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MRGPRX2 Specific Activation Signature is Enriched in Atopic Dermatitis Skin Lesions and Wheals from Chronic Spontaneous Urticaria Skin Compared to Adjacent Healthy Skin

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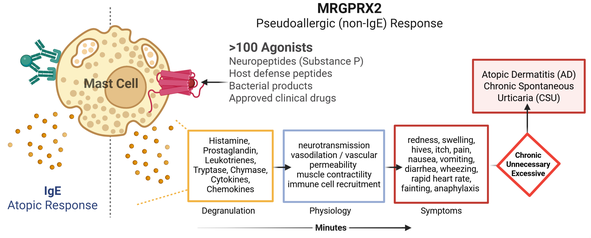
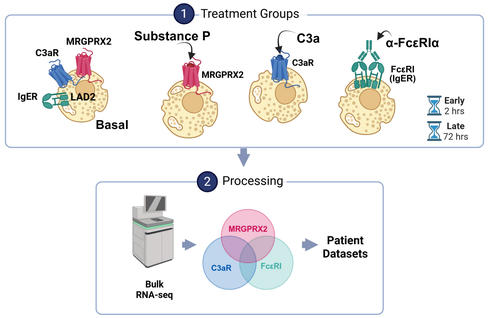
Background

Mas-related G protein-coupled receptor X2 (**MRGPRX2**) is a mast cell-specific G protein-coupled receptor (GPCR) that triggers robust mast cell activation through an IgE-independent mechanism.

Here, we utilized a propriety MRGPRX2-specific activation gene signature to probe publicly available datasets of Atopic Dermatitis (AD) and Chronic Spontaneous Urticaria (CSU) patients. We show that MRGPRX2 activation is enriched in diseased tissue from AD and CSU patients, indicating that abnormal activation of MRGPRX2 is likely driving pathophysiology.



Methods



Study Design - An MRGPRX2-specific transcriptional activation signature was generated using the LAD2 human mast cell line. LAD2s were stimulated with Substance P (MRGPRX2 agonist), C3a (C3aR agonist), or anti-FcεRIα (to activate the IgE receptor, IgER) and collected for bulk RNA sequencing at either 2- or 72-hours. Transcripts were compared to unstimulated samples to identify significantly upregulated genes, and C3a and IgER conditions were used to filter for MRGPRX2-specific activation.

Table 1 - Arcus analysis of publicly available datasets using the MRGPRX2 activation signature.

Disease	Author	Dataset	Data Type	Patients (n)
Atopic Dermatitis	Mobus[3]	GSE157194	RNAseq	57
Atopic Dermatitis	Ungar[4]	GSE137430	RNAseq	41
Atopic Dermatitis	Guttman-Yassky[5]	GSE130588	Microarray	52
Chronic Spontaneous Urticaria	Gimenez-Arnau[6]	GSE72542	Microarray	22
Chronic Spontaneous Urticaria	Patel[7]	GSE57178	Microarray	12

Results

MRGPRX2 Triggers a Distinct Activation Gene Signature in Mast Cells

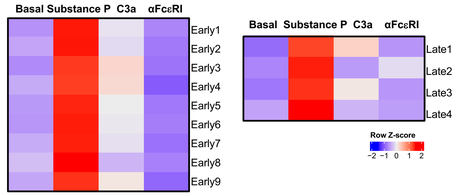


Figure 1 - Early (2-hour) and Late (72-hour) refined MRGPRX2 activation signature genes show strong enrichment over other degranulation pathways. Activation genes have at least a 2-fold enrichment in Substance P over unstimulated, but no other conditions. Heatmap shows expression of MRGPRX2 early (Early1-9) and late (Late1-4) activation signature genes across stimulation and control conditions. Values are averaged across 3 replicates, and row z-scores are plotted.

