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"New molecular insights on immediate Capsaicin-induced stinging perception and sensitive skin in vivo"

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1. Introduction

Sensitive skin is a prevalent dermatological condition characterized by heightened reactivity to environmental, chemical, and physical stimuli that are typically well-tolerated by non-sensitive skin. Individuals with sensitive skin often experience discomfort such as burning, stinging, itching, and tightness, even in the absence of visible irritation [1].

The prevalence of sensitive skin has surged in recent years, with studies indicating that approximately 60-70% of women and 50-60% of men report experiencing symptoms. Although the exact mechanisms underlying sensitive skin remain incompletely understood, research suggests that factors such as thinning of the stratum corneum, alterations in neuronal transmission, and disruptions in intracellular lipids contribute to its development. [2, 3]

Despite its prevalence and significant impact on quality of life, due to the variability in its presentation and pathogenesis, sensitive skin remains poorly understood. Most of the studies conducted to shed light on the mechanisms behind sensitive skin are based on subjective measurements such as perceived sting, questionnaires or macroscopic non-invasive measures on skin.

In this study we focused on the molecular mechanisms behind stinging perception triggered by Capsaicin—a potent TRPV1 agonist— as a widely validated experimental model to provoke and quantify this type of effect [4]. While clinical differentiation between "stingers" (individuals reporting intense discomfort) and "non-stingers" (asymptomatic controls) is well-documented [5, 6], the molecular drivers underlying this dichotomy remain poorly characterized. Recent advances in transcriptomic profiling have enabled granular exploration of cutaneous responses to irritants [7, 8], yet no studies to date have comprehensively mapped gene expression patterns specific to short-term Capsaicin-induced reactivity phenotypes in human skin.

This study presents a comparative transcriptomic analysis of stingers and non-stingers following topical Capsaicin challenge. By comparing RNA-sequencing results from skin biopsies either upon Capsaicin treatment or under homeostatic condition, we identified specific gene patterns regulated differently in stingers vs non-stingers participants.

Our findings bridge a critical gap between subjective sensory reports and objective molecular mechanisms, offering novel biomarkers Sensitive skin stratification and therapeutic targeting.

This work underscores the value of transcriptomics in deciphering interindividual variability in cutaneous neurosensory pathways, with implications for personalized dermatological care.

2. Materials and Methods

Grouping of subjects

For this study, 2 groups with 10 Caucasian female volunteers each, aged 25-60, with Fitzpatrick skin type II and III, were recruited. The volunteers were categorized as stingers (Sensitive Skin) or non-stingers (Normal Skin - 10 per group) based on capsaicin sensitivity, as described by Jourdan et al [9].

Samples collection

3-mm punch biopsies were taken by the dermatologist in the bilateral post-auricular areas. 0.075% Capsaicin cream was applied on one post-auricular area for approximately 3 minutes and then biopsied, together with the contra-lateral post-auricular area without treatment for comparison. Samples were obtained in accordance with the Declaration of Helsinki and prior approval of an external Ethical Committee. All study volunteers had given their IRB-approved informed consent prior participation.

RNA isolation and quantification

The 40 biopsies were then stored in RNAlater and kept at -80C until RNA isolation. Total RNA extraction was performed using an RNeasy Mini Kit (Qiagen) following manufacturer's instructions for fibrous samples. RNA concentration and purity were determined using Nanodrop 2000 spectrophotometer. The integrity of the RNA was analyzed using a Qbit™ RNA IQ Assay Kit. RNA samples showing 260/280nm absorbance ratios above 2, 260/230 nm ratios above 1 and RIN above 7 were used for sequencing.

Library preparation and sequencing

Using 1ug of total RNA, Poly(A) RNA sequencing libraries were prepared following Illumina's Stranded-mRNA library preparation (Illumina, CA) protocol. Poly(A) tail-containing mRNAs were purified using Oligo-(dT) magnetic beads and fragmented using fragmentation master mix in elevated temperature (94C). The fragments were then used to synthesize first-strand and second-strand cDNA using random primers and reverse transcriptase. An 'A' base was then ligated to the 3' ends of the double-stranded cDNA molecules followed by the addition of the Illumina sequencing adaptors. The cDNA fragments were then enriched using PCR and purified to create the final cDNA library. Quality control (QC) analysis of the sequencing library was performed using DNA 1000 and High Sensitivity DNA Chips on an Agilent Technologies 2100 Bioanalyzer instrument. Single-ended sequencing was performed on Illumina's Next-seq 550 Dx sequencing system.

