

Review Article

The Double Life of Shading of Cell 2 (SHOC2): Guardian of Skin Homeostasis and Accomplice of RAS- ERK Signaling

Cristina Ortiz-Gutiérrez¹, María Pilar de Lucas¹, Natasha Zarich¹, Ana Belén Cámara¹, José María Rojas^{1*} Berta Anta^{1*}

¹Unidad de Biología Celular, Unidad Funcional de Investigación de Enfermedades Crónicas (UFIEC), Instituto de Salud Carlos III, Madrid, 28220, Spain

*Correspondence author: Berta Anta and José María Rojas, Unidad de Biología Celular, Unidad Funcional de Investigación de Enfermedades Crónicas (UFIEC), Instituto de Salud Carlos III, Madrid, 28220, Spain; Email: banta@isciii.es; jmrojas@isciii.es

Citation: Ortiz-Gutiérrez C, et al. The Double Life of Shading of Cell 2 (SHOC2): Guardian of Skin Homeostasis and Accomplice of RAS-ERK Signaling. J Reg Med Biol Res. 2025;6(3):1-8.

<https://doi.org/10.46889/JRMBR.2025/>

Received Date: 31-10-2025

Accepted Date: 17-11-2025

Published Date: 24-11-2025



Copyright: © 2025 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CCBY) license (<https://creativecommons.org/licenses/by/4.0/>).

Abstract

The signaling pathway made up of RAS/RAF/MEK/ERK proteins regulates essential cellular aspects such as cell differentiation, proliferation and migration. This extracellular pathway is essential in embryonic development, tissue homeostasis and in cancer is frequently dysregulated. The scaffold protein SHOC2 is a critical modulator of ERK1/2 signals depending on the localization of the protein. Recently SHOC2 has been proposed as a therapeutic target for the treatment of different cancers alone or in combination with MEK inhibitors. In this review we have focus in the role of SHOC2 role in the epithelial skin and in the interaction of SHOC2 with other patters to understand the possible responds to SHOC2 inhibition in relation to skin toxicities.

SHOC2 interacts with RAPTOR to restrain 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 as complete mouse knockout is embryonic lethal. We have discussed other important interaction of SHOC2 in the epidermis: SCRIBBLE and ERBIN. SHOC2 acts as a signaling hub connecting RAS-ERK pathways with epithelial polarity and differentiation. Its spatial regulation ensures proper tissue homeostasis, while mutation or mis-localization drives cancer and developmental disorders as Noonan-Like Syndrome with loose anagen Hair (NSLH) with ectodermal implications. We have made also a profound revision of SHOC2 in cancers, in different context can be upregulate or down regulated. Reduction of this pathway in cancers addicted to ERK signaling can results in activation of others pathways and highlight a key role of SHOC2 in skin homeostasis and the potential skin toxicities of SHOC2 inhibitors.

Keywords: Shading of Cell 2 (SHOC2); Noonan-Like Syndrome with Loose anagen Hair (NSLH); Skin Homeostasis

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: the 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 consists 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-ERK Pathway

The RAS/RAF/MEK/ERK signaling pathway has been implicated in the regulation of keratinocytes proliferation and differentiation *in-vivo* and *in-vitro* [1].

Intracellular signaling networks depend on scaffold proteins that organize kinases and effectors (Fig. 1,2) 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 discovered in *Caenorhabditis elegans*. In mammals, it comprises a disordered N-terminal region (~90 amino acids), a core of 21 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 M-RAS 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-ERK 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. It is demonstrated that Desmoglein-1 (DSG1) promotes keratinocyte differentiation by recruiting ERBIN, which binds SHOC2 and disrupts the RAS-SHOC2 complex [14,16]. This interference lowers ERK activation and thereby supports epidermal maturation. Patients with mutations in the DSG1 cytoplasmic tail can not bind ERBIN nor 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.

SHOC2, E-Cadherin Dynamics and Epithelial Turnover

Recent findings extend SHOC2's influence beyond classical RAS-ERK modulation to the control of E-cadherin turnover and epithelial cell migration [17]. Loss of SHOC2 reduces the recycling of E-cadherin at adherents 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 at 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 [18].