The MRGPRX2 Activation Signature is Enriched in Lesions of Moderate-to-Severe Atopic Dermatitis Patients

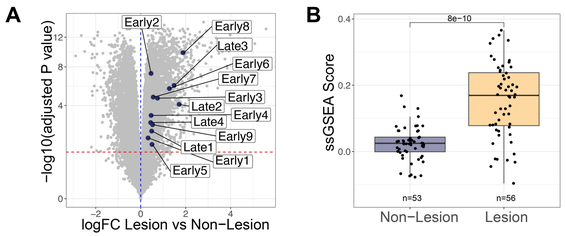


Figure 2 - MRGPRX2 Activation Signature genes are strongly enriched in untreated lesions compared to non-lesions in a dataset of moderate to severe Atopic Dermatitis patients.[3] We performed differential expression analysis on the lesions (n = 56) vs non-lesions (n = 53) in this learning dataset to refine signature genes and scoring methodology and found **(A)** 9 early and 4 late MRGPRX2 activation genes and **(B)** ssGSEA score were significantly enriched in lesions.

The MRGPRX2 Activation Signature Lesional Enrichment is Confirmed in a Second, Independent Atopic Dermatitis Dataset

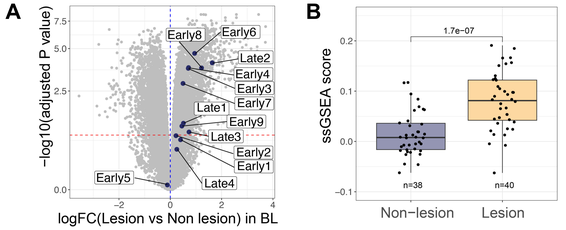


Figure 3 - A second independent dataset[4] of moderate to severe Atopic Dermatitis patients was queried similar to Figure 2. **(A)** 9/13 individual MRGPRX2 Activation Signature genes show significant upregulation, and 3 more show a trend towards upregulation, in lesions (n = 40) vs non-lesions (n = 39) prior to systemic treatment. **(B)** ssGSEA scores for the MRGPRX2 Activation Signature are significantly higher in lesion samples compared to nearby non-lesions.

Results

In a Third, Independent Dataset, MRGPRX2 Activation Signature is Enriched in Lesions of Atopic Dermatitis Patients and Correlates with Disease Severity

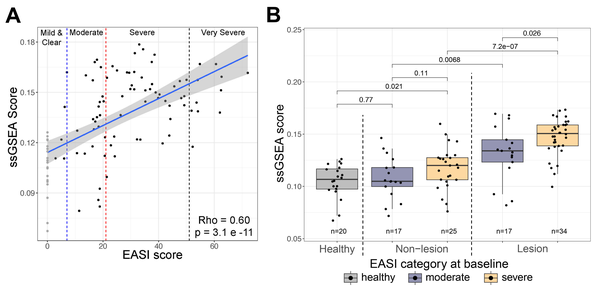


Figure 4 - MRGPRX2 Activation Signature increases with disease severity. **(A)** EASI scores of patients prior to treatment from this dataset, as well as healthy controls (EASI of 0, n = 20, in gray)[5] were compared to ssGSEA scores of the MRGPRX2 Activation Signature for lesion samples (n = 82) and were found to be significantly correlated. **(B)** ssGSEA scores were calculated for healthy controls, lesion, and non-lesion samples for moderate (EASI of 7-20), severe (EASI of 21-50), or very-severe (EASI of 51 or higher) patients. MRGPRX2 Activation Signature score was significantly elevated in Atopic dermatitis patients lesions with higher scores in severe patients.

MRGPRX2 Activation Signature is Enriched in Wheals of Chronic Spontaneous Urticaria Patients, but Not in Adjacent Healthy Skin

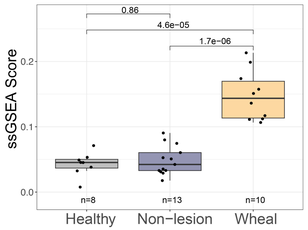


Figure 5 - MRGPRX2 Activation Signature ssGSEA scores are enriched in wheals compared to nearby non-lesional or healthy normal skin from a cohort of severely active Chronic Spontaneous Urticaria patients[6]

MRGPRX2 Activation Signature is Enriched in Wheals of Chronic Spontaneous Urticaria Patients in a Second, Independent Dataset

