

The importance of caveolins and caveolae to dermatology: Lessons from the caves and beyond

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Abstract

Caveolae are flask-shaped invaginations of the cell membrane rich in cholesterol and sphingomyelin, with caveolin proteins acting as their primary structural components that allow compartmentalization and orchestration of various signalling molecules. In this review, we discuss how pleiotropic functions of caveolin-1 (Cav1) and its intricate roles in numerous cellular functions including lipid trafficking, signalling, cell migration and proliferation, as well as cellular senescence, infection and inflammation, are integral for normal development and functioning of skin and its appendages. We then examine how disruption of the homeostatic levels of Cav1 can lead to development of various cutaneous pathophysiologies including skin cancers, cutaneous fibroses, psoriasis, alopecia, age-related changes in skin and aberrant wound healing and propose how levels of Cav1 may have theragnostic value in skin physiology/pathophysiology.

KEYWORDS

caveolae, caveolin-1, fibrosis, melanoma, psoriasis, squamous cell carcinoma, wound healing

1 | INTRODUCTION TO CAVEOLINS

Although caveolae were identified as subcellular structures in the 1950s using electron microscopy, it has taken decades of study to unravel the complex biology regulated by caveolae.^[1,2] They have initially been characterized as flask-, or omega-shaped, membrane invaginations that can be seen in most cell types.^[3,4] Caveolins are cytoplasmic proteins that were discovered in the 1990s which serve as the major structural constituents of the caveolar membrane. Much of what we fundamentally know regarding caveolins can be attributed to the work of Richard Anderson's (who discovered caveolin-1 (Cav1)), Michael Lisanti's, Robert Parton's and Tim Thompson's

groups, who developed Cav1 knockout mice and made seminal discoveries regarding its structure and oligomerization into caveolae.^[3,5-9] In addition to localizing to the cell membrane, Cav1 has been shown to be localized to ER, Golgi, mitochondria, endosomes, as well as lipid droplets, and nucleus and extracellular vesicles.^[10-16] Cellular organelles, such as the ER and Golgi apparatus, usually express both Cav1 and Cav2 which then organize into heterooligomers, that form caveolae.^[17,18] It should be noted that although it is widely accepted that caveolin expression is ubiquitous in mammalian tissues, levels of expression vary considerably between the different caveolin isoforms as well as tissue types. For example, cells with highest level of Cav1 expression tend to be those which are terminally differentiated

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(ie adipocytes, endothelia, smooth muscle cells, among others), while Cav2 usually colocalizes and mirrors expression of Cav1, whereas Cav3 expression is mainly localized to muscle cells.^[19,20] This review will specifically focus on Cav1 protein and its respective functions including lipid trafficking, membrane trafficking, signal transduction, cell migration and cell proliferation, all of which have crucial roles in normal skin functioning. We will then focus on the role of Cav1 in pathologic skin disorders related to Cav1 malfunction, such as skin cancer, scleroderma, psoriasis, alopecia, ageing-related changes in skin, as well as in non-healing chronic wounds.

2 | ROLE OF CAV1 IN CELLULAR PROCESSES CRUCIAL FOR NORMAL SKIN FUNCTION

Caveolae and Cav1 have long been known to be involved in endocytosis through various mechanisms, including regulation of early endosome migration, as well as EGF receptor (EGFR) and extracellular membrane-binding protein turnover.^[21,22] Moreover, Cav1 is extremely stable at the cellular membrane and only some Cav1 rich vesicles actually become internalized,^[23-25] which suggests that Cav1 may also act to stabilize cellular membrane and slow down membrane invagination, budding, and vesicle internalization. In other words, instead of being only structurally involved, Cav1 may take on a regulatory function of endocytosis through several different mechanisms including regulation of cholesterol content of raft domains,^[26] slowing down caveolar budding,^[27,28] or by isolation of signalling molecules necessary for caveolar endocytosis (including G proteins).^[28] Cav1 may also function in sorting proteins and lipids into distinct vesicles where Cav1 may be a platform that regulates the content of caveolar invaginations.^[29] Below, we will outline how Cav1 regulates some basic cellular functions crucial in skin physiology.

2.1 | Lipid transport

Caveolae are commonly found in areas of the cell membrane enriched in cholesterol and sphingomyelin,^[6,30] with some early in vitro studies pointing to interaction of Cav1 and cholesterol,^[31] which potentially allows its arrangement in and curvature of caveolar and cell membranes^[32-34] and to act as cholesterol transporter.^[35-38] For example, immediately after being synthesized in the ER, cholesterol migrates directly to the caveolar surface, from which it then localizes to different areas of the plasma membrane and extracellular space in a Cav1-dependent manner.^[39] Consequently, it is unsurprising that Cav1 is required for extracellular and intracellular lipid trafficking, and this could explain the relatively high expression of Cav1 by adipocytes,^[40] as well as the lipid metabolism defects observed in mice completely lacking Cav1.^[41,42] Thus, it appears that Cav1 does not act as a single molecule, but rather exists in a complex involving intracellular lipids that act to transport cholesterol and potentially

other lipids between different cellular compartments.^[43] If one considers the elaborate lipidomic profile of the stratified epidermis, elucidating the role Cav1 plays in its development and maintenance will undoubtedly provide tremendous insights into epidermal permeability barrier and treatment of various barrier function defects including atopic dermatitis, ichthyosis and psoriasis, among others.

