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Recent advances in the role of Yes-associated protein in dermatosis

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Abstract

Background: Dermatosis is a general term for diseases of the skin and skin appendages including scleroderma, psoriasis, bullous disease, atopic dermatitis, basal cell carcinoma, squamous cell carcinoma, and melanoma. These diseases affect millions of individuals globally and are a serious public health concern. However, the pathogenesis of skin diseases is not fully understood, and treatments are not optimal. Yes-associated protein (YAP) is a transcriptional coactivator that plays a role in the regulation of gene transcription and signal transduction.

Aims: To study the role of Yes-associated protein in skin diseases.

Materials and Methods: The present review summarizes recent advances in our understanding of the role of YAP in skin diseases, current treatments that target YAP, and potential avenues for novel therapies.

Results: Abnormal YAP expression has been implicated in occurrence and development of dermatosis. YAP regulates the cell homeostasis, proliferation, differentiation, apoptosis, angiopoiesis, and epithelial-to-mesenchymal transition, among other processes. As well as, it serves as a potential target in many biological processes for treating dermatosis.

Conclusions: The effects of YAP on the skin are complex and require multidimensional investigational approaches. YAP functions as an oncoprotein that can promote the occurrence and development of cancer, but there is currently limited information on the therapeutic potential of YAP inhibition for cancer treatment. Additional studies are also needed to clarify the role of YAP in the development and maturation of dermal fibroblasts; skin barrier function, homeostasis, aging, and melanin production; and dermatosis.

KEYWORDS
dermatosis, hippo signaling pathway, signal transduction, skin physiology, Yes-associated protein

Abbreviations: BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; JEB, junctional epidermolysis bullosa; ROS, reactive oxygen species; SSc, systemic sclerosis; VP, verteporfin.

1 | INTRODUCTION

The skin is the largest organ and first line of defense of the human body. Its functions include acting as a barrier, providing immune protection, maintaining electrolyte balance, and melanin metabolism, among others. However, the skin is also the most susceptible organ to external stimuli, which can lead to the development of skin diseases such as scleroderma, psoriasis, basal cell carcinoma (BCC), melanoma, cutaneous squamous cell carcinoma (cSCC), and bullous skin disease. With the aging of the global population, changes in living conditions, environmental pollution, and other factors in the last few decades, the incidence of skin diseases has increased significantly; dermatosis—a general term for diseases of the skin and skin appendages—constitutes a considerable threat to public health.[1]

Yes-associated protein (YAP) is a mammalian transcriptional accessory protein first identified in *Drosophila* with a relative molecular mass of ~65 kDa. The human *YAP* gene is located on chromosome 11q22.[2] YAP is the main effector of the Hippo signaling pathway but has functions that are independent of Hippo. In human and mouse embryo, YAP is mainly localized in the nucleus and cytoplasm of the basal layer of the epidermis. YAP expression in the nucleus declines postnatally, but it continues to be expressed in epidermal stem cells and in the nucleus of keratinocytes.[3–5] YAP functions as a transcriptional coactivator that binds to transcription factors to induce the transcription of target genes. The intracellular localization of YAP determines its transcriptional activity. In the nucleus, YAP contributes to intracellular signal transduction in collaboration with connexins to regulate proliferation, cell growth, and epithelial-to-mesenchymal transition (EMT), whereas phosphorylated YAP binds to 14-3-3 protein and accumulates in the cytoplasm, and does not participate in transcriptional coactivation.[6]

