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Inhibition of Mast Cell Specific MRGPRX2 in Dermal and Mucosal Diseases

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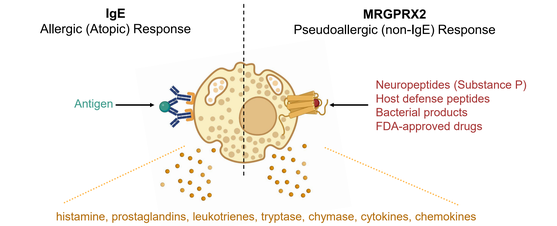
Background

- MRGPRX2 is a G-protein coupled-receptor (GPCR) that mediates mast cell degranulation and transcriptional responses to a wide variety of agonists
- MRGPRX2 is the receptor responsible for the 'pseudoallergic' response: IgE independent mast cell degranulation
- Inhibition of MRGPRX2 holds potential for the treatment of multiple conditions driven by aberrant mast cell degranulation
- Here we examined whether MRGPRX2: 1) expression is mast cell restricted, 2) common SNP variants impact responses, 3) degranulation is different from other forms, and 4) plays a role in mucosal inflammation



Results

MRGPRX2 Expression is Restricted to Human Mast Cells in Healthy Human Tissues

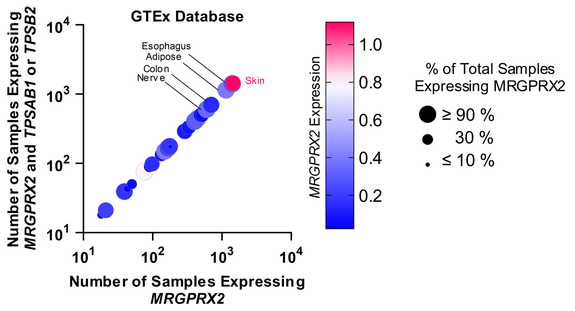


Figure 1. Analysis of 19,616 bulk RNA-sequencing samples from 30 unique tissue types collected for 946 healthy adults showed MRGPRX2 transcript is colocalized with mast cell transcripts TPSAB1 or TPSB2. Analysis of all MRGPRX2 containing samples of the GTEX database for *MRGPRX2* and *TPSAB1*/*TPSAB2* co-expression. Five tissues with highest number of *MRGPRX2* containing samples are indicated. Tissue rank order is: skin, esophagus, adipose tissue, colon, nerve, blood vessel, blood, muscle, breast, testis, heart, lung, stomach, brain, small intestine, salivary gland, spleen, vagina, thyroid, prostate, uterus, pancreas, liver, bladder, ovary, pituitary, cervix uteri, adrenal gland, fallopian tube, and kidney.

Results

MRGPRX2 is Not Detected in Human Dorsal Root Ganglion (DRG) or iPSC-Derived Sensory Neurons

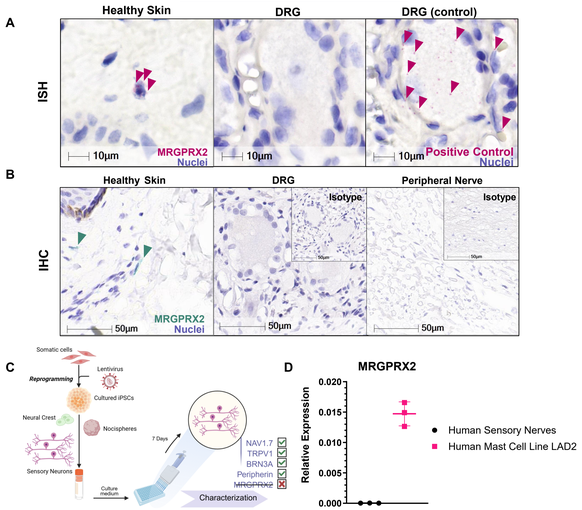


Figure 2. In situ hybridization (ISH) and Immunohistochemistry (IHC) showed no detectable MRGPRX2 transcript or protein in human DRG, and transcript was similarly not detected in iPSC-derived sensory neurons. **(A)** Skin and DRG samples were stained using ISH for MRGPRX2 transcript. A positive control for presence and RNA quality is shown on the right. Pink arrows indicate positive staining for RNA. **(B)** Human skin, DRG, and peripheral nerve samples were stained for MRGPRX2 protein using IHC. Respective isotype staining is shown on the right insets. Green arrows indicate positive staining for protein. **(C-D)** MRGPRX2 expression analysis in iPSC-derived sensory neurons and the LAD2 mast cell line.

