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Epidermal PAR2-TRPV3-IL-33 Signaling Promotes Mast Cell Recruitment and Sensory Nerve-Mast Cell Interactions in Atopic Dermatitis

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To the Editor,
Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by barrier dysfunction and heightened type 2 immunity, maintained through a complex interplay between keratinocytes, immune cells, and sensory neurons [1]. Increasing evidence points to primary sensory neurons as active participants in skin inflammation, yet the mechanisms by which epithelial ion channels regulate neuroimmune communication remain incompletely defined. The transient receptor potential vanilloid 3 (TRPV3) channel is highly expressed on keratinocytes, and pathogenic gain-of-function TRPV3 mutations in both humans and mice cause severe dermatitis with prominent mast cell (MC) accumulation [2], chronic itch, and inflammation [3, 4]. Here, we define a critical function for epidermal TRPV3 in governing MC trafficking and MC–neuron communication through an epidermal PAR2–TRPV3–IL-33 axis.

TRPV3-dependent alterations in immune composition were first analyzed using LM22 deconvolution of bulk RNA-sequencing datasets from MC903-treated wild-type or *Trpv3*$^{-/-}$ skin. Lesional skin displayed markedly increased MC abundance and activation, both of which were significantly attenuated in *Trpv3*$^{-/-}$ mice (Figure 1A). Immunohistochemistry further validated these computational findings, demonstrating striking reductions in perivascular MC density in *Trpv3*$^{-/-}$ mice (Figure 1B). Consistent with impaired MC recruitment, TRPV3 deficiency reduced vascular permeability and edema, as measured by Evans blue extravasation (Figure 1C). To determine the cell-type-specific contribution of TRPV3, the keratinocyte-specific TRPV3 knockout mice (*Trpv3*$^{\Delta Krt14}$) were generated (Table S1), which exhibited significantly fewer perivascular MCs following MC903 treatment, closely phenocopying the global knockout (Figure 1D,E). These results identify keratinocyte TRPV3 as the critical driver of MC recruitment in AD.

Building on prior work showing that protease-activated receptor 2 (PAR2) acts upstream of TRPV3 in keratinocytes to mediate itch signaling [3], we next examined PAR2–TRPV3 coupling in AD-associated inflammation. RNA transcriptomic sequencing revealed that IL-33 expression was upregulated in a mouse model of AD (Figure S1). Immunostaining confirmed that inhibition of either PAR2 or TRPV3 downregulated the expression of IL-33 in the epidermis (Figure S1). Activation of PAR2 robustly increased IL-33 production in primary keratinocytes, and the response decreased in *Trpv3-deficient keratinocytes* (Figure 1F). Conversely, pharmacologic inhibition of either

