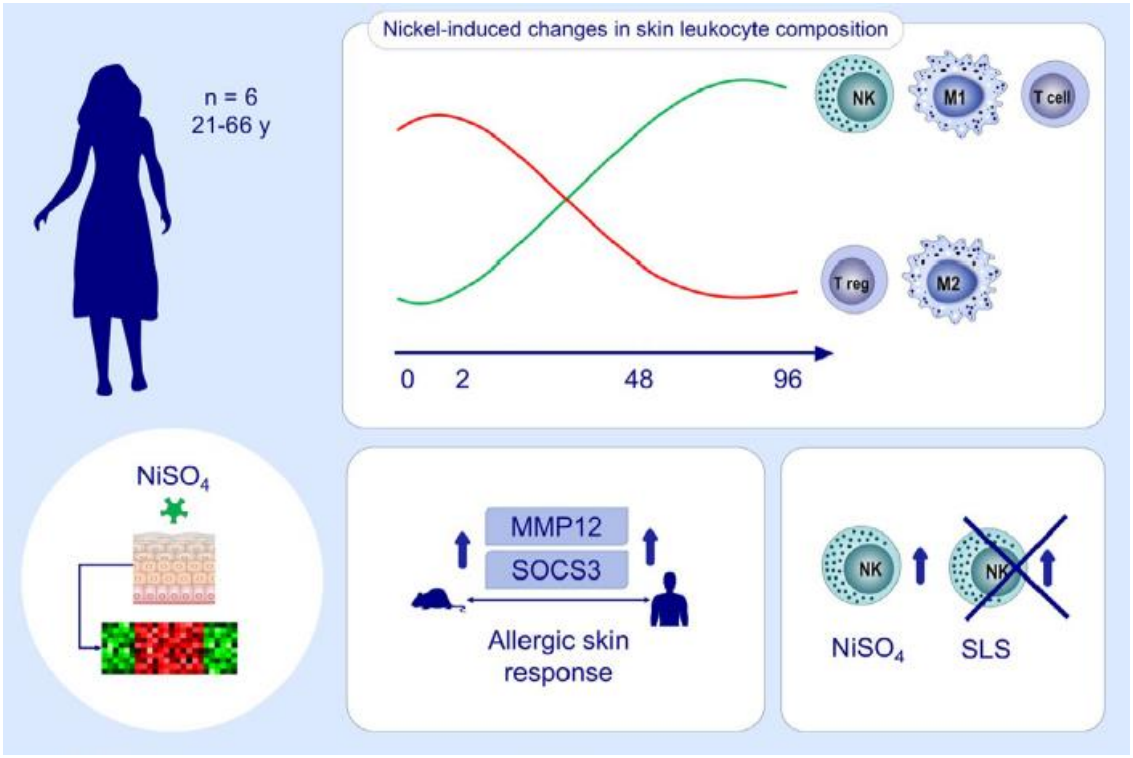
Activation of cytotoxic pathways is a major hallmarks of allergic contact dermatitis



To decipher involved immunological players and pathways, human skin biopsies were taken at 0, 2, 48, and 96 hours after nickel patch test in six nickel-allergic patients. Gene expression profiles were analyzed via microarray.

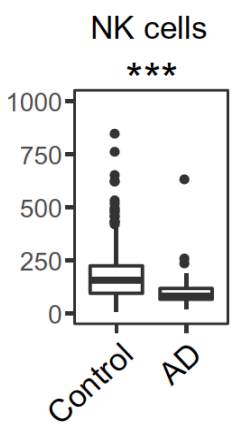
- **Late-phase nickel challenge induces major changes in leukocyte composition including influx and activation of NK cells, macrophage polarization, and T-cell immunity.**
- **NK cell infiltration and cytotoxic pathways were found to be uniquely upregulated in nickel-induced allergic skin responses compared to SLS-induced irritant skin responses.**

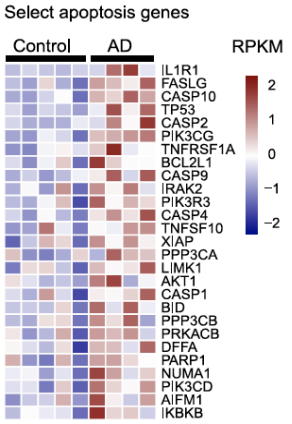
Wisgrill L, Werner P, Jalonen E, Berger A, Lauerma A, Alenius H, et al. Integrative transcriptome analysis deciphers mechanisms of nickel contact dermatitis. Allergy. 2020 Jul 24.

