Topical sulforaphane ameliorates atopic dermatitis by enhancing keratinocyte barrier function

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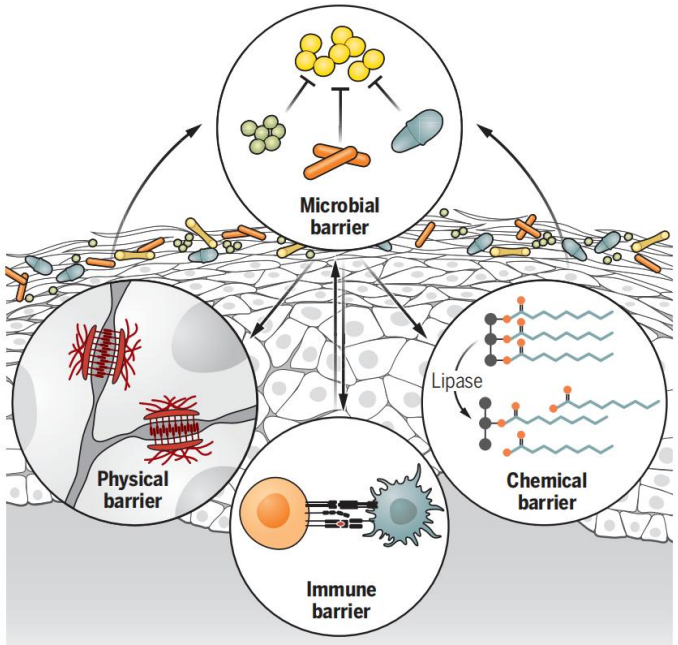
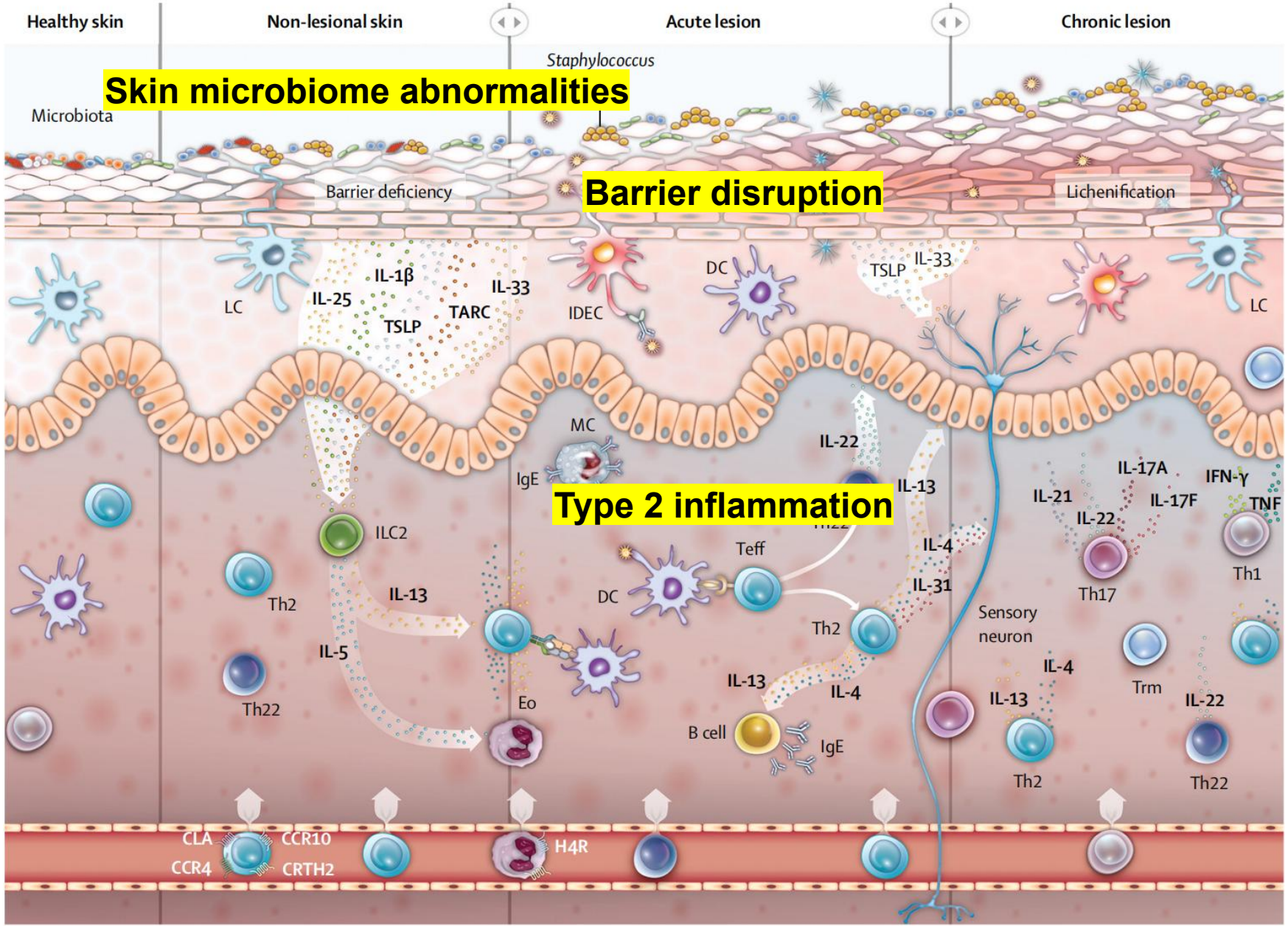
Pathogenesis and pathophysiology of AD

Mechanism of AD----a complex interplay between:

- Genomic background
- Dysfunctional epidermal barrier
- Skin microbiome abnormalities
- Predominantly type-2-skewed immune dysregulation

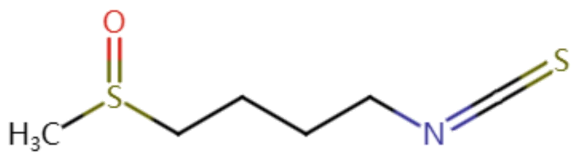


The Lancet, 396, 10247, 345 - 360.
Science 376, 940–945 (2022).



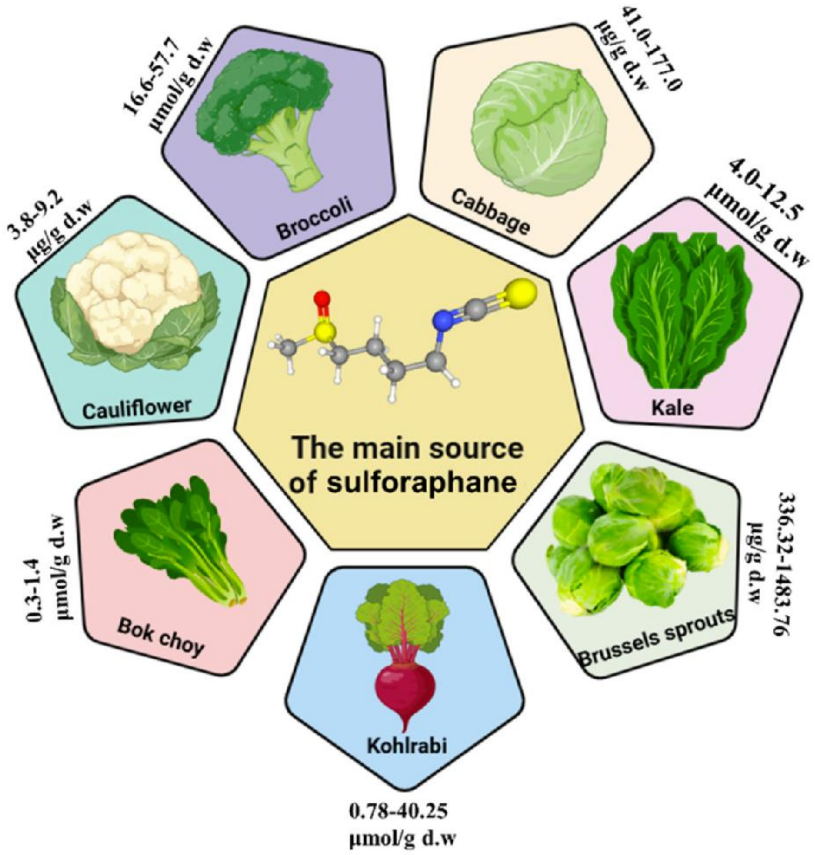
Sulforaphane (SFN)