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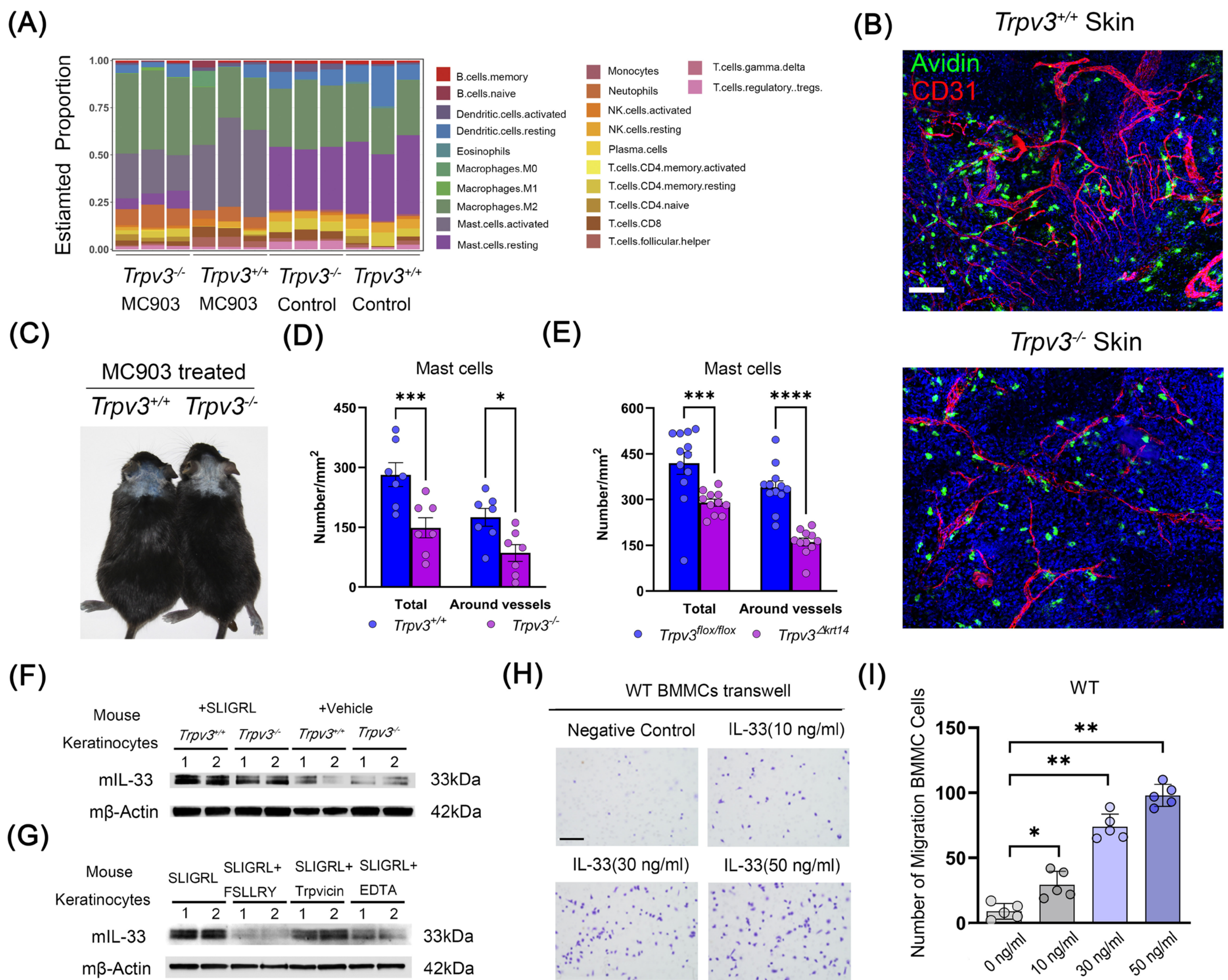

FIGURE 1 | TRPV3 deficiency attenuates skin mast-cell recruitment and suppresses IL-33-dependent inflammation. (A) CIBERSORTx immune-infiltration analysis to estimate immune cell proportion in skin from *Trpv3*$^{+/+}$ and *Trpv3*$^{-/-}$ mice with or without MC903 treatment. (B) Immunofluorescence showing the location of mast cells (Avidin) and blood vessels (CD31) in MC903-treated *Trpv3*$^{+/+}$ and *Trpv3*$^{-/-}$ mice. (C) Evans blue staining for vessel permeability in skin of MC903-treated *Trpv3*$^{+/+}$ and *Trpv3*$^{-/-}$ mice. (D, E) Quantification of total and perivascular mast cells in lesions from *Trpv3*$^{+/+}$, *Trpv3*$^{-/-}$, *Trpv3*$^{flox/flox}$, and *Trpv3*$^{\Delta Krt14}$ mice. (F, G) IL-33 expression level in primary keratinocytes from *Trpv3*$^{+/+}$ or *Trpv3*$^{-/-}$ mice under indicated stimulations. (H, I) Images and quantification of WT BMMC migration toward doses of IL-33.

PAR2 or TRPV3 markedly reduced IL-33 expression in primary keratinocytes (Figure 1G). Mechanistically, PAR2-TRPV3 signaling enhanced IL-33 transcription through phosphorylation of CaMKII and JNK and activation of the AP-1 transcriptional complex (Figure S2, Table S2).

To test how epidermal IL-33 modulates MC biology, we performed transwell assays using bone marrow-derived MCs. IL-33 induced dose-dependent MC chemotaxis (Figure 1H,I), which was substantially reduced by blocking the IL-33 receptor ST2 or using ST2 deficient (*Il1rl1*$^{-/-}$) MCs (Figure S3). Collectively, these results indicate that epidermal PAR2–TRPV3 signaling governs IL-33 expression and thereby regulates IL-33-dependent mast cell migration.