Differential gene expression analysis

Differential gene expression analysis was conducted using Illumina's BaseSpace sequence hub. The .BCL files from the sequences were converted into FASTQ format using the BCL convert app. The adapter trimming option setting was utilized while setting up the run, while the T' overhangs from FASTQ files were trimmed using FASTQ Toolkit v 2.2.6. The trimmed reads were aligned to the hg38 human reference genome, using the DRAGEN RNA v 4.2.4 application. The DRAGEN Differential Expression application v 4.3.6 was then used to run the DESeq2 algorithm on RNA quantification files produced. This identifies transcripts that are differentially expressed between the treatment group and the control group. The differentially expressed genes (DEGs) were identified using an adjusted p-value cutoff of ≤0.05 and linear fold change cutoff of >1.5 or <-1.5 (Log2FC = 0.6)

Functional pathway enrichment for DEGs

Pathway enrichment analysis (KEGG Pathways 2021 Human) and Biological Processes analysis (GO_Biological processes 2025) were performed using the EnrichR software (Enrichr). Biological Processes and KEGG pathways with p-value ≤0.05 were considered as significantly enriched. Plots were designed using the Appyter online tool (Appyter). Cross-analysis of the lists of genes was performed using the Venny 2.1.0 software (Venny 2.1.0).

3. Results

Comparison between non-stinger and stinger skin under homeostatic conditions vs Capsaicin treatment reveals a difference in gene regulation upon stress (Capsaicin) exposure

The aim of the study was to define specific patterns of genes that are actively modulated shortly after stress exposure. In this specific context, the Capsaicin sting test was performed as inducer of stress and the samples were collected either under homeostatic conditions (without treatment) or 3-5min after stress exposure to monitor the immediate changes in gene expression. Capsaicin was chosen as sting-inducer since, beside its function as agonist of TRPV1 receptor, additional molecular mechanisms involved are poorly understood. With the obtained transcriptomic profiles we firstly considered the number of Differentially Expressed Genes (DEGs) in the study group of non-stingers (normal skin) and the stingers (sensitive skin) in the comparison of Capsaicin vs untreated samples. The total number of DEGs, defined with a linear cutoff value of 1.5 / Log2Fold Change of 0.6 and a p-value ≤0.05, was not substantially different between the two groups (164 vs143), but while in the normal skin, Capsacin treatment caused a prominent down-regulation of genes (111 down vs 53 up), in sensitive skin the treatment mostly induced an up-regulation of several genes(103 up vs 40 down) (Figure 1 and Table 1). Suggesting that the mechanisms involved in the Capsaicin response between the 2 populations might be substantially different.

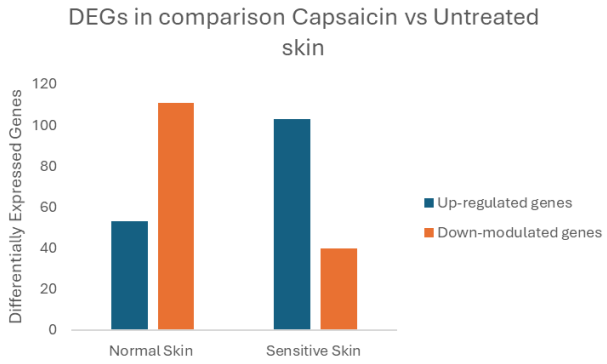

Figure 1. The plot represents the number of Differentially Expressed Genes (DEGs) in the two groups (normal skin and sensitive skin) in response to Capsaicin (analysis of Capsaicin vs untreated samples). Blue bars represent the number of up-regulated genes, while orange bars represent the number of down-regulated genes.

Table 1. Number of DEGs in the indicated comparison group. Genes were selected using a p-value ≤0.05 and a linear FC cuttoff of 1.5/log2FC cutoff=0.6, NS=normal skin, SS=sensitive skin

Comparison Group	Total number of DEGs	Up-regulated	Down-regulated
NS/Capsaicin vs NS/untreated	164	53	111
SS/Capsaicin vs SS/untreated	143	103	40

To assess whether amongst the list of DEGs in the 2 groups there could have been some common items, we crossed the full gene lists from the two populations and we found 11 genes in common (Figure 2).

