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# Spatial Transcriptomics in Darier Disease

Master's Thesis in Bioinformatics

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# Abstract

Darier disease (DD) is a genetic skin disorder caused by *ATP2A2* mutations that disrupt SERCA2-mediated calcium homeostasis, leading to epithelial stress and impaired epidermal integrity. This thesis integrates bulk RNA sequencing with single-cell spatial transcriptomics using the CosMx Spatial Molecular Imager to characterize the molecular and spatial consequences of *ATP2A2* dysfunction. Bulk RNA-seq revealed a strong IL-17/IL-36–driven inflammatory program, keratinocyte hyperproliferation, and loss of differentiation and lipid-metabolism pathways. Spatial transcriptomics resolved these global signatures into discrete keratinocyte states—including inflamed suprabasal, differentiated, and hyperproliferative basal populations—and demonstrated fragmentation of the basal layer alongside the formation of compact epithelial–immune aggregates. Spatial analysis further showed that Darier disease is characterized by spatially restricted cytokine-responsive activation rather than diffuse inflammation across the epithelium. This work highlights the value of integrating bulk and spatial transcriptomics to dissect complex skin diseases and identifies epithelial-intrinsic cytokine pathways as potential therapeutic targets.

## Declaration of GAI use

Throughout this project, I used generative AI tools (ChatGPT and Copilot) to support conceptual understanding, inform the selection and execution of analytical methods—including R code generation—and enhance the writing process by offering critical feedback on clarity, logical flow, and completeness.

## For the reader,

In this thesis, supplementary figures are hyperlinked to their placement in the end of the document, where you'll also find hyperlinks that'll take you back to the main text.

# Abbreviations

<i>ATP2A2</i>	Gene encoding SERCA2
DD	Darier Disease
SERCA2	Sarco/endoplasmic reticulum Ca <sup>2+</sup> -ATPase 2
LS	Lesional skin
NL	Non-lesional skin
FFPE	Formalin-fixed paraffin-embedded
ER	Endoplasmic reticulum
UPR	Unfolded protein response
RNA-seq	RNA sequencing
DGE	Differential gene expression
GSEA	Gene set enrichment analysis
HVG	Highly variable genes
PCA	Principal component analysis
UMAP	Uniform Manifold Approximation and Projection
kNN	k-nearest neighbors
VST	Variance stabilizing transformation
FDR	False discovery rate
NES	Normalized enrichment score
DEGs	Differentially expressed genes
CosMx SMI	CosMx Spatial Molecular Imager
ISH	In situ hybridization
MERFISH	Multiplexed Error-Robust FISH
NK	Natural killer cells
DC	Dendritic cell
IL	Interleukin (IL-1, IL-17, IL-36, etc...)

# List of Figures

Figure 1 Structure of the human epidermis. Schematic representation of the major epidermal layers and their organization above the dermis.....	1
Figure 2 Classical lesions of Darier disease in the skin and nails.....	3
Figure 3 Calcium handling in keratinocytes regulates epidermal differentiation and integrity.....	5
Figure 4 CosMx SMI chemistry and workflow.....	9
Figure 5. Overview of data modalities and analytical workflow.....	10
Figure 6 Schematic of multiscale hexagonal neighborhood definitions used for spatial analysis.....	18
Figure 7 Principal component analysis of bulk RNA seq samples.....	22
Figure 8 Sample-to-sample correlation heatmap of bulk RNA seq data.....	23
Figure 9 Differential gene expression between lesional and non-lesional skin in Darier disease.....	24
Figure 10 Hallmark pathway enrichment in lesional versus non lesional skin.....	26
Figure 11 Negatively enriched Hallmark pathways in lesional versus non lesional skin.....	28
Figure 12 UMAP embedding illustrating 16 transcriptionally distinct cell populations derived from the kNN graph (resolution = 1).....	30
Figure 13 UMAP embedding of the CosMx dataset showing the spatial organization of the 16 transcriptionally defined clusters with cell type annotations.....	32
Figure 14 Biopsy plots for two Darier disease samples (left: Biopsy #9; right: Biopsy #14).....	33
Figure 15 Global transcriptional landscape of Darier and normal skin samples visualized by UMAP.....	34
Figure 16 Cell type proportions in Darier disease and normal skin.....	35
Figure 17 Same-type proportions across cell types and neighborhood sizes (k = 6, 18, 36, 100) in Darier and normal skin.....	37
Figure 18 Spatial visualization of same-type proportions in normal and Darier skin.....	38
Figure 19 Differential gene expression between Darier disease and healthy skin.....	40
Figure 20 Number of significantly upregulated genes per cell type in Darier disease.....	42
Figure 21 Summary of significantly up-regulated genes per cell type.....	43
Figure 22 Normalized enrichment scores (NES) for the top ten Hallmark pathways enriched in Darier disease compared with healthy control skin in the CosMx dataset.....	45
Figure 23 Pathway activation across cell types in Darier skin.....	47
Figure 24 Spatial localization of IL-17 pathway activity across four Darier biopsies.....	48

# Table of Contents

<b>1 Introduction</b>	<b>1</b>
1.1 Overview of Epidermal Structure and Barrier Function	1
1.2 Genetic and Clinical Background of Darier Disease	2
1.3 SERCA2 Dysfunction and Epidermal Calcium Homeostasis	4
1.4 Multisystem Involvement and Current Management	6
1.5 Transcriptomic Approaches	7
1.5.1 CosMx Spatial Molecular Imager	8
1.6 Aim of the Study	9
<b>2 Data and Methods</b>	<b>11</b>
2.1 Data Collection	11
2.1.1 Bulk RNA-seq Dataset	12
2.1.2 CosMx SMI Dataset	12
2.1.3 Limitations of the Data	12
2.2 Preprocessing and Quality Control	13
2.2.1 Bulk RNA-seq Preprocessing and QC	13
2.2.2 CosMx Preprocessing and QC	14
2.3 Bulk RNA-seq Analyses	15
2.3.1 Differential Expression (LS vs NL)	15
2.3.2 Pathway Enrichment Analysis	15
2.4 CosMx Analyses	16
2.4.1 Dimensionality Reduction and Clustering	16
2.4.2 Cell Type Annotation	16
2.4.3 Cellular Composition Analysis	17
2.4.4 Spatial Neighborhood Analysis	17
2.4.5 Differential Expression (Darier vs Healthy)	19
2.4.6 Pathway Analyses	19
<b>3 Results and Integrated Interpretation</b>	<b>21</b>
3.1 Bulk RNA-seq	21
3.1.1 Dataset Overview and QC	21

3.1.2 Differential Gene Expression Analysis.....	23
3.1.3 Pathway Enrichment Analysis .....	25
3.1.4 Summary: Global Transcriptional Trends and Rationale for Spatial Analysis.....	29
3.2 CosMx ST.....	29
3.2.1 Clustering and UMAP Visualization .....	29
3.2.2 Cell Type Annotation.....	30
3.2.3 Epidermal Cellular Composition in Darier Disease.....	34
3.2.4 Neighborhood Analysis.....	36
3.2.5 Differential Gene Expression Analysis.....	39
3.2.6 Pathway Analyses .....	44
3.3 Integrated Interpretation of Bulk and Spatial Transcriptomics .....	49
<b>4 Future Perspectives.....</b>	<b>50</b>
<b>5 Concluding Remarks .....</b>	<b>52</b>
<b>References .....</b>	<b>53</b>
<b>Supplementary Material.....</b>	<b>56</b>
Code Availability .....	56