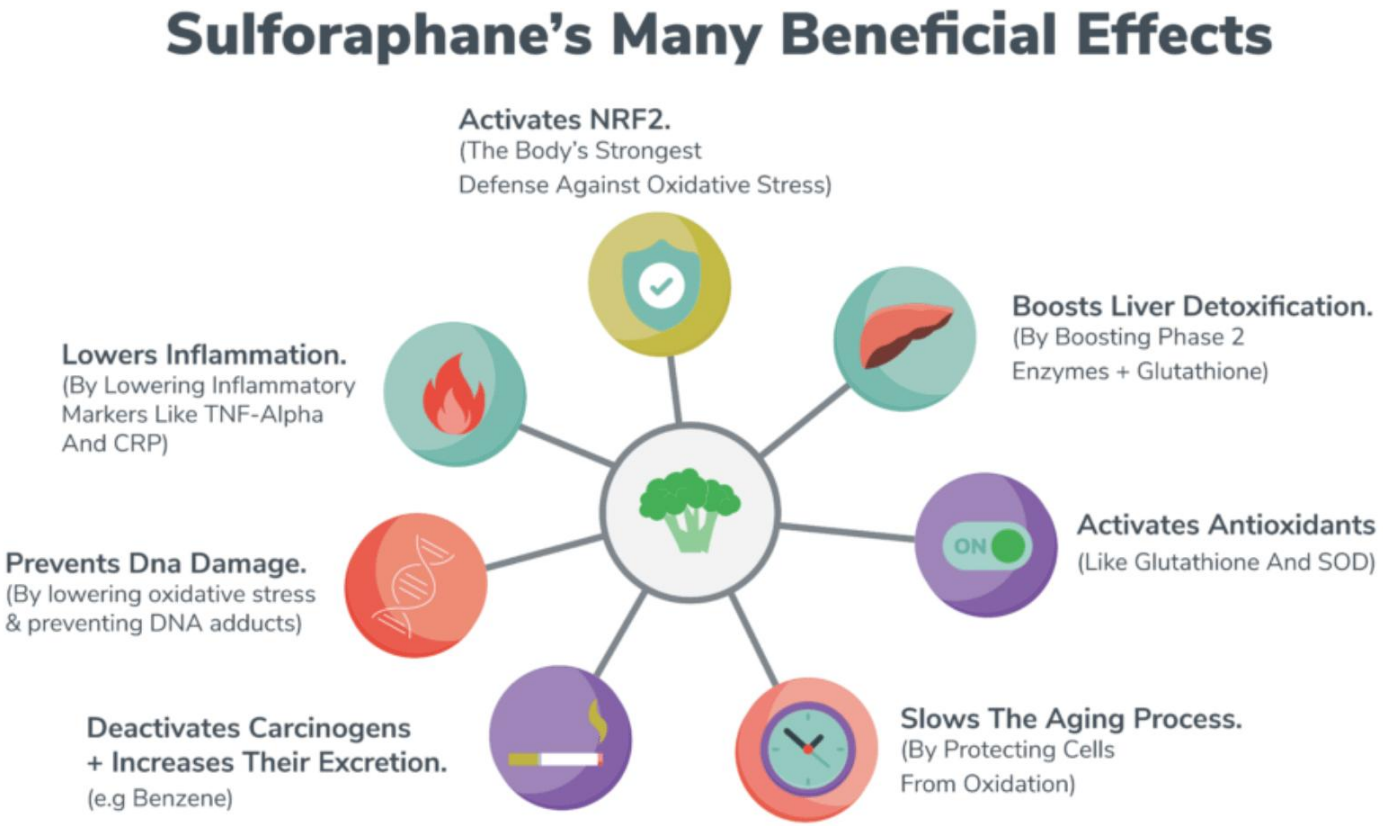
- Sulforaphane (SFN)----a bioactive compound mainly derived from brassica/cruciferous family, renowned for antioxidant, anti-tumor, anti-angiogenic, and anti-inflammatory activities.



The molecular structure of SFN

Properties	
Chemical formula	$C_6H_{11}NOS_2$
Molar mass	177.29 g/mol





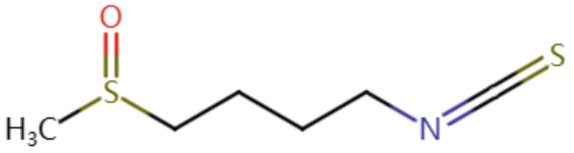
Objectives

- To investigate the potential effects of topical SFN on AD pathogenesis
- To clarify the possible mechanism of SFN-mediated role in AD

Study design (topical SFN application)

Topical application of MC903

Ctrl group (Ethanol)
AD group (MC903)
Topical SFN group (MC903 + topical SFN)



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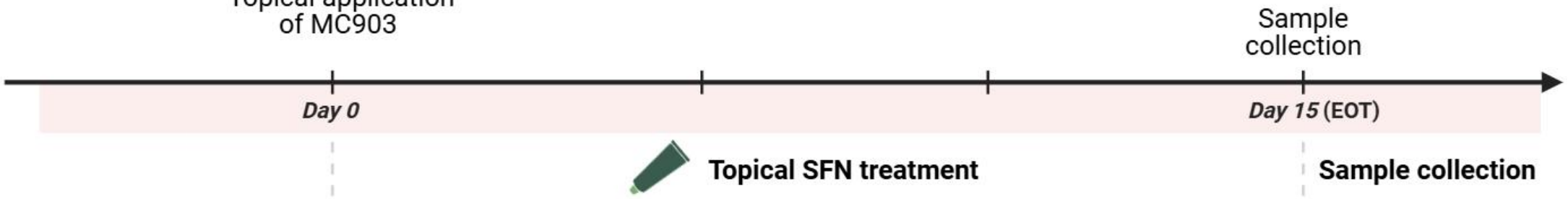
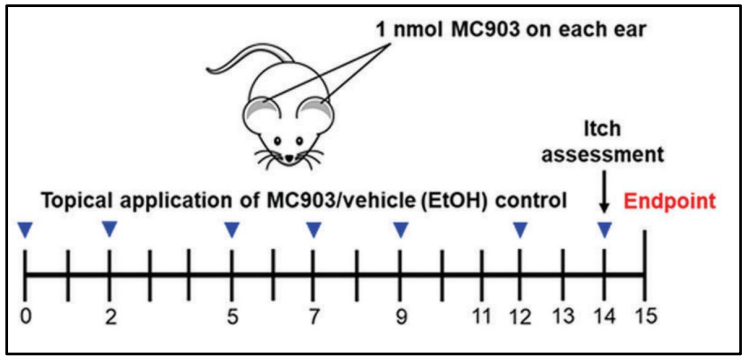


MC903 application

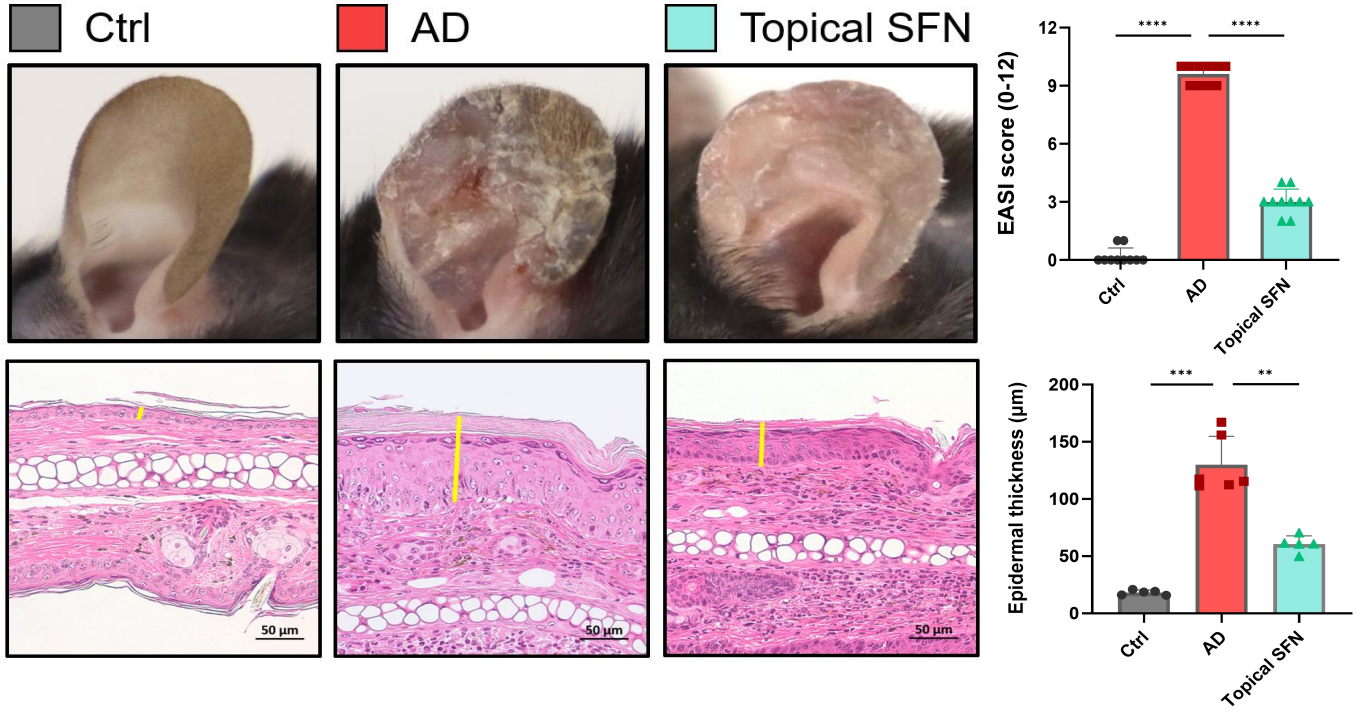


Alam, M. J., et al. Current Protocols, 2023, 3, e695.