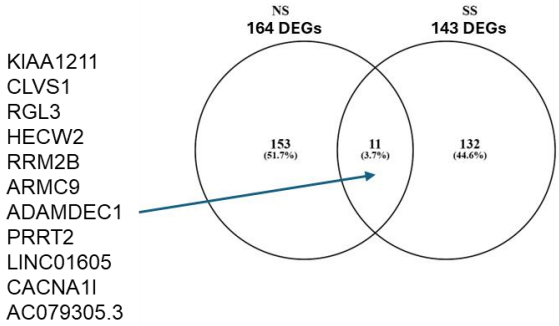

Figure 2. Crossing the full lists of DEGs (up-regulated and down-modulated genes) of Normal Skin (NS) and Sensitive Skin (SS) upon Capsaicin response. 11 genes were found in common.

However, only 3 of them were similarly modulated upon Capsaicin treatment between the 2 groups: the genes KIAA1211 and CLVS1 were consistently upregulated, while the gene CACNA1I was downregulated. This important difference in gene expression in the 2 groups could be linked with different skin sensitivity to the stressor.

Early response to Capsaicin treatment in non-stingers included neuronal processes upregulation together with a downmodulation of Cellular Defense Response

In order to first characterize the effect of short term Capsaicin exposure in non-stingers, we clustered the lists of DEGs into a KEGG 2021 Human pathway analysis and a Gene Ontology (GO) Biological Processes analyses. In the case of non-stingers, the genes modulated would lead to a lack of stinging perception. For the gene clustering analyses, the lists of upregulated and downmodulated genes were separately considered.

Amongst the upregulated genes, we found a significant enrichment of genes involved in the Thyroid Hormone Synthesis and Ribosome Biogenesis, suggesting that these pathways may be important in a non-stinging response to Capsaicin. Amongst the GO Biological Processes one of the most statistically significant was Synapse Organization, in line with a connection between Capsaicin and neural regulation, as a known agonist of the neuronal receptor TRPV1. (Figure 3)

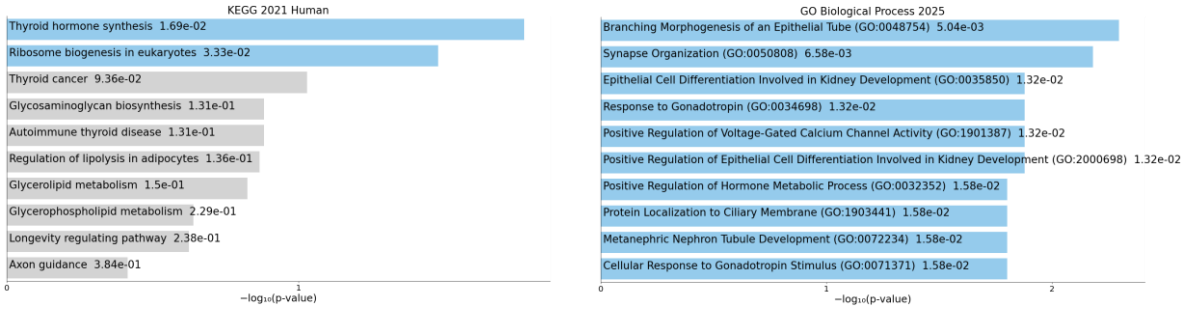

Figure 3.(Left panel) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. (Right panel) Bar chart of the top enriched terms from the GO Biological Process 2025 gene set library. The clusterings were generated from the list of DEGs upregulated in Normal Skin Capsacin vs Untreated. The top 10 enriched term in both panels are displayed based on the -log10(p-value), with the actul p-value shown next to each term.

