Multiple Mediators of Inflammation Correlate with IRAK4 Expression in the Skin of Hidradenitis Suppurativa Patients and are Blocked by the IRAK4 Degrader KT-474 in TLR-activated Monocytes

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Afsaneh Alavi

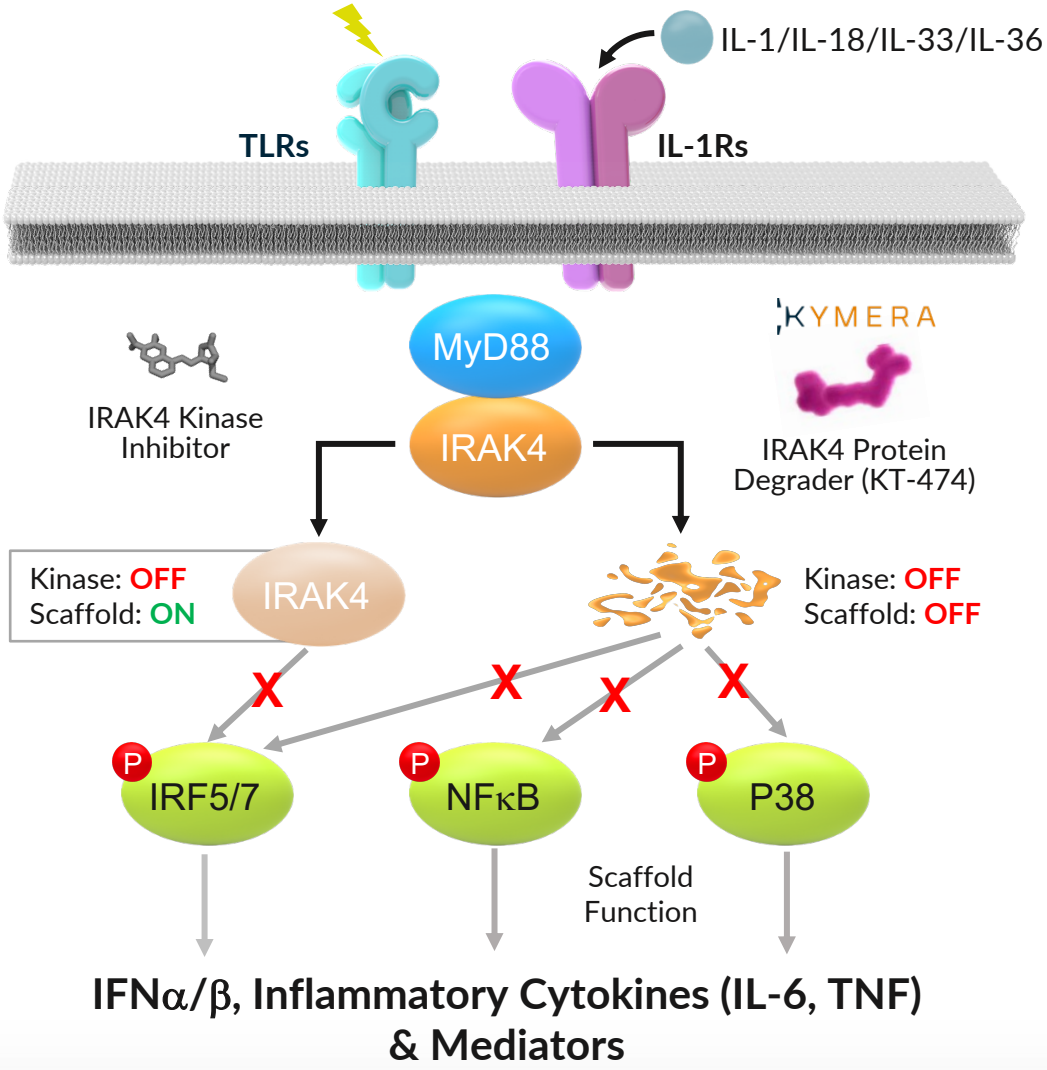
Dr. Alavi has been investigator and received honoraria from AbbVie, Arcutis, BMS, Boehringer-Ingelheim, Bausch, Celgene , Dermira, Dermovant, DSBiopharma, Eli Lilly, EMD Serono, Galderma, Glenmark, GSK, Incyte, Ilkos, Janssen, LEO Pharma, Kyowa Kirin, Kymera, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Aventis, UCB, Valeant, Xenon, and Xoma.

Veronica Campbell, Alice McDonald, Stephanie Skouras, Jeffrey Davis, Anthony Slavin, Rahul Karnik, Nello Mainolfi, Jared Gollob

Kymera Therapeutics employment and equity ownership.

Central Role of IRAK4 in TLR/IL-1R Pathway Activation

Development of Kymera IRAK4 degrader KT-474



- IRAK4 is a key component of the **myddosome complex** mediating signaling through TLRs and IL-1Rs
- Both the **scaffolding** and **kinase** functions of IRAK4 are involved in the activation of multiple downstream signaling pathways driving inflammation
- Downregulation of IRAK4 protein expression via targeted protein degradation results in **superior pathway blockade** compared to IRAK4 kinase inhibition
- Kymera is developing a selective IRAK4 protein degrader, KT-474, for the treatment of TLR/IL-1R-driven **autoimmune/autoinflammatory diseases**
- A Phase 1 trial of KT-474 is underway in healthy volunteers and patients with **hidradenitis suppurativa** (HS) or **atopic dermatitis** (AD)
- An ongoing Non-Interventional Study is characterizing **IRAK4 expression** and its relationship to **inflammatory biomarkers** in HS and AD

Non-interventional Study of IRAK4 and Inflammatory Biomarkers in HS and AD Patients

