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Review Article

The Two Faces of SHOC2: Skin Homeostasis Regulator and RAS-MAPK Pathway Enhancer

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Abstract

The signaling pathway composed of RAS-RAF-MEK-ERK proteins regulates essential cellular processes such as cell differentiation, proliferation and migration. This pathway is crucial for embryonic development and tissue homeostasis and it is frequently dysregulated in cancer. The scaffold protein SHOC2 is a key modulator of ERK1/2 signals whose activity depends on its subcellular localization. Recently, SHOC2 has been proposed as a therapeutic target for the treatment of several cancers, either alone or in combination with MEK inhibitors.

In this review we focus on the role of SHOC2 in the epithelial skin biology and its interaction with other partners to better understand the potential consequences of SHOC2 inhibition, particularly regarding skin toxicities. SHOC2 interacts with RAPTOR to limit mTORC1 activation, thereby promoting autophagy and limiting cell growth. Through its association with MRAS and PP1C, SHOC2 controls RAF1 dephosphorylation and modulates ERK output. Loss of SHOC2 disrupts E-cadherin turnover, impairing junctional dynamics and epithelial migration. In vivo, SHOC2 is essential for tissue development as complete knockout in mice results in embryonic lethality. We also discuss other important SHOC2 interactions in the epidermis including SCRIBBLE and ERBIN. SHOC2 acts as a signaling hub connecting RAS-MAPK pathways with epithelial polarity and differentiation. Its spatial regulation ensures proper tissue homeostasis, whereas mutation or mis-localization drives cancer and developmental disorders such as Noonan- like syndrome with loose anagen hair (NSLH) which has ectodermal manifestations. Finally, we review the context-dependent role of SHOC2 in cancer where it can be either upregulated or downregulated. Reduced SHOC2 activity in tumors addicted to ERK signaling may activate compensatory pathways highlighting the essential importance of SHOC2 in skin homeostasis and the potential cutaneous toxicities of SHOC2- targeted therapies.

Keywords: SHOC2; Noonan-Like Syndrome with Loose anagen Hair (NSLH); Skin Homeostasis; Cancer Therapy

Introduction

The skin is a highly specialized organ in which differentiation and proliferation are tightly coordinated to maintain barrier integrity, immune protection and sensory function. It not only shields the body from external insults but also perceives environmental stimuli such as temperature, pressure and pain, transmitting this information to the nervous system. To achieve these complex roles, the skin functions as an integrated system connected to muscles, the immune system and the brain. Structurally, the skin comprises three principal layers: epidermis, dermis and hypodermis. The outermost layer, the epidermis, consists of a multilayered epithelium termed the Interfollicular Epidermis (IFE), interspersed with appendages such as Hair Follicles (HF), sweat glands and sebaceous glands and is composed mainly of keratinocytes arranged in a spatial gradient of differentiation across the deep-to- superficial axis of the tissue. Epidermal maintenance and repair depend on distinct stem cell populations defined by specific anatomical locations and molecular markers. The skin's barrier function relies on cornified keratinocytes and Tight Junctions (TJs), a specialized adhesive structure in the granular layer that ensures epidermal sealing. To

form a functional barrier, basal keratinocytes must undergo a tightly regulated program of morphological and biochemical differentiation culminating in the cornified layer.

