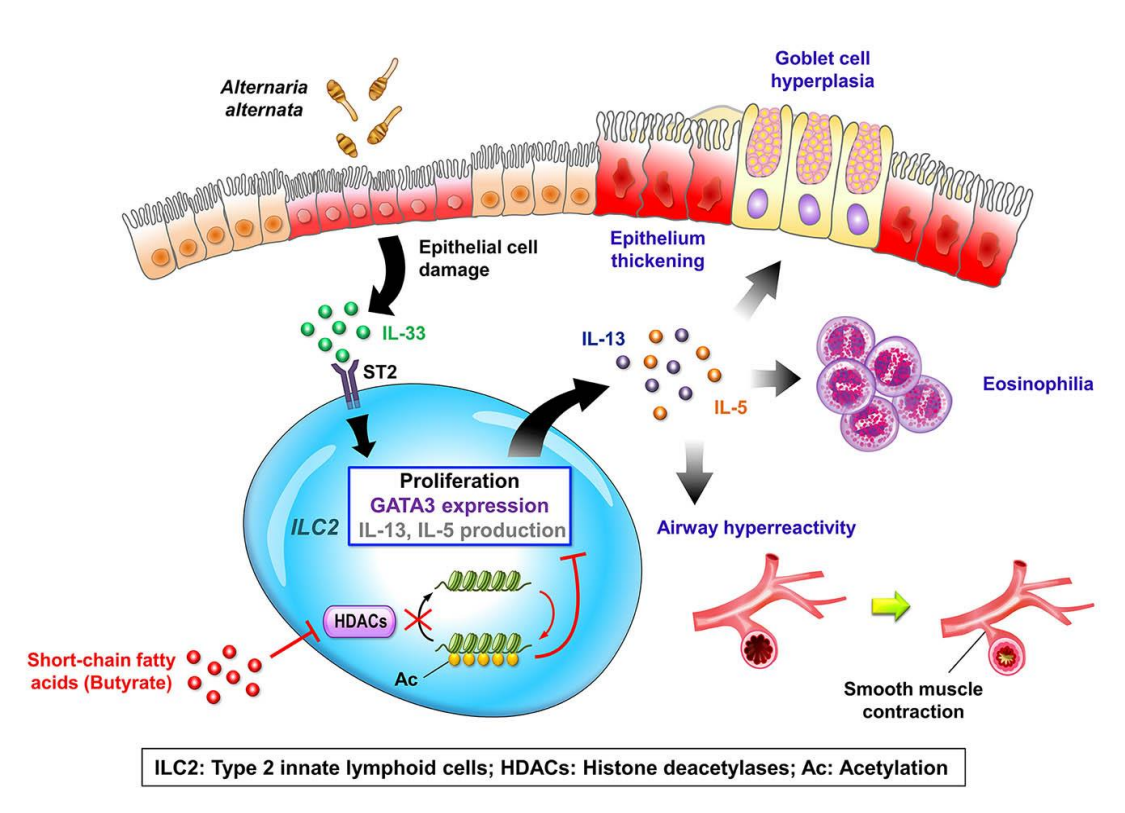
Commensal bacteria metabolite butyrate suppresses asthma caused by group 2 innate lymphoid cell

Short chain fatty acids (SCFAs) are the fermentation products of multiple bacterial phyla, including Bacteroidetes, Firmicutes and Fusobacteria, and exist naturally in our body. The immunoregulatory roles of SCFAs have been extensively studied in intestinal disorders such as inflammatory bowel disease (IBD). SCFAs have also been identified in the respiratory tract of healthy and asthmatic subjects, and a strong correlation exists between the severity of asthma and the microbial dysbiosis in the lungs. However, the role of SCFAs in lung diseases, particularly group 2 innate lymphoid cell (ILC2)-dependent asthma remains unclear. A team led by Dr Ya-Jen Chang, an Assistant Research Fellow at the Institute of Biomedical Sciences (IBMS) in Academia Sinica, discovered a new mechanism of SCFA butyrate in the regulation of ILC2 function. The research was published in the Journal of Allergy and Clinical Immunology on March 6th, 2018.

Allergic asthma is a chronic inflammatory disease of the airway characterized by hyperreactivity to inhaled antigens and Th2 response. Although the classical paradigm suggests that Th2 cells are the key players in allergic asthma, recent studies have implicated ILC2s in the pathobiology of asthma. ILC2s are innate lymphocytes present at mucosal barrier tissues such as lung, and are critical sources of innate type 2 cytokines, mainly IL-13 and IL-5, which drive airway hyperreactivity (AHR) and eosinophilia, the cardinal features of asthma. In addition, ILC2s have been shown to promote memory T cell responses to antigen re-exposure by inducing chemokine production and dendritic cell migration. Clinically, ILC2s and their activating cytokines, IL-33 and TSLP, are associated with steroid-resistant asthma exacerbated by fungal sensitization. Given their clinical importance, ILC2s represent as important target for therapeutic intervention. Despite increasing efforts, much remains to be elucidated regarding the mechanisms by which ILC2s are regulated.

In this study, Dr. Chang and her team show that the SCFA butyrate, but not propionate or acetate, directly inhibits ILC2 cytokine production. Systemic and local administration of butyrate ameliorated ILC2-induced AHR and type 2 inflammation in IL-33 and *Alternaria alternata* models of murine asthma. Mechanistically, butyrate inhibits ILC2 proliferation and GATA3 expression through histone deacetylase inhibition independently of G-coupled protein receptor 41 (GPR41) and GPR43. These results implicate a role for butyrate as a negative regulator of ILC2 function and may serve as a potential therapeutic target for the treatment of ILC2-driven asthma.



Butyrate attenuates ILC2 function by inhibiting GATA3 expression, cytokine production and cell proliferation through the inhibition of HDAC activity.

The first author Christina Li-Ping Thio is a Ph.D. student in the Taiwan International Graduate Program in Molecular Medicine (TIGP-MM) at Academia Sinica. This project is funded by the Ministry of Science and Technology and the Academia Sinica Career Development Award.

Dr. Chang and her team's research article entitled "Regulation of type 2 innate lymphoid cell-dependent airway hyperreactivity by butyrate" is available at: http://www.jacionline.org/article/S0091-6749(18)30325-7/abstract

The complete list of authors is:
Christina Li-Ping Thio, Po-Yu Chi, Alan Chuan-Ying Lai, and Ya-Jen Chang

Media contact:
Dr. Ya-Jen Chang, Institute of Biomedical Sciences, Academia Sinica
Email: yajchang@ibms.sinica.edu.tw; (Tel) +886-2-2789-9050