2 | OVERVIEW OF YAP FUNCTION

YAP regulates cell proliferation, apoptosis, and differentiation via multiple pathways and plays an important regulatory role in the development and maintenance of skin tissue structure. YAP overexpression in mice resulted in thickening of the acanthocyte and granulosa cell layers and hyperkeratosis of the interfollicular epidermis, thereby increasing epidermal thickness.[5] Meanwhile, YAP knockout mice showed thinner and more fragile skin, with loss of epidermal tissue in distal limbs, thinning of the epidermis and stratum corneum, disordered epidermal structure, basal lamina dysplasia, and decreased proliferation of epidermal stem cells.[7] In HaCaT human keratinocytes, the downregulation of YAP was associated with decreased cell proliferation and cell cycle arrest in G0/G1 phase,[8] whereas YAP activation enhanced keratinocyte proliferation via activation of WNT16/β-catenin signaling or increased expression of plasminogen activator urokinase (Plau) and transforming growth factor beta (TGF-β) type III receptor.[9–11] However, simultaneous overexpression of YAP resulted in downregulation of 14-3-3 and upregulation of DNp63a, which restored immortality in human keratinocytes.[12] Integrin/Src and epidermal growth factor receptor (EGFR)/phosphatidylinositol 3-kinase (PI3K) signaling induced YAP nuclear localization and promoted basal cell proliferation.[5] YAP was shown to interact with proteins such as baculoviral inhibitor of apoptosis (IAP) repeat-containing 5 (BIRC5), deoxyribo nucleic acid (DNA) damage-inducible transcript 4 (DDIT4), tumor necrosis factor-related apoptosis-inducing ligand, nucleosome remodeling and deacetylase (NuRD), B cell lymphoma 2 (Bcl-2), p53, caspase-3, cyclooxygenase-2 (COX2), and p21 to inhibit the apoptosis of fibroblasts. However, nuclear YAP can also combine with p73 to promote the transcription of tumor protein 53 (TP53)-regulated apoptosis inducing protein 1 (p53AIP1), Bcl2-associated X protein (Bax), death receptor 5 (DR5), promyelocytic leukemia, p21, and P53 upregulated modulator of apoptosis (PUMA), leading to fibroblast apoptosis.[13,14] This apparent paradox of YAP function can be explained by the binding of YAP to different transcription factors, although the precise mechanisms of transcriptional activation or inhibition are unclear.

YAP is known to play a role in intracellular mechanotransduction. Excessive division of epidermal cells leads to cell crowding and uneven stress distribution; high cell density or low mechanical tension affects actin contraction through the E-cadherin/β-catenin complex and acts on α-catenin, vinculin, Merlin, and LIM (Lin-11, Isl1, MEC-3) domain-containing 1 (LIMD1) to inhibit YAP activity, which in turn suppresses cell proliferation.[15] However, YAP knockout in mice did not cause pathologic changes, suggesting that the role of YAP in the regulation of epidermal regeneration is nonessential[16] (Figure 1). YAP expression is regulated by the polarity of epidermal cells, which in turn impacts skin cell differentiation. When basal cells lose contact with and delaminate from the basement membrane, they downregulate integrin/Src and EGFR/PI3K signaling, thereby inhibiting nuclear translocation of YAP and promoting cell differentiation.[5] YAP induces the proliferation of basal epidermal progenitor cells and inhibits their terminal differentiation along with the differentiation of mouse embryonic stem cells and premature differentiation of basal epidermal keratinocytes; it also regulates T cell differentiation.[17] However, the regulatory effect of YAP on the production of skin extracellular matrix (ECM) and dermis remains to be elucidated.

In light of the increasing evidence regarding the role of YAP in skin homeostasis, in this review, we summarize the relationship between YAP dysregulation and skin diseases and discuss the development of pharmacologic agents targeting YAP and their therapeutic potential for the treatment of dermatosis.

3 | RELATIONSHIP BETWEEN YAP AND SKIN DISEASES

Dysregulation of YAP expression is a feature of multiple skin diseases. YAP overexpression results in the overproliferation of cells, which is associated with malignancies.[3] YAP induces EMT via the PI3K/protein kinase B (Akt), angiomotin (AMOT), TGF-β, and WNT/β-catenin pathways, accelerating tumor invasion and metastasis and increasing mortality in patients with malignant tumors.[19–21] However, it was also shown that YAP overexpression alone is not sufficient to