2.2 | Infection and inflammation

Persistence of infection due to intracellular pathogen colonization is starting to garner a lot of interest in wound healing especially since it is now widely accepted that all chronic wounds should be considered infected, even if they do not exhibit clinical signs of infection. Interestingly, caveolae-dependent endocytosis is upregulated in chronologically aged and senescent cells, which may be one of the reasons for why the elderly are more susceptible to infections.^[44] Once vesicles are endocytosed, instead of going to the lysosomes, they are trafficked directly to the Golgi apparatus or endoplasmic reticulum^[44-46] and thus protected from degradation. As this process appears to be non-selective and is utilized by many bacteria and viruses, including *Salmonella typhimurium*, *Vibrio cholera*, *Pseudomonas aeruginosa*, Leishmania, HIV and coronavirus, this endocytic route may provide protection for these pathogens.^[44,47-53] For example, *S typhimurium* delivers SopE protein into the host cell via the type III secretion system, which binds to Cav1 and leads to Cav1-dependent Rac1 protein recruitment, which in turn promotes actin fibre rearrangement, phagocytosis and bacterial invasion of the host cell.^[44,54] Interestingly, other cells which express low levels of Cav1 exhibit increased internalization of *Staphylococcus aureus* due to enhanced membrane mobility of Cav1-deficient cells, thus arguing for more of a context-dependent role.^[55] It remains to be seen whether commensal bacteria interact with host Cav1 and how Cav1 expression correlates with development of biofilms (which comprise of diverse array of bacteria); however, considering that non-healing chronic wounds exhibit elevated levels of Cav1,^[56] understanding the role Cav1 plays in bacterial colonization will provide invaluable insights into treatment of chronic wounds.

With regard to inflammation, Cav1-null mice exhibit a systemic proinflammatory state, with a noticeable increase in cytokines including IL-6, TNF-alpha and IL-12p70^[57] (however, these results are yet to be validated in human samples). Additionally, Cav1-null mice exhibited greater chemokine-dependent immune cell recruitment when compared to controls.^[58] Interestingly, transcriptional profiling of human keratinocytes after cholesterol depletion by methyl- β -cyclodextrin (M β CD) has been shown to promote secretion of an inflammatory marker IL-8 together with plasminogen activator urokinase (PLAU), similarly to human atopic dermatitis (AD) samples.^[59] It should be noted that although the authors of this study did not observe diminished levels of Cav1 as a result of cholesterol depletion, this could be ascribed to the relatively stable nature of Cav1 and their short administration of M β CD (up to 8hrs); thus, prolonged caveolae disruption would undoubtedly lead to Cav1 downregulation as well. Consequently, it is yet

to be determined whether Cav1 levels correlate with AD; however, if downregulation of Cav1 is present in AD samples, it would be interesting to see whether topical application of caveolin scaffolding domain (CSD) peptide could alleviate IL-8 secretion and thus be used as a potential therapeutic target for treatment of AD. Cav1 has also been shown to interact with TLR4 receptor in endothelial cells and mediate activation of MyD88 signalling cascade in sepsis-induced lung inflammation,^[60] whereby Cav1 inhibition could prevent sepsis-induced lung inflammation. Thus, it becomes clear that Cav1's role in both infection and inflammation, just like the other process, is complex and further studies are necessary to elucidate these intricacies.

2.3 | Signal transduction

Shortly after the discovery of Cav1, numerous Cav1-binding partners have been discovered and attempts at understanding how they impact various cell signalling cascades have been undertaken.^[21] The tendency of Cav1 to oligomerize via N-terminal side-chain amino acids (aa 82-101) suggests that Cav1 could be a recruiter of the signalling cascade molecules via its CSD,^[61,62] leading to the Cav1 signalling hypothesis which posits that Cav1 could perhaps function as a scaffolding protein that recruits numerous signalling molecules, although that depends on the accessibility of the caveolin-binding motifs of the signalling proteins proposed to interact with Cav1.^[63]

Altogether, more than 50 studies found that Cav1 interaction with other molecules via its scaffolding domain results in deactivation of these molecules in the signalling cascade.^[64,65] There is also evidence that Cav1 may stimulate some signalling events.^[66] However, it has yet to be confirmed whether the scaffolding domain of Cav1 is directly related to its primarily suppressing and occasionally activating function, since when this region is mutated, Cav1 is unable to leave the Golgi apparatus and cell signalling transduction process in this sense becomes impossible to study.^[67] Regardless, via its scaffolding domain, Cav1 has been shown to interact with numerous receptor tyrosine kinases (EGF, TGF- β 1, Her2, PDGF, VEGF and insulin receptors),^[68-81] steroid hormone receptors (oestrogen receptor alpha, glucocorticoid and androgen receptor), G protein-coupled receptors (angiotensin II receptor and glutamate receptor),^[56,82-89] as well as with numerous intracellular signalling molecules (including but not limited to PKA, PKC, PLC, PLD, ERK1/2, Akt, Ras, Csk, Src, Irs1 and Grb2).^[26,63,66,71,90-107] Thus, it is evident that Cav1 has a tremendous network of signalling factors that may regulate numerous cellular processes. In line with its role in cholesterol recruitment, Cav1 may regulate cell signalling through lipid organization more so than through proteins. Considering that Cav1 has its role in maintaining and regulating cholesterol levels, it becomes evident how it would indirectly regulate signal cell transduction via lipids.

2.4 | Cell migration

Due to its ability to bind to and interact with such a diverse array of signalling molecules, it is unsurprising that Cav1 has been implicated

as a major regulator of cell migration.^[108-111] Immunostaining experiments show polarized Cav1 localization may be necessary for migration of endothelial cells,^[112-116] where it binds to actin cross-linking protein filamin, suggesting that Cav1 may be modulating the cytoskeleton. In line with these findings, Cav1 has been shown to affect cytoskeletal remodelling and focal adhesion assembly by differentially affecting activity Rho family of GTPases, namely RhoA, Rac1 and Cdc42 through interaction with various guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs).^[117] However, whether Cav1 promotes or inhibits cell migration is still controversial and seems to be cell- and context-dependent. For instance, Cav1 downregulation increases, while upregulation decreases the ability of EGF-stimulated cells to migrate^[56,70,118,119] and Cav1 knockdown accelerates directional cell migration.^[56] Furthermore, Cav1 has been shown to downregulate c-Src and c-met signalling, and metastatic potential of osteosarcoma cells.^[120] On the other hand, Cav1 was shown to interact with eNOS as well as integrin β 1 and urokinase receptor uPAR, resulting in cytoskeletal reorganization and cell migration.^[121-124] Moreover, Cav1^{Y14} phosphorylation leads organization of caveolae in the focal adhesions, by rearranging and co-localizing important signalling molecules necessary for cell migration.^[125-127] Its role within the extracellular matrix is evident from studies that found that Cav1 enhances cell surface plasminogen activation,^[128] and regulation of MMP-1.^[129] Therefore, the migratory potential of Cav1 is undoubtedly very complex and most likely depends not only on Cav1, but on the array of migratory proteins in its environment that directly or indirectly interact with Cav1.