Amongst the down-modulated genes, the pathways of Cell adhesion molecules, Chemokine signaling and Calcium signaling were the most significant ones, together with the Biological Processe Cellular Defense Response, in line with a reduction of the inflammatory response due to the stress, but also Oxygen Transport and Carbon Dioxide Transport. (Figure 4)

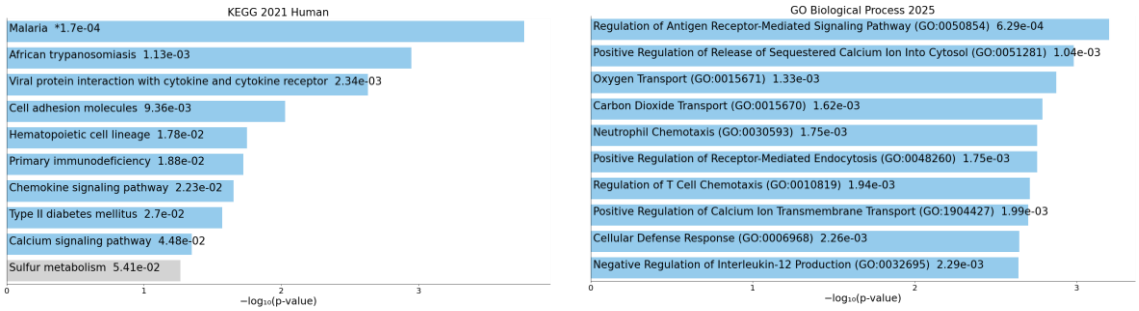

Figure 4.(Left panel) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. (Right panel) Bar chart of the top enriched terms from the GO Biological Process 2025 gene set library. The clusterings were generated from the list of DEGs downregulated in Normal Skin Capsacin vs Untreated. The top 10 enriched term in both panels are displayed based on the -log10(p-value), with the actul p-value shown next to each term.

Taken collectively these results in part recapitulate the expected response of a non-stinger to Capsaicin, whith an upregulation of neuronal pathways and control of inflammatory reaction. However, some additional new categories were highlighted giving us insights that, upon Capsaicin, other processes are involved such as hormonal regulation and metabolic modulation that could eventually take part in the protection from stinging.

Early response upon Capsaicin treatment in stinger volunteers

We then focused on the Capsaicin effect in the stinger population. We highlighted amongst the up-regulated genes, pathways linked to ECM-receptors interaction, focal adhesion, cell adhesion, and PI3K-Akt signaling pathway. While amongst the Biological Processes we identified regulation of adaptive immune response and a few items linked to immunomodulatory functions, that may be linked to an over-reaction and pro-inflammatory outcome that would lead to a sting perception (itch, burning sensations). (Figure 5)

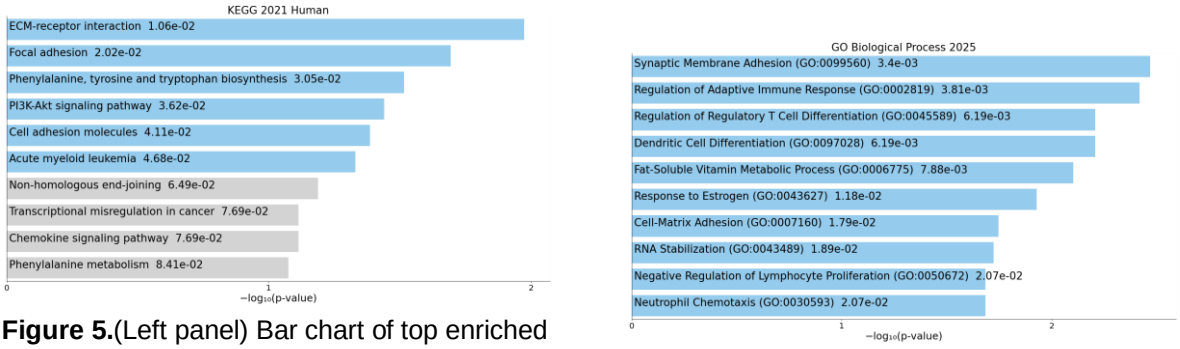

Figure 5.(Left panel) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. (Right panel) Bar chart of the top enriched terms from the GO Biological Process 2025 gene set library. The clusterings were generated from the list of DEGs upregulated in Sensitive Skin Capsacin vs Untreated. The top 10 enriched term in both panels are displayed based on the -log10(p-value), with the actul p-value shown next to each term.

