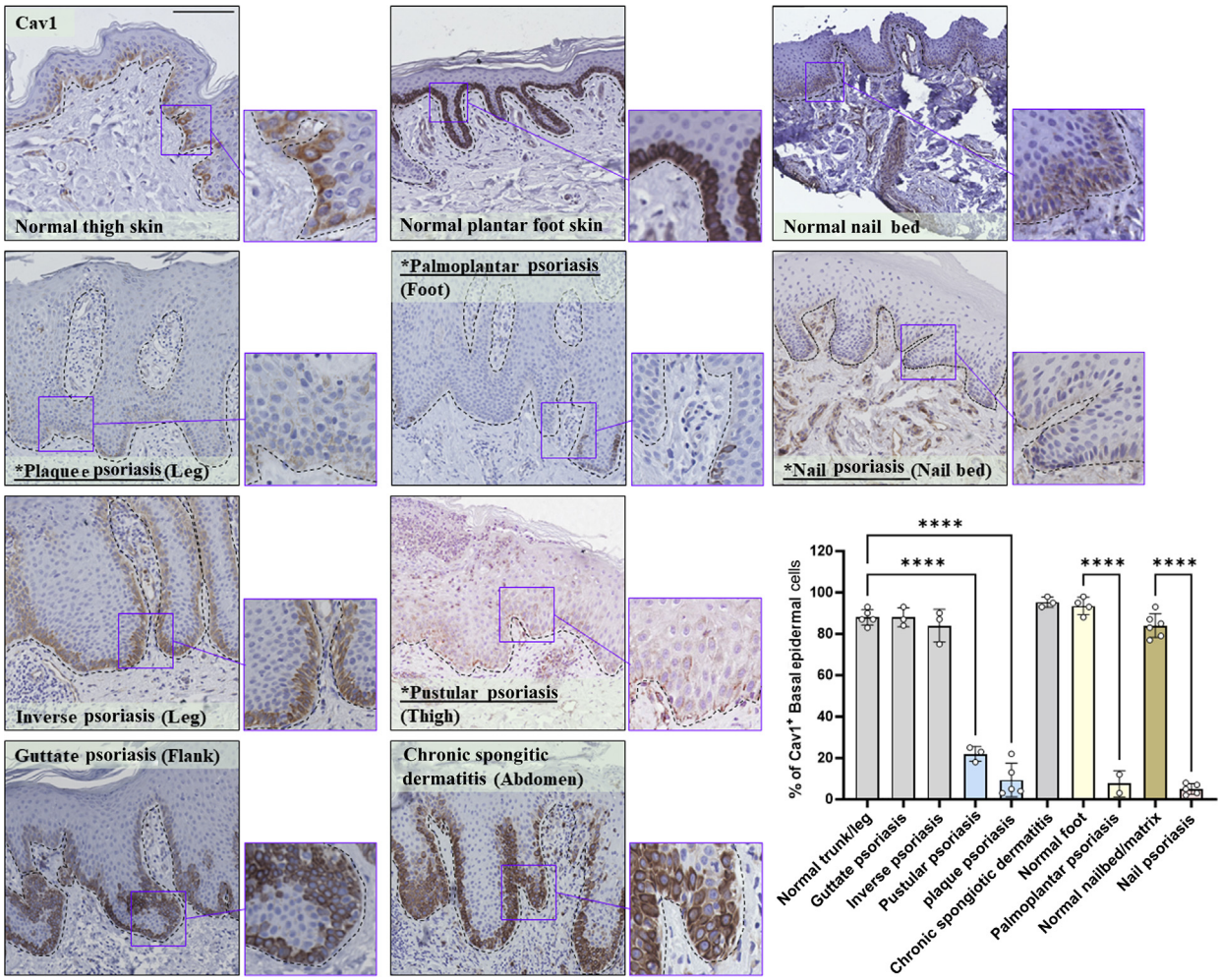

Figure 2. Downregulation of Cav1 in multiple types of psoriasiform dermatitis. Clinically confirmed cases of psoriasiform dermatitis (guttate [n = 3], inverse [n = 3], nail [n = 5], palmoplantar [n = 2], plaque [n = 5], pustular [n = 3]) were immunostained against Cav1 and counterstained with hematoxylin. Expression and localization of Cav1 were compared with those in location-matched normal skin samples, with trunk and leg skin (n = 5) serving as location-matched controls for guttate, inverse, plaque, and pustular psoriasis; normal plantar foot skin (n = 4) serving as control for palmoplantar psoriasis; and normal nail bed (n = 6) serving as location-matched control for nail psoriasis. Chronic spongiotic dermatitis (n = 3) was used as a control inflammatory skin condition (bar = 100 μm). Expression of Cav1 was quantified, and the percentage of positive basal epidermal cells in each form of psoriasis relative to location-matched control was quantified using QuPath analysis software. Each point in the bar represents an individual case, with bar graphs presented as mean ± SD from 3 independent immunostaining experiments error (2-way ANOVA: $*P < .05$, $**P < .01$, $***P < .001$, and $*P < .0001$). Cav1, Caveolin-1.

Moreover, when we compared transcriptional levels of *Cav1*, *Cav2*, and *Cavin-1* with publicly available datasets (Nattkemper et al, 2018), we confirmed the downregulation of each gene. It should be noted that this dataset sequenced bulk RNA isolated from entire skin biopsies, and as such, the contribution of other cell types could be masking the drastic changes at the protein level that we observed within the epidermis in our samples. Interestingly, only nail and pustular psoriasis types exhibited a significant reduction of Cav2 and Cavin-1, in comparison with those of skin samples of the remaining psoriasis subtypes. We were surprised to observe that downregulation of other caveolae structural components was only applicable to a few subtypes of psoriasis, suggesting that with respect to caveolar proteins, downregulation of Cav1 seems to be key rather than the downregulation of caveolae as a singular entity or its other