2.5 | Cell proliferation

Similar to cell migration, due to its ability to orchestrate compartmentalization of numerous signalling molecules, numerous studies have implicated Cav1 in regulation of cell proliferation. In general, Cav1 expression reduces cell proliferation in normal and cancer cells in early stages of cancer disease and has generally been considered a tumor suppressor.^[11] Specifically, Cav1 was found to have antiproliferative properties, causing G0/G1 cell cycle arrest, through upregulation of p53 and p21, and downregulation of cyclin D1^[130] (which is commonly upregulated downstream of many pathways including ERK1/2, PI3K and β -catenin).^[131-133] Thus, Cav1 deregulation leads to increased ERK1/2 activation, upregulation of cyclin D1, downregulation of p21 and increased proliferation.^[134] Similarly, Cav1 acts as a negative regulator of PI3K/Akt pathway^[135-137] where depletion of Cav1 leads to higher levels of Rac and Akt and increase in Cyclin D1 function.^[138] Cav1 also acts as a negative regulator of Wnt/ β -catenin canonical pathway, where Cav1 sequesters β -catenin and prevents its nuclear translocation and interaction with TCF/LEF to decrease cyclin D1 levels.^[139] Since Cav1 generally exhibits antiproliferative properties, its aberrant expression has tremendous ramifications on cutaneous hyperproliferative conditions, which will be discussed later.

TABLE 1 Role of caveolins in NMSCs

Tumor Suppressing or Promoting	Model	Translational relevance	Reference
Suppressing	In vitro	Predictive biomarker of disease severity and progression	[157]
	In vitro	Targeted therapy inducing Cav1 gene expression in cancer cells to attenuate tumor growth and metastasis	[158]
	In vivo		

2.6 | Expression of Cav1 in Skin

Due to their orchestration of a vast array of signalling molecules, it is therefore unsurprising that caveolins have been shown to have extensive roles not only in development and homeostasis of skin, but also in pathophysiology associated with skin disorders. First, Cav1 and Cav2 have been shown to exhibit differential expression in the epidermis, where Cav1 localizes primarily to undifferentiated basal keratinocytes,^[56,140,141] while Cav2 localizes to suprabasal, differentiated keratinocytes,^[140,141] suggesting possibly distinct roles in keratinocyte proliferation and differentiation for different caveolin variants. Furthermore, in vitro induction of keratinocyte differentiation has been shown to stimulate a transient drop in Cav1 expression (consistent with its absence from suprabasal levels) in the epidermis, and interestingly treatment of keratinocytes with Cav1 scaffolding domain peptide can inhibit calcium-induced keratinocyte differentiation by blocking calcium-induced increases in phosphatidylglycerol.^[142] Together these data support the role of Cav1 in inhibiting keratinocyte differentiation and thus raise intriguing possibilities for targeting Cav1 in cutaneous disorders manifested by abnormal differentiation and proliferation, including psoriasis and hypertrophic scarring.^[143–146] Interestingly, Cav1 also localizes to melanocytes and its expression can be induced by UV exposure, where it leads to changes in cell morphology and leading to increased melanin transfer and skin pigmentation as a result of changes in cAMP production.^[147]

2.7 | Expression of Cav1 in hair

Although there have been some recent studies of Cav1 expression and potential function in the skin, not much is known about Cav1 in hair development. Current knowledge comes from mouse models and studying pathologic disorders, such as different types of alopecia. For example, Selleri et al have confirmed Cav1's expression in the bulge area of the hair follicle, and its expression was not affected by doxorubicin (DXR) chemotherapy treatment. While expression of β -catenin, a marker of cell proliferation, was absent from the bulge cells post-treatment with DXR, Cav1 remained visible in all stages of hair cycle, thus suggesting a potential role in protection from permanent chemotherapy-induced alopecia, and allowing for future hair regrowth.^[148] This study also confirmed that the cells of the bulge area express Cav1 consistently regardless of the phase of the hair cycle, which posits that when cells leave the bulge area, they potentially stop expressing Cav1. Since β -catenin was shown to have

differential expression in different phases of the hair cycle, and as discussed previously, Cav1 sequesters β -catenin, proper balance between Cav1 and β -catenin may be the key to future therapies for hair regrowth. Paus' group has previously shown that selected immunophilin ligands (IPLs) and cyclosporine (CsA) also act to protect from the chemotherapy-induced alopecia and follicle dystrophy, possibly by shifting the follicle into the anagen phase. Since CsA has been previously shown to destabilize caveolae by decreasing their cholesterol content and by inhibiting the interaction of Cav1 with cyclophilin A,^[59] it would be interesting to see whether CsA treatment affects expression of Cav1, interaction of Cav1/cyclophilin A, and whether less toxic alternatives to CsA (like WAY-316606)^[149] could be used to alter Cav1 expression levels and thus promote hair growth, without eliciting the known side effects of CsA. This mechanism could also be modulating the Cav1/ β -catenin balance, and further studies are necessary to better elucidate their interplay.^[150] Further, differential expression of genes between balding (BAB) and non-balding scalp (BAN) in relation to androgen-induced alopecia found that Cav1 is downregulated in BAB in comparison to BAN.^[151] Recently, it has also been proposed that reduction of Cav1 in the hair follicle may be due to enrichment of preadipocytes during catagen phase of the hair follicle cycle, since preadipocytes have been previously shown to exhibit diminished levels of Cav1.^[152] However, it has also been demonstrated that upregulation of miR-199a-5p (miRNA that has been shown to target Cav1) can prevent lipid accumulation during preadipocyte differentiation.^[153] Thus, whether downregulation of Cav1 is the cause or consequence of balding is yet to be fully delineated. Together, these studies reveal potential therapeutic targets in clinically challenging conditions such as alopecia and further research in this area could only better our current knowledge and treatment options.