Scaffold Proteins and the RAS-MAPK Pathway

The RAS-RAF-MEK-ERK signaling pathway has been implicated in the regulation of keratinocytes proliferation and differentiation in vivo (Eckert et al. 2002) and in vitro [1]. Intracellular signaling networks depend on scaffold proteins that organize kinases and effectors (Fig. 2), thereby modulating the intensity and duration of signaling [2]. Dysregulation of such scaffolds has been implicated in human diseases, particularly cancer [3]. Examples include KSR1, paxillin, IQGAP1, MP1, caveolin-1, Sprouty family proteins and more recently, SHOC2 [4-6]. SHOC2 (also known as Sur8) is a highly conserved scaffold protein expressed in all metazoans that was first discovered in Caenorhabditis elegans. In mammals, it comprises a disordered N-terminal region (~90 amino acids), a core of twenty-one Leucine-Rich Repeats (LRRs) and a short C-terminal tail [7-10]. This horseshoe-shaped structure provides a versatile interaction platform. SHOC2 acts as a positive modulator of ERK activation and two complementary mechanisms have been proposed. Initially, it was proposed to facilitate RAS-RAF interaction [11]. Later, it was shown to form a holo-phosphatase complex with MRAS and the catalytic subunit of Protein Phosphatase 1 (PP1C), which dephosphorylates RAF at a regulatory serine residue (S259 in C-RAF), promoting RAF dimerization and activation [12]. Structural analyses have confirmed this regulatory mechanism [13]. Interactions between RAS-SHOC2-RAF and MRAS-SHOC2-PP1 are mutually exclusive, SHOC2 traps the different components directing them to the membrane [14].

The RAS-MAPK Cascade in Skin Biology

The RAS-RAF-MEK-ERK pathway orchestrates numerous epidermal processes including keratinocyte proliferation, differentiation and migration, as well as melanocyte homeostasis and hair follicle morphogenesis. Fine-tuned oscillations in ERK activity are essential for epidermal equilibrium and adaptive responses during wound healing and regeneration. Either hyperactivation or suppression of ERK signaling disrupts this balance, leading to developmental abnormalities, defective barrier formation or neoplastic transformation [15].

Excessive or sustained ERK activity impairs keratinocyte differentiation, whereas reduced ERK activity facilitates the acquisition of terminal epithelial features [14,16]. It has been demonstrated that Desmoglein-1 (DSG1) promotes keratinocyte differentiation by recruiting ERBIN, which binds SHOC2 and disrupts the RAS-SHOC2 complex. This interference lowers ERK activation and thereby supports epidermal maturation. Patients with mutations in the DSG1 cytoplasmic tail cannot bind ERBIN or SHOC2, leaving SHOC2 free in the cytoplasm and available to enhance ERK responses. Hence, ERK attenuation appears necessary for proper stratification and differentiation of keratinocytes. Consistent with this, SHOC2 overexpression has been shown to prolong ERK activation and promote neurite outgrowth in PC12 cells, whereas SHOC2 depletion impairs NGF-induced differentiation [17].

SHOC2, E-cadherin Dynamics and Epithelial Turnover

Recent findings extend SHOC2's influence beyond classical RAS-MAPK modulation to the control of E-cadherin turnover and epithelial cell migration [18]. Loss of SHOC2 reduces the recycling of E-cadherin at adherens junctions, leading to the stabilization of cell-cell adhesion and impaired epithelial turnover. Mechanistically, this effect arises because the absence of SHOC2 diminishes ERK-mediated phosphorylation of p120-catenin at threonine 310, a modification required to trigger the endocytic recycling of junctional E-cadherin. Without this phosphorylation, E-cadherin remains stably bound to the plasma membrane, restricting collective cell migration and tissue remodeling. The polarity protein SCRIBBLE could also participate in this process, although its contribution remains uncertain [19].

Tissue-Specific Regulation and Disease Relevance

Although SHOC2 was originally described as a general modulator of RAS signaling, accumulating evidence indicates that it also has tissue-specific functions. In the epidermis, SHOC2 serves as a central scaffold linking growth-factor receptor signals to adhesion and polarity complexes, thereby coordinating proliferative and morphogenetic responses (Fig. 1). Its importance for tissue homeostasis is further underscored by the observation that complete SHOC2 knockout in mice results in embryonic lethality, highlighting the essential role of SHOC2-mediated signaling in maintaining epithelial integrity during development. Interest in cutaneous SHOC2 biology intensified following the identification of Noonan Syndrome with Loose Anagen Hair

(NSLAH), caused by a recurrent SHOC2 mutation that introduces a novel myristoylation site, anchoring SHOC2 to the plasma membrane and leading to persistent ERK activation [20].