We next investigated whether TRPV3-driven IL-33 impacts sensory neurons. *Trpv3*$^{-/-}$ mice exhibited markedly reduced AD-associated substance P (SP) expression (Figure 2A–C), indicating that TRPV3-dependent IL-33 production regulates neuropeptide expression in dorsal root ganglia (DRG). Immunostaining of DRG from MC903-treated mice revealed extensive co-expression of SP and the IL-33 receptor ST2 in small-diameter neurons (Figure 2D). Functionally, oral administration of the NK1 receptor antagonist rolapitant significantly reduced skin edema, suggesting that SP-NK1R signaling mediates MC-dependent vascular permeability (Figure 2E,F). Previous ultrastructural and immunoelectron microscopy studies in urticaria have demonstrated intimate interactions between mast cells, cutaneous nerves, and vascular endothelium, whereby mast cell-derived mediators increase vascular permeability and facilitate neuroimmune–neurovascular coupling, supporting a shared mast cell-driven pathogenic circuit across allergic skin diseases [5, 6].

Finally, human data showing elevated serum IL-33 levels and perineural mast cell accumulation in AD add translational relevance (Figure 2G,H), but the small sample size and cross-sectional design represent important study limitations, restricting statistical power and precluding conclusions regarding causality or disease progression.

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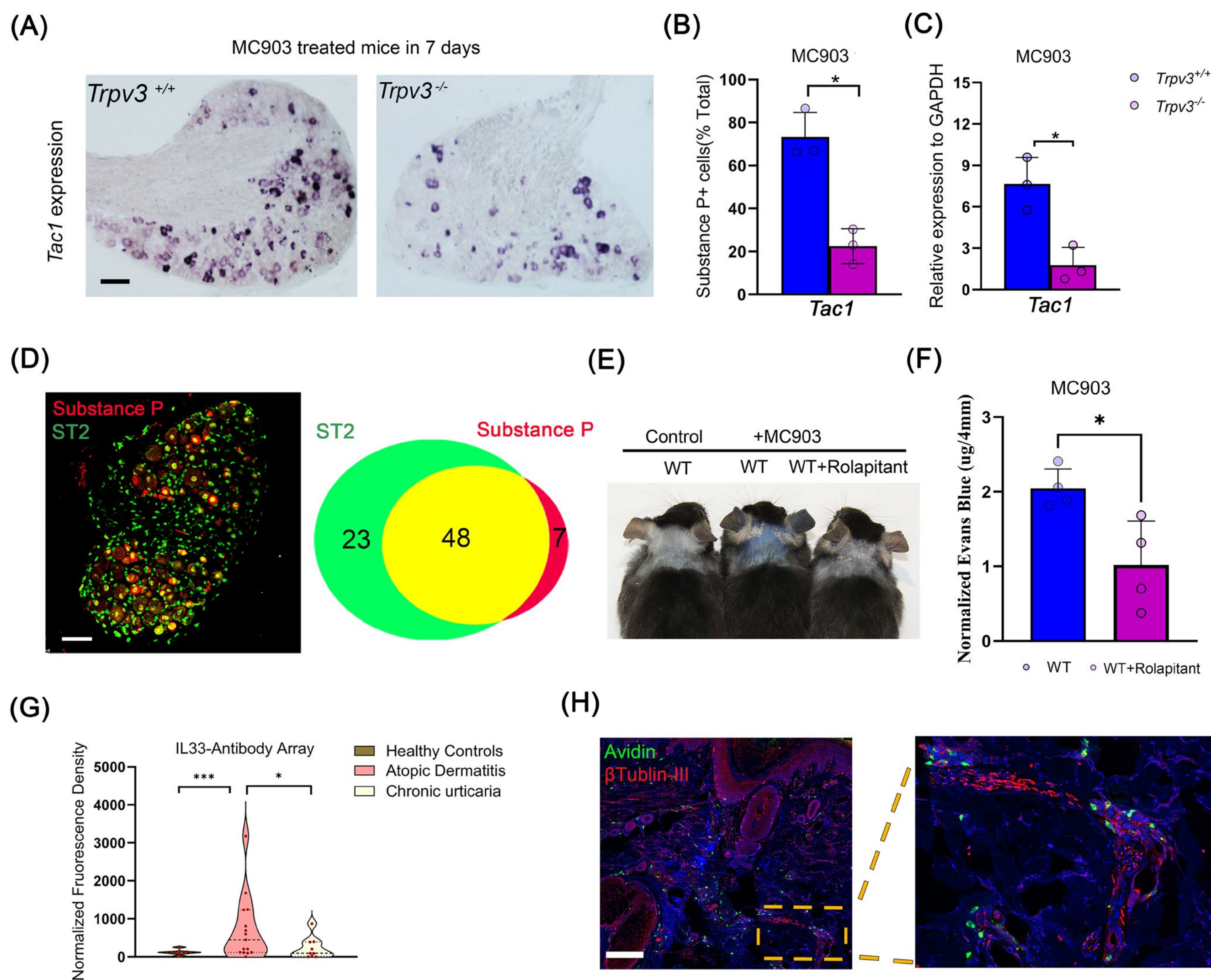