3 | ROLE OF CAVEOLINS IN SKIN CANCERS

The function of caveolins in cancer pathogenesis has been increasingly examined over the past decade. However, the role of Cav1 in carcinogenesis appears to vary with the tumor type and tumor progression. For example, its expression is associated not only with cancer suppression in oesophageal adenocarcinoma, lung adenocarcinoma, and ovarian cancer, but also with progression of prostate cancer, renal cell carcinoma, and lung squamous cell carcinoma.^[154–156] This argues for a cell-specific role where Cav1 can

Tumor promoting or suppressing	Model	Translational relevance	Reference
N/A	In vitro Ex vivo	Diagnostic and/or predictive and prognostic biomarker	[159,160,162]
Suppressing	In vitro	Targeted therapy inducing Cav1 expression in cancer cells to attenuate tumor growth and metastasis	[161,162]
Both (1° tumor promoting, metastasis suppressing)	In vitro	Targeted therapy towards balanced Cav1 expression in cancer and surrounding cells to attenuate tumor growth and metastasis	[163–165]
	In vitro In vivo	Biomarker of poor prognosis in melanoma patients undergoing surgery. Predictor of likelihood of malignancy	[165]
Promoting	In vitro In vivo	Targeted therapy suppressing Cav1 expression in cancer cells to attenuate tumor growth and metastasis	[202,203]

TABLE 2 Role of caveolins in melanoma

interact with cell type-specific proteins and thus either hinder or promote tumor progression. Below, we will outline the current understanding for the role of Cav1 in skin cancers (Tables 1 & 2).

3.1 | Role of caveolins in non-melanoma skin cancers (NMSCs)

3.1.1 | Cav1 in cutaneous squamous cell carcinomas (SCCs)

Although the role of caveolins in oesophageal, lung and other non-cutaneous forms of SCCs has been considerably explored, there are only a few studies assessing caveolin expression in cutaneous SCCs. One study compared immunohistochemical expression of Cav1 in patients with cutaneous SCC with normal control skin specimens and observed a statistically significant downregulation of Cav1 expression in SCCs compared to the control group, in both intensity and pattern of expression.^[157] Furthermore, poorly differentiated SCCs showed significantly reduced Cav1 expression compared to moderately and well-differentiated SCCs, suggesting that Cav1 downregulation not only plays a role in the promotion of SCC tumorigenesis, but also in its progression. The study went on to explore the potential role of Cav1 in the pathogenesis on non-melanoma skin cancers (NMSCs) and ultimately found that levels of Cav1 expression could be used as predictive biomarkers for patients at risk of cancer progression.^[157] Murine models of cutaneous SCC demonstrate similar relationship between Cav1 and tumor development, where mice overexpressing Cav1 exhibit decreased in vitro cell proliferation, as well as decreased in vivo tumor incidence, volume and weight.^[158] Conversely, Cav1-null mice exhibit increased cell and tumor growth, in addition to increased invasive ability and incidence of spontaneous lymph node metastasis, which is likely due to hyperactivation

of the MAPK pathway in the Cav1-null mice,^[158] thus introducing Cav1 as a potential regulator of invasion and metastasis in cutaneous SCCs.

3.1.2 | Cav1 in basal cell carcinoma (BCCs)

Although the association between Cav1-BCC development has been largely unexplored, a recent study correlated Cav1 expression with the clinicopathological parameters of BCCs.^[157] BCC samples demonstrated a statistically significant downregulation of Cav1 expression compared to specimens from healthy individuals. Additionally, localization differed between the two groups, with BCC group exhibiting only membranous localization, while the control group demonstrated both membranous and cytoplasmic. Cav1 expression also varied in BCC depending on the histopathological type, with significant downregulation being seen in aggressive types (including micronodular, infiltrative and metatypical BCC) compared to the non-aggressive types (including nodular and superficial BCC). These findings provide evidence that Cav1 expression is significantly decreased in aggressive types of BCC compared to the non-aggressive types and ultimately suggests that Cav1 may be a predictor of the biological behaviour of BCCs that could be useful in the detection of high-risk patients.

3.2 | Role of caveolins in melanoma

Whereas the literature on the role of Cav1 in NMSCs largely supports a tumor-suppressing role, research on its role in melanoma is more controversial. Some studies have demonstrated increased levels of Cav1 in melanoma patients, where baseline serum Cav1 levels were found to be significantly higher in patients with melanoma

than those in the control group (0.47 vs. 0.37 ng/ml, respectively, $P = .05$).^[159] However, the same study did not find a correlation between Cav1 levels and other known clinical variables, such as sex, location of the lesion, histology, stage of disease, or response to chemotherapy, and levels of Cav1 had no prognostic role in survival ($P = .44$). Similarly, another study examined Cav1 expression in exosomes from SCID mice engrafted with human melanoma cells and observed significantly increased levels of plasma exosomes expressing Cav1 in the melanoma group compared to healthy donors^[160]; thus, measuring Cav1 levels in exosomes in human plasma could be another non-invasive tool for melanoma screening and follow-up.

Although various studies have observed an association between caveolin and melanoma, whether this protein acts as a tumor suppressor or tumor promotor is still controversial, where in one study overexpression of Cav1 in human melanoma cell lines caused decreased cell proliferation and migration while other studies support the tumor-suppressing role of Cav1 in melanoma specifically assess its regulation of metastasis.^[161] For example, loss of Cav1 expression in melanoma cells predicts decreased survival in primary malignant melanoma as evidenced when the association of Cav1 levels and survival in both primary melanomas and melanoma lymph node metastases was examined. Furthermore, it was found that levels of Cav1 in the stroma, but not in melanoma cells, strongly predicted the clinical outcome once the tumor had metastasized and the absence of stromal Cav1 was associated with aggressive melanoma behaviour, including invasion and metastasis.^[162] This study was one of the first to propose that Cav1 may function as a metastasis suppressor in the stromal compartment of malignant melanoma, which not only suggests its potential as a new biomarker of melanoma development, but also for stromal-targeted therapies in preventing tumor progression. In another study, *in vitro* overexpression of Cav1 enhanced cell growth and increased DNA synthesis^[163]; however, when melanoma cells were implanted into mice, Cav1 overexpression appeared to suppress the ability of melanoma cells to form lung metastases by antagonizing FAK, Src and integrin $\beta 3$. Furthermore, levels of Cav1 were found to be significantly lower in human metastatic melanoma cell lines. Together, these findings suggest that Cav1 expression controls melanoma formation and progression in a stage-specific manner.