Topical SFN preparation: 1% (diluted with ethnol)

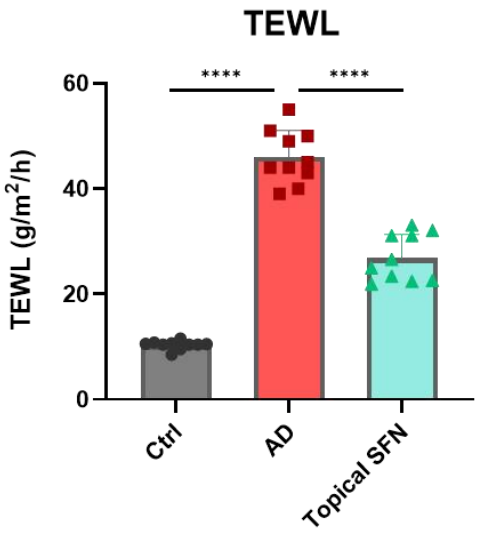
Frequency: after topical MC903 application (at least 2 hour interval)

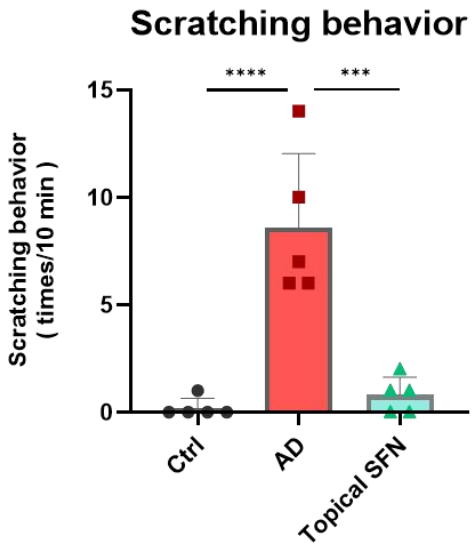
Topical SFN alleviates symptoms in AD murine model

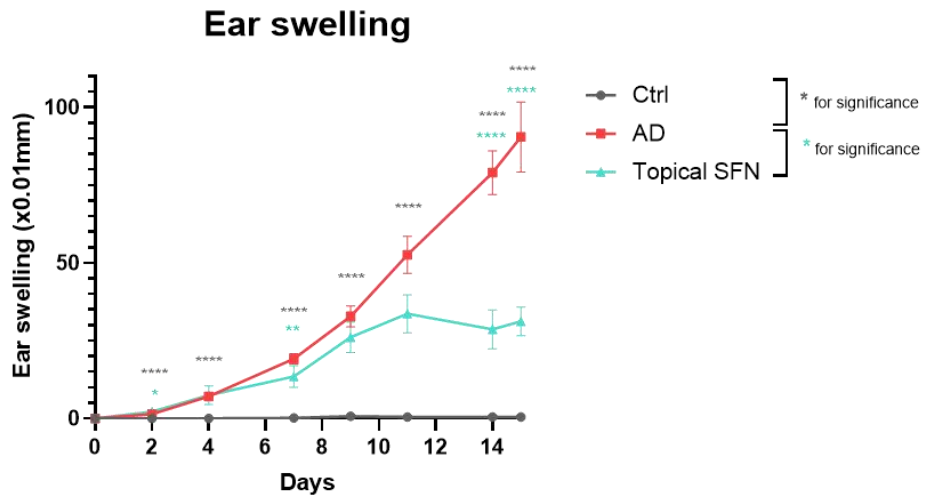


Topical SFN mice showed:

- ✓ Lower EASI score
- ✓ Lower TEWL
- ✓ Reduced ear thickness
- ✓ Slight itching symptoms
- ✓ Milder pathological inflammation and reduced epidermal thickness

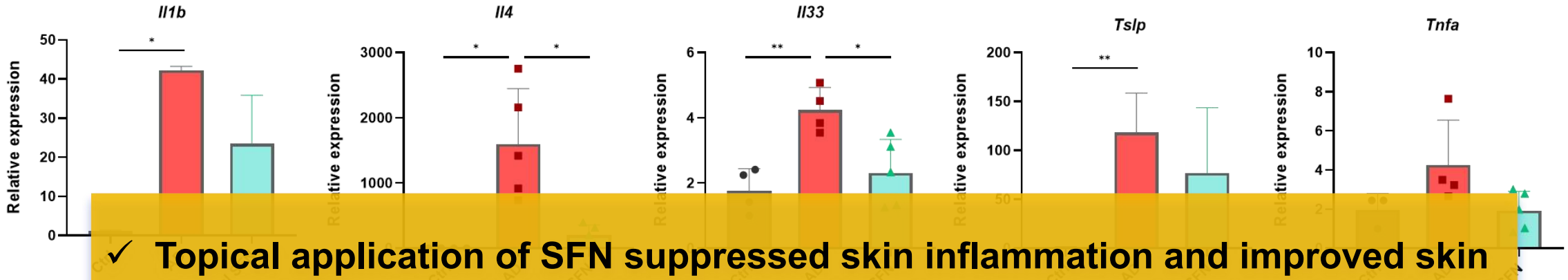






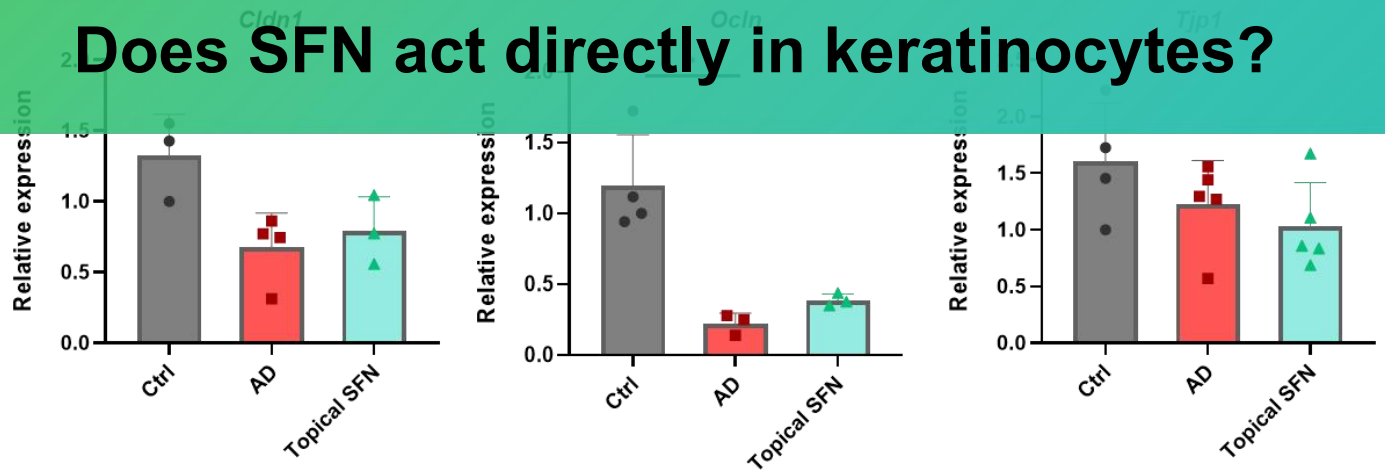
Topical SFN regulates the expression of inflammation- and barrier-related genes in AD lesional skin

Topical SFN downregulates inflammation-related genes



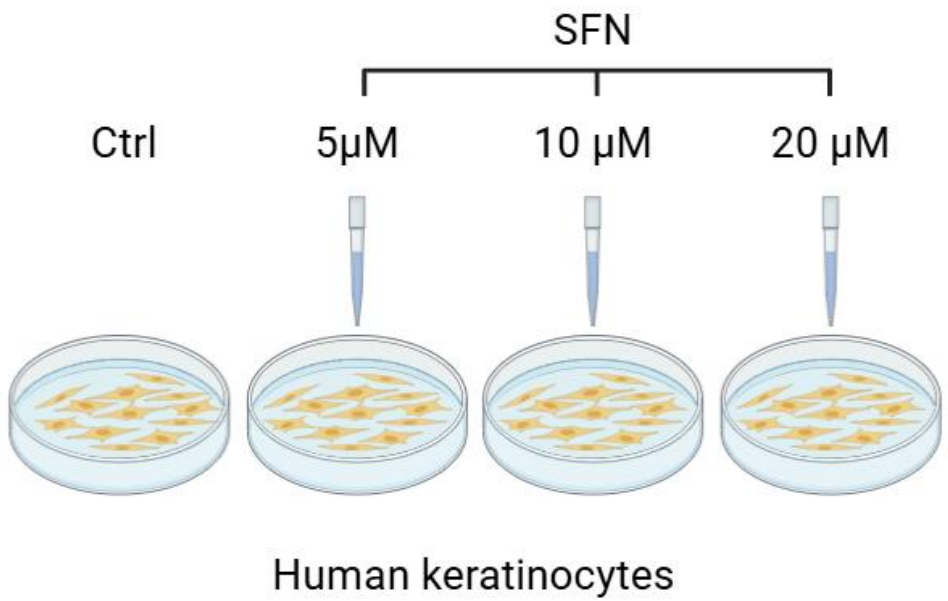
✓ **Topical application of SFN suppressed skin inflammation and improved skin barrier in an AD murine model**

