Targeting MRGPRX2 Addresses Unmet Need in Atopic Dermatitis: An *In Silico* Network Analysis

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Abstract

While IL-13/IL-4 inhibitors have transformed atopic dermatitis (AD) treatment, 30–40% of patients remain partial or non-responders. We investigated the therapeutic potential of targeting MRGPRX2, a mast cell and sensory neuron specific receptor, using a predictive computational engine to define its role in AD pathogenesis and its overlap with Type 2 immunity. We developed a MRGPRX2-specific gene signature from RNAseq data of human mast cells activated with multiple ligands in the absence or presence of the oral MRGPRX2 inhibitor EVO756. This signature was integrated into the CytoReason AD *in silico* disease model—a comprehensive computational representation of disease biology that integrates 24 RNAseq datasets, >2,000 human skin samples including clinical EASI scores and dupilumab response data. The MRGPRX2 signature was highly enriched in lesional AD tissue and associated with EASI scores. Disease features association analysis identified MRGPRX2 as a central "hub" linking T-cell effector function (Th2, Th17, Th22), neuroinflammation, pruritus, and barrier dysfunction. While MRGPRX2 and IL-13/IL-4 signatures share biology in the Th2 and neuroinflammatory space, MRGPRX2 uniquely covers "white space" pathways not addressed by IL-13/IL-4 inhibition. Critically, while dupilumab significantly reduced its primary target signatures, the MRGPRX2 signature was less downregulated in non-responders as compared to responders. These data position MRGPRX2 as a critical pathway in AD, which persists despite standard-of-care biologics treatment. Targeting MRGPRX2 via oral inhibitors like EVO756 offers a compelling strategy to address the significant unmet need in both Type 2-high and Type 2-low AD populations.

Methods

In Silico AD Model

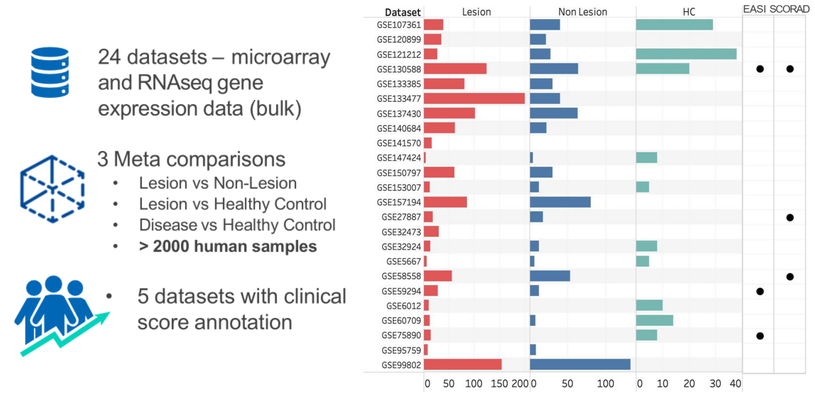


Figure 1. CytoReason Atopic Dermatitis *In Silico* Model. The AD computational disease model was constructed using a robust, clinically-anchored dataset: 24 bulk RNAseq datasets >2,000 skin biopsies, clinical disease severity measures (EASI scores), and standard-of-care treatment response data (Dupilumab treatment). This integrated approach ensures that computational findings are directly grounded in human patient biology and clinical outcomes.

