The Intestine-lung Trafficking of Memory-like Group 2 Innate Lymphoid Cells Orchestrates Asthma Relapse

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Abstract

Background: Recent works imply that immune memory might be expanded to group 2 innate lymphoid cells (ILC2s), but the cellular and molecular bases are largely unknown. Here, we investigated the memory and migrating properties of Lin $^{-}$KLRG1 $^{+}$IL-17RB $^{+}$ ILC2s (herein referred as mILC2s) and their contribution to asthma relapse. **Methods:** Clinical asthmatic subjects and HDM-induced mice asthma models were applied to investigate the memory-like characteristics of mILC2s including greater effector cytokine-producing potential and *in vivo* persistence. Parabiosis pairs of CD45.1 $^{+}$ and CD45.2 $^{+}$ mice were employed to determine whether mILC2s were circulating cells. Adoptive transplantation was performed to analyze the origin of the mILC2s accumulated in airway upon asthma relapse. CCR9 and S1P signaling blockade were used to confirm the migration of mILC2s during different asthma phases by *In vivo* imaging. KLRG1 neutralization was utilized to analyze the role of mILC2s in asthma relapse on *Rag1* $^{-/-}$ mice. **Results:** mILC2s persisted *in vivo* and retained the potency of producing IL-13 and re-inducing allergic responses. Critically, parabiosis study and *in vivo* imaging showed that the vast majority of mILC2s migrated to and resided in small intestine during asthma remission, and subsequently moved to airway upon re-encountering antigens, regulated by CCR9 and S1P signaling. Blockade of S1P signaling markedly limited secondary exposure-induced airway inflammation. Furthermore, KLRG1 neutralization attenuated asthmatic responses of *Rag1* $^{-/-}$ mice, supporting a pivotal role for mILC2s in mediating asthma relapse independent of adaptive immune cells. **Conclusion:** mILC2s exhibit memory-like and lung-small intestine migratory properties, which empowers them to drive asthma relapse.

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