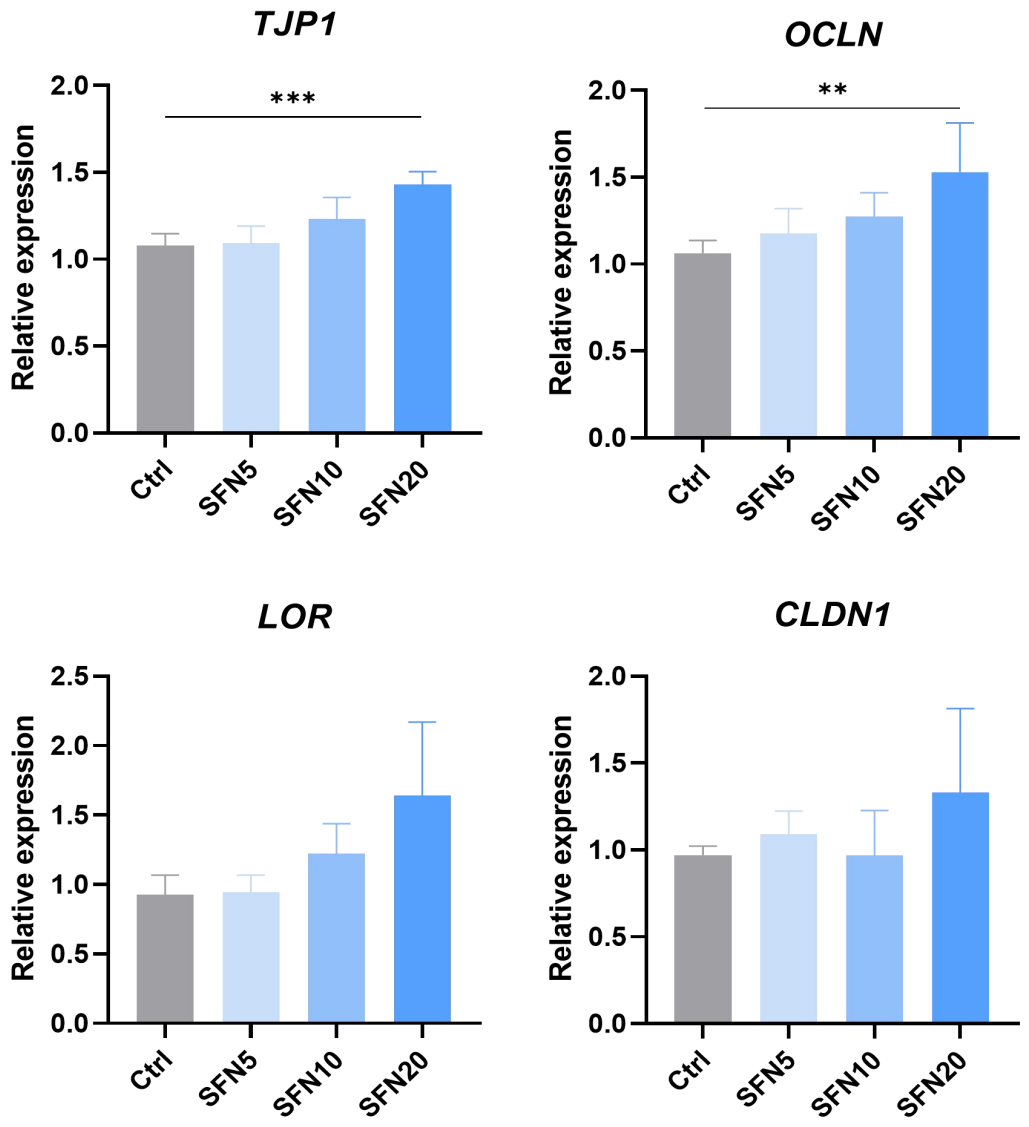
Does SFN act directly in keratinocytes?



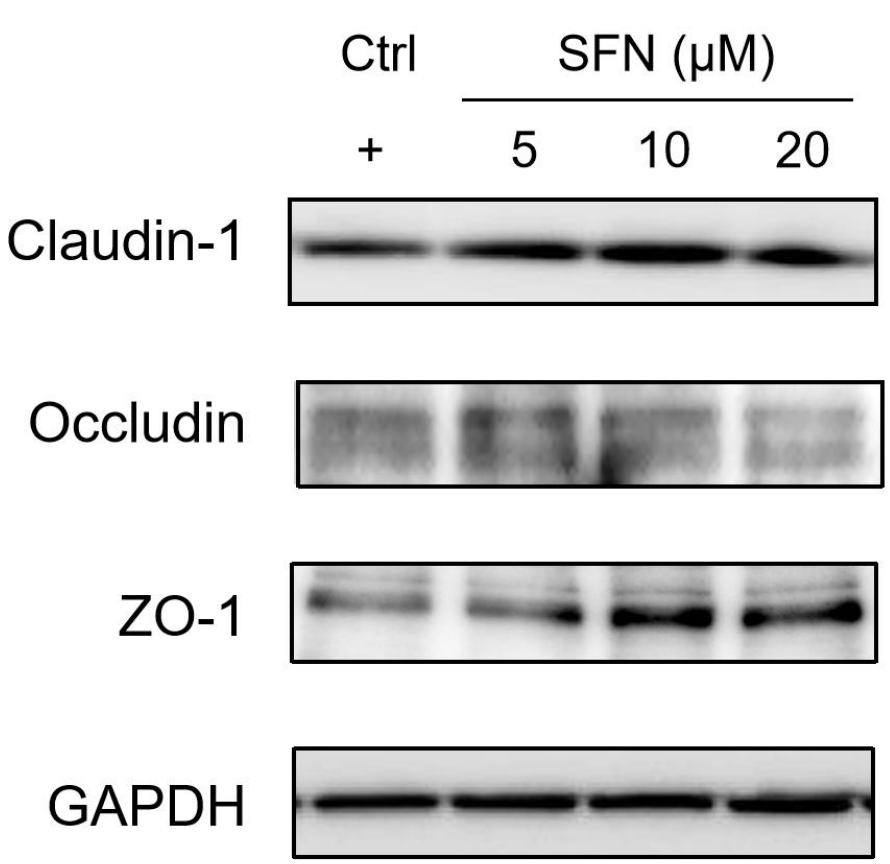
Topical SFN tends to upregulate barrier-related genes

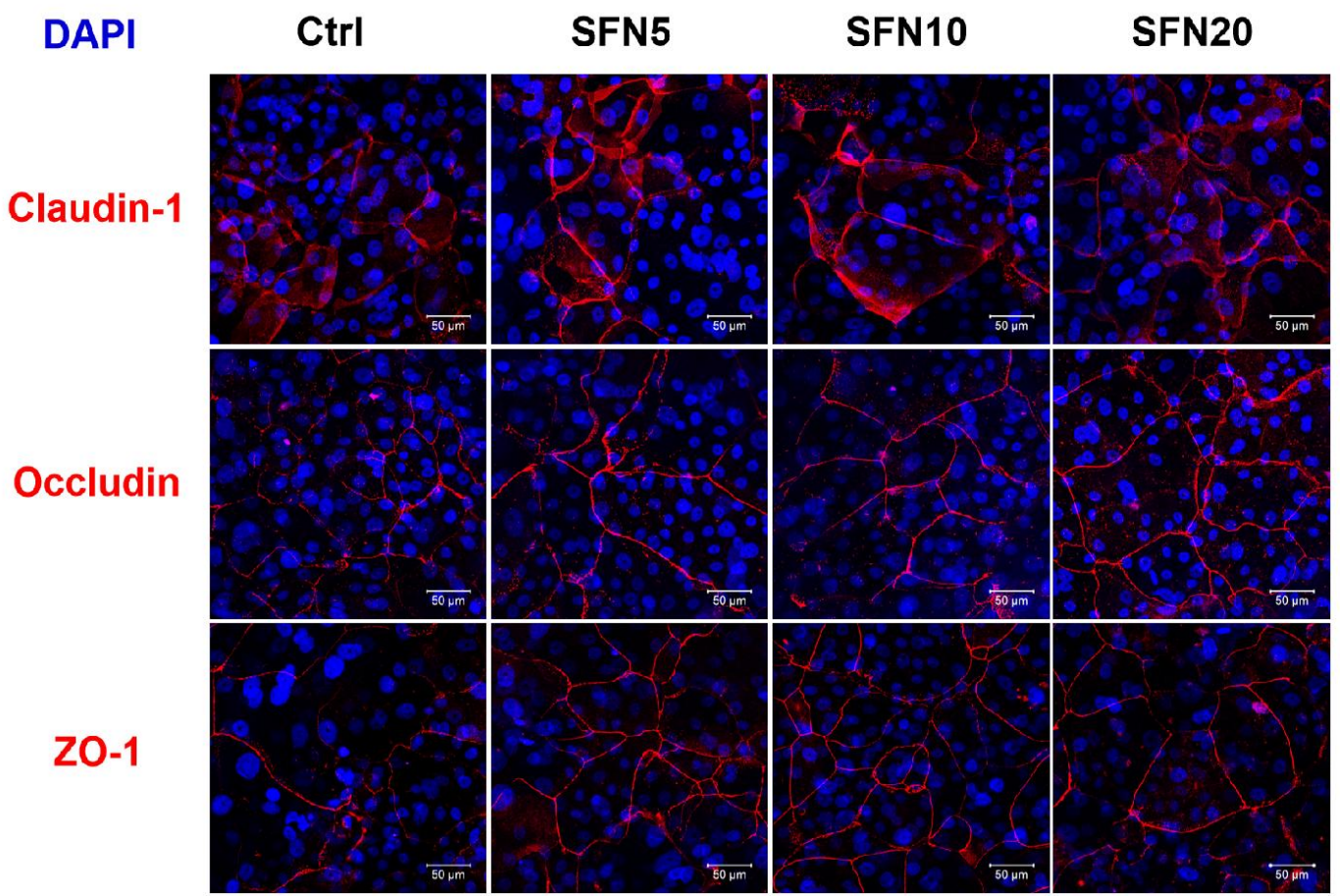
SFN enhances the expression of skin barrier-related genes in human keratinocytes





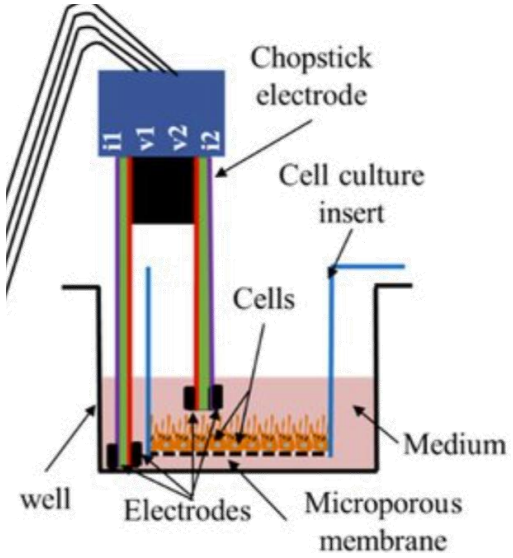
SFN upregulates the skin barrier-related protein expression in human keratinocytes