Tissue-Specific Regulation and Disease Relevance

Although SHOC2 was originally described as a general modulator of RAS signaling, accumulating evidence indicates 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. 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 causing persistent ERK activation. 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-ERK 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.

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, disrupts this control, enhancing ERK output and correlating with poor prognosis.

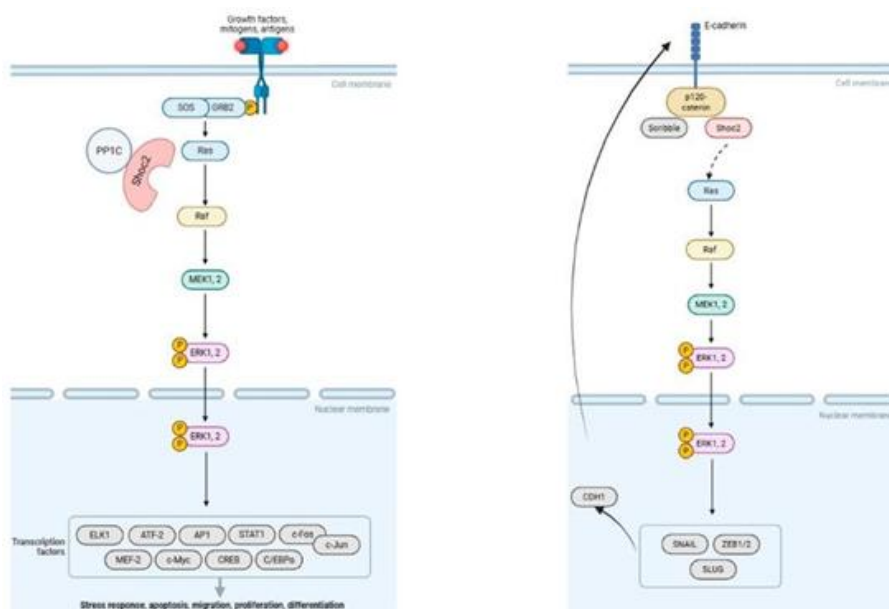


Figure 1: Diagram showing the activation of the mitogenic pathway and the holo-phosphatase complex that consist of SHOC2, PP1 and Ras, activating RAF. It also displayed the effect of E-cadherin turnover and the presence of SCRIBBLE and suspected of SHOC2.

Additionally, M-RAS has recently been proposed to act as a “broken switch”, it recruits SHOC2 to the membrane for scaffold assembly, while actual RAS activation may depend on other RAS isoforms [6,19].

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 [20]. As a result, autophagy increases and cell growth is suppressed. This interaction positions SHOC2 as a molecular switch that connects the RAS-ERK 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 [21].

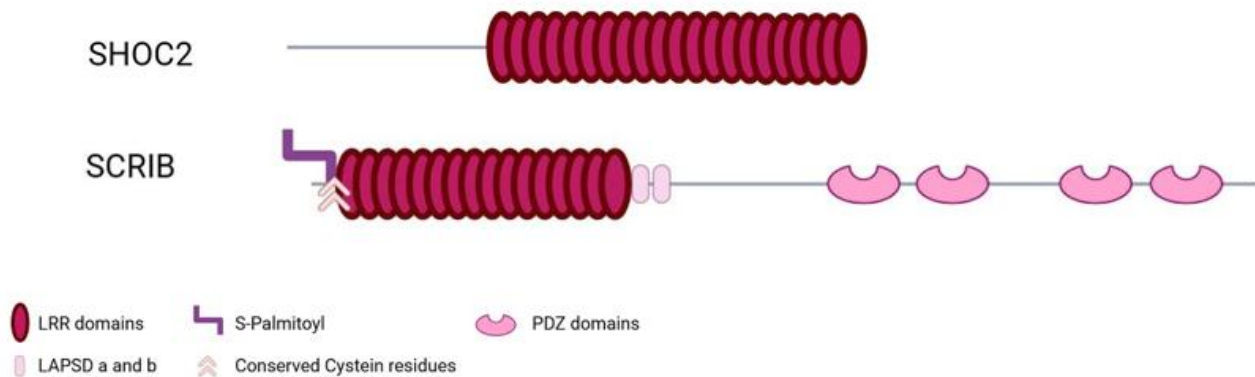


Figure 2: SCRIBBLE LAP protein shares structural homology with the LRR protein SHOC2.