The dermatologic manifestations of NSLAH highlight the critical requirement for balanced SHOC2-ERK activity in maintaining epidermal and follicular integrity, integrating upstream and feedback controls. The RAS-MAPK cascade is activated by diverse ligands-including EGF, KGF and FGF-through receptor tyrosine kinases (EGFR, FGFR), G-protein-coupled receptors or integrins. C-RAF activity is normally restrained by phosphorylation at Ser259 (Ser365 in B-RAF) and association with 14-3-3 proteins. PP1C and PP2A phosphatases remove this phosphate group, allowing RAF dimerization and membrane recruitment, culminating in phosphorylation of ERK1/2 (Thr202/Tyr204 in ERK1; Thr185/Tyr187 in ERK2). Activated ERK then phosphorylates numerous substrates-over 150 identified- including transcription factors, kinases and cytoskeletal regulators [3].

Interestingly, ERK also phosphorylates SHOC2 at Thr507, targeting it for degradation by the E3 ubiquitin ligase FBXW7. This feedback loop normally prevents sustained signaling, but SHOC2 overexpression or FBXW7 mutations, as reported in lung and pancreatic cancers, disrupt this control, enhancing ERK output and being associated with poor prognosis.

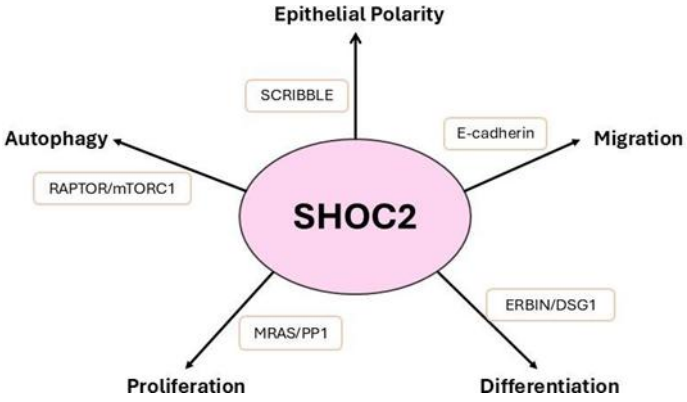

Figure 1: SHOC2 partners and pathways in epidermal regulation. SHOC2 coordinates proliferation, differentiation, migration, epithelial polarity and autophagy through interactions with MRAS/PP1, ERBIN/DSG1, E-cadherin, SCRIBBLE and RAPTOR/mTORC1.

Additionally, MRAS has recently been proposed to act as a "broken switch": recruiting SHOC2 to the plasma membrane for scaffold assembly, while actual RAS activation may depend on other RAS isoforms [6,21].

Other Molecular Patterns of SHOC2

RAPTOR is a core component of the mTORC1 complex, which regulates cell growth, metabolism and autophagy. When mTORC1 signaling is inactive, autophagy is induced. Recent findings indicate that SHOC2 can bind and sequester RAPTOR, thereby preventing mTORC1 activation [22]. As a result, autophagy increases and cell growth is suppressed. This interaction positions SHOC2 as a molecular switch that connects the RAS-MAPK and mTORC1 signaling axes, modulating the balance between proliferation and catabolic processes. Beyond its canonical scaffolding role, SHOC2 has emerged as a critical regulator of tissue homeostasis. SHOC2 fine-tunes the ERK and mTORC1 pathways to maintain lymphatic endothelial cell function, highlighting its broader contribution to cellular balance across different tissues [23].