functioning constituents. This may also suggest specific microscopic differences in the pathophysiology of nail and pustular psoriasis compared with that of other subtypes. However, given our limited sample size, there is a need for larger datasets to support these preliminary findings. Previous studies have shown Cav2 as a promising biomarker of acute kidney injury (Bulacio et al, 2019), a modulator of 17β-estradiol signaling in breast carcinoma (Totta et al, 2016), and a regulator of age-related skeletal muscle abnormalities (Schubert et al, 2007); however, its role in hyperproliferative and inflammatory skin disease is limited. Cavin-1, also known as PTRF, and its expression have been studied in its potential reduction of in vivo tumor growth in an orthotopic prostate cancer xenograft mouse model (Moon et al, 2014), although as discussed with Cav2, there is limited medical literature exploring its role in dermatological disease. Interestingly, we did not observe any changes in the expression of Cav1, Cav2, or Cavin-1 in chronic spongiotic dermatitis samples, suggesting that our observed effects seem to be specific to psoriasiform dermatitis and not a general trend for other

Table 1. Control Skin Sample Demographics

Subject	Sex	Age	Location	Type of Sample
#001	F	23	Abdomen, lower	Normal abdominal skin
#002	F	59	Breast	Normal breast skin
#003	M	41	Abdomen, lower	Normal abdominal skin
#004	F	60	Thigh	Normal thigh skin
#005	F	54	Back	Normal back skin
#006	F	35	5th toe, right matrix	Normal nail
#007	F	46	Thumb, right matrix	Normal nail
#008	F	58	3rd fingernail, right matrix	Normal nail
#009	M	71	2nd fingernail, right nail bed	Normal nail
#010	F	69	2nd fingernail, right nail bed	Normal nail
#011	M	69	1st toe, right nail bed	Normal nail
#012	M	75	3rd toe, left plantar	Normal plantar foot skin
#013	M	30	2nd toe, left plantar	Normal plantar foot skin
#014	F	59	1st toe, left plantar	Normal plantar foot skin
#015	M	67	2nd metatarsal, left	Normal foot skin
#016	M	11	Knee, left	Chronic spongiotic dermatitis
#017	F	17	Abdomen, right	Chronic spongiotic dermatitis
#018	M	53	Forearm, right ventral proximal	Chronic spongiotic dermatitis

Abbreviations: #, number; F, female; M, male.