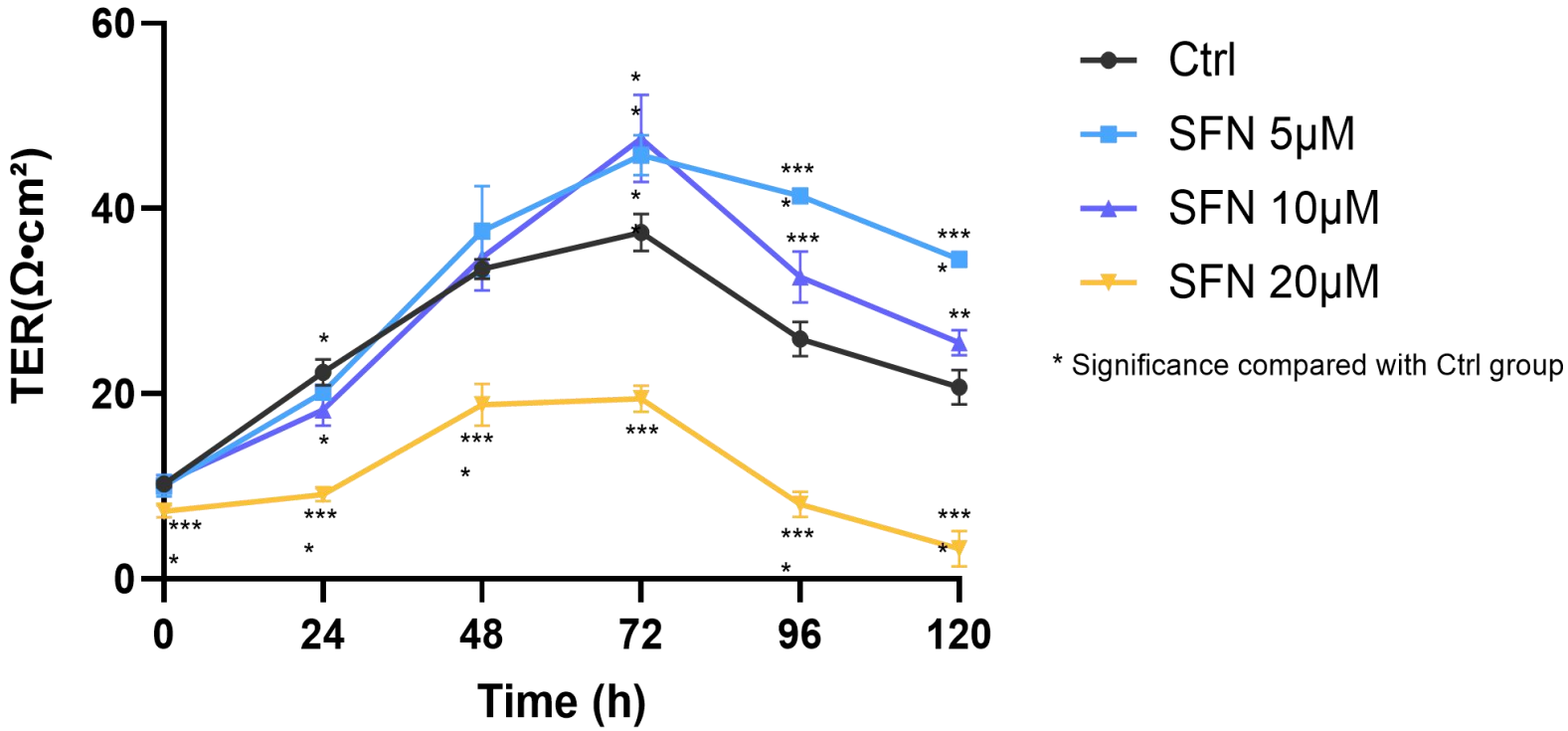




SFN enhances transepithelial electrical resistance (TER) in keratinocyte monolayers

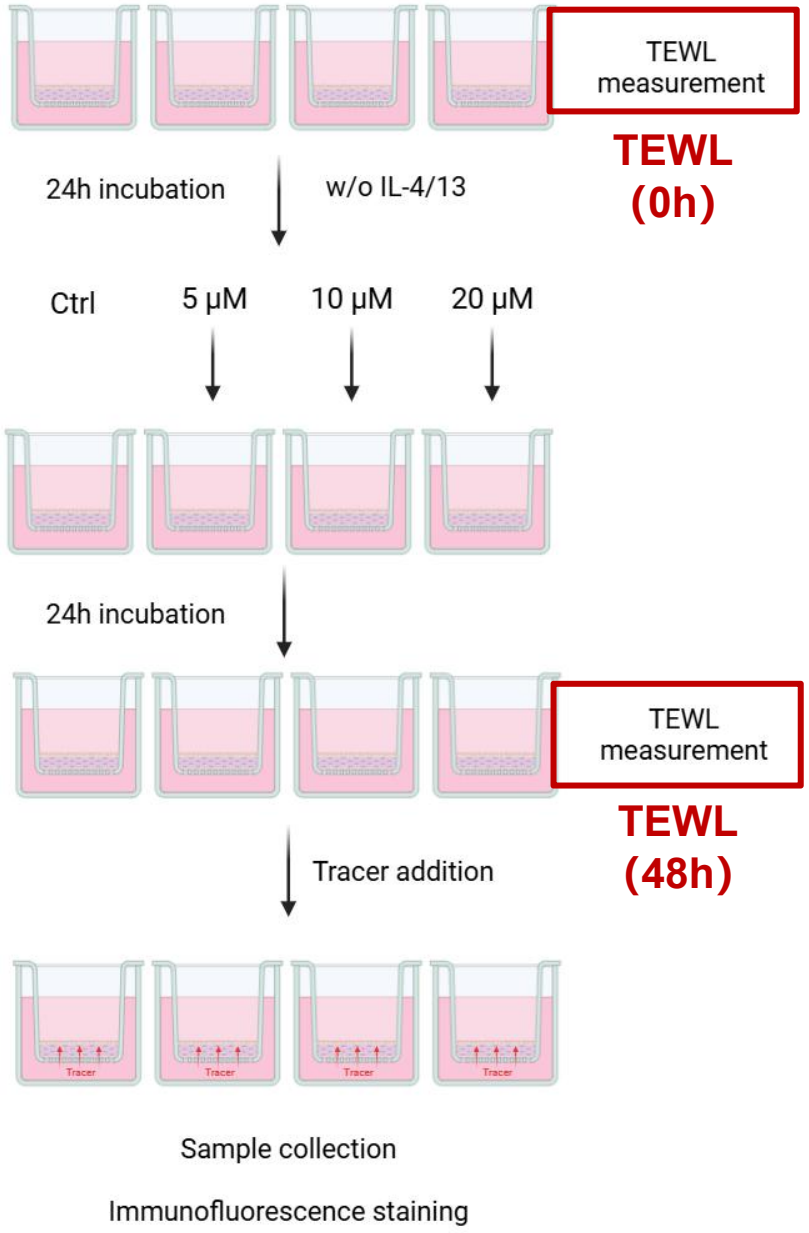
TER is positively correlated with tight junction barrier function