Design

Number of Sites	Single center (York Dermatology Clinic and Research Center, Ontario, Canada) PI: Dr. Afsaneh Alavi, MD, MSch, FRCPC, Mayo Clinic
Number of Patients	40 (30 HS and 10 AD)
Inclusion Criteria	1. Age 18 or older 2. Active Hidradenitis Suppurativa (HS) or Atopic Dermatitis (AD), diagnosed by PI 3. Mild, moderate, and severe HS (by IHS4 score) or AD (by EASI score) patients
Exclusion Criteria	1. Patients currently on a biologic or other immunosuppressive treatment for HS or AD 2. Use of biologic treatment for HS or AD within 3 months or 5 half-lives, whichever is longer 3. Use of non-biologic immunosuppressive treatment (eg. Cyclosporin) in the last 4 weeks.
Data Collection at Study Entry	Medical history, disease severity in HS (Hurley, PGA, IHS4, HASI) and AD (EASI), prior treatments, comorbidities, duration of disease
Sample Collection	Whole blood, plasma, skin (Lesion [L], Peri-lesion [PL: <2 cm away from lesion], Non-lesion [NL: >10 cm away from lesion])

Baseline Demographics & Biomarkers

Study Duration	• FPI: 28May2020 • HS and AD accrual completed: 24Mar2021
Patients Enrolled to Date	• 30 HS: 9 mild, 10 moderate, 11 severe • 10 AD: 8 mild, 1 moderate, 1 severe
Demographics	• Age 19-78 yrs • 13 male, 27 Female • Duration of disease: 1-56 years • Race: 98% were non-Hispanic or Latino
Biomarker Endpoints	• Targeted MS of IRAK4 in skin biopsies • IRAK4 immunofluorescence in skin biopsies • Proinflammatory gene transcripts in skin biopsies • Flow cytometry for IRAK4 in ex vivo treated whole blood • Cytokines from *ex vivo* treated whole blood • Plasma cytokines and acute phase reactants
Reporting Status	• Interim data on IRAK4 expression in HS skin and blood presented in October 2020 at SHSA Meeting • **Current presentation focuses on full HS skin dataset for IRAK4 protein and proinflammatory gene transcripts as well as healthy skin and monocyte controls**

Methods for Measuring IRAK4 Protein and Pro-Inflammatory Gene Transcripts in HS Skin Biopsies and Healthy Subject Skin/Monocytes

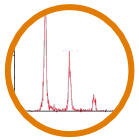
NI Study Methods

HS Skin Biopsies (N=30)

Lesion (L), Peri-lesion (PL), Non-lesion (NL)

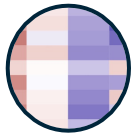
IRAK4
Immunofluorescence (IF)
Localization/ Semi-quant

1. Expression in L vs PL vs NL
2. Expression by disease severity
3. Expression in Epidermis vs Dermis



IRAK4
Mass Spectrometry (MS)
Whole Tissue/Quantitative

1. Expression in L vs PL vs NL
2. Expression by disease severity



NanoString
Gene Expression Profiling (GEP)
Whole Tissue

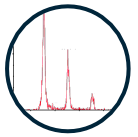
1. Significantly elevated genes in L vs NL
2. Spearman correlation of elevated genes with IRAK4 protein levels by MS and IF

Control Methods

Healthy Subject Skin Biopsies (N=10)

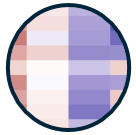
IRAK4
Immunofluorescence (IF)

1. Expression in Healthy vs HS
2. Expression in Epidermis vs Dermis



IRAK4
Mass Spectrometry (MS)

1. Expression in Healthy vs HS



NanoString
Gene Expression Profiling (GEP)

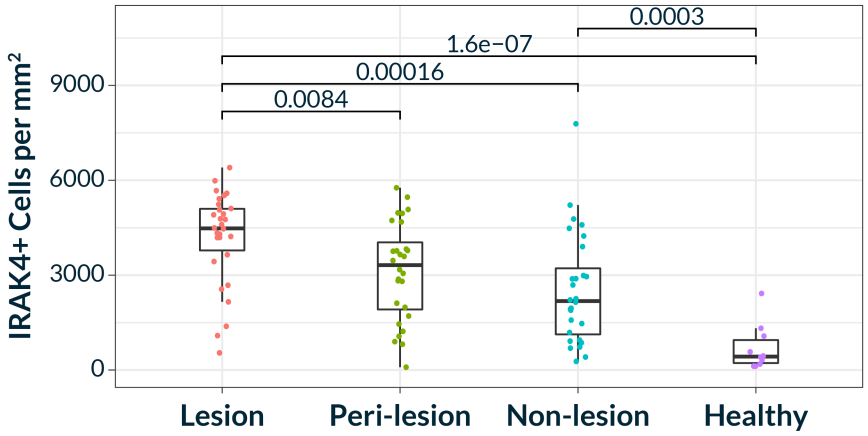
1. Significantly elevated genes in HS vs Healthy
2. Spearman correlation of elevated genes with IRAK4 protein levels by MS and IF

Ex-vivo R848-Stimulated Monocyte Methods

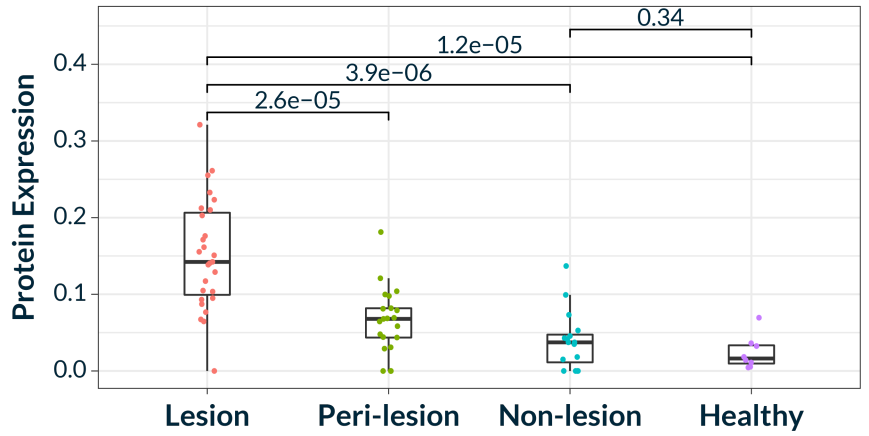
1. Mechanistic study designed to evaluate impact of IRAK4 degradation on response of healthy monocytes to TLR7/8 agonist R848
2. Monocytes isolated from blood of healthy donors (N=3), treated overnight with 500nM of IRAK4 degrader KT-474, and then stimulated with R848
3. For RNA-seq, cells were collected at 2 hours following stimulation
4. Analysis of KT-474 effect on R848 upregulation of subset of genes overexpressed in HS skin lesions that correlate with IRAK4 protein levels