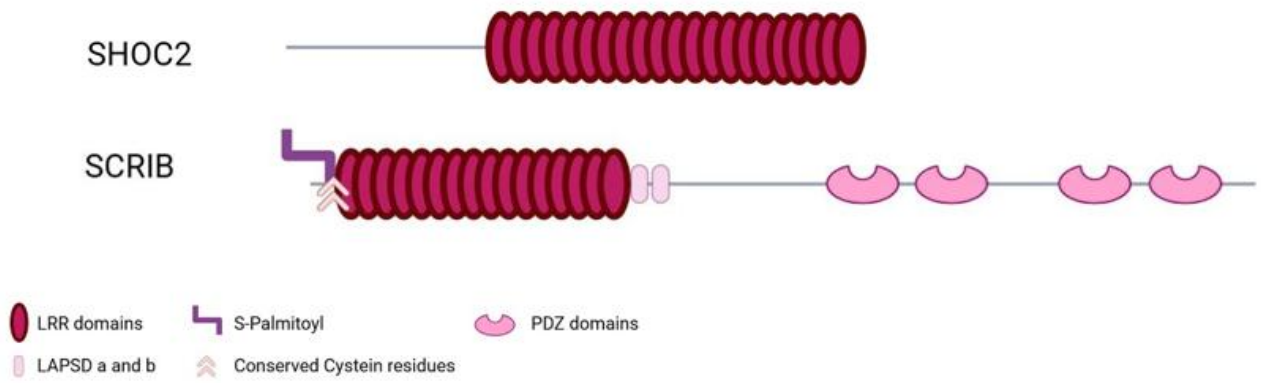

Figure 2: SCRIBBLE LAP protein shares structural homology with the LRR protein SHOC2.

SHOC2 also interacts with other leucine-rich repeat (LRR) scaffold proteins such as ERBIN and SCRIBBLE [24,25]. SCRIBBLE, ERBIN and LANO belong to the LAP family of proteins, characterized by LRR and PDZ domains, which function in junction assembly and cell polarity [26]. These three proteins redundantly regulate epithelial polarity and apical adhesion complex formation [16]. SHOC2 competes with SCRIBBLE for the PP1 phosphatase (preferably the PP1α isoform) [25]. SCRIBBLE antagonizes SHOC2- mediated RAF1 dephosphorylation and SHOC2 binds PP1 efficiently only in the presence of active MRAS, forming a ternary MRAS-SHOC2-PP1 complex [12].

SCRIBBLE is part of the polarity complex SCRIBBLE-DLG-LGLl, localized at the lateral membrane and essential for maintaining epithelial apico-basal polarity [16]. This protein plays a pleiotropic role in tissue homeostasis by interacting with multiple partners and regulating diverse signaling pathways [27]. SCRIBBLE is a known regulator of the ERK cascade, influencing not only cell polarity and migration but also proliferation and apoptosis. Its direct interaction with ERK anchors the kinase at the membrane, preventing its nuclear translocation [28]. Conversely, ERK-mediated phosphorylation of SCRIBBLE leads to its mis-localization from the membrane to the cytoplasm-a shift that, in tumor contexts, converts SCRIBBLE from a tumor suppressor into an pro-oncogenic driver [29].

E-cadherin-mediated adhesion also recruits SCRIBBLE to the basolateral membrane in epithelial cells, coupling polarity to intercellular adhesion. In cancer, SCRIBBLE often becomes mutated, mis-localized or degraded, disrupting this link and contributing to tumor progression. SCRIBBLE was originally identified in Drosophila melanogaster, where its loss produced neoplastic overgrowths in epithelial and neural tissues, highlighting its role as a tumor suppressor [30].

Consistent with these findings, it has been demonstrated that SCRIBBLE is also essential for epidermal homeostasis in vivo [31,32]. In a conditional epidermal SCRIBBLE knockout mouse model (K14-Cre; Scribflox/flox), loss of SCRIBBLE resulted in epidermal disorganization, defective differentiation and basal hyperproliferation, leading to spontaneous hyperplasia and increased susceptibility to chemical carcinogenesis. Mechanistically, SCRIBBLE deficiency caused sustained ERK and AKT activation and E-cadherin destabilization, linking polarity loss to aberrant RAS- ERK signaling. These findings support a model in which SCRIBBLE restrains ERK signaling to preserve epithelial differentiation and tissue integrity. This function complements that of SHOC2, which enhances ERK activation; thus, the balance between SHOC2 and SCRIBBLE activity appears critical for maintaining skin homeostasis and preventing neoplastic transformation. Moreover, since complete SHOC2 knockout in mice is embryonically lethal, SHOC2 is indispensable for developmental homeostasis. SCRIBBLE knockout mouse is also embryonically lethal [33,34].