Some interesting pathways were downmodulated such as Cortisol synthesis and secretion, Insulin secretion and more in general hormonal secretion, suggesting that, in the early response to Capsaicin, hormones may play a role. Amongst the Biological Pathways we could identify processes linked to Calcium fluxes together with Steroid Hormone Mediated Signaling Pathway, in line with the KEGG pathways analysis. (Figure 6)

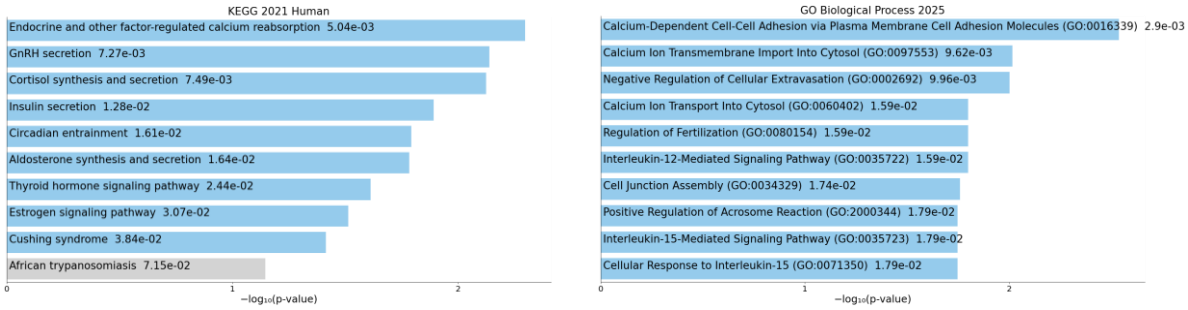

Figure 6.(Left panel) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. (Right panel) Bar chart of the top enriched terms from the GO Biological Process 2025 gene set library. The clusterings were generated from the list of DEGs downregulated in Sensitive Skin Capsacin vs Untreated. The top 10 enriched term in both panels are displayed based on the -log10(p-value), with the p-value next to each term.

Comparison between non-stingers and stingers under homeostatic condition and upon Capsaicin treatment

Lastly, we compared the treatment effects amongst the 2 panels of volunteers (stingers and non-stingers).

In this case by comparing the 2 different treatments (x-axis: untreated and Capsaicin treated) there was no prevalence of up-regulated or down-modulated genes (Figure 7) (as observed when comparing instead the stingers vs non-stingers, see Figure 1).

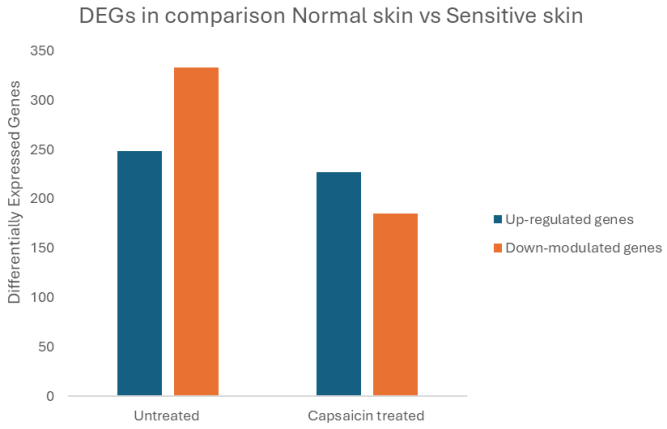

Figure 7. The left plot represents the number of DEGs in the two treatments (Untreated and Capsaicin treated) in a comparison of Stingers vs Non-stinger. Blue bars represent the number of up-regulated genes, while orange bars represent the number of down-regulated genes.

The comparison within the homeostatic condition aimed at identifying potential “stinger” and “non-stinger” gene signatures that could already give an indication of individuals who would respond or not to this specific stress.

Under the homeostatic condition the upregulated DEGs in stingers vs non-stingers were linked to Biological processes like Epidermal Development, Epithelium Development and Cell Differentiation, while amongst the downmodulated genes some relevant pathways were significant such as Wnt signaling pathway, Cell adhesion, but also Thyroid hormone signaling pathway, together with the Biological processes linked to Regulation of Immune Response and Cell Adhesion (Figure 8)