IRAK4 Protein Expression is Elevated in HS Skin Compared to Skin from Healthy Subjects

Immunofluorescence (IF)



Mass Spectrometry (MS)



Immunofluorescence (IF)

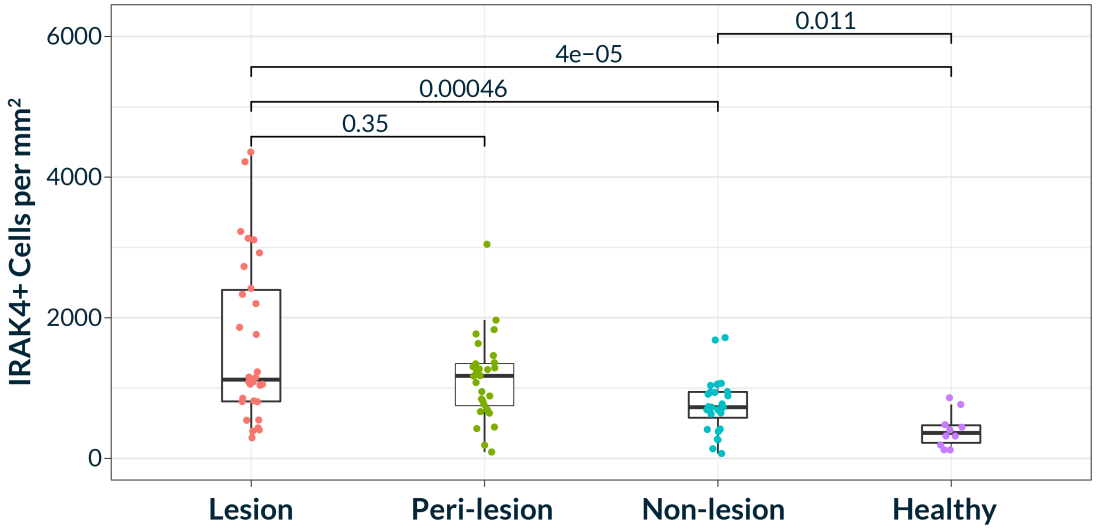
- Concordance between IF and MS for HS patients
- HS patients: Lesion > Peri-lesion > Non-lesion
- IF shows significant difference between HS Non-lesion skin and Healthy subject skin

Similar expression across disease severity*

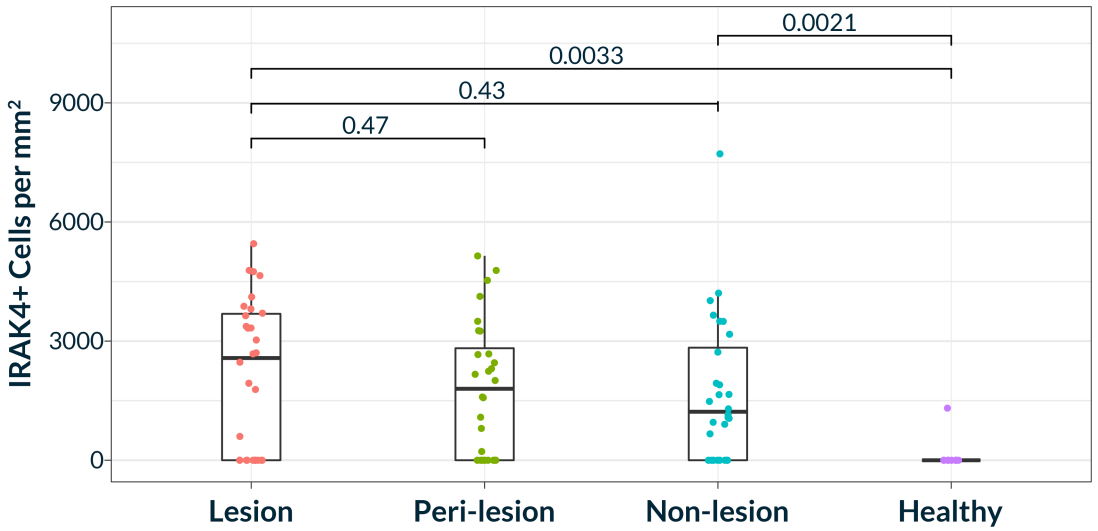
*By IHS4 severity score

IRAK4 is Upregulated in Dermis and Epidermis of HS Patients Relative to Skin of Healthy Subjects