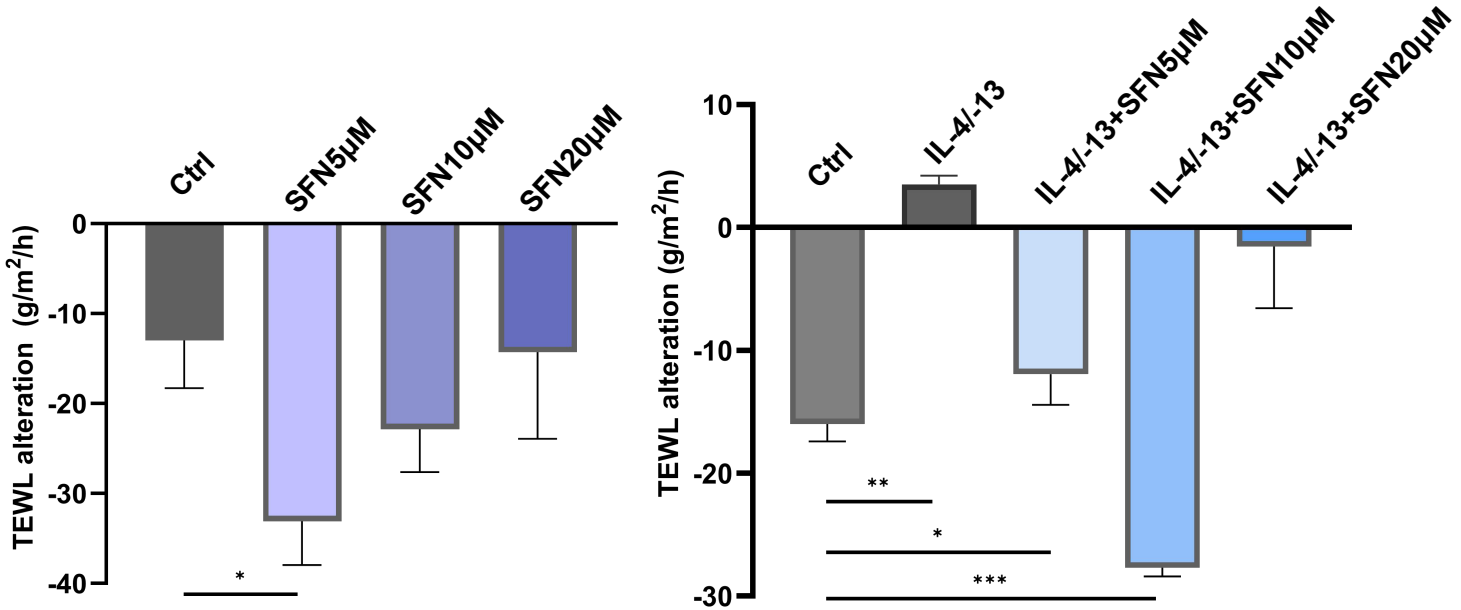


* Significance compared with Ctrl group

SFN reduces the TEWL in 3D-cultured human skin models



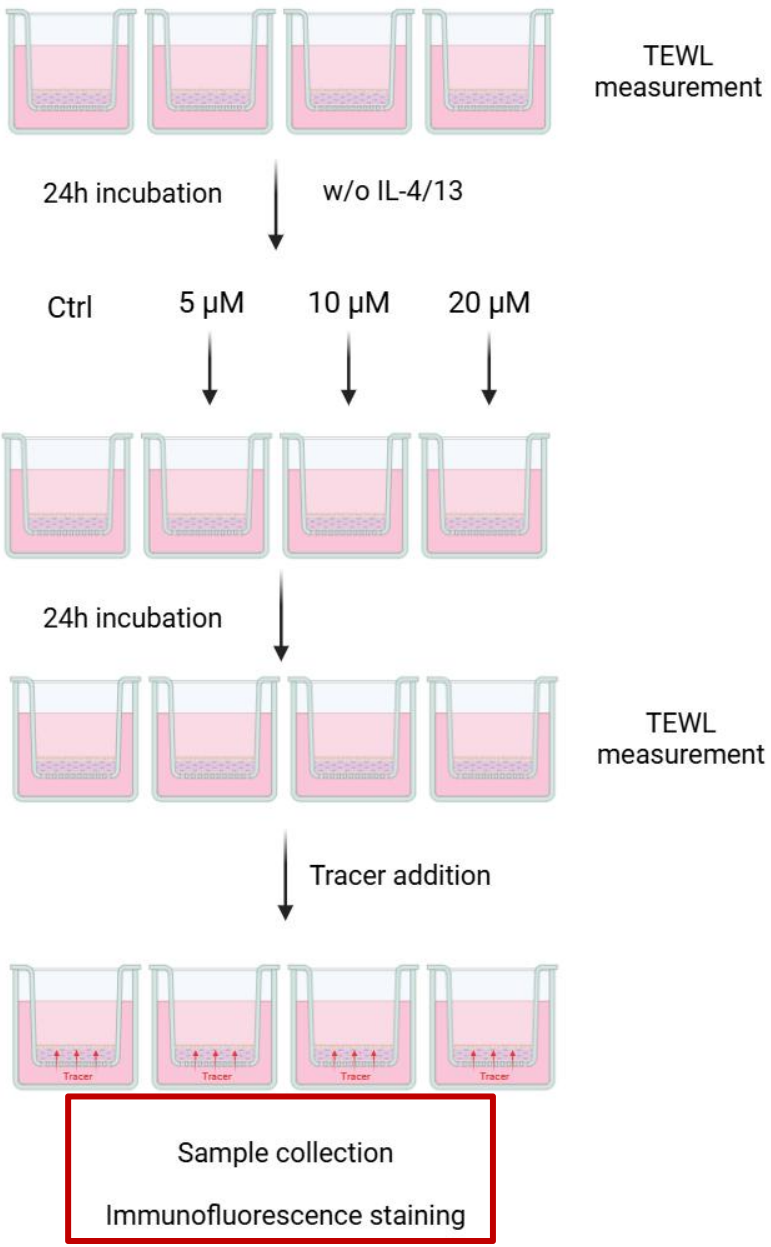
TEWL alteration = TEWL (48h) - TEWL (0h)



SFN reduced the TEWL in 3D-cultured human skin models:

- ✓ Both in normal and IL-4/-13 induced AD in-vitro model
- ✓ SFN 5μM and 10μM are optimal concentration

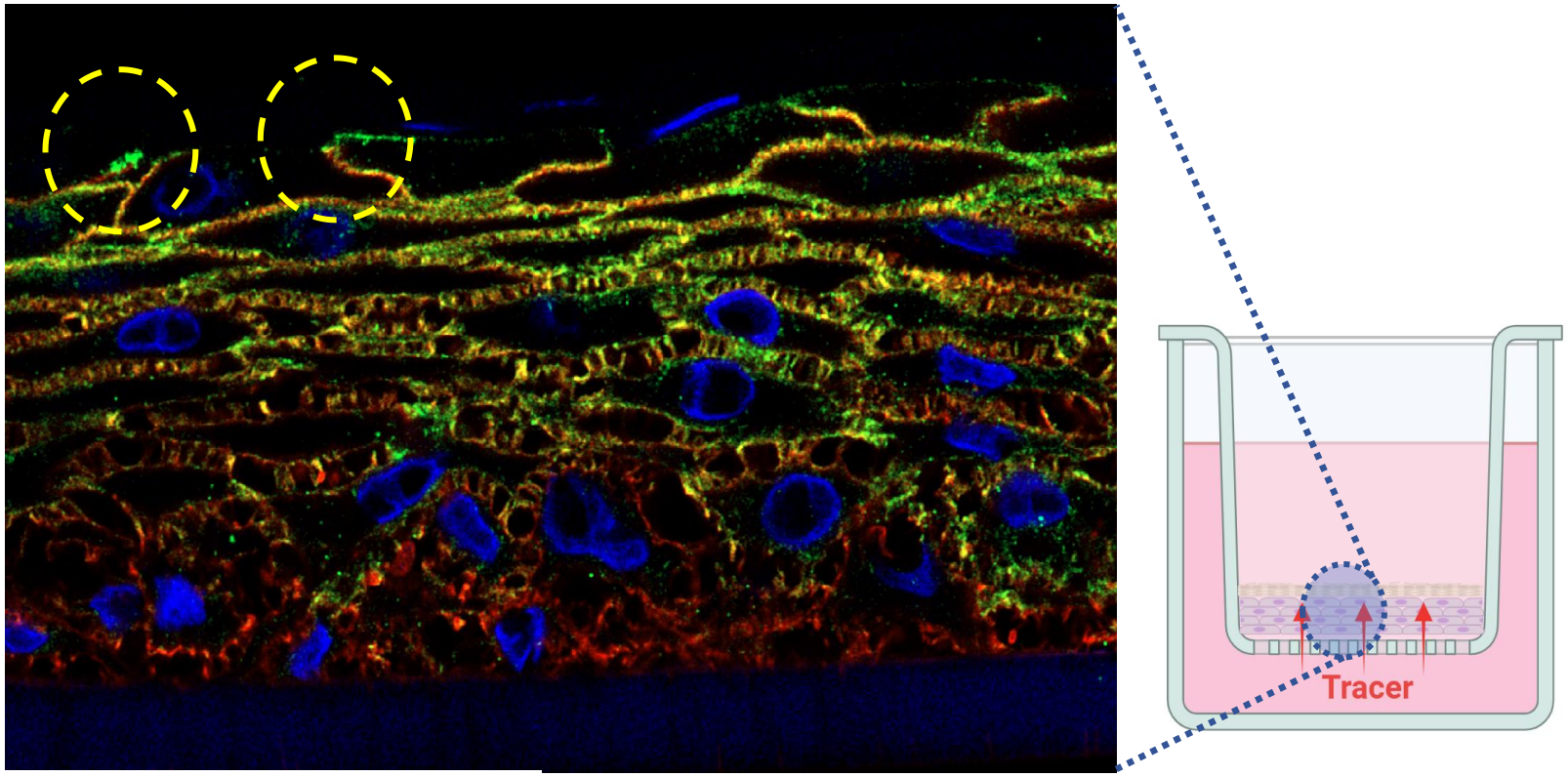
SFN enhances tight junction barrier by blocking the tracer penetration



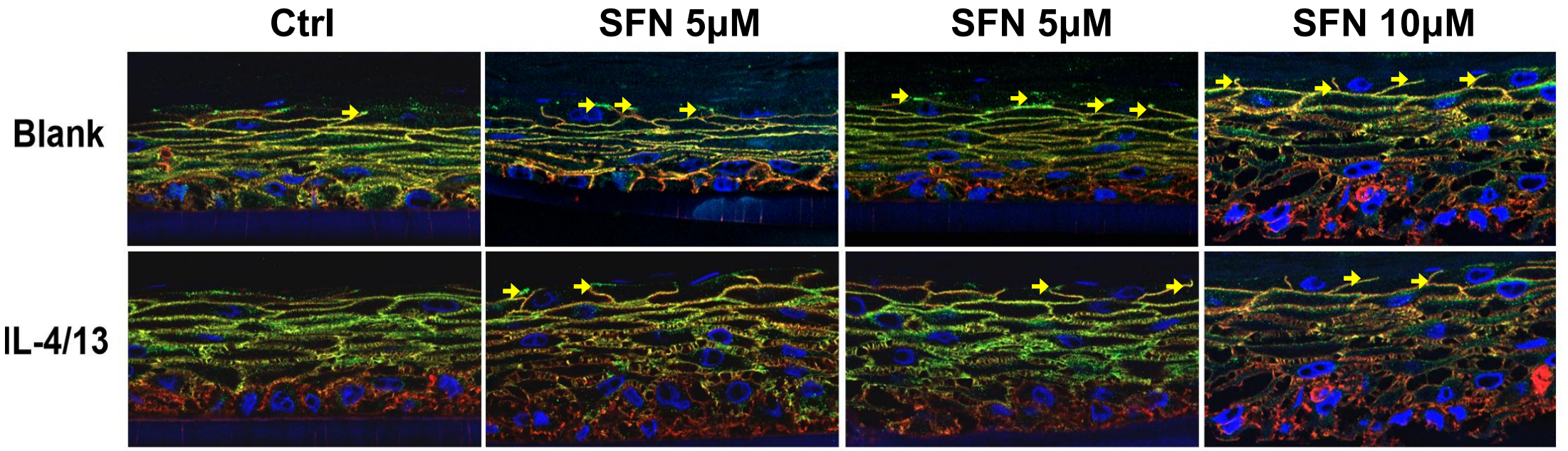
"Biotin stop"

----Refers to the site at which a biotin-based tracer is blocked by tight junctions (marked by claudin-1) in 3D skin models, indicating barrier integrity.

The more, the better barrier intergrity.