ERBIN also binds to SHOC2, sequestering it and thereby inhibiting ERK activation. ERBIN interacts with the desmosomal cadherin Desmoglein-1 (DSG1), effectively trapping SHOC2 in this membrane-associated complex. Mutations in ERBIN are linked to striate palmoplantar keratoderma, characterized by thickened skin on palms and soles. Likewise, patients with DSG1 truncations-lacking its cytoplasmic tail-display continuous RAF-MEK-ERK pathway activation, impaired keratinocyte differentiation and reduced SHOC2-ERBIN colocalization. DSG1 normally concentrates ERBIN at the plasma membrane, inhibits ERK and promotes differentiation by disrupting upstream SHOC2-RAS interactions [35].

Together, these observations reinforce that SHOC2 orchestrates the crosstalk between adhesion complexes and ERK signaling and that its activity must be precisely balanced by polarity regulators such as SCRIBBLE and ERBIN to ensure epidermal homeostasis and prevent pathological transformation [36].

SHOC2 in Noonan Syndrome-Like with Loose Anagen Hair (MIM: 607721, 617506)

Noonan syndrome with loose anagen hair (NSLAH) is an autosomal dominant RASopathy that shares many clinical features with Noonan syndrome but presents distinct ectodermal abnormalities [20]. The most characteristic manifestations include easily pluckable, sparse, thin, slow-growing hair (loose anagen hair), hyperpigmented and wrinkled skin, eczema, ichthyosis and other subtle cutaneous and ectodermal alterations. Additional ectodermal traits such as sparse eyebrows and ligamentous laxity with skin changes have also been reported in H/MRAS and PP1 mutants associated with Noonan Syndrome [37].

The syndrome is most commonly caused by the recurrent missense mutation c.4A>G (p.Ser2Gly) in SHOC2, although rare variants have been recently identified [9,20]. Mechanistically, this mutation introduces an aberrant N- myristoylation site that anchors SHOC2 to the plasma membrane lipid rafts, impairing its normal cytoplasmic-nuclear shuttling after growth factor stimulation. The result is enhanced and dysregulated RAS-MAPK signaling, leading to prolonged ERK activation and abnormal control of differentiation. Because ERK signaling is a central regulator of keratinocyte proliferation and differentiation, this dysregulation likely underlies the epidermal and hair follicle defects observed in patients.

Although direct studies in human skin or primary keratinocytes carrying SHOC2 mutations are limited, evidence from animal models supports this pathogenic mechanism. In a zebrafish model expressing SHOC2 S2G, aberrant ERK activation was detected during early embryogenesis, leading to defective craniofacial patterning, cardiac edema and abnormal melanophore migration-phenotypes that closely resemble RAS-MAPK hyperactivation syndromes [36]. These effects were rescued by MEK inhibition, confirming that the SHOC2 S2G mutation acts through constitutive ERK pathway activation.

Together, these findings indicate that the SHOC2 p.Ser2Gly mutation leads to ectopic membrane localization and chronic ERK activation, perturbing epithelial and ectodermal differentiation. This mechanism explains the cutaneous and hair phenotypes of NSLAH and provides an evolutionarily conserved model linking SHOC2-mediated ERK regulation to epithelial integrity.

SHOC2 in Cancer

Considering the RAS-MAPK pathway is central to oncogenesis, SHOC2 has been investigated for its potential role in tumor initiation and/or progression. SHOC2 activity is selectively required for the malignant properties of RAS-mutant tumors, where it promotes polarized migration [25]. SHOC2 is overexpressed in Colorectal Cancer (CRC) and enhances tumorigenic capacity irrespective of KRAS, BRAF or PI3K mutation status [38]. Furthermore, SHOC2 depletion sensitizes RAS-mutant cancers to MEK inhibition, indicating a potential synthetic lethal interaction [39,40].