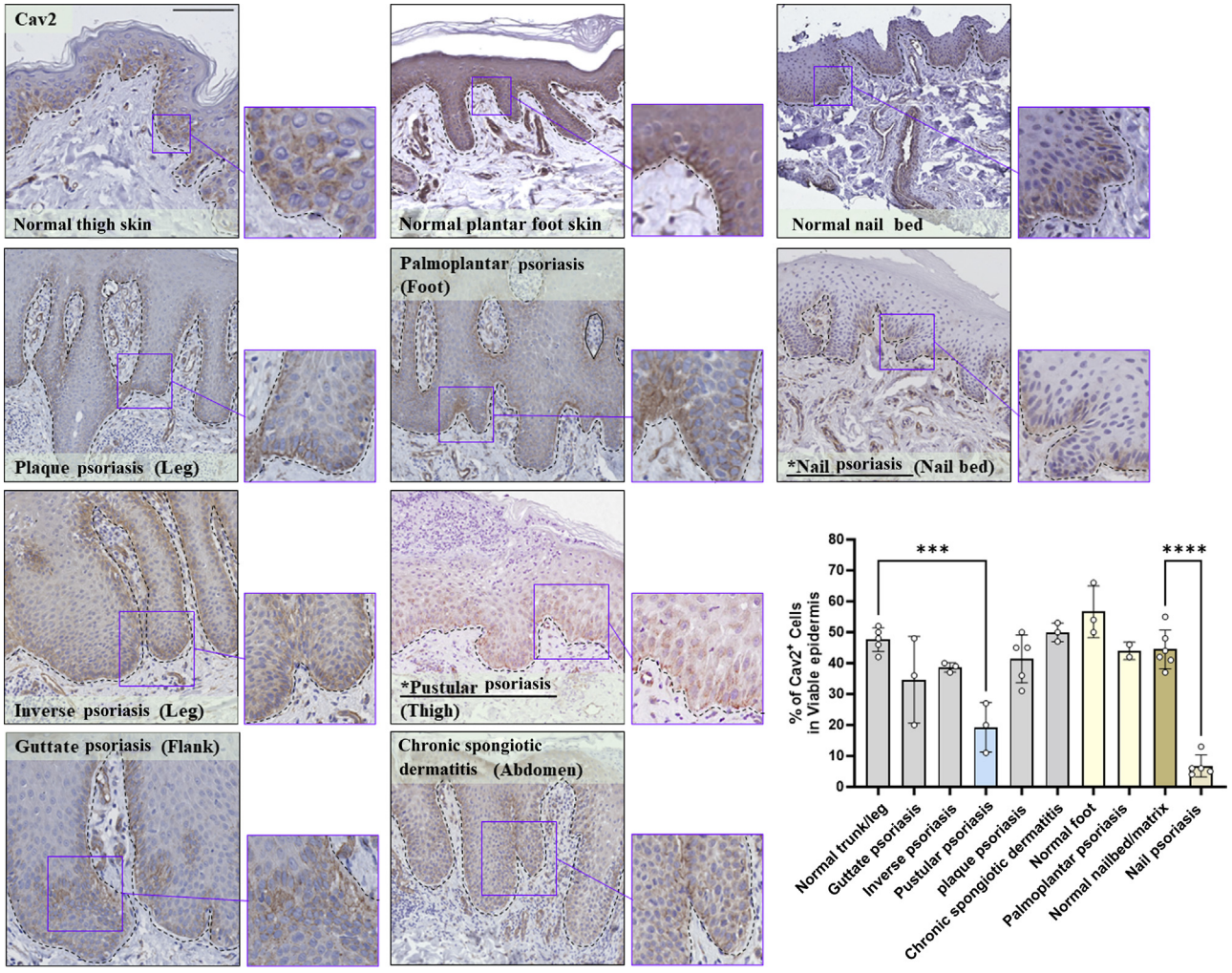

Figure 3. Downregulation of Cav2 in multiple types of psoriasiform dermatitis. Expression and localization of Cav2 were compared with those in location-matched normal skin/nail samples, with expression quantified as a percentage of positive viable epidermal keratinocytes relative to that of location-matched control (bar = 100 μm). Each point in the bar represents an individual case, with bar graphs presented as mean ± SD from 3 independent immunostaining experiments error (2-way ANOVA: $*P < .05$, $**P < .01$, $***P < .001$, and $*P < .0001$). Cav2, Caveolin-2.

