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Revolutionizing mucosal defense: IL-25-educated effector-memory ILC2s redefine innate immune memory

Hongjiao Wang[1], Pan Zhu[1], Jiamo Wang[1], Keren Chen[1], and Zuliang Jie[1,2] ✉

[1] *State Key Laboratory of Cellular Stress Biology, School of Life Sciences, Faculty of Medicine and Life Sciences, Xiamen University, Xiamen, 361102, China*

[2] *MOE Key Laboratory of Spectrochemical Analysis and Instrumentation, College of Chemistry and Chemical Engineering, State Key Laboratory of Vaccines for Infectious Diseases, Xiang An Biomedicine Laboratory, Xiamen University, Xiamen, 361102, China*

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As the primary interface for host-environment interactions, the mucosal immune system must maintain a delicate physiological homeostasis among commensal tolerance, nutrient absorption, and pathogen defense[1]. Traditional immunological paradigms have long held that "immunological memory" is the exclusive hallmark of the adaptive immune system (T and B cells), enabling rapid and highly specific responses upon secondary antigen exposure; conversely, the innate immune system has been relegated to a primary line of defense mediating immediate, non-specific responses[2,3]. Although the recent concept of "trained immunity" has revealed that myeloid cells can acquire memory-like phenotypes via epigenetic reprogramming, it remains controversial whether tissue-resident innate lymphoid cells (ILCs) possess an independent, long-lasting, and non-stem-cell-dependent mnemonic capacity[4]. A breakthrough study by Cortez et al. published in *Cell* has revolutionized this conventional understanding by identifying a novel population of "effector-memory type 2 innate lymphoid cells" (emILC2s)[5]. This study demonstrates that the cytokine IL-25 can induce persistent epigenetic reprogramming in ILC2s, thereby establishing robust defensive adaptations across multiple organs and revealing the critical role of innate immune cells as the "core drivers" in remodeling tissue homeostasis (Fig. 1).

This breakthrough in the theoretical paradigm stems from an in-depth dissection of the evolutionary adaptive mechanisms of the small intestinal mucosa. During the long-term co-evolution of the host and parasitic helminths, the small intestinal mucosa has evolved the canonical "tuft cell-ILC2 feedback circuit"[6]: chemosensory tuft cells residing in the epithelial layer secrete the alarmin IL-25 upon sensing helminth-derived signals, which specifically activate type 2 innate lymphoid cells in the lamina propria. The activated ILC2s release copious amounts of IL-13, driving the epithelial compartment toward lineage-biased differentiation into goblet and tuft cells, ultimately forming a pathogen-expulsion phenotype characterized by an enhanced protective mucus layer. Recognizing the potential plasticity of this circuit, Cortez et al. designed a longitudinal interventional model[5]. They discovered that a mere 4-week regimen of recombinant IL-25 was sufficient to induce durable tissue-level remodeling in the murine small intestine. Notably, even after treatment cessation and a resting period of up to 50 days (equivalent to more than 10 turnover cycles of the intestinal epithelium), the small intestines of these mice maintained a significantly elongated morphology, accompanied by a constitutive expansion of tuft and goblet cell numbers within the epithelial architecture. This tissue-level "memory" phenotype exhibited profound stability, persisting even 6 months post-induction. These results robustly demonstrate that IL-25 exposure does not merely trigger a transient inflammatory cascade but fundamentally reprograms the homeostatic baseline of mucosal tissues.