Treatment with KRAS G12C inhibitors has been shown to induce formation of the MRAS-SHOC2-PP1C complex in KRASG12C-mutant driven non-Small Cell Lung Cancer (NSCLC), highlighting a strong dependence of oncogenic RAS isoforms on SHOC2 for tumor growth and survival [29]. A strong dependence of the oncogenic H/K/N/RAS mutants on SHOC2 for cancer cell growth and survival has also been reported [41]. Likewise, SHOC2 also regulates E-cadherin turnover and cell-cell adhesion during collective cell migration [18].

SHOC2 can interact with the p110α subunit of PI3K, thereby coupling RAS-MAPK and PI3K-AKT [42]. In pancreatic cancer, deletion of the E3 ligase SAG/RBX2, which targets SHOC2 for degradation, results in SHOC2 accumulation and neoplastic cystic lesions, demonstrating its necessity for KRASG12D-driven tumorigenesis [43]. Disruption of the SHOC2-MRAS-PP1C complex induces autophagy inhibition and ER stress-dependent apoptosis, further confirming SHOC2's critical role in tumor cell survival [44].

Interestingly, SHOC2 upregulation has been associated with improved survival in pediatric pre-B acute lymphoid leukemia, possibly due to its modulation of p53- dependent apoptosis following DNA damage [45]. Conversely, in cholangiocarcinoma, lncRNA FALEC suppresses miR-20a-5p-a microRNA targeting SHOC2 mRNA-leading to SHOC2 upregulation and 5-FU resistance [46].

In colorectal adenocarcinoma, SHOC2 appears mostly pro-oncogenic, being overexpressed in tumor tissue and liver metastases [38]. However, some studies report lower SHOC2 levels in tumors relative to normal mucosa and associate this reduction with poor prognosis, suggesting context-dependent functions [47].

In metastatic melanoma tissues, SHOC2 expression correlates with metastatic potential; SHOC2 knockdown reduces invasiveness and modulates resistance to BRAFV600E/NRASQ61K inhibitors, such as vemurafenib [42]. A recently developed small molecule that disrupts SHOC2-NRASQ61 interaction has shown promise as a therapeutic strategy [48,49].

In breast cancer, patients with high expression of SHOC2 have worse overall survival whereas patients with high expression of MALAT1 and SHOC2 show a correlation with paclitaxel resistance [50,51]. SHOC2 inhibition enhances sensitivity of Triple-Negative Breast Cancer (TNBC) cells to everolimus (mTOR inhibitor), suggesting combined therapy may be beneficial [50].

Finally, lung cancer is the only malignancy where gain-of-function SHOC2 mutations have been described [22]. SHOC2 levels modulate response to EGFR Tyrosine Kinase Inhibitors (EGFR-TKIs) in NSCLC and pharmacological depletion (e.g., with Celastrol) phenocopies SHOC2 loss, suppressing tumor growth [52]. Additionally, pan-RAF inhibitors such as LY3009120 can paradoxically activate ERK signaling when combined with KRASG12C inhibition, a process requiring the MRAS- SHOC2 complex [53-55].

Conclusion

SHOC2 emerges as a central master coordinator of RAS-ERK signaling and epithelial architecture. Its dynamic subcellular localization determines its access to partners such as MRAS, PP1C, SCRIBBLE, ERBIN, DSG1 and RAPTOR, enabling SHOC2 to coordinate adhesion, metabolic control and MAPK-dependent signaling. When SHOC2 is mutated, mis-localized or imbalanced relative to other polarity regulators, these tightly coupled networks become uncoupled, leading to loss of epithelial integrity and homeostasis. Beyond its developmental functions, SHOC2 has clear therapeutic relevance. Given its essential role in RAS-driven oncogenic signaling, SHOC2 represents a promising therapeutic target. However, systemic inhibition may compromise skin and epithelial homeostasis, so strategies must be designed with careful consideration of its indispensable function in maintaining epithelial integrity. A deeper understanding of SHOC2's spatial and functional versatility is therefore essential for the development of interventions that balance anti-tumor efficacy with preservation of tissue architecture and function.

Conflict of Interest

The authors declare no conflicts of interest.

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