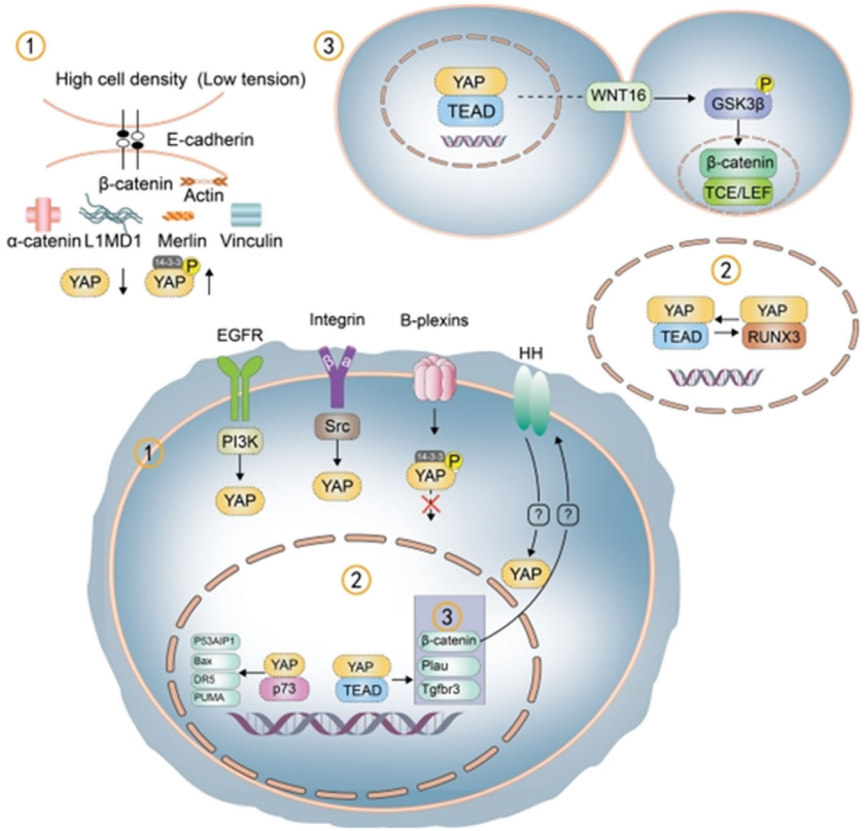

FIGURE 1 Regulatory pathways in cell proliferation and differentiation involving Yes-associated protein (YAP). (1) YAP is phosphorylated at high cell density and low mechanical tension. (2) The switch between the YAP/TEAD (transcriptional enhanced associate domain) and YAP/RUNX3 complexes—which promotes and inhibits cell proliferation, respectively—regulates the cell cycle. After entering the nucleus, YAP competes with VGLL4 for binding to the transcription factor TEAD, thereby maintaining cell proliferation.[18] (3) The YAP/TEAD complex activates WNT16/GSK3β/β-catenin to bind to TCF/LEF (transcription factor/ lymphoid enhancer binding factor), promoting cell proliferation. The integrin/Src and EGFR/PI3K pathways promote YAP nuclear localization; B-plexin phosphorylates YAP; Hedgehog (HH) signaling activates YAP; and nuclear YAP binds to β-catenin to activate HH signaling. YAP also binds to p73, increasing p53AIP1 and Bax expression, while the upregulation of DR5 and PUMA promotes cell apoptosis. YAP increases the expression of *Plau* and *Tgfbr3* to enhance keratinocyte proliferation.

promote complete EMT.[12] Excessive activation of YAP inhibits epidermal differentiation while promoting cell and vascular proliferation, expression of inflammatory factors, and T cell differentiation, which are pathophysiologic processes that are closely related to the occurrence and development of skin diseases.

3.1 | Relationship between YAP and wound healing

YAP plays an important role in skin wound repair. YAP was shown to be upregulated in the basal cell layer of injured skin[5] and localized in the nucleus of the dermis.[22] Nuclear YAP regulates cell proliferation, fibroblast activation, vascular proliferation,[23] and ECM remodeling to promote wound healing. It has been demonstrated that YAP enhanced the activation of fibroblasts and angiogenesis by increasing the expression of the target gene connective tissue growth factor (*CTGF/CCN [cellular communication network]2*), suppressing that of Mothers against decapentaplegic 7 (Smad-7), and enhancing TGF-β/Smad2/3 signaling.[22] YAP interacts with Smad2/3 through TGF-β, leading to the accumulation of phosphorylated Smad2/3 and promoting tissue repair[24] (Figure 2). In a cellular model of wound healing, HaCaT cell migration was decreased by YAP inhibition[17]; and in mouse models of type I and II diabetes, overexpression of growth differentiation factor 11 (GDF11) stimulated dermal fibrosis and accelerated skin wound closure via YAP/Smad2/3/CTGF signaling.[25] Nuclear localization of YAP was shown to be increased by treatment with calcipotriol, which induced EMT through the YAP/TGF-β/Smad pathway to