Interestingly, the opposite scenario has also been demonstrated, where injecting Cav1-deficient dermal fibroblasts with melanoma cells into mice led to increased melanoma cell growth via enhanced paracrine cytokine signalling and ShhN expression.^[164] Of note, lack of Cav2 did not have this effect, suggesting that Cav1 specifically plays a tumor-suppressing role in primary melanoma. However, the same study showed that in contrast to primary tumor growth, the Cav1-deficient mice also had reduced lung metastases. Similarly, another study specifically addressed the postsurgical setting and found that Cav1 expression suppressed tumor formation, but enhanced lung metastasis.^[165] These two studies thereby support a primary tumor-suppressing role, with a metastases-promoting role of Cav1 in melanoma.

Altogether, our current understanding of Cav1 with regard to melanoma is still not very clear. Therefore, it may not be possible to classify the protein as simply tumor suppressing or oncogenic. As many of the aforementioned studies suggested, its function may depend on timing, tumor stage, location or its interaction with other cellular proteins. Nonetheless, the established association between Cav1 and cancer stresses the need for further elucidation, as its diagnostic and therapeutic potential may be transformative in cutaneous oncology.

4 | ROLE OF CAVEOLIN-1 IN LOCALIZED AND DIFFUSE CUTANEOUS FIBROSIS

Systemic sclerosis, or scleroderma (SSc), is a connective tissue disorder of unknown aetiology characterized by localized or diffuse cutaneous fibrosis and obliterated blood vessels that may spread to internal organs, leading to death.^[166] Reduced Cav1 protein expression has been demonstrated in multiple immunohistochemical analyses of full-thickness biopsies of SSc patients,^[167,168] as well as *in vitro* studies of cultured fibroblasts from SSc patients.^[166,167,169] Similarly, the observation that Cav1 dysregulation promotes fibrosis suggests that Cav1 may also have implications in other fibrotic skin disorders, including keloids, which are characterized by excessive collagen deposition in the dermis and their formation is highly dependent on skin tension.^[170] In fact, one study found that cultured fibroblasts obtained from keloids exhibited reduced Cav1 levels compared to healthy skin.^[171] Furthermore, Cav1 downregulation has been observed in bleomycin-induced lung, and postwounding skin fibrosis, while allogeneic adipose-derived mesenchymal stromal cells (ASCs) injected mice exhibited attenuated bleomycin-induced lung and skin fibrosis and promoted faster wound healing.^[172] Reduction in Cav1 expression has been implicated in reversing several profibrotic signalling cascades contributing to fibrosis in SSc and other fibrotic skin diseases, since Cav1 downregulates TGF- β signalling by inhibiting Smad2 and Smad3 phosphorylation, ultimately inhibiting downstream ECM production and profibrotic effects.^[167,171,173] Additionally, TGF- β receptors may be inhibited directly by caveolae-mediated internalization of the receptor, subsequent degradation and turnover.^[166,171] Cav1 downregulation in keloid-derived fibroblasts has also been demonstrated to enhance TGF- β -mediated production of α -SMA, collagen type I and fibronectin, contributing to profibrotic phenotype.^[171] *In vitro* studies of human dermal fibroblasts have also demonstrated Cav1 modulation of both the activity and function of various matrix metalloproteinases (MMPs) in the skin, notably MMP1 and MMP14.^[174,175] MMP1 deregulation has been associated with collagen deposition, tissue fibrosis, impaired wound healing and cancer metastases.^[174] To this end, it has been demonstrated that an inverse relationship between Cav1 expression and increased MMP1 that was associated with activated MAP kinase pathway specifically phosphorylated Erk1/2 and Ets1.^[174] One of the recent studies argues that the plasticity of dermal adipocytes to undergo de- and re-differentiation under physiological conditions can

be disrupted by bleomycin treatment, thus leading to differentiation of preadipocytes into myofibroblasts (which have previously been shown to exhibit diminished levels of Cav1). Interestingly, myofibroblasts are commonly observed in hypertrophic and keloid scars and this new finding thus offers a novel explanation regarding pathogenesis of these cutaneous fibroses.^[152]

The pathogenesis of SSc may also involve chemotaxis of bone marrow-derived fibroblasts migrating to the dermis and expressing a profibrotic phenotype. One such study identified an increased number of monocyte-derived, Cav1 deficient, fibrocytes in the fibrotic dermis of SSc patient biopsies, compared control tissue.^[166] Additionally, SSc fibrocytes had increased expression of CCR5 and CXCR4 chemokine receptors and hypermigratory phenotype towards respective ligands MIPIa and MIPIb.^[166,176] Additionally, this trend was also seen at a lesser extent in healthy African American dermal fibroblasts, suggesting a genetic susceptibility towards developing cutaneous fibrotic disease in this ethnic population. Early studies with CSD peptide have shown promising results in treatment of lung fibrosis,^[177,178] and as such, *in vitro* and *in vivo* assays investigating reversal effects of CSD peptide in SSc found that CSD blocked hypermigration of SSc monocytes via a reduction in CXCR, CCR5, CCR1, CCR2 and CCR3 expression, indicating a potential role of Cav1 in inhibiting monocyte recruitment and migration, possibly via chemokine receptor degradation.^[166,176] Downregulation of Cav1 may also be associated with myofibroblast-mediated fibrosis contributing to vasculopathy in SSc as one study demonstrated decreased Cav1 expression was correlated with increased pigment epithelium-derived factor (PEDF) expression mediated by TGF- β induction in SSc fibroblasts, which has been associated with anti-angiogenic properties including anti-vasopermeability and neurotrophic activities.^[169]