SHOC2 also interacts with other Leucine-Rich Repeat (LRR) scaffold proteins such as ERBIN and SCRIBBLE [22,23]. 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 [24]. These three proteins regulate redundantly epithelial polarity and apical adhesion complex formation [16]. SHOC2 competes with SCRIBBLE for the PP1 phosphatase (preferably the PP1 α isoform) [23]. SCRIBBLE antagonizes SHOC2-mediated RAF1 dephosphorylation and SHOC2 binds PP1 efficiently only in the presence of active M-RAS, forming a ternary M-RAS/SHOC2/PP1 complex [12].

SCRIBBLE is part of the polarity complex SCRIBBLE-DLG-LGL1, 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 [25]. SCRIBBLE is a known regulator of the ERK cascade, influencing not only cell polarity and migration but also proliferation and apoptosis [26]. Its direct interaction with ERK anchors the kinase at the membrane, preventing its nuclear translocation. Conversely, ERK-mediated phosphorylation of SCRIBBLE leads to its mislocalization from the membrane to the cytoplasm—a shift that, in tumor contexts, converts SCRIBBLE from a tumor suppressor into an oncogenic driver [27].

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, mislocalized 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 [28].

Consistent with these findings, it has been demonstrated that SCRIBBLE is also essential for epidermal homeostasis *in-vivo* [29,30]. 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 [31]. SCRIBBLE knockout mice is also embryonically lethal [32].

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 [33].

Together, these observations reinforce that SHOC2 orchestrates the cross-talk 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 [22].

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 [34]. 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 [35].

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 [9,34]. 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 MAPK/ERK 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 evolutionary conserved model linking SHOC2-mediated ERK regulation to epithelial integrity.

SHOC2 in Cancer

Considering the RAS-ERK 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 [23]. SHOC2 is overexpressed in Colorectal Cancer (CRC) and enhances tumorigenic capacity irrespective of KRAS, BRAF or PI3K mutation status [37]. Furthermore, SHOC2 depletion sensitizes RAS-mutant cancers to MEK inhibition, indicating a potential synthetic lethal interaction [38,39].

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 [34]. It has been also detected this strong dependence of the oncogenic mutants H/K/N/Ras on SHOC2 for cancer cells on growth and survival [40]. Likewise, SHOC2 also regulates E-cadherin turnover and cell-cell adhesion during collective cell migration [17]. SHOC2 can interact with the p110 α subunit of PI3K, thereby coupling RAS-ERK and PI3K-AKT signaling [41].

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 [42]. 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 [43].

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 [44]. Conversely, in cholangiocarcinoma, lncRNA FALEC suppresses miR-20a-5p-a microRNA targeting SHOC2 mRNA-leading to SHOC2 upregulation and 5-FU resistance [45].

In colorectal adenocarcinoma, SHOC2 appears mostly pro-oncogenic, being overexpressed in tumor tissue and liver metastases [37]. However, some studies report lower SHOC2 levels in tumors relative to normal mucosa and associate its reduction with poor prognosis, suggesting context-dependent functions [46].

In metastatic melanoma tissues, SHOC2 expression correlates with metastatic potential; SHOC2 knockdown reduces invasiveness and modulates resistance to BRAFV600E/NRASQ61K inhibitors, such as vemurafenib [41]. A recently developed small molecule that disrupts SHOC2-NRASQ61 interaction has shown promise as a therapeutic strategy [47,48].

In breast cancer, patients with high expression of SHOC2 have a worse overall survival, whereas patients with high expression of MALAT1 and SHOC2 correlates with paclitaxel resistance [49,50]. SHOC2 inhibition enhances sensitivity of Triple-Negative Breast Cancer (TNBC) cells to everolimus (mTOR inhibitor), suggesting combined therapy may be beneficial [49].

Finally, lung cancer is the only malignancy where gain-of-function SHOC2 mutations have been described [20]. 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 [51]. Additionally, pan-RAF inhibitors such as LY3009120 can paradoxically activate ERK signaling when combined with KRASG12C inhibition, a process requiring the MRAS- SHOC2 complex [52-54].

