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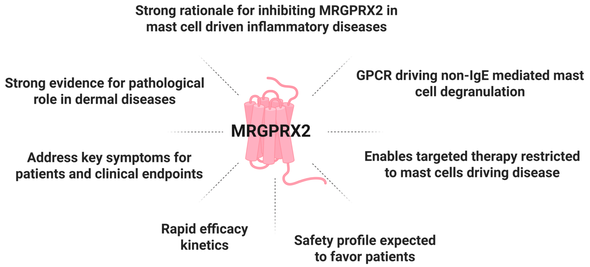
Inhibition of Mast Cell Restricted MRGPRX2 in Dermal Diseases

Nina K. Serwas, Diane Nathaniel, Emily Brown, Jenna Pappalardo, Lydia Zhang, Clement Opoku-Temeng, Jas Singh, Ehesan U. Sharif, Sean Cho, Kelsey E. Sivick, Rustom Falahati
Arcus Biosciences, Inc., Hayward, CA USA

Background

MRGPRX2 is a Mast Cell-Specific G Protein-Coupled Receptor (GPCR) That Triggers Mast Cell Activation Independent of IgE



❖ Here we evaluated MRGPRX2 activation in chronic spontaneous urticaria (CSU) and atopic dermatitis (AD) lesions and assessed whether blocking MRGPRX2 offers therapeutic benefit in preclinical models.

Results

MRGPRX2 is Highly Expressed on the Surface of Primary Human Skin Mast Cells and Human Mast Cell Line LAD2

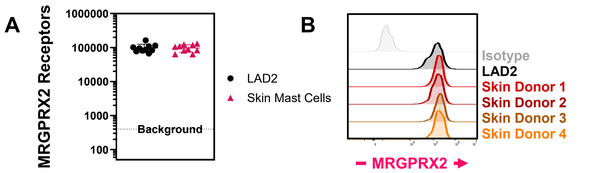


Figure 1 – **(A)** MRGPRX2 receptor density values for the LAD2 human mast cell line and human skin mast cells isolated from abdominoplasties. **(B)** Representative histogram of MRGPRX2 expression on skin mast cell populations from 4 different human donors and LAD2 cells.

MRGPRX2 Activation Drives Rapid Degranulation of Stored Inflammatory Mediators From Human Mast Cells

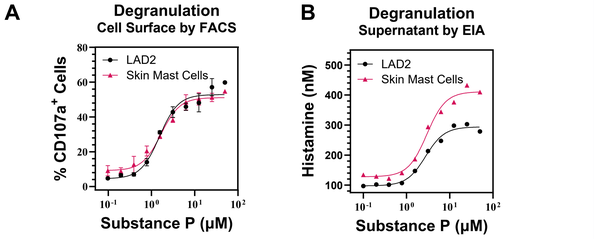


Figure 2 – **(A)** MRGPRX2 agonist substance P activated human skin mast cells and LAD2 externalized activation marker CD107a. **(B)** Concurrent quantification of histamine release by enzyme immunoassay (EIA) into cell supernatants.

Results

MRGPRX2 Triggered a Robust Mast Cell Degranulation Secretome That Was Selectively Blocked by an MRGPRX2 Antagonist

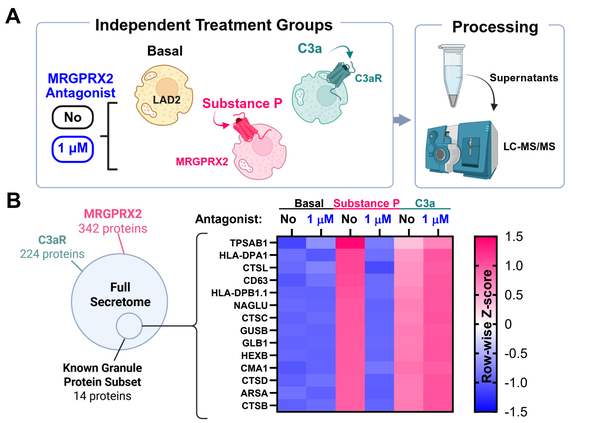


Figure 3 – **(A)** LAD2 cells were stimulated with substance P or C3a, with or without MRGPRX2 antagonist, and cell supernatants were harvested for proteomic analysis. **(B)** Protein abundances of significantly altered known granule proteins (log_2 fold change (FC) ≥ 2 and adjusted p-value ≤0.05) with row z-score of the medians for each condition are shown.