5 | ROLE OF CAVEOLIN-1 IN PSORIASIS

Campbell et al first hypothesized the role of Cav1 in pathogenesis of psoriasis back in 2000, when his group recognized the plausible connection between Cav1 regulation of proper keratinocyte proliferation, differentiation, calcium homeostasis and angiogenesis.^[143] Soon after, evidence began to emerge demonstrating the connection between downregulated Cav1 and excessive epidermal hyperplasia that is classically seen in psoriasis.^[179,180] Several immunohistochemical and histological analyses of psoriatic skin lesions demonstrated decreased expression of Cav1 compared to unaffected skin.^[143-145,181] Additionally, one study found markedly decreased expression of Cav1 in different types of psoriasis, including psoriasis vulgaris, localized pustular psoriasis and erythrodermic psoriasis, with psoriasis vulgaris having the most significant downregulation of Cav1 expression compared to the other two types.^[145] Other studies found Cav1 expression to be present throughout the full thickness of the epidermis of healthy skin, with more intense expression in the basal, upper granular and spinous layers, whereas psoriasis skin had little to no Cav1 staining

present.^[143,144] Additionally, there was intense cytoplasmic Cav1 staining in psoriatic keratinocytes.^[143] The same study looked at Cav1 expression in lesional, advancing edge and non-lesional psoriatic skin. Though there was a significant reduction in Cav1 expression in lesional skin compared to non-lesional skin, the difference in Cav1 expression in the advancing edge was equivocal, with 3 of the 9 patient samples demonstrating differential expression, and 6 of the 9 samples demonstrating no discernible difference.^[143] Another study also demonstrated an inverse relationship between Cav1 expression and psoriasis severity as measured by the PASI score, proliferation index, microvascular density at dermal papilla.^[144] Thus, the role of Cav1 in development and progression of the different forms of psoriasis needs to be explored further and higher sample numbers need to be assayed before any meaningful results can be interpreted.

6 | ROLE OF CAV1 IN CELLULAR SENEESCENCE AND SKIN AGEING

In addition to previously mentioned functions, several studies have found that Cav1 may also be related to stress-induced premature senescence in a biphasic manner. Initially, it appeared that Cav1 can be induced by sub-cytotoxic levels of H₂O₂, to accelerate premature senescence and mitochondrial dysfunction^[182-185]; however, when Cav1 expression is inhibited either in Cav1-null mice, or by using antisense Cav1, premature senescence by H₂O₂ does not occur.^[182,186] Recently, it has also been shown that strong suppression of Cav1 induces premature senescence in a p53-p21-dependent manner.^[187] Multiple studies have found Cav1 to be downregulated in fibrotic skin and lung disease where bleomycin (BLM) treated mice exhibited downregulation of Cav1, developed lung and skin fibrosis and displayed delayed wound healing.^[172,188] However, ASC injection reduced BLM-induced lung and skin fibrosis and sped up the wound healing process. Additionally, Cav1 downregulation characteristic of fibrotic tissue was also stagnated post-ASC injection.^[172] Another example is sublethal UV-C light acting to increase Cav1 expression and this way lead to premature senescence of fibroblasts.^[182] Further, Cav1 is commonly used as a marker of ageing.^[37,189,190] Specifically, senescent fibroblasts exhibit a greater level of Cav1, where it localizes in proximity to EGFR.^[69] Preliminary data from our laboratory indicate that chronologically aged human skin exhibits elevated levels of Cav1 (Figure 1); however, it should be noted that exposure to sun was not controlled for in these samples. Interestingly, other studies have recently shown that in the skin of the elderly, Cav1 promotes skin ageing via TGF- β pathway that ultimately leads to decreased collagen production by dermal fibroblasts.^[191] For further comprehensive description on the role of Cav1 in macro- and mesoscopic alterations during in skin ageing and other ageing-related diseases, please refer to previously published review articles.^[192,193] With further investigation, targeting Cav1 could potentially be beneficial in decelerating skin ageing and thus used for cosmetic purposes in the future as well.