Dermal Immune Cells



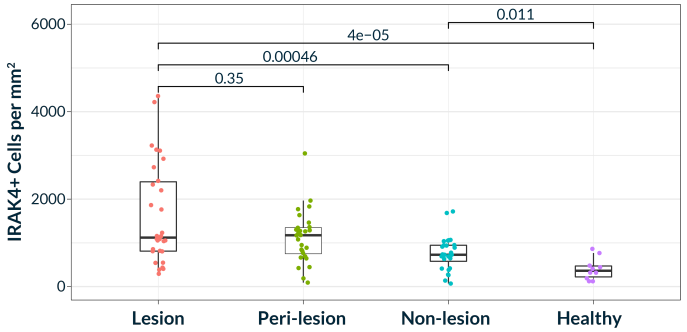
Epidermal Keratinocytes



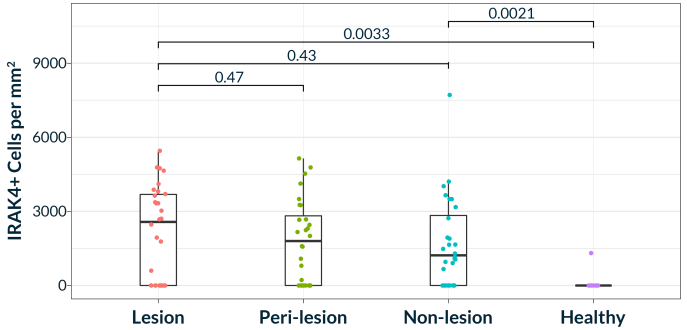
- IF shows increased number of IRAK4+ immune cells in dermis with HS Lesion/Peri-lesion > HS Non-lesion > Healthy subjects
- Epidermal IRAK4 positivity similar across biopsy sites in HS patients but significantly higher compared to Healthy subjects

IRAK4 is Upregulated in Dermis and Epidermis of HS Patients Relative to Skin of Healthy Subjects

Dermal Immune Cells



Epidermal Keratinocytes



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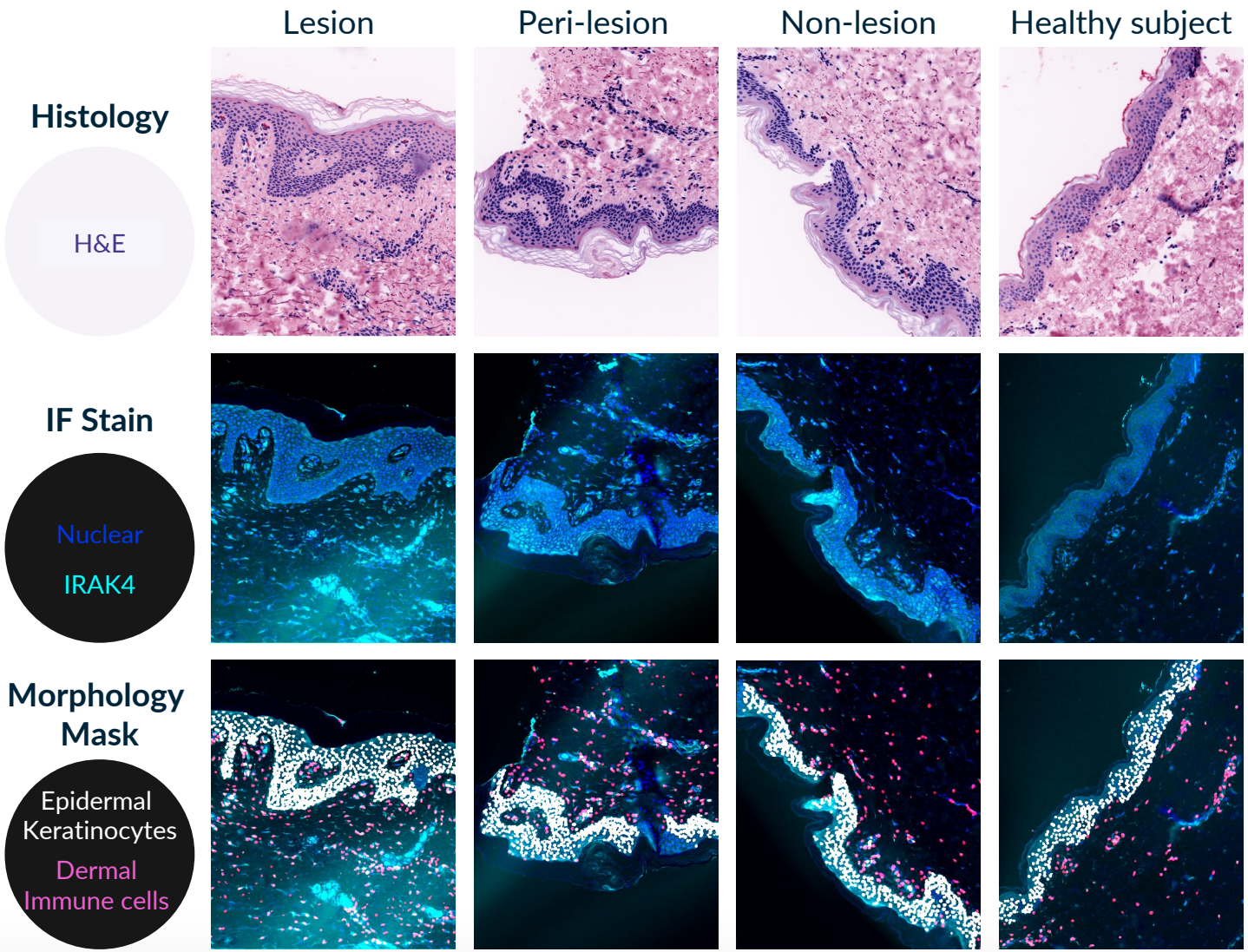
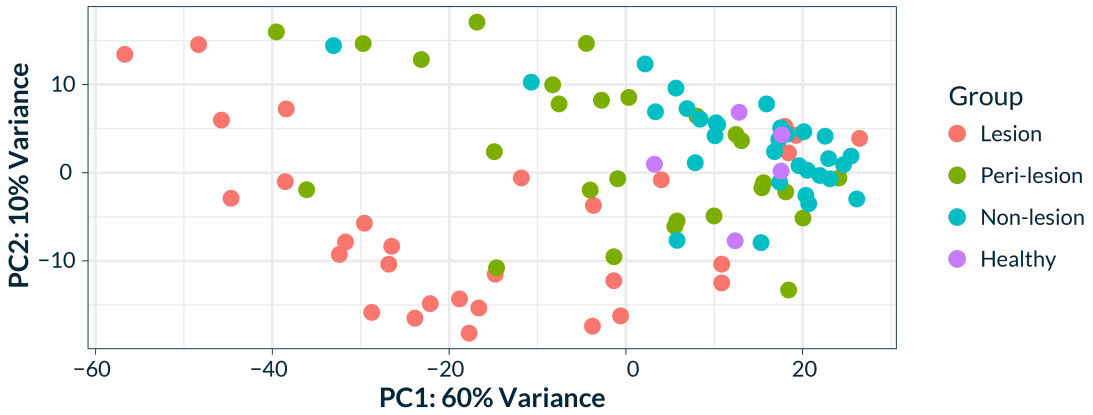
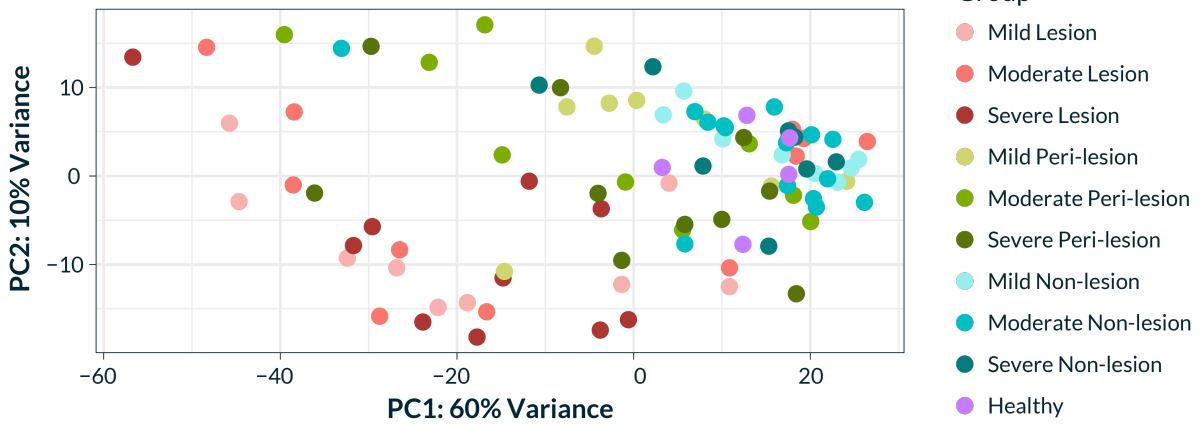