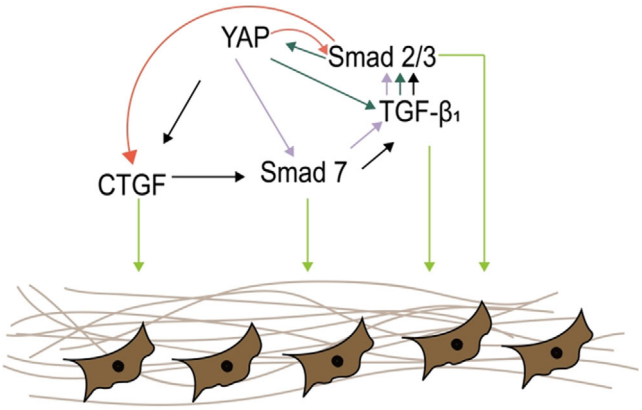

FIGURE 2 Mechanism of Yes-associated protein (YAP)/transforming growth factor beta 1 (TGF-β1)/Smad regulation in wound healing. YAP induces connective tissue growth factor (CTGF) and inhibits Smad7, thereby increasing the expression of TGF-β1 and Smad 2/3; acts directly on Smad7; and modulates TGF-β1 and Smad 2/3. YAP and TGFβ1/Smad2/3 engage in a positive feedback loop. These signaling cascades act on fibroblasts to stimulate wound healing.

accelerate tissue repair.[26] YAP/interleukin 33 (IL-33)-mediated autophagy was identified as a potential pharmacologic target for accelerating wound healing.[27] The mechanism of YAP regulation observed in spiny mice (*Acomys cahirinus*) applied to human fibroblasts cultured in vitro was shown to prevent and rescue TGF-β1–mediated myofibroblast differentiation, providing a basis for preventing scar

formation during wound healing.[28] However, treatment with the YAP inhibitor verteporfin (VP) promoted wound repair without scarring. Most of the research to date has focused on the downstream effects of YAP in wound healing, and it is not known how skin damage induces the activation of YAP. Clarifying this mechanism can reveal potential strategies for stimulating tissue repair following skin injury.

3.2 | Role of YAP in scleroderma

High YAP expression promotes skin thickening and fibrosis in systemic sclerosis (SSc) as a result of EMT of skin epithelial cells to fibroblasts (mesenchymal-like cells). Single-cell sequencing identified YAP as a potential therapeutic target for SSc.[29] Transcriptome analysis in a scleroderma model showed that *YAP* knockdown resulted in the downregulation of the profibrotic genes TGF-β1, endothelin 1 (ET-1), IL-6, TEAD1, plasminogen activator inhibitor 1 (PAI-1), cysteine-rich 61 (Cyr61/CCN1), and CCN2.[30] As a critical effector of mechanotransduction signaling, YAP nuclear accumulation and activity increased with matrix stiffness and in fibroblasts; a pathologic increase in ECM stiffness activated YAP, inducing the expression of profibrotic mediators such as PAI-1 and ECM proteins, leading to fibroblast activation and tissue fibrosis.[31] VP reduced TGF-β1–induced expression of alpha-smooth muscle actin, CCN2, and human collagen I (COLI), thereby preventing the occurrence of scleroderma fibrosis.[32] Dimethyl fumarate (DMF) exerts an antifibrotic effect by targeting YAP via the PI3K/Akt1 and TGF-β1/Akt1/glycogen synthase kinase 3-beta (GSK3β) pathways.[30] Pharmacotherapies for scleroderma mainly target inflammation, autoimmunity, vascular disease, and fibrosis. However, the precise role of YAP in immune dysregulation and vascular lesions in scleroderma is poorly understood, and additional studies are needed to determine whether pharmacologic targeting of YAP is a potential treatment strategy for SSc.