Conclusion

SHOC2 emerges as a central regulatory hub integrating RAS-ERK signaling with epithelial proliferation, differentiation and polarity. Its subcellular localization- cytoplasmic, nuclear or membrane-associated-determines its access to partners such as MRAS, PP1C, SCRIBBLE, ERBIN, DSG1 and RAPTOR, linking MAPK signaling to adhesion, metabolism and growth. Mutations or mislocalization of SHOC2 disrupt these networks, uncoupling key homeostatic mechanisms and promoting epithelial disorganization. Beyond its developmental role, SHOC2 represents a promising therapeutic target in ERK- driven cancers. However, systemic inhibition may compromise skin and epithelial homeostasis, as observed with EGFR-targeted therapies. A deeper understanding of SHOC2's spatial and functional versatility is therefore essential to develop interventions that balance anti-tumor efficacy with preservation of tissue integrity.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgement

None.

References

1. Agell N, Bachs O, Rocamora N, Villalonga P. Modulation of the Ras/Raf/MEK/ERK pathway by Ca²⁺ and calmodulin. *Cell Signal*. 2002;14(8):649-54.
2. Kolch W. Coordinating ERK/MAPK signalling through scaffolds and inhibitors. *Nat Rev Mol Cell Biol*. 2005;6(11):827-37.
3. Lavoie H, Therrien M. Regulation of RAF protein kinases in ERK signalling. *Nat Rev Mol Cell Biol*. 2015;16(5):281-98.
4. Cabrita MA, Christofori G. Sprouty proteins, masterminds of receptor tyrosine kinase signaling. *Angiogenesis*. 2008;11(1):53-62.
5. Sebolt-Leopold JS, Herrera R. Targeting the mitogen-activated protein kinase cascade to treat cancer. *Nat Rev Cancer*. 2004;4(12):937-47.
6. Kwon JJ, Hahn WC. A leucine-rich repeat protein provides a SHOC2 the RAS circuit: A structure-function perspective. *Mol Cell Biol*. 2021;41(4):e00627-20.
7. Selfors LM, Schutzman JL, Borland CZ, Stern MJ. Soc-2 encodes a leucine-rich repeat protein implicated in fibroblast growth factor receptor signaling. *Proc Natl Acad Sci U S A*. 1998;95(12):6903-8.
8. Sieburth DS, Sun Q, Han M. SUR-8, a conserved Ras-binding protein with leucine-rich repeats, positively regulates Ras-mediated signaling in *C. elegans*. *Cell*. 1998;94(1):119-30.
9. Motta M, Chillemi G, Fodale V. SHOC2 subcellular shuttling requires the KEKE motif-rich region and N-terminal leucine-rich repeat domain and impacts on ERK signalling. *Hum Mol Genet*. 2016;25(17):3824-35.
10. Bonsor DA, Simanshu DK. Structural insights into the role of SHOC2-MRAS-PP1C complex in RAF activation. *FEBS J*.

2023;290(20):4852-63.