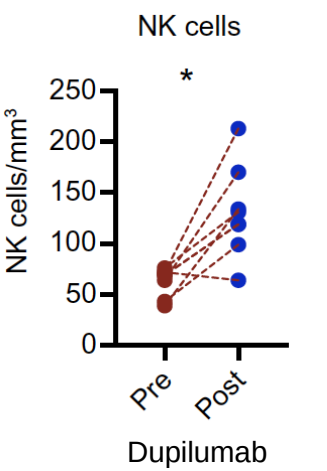
Blood natural killer cell deficiency is a diagnostic feature of atopic dermatitis and improves with therapy

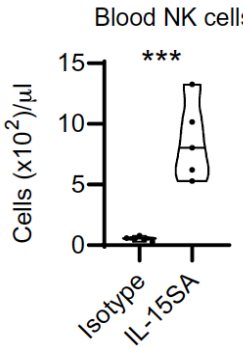
Comprehensive analysis of blood lymphocyte subpopulations in 25 adult patients with moderate-to-severe AD compared to a control cohort of 363 subjects without AD

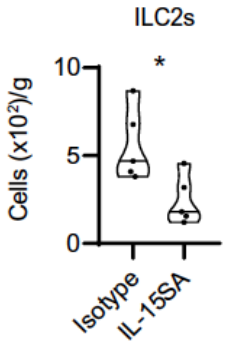
Mouse model of AD
Mice were treated with systemic IL-15 superagonist.









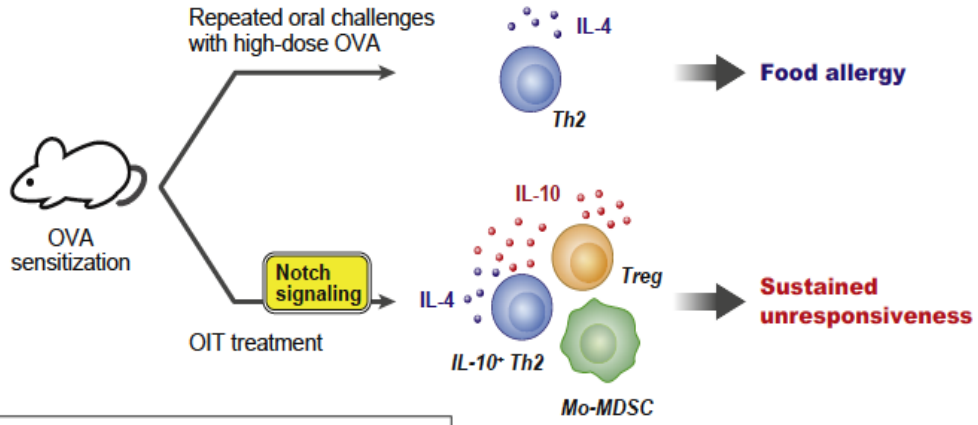


- **NK cell deficiency is a diagnostic feature of moderate-to-severe AD.**
- **AD-associated NK cells exhibit a baseline proapoptotic phenotype and are more susceptible to AICD.**
- **Type 2 cytokine blockade reverses NK cell defects in patients with AD.**
- **Restoring NK cell deficiency through IL-15 superagonism is an effective and promising therapeutic strategy for AD**
- **NK cells limit innate type 2 inflammation**

Mack MR, Brestoff JR, Berrien-Elliott MM, Trier AM, Yang T-LB, McCullen M, et al. Blood natural killer cell deficiency reveals an immunotherapy strategy for atopic dermatitis. Sci Transl Med. 2020 Feb 26;12(532).

Notch signaling contributes to the establishment of sustained unresponsiveness to food allergens by oral immunotherapy

Notch signaling contributes to expansion of immunosuppressive cells induced by oral immunotherapy



Mo-MDSC: Monocytic myeloid-derived suppressor cell
OIT: Oral immunotherapy
OVA: Ovalbumin
Th2: T helper 2
Treg: Regulatory T cell

Desensitization was assessed by OFC on day 42
SU was assessed by second OFC on day 56
Mice were injected with inhibitor of Notch signaling (DAPT)

Inhibition of Notch signaling prevents establishment of sustained unresponsiveness to food allergens induced by OIT, but it does not affect induction of desensitization.

- **Oral immunotherapy induces systemic expansion of IL- 10–producing CD4+ T cells, including TH2 cells producing both IL-4 and IL-10, and myeloid-derived suppressor cells in a mouse model of food allergy.**
- **These immunosuppressive cells contribute to induction of sustained unresponsiveness to food allergens, and Notch signaling is involved in the expansion of these cells.**