Generation of an MRGPRX2 Gene Signature

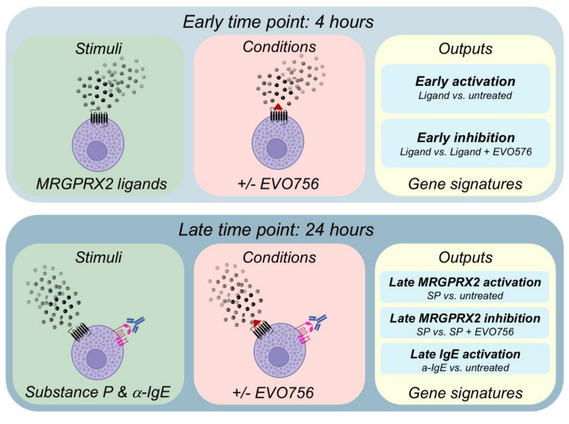
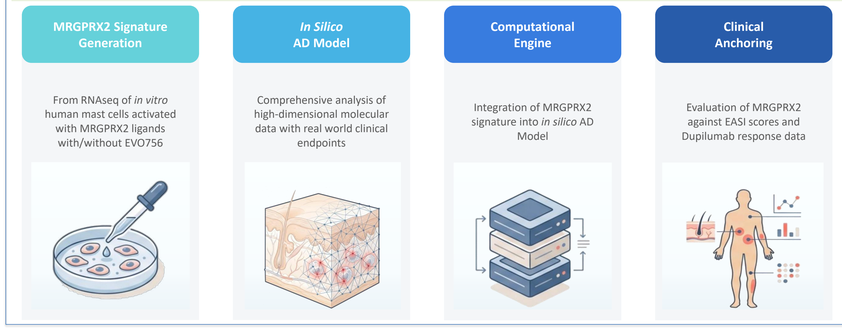


Figure 2. Evommune generation of an MRGPRX2 Gene Signature. Primary human skin mast cells were stimulated with MRGPRX2 ligands with/without EVO756 for 4 hrs or 24 hrs. Additionally, IgE-activated mast cells were also used as a comparative mast cell activation stimuli. The top 50 differentially expressed genes were identified for each condition.

Experimental + in silico approach



Results

The MRGPRX2 Pathway is Enriched in AD

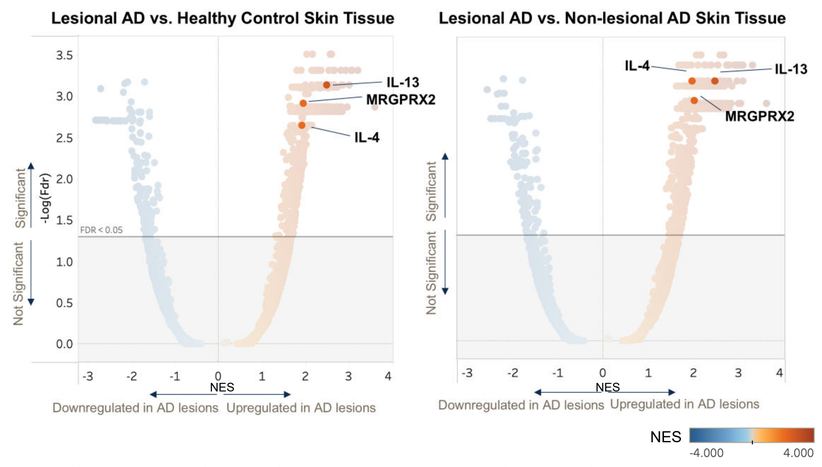


Figure 3. Volcano plots depicting up and down-regulated signatures in lesional AD skin versus either healthy (left) or non-lesional AD (right). The MRGPRX2 signature is highly and specifically upregulated in lesional AD tissues, suggesting a role specifically in active disease. Additionally, the MRGPRX2 signature is upregulated similarly to IL-4 and IL-13 signatures.

