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Commentary

Sensory neuroimmune signaling opens a new precision medicine window for Stevens–Johnson syndrome and toxic epidermal necrolysis

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Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) remain among the most devastating forms of severe cutaneous adverse reactions [1]. Although substantial progress has been made in understanding the immune basis of these syndromes, especially the central role of drug-reactive cytotoxic CD8+ T cells, the mechanisms that sustain tissue injury after the initial drug-triggered immune activation remain incompletely understood. In this context, the study by Huang and colleagues provides an important conceptual advance by identifying a sensory neuroimmune circuit that amplifies CD8+ T-cell cytotoxicity in SJS/TEN [2]. Their work places calcitonin gene-related peptide (CGRP), its receptor component RAMP1, and the downstream HCN2-dependent calcium signaling pathway at the center of a previously underappreciated mechanism linking nociceptive neural activation with persistent epidermal destruction. This is not only biologically intriguing, but also highly relevant for translational and precision medicine-oriented thinking in severe drug hypersensitivity.

A major strength of this study lies in its integration of multiple levels of evidence. Using single-cell RNA sequencing of circulating CD8+ T cells, the authors show that SJS/TEN-associated effector and effector memory T-cell populations are transcriptionally skewed toward cell migration and cytokine–cytokine receptor interactions. Among neuropeptide-related receptors, RAMP1 emerged as a particularly notable signal in effector CD8+ T cells. This transcriptomic observation was then supported by immunofluorescence data showing increased RAMP1+CD8+ T cells in lesional skin. The authors further demonstrated that affected skin contains increased nerve density, an enrichment of CGRP-positive nerve fibers, and elevated blister-fluid CGRP levels. Importantly, CGRP levels correlated with acute disease duration, suggesting that neuroimmune activation is not merely an epiphenomenon but may be linked to disease persistence and severity. Together, these findings extend the classical view of SJS/TEN from a purely immune-mediated cytotoxic disease to a neuroimmune inflammatory disorder in which sensory pathways actively shape pathogenic T-cell responses.

The mechanistic depth of the study is particularly commendable. The authors do not stop at descriptive association; rather, they establish both sufficiency and necessity for the CGRP-RAMP1 axis [3] in enhancing pathogenic immune behavior. In vitro exposure of healthy donor-derived CD8+ T cells to CGRP increased expression of IL-15Rα and IL-18Rα and augmented the release of cytotoxic mediators, including granzyme B, perforin, TNF-α, and IFN-γ. These effects were further amplified when cells were subsequently exposed to IL-15 or IL-18, consistent with the blister-fluid cytokine milieu identified in patients. Conversely, blockade of CGRP signaling with the receptor antagonist BIBN-4096 or knockdown of RAMP1 reduced IL-15Rα and IL-18Rα expression in CD8+ T cells from patients with acute SJS/TEN. This bidirectional experimental design provides compelling support for a causal pathogenic role of neuropeptide signaling in disease-associated T-cell activation.

Another important contribution is the identification of HCN2 as a downstream mediator of this pathway. Calcium imaging revealed that CGRP induces calcium influx in CD8+ T cells, and this response was attenuated by ivabradine, an HCN channel blocker already approved for cardiovascular indications. Functionally, ivabradine reduced CGRP-driven upregulation of IL-15Rα and IL-18Rα and diminished the ability of CD8+ T-cell supernatants to induce keratinocyte apoptosis in a 3-dimensional skin model. This observation is especially valuable from a translational standpoint, because it moves the study beyond target discovery toward therapeutic plausibility. When an experimental mechanism converges on a clinically available drug class, the translational distance to early proof-of-concept trials becomes shorter. In the setting of SJS/TEN, where timely intervention is critical and therapeutic options remain limited, such repositioning opportunities deserve serious attention.

From the perspective of precision medicine, this work is especially thought-provoking. SJS/TEN is already a paradigmatic disease in precision prevention because of its strong association with HLA risk alleles, such as HLA-B15:02 and HLA-B58:01 in specific drug contexts. However, precision medicine should not stop at predicting who is at risk before exposure; it should also address how to stratify patients after disease onset, identify dominant pathogenic modules in individual cases, and tailor intervention accordingly. Huang et al. provide a framework for precisely this next step. Their data suggest that not all patients with SJS/TEN may be biologically identical. Some individuals may exhibit a more pronounced neuroimmune phenotype, characterized by increased CGRP-positive innervation, elevated blister-fluid CGRP, abundant RAMP1+CD8+ T cells, and strong IL-15/IL-18 receptor upregulation. Such patients may represent a mechanistically defined subgroup particularly suitable for therapies targeting CGRP signaling or HCN2-dependent pathways.

