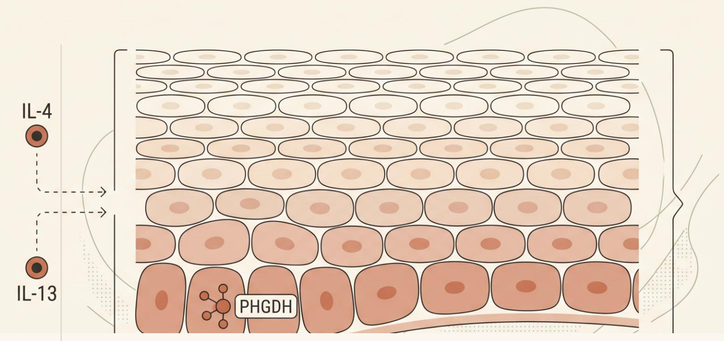
Th2 Cytokines Impair Keratinocyte Differentiation through Induction of the *Serine–Glycine Biosynthesis Pathway*

Maya Liaks-Bohnick1,2, Fadia Zagairy2, Merav Birk-Bachar1,4 Hila Belhanes-Peled3, Nofar David3, Shiran Turk3, Judith Krauz3, Timothy J. Few-Cooper1, Michael Ziv2, Eran Cohen Barak1,2

1 Rappaport Faculty of Medicine, Technion, Haifa **2** Dept. of Dermatology, Emek Medical Center, Afula **3** Dept. of Pathology, Emek Medical Center, Afula **4** Schneider Children's Medical Center, Petah Tikva

ATOPIC DERMATITIS · METABOLIC REPROGRAMMING



BACKGROUND

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting up to 20% of children and 5% of adults. Its pathogenesis is **driven by Th2 cytokines (IL-4, IL-13)**, which promote epidermal barrier dysfunction and impair keratinocyte differentiation. This inflammatory state demands significant metabolic reprogramming, yet the specific pathways activated by Th2 signaling in keratinocytes remain poorly understood.

While metabolic reprogramming is well-established in cancer and other inflammatory diseases, the role of the **serine-glycine biosynthetic pathway** in Th2-driven skin disease remains unexplored.

OBJECTIVE

To identify and functionally characterize the metabolic pathways activated by IL-4/IL-13 in keratinocytes, and to determine whether targeting these pathways can restore epidermal differentiation and reduce inflammation in AD

THE SERINE–GLYCINE BIOSYNTHESIS PATHWAY

glycolysis → **Glucose** → **3-PG** —(**PHGDH**, RATE-LIMITING)→ **3-PHP** —(**PSAT1**)→ **3-P-Serine** —(**PSPH**)→ **Serine** —(**SHMT1/2**)→ **Glycine**

↳ feeds one-carbon metabolism

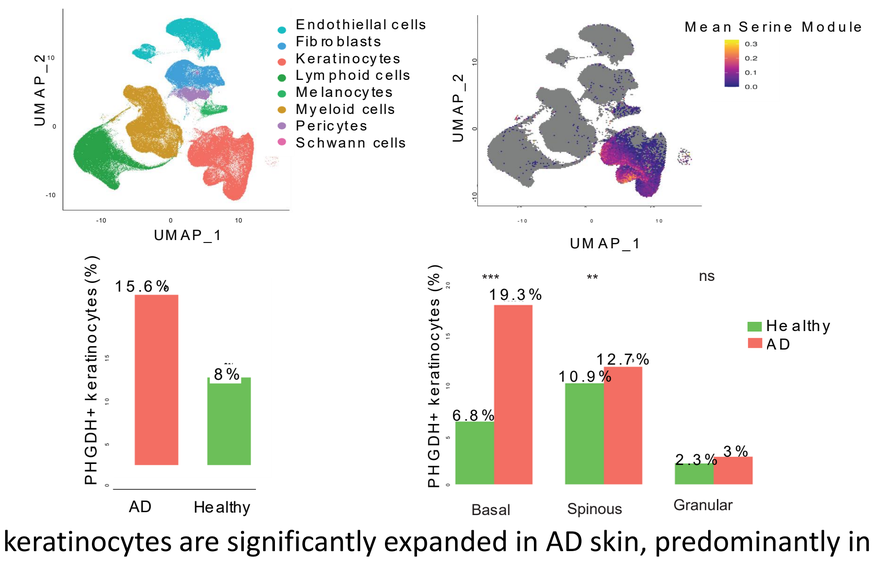
Serine → **Purines · AICAR**

Glycine → **Glutathione · GSH**

PHGDH commits 3-phosphoglycerate to *de novo* serine synthesis fuelling one-carbon metabolism, purine biosynthesis and glutathione.