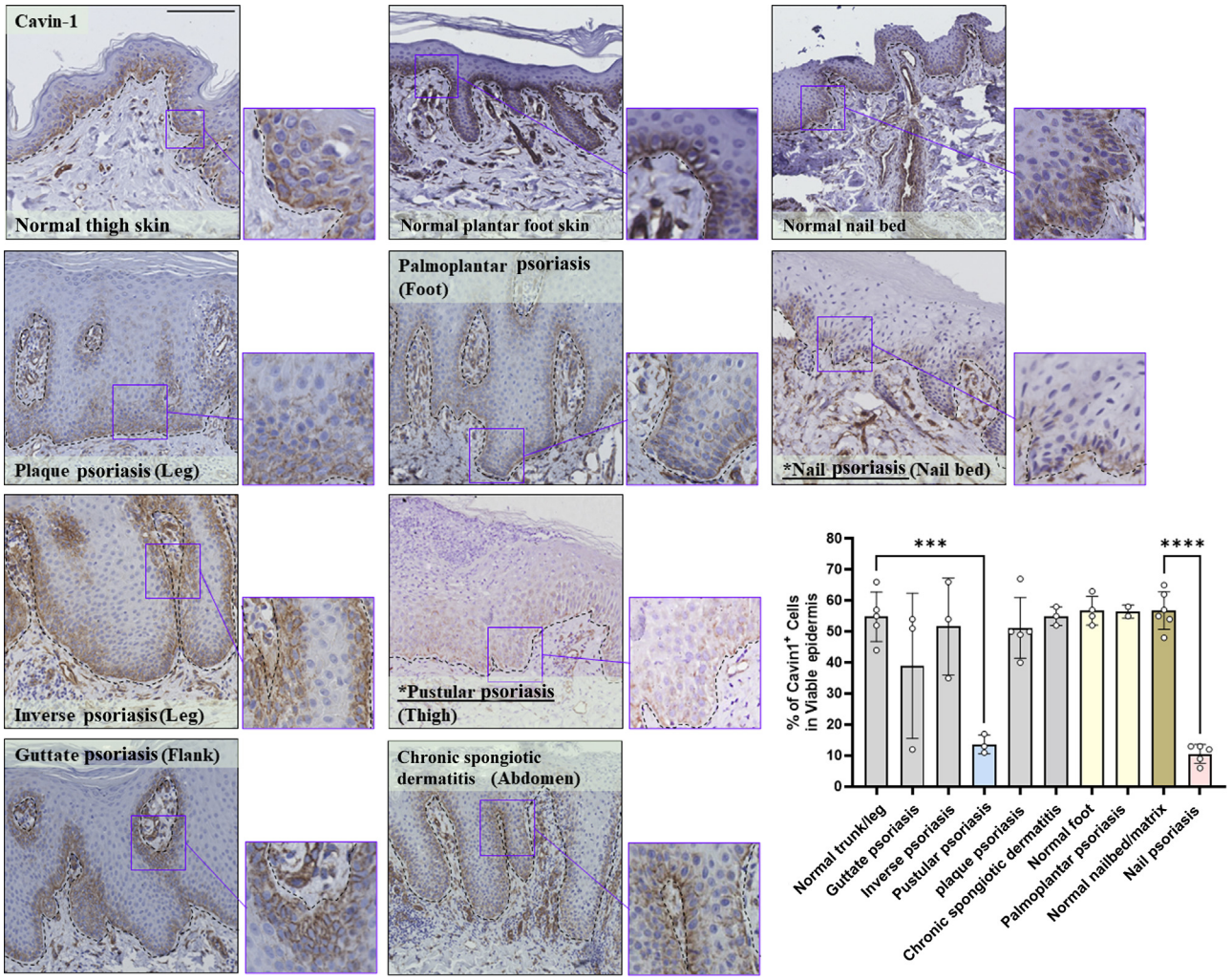

Figure 4. Downregulation of Cavin-1 in nail and pustular psoriasis samples. Expression and localization of Cavin-1 were compared with those in location-matched normal skin/nail samples, with expression quantified as a percentage of positive viable epidermal keratinocytes relative to that of location-matched control (bar = 100 μm). Each point in the bar represents an individual case, with bar graphs presented as mean ± SD from 3 independent immunostaining experiments error (2-way ANOVA: *$P < .05$, **$P < .01$, ***$P < .001$, and *$P < .0001$).