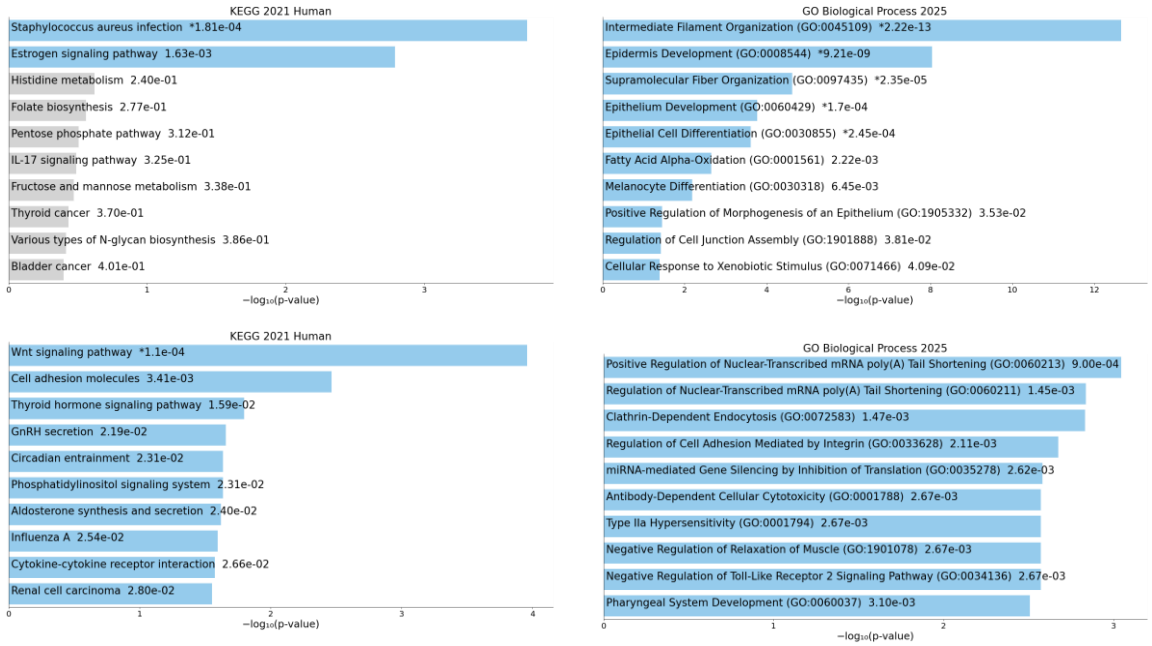

Figure 8.(Top and Bottom Left panel) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. (Top and Bottom Right panel) Bar chart of the top enriched terms from the GO Biological Process 2025 gene set library. The clusterings were generated from the list of DEGs upregulated in untreated condition by comparing Stinger vs Non-Stinger panels. In the top panels the upregulated DEGs are analyzed, while in the bottom panels the downmodulated DEGs are considered.

Upon Capsaicin treatment the situation is different since we observed Pathways linked to Chemokine singaling and Steroid hormone biosynthesis being upregulated together with processes linked to immune cells Chemotaxis and Differentiation and, immune system response. While amongst the downmodulated genes we found pathways linked to Phosphatidylinositol signaling and Cortisol synthesis together with processes involved in Neuronal development, and also unexpectedly processes such as Cell junction assembly and IGF signaling pathway.(Figure 9)