11. Matsunaga-Udagawa R, Fujita Y, Yoshiki S. The scaffold protein SHOC2/SUR-8 accelerates the interaction of Ras and Raf. *J Biol Chem*. 2010;285(10):7818-26.
12. Rodriguez-Viciana P, Oses-Prieto J, Burlingame A, Fried M, McCormick F. A phosphatase holoenzyme comprised of Shoc2/Sur8 and the catalytic subunit of PP1 functions as an M-Ras effector to modulate Raf activity. *Mol Cell*. 2006;22(2):217-30.
13. Liao NPD, Johnson MC, Izadi S. Structural basis for SHOC2 modulation of RAS signalling. *Nature*. 2022;609(7926):400-407.
14. Boned del Río I, Young LC, Sari S. SHOC2 complex-driven RAF dimerization selectively contributes to ERK pathway dynamics. *Proc Natl Acad Sci U S A*. 2019;116(27):13330-39.
15. Wortzel I, Seger R. The ERK cascade: Distinct functions within various subcellular organelles. *Genes Cancer*. 2011;2(3):195-209.
16. Choi J, Troyanovsky RB, Indra I, Mitchell BJ, Troyanovsky SM. SCRIBBLE, ERBIN and Lano redundantly regulate epithelial polarity and apical adhesion complex. *J Cell Biol*. 2019;218(7):2277-93.
17. Kota P, Terrell EM, Ritt DA, Insinna C, Westlake CJ, Morrison DK. M-Ras/SHOC2 signaling modulates E-cadherin turnover and cell-cell adhesion during collective cell migration. *Proc Natl Acad Sci USA*. 2019;116(9):3536-45.
18. Chann AS, Chen Y, Kinwel T, Humbert PO, Russell SM. SCRIBBLE and E-cadherin cooperate to control symmetric daughter cell positioning by multiple mechanisms. *J Cell Sci*. 2023;136(2):jcs260547.
19. Bernal Astrain G, Strakhova R, Jo CH, Teszner E, Killoran RC, Smith MJ. The small GTPase MRAS is a broken switch. *Nat Commun*. 2025;16(1):647.
20. Xie CM, Tan M, Lin XT. The FBXW7-SHOC2-Raptor axis controls the cross-talks between the RAS-ERK and mTORC1 signaling pathways. *Cell Rep*. 2019;26(11):3037-50.
21. Wilson P, Vishwakarma V, Norcross R. Signaling scaffold SHOC2 regulates lymphangiogenesis by suppressing mTORC1-mediated IFN responses. *bioRxiv*. 2025.
22. Jang H, Stevens P, Gao T, Galperin E. The leucine-rich repeat signaling scaffolds ShOC2 and ERBIN: Cellular mechanism and role in disease. *FEBS J*. 2021;288(3):721-39.
23. Young LC, Hartig N, Muñoz-Alegre M. An MRAS, SHOC2 and SCRIB complex coordinates ERK pathway activation with polarity and tumorigenic growth. *Mol Cell*. 2013;52(5):679-92.
24. Santoni MJ, Kashyap R, Camoin L, Borg JP. The SCRIBBLE family in cancer: Twentieth anniversary. *Oncogene*. 2020;39(47):7019-33.
25. Stephens R, Lim K, Portela M, Kvensakul M, Humbert PO, Richardson HE. The SCRIBBLE cell polarity module in the regulation of cell signaling in tissue development and tumorigenesis. *J Mol Biol*. 2018;430(19):3585-612.
26. Nagasaka K, Massimi P, Pim D. The mechanism and implications of hScrib regulation of ERK. *Small GTPases*. 2010;1(2):108-12.
27. Adachi Y, Kimura R, Hirade K. SCRIBBLE mis-localization induces adaptive resistance to KRAS G12C inhibitors through feedback activation of MAPK signaling mediated by YAP-induced MRAS. *Nat Cancer*. 2023;4(6):829-43.
28. Bilder D, Li M, Perrimon N. Cooperative regulation of cell polarity and growth by Drosophila tumor suppressors. *Science*. 2000;289(5476):113-16.
29. Pearson HB, McGlinn E, Phesse TJ. The polarity protein Scrib mediates epidermal development and exerts a tumor suppressive function during skin carcinogenesis. *Mol Cancer*. 2015;14:169.
30. Yamben IF, Rachel RA, Shatadal S. Scrib is required for epithelial cell identity and prevents epithelial to mesenchymal transition in the mouse. *Dev Biol*. 2013;384(1):55-67.
31. Yi J, Chen M, Wu X. Endothelial SUR-8 acts in an ERK-independent pathway during atrioventricular cushion development. *Dev Dyn*. 2010;239(7):2005-13.
32. Murdoch JN, Henderson DJ, Doudney K. Disruption of SCRIBBLE (Scrb1) causes severe neural tube defects in the circletail mouse. *Hum Mol Genet*. 2003;12(2):87-98.
33. Harmon RM, Simpson CL, Johnson JL. Desmoglein-1/ERBIN interaction suppresses ERK activation to support epidermal differentiation. *J Clin Invest*. 2013;123(4):1556-70.
34. Cordeddu V, Di Schiavi E, Pennacchio LA. Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. *Nat Genet*. 2009;41(9):1022-6.
35. Gripp KW, Aldinger KA, Bennett JT. A novel rasopathy caused by recurrent de novo missense mutations in PPP1CB closely