inflammatory skin conditions. We are however continuing to catalog the expression and localization of caveolar proteins in other skin conditions, including hidradenitis suppurativa and cicatricial alopecia, and hope to report on these findings soon. Importantly, however, the results of our study, coupled with the results from our previous study with murine models, support our hypothesis that there is downregulation of all caveolae structural microdomains (although these results were most apparent with nail and pustular psoriasis). Our data further confirms the downregulation of Cav1 most profoundly in nail, palmoplantar, plaque, and pustular psoriasis subtypes. Logic follows that topical preparation of cell-permeable CSD peptide may aid in reducing the inflammatory cytokines of psoriasis and transform the skin of affected patients from erythematous, hyperkeratotic plaques to normal-skin thickness and quality in all subtypes of psoriasis. To this end, topical corticosteroids have long been the first-line treatment in management of multiple grades of psoriasis (Jozic et al, 2021a; Uva et al, 2012). Interestingly, our laboratory has previously demonstrated that topical corticosteroid administration to ex vivo human skin induces expression of *Cav1* at both mRNA and protein levels (Jozic et al, 2021a), further suggesting that reintroduction of Cav1 may play an important role in the treatment of psoriasis. We are currently exploring the effect that Food and Drug Administration–approved biologics for treatment of psoriasis have on expression of caveolae-associated proteins and posit that treatment will restore the levels of each protein to homeostatic levels.

METHODS AND MATERIALS

Human skin specimens

To validate whether downregulation of Cav1 levels can be used as a diagnostic measure of disease progression, we utilized retrospectively collected human biopsies from validated cases of psoriasis vulgaris (guttate [n = 3], inverse [n = 3], nail [n = 5], palmoplantar [n = 2], plaque [n = 6], pustular [n = 2], average age at diagnosis 50.3 ± 14.48 years, 52.4% male, 47.6% female) retrieved from the specimen bank at University of Miami Hospital/Jackson Memorial Hospital obtained from consenting patients receiving standard care

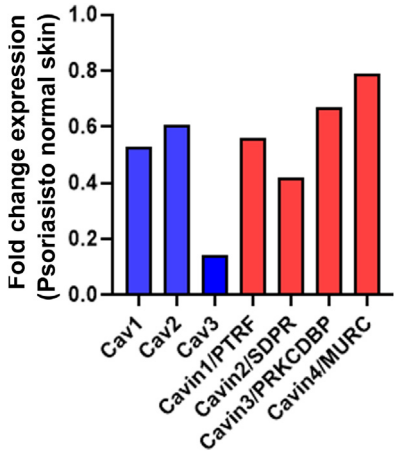

Figure 5. Confirmation of Cav1, Cav2, and Cavin-1 downregulation at transcriptional level. A publicly available dataset (Nattkemper et al, 2018) was used to compare levels of caveolar genes at the transcriptional level and represented as fold change expression in psoriasis compared with that in normal skin samples. Cav1, Caveolin-1; Cav2, Caveolin-2.

at the University of Miami Hospital with protocol approved by University of Miami Institutional Review Board (institutional review board protocol number 20220053) with written informed consent (Table 2). Chronic spongiotic dermatitis (n = 3) was used as control inflammatory skin samples without a history of psoriasis. Expressions of Cav1, Cav2, and Cavin-1 were determined by immunohistochemistry and staining compared with normal age-, sex-, and location-matched skin (n = 15) (Table 1). Control healthy human skin specimens were obtained as discarded tissue from reduction surgery procedures in accordance with institutional approvals as previously described (Jozic et al, 2021a; Sawaya et al, 2019). Specifically, the protocol to obtain unidentified, discarded human skin specimens from reduction surgery was submitted to the University of Miami Human Subject Research Office.