3.3 | Role of YAP in psoriasis

YAP is highly expressed in the skin of psoriasis patients, mainly in the basal and lower spinous layers.[8] The pathogenesis of psoriasis is related to keratinocyte activation by YAP, abnormal proliferation of blood vessels, and inflammatory cell infiltration. YAP promotes keratinocyte proliferation through positive regulation of amphiregulin (AREG)[8]; and YAP is closely related to angiogenesis, and the increase of nuclear YAP can affect the expression of other angiogenesis factors, which can promote endothelial cell proliferation, angiogenesis.[33] IL-17α was shown to promote the development of psoriasis via activation of the YAP/AREG axis.[34] Meanwhile, IL-38 inhibited the transcriptional activity of YAP to suppress keratinocyte proliferation.[35] Inhibiting YAP expression improved skin lesions by inducing cell cycle arrest in G0/G1 phase and reducing the levels of inflammatory factors as well as activation of extracellular signal-regulated kinase (ERK), signal transducer and activator of transcription 3 (STAT3), and nuclear factor kappa B signaling.[36] The mechanism by which YAP inhibits the inflammatory response is not well understood.

Mechanical stress contributes to the pathogenesis of psoriasis; continuously increasing mechanical stimulation resulted in YAP-mediated inhibition of Notch signaling and stimulated proliferation while inhibiting the differentiation of epidermal keratinocytes, leading to the formation of psoriatic skin.[37] Danshensu, a naturally derived polyphenol compound that is used in traditional Chinese medicine for its antitumor and antiangiogenic properties, was shown to prevent psoriasis by downregulating YAP expression,[38] highlighting its therapeutic potential in the treatment of psoriasis.

3.4 | Role of YAP in bullous skin disease

YAP is overexpressed around pemphigus lesions.[39] Desmoglein 3 (Dsg3) and immunoglobulin G (IgG) are essential for the induction and progression of bullous skin disease; Dsg3 is destroyed by IgG to generate reactive oxygen species (ROS), which acts directly on various signaling pathways including α-catenin, Dsg3, p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase, and protein kinase C to upregulate YAP. Increased YAP expression contributes to intraepidermal blister formation by affecting calcium channels, Dsg3, and adherens junctions.[39,40] Dsg3 was shown to form a complex with phosphorylated YAP under high mechanical tension, contradicting a previous report that phosphorylated YAP is inactive.[41] However, the function of phosphorylated YAP in keratinocytes remains to be determined. Autoantibodies against epidermal cadherin that are known to be pathogenic include anti-Dsg1 and -Dsg3 antibodies, but there have been no studies examining the relationship between Dsg1 and YAP. Unlike in pemphigus lesions, YAP expression is significantly reduced in keratinocytes of the junctional epidermolysis bullosa (JEB).[42] Laminin 332 and $\alpha6\beta4$ integrin-regulated YAP and the downstream target gene Forkhead box M1 (*FOXM1*) are involved in the repair of human epidermal stem cells, which has important implications for the treatment of JEB.[42,43] Most studies to date have focused on the effect of oxidative stress on YAP and intercellular linkages; future research directions include the impact of YAP on the apoptosis, proliferation, and T cell regulation of keratinocytes in bullous skin disease.

3.5 | Role of YAP in rosacea and atopic dermatitis

Decreased YAP expression has been reported in skin lesions of patients with atopic dermatitis. YAP promotes the differentiation of progenitor CD4+ T cells into T helper 17 cells or regulatory T cells, and its downregulation alters the ratio of these two cell types, leading to the transition of atopic dermatitis from the acute to the chronic phase.[17] At the same time, YAP expression in the epidermis is decreased, and the rate of keratinocyte proliferation is reduced, while apoptosis is accelerated, resulting in skin erosion and the progression

of atopic dermatitis.[17] The microRNA miR-375-3p was shown to attenuate inflammation by targeting the YAP/lympho-epithelial Kazal-type-related inhibitor pathway in HaCaT cells,[44] although the detailed mechanism requires clarification. The upregulation of YAP is closely related to angiogenesis, cell proliferation and maturation, and tissue remodeling,[23,45,46] which are dysregulated in rosacea. Telangiectasia and erythema in rosacea were shown to be improved upon VP-induced inhibition of vascular endothelial growth factor expression.[47] As mentioned above, angiogenesis is closely related to chronic inflammatory skin diseases. Elucidating the site of action of YAP in blood vessels in diseases such as urticaria, hidradenitis suppurativa, angioedema, and atopic dermatitis can provide a basis for developing novel treatment strategies.

