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ILC2s and miRNA regulation in allergy and asthma

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin,
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av

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Avhandlingen baseras på följande delarbeten:

I. MicroRNA-155 is a critical regulator of type 2 innate lymphoid cells and IL-33 signaling in experimental models of allergic airway inflammation.
Johansson K, Malmhäll C, Ramos-Ramírez P, Rådinger M.
J Allergy and Clin Immunol. 2017; 139(3):1007-1016.e9

II. Altered miR-155 expression in allergic asthmatic airways.
Malmhäll C, Johansson K, Winkler C, Alawieh S, Ekerljung L, Rådinger M.
Scand J Immunol. 2017; 85(4):300-307

III. Bone marrow type 2 innate lymphoid cells: a local source of interleukin-5 in interleukin-33-driven eosinophilia.
Johansson K, Malmhäll C, Ramos-Ramírez P, Rådinger M.
Immunology. 2017; 153(2):268-278

IV. MicroRNA signatures in asthmatic and healthy airway macrophages.
Johansson K, Weidner J, Malmhäll C, McCrae C, Rådinger M.
In manuscript

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ILC2s and miRNA regulation in allergy and asthma

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Abstract

Asthma is a common respiratory disease that is characterized by chronic inflammation of the airways. In most asthmatic subjects, the immune response is driven by pro-inflammatory type 2 cytokines (interleukin (IL)-4, IL-5 and IL-13) that correlate with hypersensitivity to environmental allergens and increased numbers of eosinophils in the airways and blood. In 2010, type 2 innate lymphoid cells (ILC2s) were identified as a novel type 2 cytokine-producing cell population. They were later found to promote allergen-related immune responses in the airway mucosa, where the alarmin cytokine IL-33 is an important driver.

Understanding the molecular mechanisms that cause excessive immune activation is an important area of asthma research. Gene regulatory microRNAs (miRNAs) are emerging as promising targets for modulation of type 2 immunity and play important roles in models of allergic asthma. However, miRNA expression in ILC2s and in the airways of human asthmatics is currently understudied. Using samples from asthmatic subjects and experimental mouse models of asthma we identified that miRNA-155 (miR-155) is critical for ILC2-mediated inflammation in mice (Paper I). Lung ILC2s increased miR-155 expression upon IL-33-mediated activation *in vitro* and miR-155 deficient ILC2s demonstrated decreased IL-13 production and lowered proliferative capacity to IL-33 administration *in vivo*. Importantly, this was accompanied by a severe reduction of airway eosinophils. We identified that miR-155 is differentially expressed in airways of subjects with allergic asthma compared to healthy controls (Paper II). Furthermore, induced sputum isolated from allergic asthmatics in and out of pollen season revealed that the level of miR-155 in sputum lymphocytes varied with the season. In Paper III, we identified a previously unrecognized role of ILC2s locally in murine bone marrow. We found that IL-5-producing ILC2s contribute to the development and overproduction of eosinophils that promoted airway inflammation. Finally, we identified distinct differences in miRNA expression by examining miRNA profiles in airway macrophages isolated from bronchial lavage of asthmatic and healthy individuals (Paper IV).

Taken together, these studies demonstrate that miRNAs play important roles in airway immunity; miR-155 is necessary for the pro-inflammatory function of ILC2s, miR-155 expression is altered in airway lymphocytes from asthmatic subjects and a distinct miRNA signature is present in asthmatic airway macrophages. We also demonstrated that ILC2s have additional roles in allergic immunity and support eosinophilic airway inflammation by local reactions in the bone marrow. An increased understanding of the mechanisms that promote chronic type 2 inflammation in various tissues, and in specific cells, is essential for the development of improved prevention and therapy of the disease in the future.

Keywords: microRNA, type 2 innate lymphoid cell, IL-33, IL-5, eosinophil

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