Immunohistochemistry

Formalin-fixed/paraffin-embedded tissue was cut at 5−7 μm sections using a microtome. Sections were deparaffinized with xylene (EMD Millipore) and rehydrated in graded ethanol. Endogenous peroxidase activity was quenched with 0.3% hydrogen peroxide in methanol and washed with distilled water. Slides were then incubated in sodium citrate buffer (10 mM sodium citrate, 0.05% Tween-20, pH 6.0) for 30 minutes at 95 °C for antigen retrieval, allowed to cool, and then treated with Background Punisher (Biocare Medical). Antibodies used were polyclonal rabbit anti-Cav1 (1:200, Sigma-Aldrich, number HPA049326), polyclonal rabbit anti-Cav2 (1:200, Sigma-Aldrich, number HPA044810), and monoclonal rabbit anti−cavin-1 (1:500, Cell Signaling Technology, number 69036). Antibodies were diluted in 2% normal goat serum (Sigma-Aldrich) in PBS with 0.1% Tween-20 and applied to the samples for overnight incubation at 4 °C. The detection and chromogenic reaction were carried out using the Universal anti-rabbit HRP-Polymer Detection system (Biocare Medical), following the manufacturer's instructions. Slides were counterstained using Harris hematoxylin (Leica Microsystems) and then dehydrated in graded ethanol and xylene. Full slides were imaged, and corresponding TIFF images were exported using a VS120 slide scanning microscope.

Quantification of immunohistochemical staining

Bioimage analysis was performed using QuPath bioimage analysis software, as previously described (Bankhead et al, 2017; Emmanuel et al, 2022; Palomäki et al, 2022). Briefly, images were imported into QuPath, and regions of interest were annotated using polygon features within the software focusing on basal epidermal cells for Cav1 and all viable epidermis for Cav2 and Cavin-1. Analysis of positive staining was determined using positive cell detection commands

Table 2. Psoriatic Skin Sample Demographics

Subject	Sex	Age	Location	Type of Sample
#001	M	22	Back, right lower	Guttate psoriasis
#002	M	32	Flank, right	Guttate psoriasis
#003	M	61	Chest, left	Guttate psoriasis
#004	F	59	Breast, left	Inverse psoriasis
#005	F	60	Abdomen, lower	Inverse psoriasis
#006	M	53	Penile	Inverse Psoriasis
#007	F	28	5th finger, left nailbed	Nail Psoriasis
#008	F	58	2nd finger, left nailbed	Nail Psoriasis
#009	M	29	5th finger, right nailbed	Nail Psoriasis
#010	M	58	3rd toenail, right nailbed	Nail Psoriasis
#011	M	71	5th finger, right nailbed	Nail Psoriasis
#012	F	59	Hand, left palm	Palmoplantar psoriasis
#013	M	58	Foot, right	Palmoplantar psoriasis
#014	F	51	Elbow	Plaque Psoriasis
#015	F	55	Leg, right lower	Plaque psoriasis
#016	F	57	Hand, left lateral	Plaque psoriasis
#017	F	75	Leg, right anterior	Plaque psoriasis
#018	M	37	Leg, left lower	Plaque psoriasis
#019	M	57	Leg, right posterior	Pustular psoriasis
#020	M	31	Thigh, right	Pustular psoriasis
#021	F	47	Thigh, left	Pustular psoriasis

Abbreviations: #, number; F, female; M, male.

within the software quantified as DAB+ cells over hematoxylin-stained nuclei (Figure 1 shows sample quantification). For each biopsy, 3 independent sections were immunostained and quantified. Depending on the size of each biopsy, this resulted in quantification of anywhere between 6000 and 10,000 cells per section.

Statistical analysis

The number of positive cells and area detected were used to calculate the percentage of positive cells/mm^2, which were then exported to GraphPad Prism for statistical analysis. Two-way ANOVA, followed by Tukey's multiple comparisons test, was then used to assess statistical significance, with $*P < .05$, $**P < .01$, $***P < .001$, and $****P < .0001$ being used as a determinant of which means among the set of means differed from the rest.

ETHICS STATEMENT

All experiments were approved by the University of Miami Institutional Review Board (institutional review board protocol number 20220053), with written informed consent obtained from each participant in the study.

DATA AVAILABILITY STATEMENT

No large datasets were generated during this study; however, we did utilize a publicly available dataset (Nattkemper et al, 2018) to compare normal with psoriatic skin samples and validate our protein findings on the transcriptomic level. Minimal datasets necessary to interpret and/or replicate data in this paper are available upon request to the corresponding author.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: IJ, PR, BM; Data Curation: IJ, DAL; Formal Analysis: IJ, DAL, BAA, LN, SR; Methodology: DAL, BAA, LN, SR; Resources: IJ, LN; Writing – Review and Editing: DAL, BAA, SR, LN, BM, PR, IJ

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