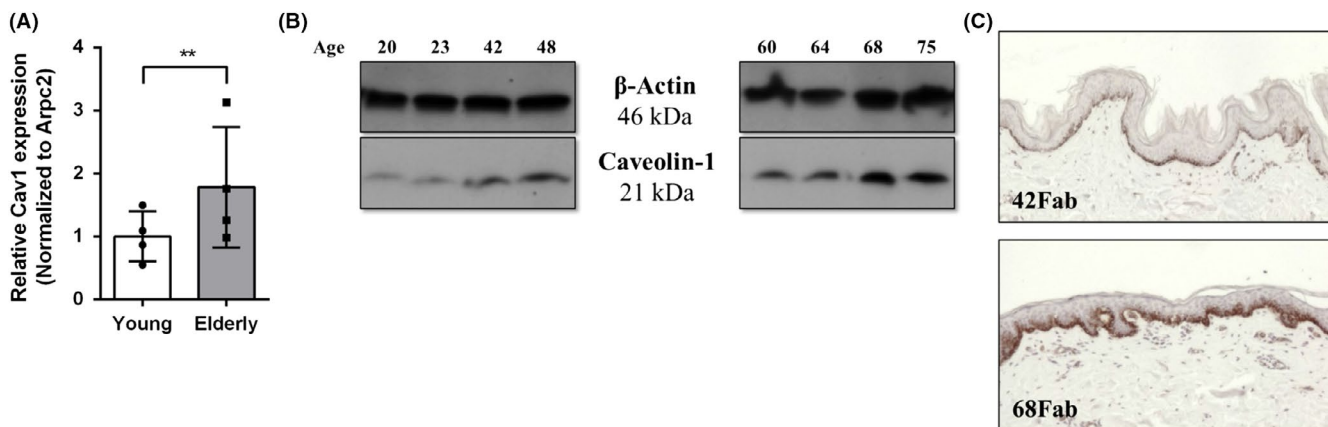


FIGURE 1 Elevated expression of Cav1 in chronologically aged skin. Levels of Cav1 from 4 young (<50 years of age) and 4 elderly (>60 years of age) female abdominal skin (Fab) skin were assessed by qRT-PCR (A), Western blotting (B) with Arpc2 and β -actin serving as normalizing and loading controls, respectively. Briefly, sex-matched skin (N = 8) from patients undergoing routine reduction surgeries (abdominoplasties), composed of both dermis and epidermis, was used to assess Cav1 levels which were determined by qRT-PCR and Western, blotting, respectively (Arpc2 forward primer (5'-TCCGGGACTACTGCACTAC-3') and reverse primer (5'-GGTTCAGCACCTTGAGGAAG-3'); Cav1 forward primer (5'-GCGACCTAAACACCTCAAC -3') and reverse primer (5'-ATGCCGTCAAACACTGTGTGTC-3')). Protein levels were validated by immunoperoxidase staining using Cav1 antibody (Sigma HPA049326) in chronologically aged skin. Expression of Cav1 was found to positively correlate with increasing age (Pearson's correlation coefficient $r(6)=0.7509$, $P=.031$). Error bars correspond to standard deviation from 4 biological samples from each category. $**P < .01$ (Student's t test). (C). Immunoperoxidase staining of representative young (42-year-old) and elderly (68-year-old) skin was used to validate upregulation of Cav1 in chronologically aged skin. Control healthy human skin specimens were obtained as discarded tissue from reduction surgery procedures in accordance to institutional approvals. Specifically, protocol to obtain unidentified skin specimens was submitted to University of Miami Human Subject Research Office (HSRO). Upon review conducted by University of Miami Institutional Review Board (IRB), it was determined that such protocol does not constitute Human Subject Research per 45 CFR46.101.2

7 | ROLE OF CAV1 IN WOUND HEALING

In one of the first studies on the role of Cav1 in wound healing, Rhim et al looked at Cav1 expression in corneal epithelium and its effect on wound healing and observed Cav1 overexpression in aged compared to young corneal epithelium, which was associated with delayed wound healing post-LASEK surgery.^[194,195] Along these lines, Cav1 knockout mice have also shown increased concentration of NO, leading to greater MMP-13 nitration, and faster wound healing.^[196] Interestingly, our team has also shown significant Cav1 overexpression in wound edge biopsies of patients with non-healing chronic wounds. Likewise, we have shown that Cav1 negatively correlates with healing in acute wounds, where it needs to be spatiotemporally downregulated in the migrating epithelial tongue in order to allow for proliferation and migration of keratinocytes from the wound edge into the wound bed using in vitro, in vivo (mouse and porcine) and human ex vivo models of wound healing.^[56] Interestingly, we observed that Cav1 can be used as a bona fide marker of the wound healing edge, where it localizes to the basal keratinocytes proximal to the wound. When co-stained with keratin 6 (which demarcates activated migrating keratinocytes of the healing migrating epithelial tongue), we observed a distinct localization and absence of Cav1 from the migrating epithelial tongue using skin equivalent organotypics, human ex vivo wound, as well as murine and porcine in vivo wound models. Upregulation of Cav1, as seen in non-healing chronic wounds (diabetic foot ulcers and venous leg ulcers), results in increased Cav1 interaction

with membranous glucocorticoid receptor (which potentiates wound healing-inhibitory signalling events), as well as sequestration of EGFR signalling, which altogether results in inhibition of keratinocyte migration and subsequent wound closure. Interestingly, topical administration of cholesterol depleting agents, including (M β CD and Mevasatin), reversed the Cav1-mediated inhibition of migration and resulted in accelerated wound closure.^[56,197] However, it is yet to be established whether the same is true for pressure ulcers.

Other studies however have shown Cav1 to be crucial as a promoter of the wound healing process. Specifically, overexpression of Cav1 in epidermal stem cells (EpiSCs) enhanced wound re-epithelization and cellularity, and improved wound vasculature and overall healing scores. As such, Cav1 appears to be crucial in future wound healing therapies involving EpiSCs.^[198] Furthermore, another study demonstrated that disruption of either syndecan-4 or Cav1 could lead to impaired wound closure in mice.^[199] Thus, it should be noted that therapeutic targeting of Cav1 in wound healing should be interpreted in the context of each type of wound. For example, burns and other types of acute wounds will require temporal downregulation of Cav1 expression, whereas inability to normalize homeostatic levels could result in aberrant inflammatory response, infection, hyperproliferation as well as excessive collagen deposition and thus yield undesirable healing outcomes (chronic wounds or hypertrophic scars). Therefore, as with other roles discussed above, Cav1's role in wound healing is complex and environment-dependent, but it is clear how understanding its role