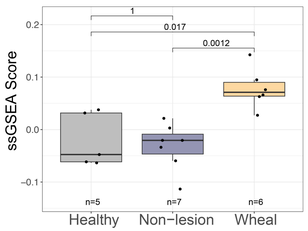


Figure 6 - MRGPRX2 Activation Signature ssGSEA scores are enriched in wheals compared to nearby non-lesional or healthy donor skin from a second cohort of Chronic Spontaneous Urticaria patients.[7]

Results

Atopic Dermatitis and Chronic Spontaneous Urticaria Show Broad Enrichment of MRGPRX2 Activation Signature Specifically at Disease Sites

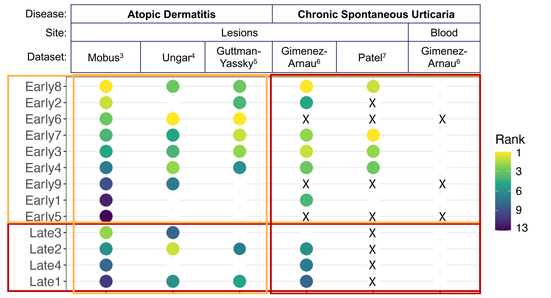
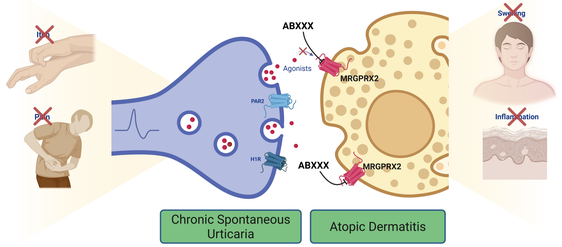


Figure 7- Large number of individual genes from the MRGPRX2 Activation Signature show significant upregulation in affected lesions across datasets in both Atopic Dermatitis and Chronic Spontaneous Urticaria. This contrasts with MRGPRX2 transcript, mast cell, complement activation, and IgE activation signatures, which are unchanged or do not show consistent enrichment in Atopic Dermatitis or Chronic Spontaneous Urticaria lesions (data not shown). Filled circles indicate a gene is significantly upregulated compared to non-lesion samples, with the color scale indicating the rank of the gene in each dataset. "X" indicates genes that were below the background expression level, and therefore not evaluable.

Summary

- We identified an MRGPRX2-specific 13-gene Activation Signature distinct from complement or IgE-mediated forms of mast cell degranulation **(Figure 1)**.
- The MRGPRX2 Activation Signature is highly enriched in Atopic Dermatitis lesions as compared to nearby non-lesions in three independent datasets **(Figures 2-4)**.
- The MRGPRX2 Activation Signature positively correlates with Eczema Area and Severity Index (EASI) scores, a measure of disease severity, in Atopic Dermatitis **(Figure 4)**.
- MRGPRX2 Activation is enriched in wheals of Chronic Spontaneous Urticaria patients, as compared to non-lesions and healthy controls, in two independent datasets **(Figure 5-6)**.
- Large number of individual MRGPRX2 Activation Signature genes show robust and selective enrichment in diseased skin tissue across numerous independent datasets with relevant Atopic Dermatitis and Chronic Spontaneous Urticaria patients. **(Figure 7)**.

In conclusion, MRGPRX2 robust mast cell degranulation biology and enrichment of Arcus MRGPRX2 activation signature in diseased skin tissue supports targeting MRGPRX2 in Chronic Spontaneous Urticaria and Atopic Dermatitis. Our signature provides a useful tool to build evidence to target other mast-cell driven diseases.



References: 1. Mc Neil BD et al. (2015) *Nature*; 2. Gour N et al. (2024) *Immunity*; 3. Mobus et al (2021) *J Allergy Clin Immunol*; 4. Ungar et al. (2021) *Immunol*; 5. Guttman-Yassky (2019) *J Allergy Clin Immunol*; 6. Gimenez-Arnau et al (2017) *Allergy*; 7. Patel et al (2015) *Allergy Rhinol*. LAD2 human mast cells were kindly provided by A Kirshenbaum and D. Metcalfe (NIH, USA). Illustrations made with BioRender.