This possibility opens several clinically meaningful avenues. First, the molecules highlighted in this study could serve as candidate biomarkers for patient stratification. Blister-fluid CGRP is especially attractive because it is measurable, reflects local tissue biology, and appears to correlate with acute disease duration. Tissue RAMP1 expression on infiltrating CD8+ T cells may further help define a neuroimmune-high endotype. Likewise, IL-15Rα and IL-18Rα expression on circulating or lesional CD8+ T cells could function as dynamic immune readouts of pathway activation. In an ideal precision medicine framework, these markers could be combined with known genetic susceptibility factors, culprit-drug information, clinical

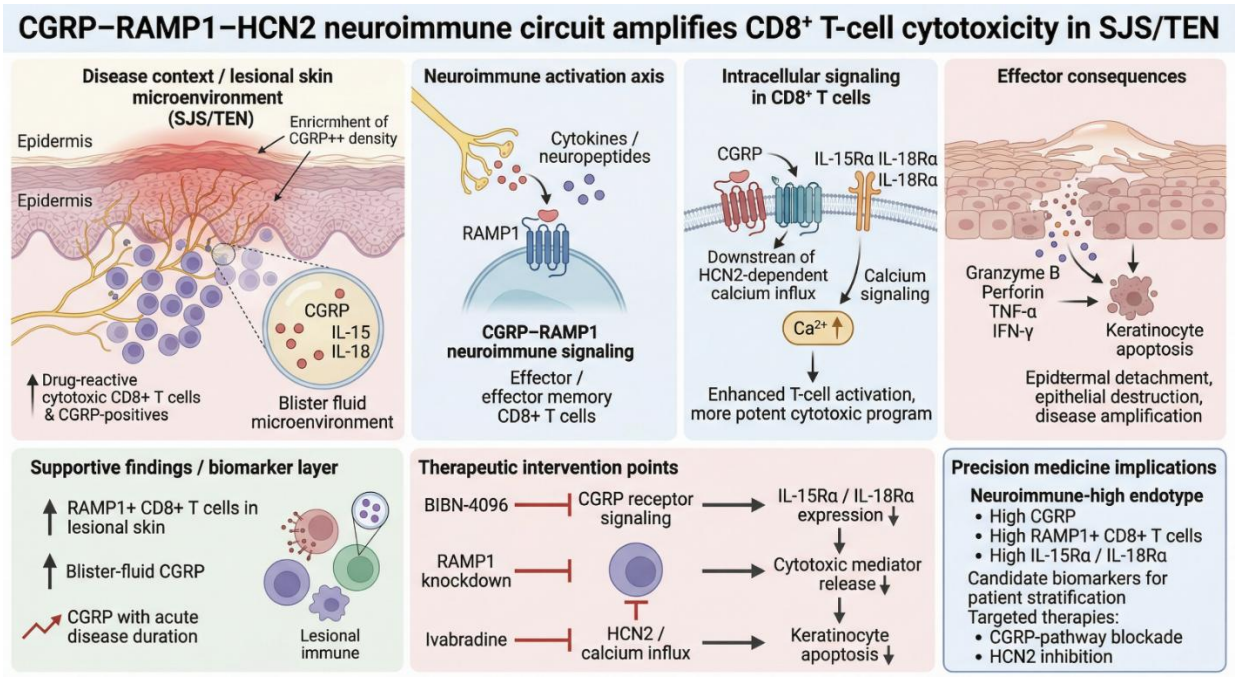

Figure 1. Proposed model illustrating how a sensory neuroimmune circuit sustains and amplifies tissue injury in Stevens–Johnson syndrome/toxic epidermal necrolysis. In this framework, CGRP released from nociceptive nerve fibers engages RAMP1 on effector CD8⁺ T cells, activating an HCN2-dependent calcium signaling pathway that enhances responsiveness to IL-15 and IL-18 and potentiates cytotoxic effector functions. This feed-forward loop promotes keratinocyte apoptosis and ongoing epidermal destruction beyond the initial drug-triggered immune response. The pathway is supported by biomarker evidence in lesional tissue and blister fluid and identifies a neuroimmune-high endotype with potential for targeted therapeutic intervention.

severity indices, and perhaps early omics-based signatures to generate a multidimensional model for prognosis and treatment selection.

Beyond its mechanistic depth, the study also prompts a reconsideration of how SJS/TEN is biologically stratified. Traditionally, the disease has been viewed through the lens of drug-specific immune activation, with genetic predisposition, particularly HLA alleles, guiding risk prediction prior to exposure. However, once the disease is established, patients are often managed as a relatively homogeneous group despite marked variability in clinical course and outcomes. The findings presented here suggest that a neuroimmune dimension may contribute to this heterogeneity. The degree of CGRP signaling, RAMP1 expression, and downstream cytokine receptor upregulation could reflect a distinct pathogenic axis that varies among patients. This raises the possibility that SJS/TEN encompasses biologically diverse endotypes rather than a single uniform process.