- resembles Noonan syndrome with loose anagen hair. *Am J Med Genet A*. 2016;170(9):2237-47.
36. Jang H, Oakley E, Forbes-Osborne M. Hematopoietic and neural crest defects in zebrafish *shoc2* mutants: A novel vertebrate model for Noonan-like syndrome. *Hum Mol Genet*. 2019;28(3):501-14.
 37. Lee YM, Kaduwal S, Lee KH, Park JC, Jeong WJ, Choi KY. Sur8 mediates tumorigenesis and metastasis in colorectal cancer. *Exp Mol Med*. 2016;48(7):e249.
 38. Wang T, Yu H, Hughes NW. Gene essentiality profiling reveals gene networks and synthetic lethal interactions with oncogenic Ras. *Cell*. 2017;168(5):890-903.
 39. Sulahian R, Kwon JJ, Walsh KH. Synthetic lethal interaction of SHOC2 depletion with MEK inhibition in RAS-driven cancers. *Cell Rep*. 2019;29(1):118-34.
 40. Tsherniak A, Vazquez F, Montgomery PG. Defining a cancer dependency map. *Cell*. 2017;170(3):564-76.
 41. Kaduwal S, Jeong WJ, Park JC. Sur8/Shoc2 promotes cell motility and metastasis through activation of Ras-PI3K signaling. *Oncotarget*. 2015;6(32):33091-105.
 42. Tan M, Chang Y, Liu X. The Sag-Shoc2 axis regulates conversion of mPanINs to cystic lesions in KRAS pancreatic tumor model. *Cell Rep*. 2022;41(12):111837.
 43. Montenegro MF, Martí-Díaz R, Navarro A. Targeting protein methylation in pancreatic cancer cells results in KRAS signaling imbalance and inhibition of autophagy. *Cell Death Dis*. 2023;14(11):761.
 44. Silveira VS, Borges KS, Santos VS. SHOC2 scaffold protein modulates daunorubicin-induced cell death through p53 modulation in lymphoid leukemia cells. *Sci Rep*. 2020;10(1):15193.
 45. Du H, Hou S, Zhang L, Liu C, Yu T, Zhang W. LncRNA FALEC increases the proliferation, migration and drug resistance of cholangiocarcinoma through competitive regulation of miR-20a-5p/SHOC2 axis. *Aging*. 2023;15(9):3759-70.
 46. Piepoli A, Palmieri O, Maglietta R. The expression of leucine-rich repeat gene family members in colorectal cancer. *Exp Biol Med*. 2012;237(10):1123-8.
 47. Kaplan FM, Kugel CH, Dadpey N, Shao Y, Abel EV, Aplin AE. SHOC2 and CRAF mediate ERK1/2 reactivation in mutant NRAS-mediated resistance to RAF inhibitor. *J Biol Chem*. 2012;287(50):41797-807.
 48. Hauseman ZJ, Stauffer F, Beyer KS. Targeting the SHOC2-RAS interaction in RAS-mutant cancers. *Nature*. 2025;642(8066):232-41.
 49. Geng W, Cao M, Dong K, An J, Gao H. SHOC2 mediates the drug-resistance of triple-negative breast cancer cells to everolimus. *Cancer Biol Ther*. 2023;24(1):2206362.
 50. Shi C, Ren S, Zhao X, Li Q. lncRNA MALAT1 regulates the resistance of breast cancer cells to paclitaxel via the miR-497-5p/SHOC2 axis. *Pharmacogenomics*. 2022;23(18):973-85.
 51. Terai H, Hamamoto J, Emoto K. SHOC2 is a critical modulator of sensitivity to EGFR-TKIs in non-small cell lung cancer cells. *Mol Cancer Res*. 2021;19(2):317-28.
 52. Jones GG, Boned del Río I, Sari S. SHOC2 phosphatase-dependent RAF dimerization mediates resistance to MEK inhibition in RAS-mutant cancers. *Nat Commun*. 2019;10(1):2532.
 53. Eckert RL, Efimova T, Dashti SR. Keratinocyte survival, differentiation and death: Many roads lead to mitogen-activated protein kinase. *J Invest Dermatol Symp Proc*. 2002;7(1):36-40.
 54. Motta M, Solman M, Bonnard AA. Expanding the molecular spectrum of pathogenic SHOC2 variants underlying Mazzanti syndrome. *Hum Mol Genet*. 2022;31(16):2766-78.