Given the extreme durability of this mucosal tissue remodeling, identifying the cellular basis sustaining this long-term "tissue memory" became a central question[7]. Considering the high turnover rate of intestinal epithelial cells[8], prevailing theories postulated that such long-lasting tissue adaptation arises either from the intrinsic epigenetic reprogramming of long-lived intestinal stem cells (Lgr5$^+$ ISCs)[9] or from compositional shifts in the commensal microbiota[10]. However, Cortez et al. rigorously excluded both mechanisms through in vivo and in vitro validations[5]. The study showed that neither co-housing nor cecal microbiota transfer could transmit the defensive phenotype, and germ-free mice established identical tissue adaptation following IL-25 intervention, directly ruling out the necessity of the microbiota. Concurrently, single-cell RNA sequencing (scRNA-seq) and Assay for Transposase-Accessible Chromatin sequencing (ATAC-seq) revealed that IL-25-induced Lgr5$^+$ ISCs were essentially indistinguishable from controls at both the transcriptomic and epigenetic levels. Furthermore, organoid co-culture experiments confirmed that the lineage-biased differentiation of the epithelium toward tuft cells was entirely dependent on effector-memory ILC2s (emILC2s) and their secreted IL-13. This series of findings poses a substantial challenge to the recently prevalent model of "stem cell training" mediating tissue memory, confirming that, in this context of mucosal adaptation, epithelial stem cells act merely as passive effector units responding to local microenvironmental cues, rather than as the true repository of the memory imprint.

Having systematically ruled out the aforementioned possibilities, the investigation ultimately focused on the immune cells themselves. By utilizing Rag1-deficient mice to exclude the involvement of adaptive lymphocytes (T/B cells), the researchers confirmed that the IL-25-induced tissue adaptation persisted long-term; conversely, targeted depletion of ILC2s using genetic models or blockade of IL-4Rα/IL-13 signaling led to a rapid collapse of the

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✉Address correspondence to Zuliang Jie, jiezuliang@xmu.edu.cn

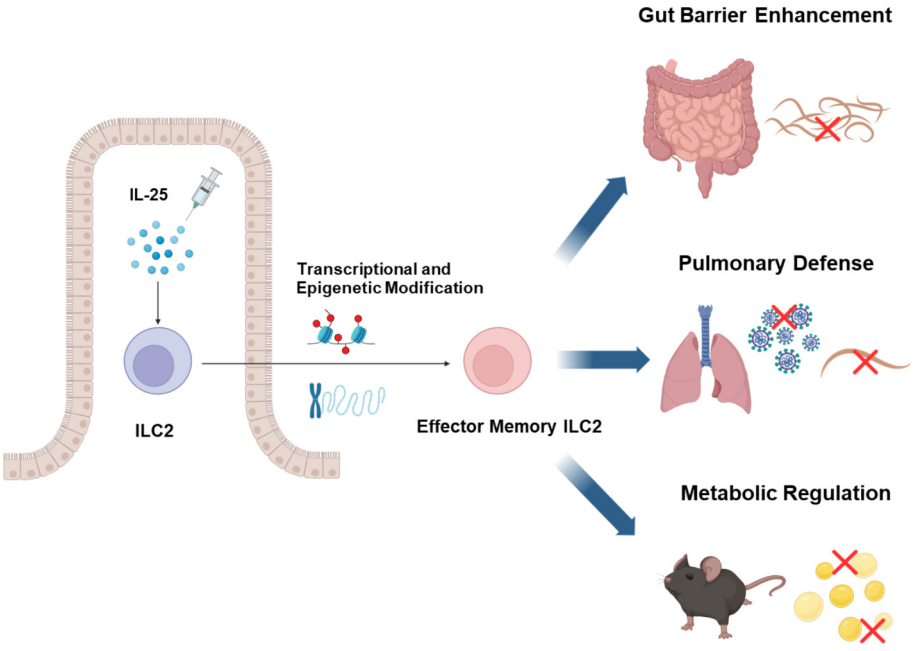

Figure 1 IL-25-driven memory type 2 innate lymphoid cells underpin mucosal immunity. Cortez et al. showed that administering IL-25 alone is sufficient to induce long-lasting anatomical and immunological adaptations in the small intestine. These changes persist for months and confer broad resistance to barrier pathogens, even at distal sites such as the lung. This adapted state is maintained by a distinct population of transcriptionally and epigenetically reprogrammed effector-memory ILC2s (emILC2s), which remain active independently of canonical alarmins and do not promote chronic inflammation. The figure was created with BioRender.com.

