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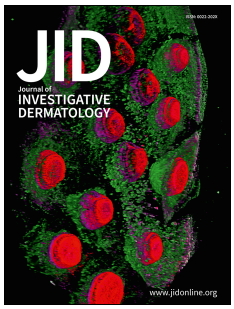

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Psychological stress delays inflammatory resolution and promotes sustained sensory sensitization during recovery from atopic dermatitis

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Stress sustains sensitization during recovery from atopic dermatitis

TO THE EDITOR,

Atopic dermatitis (AD) is a chronic inflammatory disorder characterized by pruritus, eczematous lesions, and epidermal barrier dysfunction, with substantial impact on quality of life (Weidinger and Novak 2016). Its pathogenesis reflects a complex interplay between barrier impairment, immune dysregulation, and environmental triggers, resulting in heterogeneous phenotypes (Kim, Kim et al. 2019). While mechanisms driving onset and exacerbation have been extensively studied, the processes governing disease resolution remain poorly understood. Inflammatory resolution is increasingly recognized as an active process involving immune reprogramming, tissue repair, and restoration of homeostasis rather than a passive decline in inflammation (Oetjen, Mack et al. 2017). Disruption of this process may contribute to persistent symptoms and chronic disease activity. However, the factors that impair inflammatory resolution in AD remain poorly understood.

Psychological stress is a recognized modifier of AD, associated with worsened pruritus and disease persistence. Experimental incorporation of stress paradigms has improved the translational relevance of AD models (Hall, Cruser et al. 2012). Restraint stress (RS), a model of psychological stress in rodents, activates the hypothalamic-pituitary-adrenal (HPA) axis and may enhance DRG neuronal excitability through glucocorticoid and sympathetic signaling, thereby facilitating Aβ fiber–mediated mechanical alloknesis (Buynitsky and Mostofsky 2009). However, prior work has focused largely on stress during active inflammation, emphasizing exacerbation rather than recovery. We hypothesized that psychological stress disrupts the transition to resolution without amplifying peak inflammation, thereby sustaining sensory sensitization during recovery.

To address this, we applied RS during the recovery phase of a murine AD model and performed longitudinal analyses of barrier function, inflammatory markers, tissue pathology, and itch-related behaviors to evaluate changes in recovery dynamics. In our model, the recovery phase was defined as the period immediately after induction, when inflammation transitions from peak toward resolution and repair (Pellefigues, Naidoo et al. 2021).

RS induced transient epidermal remodeling, with greater epidermal thickness and previously validated dermatitis scores (Zhao, Tominaga et al. 2024) observed at week 1 but not at week 2 (Figure 1a-c). Transepidermal water loss (TEWL) declined over time in both groups without intergroup differences, and hydration remained unchanged (Figure 1d-e), indicating comparable barrier recovery despite stress exposure.

The AD+RS mice showed higher urinary corticosterone levels than the AD-alone mice at week 1 (Figure 1f).

Serum IgE levels diverged at week 2, presenting higher concentrations in the AD+RS mice, while no difference was observed in week 1 (Figure 1g). IL-13 remained stable in the AD+RS mice and was consequently elevated than in the AD-alone mice across both time points, whereas IL-31 remained stable in the two groups and showed no temporal or intergroup variation (Figure 1h-i). CCL-2 displayed dynamic regulations in the AD-alone mice, with higher levels at week 1 followed by a decline at week 2, while remaining relatively stable under RS (Figure 1j). These findings suggest that stress selectively reshapes type 2 immune signaling during recovery.

Mechanical alloknesis was higher in the AD+RS at both filament forces and time points (Figure 1k-n), while spontaneous scratching bouts were more pronounced at week 2 (Figure 1o). These findings indicate that RS potentiates both evoked and spontaneous itch behaviors, consistent with progressive peripheral sensitization.

In the skin, RS was associated with progressive $CD4^+$ T-cell accumulation, with greater infiltration observed in the AD+RS mice across time points (Figure 2a-c). Apoptotic activity showed a similar pattern, with higher TUNEL-positive cell counts in the AD+RS and further elevation at week 2 (Figure 2d-f), indicating sustained structural alterations during recovery. In parallel, TRPV1 expression in the skin was stronger in the AD+RS and more evident at week 2 (Figure 2g-h). The temporal association between TRPV1 upregulation and itch-related behaviors suggests that stress enhances sensory sensitization, thereby altering disease trajectory in the AD+RS mice.

Collectively, these findings indicate that psychological stress does not simply intensify inflammation but alters the trajectory of disease resolution. Rather than broadly affecting all mediators, RS selectively sustains key immune and neuroimmune pathways. Sustained IL-13 and IgE levels may contribute to persistent pruritus by promoting neuroimmune sensitization. IL-13 can enhance sensory neuron responsiveness and potentially increase C-fiber excitability, while IgE- and eosinophil-mediated mast cell activation may promote the release of pruritogenic mediators that sensitize peripheral nerve endings. (Tian, Cao et al. 2026). Although IL-31 levels remained unchanged, its established interaction with sensory neurons suggests that itch amplification may arise from increased neuronal sensitivity rather than cytokine abundance.

The observed elevation in TRPV1 expression provides a mechanistic link between stress and sustained sensory sensitization. TRPV1, a non-selective cation channel expressed in sensory

neurons and skin cells, plays a central role in itch transmission and neurogenic inflammation and is known to be upregulated in AD (Tang, Gao et al. 2022). Its higher expression in the AD+RS mice, together with enhanced scratching and alloknesis, supports a model in which stress lowers the threshold for peripheral sensory activation, promoting persistent itch despite partial inflammatory resolution.