Transcriptional Profiling Shows Clear Differences Between HS Skin Biopsy Sites, But Not Across Disease Severity

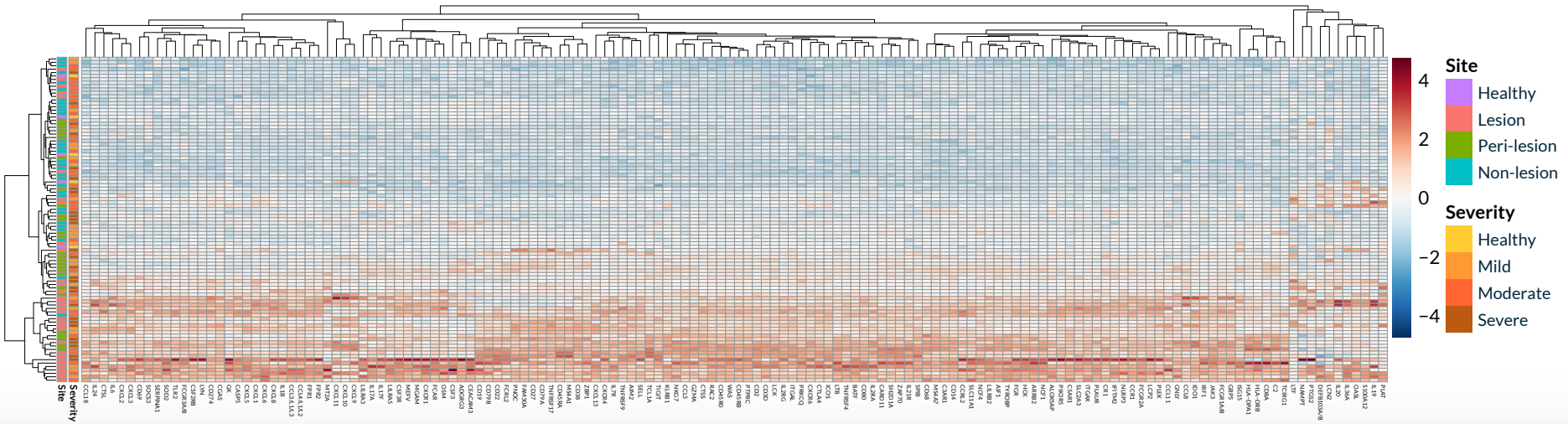
Lesion Samples Cluster Separately in PCA Plot of Transcript Profiles