MRGPRX2 Mediates a Distinct Activation Gene Signature in Human Mast Cells

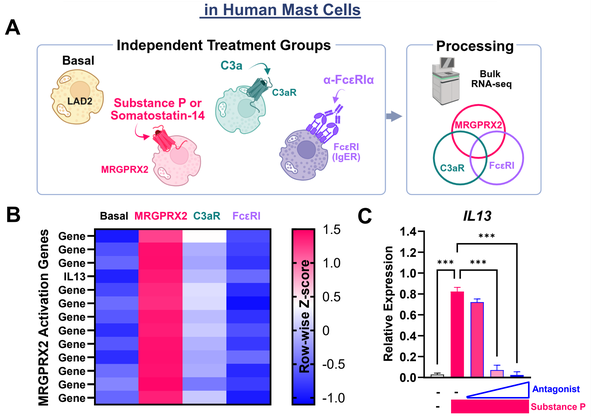


Figure 4 – **(A)** Schematic of LAD2 cells stimulated through MRGPRX2, C3a receptor (C3aR), or high-affinity IgE receptor (FcεRI) using EC_{90} of each respective ligand/agonist. Transcriptional changes were analyzed by bulk RNA sequencing. MRGPRX2-specific genes were determined as genes with at least 2-fold upregulation after substance P or somatostatin stimulation and no upregulation after C3aR or FcεRI activation. **(B)** Median LAD2 expression data (row z-scores) of the final 13-gene MRGPRX2 activation signature in RNAseq dataset shows high enrichment of expression in MRGPRX2 stimulated LAD2 human mast cell line. **(C)** Independent confirmation of MRGPRX2-specific upregulation of IL-13 gene following incubation with substance P that was inhibited by pre-incubation of cells with MRGPRX2 antagonist.

Results

MRGPRX2 Activation Signature is Enriched in Wheals From CSU Patients

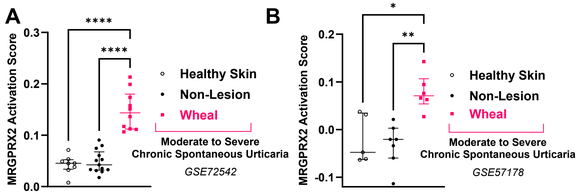


Figure 5 – **(A)** Analysis of transcript dataset[1] from healthy individuals or moderate to severe chronic spontaneous urticaria (CSU) patients (wheal and nearby non-lesional tissue) shows high enrichment of MRGPRX2 activation ssGSEA score in wheals of patients. **(B)** A second independent dataset[2] shows comparable enrichment of the MRGPRX2 activation ssGSEA score in wheals of moderate to severe CSU patients over matched non-lesional samples or healthy controls.

Oral MRGPRX2 Antagonist Inhibits Wheal Response in MRGPRX2 KI Mice

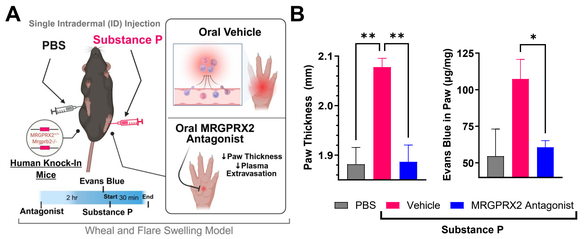


Figure 6 – **(A)** Human MRGPRX2 Knock-In (KI) mice were treated orally (PO) with MRGPRX2 antagonist prior to Evans Blue intravenously followed by intradermal injection of substance P or PBS. **(B)** Paw Thickness was measured 30 min after injection (LEFT). Evans Blue was extracted from dried paws using formamide and normalized to dry tissue weight (RIGHT).