This perspective has several practical implications. Molecules identified in this study, such as CGRP in blister fluid or RAMP1 expression on infiltrating CD8+ T cells, may serve as accessible indicators of pathway activation. Their correlation with disease features, including duration and inflammatory intensity, suggests potential utility in monitoring disease dynamics. At the same time, the link between nociceptive signaling and immune activation provides a conceptual bridge between symptomatology and pathogenesis. Pain, a prominent and often debilitating feature of SJS/TEN, may not simply be a consequence of tissue injury but could also reflect ongoing neuroimmune interactions that sustain inflammation. Recognizing this connection could shift the clinical interpretation of symptoms from passive observations to biologically informative signals.

That said, several questions remain before this work can be translated into routine clinical practice. The sample size is understandable given the rarity and severity of SJS/TEN, but still relatively limited. Independent validation in multicenter cohorts will be essential to confirm the robustness and generalizability of the proposed pathway. It will also be important to define how specific this neuroimmune signature is for SJS/TEN compared with other severe inflammatory blistering or drug-induced skin disorders. Although the authors included some comparator conditions, larger disease-control analyses would help determine whether CGRP-RAMP1 activation is truly distinctive enough for biomarker-guided application.

In addition, the temporal dynamics of this pathway deserve closer study. Is CGRP signaling an early amplifier, a late sustainer, or both? Does it differ according to culprit drug, HLA background, mucosal severity, or systemic involvement? Can circulating biomarkers reliably substitute for tissue assessment in critically ill patients? Precision medicine depends not merely on identifying a target, but on knowing when, in whom, and how intensely that target matters. Longitudinal sampling and integrated clinical-pathobiological modeling will therefore be important next steps.

Another key issue is therapeutic safety. Because SJS/TEN patients are often acutely ill, vulnerable to infection, fluid loss, and multiorgan complications, any new intervention must be evaluated with extreme caution. Neuroimmune modulation may carry consequences beyond the skin, and CGRP itself has physiological roles in vascular and tissue homeostasis. Precision medicine here should therefore mean more than biomarker enrichment; it should include careful benefit-risk selection, dose optimization, and perhaps combination strategies tailored to disease phase.

Despite these caveats, the conceptual importance of this study is

undeniable. It challenges the field to move beyond a predominantly immunocentric model and to recognize that pathogenic tissue injury in severe drug reactions may be sustained by structured interactions between nerves, immune cells, and epithelial targets. Such a framework resonates strongly with the broader goals of precision medicine: identifying disease-relevant circuits rather than isolated molecules, classifying patients by mechanism rather than phenotype alone, and matching therapies to dominant pathogenic programs.

In conclusion, Huang and colleagues delineate a neuroimmune circuit in which CGRP-RAMP1 signaling enhances CD8+ T-cell effector function through an HCN2-dependent mechanism, thereby promoting keratinocyte apoptosis in SJS/TEN. Beyond advancing our understanding of disease pathogenesis, this work highlights the importance of integrating neural and immune components into the conceptual framework of severe drug reactions. It also suggests that future progress may depend on identifying biologically defined patient subsets and aligning therapeutic strategies with dominant pathogenic pathways. In this regard, neuroimmune signaling represents not only mechanistic insight but also a potential entry point for more individualized approaches to treatment in SJS/TEN.

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Declaration of competing interest

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Reference

1. Justice J, Mukherjee E, Martin-Pozo M, Phillips E. Updates in the pathogenesis of SJS/TEN. Allergol Int. 2025 Jul;74(3):361-371. doi: 10.1016/j.alit.2025.05.002. Epub 2025 Jun 4. PMID: 40473510; PMCID: PMC12256649.

2. Huang X, Ao S, Xu R, Gao X, Qi S, Liang Y, Feng P, Xue R, Ren Y, Han J, Li F, Chu C, Wang F. Sensory neuroimmune signaling in the pathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis. J Allergy Clin Immunol. 2025 Feb;155(2):533-546. doi: 10.1016/j.jaci.2024.10.015. Epub 2024 Oct 29. PMID: 39481654.

3. Kulalert W, Wells AC, Link VM, Lim AI, Bouladoux N, Nagai M, Harrison OJ, Kamenyeva O, Kabat J, Enamorado M, Chiu IM, Belkaid Y. The neuroimmune CGRP-RAMP1 axis tunes cutaneous adaptive immunity to the microbiota. Proc Natl Acad Sci U S A. 2024 Mar 12;121(11):e2322574121. doi: 10.1073/pnas.2322574121. Epub 2024 Mar 7. PMID: 38451947; PMCID: PMC10945812.