Transcript Profiles are not Differentiated by Disease Severity



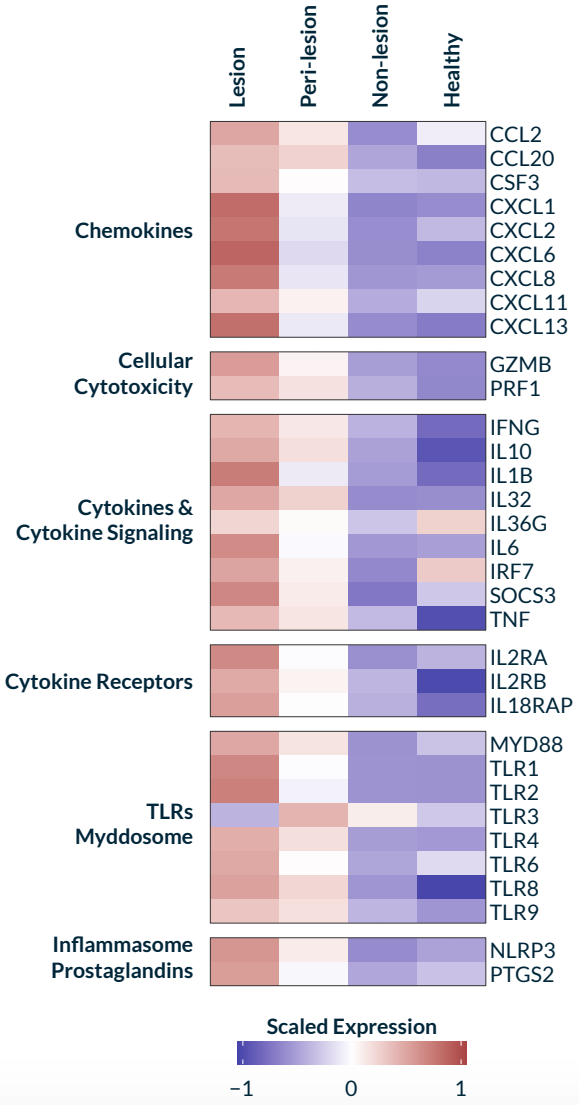
Differentially Expressed Genes – Lesion vs Non-lesion

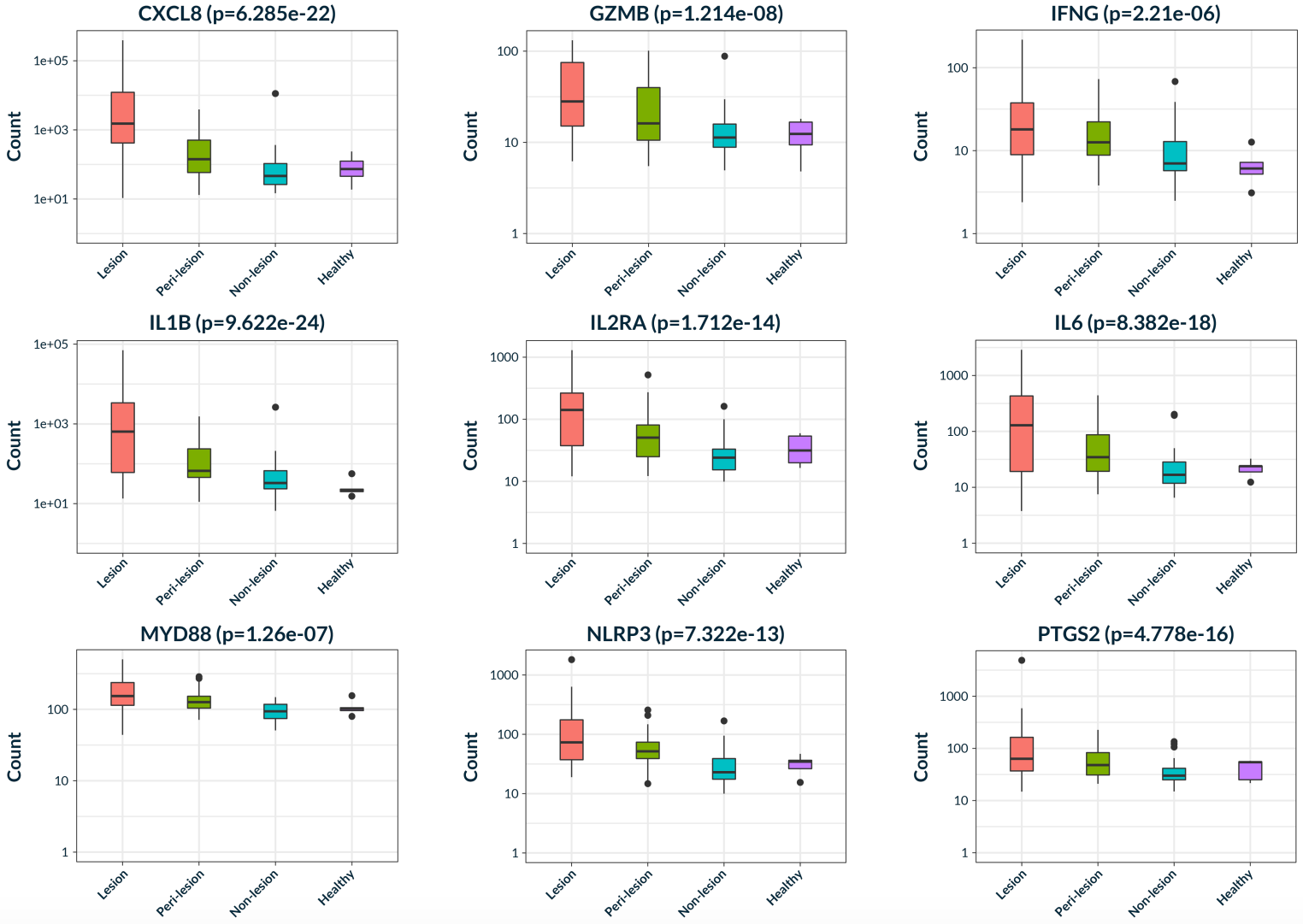


p-value < 0.0001,
fold change >= 4

Lesion samples show many upregulated genes relative to Peri- and Non-lesion samples