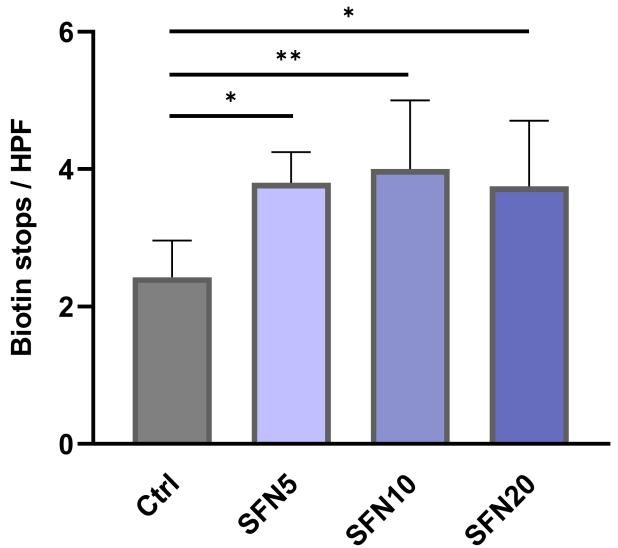


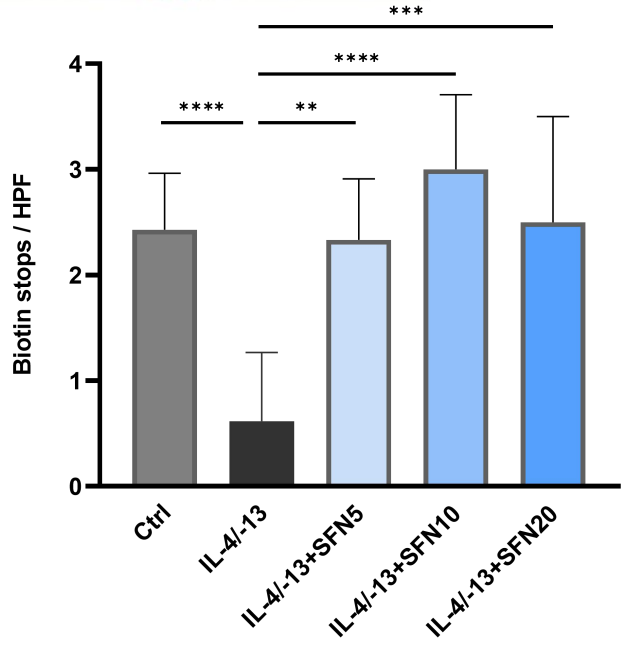
SFN increases the barrier intergrity in 3D cultured human skin model



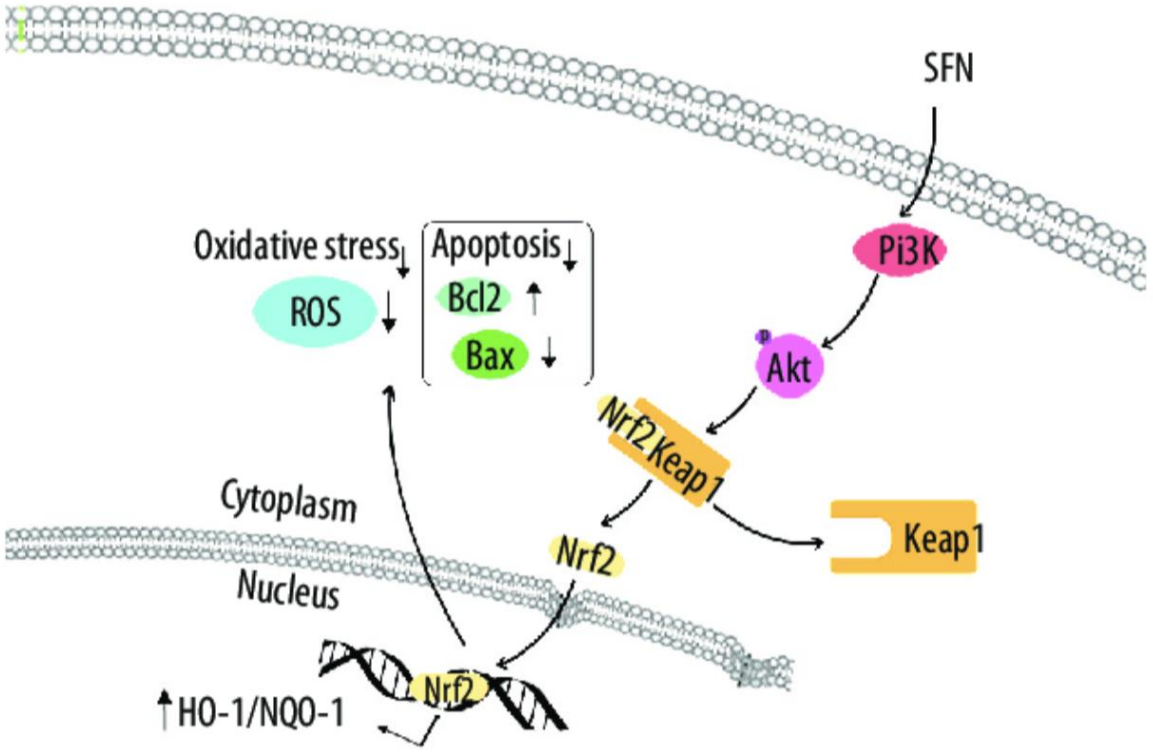
SFN increased the number of biotin stops in 3D cultured human skin model:

- ✓ Both in normal and IL-4/-13 induced AD in-vitro model
- ✓ 10μM SFN is the best optimal concentration





SFN is a known nuclearfactor-E2-related factor 2 (Nrf2) activator



Sulforaphane (SFN) exerts antioxidant stress through PI3K/Akt and Nrf2 signaling pathways. SFN, as a new type of Nrf2 agonist, activate Nrf2 by promoting PI3K/Akt signaling pathways, mainly enhancing the phosphorylation of Akt. Nrf2 is translocated into nuclei after released from Keap1 to induce the transcription of phase II antioxidative enzymes NQO-1, HO-1, GCLC, and GCLM.

Nrf2 activator, **sulforaphane** ameliorates autism-like symptoms through suppression of Th17 related signaling and rectification of oxidant-antioxidant imbalance in periphery and brain of BTBR T+tf/J mice.

Nadeem A, Ahmad SF, Al-Harbi NO, Attia SM, Bakheet SA, Ibrahim KE, Alqahtani F, Alqinyah M.

Behav Brain Res. 2019 May 17;364:213-224. doi: 10.1016/j.bbr.2019.02.031. Epub 2019 Feb 19.

PMID: 30790585

Sulforaphane induced **NRF2 activation** in obese pregnancy attenuates developmental redox imbalance and improves early-life cardiovascular function in offspring.

Psefteli PM, Morris JK, Ehler E, Smith L, Bowe J, Mann GE, Taylor PD, Chapple SJ.

Redox Biol. 2023 Nov;67:102883. doi: 10.1016/j.redox.2023.102883. Epub 2023 Sep 18.

PMID: 37774548 Free PMC article.

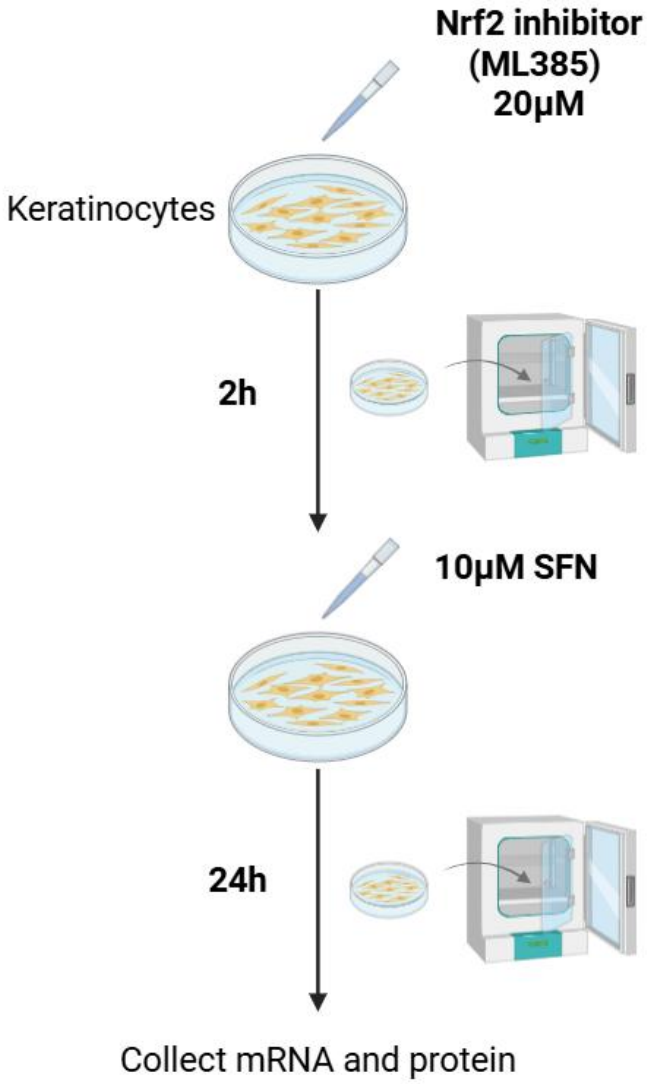
Protective Effects of **NRF2 Activator Sulforaphane** in Polyinosinic:Polycytidylic Acid-Induced In Vitro and In Vivo Model.