MRGPRX2 is Not Expressed on Resting or Activated Primary Human Basophils or Eosinophils

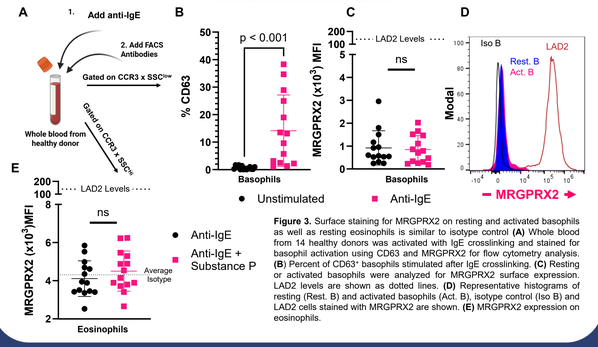


Figure 3. Surface staining for MRGPRX2 on resting and activated basophils as well as resting eosinophils is similar to isotype control **(A)** Whole blood from 14 healthy donors was activated with IgE crosslinking and stained for basophil activation using CD63 and MRGPRX2 for flow cytometry analysis. **(B)** Percent of CD63⁺ basophils stimulated after IgE crosslinking. **(C)** Resting or activated basophils were analyzed for MRGPRX2 surface expression. LAD2 levels are shown as dotted lines. **(D)** Representative histograms of resting (Rest. B) and activated basophils (Act. B), isotype control (Iso B) and LAD2 cells stained with MRGPRX2 are shown. **(E)** MRGPRX2 expression on eosinophils.

Results

MRGPRX2 Mediates Robust Degranulation in Human Mast Cells That Can Be Globally Inhibited by Small Molecule Antagonist

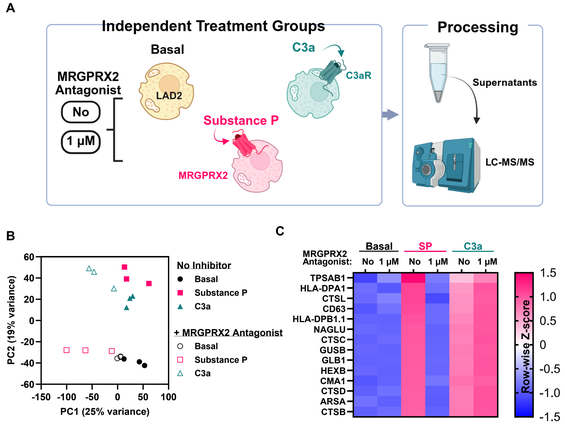


Figure 4. Analysis of activated LAD2 supernatants by mass spectrometry reveals a broad degranulation secretome that is inhibited by tool antagonist. **(A)** LAD2 cells were stimulated with substance P (SP) or C3a, with or without the presence of antagonist. Cell supernatants were harvested after 2 hours and prepared for proteomics analysis. **(B)** Principal Component (PC) analysis of secreted proteins shows separation of samples by stimulation. **(C)** Protein abundances of known granule proteins ($log_2FC \geq 2$ and adjusted p-value ≤ 0.05) in stimulated conditions from cell supernatants of all 6 conditions are shown. For each condition, the median value of 3 replicates was calculated, and the row z-score of the medians are shown; granule proteins are sorted in descending order by z-score in MRGPRX2 (substance P) stimulated conditions.