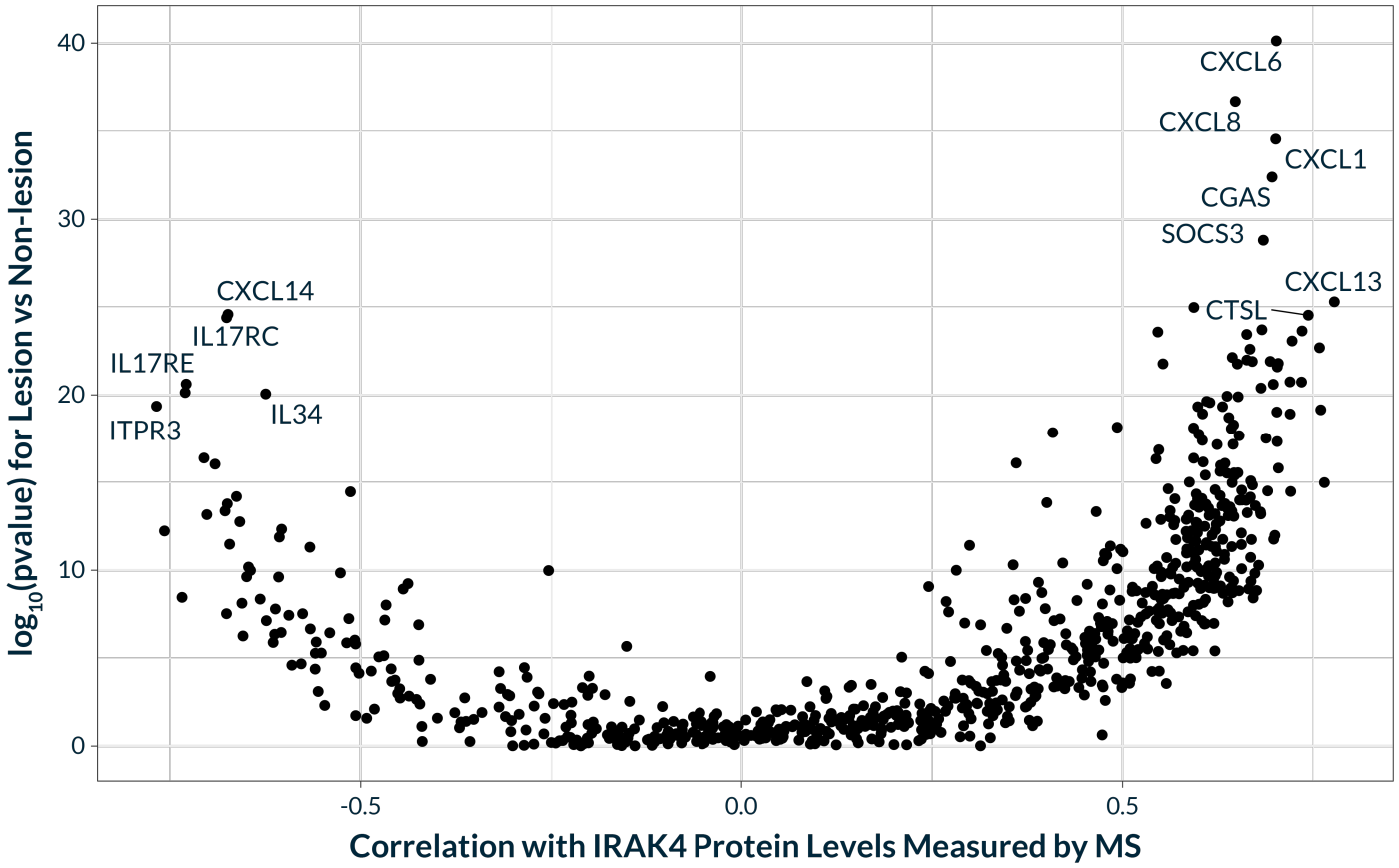
Transcripts for Multiple Mediators of Inflammation are Upregulated in HS Skin Lesions

