The role of the neutrophil receptor Mrgpra2 in neuroimmune regulation of itch in atopic dermatitis

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Background: Atopic dermatitis (AD) is a chronic inflammatory skin disease often accompanied by persistent itch. Classically, AD is considered a T-cell mediated disease, however recent evidence suggests an emerging role of neutrophils as key contributors to neuroinflammation and pruriceptor sensitization in AD, in part through release of inflammatory mediators such as Cxcl10. In the present work, we investigated whether Mas-related G protein-coupled receptor A2 (Mrgpra2), a neutrophil-specific receptor known to regulate neutrophil responses during bacterial skin infection, contributed to inflammation and pruritus in context of AD-associated itch.

Methods: Wild-type (WT) and Mrgpra2 knockout (A2KO) mice received daily topical MC903 for seven days to model AD. Scratching behavior, epidermal thickness, transepidermal water loss (TEWL), and neutrophil infiltration were assessed throughout disease progression by behavioral scoring, histology, and flow cytometry. Neutrophil intrinsic changes were accessed through RT-qPCR of FACs sorted neutrophils, collected from MC903 treated skin of WT and A2KO mice.

Results: We observed that A2KO mice exhibited significantly reduced scratching behavior, epidermal thickness, and TEWL compared to WT controls, particularly on day 7 of treatment.

We observed a significant increase in the recruitment of neutrophils to the skin over disease progression, however there was no significant effect in recruitment between WT and A2KO mice. RNA expression from sorted neutrophils showed significantly reduced expression of Cxcr2 and the signaling cytokines Il1b, Cxcl2, and Cxcl10 from A2KO mice relative to WT (Fig. 1).

Conclusion: These findings indicate that Mrgpra2 drives AD-associated itch through modulation of neutrophil derived cytokine release, and not through regulation of neutrophil recruitment. In particular, Cxcl10 has been shown to directly sensitizes pruriceptors (and infiltrating neutrophils localize proximal to cutaneous primary nerve endings. Our results suggest that Mrgpra2 affects AD pathology primarily through modulation of neutrophil derived pruritic signaling cytokines, and offer key insights into the neuroimmune regulation of neutrophils which contribute to the pruritic aspects of AD.

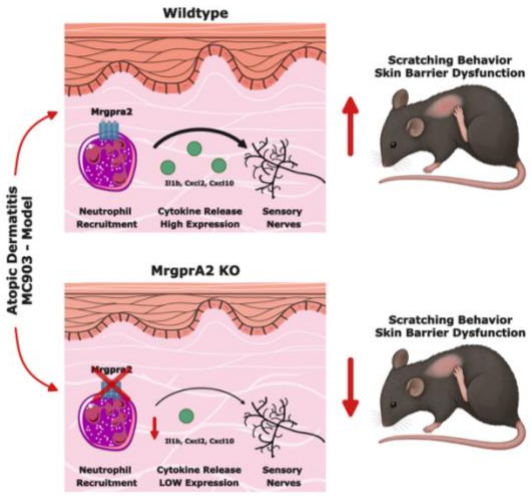


Figure 1: Graphical Abstract

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