MRGPRX2 is Associated with AD Disease Pathways and Clinical severity score

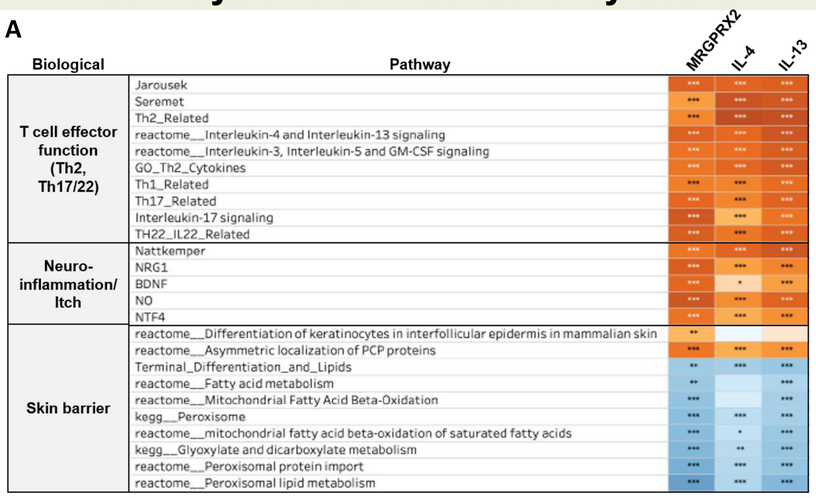


Figure 4. Significant associations with MRGPRX2, IL-4, or IL-13 gene signatures and key biological pathways in AD or EASI score. (A) The MRGPRX2 signature is significantly correlated with critical drivers of disease including Th2 and itch. MRGPRX2 signature also significantly correlated with additional pathways present in disease (Th1, Th17, Th22, neuro-inflammation and barrier dysfunction) (B) MRGPRX2 target signatures are correlated to disease severity EASI scores. MRGPRX2 signatures, positive controls (IL4 and IL13), and negative controls were evaluated for positive correlation with EASI score

MRGPRX2 is an Important Node in the AD Network with Potential Strong Functional Role in Disease

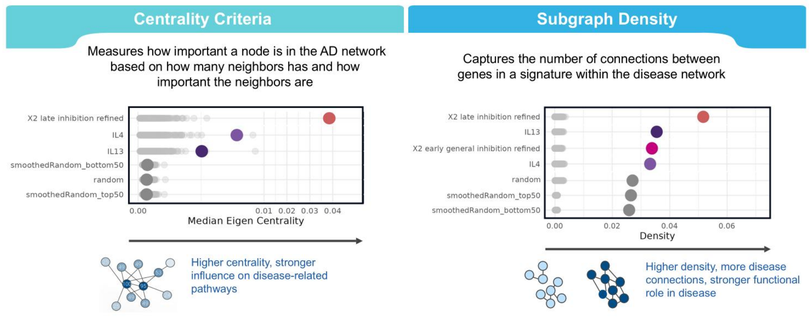


Figure 5. Median Eigen Centrality and Density of the MRGPRX2 signature in the *in silico* AD model, compared to positive and negative controls (grey circles). The MRGPRX2 signature demonstrates stronger median Eigen centrality and density compared the signatures of current standard of care therapeutic targets (e.g. IL-4 and IL-13), placing MRGPRX2 as a central node.