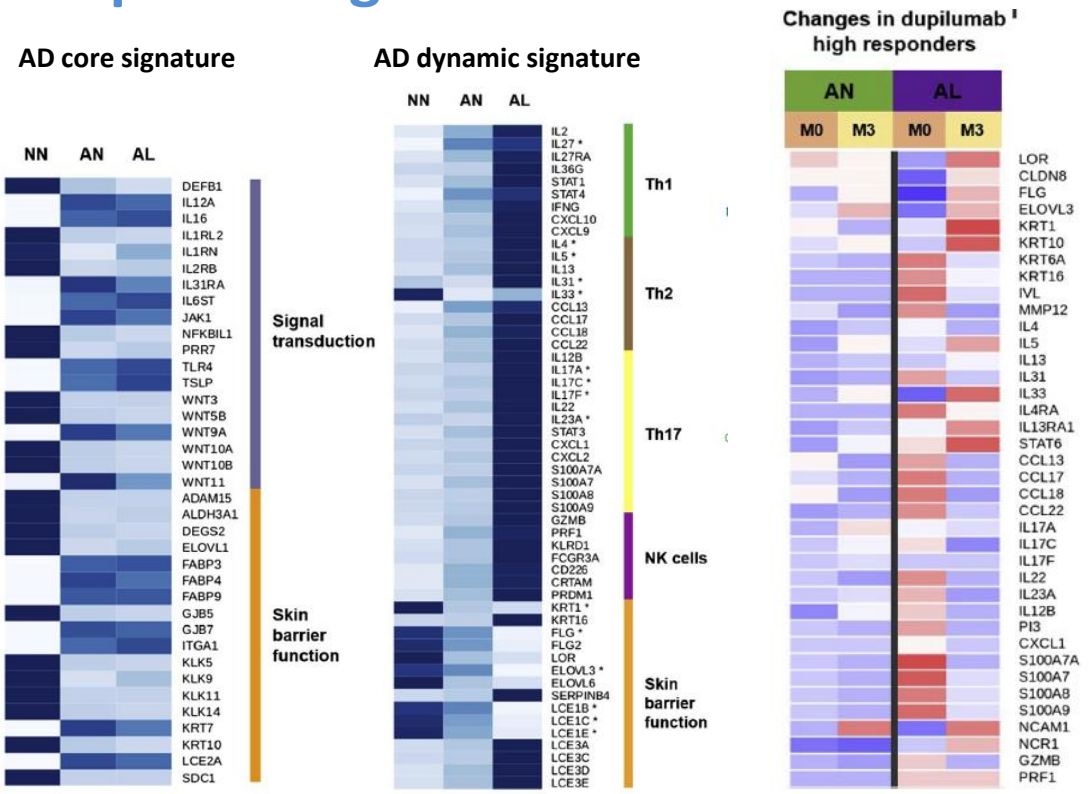
Yoneyama T, Nakano N, Hara M, Yamada H, Izawa K, Uchida K, et al. Notch signaling contributes to the establishment of sustained unresponsiveness to food allergens by oral immunotherapy. J Allergy Clin Immunol. 2020 Jul 24.

Atopic dermatitis displays stable and dynamic skin transcriptome signatures

Biopsy specimens from :
- 59 patients with AD before treatment
- 30 patients 12 weeks after start of dupilumab or cyclosporine
- 31 healthy controls

→ mRNA sequencing.

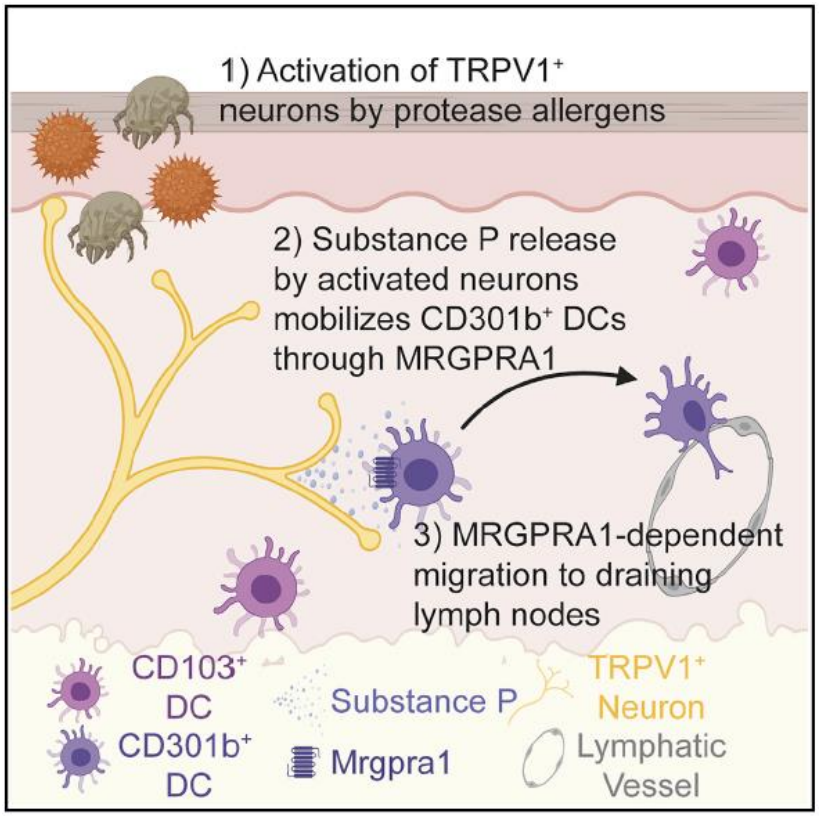
Differential expression, pathway enrichment, correlation, and coexpression network analysis were conducted.