established tissue adaptation, with the epithelial architecture reverting to baseline. This series of in vivo experiments definitively localized the vehicle of mucosal memory to a population of IL-25-educated "effector-memory ILC2s" (emILC2s). This newly identified cellular subset differs fundamentally from resting-state ILC2s in its biological properties. Phenotypically, emILC2s downregulate canonical markers such as CD25, CD127, and Sca-1, and upregulate PD-1 and CTLA-4; however, this seemingly "exhausted" surface profile belies a potent, constitutively active state. Functionally, even in quadruple-knockout mice simultaneously lacking the four key alarmin signals (IL-25, IL-33, TSLP, and IL-18), emILC2s, once induced, can survive long-term in situ and maintain high levels of cytokine expression. The molecular mechanism underlying this functional independence originates from their persistent epigenetic reprogramming—ATAC-seq data revealed that emILC2s acquire a more prominent open chromatin conformation at core type 2 cytokine loci (including Il13, Il5, and adjacent regulatory regions such as Rad50). This epigenetic remodeling keeps key defensive genes in a "poised" state, maintaining basal cytokine transcription without the need for intense triggering by exogenous alarmins.

Notably, Cortez et al. further revealed that the impact of emILC2s is not restricted to the local intestinal environment but establishes a distributed, multi-tissue defensive network via systemic migration. The emILC2s activated in the small intestine can enter the circulation, migrate to, and colonize the lungs, large intestine, and adipose tissue, while retaining their distinct epigenetic imprints and potential for high effector cytokine expression. This systemic immune remodeling confers broad-spectrum adaptability upon the host to counter diverse environmental stressors: in a model of enteric bacterial infection (Salmonella typhimurium), emILC2s significantly reduced bacterial burdens in the spleen and mesenteric lymph nodes, promoting pathogen clearance; during respiratory viral infection (SARS-CoV-2), although overall survival rates were not significantly altered, emILC2s enhanced the host's "disease tolerance," enabling infected mice to recover from severe weight loss rapidly. Even more strikingly, the physiological function of this immune memory extends to systemic metabolic regulation—emILC2s residing in adipose tissue significantly reduced fat accumulation in mice, thereby restricting overall weight gain while maintaining lean mass. This body of evidence indicates that emILC2s are not merely "broad-spectrum defenders" against multiple classes of pathogens, but also serve as core cross-organ hubs coordinating immunity and metabolic homeostasis, allowing the host to maintain health at a lower physiological cost when facing exogenous infections or endogenous metabolic pressures.

This series of groundbreaking discoveries not only fills a theoretical void regarding innate immune memory but also provides crucial mechanistic insights for the innovation of clinical intervention strategies. Cortez et al. demonstrated that emILC2s acquire durable tissue adaptability through epigenetic remodeling, and the maintenance of their effector functions is entirely independent of classical alarmin signals such as IL-33 and TSLP. This alarmin independence suggests, on the one hand, that antibody blockade therapies targeting upstream cytokines may struggle to reverse cellular memories that have already been epigenetically "hard-wired," implying that future interventions for chronic inflammation may need to pivot toward targeting the underlying epigenetic modification machinery. On the other hand, it also reveals that emILC2s can safely and autonomously maintain mucosal immune resilience without triggering pathogenic allergic reactions. Building on this, the research team proposed a novel strategy utilizing specific cytokine-driven approaches (e.g., IL-25) to enhance the long-term defensive capacity of the mucosal barrier systemically. Distinct from traditional paradigms reliant on antigen-specific recognition, inducing and modulating emILC2s could establish a broad-spectrum, cross-organ protective barrier of pre-adaptation for the host. In conclusion, this study establishes the central position of emILC2s in tissue adaptation, proving their ability to translate transient environmental stimuli into durable,

multi-tissue defense and metabolic homeostasis; this paradigm shift in our understanding not only deepens our knowledge of how the innate immune system orchestrates tissue homeostasis but also points the way toward the development of novel mucosal interventions designed to boost broad-spectrum host resilience while avoiding immunopathological damage.

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Ethics approval and consent

N/A

Consent for publication

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Conflicts of interest

The authors declare no competing financial interests.

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