1 DISCOVERY SCRNA-SEQ

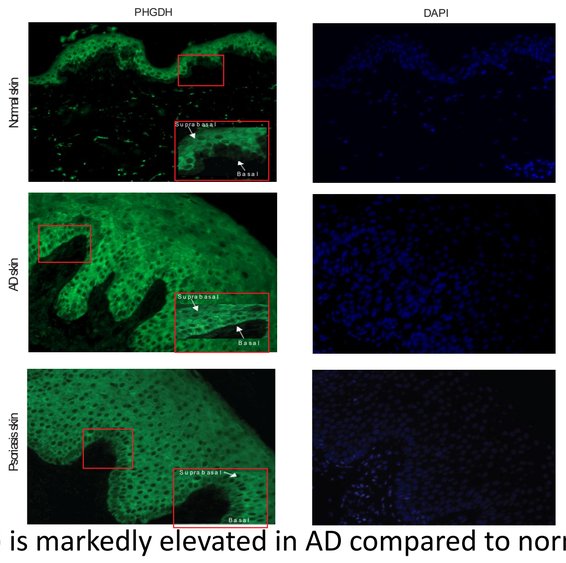
Serine-glycine genes are up-regulated in AD keratinocytes



PHGDH⁺ keratinocytes are significantly expanded in AD skin, predominantly in the basal and spinous layers.

2 TISSUE VALIDATION · IMMUNOFLUORESCENCE

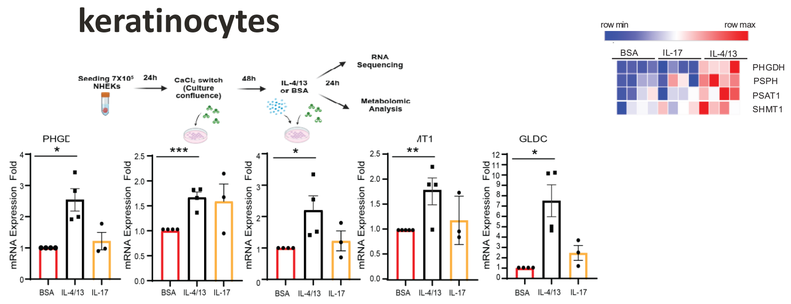
PHGDH protein is elevated in AD skin -Th2-specific



PHGDH (green) is markedly elevated in AD compared to normal skin, with the strongest signal in the basal layer. No upregulation is seen in psoriasis, confirming Th2-specific expression at the protein level.

3 IN VITRO VALIDATION · KERATINOCYTE CULTURES

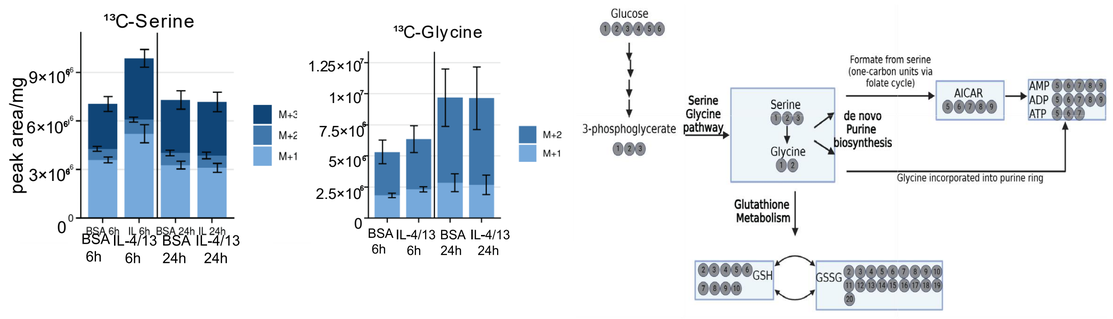
Th2 cytokines selectively upregulate the serine-glycine pathway in keratinocytes



IL-4/IL-13 specifically upregulate serine-glycine pathway enzymes (PHGDH, SHMT1, PSAT1) in primary keratinocytes, an effect not seen with IL-17, confirming Th2-selectivity.