- **AD core signature is characterized by a dysregulation of genes driving skin barrier dysfunction and itch signaling, whereas a second, more dynamic signature reflects progressive inflammatory mechanisms such as activation of type 2, TH17, and NK cell function.**
- **Both dupilumab and cyclosporine led to a strong downregulation of type 2 markers, but overall the residual profile was still profoundly different from that of healthy skin.**

Möbus L, Rodriguez E, Harder I, Stölzl D, Boraczynski N, Gerdes S, et al. Atopic dermatitis displays stable and dynamic skin transcriptome signatures. J Allergy Clin Immunol. 2020 Jun 29.

Substance P Release by Sensory Neurons Triggers Dendritic Cell Migration and Initiates the Type-2 Immune Response to Allergens



In vivo mouse model: cysteine protease allergen papain.
Depletion of TRPV1+ neurons, inhibition of sensory neuronal activation, or ablation of Mrgpra1 from CD301b+ DCs led to a defect in CD301b+ DC migration and as a direct consequence, Th2 cell differentiation.

- **Allergens activate TRPV1+ sensory neurons to induce itch responses and Substance P release.**
- **Substance P stimulate proximally cDC2 through MRGPRA1 and trigger cDC2 migration to the draining lymph node where they inititate Th2 cell differentiation.**
- **TRPV1+ neurons are required for allergen recognition, DC activation and initiation of the allergic immune response.**

Perner C, Flayer CH, Zhu X, Aderhold PA, Dewan ZNA, Voisin T, et al. Substance P Release by Sensory Neurons Triggers Dendritic Cell Migration and Initiates the Type-2 Immune Response to Allergens. Immunity. 2020 Nov 17;53(5):1063-1077.e7.

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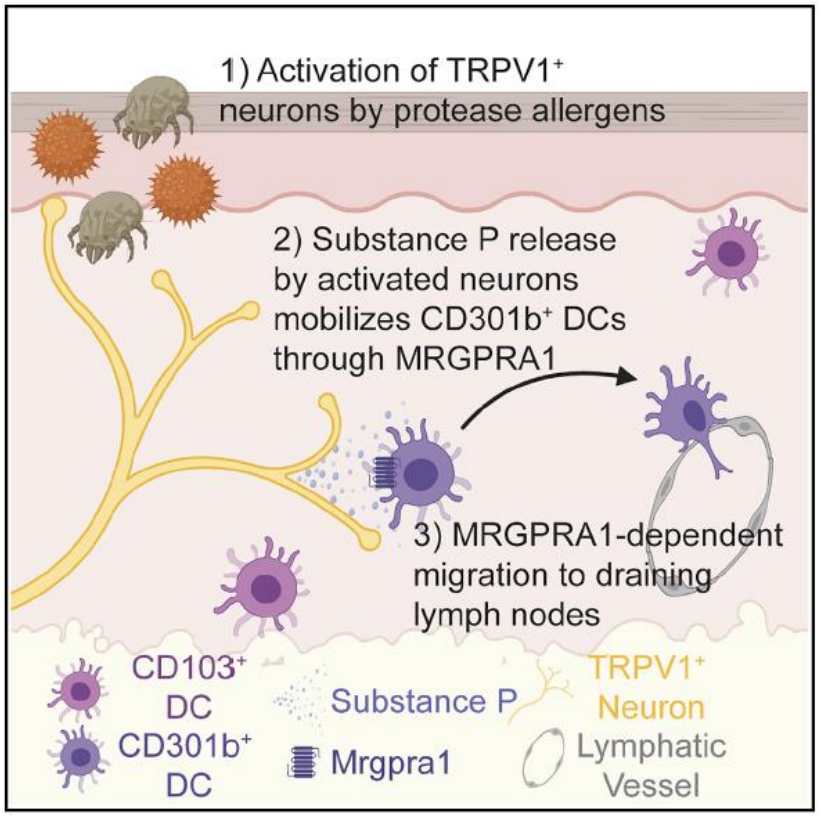
Substance P Release by Sensory Neurons Triggers Dendritic Cell Migration and Initiates the Type-2 Immune Response to Allergens



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