Introduction

- Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease.
- HS is characterised by the formation of inflammatory nodules and fibrotic scarring.
- Adalimumab (anti-TNF) is the only approved targeted therapy for HS, however only ~50% respond to treatment.
- Hyperkeratosis is an important event in HS pathogenesis, suggesting that keratinocytes are key players in HS.

HS pathogenesis remains unclear and the role for non-immune cells has yet to be elucidated.

Methods

- Pseudotime trajectory analysis demonstrates that hyperproliferative keratinocytes have an altered differentiation program to normal spinous keratinocytes.
- Key inflammatory cytokines, chemokines and anti-microbial peptides are expressed in hyperproliferative keratinocytes.
- Metabolic pathway activity increases in HS lesional keratinocytes compared with healthy control keratinocytes.

Results

- Hyperproliferative keratinocytes are enriched in HS lesions compared with healthy control skin.
- Anti-microbial peptides, IL-17 signaling and oxidative phosphorylation are enriched in HS keratinocytes.
- Th17-derived ligands interact with hyperproliferative keratinocytes, inducing the expression of significantly differentially expressed genes.

Findings

- scRNA-seq identified 23 distinct cell clusters in CD45- cells derived from HS lesional and healthy control skin.
- 6 keratinocyte populations were identified, with hyperproliferative keratinocytes significantly increased in HS lesions compared with healthy controls.
- Th17 cells likely interact with hyperproliferative keratinocytes inducing the expression of antimicrobial peptides (S100A8, S100A9) and proinflammatory mediators (CXCL1, CXCL8).
- Hyperproliferative keratinocytes have a dysregulated differentiation program compared with healthy keratinocytes.
- Hyperproliferative keratinocytes have altered metabolic activity compared with healthy keratinocytes.

Next steps

1. Identify key transcription factors driving this dysregulated differentiation program in hyperproliferative keratinocytes
2. Validate the findings of an altered metabolic profile in HS keratinocytes ex vivo
3. Evaluate the expression and release of key inflammatory mediators from HS keratinocytes following treatment with novel targeted therapies.

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