3.6 | Role of YAP in epidermal BCC

Genome-wide analysis of BCC samples has revealed an upregulation of YAP target genes.[48] In YAP-overexpressing mouse BCC cell lines, the rate of proliferation rate was found to be increased 2.1 fold relative to control cells.[49] Aberrant WNT and Hedgehog signaling is thought to underlie BCC.[50] The interaction between Hedgehog and YAP also controls epidermis development and homeostasis,[51] and a positive feedback interaction between these factors can promote the development of BCC.[52] Disruption of the Gαs/PKA interaction induced cell-autonomous Hedgehog signaling and activation of YAP, leading to the development of mouse and human BCC.[53] Hyperactivation of Hippo/YAP and WNT pathways was observed in intrinsically resistant BCC.[49] At the same time, YAP promotes the development of BCC through the c-JUN/activator protein 1 (AP1) axis independent of the WNT and Hedgehog pathways.[16] YAP and its downstream effectors CCN1 and CCN2 were found to be upregulated in the skin of patients with BCC, and elevated levels of CCN family proteins were significantly correlated with tumor malignancy. CCN1 regulates the proliferation of abnormal keratinocytes whereas CCN2 regulates tumor stromal cell activation and remodeling.[54] Epidermal stem cells lacking B-plexins are unable to sense mechanical compression, leading to disinhibition of YAP, cell hyperproliferation, and tissue overgrowth.[37,55] B-plexins and protein tyrosine phosphatase nonreceptor type 14 (PTPN14) inhibit YAP to inhibit the development of BCC.[37,48] An analysis of skin samples of patients with BCC found no difference in YAP expression levels between recurrent and nonrecurrent disease,[56] and activating mutations of YAP did not result in the development of BCC-like lesions. Although the precise role of YAP in BCC requires clarification, targeting YAP or its up- or downstream factors may be a promising treatment approach.

3.7 | Role of YAP in cSCC

YAP is highly expressed in poorly differentiated (precancerous) cSCC,[57–59] and the expression level is positively correlated with the progression of cSCC and actinic keratosis as well as Bowen disease, a precancerous lesion of squamous cell carcinoma.[60] Another study found that at the site of epithelial scratches, YAP induced the transformation of cSCC to spindle cell carcinoma through zinc finger E-box binding homeobox 1 (ZEB1)-mediated EMT.[61] Additionally, YAP activation was observed in most cSCC patients who experienced treatment failure and relapse.[62] Following α-catenin/YAP overexpression in the dermis, tumors showed signs of EMT, leading to the development of tumors that were morphologically similar to human cSCC.[7] Loss of YAP resulted in the arrest of cSCC cells in G1/S phase and the cell cycle regulators cyclin A, B1, D1, and E and cyclin-dependent kinase 2 (CDK2) and CD25A were all downregulated, resulting in decreased cell proliferation.[57] YAP was also found to promote EGFR/RAS signaling by regulating TP53, NOTCH1, NOTCH2, histone-lysine N-methyltransferase 2D (KMT2D), fat atypical cadherin 1—4 (FAT1—4), and other genes[63] or AREG transcription to enhance EGFR/RAS signaling; RAS further activated the RAF/MEK (MAP/ERK kinase)/ERK and PI3K/Akt pathways,[57] thereby enhancing the proliferation and invasion of cSCC. Oncogenic activation of YAP expression by integrin β4-src signaling was shown to be inhibited by ε-catenin.[64] YAP/NUAK2 is a potential target in the treatment of cSCC.[58] Knockdown of the long noncoding RNA p38-inhibited cutaneous squamous cell carcinoma-associated lincRNA (PICSAR) suppressed the proliferation and invasion of cSCC cells through regulation of the miR-125b/YAP1 axis and promoted the apoptosis of cSCC cells,[65] suggesting another avenue for cSCC treatment.