In addition, sustained $CD4^+$ T-cell infiltration and elevated apoptosis suggest impaired coordination of tissue repair. Disruption of barrier restoration may perpetuate antigen exposure and inflammatory signaling, reinforcing a self-sustaining inflammatory loop. These findings support that stress interferes with the transition from inflammation to tissue repair, essential for restoring cutaneous homeostasis.

In our study, male mice were used to minimize variability associated with estrous cycle–dependent hormonal fluctuations (Klein and Flanagan 2016); future studies including both sexes are needed. In addition, the absence of concurrent normal control and RS-only groups limits the strict separation of AD- and stress-related effects.

Our data supports a potential shift in perspective: stress may act as a disease-modifying factor that delays resolution rather than amplifying peak inflammation in this mouse model. This distinction potentially has translational relevance, as it suggests that persistent symptoms in AD may reflect impaired recovery dynamics driven by neuroimmune interactions. Addressing both immune and sensory pathways, as well as incorporating stress-related factors into therapeutic strategies, has the potential to impact disease outcomes.

In conclusion, this study demonstrates that psychological stress disrupts the resolution phase in a mouse model of AD, promoting sustained immune activation and peripheral sensory sensitization (Figure 2i)

ETHICAL STATEMENT

Collection of animal tissue samples for this study was approved as part of the study protocol. This animal study was approved by Experimental protocols were approved by the Ethical Committee of Research Animal Use of Juntendo University - approval: Approval NO.2024124, No. 2025083. All animal experiments adhered to National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. Mice were housed under standard laboratory conditions. Stress procedures were carefully designed and monitored to minimize unnecessary distress. All efforts were made to reduce animal suffering and the number of animals used.

DATA AVAILABILITY STATEMENT

Lead Contact: Requests for further information, resources, and data should be directed to and will be fulfilled by the lead contacts Qiaofeng Zhao (zhao@juntendo.ac.jp) and Kenji Takamori (ktakamor@juntendo.ac.jp)

Materials Availability: This study did not generate new unique reagents

Data and Code Availability: Data are available from the corresponding author upon reasonable request. No code was used in this study

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CONFLICT OF INTEREST

The authors state no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization, Q.Z., M.T. and K.T.; Data creation, Q.Z.; methodology, Q.Z., M.T., Y.K. and A.K.; formal analysis, Q.Z., A.L-R. and M.T.; investigation, Q.Z.; writing-original draft preparation, Q.Z., and A.L-R.; writing-review and editing, Q.Z., A.L-R., M.T., Y.K., A.K., H.W., Y.R. and K.T.; supervision, M.T. and K.T.; funding acquisition, Q.Z., M.T. and K.T.. All authors have read and agreed to the published version of the manuscript.

DECLARATION OF AI/LLM USE

During the preparation of this work, the authors used ChatGPT (Open AI) solely for language polishing and grammatical refinement of non-scientific content. All critical scientific components including research design, data analysis, and result interpretation, were exclusively conducted by human authors. The final manuscript has been thoroughly reviewed and approved by all coauthors who take full responsibility for its academic integrity and accuracy.

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FIGURE LEGENDS

Figure 1. Restraint stress reshapes recovery dynamics in atopic dermatitis by sustaining type 2 immunity and enhancing itch-related behaviors.

(a) H&E-stained skin. (b) Epidermal thickness was increased in AD+RS vs AD-alone at week 1, but not week 2 (ns, n = 8). (c) Dermatitis scores were higher in AD+RS at week 1, not week 2 (ns, n = 12). (d) TEWL decreased over time in both groups without intergroup differences (n = 12). (e) Skin hydration showed no differences (n = 12).

(f) Urinary corticosterone was elevated in AD+RS at week 1 (n = 12).

(g-j) IgE increased in AD+RS at week 2 (n = 8-9). IL-13 declined in AD-alone but remained stable in AD+RS, yielding higher levels at week 1 and week 2 (n = 9-12). IL-31 was unchanged (n = 10-20). CCL-2 showed a transient increase in AD-alone at week 1 followed by reduction (n = 13-15).

(k-o) Alloknesis increased in AD+RS at both forces and scratching increased at week 2 (n = 12).

Data represented as mean ± SEM. ns = not significant, $*p < 0.05$, $**p < 0.01$ and $***p < 0.001$. Two-way ANOVA or Welch's t-test.

Figure 2. Restraint stress sustains cutaneous immune activation and apoptosis, enhancing TRPV1-mediated sensory signaling during atopic dermatitis recovery.

(a) Representative immunofluorescence images of dermal $CD4^+$ T-cell infiltration (scale bar = 100 µm). (b, c) $CD4^+$ cell number and area were higher in AD+RS vs AD-alone at both weeks (n = 8).

(d) Representative TUNEL staining (scale bar = 100 µm). (e, f) Apoptosis was increased in AD+RS, with higher $TUNEL^+$/DAPI and $TUNEL^+$ area/DAPI at both time points (n = 6-14).

(g) Representative TRPV1 staining (scale bar = 100 µm). (h) TRPV1 MFI was higher in AD+RS at both weeks (n = 8).

(i) Schematic of the proposed mechanism: Stress delays resolution and sustains sensory sensitization in AD via corticosterone-mediated immune–neuronal crosstalk, TRPV1-dependent C-fiber sensitization, and increased DRG excitability (Aβ fiber).

Data represented as mean ± SEM. ns = not significant, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ and $****p < 0.0001$. Two-way ANOVA with Tukey's test.