4 METABOLIC FLUX · $^{13}C_6$-GLUCOSE TRACING

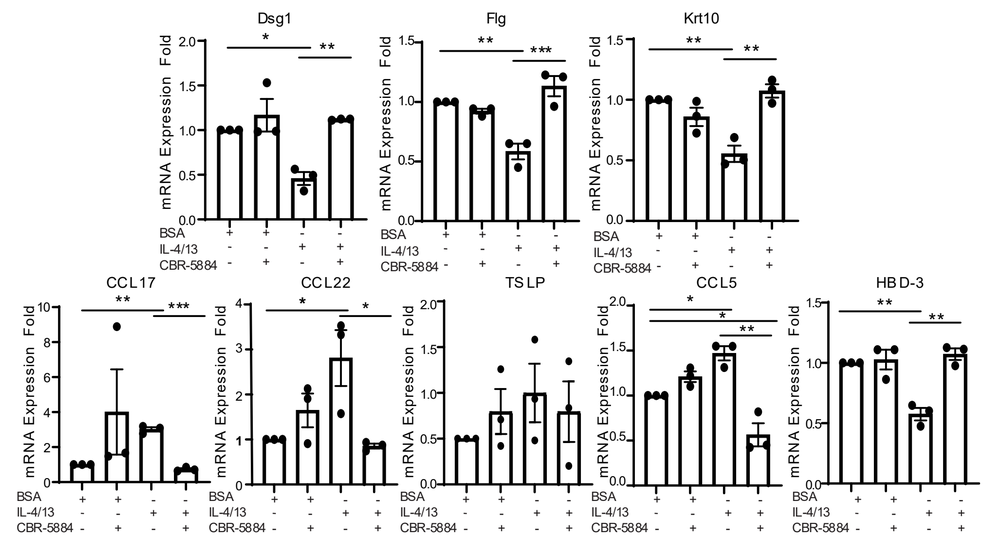
IL-4/IL-13 increase metabolic flux through the serine-glycine pathway



^{13}C glucose tracing confirms increased carbon flux into serine, glycine, and downstream purine intermediates in IL-4/IL-13-stimulated keratinocytes.

5 THERAPEUTIC TARGET · PHGDH INHIBITION

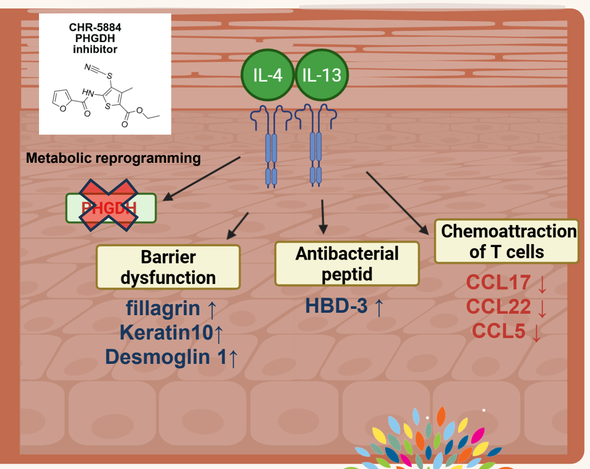
PHGDH inhibition (CBR-5884) restores differentiation and reduces inflammatory chemokines



Pharmacological inhibition of PHGDH reverses IL-4/IL-13-induced differentiation impairment and reduces Th2-associated chemokine expression, identifying PHGDH as a potential therapeutic target in AD.

KEY FINDING

- **Serine-glycine pathway is selectively upregulated by Th2 cytokines in keratinocytes**
- **PHGDH is the key driver, elevated in AD skin but not psoriasis**
- **PHGDH inhibition restores barrier proteins and reduces inflammatory chemokines**



CONCLUSIONS

PHGDH-dependent serine biosynthesis links Th2 inflammation to epidermal barrier dysfunction, representing a novel and targetable metabolic vulnerability in atopic dermatitis. Pharmacological inhibition of PHGDH restores keratinocyte differentiation and reduces inflammatory chemokines, offering a potential new therapeutic strategy for AD.

REFERENCES

1. Weidinger S et al. *Nat Rev Dis Primers.* 2018;4(1):1.
2. Guttman-Yassky E et al. *J Allergy Clin Immunol.* 2019;143(1):36–55.
3. Reynolds G et al. *Science.* 2021;371(6527):eaba6500.

מדע בונה חברה
אייסף ISEF ISRAEL SCHOLARSHIP EDUCATION FOUNDATION הקרן הבינלאומית לחינוך ע"ר
מרכז רפואי העמק רפואה מתקדמת בדיוק בשבילך
הטכניון מכון טכנולוגי לישראל