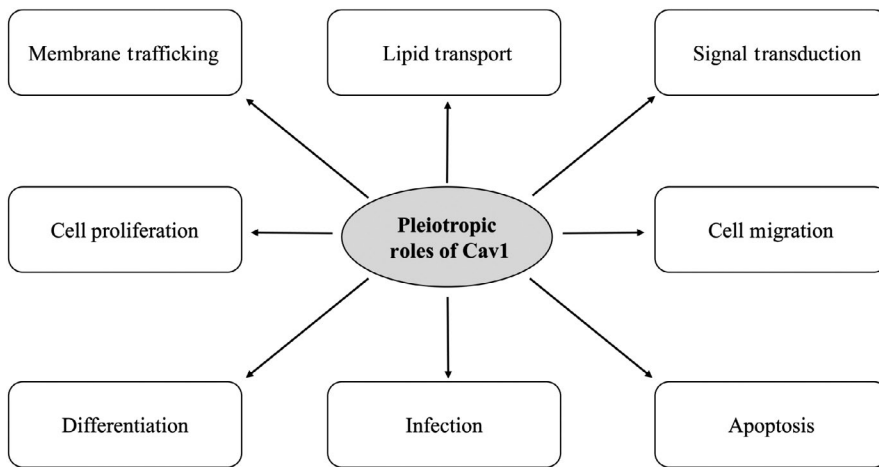


FIGURE 2 Pleiotropic Roles of Cav1 in Skin Physiology

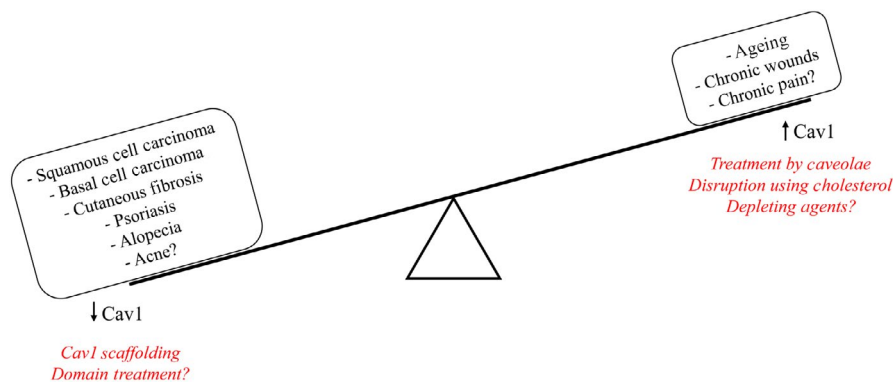


FIGURE 3 Skin Pathophysiology associated with deregulation of homeostatic Cav1 levels. It is the fine balance of Cav1 that is key to physiologic skin structure and function, as the slight imbalance in one direction or another affects localization and activation of various key signalling molecules and can tip the scale towards one of numerous skin pathologies. On one side, upregulation of Cav1 has been implicated in skin ageing, development of non-healing chronic wounds and, whereas downregulation has been associated with squamous cell carcinoma, basal cell carcinoma, cutaneous fibroses, psoriasis and alopecia

is important for developing potential therapies with many patients with non-healing chronic wounds, considering that the last biologic for treatment of chronic wounds was approved by the FDA over 20 years ago.

8 | CONCLUSIONS AND TRANSLATIONAL PERSPECTIVES

The signalling pathways that regulate various cellular functions ranging from migration, proliferation and differentiation, to endocytosis and cellular senescence, are of integral importance to development and normal functioning of skin. There is abundant evidence reviewed here that supports the role of Cav1 in all the aforementioned cellular processes and thus brings about a new spotlight on Cav1 in development and progression of numerous cutaneous disorders (Figure 2). Specifically, it is the fine balance of Cav1 that is key to physiologic skin structure and function, as the slight imbalance in one direction or another affects localization and activation of various key signalling molecules and can tip the scale towards one of the skin pathologies (Figure 3).

Thus, by studying the cellular and molecular mechanisms of Cav1 balance and imbalance in physiologic and pathologic skin conditions, respectively, one can arrive at a better understanding of commonly encountered and challenging to manage skin diseases, including skin cancer, psoriasis, scleroderma, skin ageing and senescence, wound healing and others. For example, spatiotemporal downregulation of Cav1 may be beneficial for proper wound closure, but sustained downregulation of Cav1 may bring about prominent changes in cell proliferation and collagen production and thus yield undesirable outcomes in line with non-melanoma skin cancers, psoriasis and cutaneous fibroses. On the other hand, overexpression of Cav1 can also alter cellular migration and lead to decreased collagen deposition and thus have unfavourable outcomes in wound closure, cellular senescence and the resulting age-related changes in skin as well as in progression of melanoma. Not only would it be of interested to target Cav1 expression in various cutaneous pathologies outlined above, but if Cav1 expression is confirmed to be either up- or downregulated in specific conditions by studies with larger samples sizes, Cav1 may become a very useful theragnostic (therapeutic and diagnostic) tool in dermatology.

It is also important to note that some of the observed effects of Cav1 on certain cutaneous disorders come from animal models (ie Cav1-null mice) which do not always recapitulate human conditions and thus should be taken cautiously. Therefore, our understanding of the role Cav1 plays in development and progression of numerous cutaneous disorders may be limited by those models and highlights the need for development of better models which more closely mirror the human condition. Further, current therapeutic strategies in conditions such as psoriasis, scleroderma, ageing and especially wound healing have their limitations and beget newly discovered targets. At the same time, current strategies do not target Cav1, which evidently plays a role in these pathologies, and has now become the spotlight as a potential new and exciting therapeutic target candidate. While many of the aforementioned functions may not be confirmed in humans, are not fully elucidated and in some cases even controversial, the vast preclinical data discussed are certainly promising and exciting for both scientists as well as clinicians and should serve as a large stepping stone towards more confirmatory and useful clinical and therapeutic innovations. Likewise, there are still many unanswered questions regarding the role of Cav1 in development of other cutaneous pathophysiology not highlighted in this review. For example, although there is ample evidence supporting the role of Cav1 in internalization of various aforementioned bacteria, does Cav1 also regulate internalization of *Cutibacterium acnes*, and thus can Cav1 be targeted in treatment of acne? Also, why is Cav1 expression consistently low in most neuronal cells and what implications does this have on development of pruritus and/or various cutaneous neuropathies? There is some evidence from mouse studies that point to persistent upregulation and activation of Cav1 in the anterior cingulate cortex neurons after chronic constriction injury,^[200] suggesting a possible role for Cav1 in neuronal transmission pathways associated with pain modulation; however, these are still very preliminary. Lastly, Tim Thompson's group has identified differentially expressed levels of Cav1 in White American vs African American prostate cancer patients^[201]; thus, it would be of great interest to elucidate whether such ethnic/racial disparities of Cav1 expression are present in cutaneous disorders that are known to disproportionately affect ethnic/racial minorities including melanoma and non-melanoma skin cancers as well as atopic dermatitis (among others). In all, the vast aforementioned preclinical data on Cav1 are certainly inspiring, and as it becomes more clear-cut, and is recapitulated in humans in the future, it should serve as a large stepping stone towards more confirmatory and useful clinical and therapeutic innovations, ultimately leading to a more effective and successful management of cancerous, psoriatic, senescent, fibrotic and non-healing skin lesions.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing conflicts of interest.

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AUTHOR CONTRIBUTIONS

IJ designed the manuscript and ANE, AR, NMW, SRR, JDF, LLW and IJ wrote the manuscript cooperatively.

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