3.8 | Role of YAP in melanoma

YAP regulates the proliferation, apoptosis, and invasion of melanocytes through various pathways. The main driving force of melanoma development is the activation of BRAF and MAPK signaling. BRAF mutations are detected in about half of melanomas, and YAP causes T cell exhaustion by inducing the upregulation of programmed death ligand 1, resulting in immune evasion and BRAF inhibitor resistance.[66] Silencing ubiquitin-specific peptidase 22 expression resulted in the upregulation of YAP, leading to BRAF inhibitor resistance.[67] As YAP activation has been linked to increased resistance to BRAF and/or MEK inhibitors,[68,69] simultaneous BRAF/MEK inhibition is a potential treatment for BRAF-mutant melanoma.

The TGFβ/Smad and YAP signaling pathways interact to induce melanoma cell proliferation and their transformation to an aggressive phenotype; thus, these pathways are suitable therapeutic targets for blocking melanoma progression, metastasis, and drug resistance.[70] YAP activation may promote the proliferation and migration of melanoma cells through MAPK, Akt, and other signaling pathways.[71] As a classic mechanical sensor, YAP is modulated by static mechanical stimulation of the actin cytoskeleton. In melanoma models, semaphorin 6A (SEMA6A) was shown to activate the RhoA/YAP axis, which remolded the actin cytoskeleton and predicted shorter recurrence-free interval in patients.[72] Upstream of RhoA/YAP, PPARG coactivator 1 alpha inhibition increased the expression of WNT5A and activated RhoA to increase the level of YAP, thereby increasing melanoma

invasion[73] through the regulation of actin-related protein 2/3 complex subunit 5, which is associated with melanocyte adhesion.[74]

YAP is also affected by dynamic mechanical stress, which plays a role in the pathology of melanoma. In plantar melanoma, continuous mechanical stress caused by weight-bearing activities activated the expression of YAP, stimulating the proliferation of melanoma cells.[75] YAP activity is also positively regulated by the ECM[76]; ECM-mediated signaling induced by changes in cytoskeletal structure promoted tumor development through increased collagen production and remodeling, while the HU177 epitope was shown to promote melanoma cell metastasis through CDK5/YAP signaling.[77] High fibromodulin expression in the tumor microenvironment stimualted ECM remodeling, activated the integrin/focal adhesion kinase pathway, and induced YAP nuclear translocation and metastatic growth and vasculogenic mimicry.[78] Fibroblast reticulocyte relaxation depends on constitutive inhibition of Janus kinase 1 (JAK1)/STAT3 and YAP signaling, which resulted in lymph node expansion and increased melanoma invasiveness.[79] DMF combined with vemurafenib improved therapeutic response in melanoma by inhibiting YAP[80]; however, VP was found to be ineffective in inhibiting melanoma progression in a mouse model.[81] Additional studies are needed to resolve these contradictory findings.

4 | YAP IN CLINICAL DIAGNOSIS AND TREATMENT

Immunohistochemical detection of the YAP1 C terminus has allowed the classification of hole-like lesions in NUT carcinoma.[82] Elevated

TABLE 1 Summary of YAP pathways and functions.

