Neuro-immune crosstalk and neuronal sensitization in atopic dermatitis: a translational approach to itch and neuronal memory

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Abstract: Atopic dermatitis (AD) is an inflammatory skin disease characterized by immune dysregulation, chronic inflammation, and itch. Yet, the mechanisms underlying its persistence and recurrence remain largely unexplored. Furthermore, itch severity often does not correlate with clinical signs of inflammation. Understanding the mechanisms underlying this mismatch may help identify why itch persists in some patients independently of clinical disease activity.

Current literature has highlighted the role of neuro-immune crosstalk in the relationship between itch and AD, with growing interest in the concept of neuronal memory, where prior inflammatory events induce long-lasting changes in sensory pathways. This study aims to investigate mechanisms underlying persistent itch in AD by combining human and experimental approaches, with a particular focus on peripheral sensory neurons, (Remak) Schwann cells, and central neuronal circuits.

Using the MC903-induced mouse model of AD, we performed an initial pilot study in which ear skin, dorsal root ganglia (DRG), and brain tissues were collected for analysis of neuronal innervation, activation, and inflammatory signaling. Immunofluorescence and

confocal microscopy will be used to quantify cutaneous innervation ($PGP9.5^+$ fibers) and will be further expanded to expression of itch-associated markers such as TRPV1. Complementary molecular analyses, including qPCR, FACS, and serum proteomics, will evaluate neuropeptide and cytokine profiles associated with sensory sensitization, as well as the role of (Remak) Schwann cells and other peripheral cells.

To address the mismatch between itch and inflammation, behavioral readouts of scratching will be integrated with histological, molecular and cellular profiling. Mice will be stratified based on itch and inflammatory severity to identify signatures associated with high-itch/low-inflammation versus low-itch/high-inflammation, providing an experimental framework to investigate the clinical heterogeneity observed in patients. To further explore neuronal memory, we will investigate whether neuronal changes persist beyond the resolution of visible inflammation. FosTRAP-based labeling will be used to identify neuronal populations activated during itch and assess their reactivation during a later inflammatory episode. Brain regions involved in itch processing will be identified using activity-dependent markers and transcriptomic approaches to identify potential "itch engrams".

Human AD samples and clinical data will be analyzed to assess neuro-immune pathways using molecular data of human serum and PBMCs to investigate neuro-immune mediators, and human skin biopsies to assess cutaneous innervation and hyperinnervation. Preliminary analysis of clinical data from 96 patients demonstrates that itch and clinical disease severity can be discordant, with mismatched itch-disease profiles observed using both SCORAD and EASI. These molecular and structural findings

will be compared with clinical data, with a particular focus on itch scores, to identify neuro-immune features associated with persistent or high itch.

By integrating human and experimental data with behavioral, molecular, and neuronal approaches, this study aims to define mechanisms by which neuro-immune crosstalk and neuronal memory sustain chronic itch. These insights may explain clinical heterogeneity in AD and reveal novel therapeutic strategies targeting neural pathways rather than immune suppression alone.

Keywords: Atopic dermatitis, chronic itch, neuro-immune crosstalk, neuronal memory, hyperinnervation, MC903 mouse model

Acknowledgements and funding: CK-CARE by Kühne Foundation