FIGURE 2 | TRPV3–IL-33 axis regulates substance P expression and neuro–mast cell interactions. (A) In situ hybridization of *Tac1* mRNA in DRGs from MC903-treated $Trpv3^{+/+}$ and $Trpv3^{-/-}$ mice. Scale bar, 50 μm. (B) Quantification of $Tac1^{+}$ DRGs in both genotypes. (C) qRT-PCR analysis of *Tac1* mRNA in MC903-treated DRGs. (D) Immunofluorescence of ST2 (green) and substance P (red) in DRGs, and the Venn diagram displays the proportions of each cell population and their overlap. Scale bar, 100 μm. (E, F) Images and quantification of the Evans blue penetration in control or MC903-treated mice with or without oral NK1 receptor antagonist rolapitant treatment. (G) Serum IL-33 levels in healthy individuals, AD patients, and chronic urticaria patients. (H) Immunofluorescence of mast cells (avidin) and terminal fibers (β-tubulin III) in skin lesions from AD patients. Scale bar, 50 μm.

Together, our findings identify an epidermal PAR2–TRPV3–IL-33 axis as a central orchestrator of barrier–immune–neural interactions in AD. This pathway integrates environmental and proteolytic cues through PAR2, amplifies inflammation through IL-33-mediated MC recruitment and promotes neuropeptide-driven neurogenic inflammation. Targeting components of this axis, including PAR2, TRPV3, IL-33, or NK1R, may offer a rational strategy to attenuate inflammation and pruritus in AD and other allergic dermatoses characterized by neuroimmune dysregulation.

Author Contributions

J.Z. and M.J. conceived the study. J.Z. and L.Z., C.W., and X.Y. acquired the data. L.Z., C.W., Z.R., X.Y., and J.C. performed data analysis. M.J., J.Z., L.Z., C.W., and Z.R. drafted the original manuscript. M.J., J.Z., D.Z., Y.S., Y.C., and R.L. revised the manuscript.

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Ethics Statement

All experimental procedures followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by

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the Animal Studies Committee at the Peking University First Hospital (J202034 and J2023084). The study involving human participants was conducted in accordance with ethical guidelines and was approved by the Institutional Review Board (ChiECRCT20190208). Blood samples were collected from patients undergoing clinical testing, and all participants provided written informed consent prior to inclusion in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online Supporting Information (Table S3). The RNA-seq data presented in this study are deposited in the GEO repository, accession number is https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE297292. Further inquiries can be directed to the corresponding authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** PAR2-TRPV3 signaling induces IL-33 expression in a mouse model of AD. **Figure S2:** PAR2-TRPV3 signaling axis promotes IL-33 expression in keratinocytes through the CaMKII and JNK phosphorylation pathways. **Figure S3:** IL-33-ST2 signaling regulates mast cell chemotaxis. **Table S1:** Experimental models: organisms/strains. **Table S2:** Primers for quantitative PCR. **Table S3:** Regents used in this study.

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