YAP pathway or related process	Effect	Reference
YAP/P73/p53AIP1, BAX, DR5, PUMA	Promote apoptosis	13,14
Integrin/Src/YAP, EGFR/PI3K/YAP	Promote proliferation	5
YAP/WNT16/β-catenin	Promote proliferation	9
YAP/PLAU, YAP/TgFbr3	Promote proliferation	11
Conversion between YAP-TEAD4 and YAP-RUNX3	Cell cycle regulation	18
Hedgehog/YAP	Control tissue regeneration	51
High cell density or low mechanical tension	Inhibit excess cell proliferation	15
B-plexins/YAP	Inhibit excess cell proliferation	37
YAP/PI3K/Akt, YAP/AMOT, YAP/TGFβ-Smad, YAP/WNT/β-catenin	Induce EMT occurrence, accelerate tumorigenesis and metastasis	19,20,21
YAP/CTGF/Smad7/TGF-β/Smad	Promote wound healing	22
YAP/Smad2/3/CTGF	Promote wound healing	24
YAP/IL-33autophagy pathway	Promote wound healing	27
PI3K/Akt1/YAP, TGF-β1/Akt1/GSK3β/YAP	Target YAP to inhibit fibrosis	30
YAP/AREG	Promote keratinocyte proliferation	8
YAP/ERK, STAT3, NF-KB	Proinflammatory effect	36
YAP/Th17, Treg	Associated with atopic dermatitis	17
YAP/VEGF	Associated with rosacea	47
YAP-TEAD/c-JUN/AP1	Promote BCC tumorigenesis	16
YAP/CCN1, CCN2	Promote BCC tumorigenesis	54
PTPN14/YAP, B-plexin/YAP	Inhibition of YAP and BCC generation and development	23,76
YAP/AREG/EGFR/RAS/RAF/MEK/ERK	Promote CSCC occurrence and development	57
YAP/AREG/EGFR/RAS/PI3K/Akt	Promote CSCC occurrence and development	57
YAP/TP53, NOTCH1, NOTCH2, KMT2D, FAT1-4	Promote CSCC occurrence and development	63
YAP/NUAK2	Promote CSCC occurrence and development	58
USP22/YAP/CCN1, CCN2	Promote melanoma tumorigenesis	67
YAP/PD-L1/T cell	T cell immune escape, BRAF inhibitor resistance	66
YAP/LRP1/MAPK, Akt	Promote melanoma proliferation and migration	71
PGC1α/WNT5A/RhoA GTPase/YAP	Inhibit melanoma cell invasion	73

Abbreviations: BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; EMT, epithelial-to-mesenchymal transition; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

YAP expression may be a useful indicator for clinical staging, monitoring postoperative survival, and predicting prognosis of malignant melanoma.[83] YAP is a downstream effector of C-Jun–mediated apoptosis following cisplatin treatment and may be a key predictor of chemotherapy response and treatment outcome.[84] Aberrant YAP expression is observed in many skin diseases and its clinical potential for disease diagnosis, staging, and prognostic assessment is warranted to guide clinical treatment. The YAP inhibitor VP is approved for the treatment of age-related macular degeneration[85,86] and its antitumor potential has also been reported. YAP is involved in apoptosis signaling downstream of chemotherapeutic agents such as cisplatin, ionizing radiation, and Fas ligand-targeted therapy.[87–89] In an in vitro study, dabrafafenib alone or in combination with trametinib induced the expression of SEMA6A and activated the RhoA/YAP axis.[68] The combination of Neratinib and pemetrexed increased the phosphorylation of YAP resulting in the loss of YAP transcriptional activity.[90] Topical administration of the YAP inhibitor danshensu had a therapeutic effect in psoriasis model mice[38]; and topical application of GDF1 increased YAP expression to accelerate skin wound healing in a mouse model of diabetes[91]. DMF injection targeting YAP relieved symptoms of scleroderma.[20] Inhibiting YAP activity in T cells is an important mechanism in T cell therapy for cancer and other diseases[92]; YAP agonists such as XMU-MP-1[93] have not been applied to skin diseases but are worth exploring in the future. The evidence to date indicates that targeting YAP or its up- and downstream genes is a promising treatment strategy for skin diseases. However, as circulating levels of YAP are low, treatment response monitoring is currently limited to epidermal sampling. Identifying biomarkers for this purpose is an important future research direction.

5 | CONCLUSION AND OUTLOOK

The effects of YAP on the skin are complex and require multidimensional investigational approaches. YAP functions as an oncoprotein that can promote the occurrence and development of cancer (Table 1), but there is currently limited information on the therapeutic potential of YAP inhibition for cancer treatment. Additional studies are also needed to clarify the role of YAP in the development and maturation of dermal fibroblasts; skin barrier function, homeostasis, aging, and melanin production; and dermatosis. This will require systematic investigation of the molecular pathways and mechanisms of YAP in skin development and maintenance, which would provide a basis for the development of pharmacotherapies targeting YAP and related pathways for the prevention and treatment of skin diseases.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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