AARHUS UNIVERSITY · DEPARTMENT OF BIOINFORMATICS

Spatial Transcriptomics in Psoriasis

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Abstract

This thesis is part of the Dermatology Research Across Multiple Disciplines (DREAM) project, a systems medicine initiative studying immune-mediated inflammatory diseases using skin as a clinical entry point. Psoriasis is a chronic inflammatory skin disease affecting 2–3% of the global population, characterised by keratinocyte hyperproliferation, impaired differentiation, and dysregulated crosstalk between resident skin cells and infiltrating immune populations. Despite well-characterised immunopathology, the molecular, morphological, and spatial basis of lesion formation remains incompletely understood, and substantial heterogeneity in disease phenotype and treatment response highlights the need for approaches that can characterise the disease across multiple biological levels simultaneously.

To address this, a spatial single-cell transcriptomic analysis was performed on paired lesional and non-lesional skin biopsies from seven psoriasis patients profiled using the CosMX Spatial Molecular Imager with a 6,000-plex RNA panel. Two complementary aims were pursued: a biological aim to characterise the molecular, morphological, and spatial architecture of psoriatic skin, and a methodological aim to evaluate what insights can be gained from spatial single-cell transcriptomic data. Analyses combined dimensionality reduction, proliferation analysis, differential gene expression, morphological quantification, spatial autocorrelation, and cell-cell communication inference using SpatialCellChat.

Across all analytical frameworks, lesional skin was consistently distinguished from non-lesional skin by coordinated remodelling of tissue architecture rather than simple changes in gene expression. Inflammatory and hyperproliferative keratinocyte populations were numerically expanded, transcriptionally heterogeneous, and physically aggregated into spatially coherent inflammatory foci, while immune cell infiltration and stromal remodelling were reflected in both differential gene expression and elevated spatial clustering. Morphological analysis revealed cell-type-specific enlargement and nuclear rounding in lesional skin independently of proliferative activity, consistent with cytokine-driven remodelling rather than cell cycle effects. Differential expression confirmed broad upregulation of alarmin, stress keratin, and antigen presentation signatures across multiple cell types, suggesting a tissue-wide inflammatory response extending beyond the keratinocyte compartment. Cell-cell communication analysis showed that lesional skin is characterised by amplified signalling intensity and lesion-enriched pathway activity, with ECM remodelling, immune recruitment, and epithelial integrity pathways most significantly upregulated. Across all frameworks, homeostatic populations including differentiated keratinocytes showed remarkable stability regardless of lesional status, forming a coherent counterpoint to the activated compartments.

Together, these findings demonstrate that spatially resolved transcriptomics can capture tissue organisation, cellular morphology, and intercellular communication alongside gene expression within a single experiment. The analytical infrastructure established here provides a direct foundation for the DREAM project's broader ambition of understanding how disease

heterogeneity and treatment response may be encoded across these dimensions in inflamed tissue.

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Thesis overview

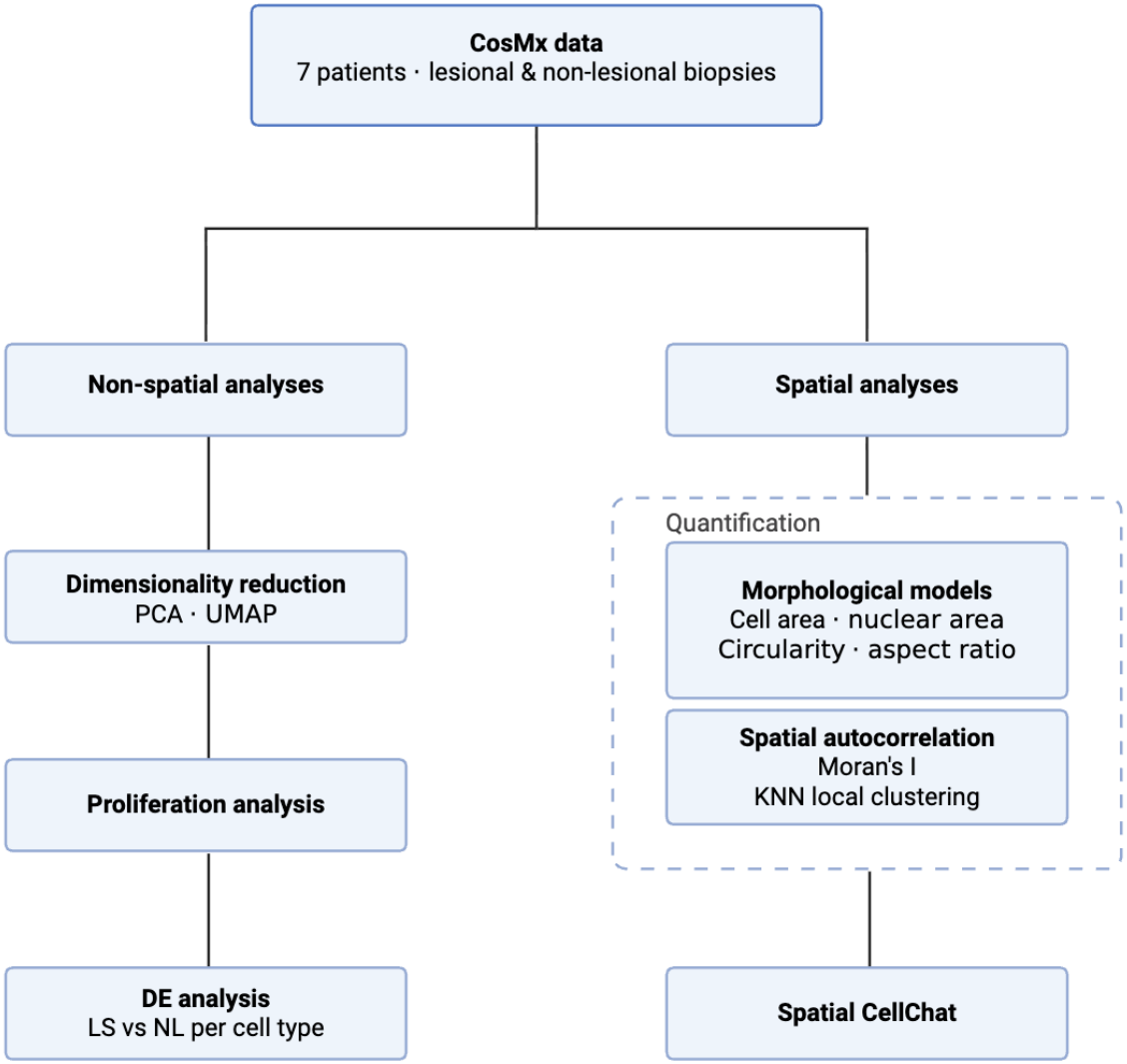

Figure 1. Thesis overview. *Spatial transcriptomic data were obtained from paired lesional and non-lesional skin biopsies from 7 psoriasis patients using CosMX SMI, with each patient serving as their own control. Data were analysed across two independent tracks: non-spatial analyses including dimensionality reduction (PCA and UMAP), proliferation analysis and DE analysis, and spatial analyses comprising morphological mixed models, spatial autocorrelation (Moran's I and KNN local clustering), and spatial CellChat.*

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