Dupilumab Targets Type 2 Pathways – Leaves MRGPRX2 Signature Largely Intact

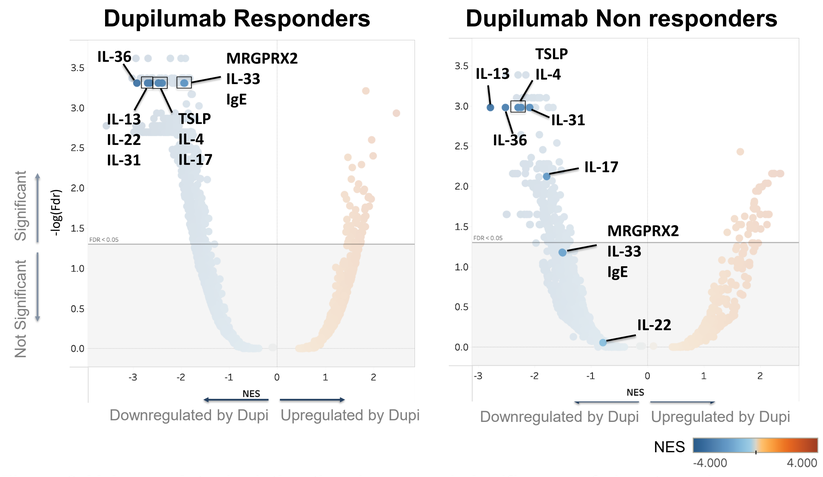


Figure 6. Volcano plots depicting the change and significance of signatures in Dupilumab responders and non-responders. 4 weeks of Dupilumab treatment significantly decreases target signature for expected MoA (IL-4 and IL-13) and other relevant AD targets. In non-responders, MRGPRX2 target signature is not significantly impacted suggesting MRGPRX2-associated unmet need.

MRGPRX2 Provides Additional Disease-Associated Coverage beyond IL-13 and IL-4

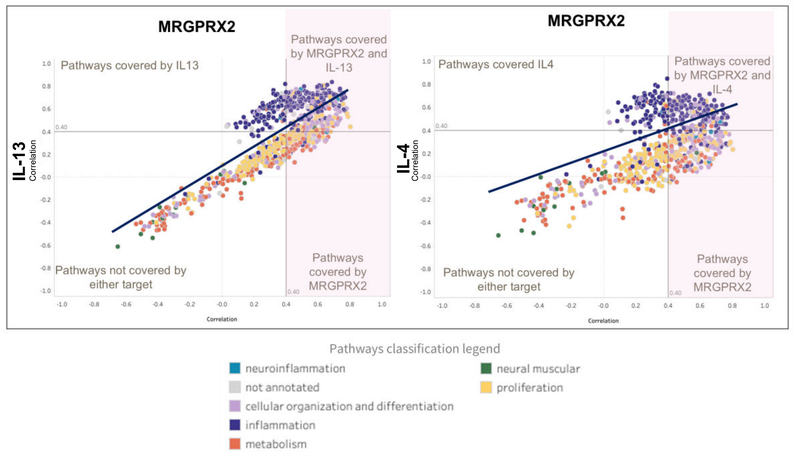


Figure 7. Pathway co-correlation of MRGPRX2 with IL-13, or IL-4 signatures in the *in silico* AD model. The MRGPRX2 target signature is more correlated with IL-13 signature (left), compared to the IL-4 signature (right), indicating mechanistic similarity to IL-13. The MRGPRX2 and IL-13/IL-4 signatures cover shared biology, including Th2 inflammation, and neuroinflammation spaces. However, the MRGPRX2 signature covers pathways that are not covered by IL-13/IL-4 including proliferation and epidermal pathways consistent with complementarity and target differentiation.

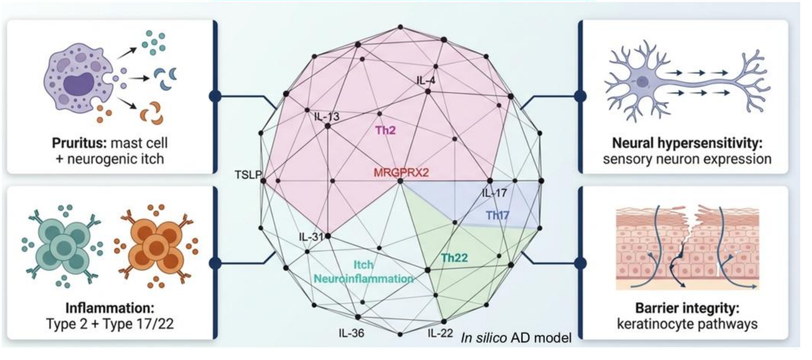
Conclusions

Computational Validation Increases Conviction of MRGPRX2 as a Competitive Target in AD

MRGPRX2 inhibition: Therapy for a wide range of patients, Type 2 and beyond

MRGPRX2 handles 4 pillars of AD pathophysiology

MRGPRX2 is a hub of multiple disease-driving pathways



Acknowledgements and Disclosures

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