Delivery of contact sensizers and neuropephin 1 receptor antagonists by microneedle arrays targets different skin cells to abrogate contact dermatitis

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Development of contact dermatitis (CD) relies on innate and adaptive immunity that promote the activation of CD4 T helper 1 (Th1) and CD8 T cytotoxic (Tc1) cell biased cell. Signaling via the neuropephin 1 receptor (NKIR) by the proinflammatory peptid subsequence P and hemekinin 1, triggers skin neuroinflammation and supports Th1 and Tc1 immunity. Thus, we hypothesized that limiting neuroinflammation during skin Ag entry induces an immune-suppressive environment that limits the function of activated T cells that cause CD. Using self-developing microneedle arrays, we efficiently co-delivered 2,4-dinitrochlorobenzene (DNCB) or OVA and two different NKIR antagonists to the skin of C57Bl/6 mice during sensitization (protection) or between relapses (therapy) of CD. This approach resulted in significant decrease of local and systemic CD in an Ag specific manner. Using NKIR knockout (KO) bone marrow chimeras and the Cre-Lox system, we demonstrate that absence of functional NKIR in keratinocytes but not in leukocytes decreased IL-1β and IL-6, and inhibited the sensitization phase of CD. Absence of functional NKIR in keratinocytes or dendritic cells, but not in mast cells abrogated the adaptive immunity of CD. Mechanistic studies using DNBC biosynthesis (polycyclonial) or OVA OVA1 and OT2 (monoclonal) models showed expansion of regulatory T cells, death of activated Th1 and Tc1 cells, decreased IFN-γ and, increased IL-10 in skin draining lymph nodes. Together these results suggested a diminished T cell homing in the skin after re-exposure to OVA or DNBC. Our data demonstrate the possibility of preventing sensitization and relapses of CD by an immune-suppressive mechanism based on restraining neuroinflammation during skin Ag penetration.

Hidradenitis suppurativa RNA-seq skin transcriptome overlaps with psoriasis vulgaris and reveals a marked upregulation of multiple targetable cytokines

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Hidradenitis Suppurativa (HS) is a chronic inflammatory dermatosis of inguinal, axillary, and submaxillary skin. Using established consensus definitions, unaffected, perilesional and lesional HS skin samples were collected and RNA-seq performed. A mixed-effect model was estimated. Hypotheses were tested under the general framework for linear models in the R language package. P values from t-tests were adjusted for multiple hypotheses using the Benjamini-Hochberg procedure. Statistical analysis revealed a HS transcriptome of approximately 5000 genes (FDR < 0.05). HS and psoriasis vulgaris (PV) were shown to share a common signature of pro-inflammatory cytokines and chemokines, which was not present in normal skin. This signature was shared with a number of cytokines and chemokines that have been implicated in both HS and PV, including IL-17A, IL-17F, IL-22, IL-6, IL-36A and IL-36G in HS skin, with increased expression between unaffected, perilesional and lesional skin. HS lesional skin had similar or higher levels of the pro-inflammatory cytokines seen in psoriasis. Unaffected HS skin had higher expression of these cytokines compared to healthy controls, suggesting that even unaffected skin is inflammation-prone. This suggests that HS is a systemic disorder that initiates in the skin but spreads via lymphatic drainage to other inflammatory tissues. This data establishes parallels between HS and psoriasis, suggesting that psoriasis-like feed-forward mechanisms may be involved in disease pathology.