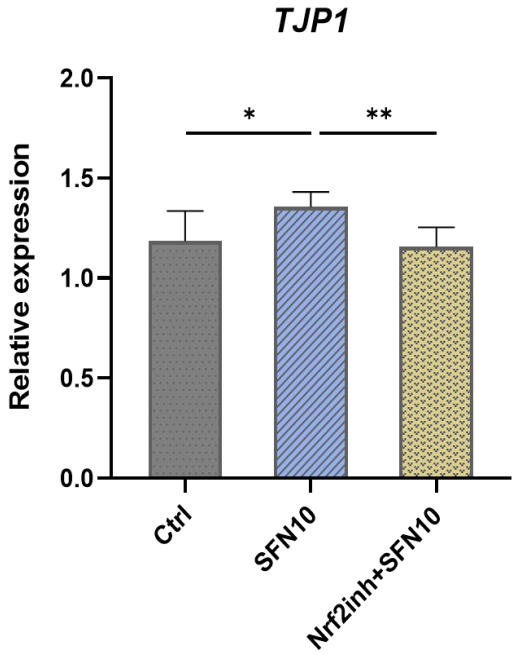
Matsagar SV, Singh RK.

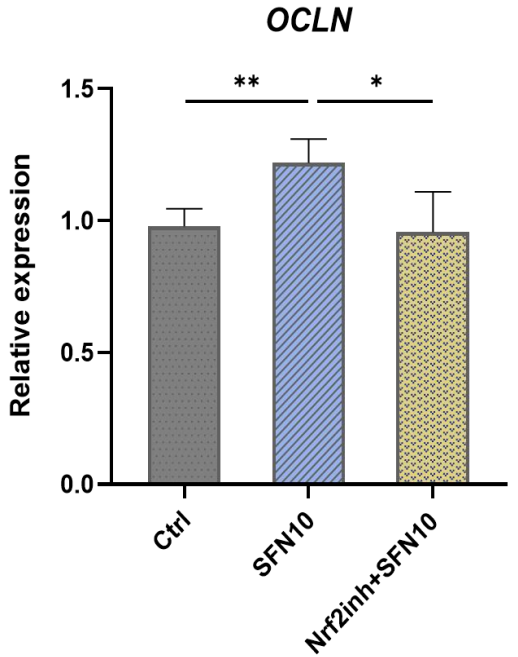
J Biochem Mol Toxicol. 2024 Dec;38(12):e70086. doi: 10.1002/jbt.70086.

PMID: 39635763

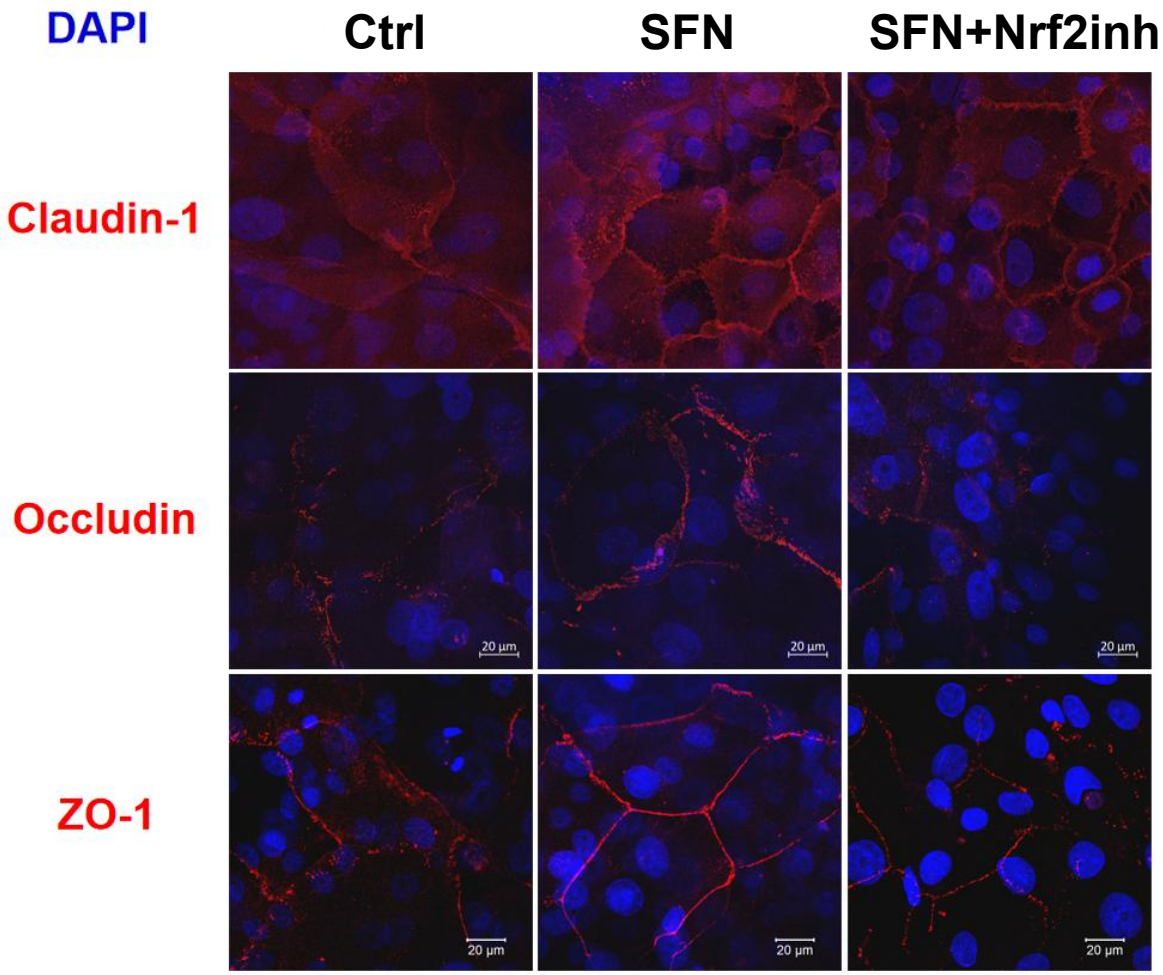
Nrf2 inhibitor supresses the enhancing effect of SFN on keratinocytes

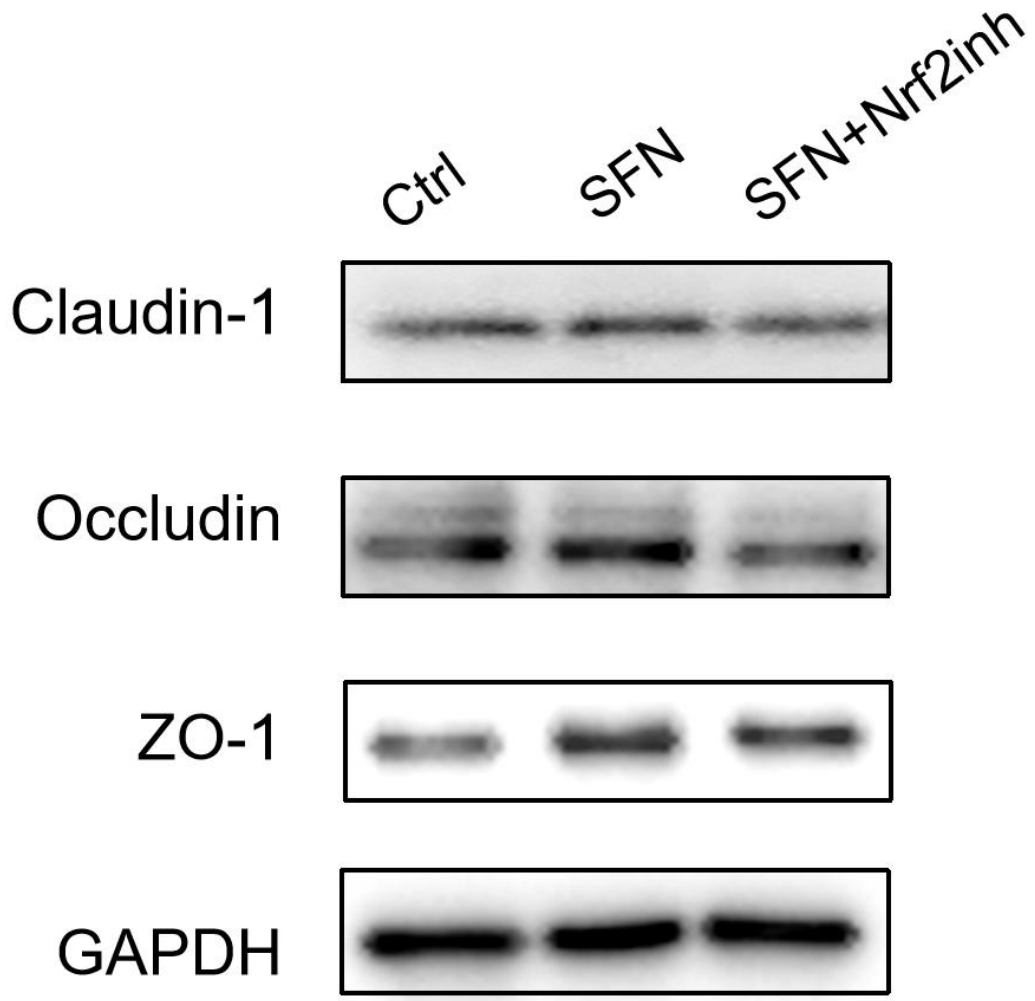






Nrf2 inhibitor supressed SFN-mediated expression and distribution of barrier-related protein in keratinocytes





Summary and Conclusion

Summary:

1. Topical SFN suppresses skin inflammation and improves skin barrier in an AD murine model.

2. SFN enhances keratinocyte barrier function through upregulation of tight junction-related proteins.

3. SFN enhances barrier function through Nrf2 signaling pathway.

Conclusion:

SFN is suggested as a potential topical therapeutic agent for AD.

Acknowledgement

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Assoc. Prof. Ying Liu

Assoc. Prof. Dan Yu

Ms. Yuanyuan Tian

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All my colleagues

from the Dermatology Department