Human MRGPRX2 Single Nucleotide Polymorphism Variants Expressed by CHO Cells Show Comparable MRGPRX2 Activation and Small Molecule Antagonist Inhibition

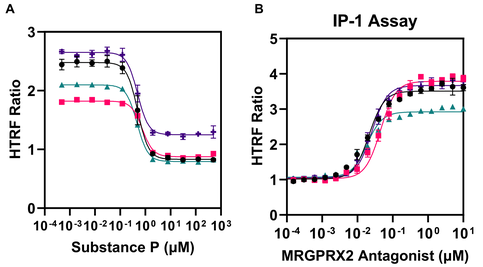


Figure 5. MRGPRX2 single-nucleotide polymorphism (SNP) variants (N16H, N62S, S313R) are comparable to the wild-type (WT) consensus sequence by myo-inositol 1-phosphate (IP1) assay. **(A)** CHO cells stably expressing WT MRGPRX2 or MRGPRX2 containing indicated variants were stimulated with substance P. Activity was determined through quantification of IP1. **(B)** WT MRGPRX2 or MRGPRX2 variant-overexpressing CHO cells were incubated with the MRGPRX2 antagonist prior to stimulation with EC_{80} of substance P and MRGPRX2 activity was measured with IP1.

Results

MRGPRX2 Activation Gene Signature is Most Pronounced in Chronic Spontaneous Urticaria and Atopic Dermatitis Skin Lesions

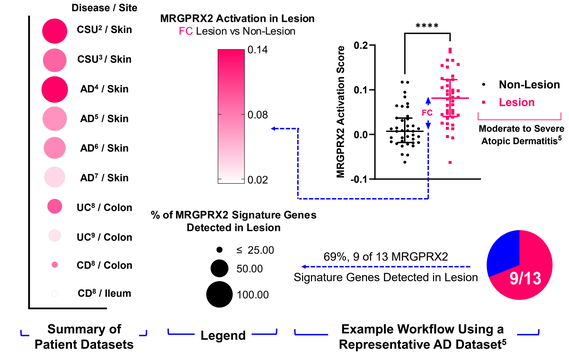


Figure 6. The enrichment of a 13 MRGPRX2 specific activation gene signature[1], derived on LAD2 cells and refined for tissue analysis on an atopic dermatitis training dataset[4] was evaluated in chronic spontaneous urticaria (CSU)[2,3], atopic dermatitis (AD)[6,7] ulcerative colitis (UC)[8,9] or Crohn's disease (CD)[8] datasets. The fold change (FC) of MRGPRX2 activation signature observed in lesional versus non-lesional, and the percentage of the 13 genes significantly upregulated in lesional samples were determined and plotted for all datasets. Data from an average representative dataset[5] from AD patients are shown to illustrate the processing workflow. The color scale indicates the fold change of MRGPRX2 activation signature in lesional over non-lesional samples in each disease dataset. Size of circles indicates the percent of the MRGPRX2 activation gene signature detected in lesional samples

Summary

- *MRGPRX2* expression is restricted to human samples containing mast cell markers such as *TPSAB1* and *TPSB2* (Figure 1).
- *MRGPRX2* was not detected by protein or transcript on human dorsal root ganglion or iPSC-derived sensory neurons (Figure 2).
- MRGPRX2 was not detected on human basophils and eosinophils (Figure 3).
- MRGPRX2 drives a robust degranulation secretome in mast cells that can be blocked by a small molecule MRGPRX2 antagonist (Figure 4).
- Engineered cell lines expressing predominant low-frequency MRGPRX2 missense single nucleotide polymorphism variants responded similarly to the consensus wild-type receptor (Figure 5).
- Atopic dermatitis and chronic spontaneous urticaria skin lesions showed broad enrichment of MRGPRX2 activation gene signature (Figure 6).

References: [1]E. Brown, (2025) EAACI Congress Poster Board # D3.412; [2]Gimenez-Arnau (2017) Allergy GSE72542; [3]Patel (2015) Allergy and Rhinol GSE57178; [4]Mobus (2021) J Allergy Clin Immunol GSE157194; [5]Ungar (2021) J Allergy Clin Immunol GSE137430; [6]Tsoi (2019) J Invest Dermatol GSE121212; [7]Guttman-Yassky (2019) J Allergy Clin Immunol GSE130588; [8]Weir (2021) J Immunol GSE179285; [9]Noble (2008) Gut GSE11223. Some images made with BioRender. LAD2 human mast cells were kindly provided by A. Kirshenbaum and D. Metcalfe (NIH, USA).

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