MRGPRX2 Activation Signature is Enriched in Lesions From AD Patients

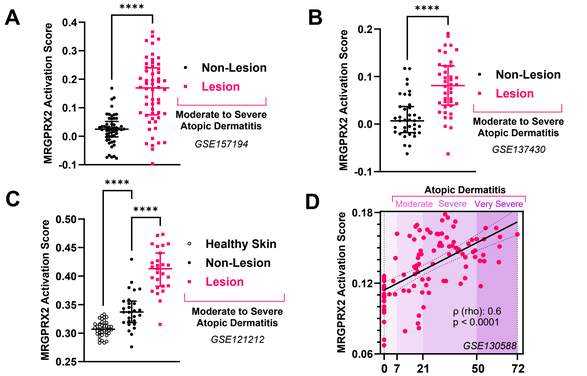


Figure 7 – **(A)** Lesional skin samples of atopic dermatitis (AD) patients have significantly increased MRGPRX2 signature ssGSEA scores in a training dataset[3]. **(B)** A second independent RNAseq AD dataset[4] showed comparable lesional enrichment. **(C)** Confirmation of ssGSEA score enrichment in AD lesions in a third independent RNAseq dataset[5] is shown. **(D)** In a fourth independent AD RNAseq dataset[6], ssGSEA scores show high correlation with reported EASI scores.

Results

MRGPRX2 Antagonist Inhibits Atopic Dermatitis Like Skin Inflammation in MRGPRX2 Knock-In Mice

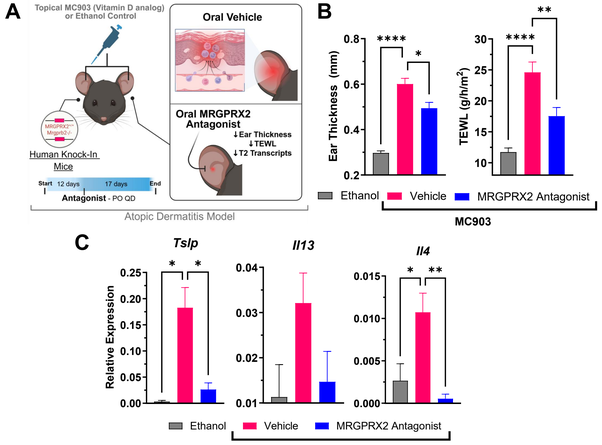
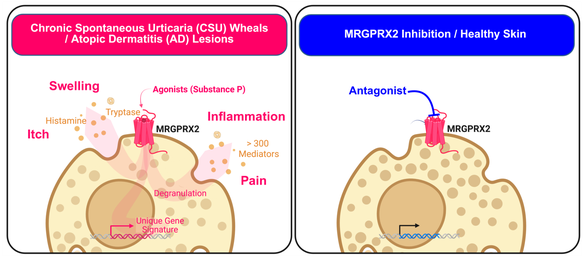


Figure 8 – **(A)** MRGPRX2 KI mice receiving topical applications of MC903 or EtOH control on ears were treated therapeutically with oral once-daily administrations of vehicle or MRGPRX2 antagonist. **(B)** Ear thickness (LEFT) and transepidermal water loss (TEWL) (RIGHT) were measured on study day 28. **(C)** Analysis of *Tslp*, *Il13*, and *Il4* transcript in the ear on study day 29.

Summary



❖ MRGPRX2 mast cell activation results in rapid and robust degranulation of key inflammatory mediators that can be fully and selectively inhibited with small molecule antagonist (Figures 1-3).

❖ MRGPRX2 activation results in a distinct gene expression signature (Figure 4) that is selectively elevated in CSU and AD patient lesional skin (Figure 5, 7).

❖ Oral administration of MRGPRX2 antagonist can fully inhibit MRGPRX2-mediated paw swelling in a wheal-and-flare model (Figure 6) and MC903-induced skin inflammation in an atopic dermatitis model in human MRGPRX2 KI mice (Figure 8).

References: 1. Gimenez-Arnau et al (2017) *Allergy*; 2. Patel et al (2015) *Allergy and Rhinol* 3. Mobus et al (2021) *J Allergy Clin Immunol*; 4. Ungar et al (2021) *J Allergy Clin Immunol*; 5. Tsoi et al (2019) *J Invest Dermatol*; 6. Guttman-Yassky et al (2019) *J Allergy Clin Immunol.* Some images made with BioRender. LAD2 human mast cells were kindly provided by A. Kirshenbaum and D. Metcalfe (NIH, USA).

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