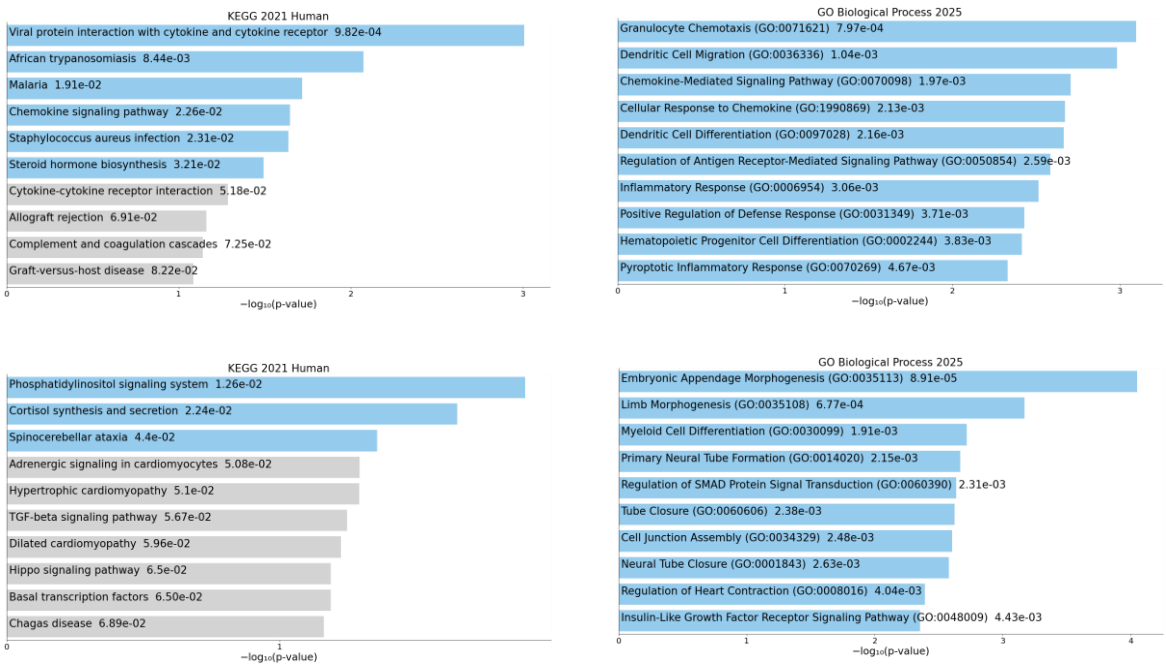

Figure 9.(Top and Bottom Left panel) Bar chart of top enriched terms from the KEGG 2021 Human gene set library. (Top and Bottom Right panel) Bar chart of the top enriched terms from the GO Biological Process 2025 gene set library. The clusterings were generated from the list of DEGs upregulated in Capsaicin Treatment by comparing Stinger vs Non-Stinger panels. In the top panels the upregulated DEGs are analyzed, while in the bottom panels the downmodulated DEGs are considered.

Finally, in order to identify gene signatures consistently different between the 2 subgroups and independent from the treatment, we crossed the obtained lists of DEGs and identified 116 genes differentially regulated in the two subgroups independently from the treatment. Out of these 116, 111 genes were similarly regulated, suggesting that the pathways involved might be relevant for the distinction of the 2 subgroups regardless of the type of stress (Figure 10).

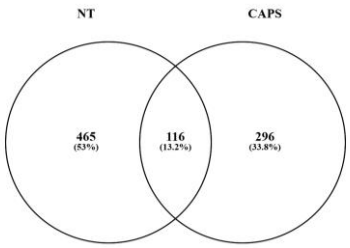

Figure 10. The Venn diagram represents the crossing of the full lists of DEGs (up-regulated and down-modulated genes) of Non treated and upon Capsaicin treatment in Stingers vs Non-stingers. 116 genes were found in common.

4. Discussion

The aim of this study was to elucidate the molecular mechanisms triggered by short-term capsaicin treatment in groups of stinger and non-stinger individuals. Capsaicin elicited markedly different transcriptomic responses in the two groups: non-stingers predominantly exhibited downregulation of gene expression, whereas stingers showed a general upregulation of genes (Figure 1). Only three differentially expressed genes (DEGs) were commonly regulated between the groups, indicating highly specific and distinct activation patterns.

In non-stingers, upregulated genes were primarily associated with neuronal processes, consistent with direct TRPV1 activation by capsaicin [10]. Additionally, there was an increase in genes linked to thyroid hormone synthesis and ribosome biogenesis, while genes involved in chemokine signaling, cellular defense, and metabolic pathways were downregulated (Figure 3 and 4). This pattern suggests a reduction in inflammatory responses and metabolic activity, aligning with the known effects of TRPV1 activation in modulating neuronal and inflammatory pathways.

Conversely, stingers demonstrated upregulation of pathways related to extracellular matrix (ECM) structure, cell adhesion, inflammatory processes, and PI3K-Akt signaling, alongside downregulation of genes involved in cortisol synthesis, insulin secretion, calcium flux, and steroid hormone pathways (Figure 5 and 6). Notably, the PI3K-Akt pathway has been implicated in capsaicin-induced cellular responses, including apoptosis and modulation of inflammatory signaling [11]. These findings underscore profound differences in capsaicin response between the two populations and suggest a potential role for hormones—thyroid hormones in non-stingers and corticosteroids in stingers—in mediating the stinging response.

Further comparative analysis under homeostatic conditions revealed that stingers had pre-existing upregulation of genes associated with epidermal development and cell differentiation, as well as downregulation of thyroid hormone regulation, Wnt signaling, and cell adhesion pathways (Figure 8). These gene signatures may serve as potential markers for early identification of stingers and non-stingers, facilitating the development of non-invasive diagnostic methods and providing insight into the molecular distinction between these groups as already highlighted in other contexts [12].