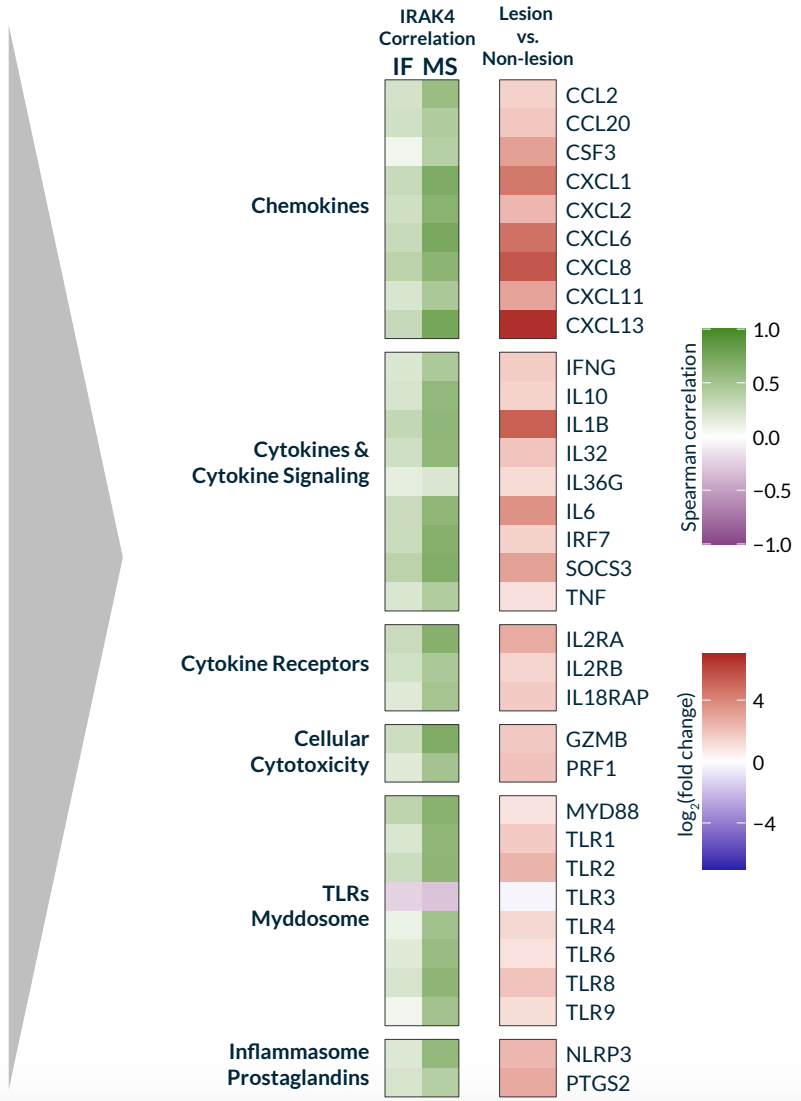




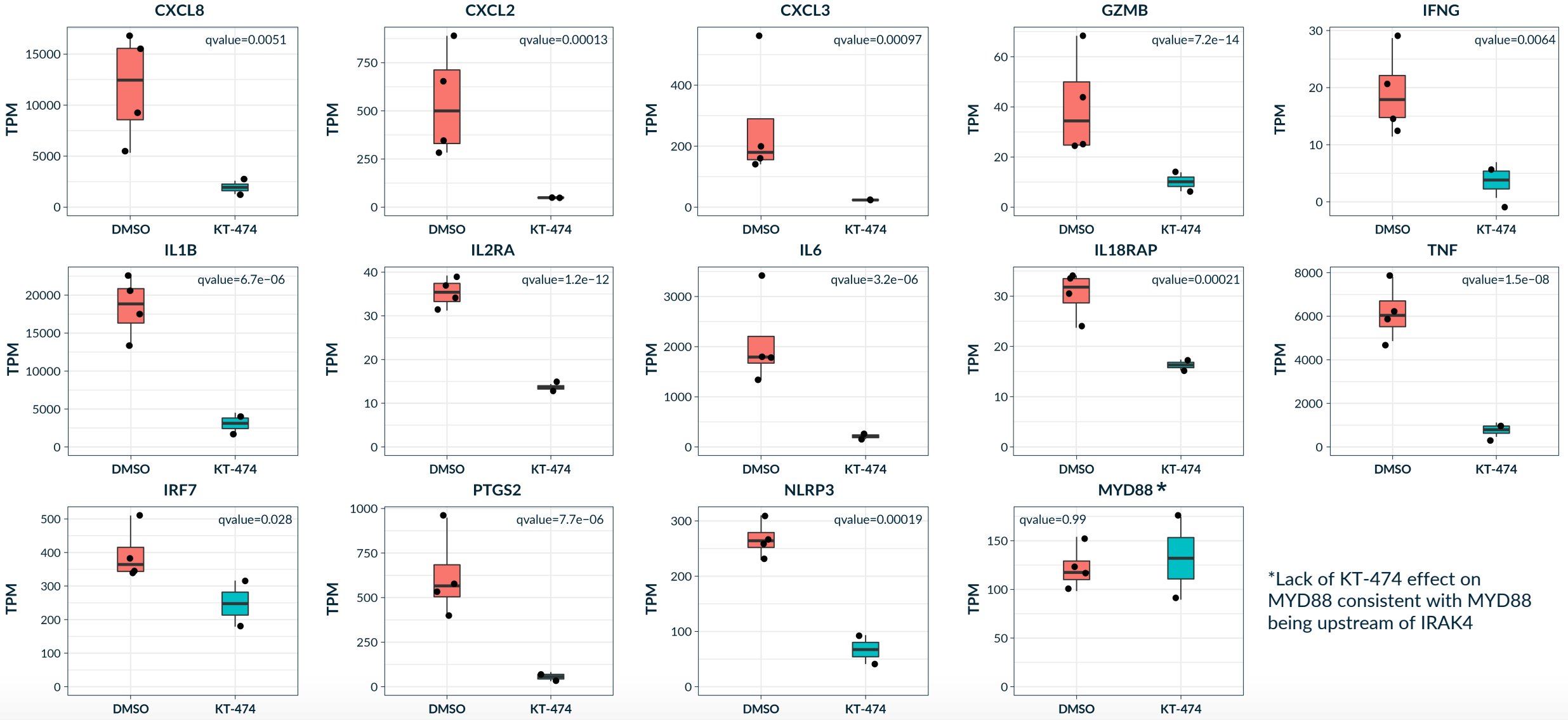
All p-values are for differential expression in Lesions vs Non-lesions

Multiple Proinflammatory Transcripts Correlate with IRAK4 Protein Levels in HS Skin Lesions





IRAK4 Degrader KT-474 Inhibits TLR-Mediated Induction of HS-Overexpressed Proinflammatory Transcripts in Healthy Monocytes



*Lack of KT-474 effect on MYD88 consistent with MYD88 being upstream of IRAK4

Conclusions

- **IRAK4 is overexpressed in HS skin relative to healthy subjects due to increase in number of IRAK4+ dermal immune cells and epidermal keratinocytes**
  - Higher expression in active HS skin Lesions compared to Peri-lesion and/or Non-lesion skin associated with increase in infiltrating IRAK4+ dermal immune cells
  - Higher expression in dermis and epidermis of Non-lesion skin compared to skin of Healthy subjects raises possibility that IRAK4 overexpression may predispose to inflammatory lesion formation in HS
- **Gene expression profiling shows upregulation of multiple mediators of inflammation in HS skin lesions that correlates with IRAK4 protein overexpression**
  - Includes genes involved in TLR/myddosome signaling, inflammasome activity, prostaglandin generation, Th1 and Th17 inflammation, and monocyte/neutrophil migration and activation, thereby linking IRAK4 to the pleiotropic inflammation in HS
  - Neither proinflammatory gene expression nor IRAK4 protein expression correlated with disease severity, suggesting common pathophysiology underlying inflammation in active lesions irrespective of disease stage
- **IRAK4 degrader KT-474 inhibits TLR-stimulated upregulation of HS-overexpressed inflammatory genes in monocytes from healthy subjects**
  - Provides further evidence for role of IRAK4 in overexpression of these mediators of inflammation in HS skin Lesions and rationale for targeting IRAK4 with KT-474 for the treatment of patients with HS
  - Phase 1 trial of KT-474 in healthy volunteers and patients with HS or AD is ongoing and includes pre- and post-treatment skin biopsies and blood sampling to assess the effect of KT-474 on the expression of IRAK4 and associated biomarkers of inflammation