Upon capsaicin treatment, stingers uniquely activated pathways such as chemokine signaling and steroid hormone synthesis, while downregulating genes related to Phosphatidylinositol signaling, cortisol synthesis, cell junctions, and IGF signaling (Figure 9). These stinger-specific pathways could represent novel targets for personalized interventions aimed at mitigating the stinging response to irritants.

A comprehensive comparison of DEGs identified 111 genes that were consistently differentially expressed between the two groups, independent of treatment. These data provide, for the first time, insight into the short-term molecular mechanisms activated by capsaicin exposure. The results not only improve our understanding of the biological basis for stinging perception in a subset of the population but also highlight candidate genes for the development of innovative cosmetic products designed to alleviate irritant-induced stinging.

Future studies should focus on validating the most promising candidate genes and pathways, with the goal of identifying robust biomarkers for stinger and non-stinger phenotypes and discovering new therapeutic targets.

5. Conclusion

The results of this study provide the first detailed insight into the short-term molecular mechanisms activated by capsaicin exposure. Our findings identify novel key markers that can distinguish stinger and non-stinger populations and clarify the specific pathways contributing to stinging sensations in a subset of individuals. Additionally, we have highlighted new candidate genes and pathways as potential targets for innovative cosmetic interventions aimed at alleviating irritant-induced stinging reactions.

By adding a molecular perspective to the complex phenomenon of sensitive skin, this study advances our understanding of the underlying biological processes and introduces specific molecular players that can be linked to clinical skin measurements. These insights pave the way for the development of more precise and personalized solutions for managing skin discomfort associated with sensitivity and stinging responses.

Future research should focus on validating these identified markers and pathways, as well as integrating molecular findings with clinical outcomes, to further refine new cosmetic strategies for sensitive skin.

References

1. Berardesca, E., M. Farage, and H. Maibach, *Sensitive skin: an overview.* Int J Cosmet Sci, 2013. **35**(1): p. 2-8.
2. Farage, M.A., *The Prevalence of Sensitive Skin.* Front Med (Lausanne), 2019. **6**: p. 98.
3. Buhe, V., et al., *Pathophysiological Study of Sensitive Skin.* Acta Derm Venereol, 2016. **96**(3): p. 314-8.
4. Ilie, M.A., et al., *Capsaicin: Physicochemical properties, cutaneous reactions and potential applications in painful and inflammatory conditions.* Exp Ther Med, 2019. **18**(2): p. 916-925.
5. Li, Q., et al., *Lactic acid sting test and capsaicin test differentially induce facial erythematous reaction in subjects with sensitive skin.* J Cosmet Dermatol, 2024. **23**(3): p. 1009-1014.
6. Yu, L.L., et al., *Correlation between the capsaicin test and objective skin measurements in evaluating sensitive skin in Chinese females.* J Dermatol Sci, 2012. **68**(2): p. 108-9.
7. Jansen, B.J. and J. Schalkwijk, *Transcriptomics and proteomics of human skin.* Brief Funct Genomic Proteomic, 2003. **1**(4): p. 326-41.
8. Kuehne, A., et al., *An integrative metabolomics and transcriptomics study to identify metabolic alterations in aged skin of humans in vivo.* BMC Genomics, 2017. **18**(1): p. 169.
9. Jourdain, R., et al., *Detection thresholds of capsaicin: a new test to assess facial skin neurosensitivity.* J Cosmet Sci, 2005. **56**(3): p. 153-66.
10. Braga Ferreira, L.G., et al., *Capsaicin: TRPV1-independent mechanisms and novel therapeutic possibilities.* Eur J Pharmacol, 2020. **887**: p. 173356.
11. Zhang, J.H., et al., *Involvement of the phosphoinositide 3-kinase/Akt pathway in apoptosis induced by capsaicin in the human pancreatic cancer cell line PANC-1.* Oncol Lett, 2013. **5**(1): p. 43-48.
12. Wu, D., et al., *Capsaicin suppresses breast cancer cell viability by regulating the CDK8/PI3K/Akt/Wnt/beta-catenin signaling pathway.* Mol Med Rep, 2020. **22**(6): p. 4868-4876.